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Are patients with Parkinson's disease who have either mild to moderate microsmia, severe microsmia or anosmia clinically different?

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ABSTRACT

Introduction

Olfactory loss is a common non-motor symptom of Parkinson's disease (PD), which has the potential to have a negative effect on quality of life. However, research examining PD patients with varying degrees of loss of sense of smell and whether they are clinically distinct and the implications of the loss of sense of smell when nursing a patient with PD appears to be poorly explained.

Objective

To investigate whether patients with PD who have either mild/moderate microsmia, severe microsmia or anosmia (as measured by the University of Pennsylvania Smell Identification Test (UPSIT)) were clinically different when compared across a range of motor, non-motor and quality of life domains.

Methodology

This is an open cross-sectional observational study, involving 112 patients (of both genders) who have a diagnosis of PD. Tools and scales used include the motor rating subscales in the Unified Parkinson's Disease Rating Scale (UPDRS), the Non-motor Symptoms Questionnaire (NMSQ), the PDQ39 Quality of Life Questionnaire (PDQ39), the Hoehn and Yahr scale (H&Y), the Rapid Eye Movement Behaviour Disorder Screening Questionnaire, (RBD) and the Montreal Cognitive Assessment (MoCA).

Results

Seventy-two males and forty females have been recruited for this study. Age ranged from 49 - 89 years (mean age 71 years). Eight-five (77%) of the PD patients were at stage 1 or 2 Hoehn and Yahr staging highlighting the study sample mainly consisted of PD patients with minimal or no functional impairment, without impairment of balance. Disease duration ranged from 6 months to 19 years (mean duration 5.5 years). All PD patients (except two) were considered to have either normal cognition or mild cognitive impairment, defined by the MoCA (mean MoCA 26.1).

All the PD patients recruited for this study had loss of sense of smell and 91% had -in fact- severe microsmia or anosmia. Seventy-nine (70.5%) PD patients correctly detected a reduced sense of smell. Twenty-nine out of the 33 PD patients (97%) (self-reporting a normal sense of smell) had, in fact, a severe degree of loss of sense of smell (Mean UPSIT 16) without realising it.

Overall loss of sense of smell was not correlated with severity or stage of PD, duration of disease, medication, smoking, the environment in which the PD patient was tested, whether they had phantosmia (persistent pleasant or disgusting smell) or taste problems. There was also no correlation between the motor, non-motor, rapid eye movement disorder and quality of life themes during whole group analysis. However, on sub-group analysis, a positive correlation was noted between sense of smell score and PD patients with normal cognition compared to those with mild cognitive impairment using MoCA (r_s=0.213, p=0.024) and non-motor symptom dribbling of saliva during the day (p=0.003), There was also a negative correlation in PDQ39 cognition theme (score r_s=-0.012 p=0.036), minutes since last PD medication taken (r_s=-0.2634, p=0.008), timing of levodopa dose (r_s=-0.1875, p=0.015), and individual domains of the UPDRS motor scores, including posture (r_s= -.231 p=0.014) facial expression (r_s=-0.207 p=0.029) and arising from a chair (r_s=-0.190 p=0.045).

Conclusion

This study raises three important points; (i) all the PD patients in this study had abnormal sense of smell, highlighting that loss of sense of smell in PD is very common, (ii) PD patients need to be formally tested to assess their degree of smell loss as their ability to recognise this cannot be relied upon and (iii) olfactory loss can be profound even in in the early stage and duration of PD.

However, there were several limitations to the present PhD study due to a possible sample size effect and some aspects of this study relied on self-reported data in the form of questionnaires which could be a potential source of bias.

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PREFACE/ACKNOWLEDGEMENT

I started my PhD study with the intent to put back, in some small way, knowledge about the sense of smell and its correlation to other Parkinson's disease symptoms. This PhD thesis is the report of this process. I cannot express the long days spent researching olfaction, sense of smell, hyposmia, anosmia, microsmia, phantosmia and any number of other names describing the human sense of smell, the battle of the p values, medians, standard deviations correlations and a host of other analytical statistics, getting to grips with the pathology the olfactory bulb, anterior olfactory nucleus, cerebellum and lewy bodies, the relentless reading of every sentence, paragraph and chapter of this paper and and the heartache with each failed attempt. However, the joy of completing each milestone, the hope for original results, and the expansion of knowledge makes it all worthwhile.

Along this journey I have met and had the pleasure of working with some quite exceptional people. I would like to therefore personally thank; Ahmed Khattab, Professor of research for being such a great supervisor. Always on hand to help and to nudge me in the right direction. I truly could not have found anybody better to get me through the graduate experience. Khaled Amar, a medical consultant colleague for two decades and supervisor. Thank you for believing in me and encouraging me to do this. It has provided me with an experience I will never forget and for that I am eternally grateful. Michele Board, fellow PhD student, fellow nursing colleague and dear friend. Encouraged always by her words of wisdom, determination and dedication to nursing and research. Sharon Atkins and Chantel Cox both exceptional nursing colleagues whom not only went out their way to ensure I had the appropriate study sample but then contacted those willing to participate in this study to avoid research bias. Janine Faulkner and Pam Lovell my admin support workers who helped immensely to take the pressure off completing a part time PhD whist still trying to run a Parkinson's disease service.

I would also like to sincerely thank my family. Those most affected by this journey. My partner Tony Dorey, my rock, supporting me in so many ways that only your partner and friend can. Tony's children Frazer and Elliot Dorey always keen to see how I was getting on and always ready to help. My children Louis, Janie and Emily Thompson for their youthful enthusiasm, encouragement and help with referencing.

My friends, Pauline Cartmell and Julie Carter who between them didn't have a clue what I was talking about but still listened intently and finally the person that gave me the strength to face challenges with confidence, and the most important person of all, my mother, Peggy Marguerite Cox. I would have made her very proud.

DECLARATION OF AUTHORSHIP

I, Cindy Marguerite Cox

declare that this thesis entitled

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and the work presented in this thesis are both my own and has been generated by me as the result of my own original research.

I confirm that that:

1. This work was done wholly or mainly while in candidature for a research degree at this University;

2. Where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

3. Where I have consulted the published work of others, this is always clearly attributed;

4. Where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;

5. I have acknowledged all main sources of help;

6. Where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

7. parts of this work have been published as:

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- Cindy Cox Ahmed Khattab, Khaled Amar. Non-motor symptoms in a cross section of PD patients with varying degrees of smell loss. Poster presentation. International Congress of Parkinson 's disease and Movement Disorders. Vancouver Canada 2017.

Signature of candidate

Date 12/6/18

CHAPTER 1

INTRODUCTION

1.1 OVERVIEW

The clinical diagnosis of Parkinson's disease (PD) is currently outlined by the UK Parkinson's Disease Brain Bank Clinical Diagnostic Criteria and relies on the presence of bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions) and at least one of the following:- muscular rigidity, 4-6 Hz rest tremor and postural instability, not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction (Hughes et al 1992). Despite these diagnostic criteria, the accuracy of such a diagnosis, even after long term follow-up (applied by experts), has at its best 84%-90% sensitivity (Rizzo et al 2016, Brooks 2012, Hughes et al 2001).

It is now known however, that non-motor symptoms as well as the typical motor features are well recognised in PD (Chaudhuri et al 2006). These include sensory disturbances such as visual contrast sensitivity, colour perception, and sensations associated with proprioception (such as numbness and tingling) (Doty et al 1995). However, the most consistent sensory deficit in PD is olfactory impairment (Tissingh et al 2001). The neuropathological basis of this dysfunction is neuronal damage in the olfactory system, including the olfactory bulb and the anterior olfactory nucleus (Braak et al 2003).

Impairment of olfaction in PD was first recognised in the 1970s (Ansari and Johnson 1975, Constandinidia et al 1970). There is now good research evidence that the ability to smell is significantly affected in PD compared to the general population (Cajuns et al 2013, Latvian et al 2003, Artmaker et al 2002, Hawkes et al 1999, Hawkes and Shephard 1998, Mesholam et al 1998, Hawkes et al 1997, Doty et al 1988, Quinn et al 1987) and affects at least 80% of PD patients (Double et al 2003, Mesholam et al 1998, Hawkes

et al 1997). There is also evidence that impaired olfaction may precede the classical motor manifestations by several years (Ross et al 2008, Haehner et al 2007, Stiasny-Kolster et al 2005, Pones et al 2004, Hawkes 2003, Berendsen et al 2001, Doty et al 1988), suggesting that neuronal damage occurs early in the diagnosis before the classical motor signs are evident (Braak et al 2003).

Although olfactory deficits are now considered a highly characteristic feature of PD (Katzenschlarger and Lees 2004), several studies suggest that olfactory deficits in PD are unrelated to factors such as disease stage and duration (Haehner et al 2009, Hawkes et al 1997, Doty et al 1988, Quinn et al 1987, Ward et al 1983). However, a study by Tissingh et al (2001) highlighted that smell discrimination scores were related to disease severity, suggesting that at least some aspects of olfactory dysfunction in PD patients may be secondary to ongoing degenerative processes in PD.

Interest in the phenomenon has grown markedly in the past few years, driven by the hope of developing neuroprotection treatment for patients in the early stage of the disorder. This PhD study however, aims to explore the relationship between olfactory dysfunction in PD and disease severity, within the motor, non-motor and quality of life domains. Patients with PD were divided (depending on their sense of smell scores) into three sub-groups (mild/moderate microsmia, severe microsmia and anosmia) to see if they are clinically different. This study also addresses the implications of the loss of sense of smell for nursing a patient with PD.

1.1.1. Prevalence of PD

Parkinson's disease is the second most common chronic neurodegenerative condition in older people especially beyond the age of sixty (Office for National Statistics. Age structure: Census 2001, Spillantini and Goedert 2000, De Rijk et al 1997). It occurs because of the progressive loss of dopamine-producing nerve cells in a region of the brain called the substantia nigra.

There are a limited number of prevalence studies that have been carried out in various United Kingdom (UK) regions over the last two decades (Walker et al 2010, Wickremaratchi et al 2009, Porter et al 2006, Hobson et al 2005, Schrag et al 2000, Mutch et al 1986). Their results on prevalence ranged from 105 to 178 persons with Parkinson's per 100,000 of the population. The possible reasons for such a varied range of prevalence may be attributed to the fact that all these studies have been performed in specific regions, biased by the characteristics of the populations studied. Therefore, access to and quality of health care services and the accuracy of diagnosis at local level may be factors affecting the differences in prevalence (Parkinson's UK 2009) A relatively more recent study (Parkinson's UK 2009) calculated the prevalence of PD (using the clinical practice research datalink) as 27.4/10,000 which is equivalent to 126,893 cases when scaled up to the total UK population of whom 69,850 were males and 57,043 were females (males are 1.5:1 times more likely to develop PD than females (Wooten et al 2004). The highest prevalence rate of Parkinson's was among those aged > 80 years. Future trends suggest the number of people with Parkinson's will increase to 162,000 in 2020 which represents a 28% increase on the 2009 figure with particular increase in the older age group (Parkinson's prevalence in the UK 2012). Currently, over 500 people with a diagnosis of PD are registered on the local PD Trust database.

1.1.2. Socio-Economic Burden of PD

Few studies have examined the cost of PD in the UK. An early study conducted by West (1991) reported an annual cost to the National Health Service of £126 million. This figure was based on national statistics and considered direct costs only. A more recent study (Findley et al 2003), used a cross-sectional, survey-based approach through interviews and study questionnaires to 432 PD patients, in which three categories of direct costs were included: NHS costs, social service costs and private PD-related expenditures. Costs were analysed according to age and disease severity (Hoehn and Yahr stage) of PD. Direct costs in the UK were estimated at £5993 per patient per year, NHS costs (38%) social services costs (35%) and

private expenditure (27%). This equates to £288 million annual costs to the National Health Service, £266 million annual costs to social services and £205 million annual costs to private expenditure. In clinical practice, the rise in social services costs is particularly influenced by the degree of disability (Hoehn and Yahr stage). Findley et al (2003) in their study identified that disease severity was a crucial factor associated cost. Thus, total cost of PD in the UK, using the recent Parkinson's disease UK (2006) prevalence study on direct costs might be as high as £760 million annually.

Therefore, the cost of PD is extremely high in both economic terms and in terms of the impact on patients' lives. For these reasons, strategies that maximise quality of life, while minimising the impact of disease progression, are paramount. This can be achieved by not only optimising therapies to treat motor symptoms but also by addressing non-motor complications and quality of life issues, such as those that are (and might be) associated with a reduced sense of smell.

1.1.3 Implications for Nursing

The sense of smell is an important chemical warning system that regulates food intake and is involved in social and personal interactions and relationships and is linked to our memories and places. Consequently, adverse effects in patients with olfactory disorders have been reported with regards to poor safety, difficulties cooking and detecting spoiled food, decreased food enjoyment and poor appetite, change in body weight, worries about personal hygiene, depression and mood changes, feelings of vulnerability, and deterioration in work life, social interactions and sexual life (Hummel and Nordin 2005). This highlights that reduced sense of smell is associated with reduced quality of life.

There appears, at this present time, no evidence in the literature that any treatment exists to reverse, protect or slow down the loss of sense of smell seen in PD and therefore coping strategies play a vital role in dealing with everyday problems. Nurses, not only due to their expertise in the bio-

psychosocial approach to care, but also because they are direct care providers are in an ideal position to advise on coping strategies and refer to other members of the multi-disciplinary team.

As a nurse consultant working with patients with Parkinson's disease and allied conditions, the role, although diverse, is also firmly grounded in direct care provision or clinical work with patients and families. However, unlike general nurses this involves regular reviews via nurse led clinics, home visits, in-patient visits, and telephone consultations. The role requires advanced skills in physical examinations, interpreting diagnostic tests, communication, prescribing medication and monitoring the effectiveness of therapeutic interventions. The ability to comprehensively assess patients for risk factors and early signs of illness due to the complex and unpredictable care events that PD patients encounter is paramount.

1.2. GENERAL REVIEW OF THE LITERATURE EXPLORING THE GAPS IN CURRENT KNOWLEDGE AROUND THE LOSS OF SENSE OF SMELL IN PD

The major objectives of this literature review were to: (i) explore the sense of smell in relation to PD and the significance of this for PD patients, (ii) identify gaps in the current body of knowledge and (iii) identify a place where a new contribution could be made. This helped to set the scene for the main research question itself and the most appropriate methodology (see figure 1.1 for elements of literature review).

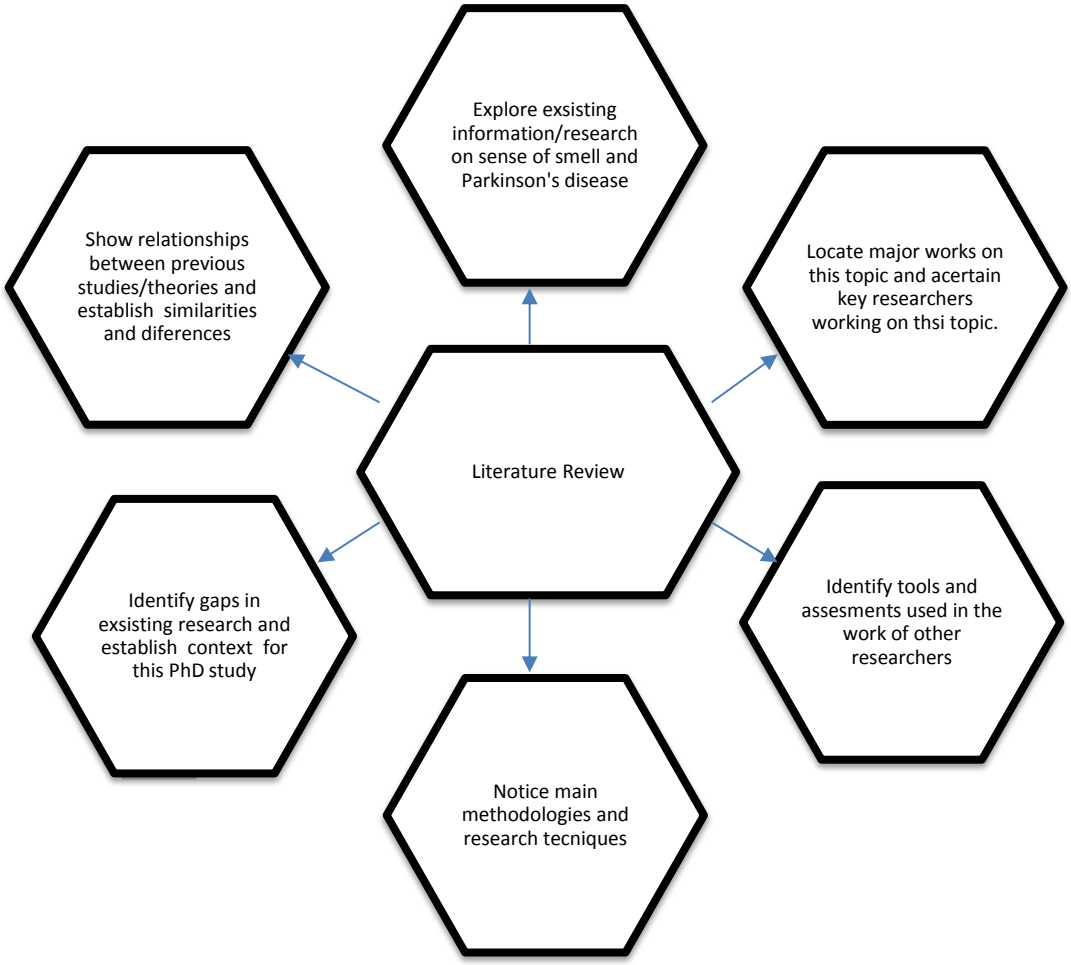


Figure 1.1 Elements of Literature Review

An initial search was conducted between August 2010 and January 2011 using electronic citation databases, CINAHL, BNI Medline, PubMed, and PubMed Related Articles' (this includes PubMed Central, Medline, Embase and the Cochrane central trials Registry). Subsequent major literature searches were performed between July 2012 and December 2012 after the study proposal was accepted, between June 2014 and December 2014 prior to voice viva to transfer to PhD and between April 2016 and August 2016 prior to final voice viva. However, this was an ongoing process throughout this study.

There was a variety of search terms used for each section. For example, "olfaction" "olfactory" "smell" "anosmia," "hyposmia", "microsmia" and "odour" were all used to look for smell and smoking, smokers, cigarette, nicotine Parkinson's disease, PD, sense of smell, olfaction, smell and odour for one

section (see section 3.1.4). The thesaurus of synonyms was also used to expand on search terms.

Some research articles offered links to the full-text material. In addition, web-based search engines, i.e., Google and Google Scholar were also accessed as well as accessing papers through ResearchGate. However, if any core journal references were unavailable in full text from the databases searched the Online Library was accessed to see if the full text of the article is available from any other database by using Article Linker or through the Trusts library service.

When searching these databases, emphasis was given to primary articles where possible, such as expert's new evidence, proposals, case reports, clinical trials and conference papers, although secondary articles such as peer reviews were also considered an important part of the analysis. The researcher also became a member of respected journals on movement disorders, neurology and olfaction to eliminate any frustrations encountered by being denied access to scholarly papers. The researcher also discussed with colleagues and eminent researchers in the field of PD and olfaction the topic under investigation and the most appropriate tools to use for data collection and the most appropriate method to disseminate this information.

Also, several frequently cited variables that could affect a patient’s perceived or actual sense of smell were noted during initial analysis, (see sections 1.2.2 to 1.2.7).

The researcher initially started with the most recently published papers and worked backwards until the earliest records of smell loss was found. This was to establish current issues. However, it was soon apparent who the important authors were in this field and therefore some searches included looking for specific authors and sense of smell.

The researcher looked for rigour, credibility, relevance’ and particularly the number of citations and started looking at references cited in highly relevant

articles. The researcher also combined keywords, for example, “Parkinson’s and olfaction”. Furthermore, the link entitled ‘Related Articles’ in PubMed was used to searches for similar citations which scans titles, abstracts and Medical Subject headings.

Firstly, all study titles and abstracts were screened and studies that clearly did not meet the inclusion criteria were excluded (i.e. loss of sense of smell reported for other known conditions besides PD such as post-viral or post-traumatic injury or since birth). The articles were then grouped into; A= must read (highly relevant, high quality), B = unsure, probably relevant, but not yet sure how and C= probably irrelevant, not what you thought it was when you read the title. Throughout the study all articles were then filed into sub-sections. For example, folders were named, smoking, cognition, tools for assessment, pathology and put into alphabetical order of first author’s surname. A language criterion was not set. However, all the papers found were available in the English or American language.

It is important to highlight that due to a plethora of information on PD and sense of smell, those authors that consider their argument, are most convincing of their opinions and make the greatest contribution to the understanding and development of this area, have been referenced. This was achieved by working systematically through each article using Holland and Rees (2010) critiquing framework for both qualitative (see appendix 1) and quantitative (see appendix 2) research.

The literature revealed that although there were wide variations in the prevalence of smell loss, the consensus now is that at least 80% of people with PD do have some degree of smell loss (Haehner et al 2009, Double et al 2003, Mesholam et al 1998, Hawkes et al 1997). This means that 101,000 out of the 127,000 PD patients in the UK have a loss of sense of smell. Given the significance of this, it was deemed important to establish whether the sense of smell progresses alongside the natural history of PD, in the motor, non-motor and quality of life domains. The literature review revealed

that although the sense of smell in PD has been extensively explored, particularly trying to establish a link between the loss of sense of smell and the well-known motor aspects of PD (Casjens et al 2013, Litvan et al 2003, Ramaker et al 2002, Hawkes et al 1999, Hawkes and Shephard 1998, Mesholam et al 1998, Hawkes et al 1997, Doty et al 1988, Quinn et al 1987), no studies were found so far, that have explored the link between the sense of smell and other non-motor or quality of life symptoms frequently seen in patients with PD. Therefore, such a narrow focus may not fully explain the link between the sense of smell and the diverse symptoms seen in PD. This PhD study addresses this by looking at the correlation between the sense of smell and other non-motor and quality of life symptoms, as well as re-examining the typical individual motor symptoms seen in PD. Clarifying the link with the motor, non-motor and quality of life symptoms and degree of smell loss could not be justified with the present available evidence as no research -to date- had further sub-divided patients per their degree of smell loss. The researcher therefore divided the patients' sense of smell into three sub-groups (mild/moderate microsmia, severe microsmia and anosmia) to see if they were clinically different. This will also allow the researcher to establish whether the degree of smell loss might predict symptoms likely to be encountered by people with PD.

1.2.1. Impairment in Olfaction

Olfactory dysfunction (or disorders) can be generally classified into: (i) conductive disorders caused by the interference with the access of odorants to the olfactory receptors, (ii) peripheral sensorineural disorders resulting from injury to the olfactory receptors and (iii) central neural disorders of the olfactory bulb or tract or related parts of the central nervous system such as the temporal lobe (Doty 2003).

1.2.1.1. Terminology

Olfactory dysfunction is defined in terms of its severity, using a wide range of terminology. Anosmia is the inability to perceive odour or a lack of

functioning olfaction (also called olfactory anaesthesia). Microsmia (also called hyposmia) is defined as a reduced or lessened ability to detect odours and normosmia is defined as normal sense of smell.

For this study, a specific classification scoring system and terminology were used (see section 2.4.6). This classification scheme has been developed by Doty in 2003 for establishing an adult patient's olfactory diagnosis using the 40 item University of Pennsylvania Smell Identification Test (UPSIT) (Doty 2003).
In this classification scheme (Doty 2003), anosmia is defined as total inability to perceive odour sensations, whereas microsmia is defined operationally as decreased smell ability. The term microsmia was chosen for this study to specifically relate to the scores on the Smell Identification Test (UPSIT) (Doty 2003) (see section 2.4.6) and does not draw a distinction between "Partial Anosmia" and "Hyposmia". Doty (2003) further subdivides the microsmia category into "severe", "moderate" and "mild" classes.

1.2.1.2. Pathophysiology of Olfaction in PD

As previously stated, olfaction is markedly reduced in PD compared to the general population (Casjens et al 2013, Litvan et al 2003, Ramaker et al 2002, Hawkes et al 1999, Hawkes and Shephard 1998, Mesholam et al 1998, Barz et al 1997, Hawkes et al 1997, Hawkes and Shephard 1993, Hummel et al 1993, Doty et al 1988, Quinn et al 1987, Ward et al 1983). There is also evidence that olfactory dysfunction is more prevalent than the cardinal sign of a resting tremor (approximately 70%) of PD patients (Alves et al 2008) and equal to rigidity and bradykinesia (Alves et al 2008, Hawkes et al 1999, Hoehn and Yahr 1967). There is also evidence that olfactory loss significantly affects quality of life (Politis et al 2010). Indeed, according to Politis et al (2010), olfactory loss belongs to the top five most prevalent symptoms (both from a motor and non-motor perspective) that have affected the quality of life of PD patients. This highlights the importance of smell loss in PD not only as a biomarker and as an aid to diagnosis, but also the effect this has on the PD patient's quality of life. This concurs with the results of a

case-control study on 90 PD patients and healthy controls by Bohnen et al (2010) who found that the accuracy of smell testing in PD diagnosis outweighs the accuracy of motor test batteries, and other non-motor tests of, for example, depression and anxiety.

The cause of impairment of olfaction in PD is likely to be due to the presence of Lewy bodies (abnormal aggregates of protein that develop inside nerve cells in PD and other Lewy body pathologies) and neuritis in the olfactory bulb and its projections through the olfactory tract to the anterior olfactory nucleus (Kranick and Duda 2008, Braak et al 2003, Pearce et al 1995). It is, therefore, more likely to be a central neural disorder than a peripheral disorder (Haehner et al 2011, Hummel et al 2010, Witt et al 2009, Silveira-Moriyama et al 2009, Westermann et al 2008, Muller et al 2005). However, there is also some debate as to whether PD related olfactory deficit is directly associated with specific changes at the peripheral level of the olfactory system (such as the olfactory mucosa). Crino et al (1995) in their research conclude PD sufferers show dystrophic axons in the lamina propria of the olfactory mucosa but this is not specific for PD and occurs also in Alzheimer's disease (AD) and even in healthy individuals. Furthermore, Witt et al (2009) found no specific changes in the nasal mucosa of PD patients compared with patients who had microsmia for other reasons. Therefore, PD-related olfactory impairment does not seem to be directly associated with specific changes in the olfactory mucosa, further clarifying that it is likely to be a central neural disorder and therefore irreversible.

However, most olfactory studies in PD have used clinical diagnostic criteria and none have post mortem validation to confirm the diagnosis. This is reasonable, considering particularly the ethical, scientific, legal and cost implications associated with post-mortem procedures (Brain Procurement Programme 2015). However, post-mortem validation is of considerable relevance in PD as it has been estimated that the diagnostic error rate made in the community by non-experts, currently diagnosing PD is usually in the range of a 25% (Brooks 2012); this can be reduced to a 10% error rate if the established brain bank criteria is applied by experts (Brooks 2012, Hughes et

al 2001, Hughes et al 1992). Despite this, it is reasonable to propose that patients with PD have profound disorder of olfactory function. This observation is based on pathological abnormality, psychophysical tests, and evoked potential studies (Hummel et al 2013, Litvan et al 2003, Ramaker et al 2002, Hawkes et al 1999, Hawkes and Shephard 1998, Doty et al 1988, Quinn et al 1987, Ward et al 1983). This means that testing a patient's sense of smell may reduce the diagnostic error rate and may need to be considered as part of the brain bank criteria.

Although, research suggests approximately 80% of PD patients have olfactory loss (Haehner et al 2009, Herting et al 2008, Double et al 2003, Muller et al 2002, Daum et al 2000, Meshholam et al 1998, Hawkes and Shephard 1998, Hawkes et al 1997, Hummel et al 1997, Wenning et al 1995, Doty et al 1988, Quinn et al 1987), two other studies concluded that 100% of PD patients had olfactory loss (Herting et al 2008, Hummel et al 1997). Hummel et al (1997) states the diagnosis of PD should be reconsidered if olfaction is normal on testing by reliable methods such as University of Pennsylvania Smell Identification Test (UPSIT) or the Brief Smell Identification Test (BSIT). (Doty et al 1984).

Furthermore, olfactory deficits are now considered a highly characteristic feature of PD (Katzenschlarger and Lees 2004), several studies suggest that olfactory deficits in PD are unrelated to factors such as disease stage and duration, and are therefore non-progressive (Meusel et al 2010, Stern et al 1994, Doty et al 1992, Doty et al 1988, Quinn et al 1987, Ward et al 1983) (see table 1.1). However, three later studies highlighted that odour discrimination scores correlate well with disease stage and severity, and therefore sense of smell loss may be progressive (Deeb et al 2010, Boesveldt et al 2008, Tissingh et al 2001) (see table 1.2). In addition, odour discrimination performance (in patients with PD) improves concurrent with clinical motor improvement after stereotactic neurosurgical treatment using deep brain stimulation (Hummel et al 2005). This possibly indicates that at least some aspects of olfactory dysfunction in PD may be secondary to on-going degenerative processes in PD. As this study is an open cross-

sectional study (and not a longitudinal study), this issue was not assessed. However, none of the above studies investigated patients according to severity of smell loss which this PhD study addresses.

Table 1.1 Studies that Show Loss of Sense of Smell does not Correlate with Disease Stage or Duration

Author-Year	Study	Number of Cases	Follow-up	Assessment	Conclusion
Meusel et al 2010	Retrospective, Longitudinal	19 PD patients	5 years	Psychophysical tests including "Sniffin Sticks",	Fluctuations seen in olfactory loss but did not predict the course of PD.
Doty et al 1992	Comparative Study	40 PD patients (20 early-stage non-treated and 20 early-stage treated) and 20 controls	NA	UPSIT	No relation was present between the olfactory test scores and the degree of tremor, rigidity and bradykinesia or gait disturbance at the time of testing.
Doty et al 1988	Longitudinal Study	81 PD patients	5-39 months. Re-test 24 patients	UPSIT 40 Phenyl ethyl alcohol odour detection test	Consistent and marked olfactory impairment. No evidence of longitudinal change.
Stern et al 1994	Comparative Study	118 PD patients	NA	UPSIT 40	No significant correlation.
Hawkes et al 1997	Case Control	96 PD patients, 96 controls	NA	UPSIT Olfactory Evoked Potentials,	Olfactory damage in Parkinson's disease is consistent and severe.

Table 1.2 Studies that Show Loss of Sense of Smell Correlates with Disease Severity/Duration

Author-Year	Study	Number of Cases	Follow-up	Assessment	Conclusion
Tissingh et al 2001	Case Control	41 PD patients, 18 healthy controls	NA	Odour Detection, Discrimination and Identification Test	Odour discrimination measures were related to disease severity.
Boesveldt et al 2008	Comparative Study	404 PD patients 150 controls	NA	Sniffin Sticks Battery	The impairment in odour discrimination appears to increase with disease duration whereas odour identification did not.
Deeb et al 2010	Longitudinal	73 early PD patients	15 months (mean)	UPDRS, DaTSCAN, Electrogustometry (EGM), UPSIT, Olfactory Event-Related Potentials (OERP)	Early PD patients have a frequent and severe olfactory deficit that correlates with disease severity, symptom duration and DaTSCAN but not EGM.

1.2.2. Why do Clinicians Need to Test for Sense of Smell Formally in PD Patients?

According to some clinical studies, PD patients frequently complain of impaired sense of smell years prior to the appearance of motor impairments (Wolters et al 2000, Hawkes et al 1999, Mesholam et al 1998, Hawkes et al 1997). However, self-reporting of smell dysfunction is regarded as too unreliable as between 40% and up to 76% of PD patients with smell dysfunction on formal smell testing have failed to notice it (Muller et al 2002, Doty et al 1988, Doty et al 1992, Hawkes and Doty 2009). Hawkes and Doty (2009) reported in their study, that those who are unaware of their smell dysfunction probably have mild/moderate microsmia. Regardless of this, the evidence highlights that simply asking a patient about their sense of smell is unreliable and it must be properly measured. This is important in counselling the patient and ensuring that the patient is aware of the dangers faced from compromised smell function (Doty et al 1988), which include fire risk and food poisoning (Santos et al 2004).

Smell tests are cheap and quick (Deeb et al 2010, Hummel et al 2001, Davidson et al 1998) and therefore suited for routine use in everyday clinical practice (presently The University of Pennsylvania Smell Identification Test (UPSIT 40) costs £2.50 each compared to approximately £1,500 for a DaTSCAN in 2017. The UPSIT 40 can have up to 86% sensitivity and 82% specificity (Picillo et al 2014). In contrast, dopamine transporter imaging (DaTSCAN) can have up to 92% sensitivity and 100% specificity in the demonstration of nigrostriatal dopamine deficiency in individuals with suspected pre-synaptic Parkinsonism (Picillo et al 2014, Jennings et al 2004). Although, the DaTSCAN may be more sensitive and specific than smell tests, in practice, they are expensive to perform and not readily available. There are also still technical issues with these scans which can lead to difficulties with interpretation of findings in borderline cases. It is also important to recognise that patients who are claustrophobic refuse to have these scans. In fact, although not specific to dopamine transporter imaging, estimates highlight that between 4–37% of patients refuse to go through with

any form of brain scan, (MRI, DaTSCAN, PET Scan) for precisely this reason (Dewey et al 2007).

1.2.3. Ageing and Olfaction

The incidence of olfactory dysfunction in the general population is a matter of debate (Murphy et al 2002, Hoffman et al 1994, Wysocki et al 1989). However, most authors reported frequencies of 1% to 3%. At least 1% of the general population have total inability to perceive odour sensations (anosmia) and approximately 5-10% has reduced olfactory function (microsmia) (Wysocki and Gilbert 1989). It is known that ageing is among the factors that put an individual at risk of developing olfactory dysfunction (Hawkes 2008, Doty 1995, Doty et al 1984) and about 25% of people older than 53 years exhibit varying degrees of loss of sense of smell (Murphy et al 2002). The decrease in the olfactory ability with age is in part attributed to structural modifications in the olfactory system, particularly due to age-related decreases in the number of olfactory receptor cells (Jafari et al 2008). This can be due to vascular or metabolic insufficiency, loss of specific neurotrophic factors (leading to age related atrophy of the olfactory receptors), viral damage (Rombaux et al 2012, Jafek et al 1990, Douek et al 1975), nutritional deficiencies, air pollution (Hudson et al 2006), as well as several age-related diseases (Rombaux et al 2009, Doty 1989).

However, recent research has found that some impaired olfaction in old age is associated with post-mortem evidence of neurodegenerative disease, including Lewy bodies, the pathological hallmark for PD (Ross et al 2006). Using statistics from the UK, it is noted that 2 million people in the UK exhibit varying degrees of smell loss (The Ageing Population, Key Issues for the 2010 Parliament). Out of these 2 million, neurodegenerative diseases, particularly synucleinopathies such as Parkinson's disease (PD), dementia with Lewy bodies (DLB) and multiple system atrophy (MSA) could account for 224,000 people over the age of 65 with significant smell loss. These can be broken down into 121,000 people with DLB (Dementia with Lewy bodies - Alzheimer's Research UK 2016), 3,000 people with MSA (MSA Trust

Research Strategy 2016) and 127,000 with PD (Parkinson's UK 2009). (See table 1.3).

Table1.3: UK Population of People with Varying Degrees of Smell Loss and Those with a Synucleinopathology

People with varying degrees of smell loss (UK)	Parkinson's disease	Dementia with Lewy Bodies	Multiple System Atrophy
2,000,000	127,000	121,000	3,000

Taken from The Ageing Population. Key Issues for the 2010 Parliament and calculated from the findings of Murphy et al (2002) by the researcher.

Also, when specifically looking at PD, Hawkes (2008) suggests it is unlikely that the PD olfactory defect is due to simple ageing and suggests a healthy person would need to live until the age of 106 to 160 years to exhibit the degree of smell loss shown by a typical PD patient aged 60 years.

1.2.4. Sniff Vigour and Olfaction

Sniffing enhances smell detection and, apart from redirection of airflow to the olfactory neuroepithelium, functional magnetic resonance imaging studies have shown that it activates the pyriform and orbitofrontal cortices of the brain (Sobel et al 1998).

In PD, mechanical aspects of sniffing may also play a role in the odour sensory deficits. Indeed, Sobel et al (2001) showed that sniffing caused a slight reduction in patients with PD performance on identification (using UPSIT 40) and detection thresholds, (using the odourants vanillin and protonic acid and a two-alternative forced-choice paradigm during which sniff parameters were recorded with a pneomatotachograph-coupled spirometre. Practically, this is said to equate to a mean reduction of around two to three points on the 40-odour University of Pennsylvania smell Identification (UPSIT-40) test (Doty et al 1984) in PD patient. Studies have not allowed for this effect and therefore may exaggerate slightly the severity of any smell

defect, especially where bulbar function is involved. However, Sobel et al (2001) observed that olfactory function improved with increased sniff vigour.

1.2.5. Parkinson's Disease Medication and Olfaction

Most present anti-parkinsonian medication works on the dopaminergic system (for a list of present UK drugs used to treat PD see Appendix 3). These drugs aim to increase dopamine in the brain, by increasing its production or altering its metabolism. (See figure 1.2 for drugs that affect the metabolism of levodopa).

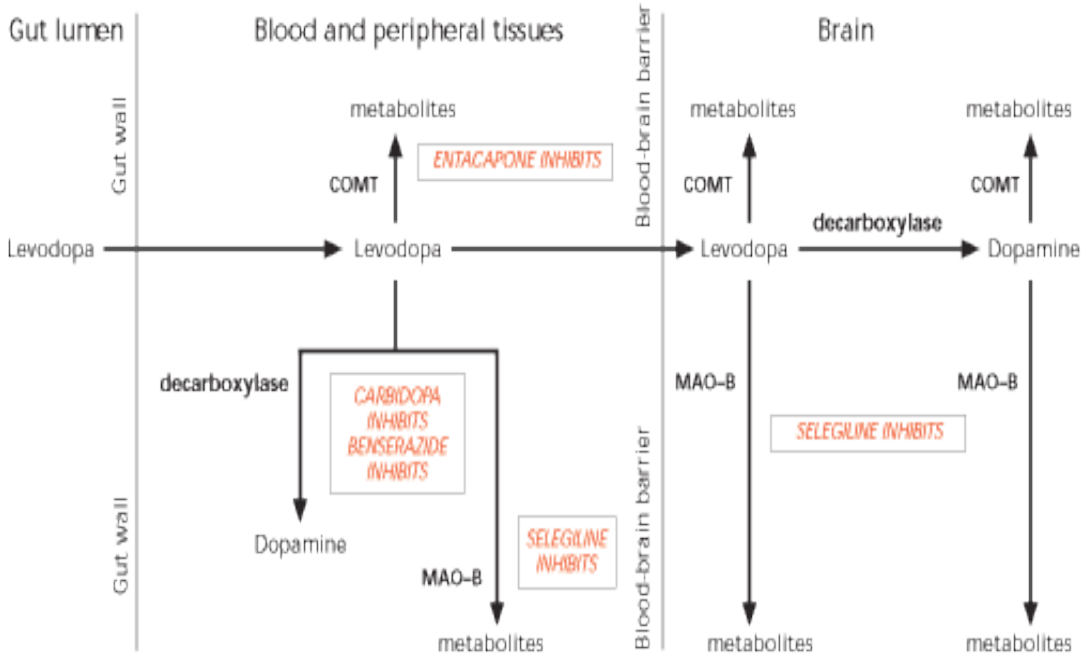


Figure 1.2 Drugs Affecting the Metabolism of Levodopa.

Key: Enzymes in bold. COMT = Catechol-O-methyltransferase. MAO-B = monoamine oxidase B. Drugs with alter metabolism in boxed red italics. (Fung et al 2001).

As far back as 1975 when Ansari and Johnson (1975) first recognised impairment in olfaction in PD, it appeared unlikely that PD medications affect or restore olfactory function, even in patients who were taking drugs with anticholinergic effects with the possible drying up effect of the olfactory mucosa. However, no firm conclusions could be made -at that time- due to the small number of patients recruited (22 males with PD).

Since then, several studies have explored this phenomenon and reported that olfactory function remains unaffected by anti-parkinsonian medication (Doty et al 1992, Quinn et al 1987, Ward et al 1983), including the potent dopamine agonist Apomorphine (Roth et al 1998).

However, although there are several types of interneurons in the olfactory bulb, most of them are dopaminergic. As most PD symptoms are due to a lack of dopaminergic neurons (Braak et al 2003), you would expect that there would be a reduction in dopaminergic neurons in the olfactory bulb. However, in 2004 Huisman et al (2004) noted a significant increase (more than 100%) of Tyrosine Hydroxylase-expressing cells in the olfactory bulb of PD patients. Tyrosine Hydroxylase is the enzyme responsible for catalysing the conversion of the amino acid L-tyrosine to L-3, 4-dihydroxphenlalanine (L-DOPA). L-DOPA is the precursor to the neurotransmitters dopamine, norepinephrine (noradrenaline) and epinephrine (adrenaline), collectively known as catecholamines (Nakashima et al 2009). See figure 1.3

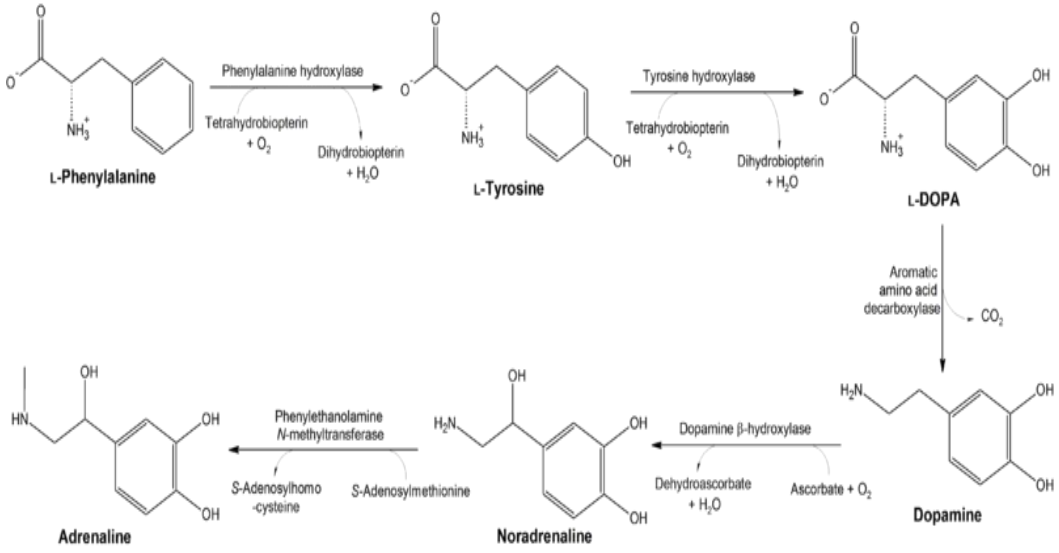


Figure 1.3: Role of N-terminus of Tyrosine Hydroxylase in the Biosynthesis of Catecholamines (Nakashima et al 2009).

The increase in the number of dopaminergic neurons (that inhibit olfaction) in the olfactory bulbs in PD patients (as shown in Huisman et al 2004 study), makes it understandable why olfaction is not improved in PD patients treated

with L-dopa (as dopamine is known to inhibit olfactory transmission in the olfactory bulb) (Hsia et al 1999, Koster et al 1999, Duchamp-Viret 1997, Wilson and Sullivan 1995, Doty et al 1992). This proposes that the increase in dopaminergic neurons in the olfactory bulbs may be responsible for the olfactory dysfunction seen in PD patients. However, results of a follow-up study (Huisman et al 2008) indicated that although the number of tyrosine hydroxylase cells in control females is significantly lower than those in control males, the number of dopaminergic (inhibitory) cells in the olfactory bulbs of both male and female Parkinson's patients equals that of healthy males of the same age group, concluding that the hyposmia in Parkinson's disease patients cannot simply be ascribed to dopamine in the olfactory bulb.

Therefore, perhaps impaired olfactory threshold in PD patients might be due to cholinergic rather than dopaminergic disturbance, not only because of the increased dopamine levels in the olfactory bulb but also because in AD there is reduced choline acetyltransferase activity in the olfactory tubercle (Simpson et al 1984) and in AD and Parkinson's Disease Dementia (PDD), defective olfactory recognition has been reported (Serby et al 1985). However, to date the lack of olfactory response to L-Dopa treatment remains inconclusive.

1.2.6. Cognition and Olfaction

Odour identification has been linked in some studies to language, verbal memory, and processing speed in healthy elderly (Westervelt et al 2005, Swan and Carmelli 2002), whilst in other studies this has not been found (Hawkes et al 1997, Doty et al 1989, Quinn et al 1987). However, this link between cognitive impairment and olfactory loss remains poorly explored in PD. Postuma and Gagnon (2010) have recently reported significant correlations between verbal and nonverbal memory and olfactory loss in PD. Furthermore, Bohnen et al (2010) found a positive correlation between odour identification scores and verbal memory in patients with PD who have olfactory loss. Bohnen et al (2010) implicated limbic cholinergic denervation and suggests that this cholinergic denervation may be more pronounced in a

subset of PD patients with early emerging cognitive deficits and that greater deficits in odour identification may identify patients at risk of clinically significant cognitive impairment (Bohnen et al 2010, Bohnen and Albin 2010).

1.2.7. Gender and Olfaction

In general, women have a better sense of smell than men (Oliveira-Pinto et al 2014, Liu et al 1995). The discussion as to why these effects should occur is inconclusive. So far, the increased olfactory sensitivity has been speculated to be attributed to numerous factors including hormonal effects (Doty 1986), verbal skills (Larsson et al 2004), congenital factors (Schaal et al 2004) or more recently the discovery that women have more olfactory bulb cells than men (Olveria-Pinto et al 2014). This observation has been made by numerous investigators using psychophysical, electrophysical and imaging techniques (Lundstrom et al 2006, Dalton et al 2002, Brand and Millot 2001, Cain 1982).

The superiority of women's sense of smell can be observed very early on in childhood, even as early as 4 years of age, and is evidenced by several cultures (Liu et al 1995). This superiority in women also increases with age (Liu et al 1995). This agrees with normative data for the UPSIT-40 in the United States showing considerable influence of gender (Doty 1995). This was also supported by the Silveria-Moriyama et al (2008) study which found that gender was an independent predictor of the UPSIT-40 score. (The UPSIT 40 has allowed for both male and female percentile scores and can be seen in appendix 4).

1.3. LOSS OF SENSE OF SMELL NOTED IN OTHER PARKINSONIAN DISORDERS

1.3.1. Conditions that can be misdiagnosed as Parkinson's disease

Parkinsonian disorders include Lewy Body Dementia (LBD), Multi System Atrophy (MSA), Progressive Supranuclear Palsy (PSP), Drug-Induced PD (DIPD) and Essential Tremor (ET). These conditions have been chosen as they are the most likely conditions to be referred to a PD clinic and the most likely conditions that can be misdiagnosed as PD. They will now be discussed individually.

1.3.1.1. Lewy Body Dementia (LBD)

In comparison to PD, this parkinsonian disorder is characterised by a more rapid course, early onset of confusion, hallucinations, drug sensitivity, and dementia. However, it is a disorder with synuclein pathology and therefore the pathology differs only quantitatively from typical PD. In one study of clinically defined LBD, severe impairment of olfactory identification and detection threshold was observed, and test scores were independent of disease stage and duration (Liberini et al 2000, Liberini et al 1999). In another study (McShane et al 2001), simple smell perception to one odour (lavender water) was examined in 92 patients with dementia (confirmed on post mortem) of whom 22 had LBD and 43 had AD; they were compared to 94 age-matched controls. The main finding was of impaired smell perception in the LBD group and little or no defect in the AD patients. Although only one odorant was used for perception tests, the study confirms at clinical and pathological level the clinically based conclusions (Liberini et al 2000, Liberini et al 1999) that impairment of smell is significant in LBD. Those who consider LBD to be no more than severe PD would not be surprised by this observation. Therefore, reduced olfaction may be associated with Lewy bodies (McShane et al 2001).

1.3.1.2. Multiple System Atrophy (MSA).

This is a rapidly progressive form of Parkinsonism in which autonomic dysfunction predominates, particularly affecting bladder and orthostatic blood pressure control. In the only study of identification in 29 patients with a clinical diagnosis of MSA, mild impairment of UPSIT-40 score was demonstrated. The mean UPSIT score was 26.7 compared to the control mean of 33.5 (Wenning et al 1993).

The discovery of alpha-synuclein in MSA has provided an elusive link with Parkinson's disease. Nevertheless, MSA is distinguished from other neurodegenerative diseases by the prominent, if not primary, involvement of the glial cells. Glial cytoplasmic inclusions (GCIs) are present in all the olfactory bulbs from MSA cases and are a diagnostic hallmark. Additionally, neuronal loss is present in the Anterior Olfactory Nucleus. These pathological changes might be responsible for the olfactory dysfunction seen. This may well have significance when testing the sense of smell.

1.3.1.3. Progressive Supranuclear Palsy (PSP).

The classic clinical features of Progressive Supranuclear Palsy (PSP) include supranuclear vertical ophthalmoplegia, severe postural instability with early falls, (Steele and Richardson 1964, Richardson et al 1963) and subcortical dementia (Albert et al 1974) most commonly developing in the seventh decade of life.

PSP-P (PSP-parkinsonism), an atypical clinical presentation of PSP-type tauopathy which presents with less cognitive decline (O'Sullivan et al 2008, Williams et al 2005), is more likely to be confused with PD and shares many common features with PD (Williams et al 2005, Hughes et al 2002).

Previous studies have suggested that microsmia is not present in PSP-P (Wenning et al 1995, Doty et al 1993). A later study suggests smell tests might differentiate PSP-P from PD (Silveria-Moriyama et al 2010) particularly

when UPSIT scores are lower than 14/40 (a cut-off that provides a sensitivity of 97.3%) although they do conclude, as a generalization, smell sense is better preserved in PSP-P than PD.

1.3.1.4. Drug-Induced Parkinsonism (DIP).

There are reported to be 261 suspected drugs that might cause DIP, most involve central dopaminergic antagonists, followed by antidepressants, calcium channel blockers, peripheral dopaminergic antagonists and H1 antihistamines that cause DIP (see appendix 5).

Clinically, drug induced parkinsonism is almost indistinguishable from PD (Bondon-Guitton et al 2011, Benito-Leon et al 2004, de Lau et al 2004), which constitutes 15 - 60% of all parkinsonism cases and represents the second most frequent cause of akinetic rigid syndromes in the western world, with a prevalence nearly approaching that of PD due to the increased use of polypharmacotherapy (Mena and de Yebenes 2006).

Although it can be serious, it is often reversible once the drug is withdrawn in 90% of cases (Bondon-Guitton et al 2011). However, DIP is not always reversible; it has been reported that PD can develop after apparent recovery from DIP (Burn and Brooks 1993, Hardie and Lees 1988, Stephen and Williamson 1984).

From the research available, it appears this subset of patients could well have subclinical PD (Morley et al 2014, Lee et al 2007) and the offending drug has simply unmasked emerging PD. It could be argued then the results of these research studies suggest that the presence of smell deficits in DIP patients might be more associated with dopaminergic loss rather than with a drug-mediated dopamine receptor blockade.

These preliminary results might have prognostic and therapeutic implications, as abnormalities in these individuals may be suggestive of an underlying PD-like neurodegenerative process (Bovi et al 2010). Indeed, in a recent study,

Morley et al (2014) highlight that olfactory testing may offer a simple and inexpensive method to help predict outcomes in drug-induced parkinsonism and, potentially, identify a cohort of pre-motor Parkinson's disease.

1.3.1.5. Essential Tremor.

Classical essential tremor is usually diagnosed easily but there are problems when the tremor seems to be dystonic or there is co-existing rigidity. In one small study of odour identification ability in 15 patients with benign essential tremor, all were normal (Busenbark et al 1992). If this phenomenon is correct, it might be useful in distinguishing essential tremor from parkinsonian tremor although females (with tremor dominant PD) are thought to be less liable to have olfactory impairment (Stern et al 1994). However, In Louis et al (2002) study of 37 patients with essential tremor, modestly impaired olfaction was noted. This may relate to the newly claimed function of the cerebellum in olfactory processing. Once more, the diagnosis in this present study was not established by reference to agreed criteria, and confirmation from imaging (e.g., DaTSCAN, PET) or post mortem was not undertaken. Accordingly, their finding must be regarded as provisional.

1.4. RATIONALE

Although sense of smell in PD has been extensively explored; particularly with regards to the motor aspects of PD, the researcher was unable to find any studies that have explored the link between the sense of smell and a majority of other non-motor and quality of life symptoms frequently seen in patients with PD. This PhD study addresses this by looking at the correlation between the sense of smell and other non-motor and quality of life symptoms as well as re-examining the typical individual motor symptoms seen in PD. Therefore, this study will add new evidence to this topic and support or refute previous research.

This study also addresses the link between varying degrees of loss of sense of smell (mild/moderate microsmia, severe microsmia and anosmia), both in the motor, non-motor and quality of life symptoms and whether the degree of smell loss itself might predict symptoms likely to be encountered by people with PD.

Testing loss of sense of smell may also provide a supportive diagnostic tool for PD, which is of great interest when examining the literature and in clinical practice, particularly for specialists working in the field of PD. This is because aalthough less severe, olfactory loss may be found in multiple system atrophy (Shah et al 2008) and dementia with Lewy bodies (DLB) (Olichney et al 2005), but uncommonly in progressive supranuclear palsy (PSP/PSP-P) (Silveria-Moriyama et al 2010), drug-induced parkinsonism (DIP) (Kruger et al 2008) and essential tremor (ET) (Shah et al 2008). Therefore, from the evidence so far, data does suggest that olfactory function may be a useful tool for the discriminative diagnosis of PD from other parkinsonian disorders. This is extremely important when a patient with parkinsonian symptoms is assessed, as the sense of smell may well be a significant indicator as to what type of parkinsonian condition the patient has, as atypical symptoms may come much later in the disease progression.

This research will also address implications of the loss of sense of smell for nursing a patient with PD as there is no preceding evidence that this has been explored before. This is to raise awareness of the prevalence and implications of smell loss in PD, including the increased risk of hazards, and to ensure the nurse implements or advises on coping mechanisms required to improve safety, well-being and quality of life.
This study also explores whether there is a link between the sense of smell and Rapid Eye Movement Behavioural Disorder (RBD) (Yoritaka et al 2009, Gjerstad et al 2008, De Cock et al 2007). This is because both symptoms are known to be early biomarkers for a diagnosis of PD and loss of sense of smell alone would not be specific to PD.
Therefore, if there is a statistically significant link between the degree of smell loss seen in PD patients and certain motor and non-motor symptoms this

may then support the need to review the Parkinson's Disease National Institute for Health and Clinical Excellence Guideline Number 35 (NICE) (2006) on treatment and management for Parkinson's disease which could have improved outcomes for patients with PD.

Also, if smell function is associated with a certain PD phenotype or prognosis, this can pave the way for a (bio)marker that can be obtained easily and relatively cheaply at the bedside.

Finally, the researcher is best placed to conduct this study having worked in the field of PD as a clinician for two decades. The exsisting knowledge and expereince of assessing and interpreting tests will be of significant value not only for other clinicians but to the PD patients themselves. The researcher is also in a prime position to disseminate and act upon the research findings, particularly in the field of nursing.

1.5 AIMS OF THIS STUDY

This study will investigate whether patients with PD who have mild/moderate microsmia, severe microsmia or anosmia are clinically different when comparing their PD in terms of the motor, non-motor, disease stage and quality of life domains, using a range of validated scales and questionnaires. This study will also analyse tremor dominant PD compared to akinetic-rigid type PD (which presents with little or no tremor but increased bradykinesia and rigidity) as tremor dominant PD is said to have a more preserved sense of smell (Quinn 1995) and whether PD patients with RBD (or not) have a more preserved sense of smell.

1.6. OBJECTIVES OF THE RESEARCH

- The objectives of the research are to establish:The prevalence of mild/moderate microsmia, severe microsmia or anosmia in this study group. (See chapter 3).

- Whether gender, age, smoking or disease duration has an impact on the sense of smell. (See chapter 3).

- Whether taste is related to the degree of smell loss in this PD study group. (See chapter 3).

- Whether cognition has an impact on the sense of smell (N.B. PD patients with significant cognitive problems have been excluded from this study). (See chapter 3).

- Whether there is a link between motor function, (as measured by UPDRS III (see appendix 7)) and the degree of loss of sense of smell (mild/moderate microsmia, severe microsmia or anosmia) in this study group. (See chapter 4).

- Whether there is a link between disease severity (using Hoehn and Yahr Staging) (see appendix 10)) and the degree of loss of sense of smell in this study group. (See chapter 4).

- Whether PD patients with mild/moderate microsmia are less(or --more likely to have a rapid eye movement behaviour disorder (see chapter 4) in comparison with PD patients who have severe microsmia or anosmia (using Rapid Eye Movement Behaviour Sleep Disorder Questionnaire. See appendix 11).

- Whether PD patients with tremor dominant PD are less (or more) likely to have reduced sense of smell compared with PD patients who have akinetic-rigid type PD.

- Whether PD patients with mild/moderate microsmia are less (or more) likely to have prominent non-motor features (such as hallucinations, sleep disturbance, cognitive or autonomic features) (see chapter 5) in comparison with PD patients who have severe microsmia or anosmia (using the Non-Motor Symptoms Questionnaire. See appendix 8).

- Whether PD patients with mild/moderate microsmia are less(or more) likely to have prominent quality of life features, indicating the impact of PD (such as emotional well-being, activities of daily living or stigma) (see chapter 5) in comparison with PD patients who have severe microsmia or anosmia (using the PDQ39. See appendix 9).

- Whether different classes of PD medication, the timing of medication , the environment (in which the smell test was conducted) and handedness has an impact on sense of smell. (See chapter 6).

- Whether sniff vigour fatigues during the UPSIT 40 smell test which may contribute to lower UPSIT scores seen in patients with PD in this study group. (See chapter 6).

- Whether PD patients in this study group are aware of any impairment of their sense of smell (i.e. perceived sense of smell) and whether PD patients reporting a recovery or fluctuation of their sense of smell affects UPSIT scores. (See chapter 7 (See chapter 7).

- If there is any evidence of phantosmia and whether phantosmia affects UPSIT scores. (See chapter 7).

- The profile of the 40 odours presented and number/percentage of patients correctly identifying each individual odour. (See chapter 7).

CHAPTER 2

METHODOLOGY

2.1. STUDY DESIGN AND SAMPLE SIZE

This is an open cross-sectional observational study, involving 112 patients (of both genders) who have a diagnosis of Parkinson's disease. This was considered the most appropriate study design in order to examine the relationship between the sense of smell and the motor, non-motor and quality of life domains in people with PD who had anosmia, severe microsmia or mild/moderate microsmia. The intention was not to assign exposures or have a comparison between exposed and non-exposed groups and at this point this study does not want to establish whether the sense of smell progresses alongside the natural history of PD or how the sense of smell affects a patient with PD, over a period (i.e. no follow up).

The individuals recruited for this study appear to represent the general white British older PD population (as none of the PD patients recruited to this study were of ethnic minority race). This is based on the fact that there is 33% higher than the national average of older people in the study area. A majority of these have migrated, through retirement, from other parts of the United Kingdom, therefore, there is a mixture of patients who are either local to the area or from other regions of the UK.

During the initial proposal it was estimated from the literature review that between 10 - 20% of PD patients have a preserved sense of smell. Therefore the original plan was to subdivide the patients into five groups (i) normosmia, (ii) mild microsmia (iii) moderate microsmia (iv) severe microsmia (v) anosmia. However, as no patients were found to be normosmic in this particular study, patients were divided into (i) mild/moderate microsmia, (ii) severe microsmia and (iii) anosmia sense of smell sub-groups. (For sense of smell test scores and therefore category of loss of sense of smell see section 2.4.6).

Patients were assessed, and data collected from March 2013 to November 2013. All patients provided written informed consent. Data collection was performed on a convenient day for patients and included weekends and evenings. Lone Worker Policy was adhered to (see appendix 6).

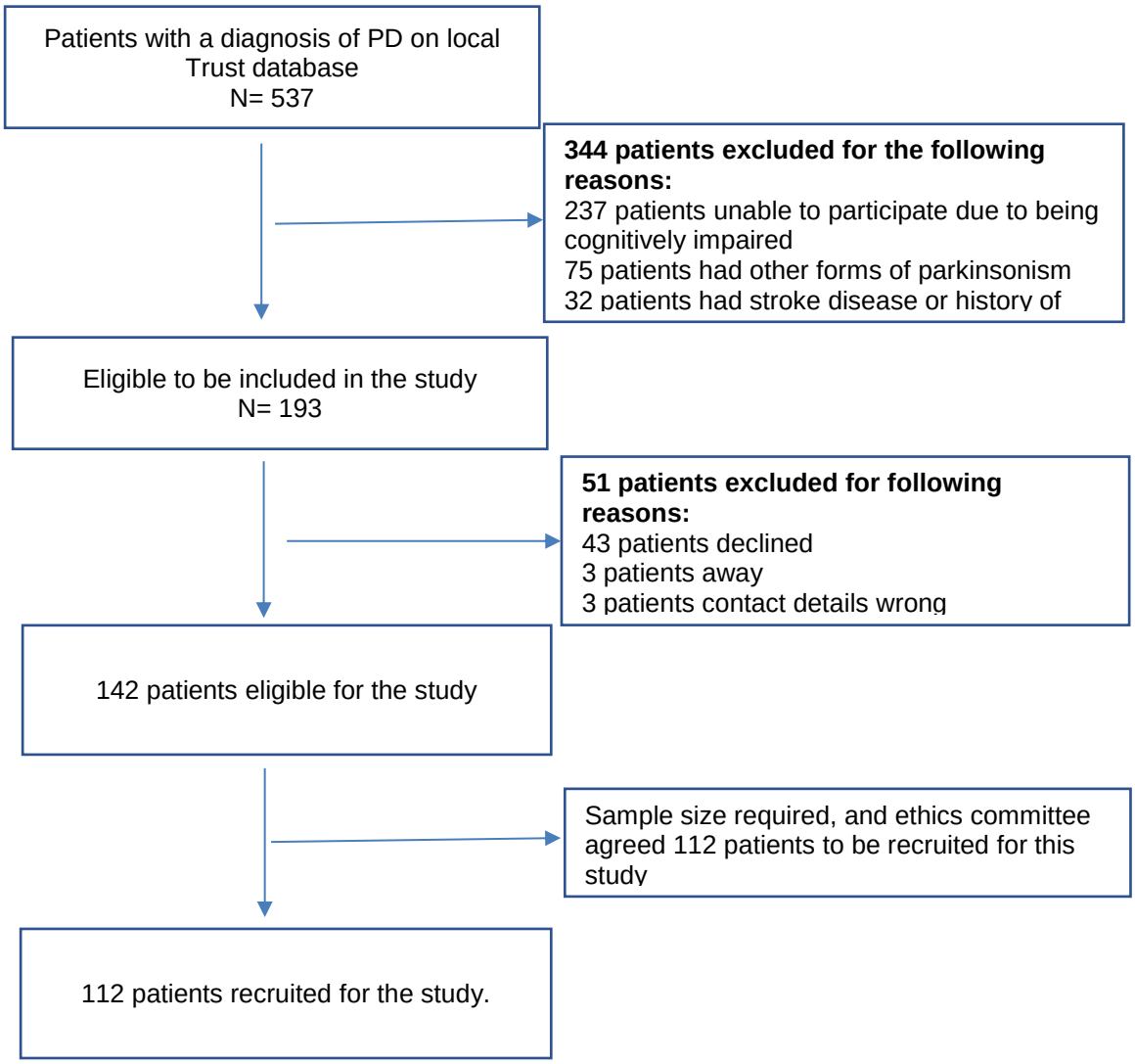
2.1.1. Study sample recruitment process

The preparatory work by the researcher during the recruitment process was to initially identify eligible patients from a local NHS PD Trust database. This was achieved by screening patient's records to exclude patients who did not meet the inclusion or exclusion criteria (see section 2.2). Once eligible patients were found a list was compiled which contained the patient's hospital number and telephone contact details. This list was then forwarded to two nursing colleagues, both covering different areas within the local trusts catchment area. The nursing colleagues then contacted these patients either via a telephone call, during an out-patient appointment or during a home visit. The researcher did not make the initial contact to avoid research bias. If the patient agreed the two nursing colleagues sent invitation letters (see appendix 16). All reply slips came directly back to the researcher and from then on, all tasks were the responsibility of the researcher. This included preparing appropriate recruitment material, completing all assessments and ensuring that the relevant clinicians were fully informed about the study (details of this process can be seen in Figure 2.1 flow diagram).

As previously stated a sample size of 112 PD patients was required. This sample size was obtained by statistical analysis by the head statitician at the university that supported the researcher to complete this PhD study. This sample size was then agreed by the ethics committee. The process of gaining the is sample can be seen in figure 2.2. Due to the researcher being the only person carrying out all the assessments it was agreed that patients would be contacted in batches of 40 at a time and to await response before contacting another 40 patients. As the two nursing colleagues shared an office with the researcher this was managable. The researcher started the

recruitment process as soon as a patient accepted. The aim was to ensure patients were seen in a timely manner rather than sending out information and then not being seen for some time afterwards. Althogh there were 30 remaining patients eleigible for the study the researcher would have needed to go back to the ethics committee for their approval and this would have been time consuming. Also the researcher was aware that there was going to be a significant amount of data collected and more patients in the study would have increased the researchers time carrying out all the assessments and arranging home visits or aseesment in an allocated research office.

Figure 2.1 Parkinson's disease out-patient's recruitment chart



2.2. INCLUSION AND EXCLUSION CRITERIA

2.2.1. Inclusion criteria

- Aged 18 years or above
- Confirmed clinical diagnosis of Parkinson's disease
- No other recognised causes of loss of sense of smell
- No current medical history of using sedatives (or any other medication that may interfere with perception of symptoms or performance of measurements)
- Able to provide informed consent

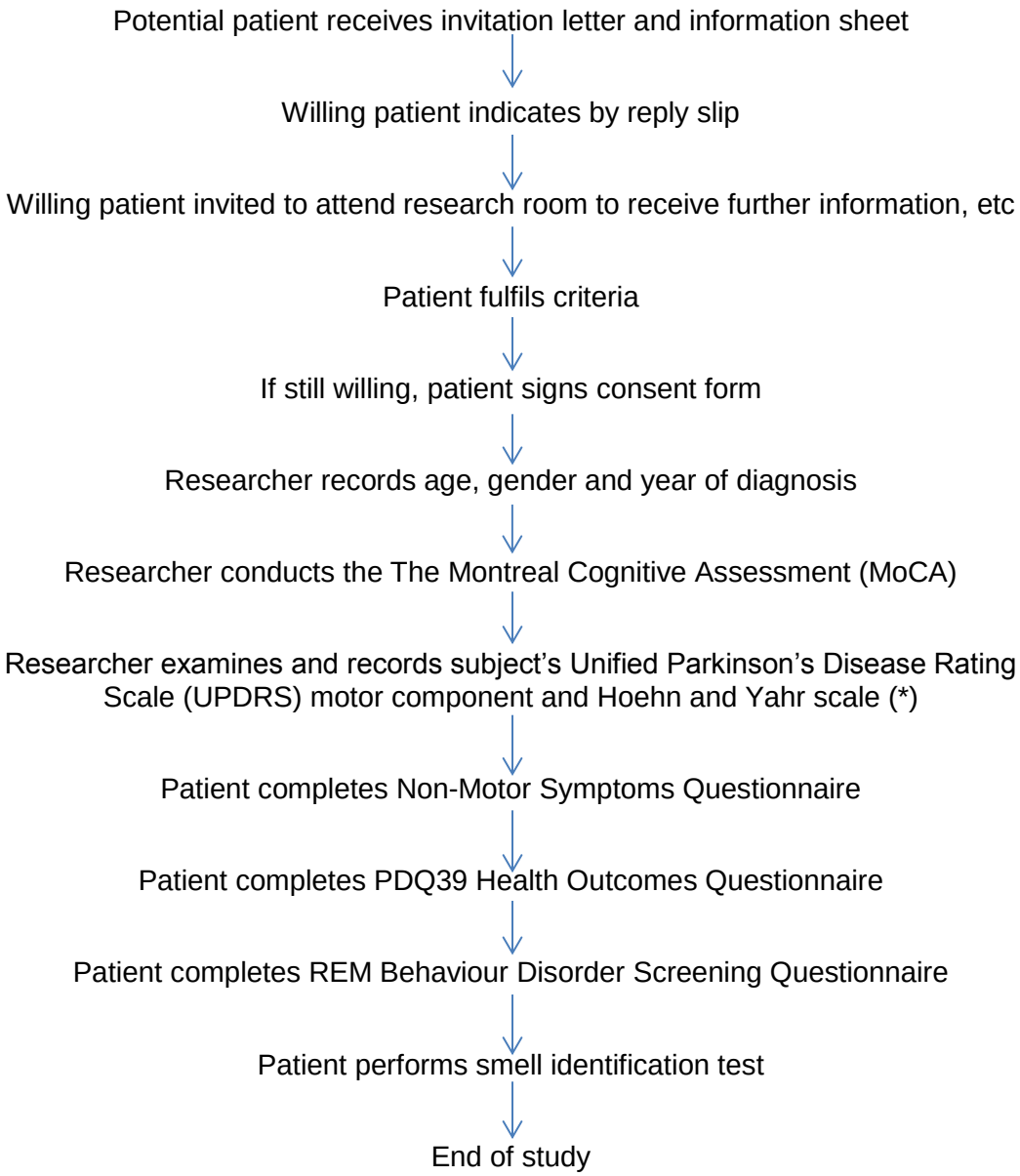
2.2.2. Exclusion criteria

- Known physical impairment (i.e.stroke/rheumatoid disease) that may influence compliance with protocol
- Confirmed medical history of surgery or trauma to the nose resulting in the inability to smell properly
- Known current infection (i.e. chest/sinus infections) that may interfere with the sense of smell
- Unable to provide informed consent.

2.3. STUDY PROTOCOL

The flow chart highlighing the study protocol and methods used for data collection can be seen in Figure 2.2.

FLOW DIAGRAM OF THE STUDY



(*) Patients will be required to be examined in order to test their motor ability which is routine in clinical practice .This is a non invasive procedure

Figure 2.2: Flow Diagram of the Study.

2.4. RATING SCALES AND TOOLS USED IN THE STUDY

Specific scales and questionnaires that cover the different clinical symptoms noted in patients with PD have been chosen (see section 2.4.1 - 2.4.7). This is to ensure that a wide variety of symptoms (present in PD), which particularly include the non-motor deficits, can be captured and analysed. This may highlight whether in fact the olfactory system is connected to or deteriorates parallel to a particular symptom. This study will also investigate Rapid Eye Movement Behaviour Disorder and its correlation with olfactory dysfunction in PD patients. These scales and questionnaires are discussed below.

2.4.1. Unified Parkinson's Disease Rating Scale

The UPDRS developed by Fahn and Elton (1987) is a rating tool to follow the longitudinal course of Parkinson's disease. It is the most widely used standardised scale to assess parkinsonism (Rascol et al 2002, Mitchell et al 2000). The UPDRS demonstrates high internal consistency and inter-rater reliability, shows moderate construct validity and has stable factor structure (Stebbins and Gotez 1998, Nouzeilles and Merello 1997, Rabey et al 1997, Richards et al 1994).

The motor subscales of the UPDRS provide a measure of key motor symptoms and examines speech, facial expression, tremor - both action and at rest, rigidity, finger taps, hand movements, hand pronation and supination, leg agility, arising from a chair, posture, gait, postural stability and body bradykinesia. It contains fourteen questions, each measured on a 5-point scale (0 - 4) (see appendix 7). The higher the score the worse the disability.

There are three other muti modular scales containing both impairment and disability sections found in the literature. These are the New York University Parkinson's disease Evaluation (NYU) (Lieberman et al in Goldstien 1980 pages 227-286), the University of California Los Angeles scale (UCLA) (Martinez-Martin et al 1988) and the Short Parkinson's Disease Evaluation

Scale (SPES) (Rabey et al 1997). Of these scales the SPES appears to be the most valid and reliable scale but none of these have been subjected to an extensive clinometric evaluation and have only been evaluated by their designers. Therefore, the researcher did not consider these scales for this particular research as no recommendations for the use of these scales is available.

2.4.2 Non-Motor Symptoms Questionnaire

The Non-motor Symptoms Questionnaire (Chaudhuri et al 2006) is a validated questionnaire which shows modest association with indicators of motor symptom severity and disease progression but a high correlation with other measures of NMS (NMSQuest) and health-related quality of life measure (PDQ-8) (both, r_s = 0.70). It has also been validated in several European and Asian languages (see Chaudhuri et al 2007). It is a self reported questionnaire specifically designed for PD patients. It comprises 30 common non-motor symptoms and is designed to provide a rapid screen for problematic non-motor symptoms (see Appendix 8). It is not a rating scale and is not intended to evaluate the effect of treatment. In this research study, it will simply highlight if there is a link between any of the non-motor symptoms and degree of olfactory function. It is now an integral part of the assessment of patients with Parkinson's disease and contributes to the management of the disease. This scale was chosen as there are no other non-motor symptoms questionnaires for PD available in practice.

2.4.3. PDQ39 Quality of Life Questionnaire

The PDQ39 Quality of Life Questionnaire (Jenkinson et al 2008, Peto et al 1995) has been translated into more than 80 other languages. The PDQ39 is a self reported questionnaire that is a disease-specific measure of subjective health status (see Appendix 9). The PDQ-39 produces a profile of scores indicating the impact of Parkinson's disease in eight important areas of health status which are;

- mobility (10 items)
- activities of daily living (6 items)
- emotional well-being (6 items)
- stigma (4 items)
- social support (3 items)
- cognition (4 items)
- communication (3 items)
- bodily discomfort (3 items)

Patients are asked to think about their health and general well-being and to consider how often, in the last month, they have experienced certain events (e.g. difficulty walking 100 yards). Patients are asked to indicate the frequency of each event by selecting one of 5 options (Likert Scale): never/occasionally/sometimes/often/always or cannot do at all.

The PDQ 39 is shown to have high levels of reliability and validity (Damiano et al, 1999, Jenkinson et al, 1997, Peto et al 1998). It is the most widely used specific health related quality of life scale and the most thoroughly tested and used in clinical studies. Its disease specificity and the single summary index offer the opportunity to assess the overall impact of illness, and it is easy to interpret (Jenkinson et al 1997).

There are other scales used to measure health related quality of life issues such as the Parkinson's Disease Questionnaire Short form (PDQ-8) (Jenkinson et al 1997), the Parkinson's Disease Quality of Life (PDQL) (de Boer et al 1996), the Parkinson's Impact Scale (PIMS) (Calne et al 1996) and Scales for Outcomes in Parkinson's Disease - Psychosocial (SCOPA-PS) (Marinus et al 2003).

The PDQ-8 is the short version of the PDQ-39. However, it has lower reliability and validity than the PDQ-39 and was therefore not chosen. The PDQL is the second most frequently used health related questionnaire specific for PD. However, it does not adequately cover self-care, sleep,

cognition, close relationships and role functioning (Marinus et al 2002, Damiao et al 1999). These are considered important to the researcher. The PIMS has very few independent and cross cultural validation studies (Serrano-Duenas et al 2008) and is rarely used in research and the SCOPA-PS is focused on psychological adjustment rather than health related quality of life. This is why PDQ39 was chosen.

2.4.4. Hoehn and Yahr Scale

Hoehn and Yahr scale (Hoehn and Yahr 1967) measures disease stage (see Appendix 10). There is no other scale available that provides a method of establishing the severity of PD with a simple staging assessment and this is why it has been chosen for this research. Since its introduction, the Hoehn and Yahr scale has remained the most commonly and most widely used scale to describe severity of PD worldwide (Mitchell et al 2000). It is the standard staging system used to describe patient populations enrolled in clinical trials of antiparkinsonian interventions and the second most frequently used outcome measure after the UPDRS in all randomly ordered drug trials for PD published between 1966 and 1998 (Mitchell et al 2000). It provides an overall assessment of severity based on clinical features and functional disability (Diamond and Markham 1983) and is easy to apply, quick to complete and practical to use both in research and clinical practice. The Hoehn and Yahr scale has been successfully used by raters with or without movement disorder expertise (Geminiani et al 1991).

Most assessments of the validity and reliability of the Hoehn and Yahr scale have been limited to the assessment of reliability and report a moderate to significant level of inter-rater reliability (Geminiani et al 1991). No formal assessments of test-retest reliability (intra-rater reliability) or validity could be found. Most studies have used the Hoehn and Yahr scale as the gold standard against which the validity of other scales is assessed. Although these studies cannot be considered examinations of Hoehn and Yahr scale validity, they do provide some assessment of the relationship between Hoehn and Yahr staging and other measures of PD impairment/disability. Most

studies report significant correlations between Hoehn and Yahr stage and the UPDRS (van Hilten et al 1994), which is another reason for using this scale.

Hoehn and Yahr staging is a quick, simple and commonly used tool both in research and clinical practice as an aid to assess the severity of PD. The lower the score the less disability (for example 0= no signs of disease and 5=Wheelchair bound or bedridden unless aided), (see Appendix 10).

2.4.5 Rapid Eye Movement Behaviour Disorder Screening Questionnaire

RBD Screening Questionnaire (Stiasny-Kolster et al 2007) is a relatively new screening questionnaire with high sensitivity. This questionnaire was chosen as it specifically deals with RBD. Other sleep scales are widely used in clinical practice such as the Pittsburgh Sleep Quality Index (PSQI) (Buysse et al 1989), and the Epworth Sleepiness Scale (ESS) (Johns 1991). The PSQI is designed to assess sleep quality during the past month and has been used, for example, to measure sleep quality among truck drivers (Souza et al 2005) and to test the effects of a drug on sleep quality in a randomized placebo controlled trial (Johnson et al 2005). The ESS is an 8-item questionnaire designed to assess general level of daytime sleepiness, and has been used in studies that have examined daytime sleepiness in medical interns (Rosen et al 2006) and in patients with multiple sclerosis (Heesen et al 2006) and it was a main outcome measure of the effects of didgeridoo playing in patients with moderate obstructive sleep apnea (Puhan et al 2006). Both scales are highly reproducible (Knutson et al 2006) and reliable (Backhaus et al 2002, Johns 1992).

However, RBD is a parasomnia, characterised by loss of normal skeletal muscle atonia during rapid eye movement sleep, thus enabling the patient to physically enact their dreams and, in some, vocalisations and abnormal movements are reported by bed partners (Comella et al 1993). Many patients with PD complain of RBD. Early detection of these patients is clinically relevant for long-term perspective as well as future neuroprotective

studies. This present study will attempt to see if the degree of olfactory dysfunction correlates with the degree of severity of RBD.

The questionnaire is a 10 item patient self rating instrument (maximum total score 13 points), covering the clinical features of RBD (spouse or carers observations can also be included during the assessment if appropriate). Items 1 to 4 address the frequency and content of dreams and their relationship to nocturnal movements and behaviour. Item 5 asks about self-injuries and injuries of the bed partner. Item 6 consists of four sub items that assess nocturnal motor behaviour more specifically, e.g. questions about nocturnal vocalization, sudden limb movements, complex movements, or items around the bed that fell down. Items 7 and 8 address nocturnal awakenings. Item 9 focuses on disturbed sleep in general and item 10 on the presence of any neurological disorder. A score of five points or more, based on The International Classification of Sleep Disorders (American Sleep Disorders Association 2001), is considered as a positive test result for a clinical diagnosis of RBD (see Appendix 11). However, for a definite diagnostic decision, a polysomnography is required predominantly to definitely rule out differential diagnoses such as sleep related epileptic seizures, non-REM parasomnias (eg. sleep walking, obstructive sleep apnea or nocturnal periodic leg movements).

2.4.6 University of Pennsylvania Smell Identification Test

Numerous clinical olfactory tests have been described in the literature, including ones incorporating psychophysical, electrophysiological, and psychophysiological methods (for reviews, see Doty and Laing 2003, Kobal 2003). Such tests range from simple single-item odour identification screening tests to complex electrophysiological tests employing sophisticated olfactometers. Briefly, these can be devided into three catogories; (i) psychophysical techniques (ii) electrophysiological techniques and (iii) imaging techniques.

(i) Psychophysical techniques are those where stimuli are varied in some manner (e.g., in concentration or quality) and the patient is required to indicate whether the stimulus is perceived (e.g., detection, discrimination and identification).

(ii) Electrophysiological techniques evaluate either summated electrical activity at the surface of the olfactory receptor epithelium (i.e., the electro-olfactogram or EOG) or integrated electrical activity at the surface of the scalp (e.g., odour event-related potentials or OERPs) (Hawkes and Doty 2009).

(iii) Imaging techniques assess stimulation of the left orbitofrontal region, right pyriform cortex or bilateral occipital cortex amongst other regions (see section 1.3.1).

Olfactory perception was tested through a psychophysical test. One advantage of this 'low-tech' approach over other methods is the speed of testing, allowing for rapid screening of olfactory function (Davidson et al 1998, Hummel et al 2001). There are three main psychophysical assessments highlighted in the literature: odour identification (Doty et al 1984), odour discrimination (Hummel et al 1997) and odour thresholds. (Lotsch et al 2004, Ehrenstein and Ehrenstein 1999).

Recent research (Lotsch et al (2008), Larron et al (2004) indicates that the three individual subtests describe different aspects of olfactory function. Lötsch et al (2008) found that odour thresholds can be separated from those of odour identification and odour discrimination. Furthermore, Larsson et al (2004) report that odour discrimination is more strongly influenced by memory function than odour identification or odour thresholds.

Thus, it would be best to perform all three subtests to obtain a maximum amount of reliable information. However, this would be time consuming and involve storage of chemicals and equipment. Furthermore, most olfactory psychophysical tests are positively correlated with one another and measure

common attributes (Frank et al 2003, Hummel et al 1997, Doty et al 1995, Cain and Rabin 1989, Doty et al 1985, Doty et al 1984). For these reasons odour identification will be used to measure olfaction.

Odour identification is the most frequently used measure of olfaction. Several test kits are commercially available, with the University of Pennsylvania Smell Identification Test (UPSIT) (Doty et al 1984) being the most widely used. It has well-validated psychometric properties (Doty et al 1984, Doty et al 1995) This test will be used in this study and consists of 4 booklets each having 10 different odours to identify, which are microencapsulated in paper strips and are released by scratching with a pencil (see appendix 12). A forced choice for each odour is required from four possible answers, even if no odour is perceived. This forced-choice procedure controls the patient's response bias. There is an answer column on the back of the test booklet, and the test is scored out of 40 items. The score is compared to scores in a normative database from 4000 normal individuals. This records the level of absolute smell function (Doty et al 1984). The score also indicates how the patient does in accordance to their age group and gender. The test has been validated and normal age and sex-related values are available (Doty et al 1995).

For this study, a specific classification scoring system and terminology were used. This classification scheme has been developed by Doty in 2003 for establishing an adult patient's olfactory diagnosis using the 40 item University of Pennsylvania Smell Identification Test (UPSIT) (Doty 2003). (See table 2.1).

Table 2.1. Classification Scoring System of UPSIT 40

Test score	Olfactory Diagnosis
00-05	Probable Malingering
06-18	Total Anosmia
19-25	Severe Microsmia
26-29	Moderate Microsmia (Males)
26-30	Moderate Microsmia (Females)
30-33	Mild Microsmia (Males)
31-34	Mild Microsmia (Females)
34-40	Normosmia (Males)
35-40	Normosmia (Females)

(See appendix 4 for female and male percentile values).

2.4.7. The Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) (Nasreddine et al 2005). is a brief tool developed to detect mild cognitive impairment that assesses a broader range of domains frequently affected in Parkinson's disease, in particular, executive functions (see appendix 13). Although the Mini-Mental State Examination (MMSE) (Folsten et al 1975) is widely used in research and clinical practice, research highlights that the MMSE is particularly insensitive to mild cognitive impairment and lacks adequate sampling of executive functions. It may therefore, not detect cognitive deficits common to Parkinson's disease, especially in the early stages of disease (Zadikoff et al 2008, Athey et al 2005, Tang-Wai et al 2003, Wind et al 1997, Tombaugh and Mcintyre 1992). This is important because dementia is an important and increasingly recognised problem in PD and depending on the method of ascertainment of cases, 20 - 80% of patients with PD will develop dementia over time (Svenningsson et al 2012, Butler et al 2008, Aarsland et al 2001, Sutcliffe and Meara 1995).

MoCA has been shown to have good validity, reliabilty and consistency by the original test authors (Nasreddine et al 2005) and since then has been shown to have a good test-retest reliabily, inter rater reliabilty, and

convergent validity with a neuropsychological battery in a small sample of patients with PD (Gill et al 2008).

All these tools/scales used for data collection are presently used in clinical practice and provide simple, user friendly and inexpensive tools/scales across the field of PD ensuring colleagues can readily interpret data presented. These tools/scales chosen from the researcher's perspective particularly appealed to address the balance between the required information and the burden to the patients participating in this study.

2.5. SAMPLE SIZE CALCULATIONS AND STATISTICAL ANALYSIS

A sample size of 112 was required (Faul et al 2009) for 90% power, assuming a two-sided 0.05 significance level and a weak correlation coefficient of 0.3 (Swinscow, 1997). Over-recruitment was not accounted for since there is no follow-up and missing data was anticipated to be negligible. Although there are four outcomes of interest, motor-skills are considered the most important and therefore are considered the primary outcome on which the sample size was based.

Spearman's Rank was the most appropriate statistical test to investigate the association between sense of smell and motor symptoms and disease stage; in the meantime Pearson's correlation coefficient was the most appropriate to investigate the association between sense of smell and quality of life and the sense of smell of those with and without the 30 non-motor symptoms was investigated using chi square test.
Following on from the data collection, correlations were used to investigate the associations between sense of smell and most of the outcome variables.

2.6. ETHICAL CONSIDERATIONS

Full NHS ethical approval was obtained from the National Research Ethics Service (NRES) Committee South Central Southampton B and The Royal Bournemouth and Christchurch NHS Foundation Trust Research and Development Department (IRAS project ID 87288 REC reference number 12/SC/0705). (See appendix 15).

The study is based on voluntary participation. Patients were posted an invitation letter (see appendix 16) and information sheet (see appendix 17) by the researcher following an initial telephone consultation, or face to face meeting from another member of the PD team (during routine follow-up appointments) or from a local research nurse working in the field of neurodegenerative conditions. An attached reply slip and a self addressed, postage paid envelope was then sent to the patients. This allowed patients time to digest the information and decide if they wished to participate. It also gave them the opportunity to discuss it with others and ask if there was anything that was not clear or if they would like more information. Therefore, further information would be provided prior to participation if requested.

All procedures were explained before performing the tests. All tests, apart from the smell test, were considered entirely free of risks. There were some concerns as to whether the smell test could cause a migrane or nausea. This was not seen in the study or during routine clinical testing. The only disadvantage to the patient was the donation of an hour of their time. Patients chose dates that were convenient to them for assessment.

Written consent (see appendix 18) was obtained by the researcher from patients who were willing to participate in the study once they had read and understood the information that was given to them in advance, and they are made fully aware of the expectations of them in the study and the researcher is satisfied they have understood. Patients were informed that they were not likely to benefit personally from taking part in the research. However because the research will give us a better understanding as to whether the

sense of smell and the progression of Parkinson's disease may be linked this could influence our understanding and treatment of individual Parkinson's disease patients in the future.

Patients were consented in a quiet room away from the clinical areas or at their home. This was to avoid patients feeling pressurised into consenting. A statement highlighted that it was entirely up to the patient to decide whether or not to take part, and if that if they agreed to take part, they were free to withdraw at any time should they so decide. The invitation letter also highlighted that the patient did not have to give any reasons for withdrawing and this would not affect the standard of care they receive or have any adverse effects on their treatment (see appendix 16). Respect for human dignity and privacy was maintained at all times and patients were assured that their participation in the study was confidential. All records remain anonymous and are stored in a secure place on a local hospital Trust site.

All patients who participated agreed to their GP being informed and a letter was sent to the GP accordingly (see appendix 19).

CHAPTER 3

SENSE OF SMELL AND THE DEMOGRAPHIC FEATURES OF THE PARKINSONS DISEASE PATIENTS PARTICIPATING IN THIS STUDY

3.1 OVERVIEW

This chapter will address the link between the sense of smell (as measured by UPSIT 40) and the typical characteristics and demographic features of the study group, including UPSIT 40 sense of smell scores, gender, age, smoking history, taste reported, disease duration and cognitive function in each sense of smell sub-group. All these demographic features were chosen as they may contribute to loss of sense of smell seen in PD patients.

3.1.1. Parkinson's Disease and Sense of Smell

There is now good research evidence that the ability to smell is significantly affected in PD compared to the general population (Casjens et al 2013, Litvan et al 2003, Ramaker et al 2002, Hawkes et al 1999, Hawkes and Shephard 1998, Mesholam et al 1998, Hawkes et al 1997, Doty et al 1988, Quinn et al 1987), with at least 80% of PD patients affected (Double et al 2003, Mesholam et al 1998, Hawkes et al 1997) (see section 1.2.1.2.). There is also evidence that impaired olfaction may precede the classical motor manifestations of PD by several years (Ross et al 2008, Haehner et al 2007, Stiasny-Kolster et al 2005, Ponsen et al 2004, Hawkes 2003, Berendse et al 2001, Doty et al 1988) (see section 1.2.1.2), suggesting that neuronal damage occurs early in the diagnosis, even before the classical motor signs are evident (Braak et al 2003) (see section 8.1 figure 8.2). Interest in the loss of sense of smell (seen in PD patients) has grown markedly in the past few years, driven by the hope of developing neuroprotection treatment for PD patients in the early stage of the disorder. Therefore, one of the aims of this chapter is to study the pattern of distribution of mild/moderate microsmia, severe microsmia and anosmia in PD patients selected for this PhD study.

3.1.2. Gender and Sense of Smell

In general, females have a better sense of smell than males (Liu et al 1995). This observation has been made by numerous investigators, using psychophysical, electrophysical and imaging techniques (Lundstrom et al 2006, Dalton et al 2002, Brand and Millot 2001, Cain 1982). The discussion as to why these effects should occur is inconclusive. So far, the increased olfactory sensitivity in females has been speculated to be attributed to numerous factors including hormonal effects (Doty 1986), verbal skills (Larsson et al 2004) or congenital factors (Schaal et al 2004). This agrees with normative data for the UPSIT-40 in the United States, showing considerable influence of gender (Doty 1995). This was also supported by the Silveria-Moriyama et al (2008) study which found that gender was an independent predictor of the UPSIT-40 score. The UPSIT-40 has therefore adjusted for this and both female and male percentile scores can be seen in appendix 4. Therefore, one of the objectives of this chapter is to confirm or refute whether females in this PD study group do -in fact- have a better sense of smell compared to males.

3.1.3. Ageing and Sense of Smell

As previously mentioned (in section 1.2.3.) ageing is among the factors that put an individual at risk of developing olfactory dysfunction (Hawkes 2008, Doty 1995, Doty et al 1984). However, it is also known it is unlikely that the PD olfactory defect is simply due to ageing (Hawkes 2008). Therefore, one of the objectives of this chapter is to confirm or refute whether ageing does have an impact on loss of sense of smell in PD and to what degree.

3.1.4. Smoking and Sense of Smell

Little is known about the effect of cigarette smoking on the ability to smell. Previous studies on this topic have led to inconsistent findings. For example, Frye et al (1990) found that smoking causes long-term but reversible adverse effect on the ability to smell. This was not replicated by Ishimaru and Fujii

(2007) research who found that although smoking reduces the sense of smell function, recovery of sense of smell after cessation of smoking appears to be exceptional. Katotomichelakis et al. 2007, in their study found smoking to be adversely associated with the olfactory ability in a dose-related manner and that smokers were found to be nearly six times as likely to have evidence of an olfactory deficit as non-smokers. This was supported by Vennemann et al (2008). However, a study by Lucassen et al (2014) showed that a history of smoking was associated with better olfaction among PD. Lucassen et al (2014) conclude that although the interaction between smoke and the olfactory system at a peripheral level is a very intriguing hypothesis, it is also possible that cigarette smoke may protect olfactory structures within the brain. This is supported by the fact that more than 60 epidemiological studies are consistent in reporting that smokers have a lower risk for developing PD (Li et al 2015, Burton et al 2013, Hawkes et al 2007, Hawkes et al 2009, Allam et al 2004). However, the mechanism(s) by which cigarette smoking may confer a protective effect in PD is unknown and warrants further study.

3.1.5. Taste and Sense of Smell

Since brain stem regions associated with early Parkinson's disease (PD) pathology encroach upon those involved in taste function (caudal orbitofrontal cortex and immediately adjacent agranular insula) (Welge-Lussen et al 2005, De Araujo et al 2003), the ability to taste may be compromised in PD (Doty et al 2015). However, studies regarding the link between taste and sense of smell generally have been contradictory. Sienkiewicz-Jarosz et al (2005) report in their study that taste is unaffected by PD, Shah et al (2008) suggest that up to 28% of patients with established disease also have taste problems but Deems et al (1991) in their early research reported that 87% of those who report a taste problem -in fact- have no measurable taste deficit (false-positive rate).

Although it is suggested there can be a central cause of taste loss, Hawkes and Doty (2009) suggest this appears to be due to retro nasal olfaction as

odorants released from food escapes into the retropharyngeal space. Therefore, it appears any food entering the mouth will evoke a sensation of both taste and smell, unless it is pure odourless tastant evoking solely sweet, sour, salt, bitter or savoury taste qualities.

Overall, at this present time, it appears the coexistence of taste impairment with PD is not typical of PD (Sienkiewicz-Jarosz et al 2005) and Fernando et al (2005) suggest if it does occur at all it is probably a late feature of PD.

3.1.6. Disease Duration and Sense of Smell

The question of whether olfactory deficits in PD are related or unrelated to factors such as disease duration has been of considerable debate over the last 40 years. Some researchers report no associations (Haehner et al 2009, Hawkes et al 1997, Doty et al 1992, Doty et al 1988, Quinn et al 1987, Ward et al 1983), whilst others note associations (Cavaco et al 2015, Debb et al 2010, Tissingh et al 2001, Stern et al 1994, Ansari and Johnson 1975). These inconsistent findings may be related to procedural differences in measuring olfactory dysfunction (e.g., use of different assessment instruments, different methods used in the interpretation of olfactory performance (see table 1.1 and 1.2 section 1.2.1.). However, interestingly, odour discrimination performance (in patients with PD) improves concurrently with clinical motor improvement after stereotactic neurosurgical treatment using deep brain stimulation (Hummel et al 2005). This possibly indicates that at least some aspects of olfactory dysfunction in PD may be secondary to on-going degenerative processes in PD.

However, none of the above studies have divided patients according to their severity of smell loss and disease duration. This section will address this by, firstly examining the whole group and then dividing the duration of disease into 5-year intervals. The PD patients will then be analysed according to their degree of smell loss (mild/moderate microsmia, severe microsmia or anosmia).

3.1.7. Cognitive Function and Sense of Smell

Odour identification has been linked in some studies to language, verbal memory, and processing speed in healthy elderly (Westervelt et al 2005, Swan and Carmelli 2002). Whilst in other studies, this has not been proposed (Hawkes et al 1997, Doty et al 1989, Quinn et al 1987). However, this link between cognitive impairment and olfactory loss remains poorly explored in PD, although, Postuma and Gagnon (2010) recently reported significant correlations between verbal and nonverbal memory and olfactory loss in PD. Furthermore, Bohnen et al (2010) found a positive correlation between odour identification scores and verbal memory in patients with PD who have olfactory loss. Bohnen et al (2010) implicated limbic cholinergic denervation and suggests that this cholinergic denervation may be more pronounced in a subset of PD patients with early emerging cognitive deficits and that greater deficits in odour identification may identify patients at risk of clinically significant cognitive impairment (Bohnen et al 2010, Bohnen and Albin 2010).

Part of this chapter aims to confirm or refute whether cognition has an impact on sense of smell in this PD patient study group.

3.2. AIM

The aim of this chapter is to establish the pattern of distribution of mild/moderate microsmia, severe microsmia and anosmia in PD patients in this PhD study and relate it to gender, age, smoking history, taste reported, disease duration and cognitive function.

3.3 OBJECTIVES

(i) To establish the prevalence of mild/moderate microsmia, severe microsmia or anosmia in this study group.

(ii) To establish whether females in this study group do in fact have a better sense of smell than males.

(iii) To confirm or refute whether age has an impact on the sense of smell.

(iv) To establish the smoking status of PD patients in this study group and to confirm or refute whether smoking status has an impact on the sense of smell.

(v) To confirm or refute whether taste is related to the degree of smell loss in this PD study group.

(vi) To confirm or refute whether disease duration has an impact on the sense of smell and degree of smell loss.

(vii) To ascertain whether cognition has an impact on the sense of smell.

3.4. OUTLINE OF THE METHODS

(i) The sense of smell was evaluated using the 40 items University of Pennsylvania Smell Identification Test (UPSIT) (as detailed in section 2.4.6).

(ii) Gender, age, smoking history, taste reported, and duration of disease were all recorded on the Odour Detection in Parkinson's Disease Participants Questionnaire (see appendix 14).

(iii) Cognition was measured using the Montreal Cognitive Assessment tool (MoCA), (see appendix 13), (as detailed in chapter 2.4.7).

3.5 RESULTS

This study was performed on 112 PD patients. All patients were enrolled from a local Trust PD database and had a confirmed diagnosis of PD, using the UK Parkinson's Disease Brain Bank Clinical Diagnostic Criteria (Hughes et al 1992). All patients were out-patients. No in-patients were included in the study. All patients reported no olfactory system damage from any other cause at the time of testing. No attempt was made to capture environmental exposures or family history of PD and none of the patients were related.

Of the 112 PD patients, 72 were males and 40 were females which represent a ratio of 1.8:1, age ranged from 49-89 years (mean age 71 years). Out of 112 patients, 61 patients have never smoked, 47 patients were ex-smokers and 4 patients still smoke. Thirty patients also reported a decrease in taste.

Disease duration ranged from 6 months to 19 years (mean duration 5.5 years). All patients (except two scoring less than 18 on The MoCA) were considered to have either normal or mild cognitive impairment (normal score for the MoCA questionnaire is 27 and above and mild cognitive impairment ranges from 18-26) (Nasreddine et al 2005). See table 3.1 for the demographics and clinical characteristics of PD patients in this study.

Table 3.1: Demographics and Clinical Characteristics of PD Patients in This Study

Variable		All patients (N=112)	Mild/Moderate Microsmia (N=10)	Severe Microsmia (n=27)	Anosmia (N=75)	Total (N=112)
Sense of smell (UPSIT) Score	Mean Median (±SD)	17 16	M=27 F=27 M=27 F=27 1.509	M=22 F=22 M=22 F=22 1.884	M=13 F=15 M=16 F=16 3.067	
Gender	Males (N=72) Females (N=40)		4 6	17 10	51 24	
Age (years) Males	Males Mean Median (±SD) IQ	N=72 70 7.951 10.5	66	70	72	
Age (years) Females	Females Mean Median (±SD) IQ	N=40 70 7.628 10	65	66	70	
Age (years) Males and Females	Males and Females Mean Median (±SD) IQ	71 71 7.820 9.5	65 7.130	69 7.785	72 9.764	
Smoking	Non-Smokers Ex-Smokers Current Smokers		7 3 -	12 13 2	42 31 2	61 47 4
Taste	Mild Moderate Severe		1 1 -	2 3 1	7 13 2	10 17 3
Duration of Disease	Mean Median (±SD) Range (IQ)		5 4 5.31 7.5	5 3 4.57 5.5	6 5 5.91 5	
Cognition (MoCA) Score	Mean Median (±SD) Range (IQ)		27.5 27 2.699 3.75	26 23 1.881 2	26 26 2.991 3.5	

Data are presented in mean, medians, SD, IQ range.

3.5.1. Male to Female Ratio

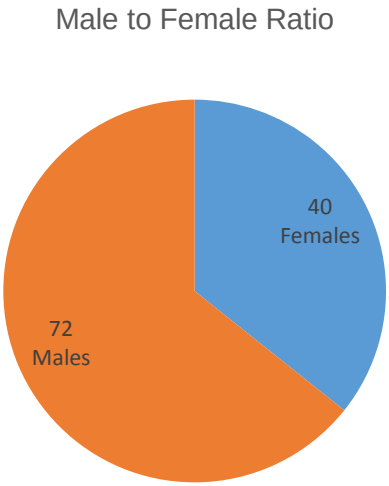


Figure 3.1: Male to Female Ratio

72 patients were males (64%) and 40 were females (36%). This represents a ratio of 1.8:1.

3.5.2. Age Range and Gender of PD Patients

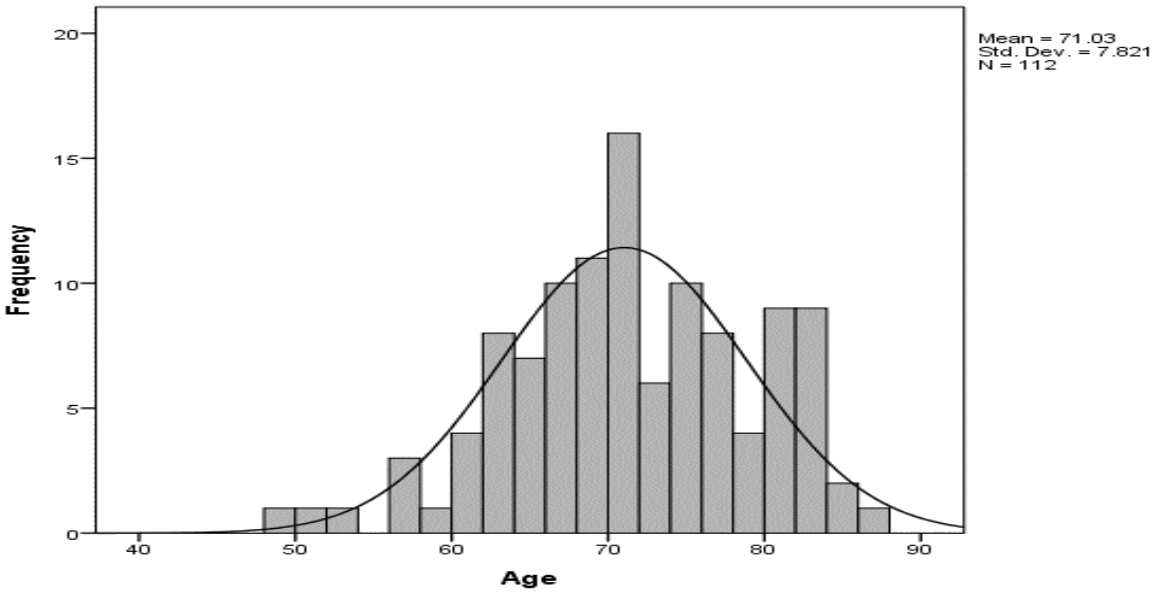


Figure 3.2: Age of Patients Enrolled in this Study

The distribution of age within this study group is roughly symmetric with no major outliers. The mean age is 71 years and there is a cluster of patients around this age. SD=7.821.

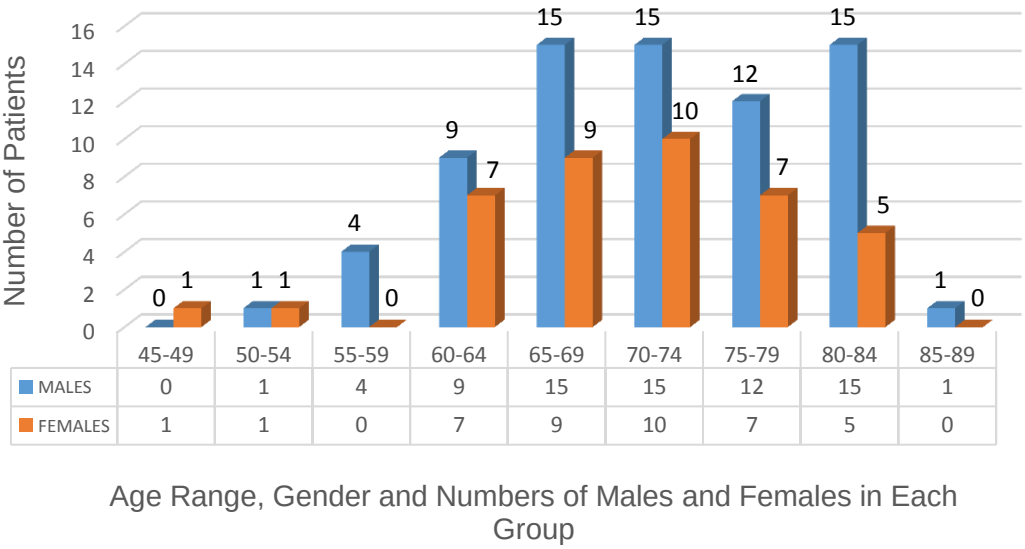


Figure 3.3: Age Range, Gender and Numbers of Male and Females in Each Group. *Most of the patients enrolled in this study are between 70-74 age groups (22%) in both genders. Another peak in age can be seen among both genders in the 65-69 age groups (21%). PD patients between the age of 45-59 (6%) and 85-89 (> 1%) in both genders represent the smallest sample of age range in this study. Males are predominantly more representative in the 80-84 age group (13%) compared to females (4%).*

3.5.3 Sense of Smell (UPSIT) Scores

Of the 112 PD patients recruited to this study, 75 patients had anosmia, 27 patients had severe microsmia, 9 had moderate microsmia and one patient had mild microsmia. No PD patients had a normal sense of smell (figure 3.4).

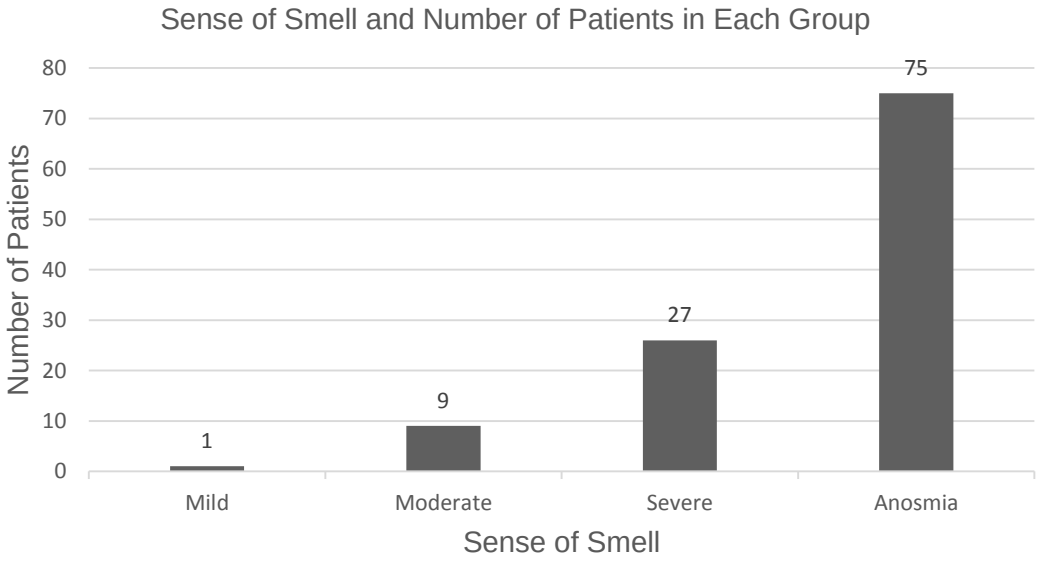


Figure 3.4: Sense of Smell and Numbers of PD Patients in Each Sub-Group

Most PD Patients (75) have anosmia which is 67% of the study sample size. The female and male normal percentile values per the age of patients and test scores can be seen in Appendix 4.

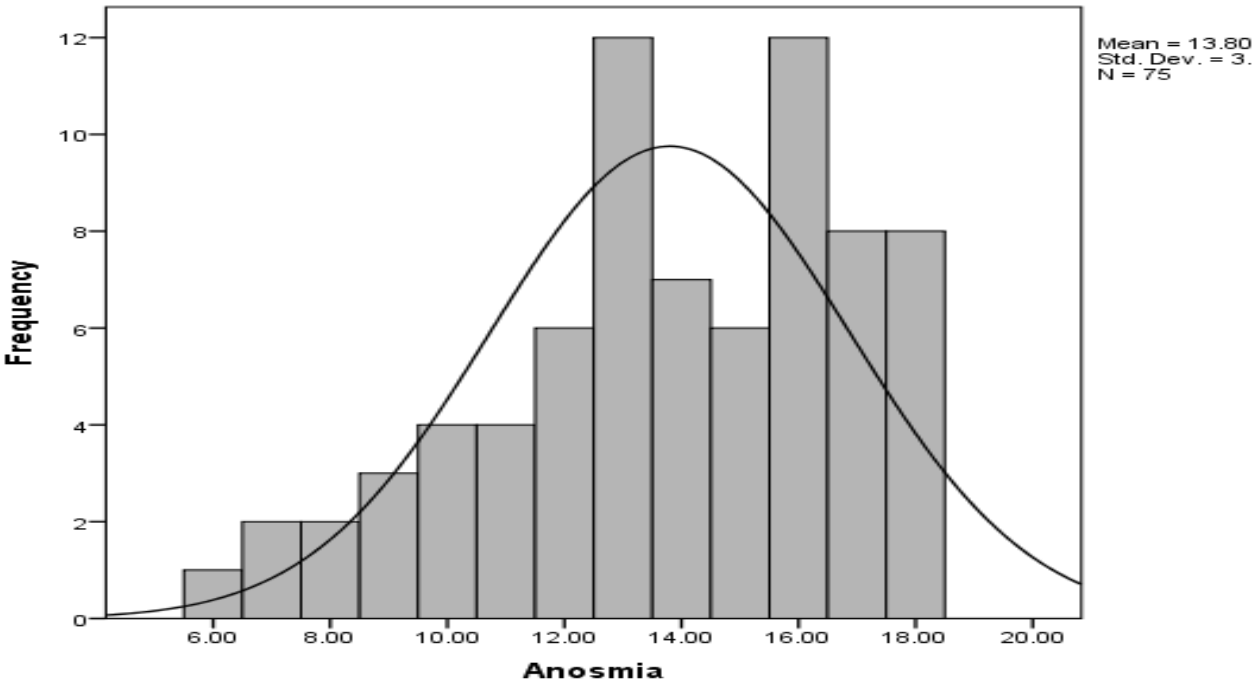


Figure 3.5 UPSIT Scores in Anosmia Group

The UPSIT 40 scores show a double peak distribution at 13 and 16. Both represent 12 patients out of 75 anosmic patients and therefore 9% each of the whole anosmic group. The mean is 13.80 and SD=3.067.

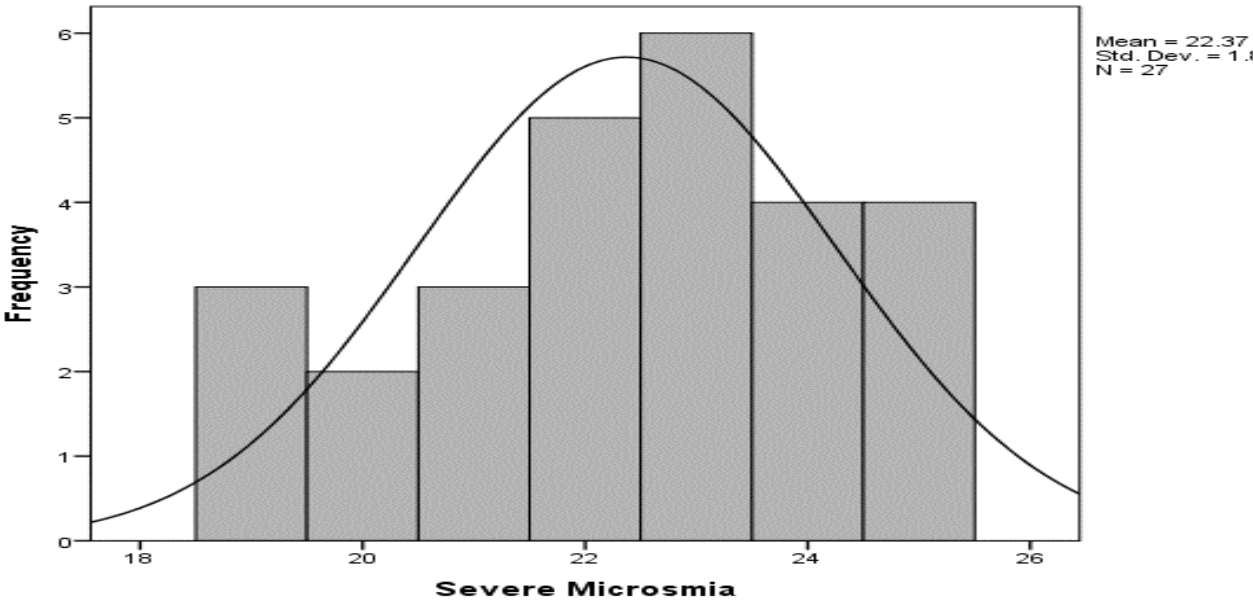


Figure 3.6: UPSIT Scores in Severe Microsmia Group

Distribution of UPSIT 40 scores in 27 patients with severe microsmia. The mean UPSIT is 22.37 and SD=1.884.

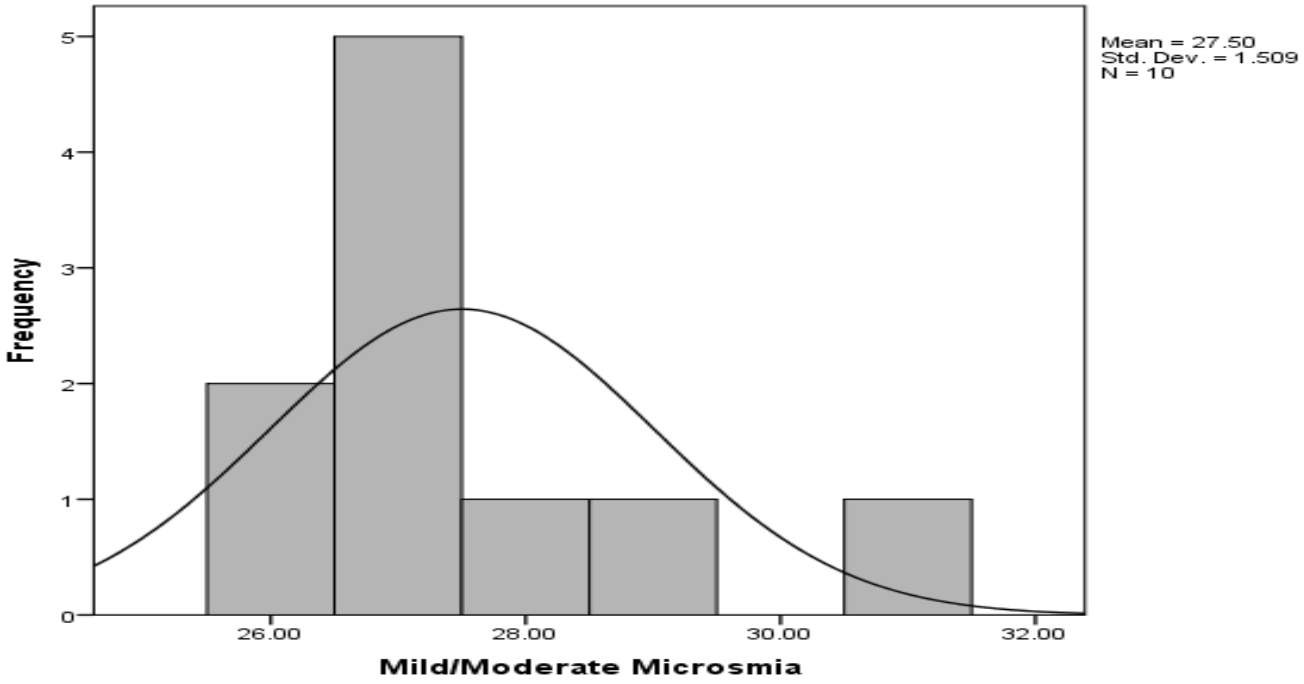


Figure 3.7 UPSIT Scores in the Mild/Moderate Microsmia Group

Distribution of UPSIT 40 scores in 10 PD patients with mild to moderate microsmia. There is a peak at UPSIT score 27 and represents 5 PD patients (50%) of the mild/moderate group. Only one patient had mild microsmia possibly representing an outlier. The mean UPSIT is 27.50 and SD=1.509.

3.6. FACTORS AFFECTING SENSE OF SMELL

In this section data will be analysed for the whole group as a continuous parameter to ascertain the effects of certain factors that might affect the sense of smell.

3.6.1. Gender Differences and Sense of Smell

Figure 3.8 demonstrates that females have a better sense of smell and an overall higher median UPSIT score than males in this group of PD patients.

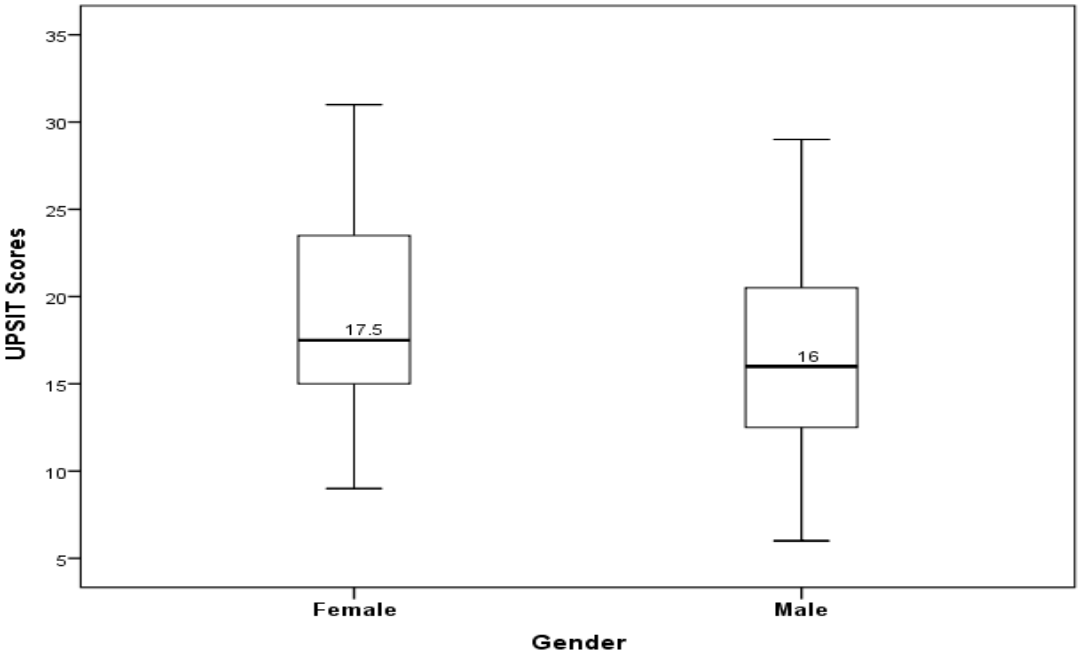


Figure 3.8: UPSIT Scores and Gender

Females have an overall higher median UPSIT score of 17.5 compared to males with a median UPSIT score of 16 in this group of PD patients, which is statistically significant (p= 0.024). (Number of males =72. Number of females = 40).

An independent samples t-test has been conducted to provide further statistical analysis on gender differences regarding the sense of smell. These are statistically significant in females (M=18.68, SD 5.498) compared to males (M=16.21, SD 5.467: t (112) = 2.283. p=0.024.

3.6.2 Age and Sense of Smell

UPSIT scores of patients with PD according to their age are shown in Figure 3.9. The data show a trend of a reduction in the sense of smell as PD patients get older. Furthermore, there is a negative correlation between age and UPSIT r_s = -0.210, which is statistically significant (p=0.026).

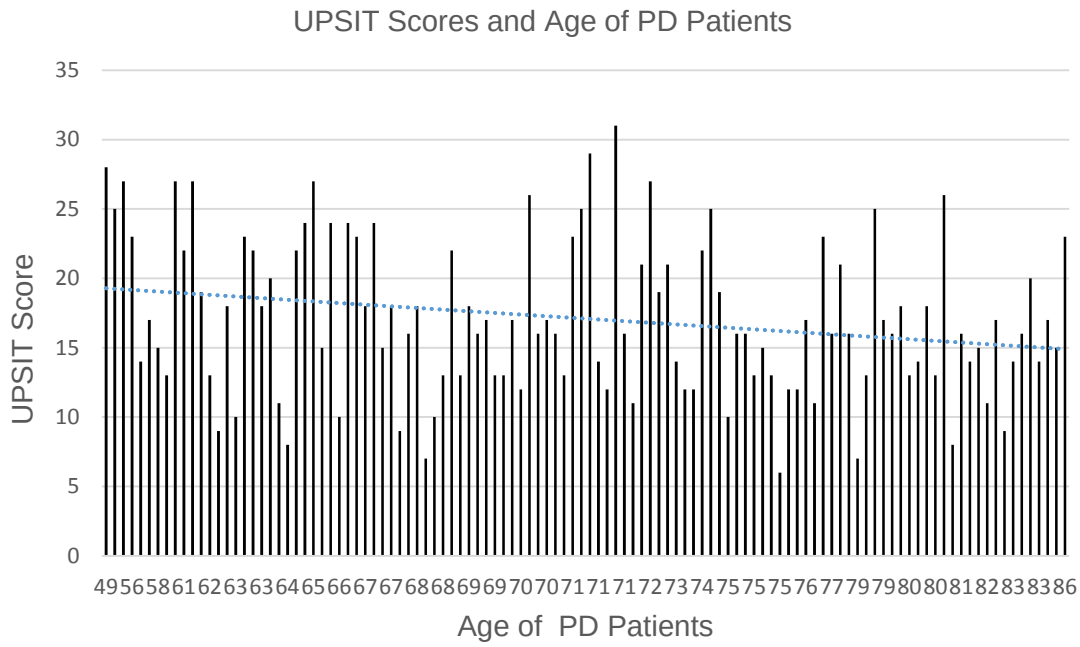


Figure 3.9: UPSIT Scores and Age of PD Patients

Distribution of the UPSIT score for 112 PD patients age recruited for this study. The mean age is 71 years for both males and females. SD=7.820 (see table 3.1).

3.6.3. Smoking and Sense of Smell

Figurer 3.10 shows UPSIT scores for non-smokers, ex-smokers and current smokers. The median UPSIT of present smokers is less than ex-smokers and non-smokers.

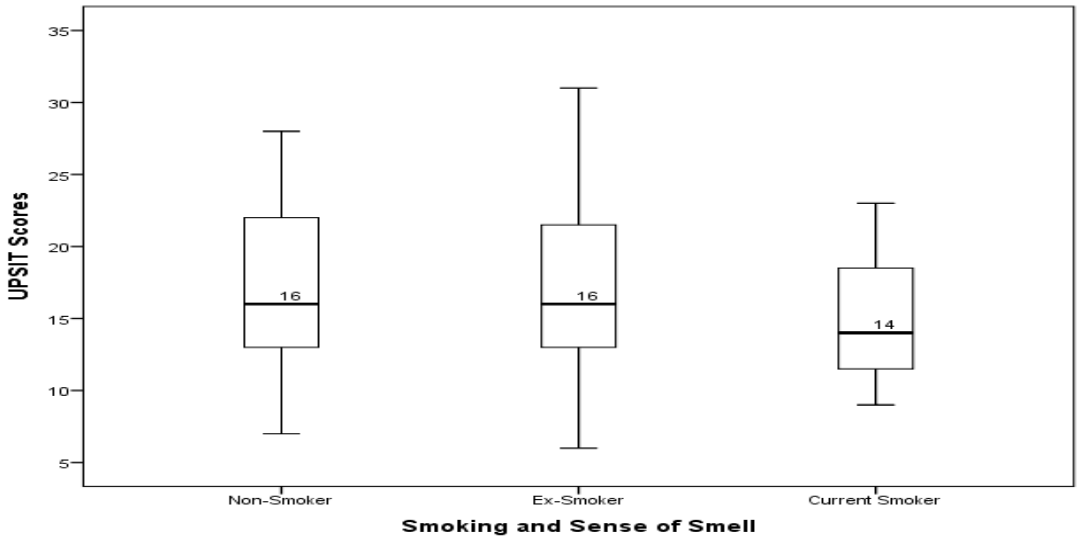


Figure 3.10: UPSIT Scores, Smoking and Sense of Smell

Smoking status and median UPSIT score for each subgroup. There are 61 non-smokers (median UPSIT 16), 47 ex-smokers (median UPSIT 16) and 4 current smokers (median UPSIT 14).

Figure 3.11 shows the years since 47 ex-smokers quit smoking. This ranges from 1 year to 60 years and UPSIT scores range from 6-31. A Spearman's correlation was run to determine the relationship between number of years since ceasing smoking and the sense of smell using UPSIT 40 scores. There was a weak positive correlation between the years since ceasing smoking and the degree of smell loss (r_s=0.107, n=47), which did not reach statistical significance (p=0.472).

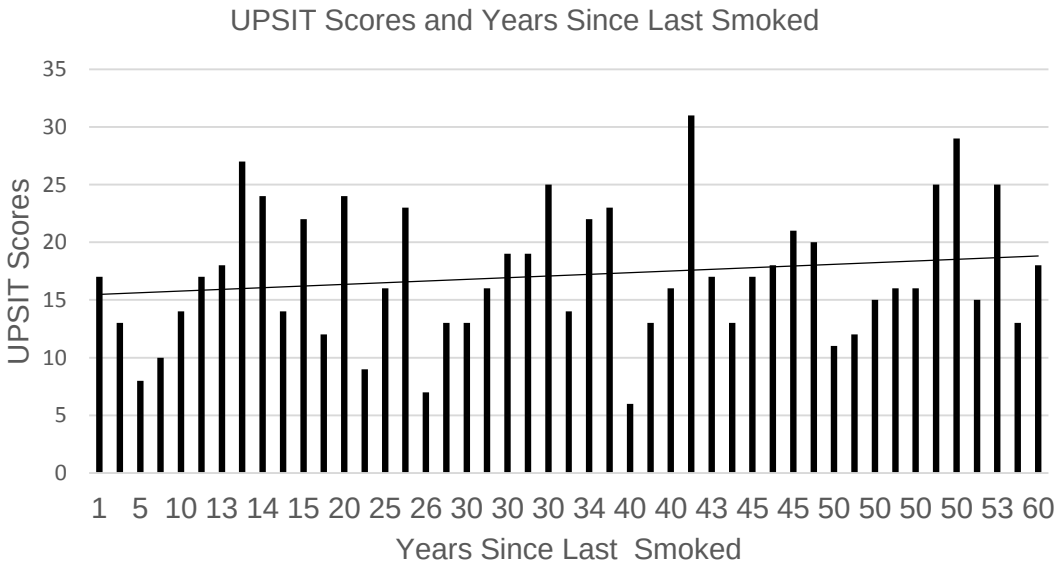


Figure 3.11: UPSIT Scores and Years Since Last Smoked

Distribution of 47 ex-smokers' UPSIT scores and years since last smoked. This ranges from 1 year to 60 years and UPSIT scores range from 6-31. It appears UPSIT scores improve alongside years from quitting smoking. However, on further statistical analysis this did not reach statistical significance (r_s =0.107, n=47, p=0.472).

3.6.4. Taste Perception and Sense of Smell

Of the 112 PD patients recruited to this study, 82 patients (73%) self-reported no taste problems and 30 patients (27%) self-reported taste problems (figure 3.12). The median UPSIT is lower in patients with self-reported taste problems (14.5) and the mean is 15.70, compared to those PD patients with no taste problems (median 17, mean 17.60) (see figure 3.12).

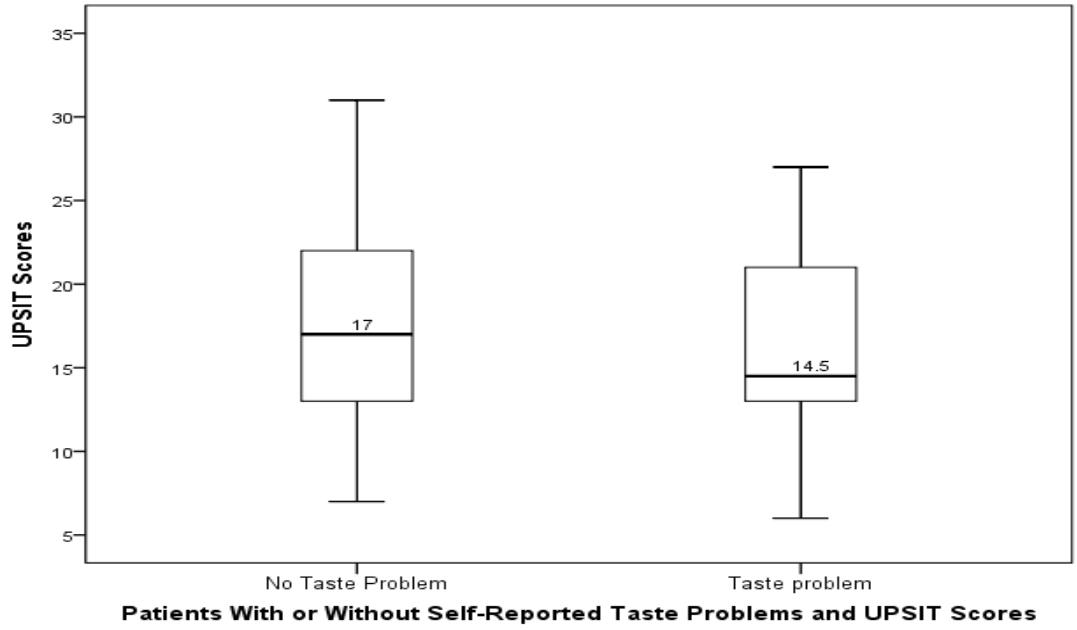


Figure 3.12: Patients with or Without Self-Reported Taste Problems and UPSIT Scores. *Eighty-two PD patients reported no taste problems and thirty PD patients had taste problems. The median UPSIT is lower in patients with self-reported taste problems (14.5) and the mean is 15.70, compared to those PD patients with no taste problems (median 17. Mean 17.60).*

Further statistical analysis using independent-samples t-test was conducted to compare UPSIT scores with patients self-reporting loss or changes in taste perception or not and sense of smell. There was not a significant difference in the scores for patients self-reporting no changes (M=17.60, SD 5.584) and those patients self-reporting changes (M=15.70, SD 5.421): t (110) =1.605, p=0.111 in their ability to taste. These results suggest that the perceived ability to be aware of loss or change in ability to taste does not correlate with the degree of loss of sense of smell.

Further subgroup analysis of the degree of self-reported taste loss by 30 PD patients and UPSIT scores is shown in figure 3.13 (mild, moderate or severe as per odour detection in Parkinson's disease questionnaire), (see appendix 14). Figure 3.13 demonstrates those PD patients self-reporting mild taste loss appear to have an improved sense of smell.

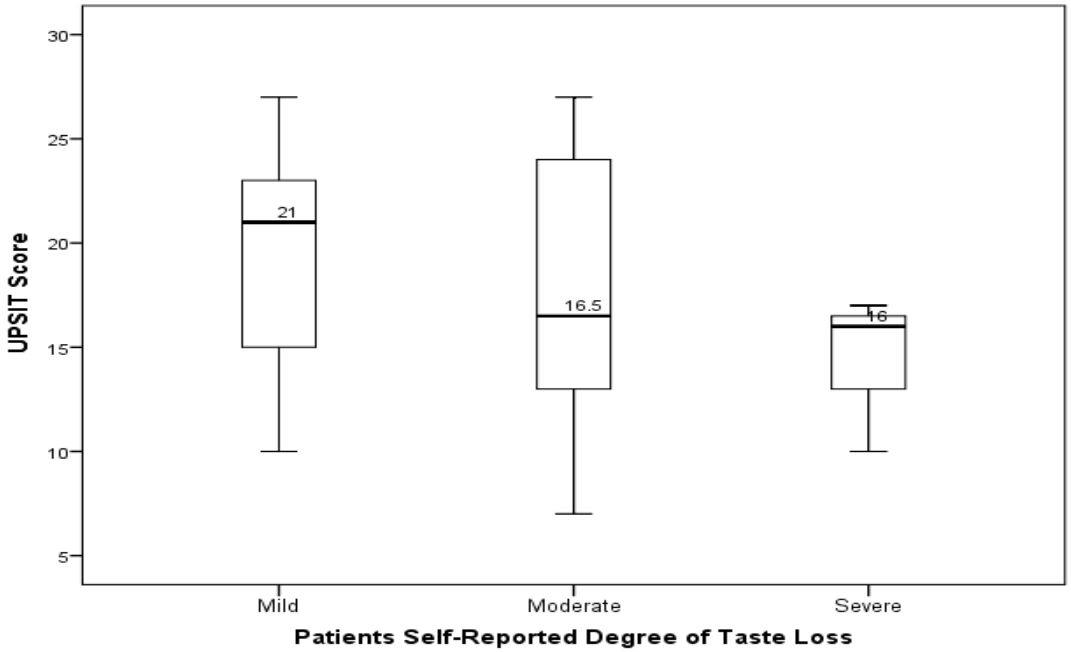


Figure 3:13: Patients Self-Reported Degree of Taste Loss by 30 PD Patients in the Study Group and UPSIT Scores

Ten PD patients reported mild taste problems, 17 PD patients reported moderate taste problems and three PD patients reported severe taste problems. The median UPSIT is higher in PD patients reporting mild taste problems (21) than the PD patients reporting moderate (median 16.5) and severe (median 16) taste problems.

An independent sample Kruskal-Wallis test was run to determine the relationship between self-reported mild, moderate and severe taste problems and the sense of smell (using UPSIT 40 scores). This did not reach statistical significance (p=0.570).

3.6.5. Duration of PD and Sense of Smell

The results showed that the duration of PD in the study group ranged from 6 months to 19 years and that olfactory dysfunction is present to a relatively high degree even in early stages of the disease process (figure 3.14). The mean duration is 5.5 years (SD=3.887), median is 4 years (IQ range=6). Further statistical analysis using Pearson's correlation shows that there was no correlation between duration of PD and severity of olfactory dysfunction, (as measure by UPSIT score), (r_s=0.043, p=0.649).

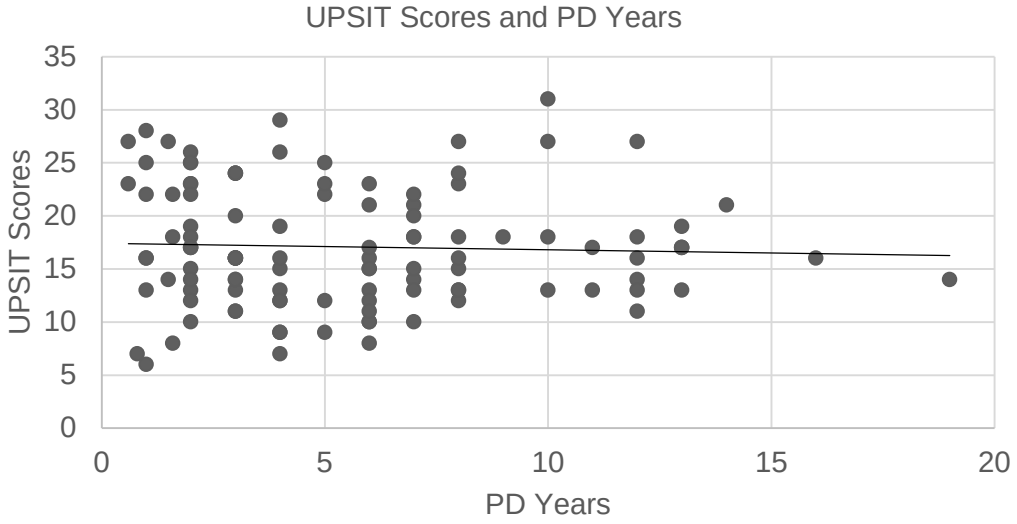


Figure 3.14: UPSIT and PD Years

The duration of PD in the study group ranged from 6 months to 19 years. On visual inspection, there appears to be a cluster of PD patients around two and six years with the widest range of UPSIT at one year (UPSIT range 6-28).

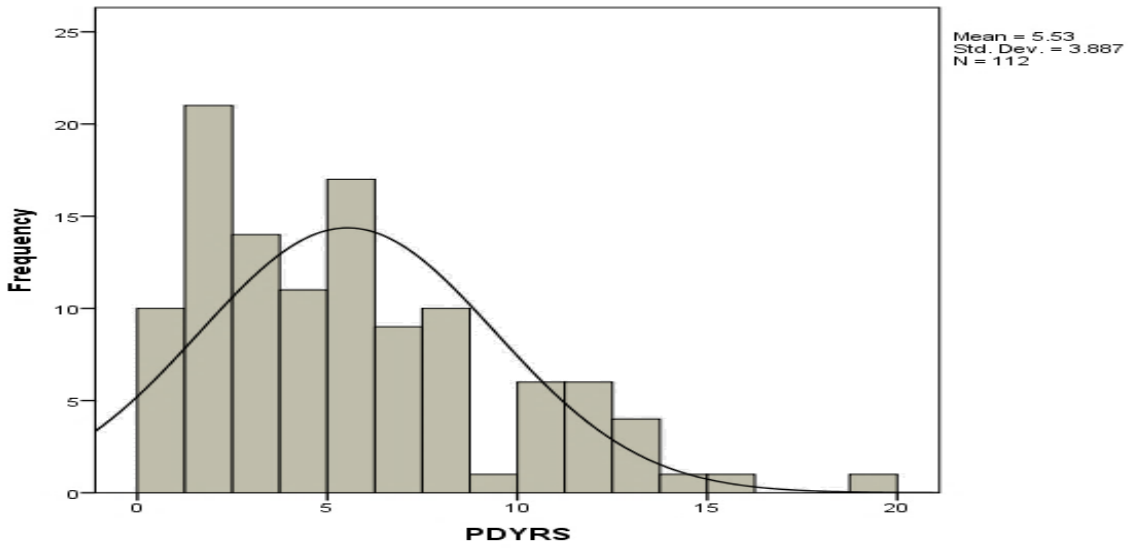


Figure 3.15: Frequency of PD Years

The mean duration is 5.5 years, median is 4 years, SD=3.887 and IQ range=6. Further statistical analysis shows that duration of PD and UPSIT Scores did not reach statistical significance r_s*=0.043, p=0.649.*

Duration of the disease has been analysed further by dividing the years into 5-year intervals (i.e., 0.6-5, 6-10, 11-15 and 16-19 years) since being initially diagnosed with PD. These intervals were linked with UPSIT mean, median and range and can be seen in table 3.2.

Table 3.2 shows that most patients (61=54%) have PD for five years or less, with the next group of patients having PD between 6-10 years (35= 31%). The group least representative in this study is patients with PD for 16 years or more and only accounts for less than 2% of the overall sample size. There appears to be a slight difference between the mean and median UPSIT scores in each 5-year duration of PD subgroup.

Table 3.2: PD Years, Number of Patients, UPSIT Scores (Mean, Media and Range).

PD Years (Since diagnosis)	Number of Patients	UPSIT (Mean)	UPSIT (Median)	UPSIT (Range)
0.6-5	61	17 (SD = 8.602)	16 (IQR = 10)	6-29
6-10	35	18 (SD = 6.167)	16 (IQR = 7.25)	8-31
11-15	14	17 (SD = 3.701)	17 (IQR = 5)	11-27
16-19	2	15 (SD = 2.061	15 (IQR = 1)	14-16

3.6.6. Cognitive Function and Sense of Smell

MoCA was used to assess cognitive function in patients with PD in this study (see section 2.4.2). The minimum recorded MoCA for this PD study group is 16 and the maximum is 30. The mean MoCA is 26.1 (SD=2.787).

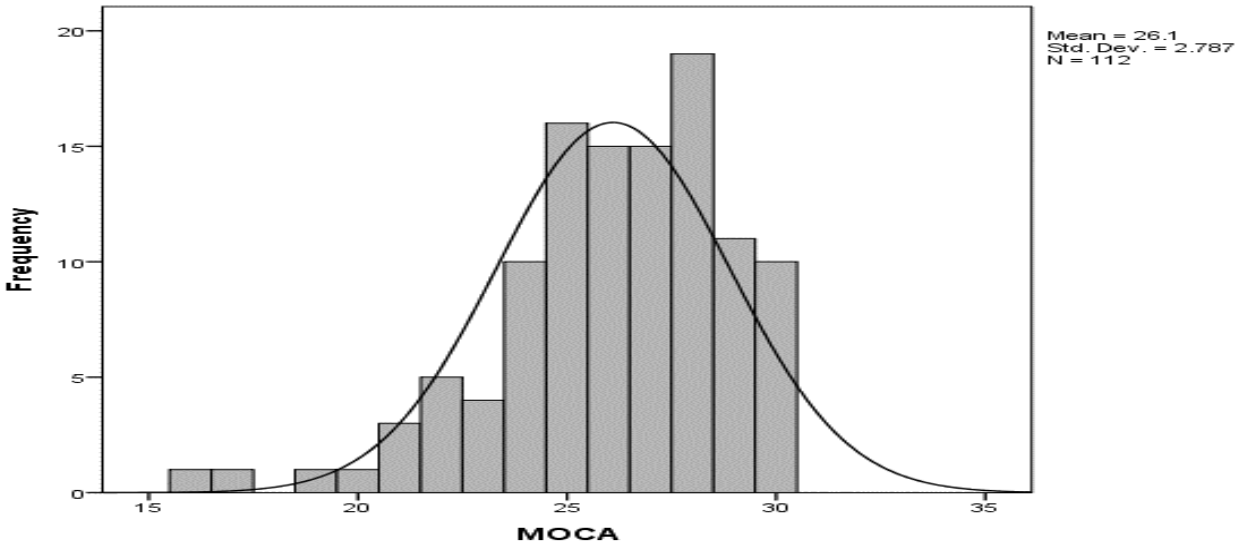


Figure 3.16: Frequency of MoCA Scores

Mean MoCA score is 26.1 SD=2.787. Median is 26 and Mode is 28.

Figure 3.17 shows the UPSIT and MoCA scores for the whole PD group. There appears to be a trend for UPSIT scores to increase alongside an increase in MoCA scores. Therefore, a Spearman's correlation was conducted on all PD patients MoCA and UPSIT scores. There is a weak positive correlation between cognition and UPSIT which is statistically significant. (r_s=0.213 p=0.024).

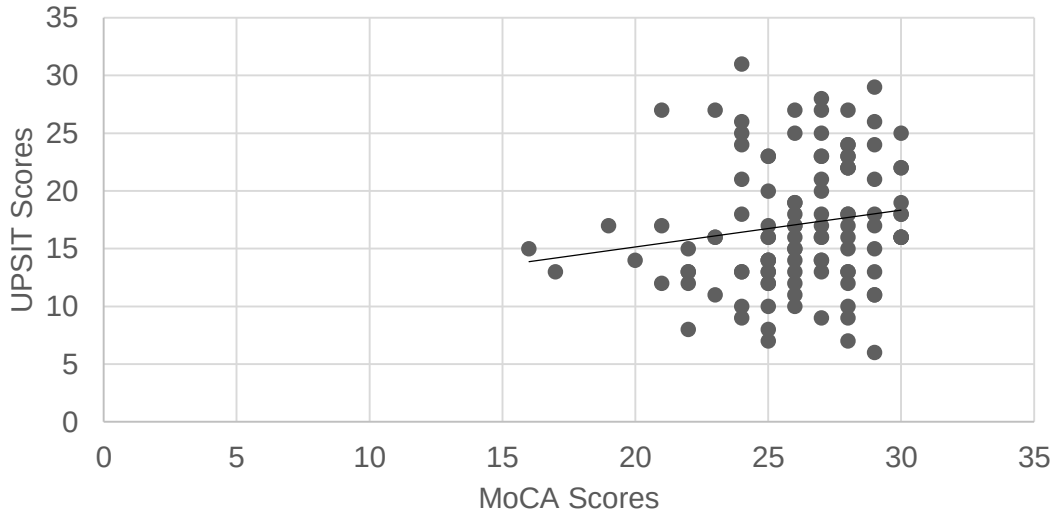


Figure 3.17: UPSIT and MoCA Scores of Study Group

The mean MoCA is 26.1 (SD=2.787). However, there appears, to be a trend for UPSIT scores to increase alongside an increase in MoCA scores. On further analysis, there was a positive correlation between cognition and UPSIT (r_s=0.213), which is statistically significant (p=0.024).

Further sub-group analysis was conducted by dividing patients into those with normal and those with mild impaired cognition (figure 3.18).

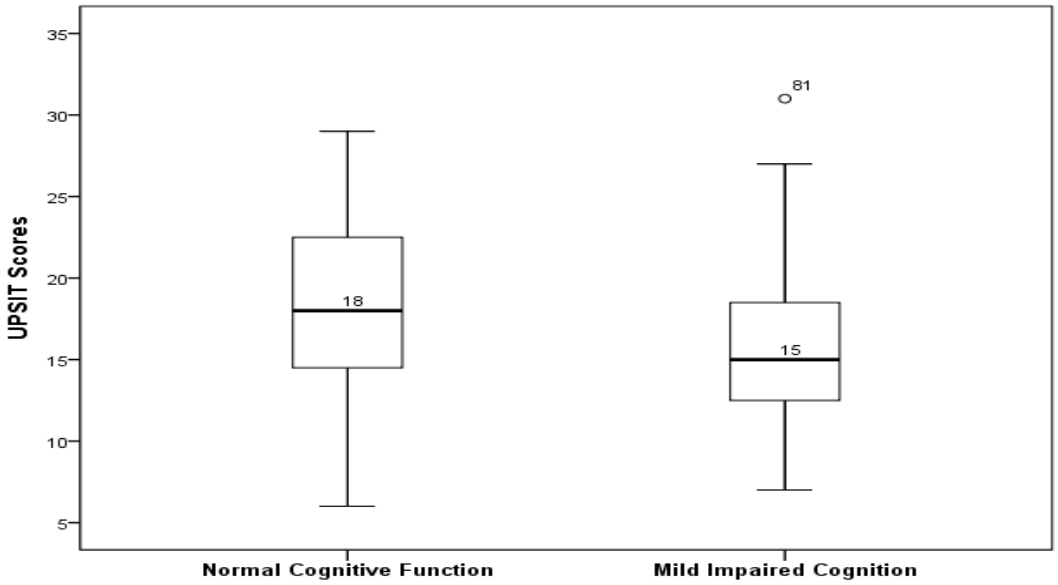


Figure 3.18: UPSIT Scores and Patients with Normal or Mild Cognitive Impairment

Fifty-seven PD patients had normal cognitive function and 55 PD patients had mild impaired cognition (normal score for MoCA is 27 and above and mild cognitive impairment ranges from 18-26 (although two patients included in the study had MoCA's of 16 and 17). (See Appendix 13). Initial analysis appears to show UPSIT scores decrease alongside the degree of impaired cognition.

Figure 3.18 demonstrates that UPSIT score are slightly less in fifty-seven PD patients with mild impaired cognition (median 15, mean 16, SD= 5.470) compared to the fifty-five PD patients with normal cognitive function (median 18, mean 18 SD= 5.546). An independent samples t-test showed a statistically significant difference in the sense of smell (p=0.049) between PD patients with normal cognitive impairment compared to PD patients with mild cognitive impairment.

3.7 DISCUSSION

3.7.1. Demographic Features of the PD Study Group

In this PhD study group, the male (64%, n=72) to female (36%, n=40) ratio (see figure 3.1) appears to be slightly higher at 1.8:1 ratio than that considered representative of the general PD population at 1.5:1 ratio (Wooten et al 2004). This however, seems to vary throughout the PD research with Hearting et al (2008) study reported a 1.5:1 ratio but Doty et al 1988 study reported a ratio of 1.3:1. Most patients (44%) were between the 65-74 age group in both genders and 80+ age group in the males (see figure 3.2). This is not surprising as the researcher has predominantly older patients on the Trust database. This is not only due to predominantly working alongside an elderly care physician but also because local demographics of the area, where the study was conducted, holds the highest concentration of the elderly in the United Kingdom with 33.2% of its population over the age of 65. This is almost double the existing UK figure of 16.5%. (Office for National Statistics 2011). However, it is also worth noting that the prevalence rate of PD is set to increase by 28% by 2020 particularly in the older age groups highlighted in this study (65-74 and 80 + years) (Parkinson's Prevalence in the UK 2012) and therefore could also represent the general age of the PD population.

The distribution of age of PD patients (in years) within this study group is roughly symmetric (Figure 3.2), with no major outliers. The mean age is 71 years and there is a cluster of patients around this age (SD=7.821). This is higher than Herting et al (2008) who examined 27 patients (5 women, 22 men) and had a predominantly younger age range 27–64 years (mean age 49 years), but lower than to Doty et al (1988), who examined 81 patients (46 men 35 women using UPSIT 40) and had a slightly larger mean age at 77.2 years.

3.7.2 The Link Between Sense of Smell and PD

Although the UPSIT is a self-administered test and safe, a member of the ethics committee referred to potential side effects of the sniff test (such as nausea or headaches), which are very rare and have not been encountered in clinical practice. In view of this, the researcher administered the test to all PD patients in this study. This has been done in previous research but for ease of data collecting and to reduce potential sources of variance rather than for possible side effects (Sobel et al 2001, Doty et al 1988).

Results of this study show at least 90% of the patients recruited for this study have either anosmia or severe microsmia with the remainder of the patients having mild/moderate microsmia (figure 3.3). This finding concludes that 100% of this study sample had an abnormal sense of smell. However, this is not mirrored by others. For example, Haehner et al (2009) in their large-scale study of 400 patients of 3 individual populations reported 96% of their PD patients had olfactory loss, however, when normative data in relationship to the subjects age and sex was applied 74.5% of the study population was diagnosed with olfactory loss, highlighting that olfactory loss needs to be qualified in terms of the olfactory test used and normative data being applied. Therefore, the reasons for these inconsistent findings may be due to procedural differences in measuring olfactory dysfunction (e.g., use of different assessment instruments, interpretation of olfactory performance and demographic confounding factors) (which varied between these investigations)

Herting et al (2008) is the only other researcher who found no patients had normosmia. They conducted a longitudinal study over 4.4 years rather than an open cross-sectional study. Although the sample size was smaller (27 PD patients were examined of whom 5 were women and 22 were men) with a predominantly younger age range of 27–64 years their study had PD patients with similar duration of disease recorded in this PhD is study (0 to 19 years).

However, if between 80-100% of PD patients have a degree of loss of sense of smell, this further emphasises that testing a patient's sense of smell may improve the diagnostic accuracy of PD and may need to be considered as part of the brain bank criteria. The researcher believes the more cardinal symptoms associated with a diagnosis of PD can only contribute to a more accurate diagnosis particularly as (i) PD is a devastating relentless condition (ii) the diagnostic accuracy is at best 84%-90% accurate even by an expert (Rizzo et al 2016, Brooks 2012, Hughes et al 2001) and, (iii) in practice, some patients make drastic lifestyle changes and alter their upcoming plans based on the diagnosis.

In practice, the UPSIT was a simple test to administer and took on average 5 minutes to complete. One patient however, did struggle to accept she could not smell anything and was determined to smell the odour presented (she was anosmic) and for this reason the test took 45 minutes to complete. There were also several patients who commented that they had not smelt the occasional odour presented on the cards such as liquorice or skunk but there were other odours on the card that were familiar to them. None of the odours the patients had not smelt before were in fact the presenting odour which re-assured the researcher that the test score was in fact correct. Interestingly, 8 patients commented that all the smells smelt of cardboard. A couple of PD patients also commented that there were a lot of odours to sniff but in general it was received well.

Interestingly, there is one major outlier in the groups and this is the only patient who had mild loss of sense of smell (UPSIT 31), who later went on to be diagnosed with PSP-P.

Further clarification on the distribution of UPSIT scores in each sub-group can be found in figures 3.5-3.7 (see section 3.4.3).

3.7.3. Age and Sense of Smell

Results of this study showed that there is a trend in reduction in the sense of smell as PD patients get older (figure 3.9). There are numerous theories on why the sense of smell deteriorates as we age (see section 3.1.3). However, it is beyond this study to examine these theories in any detail. Furthermore, there is a negative correlation between age and UPSIT (r=-0.210), which is statistically significant (p=0.026). This is in support of the findings of not only PD patients but non-PD patients. For example; Doty et al (1984), examined over 1600 subjects (see section 1.2.3) and noted age has an impact on sense of smell. Hawkes (2008) suggests it is unlikely that the PD olfactory defect is due to simple ageing and suggests a healthy person would need to live until the age of 106 to 160 years to exhibit the degree of smell loss shown by a typical PD patient aged 60 years. However, it is worth remembering that although ageing (Jafari et al 2008, Murphy et al 2002) and PD (Casjens et al 2013, Litvan et al 2003, Ramaker et al 2002, Hawkes et al 1999, Hawkes and Shephard 1998, Mesholam et al 1998, Barz et al 1997, Hawkes et al 1997, Hawkes and Shephard 1993, Hummel et al 1993, Doty et al 1988, Quinn et al 1987, Ward et al 1983) are among the factors that put an individual at risk of developing olfactory dysfunction, other factors can cause olfactory loss such as vascular and metabolic insufficiency, (e g hypothyroidism or cirrhosis of the liver) viral/ inflammatory damage (e.g. allergic rhinitis) (Rombaux et al 2012, Jafek et al 1990, Douek et al 1975) nutritional deficiencies, (such as B12 and Zinc) air pollution (such as paint solvents and acetone) (Hudson et al 2006), as well as a number of age related diseases , e.g. PD and AD (Rombaux et al 2005, Doty 1989) (For a list of related medical conditions that affect sense of smell see appendix 20) and medications such as ampicillin to treat infections and dexamethasone to treat pain (see appendix 21) (Doty et al 2008, Seiberling and Conley 2004, Schiffman and Graham 2000), can affectsense of smell.

3.7.4. Gender Differences and Sense of Smell

Results of this study showed that females have an overall higher median UPSIT score than males in this group of PD patients (figure 3.9). This difference was statistically significant (p= 0.024). This is consistent with the published work by Silveria-Moriyama et al (2008), Doty (1995) and Liu et al (1995) in patients with PD and has also been observed in general by numerous investigators, using psychophysical, electrophysical and imaging techniques (Lundstrom et al 2006, Dalton et al 2002, Brand and Millot 2001, Cain 1982), (as briefly described in section 1.2.7.). Therefore, this study agrees with normative data for the UPSIT-40 showing a considerable influence of gender (Silveria-Moriyama et al 2008, Doty 1995).

It is also worth considering that gender differences are significant despite adjustment using percentile values allowed for by Doty (2003) (See Appendix 4) and possibly suggest that percentile values are in fact much higher in females than previously stated.

Many studies report females outperform males on tests of odour identification regardless if they have PD or not (Fusari et al 2008, Doty et al 1984, Cain 1982). These observations have been made by numerous investigators using psychophysical, electrophysical and imaging techniques (Lundstrom et al 2006, Dalton et al 2002, Brand and Millot 2001, Doty et al 1984, Cain 1982), (see section 2.4.6). For example, Doty et al 1984 found in a study of 455 men and 742 women asked to identify each of 50 odours being evaluated for inclusion in a standardized smell identification test. Women outperformed men on 45 of the 50 stimuli (90%). However, this is not mirrored by all researchers and some studies fail to find any significant differences between male and females in sensitivity for some odours for example pyridine (spoiled-milk odour) (Dorries et al 1989) and phenyl ethyl alcohol (rose like), (Segal et al 1995). However, these studies are rare. The discussion as to why women outperform men is inconclusive. So far, the increased olfactory sensitivity has been speculated to be attributed to numerous factors such as hormonal effects and verbal skills.

With regards to hormonal effects, well-known examples are the variations in the sensitivity of women during their menstrual cycle. Olfactory performance reaches a peak during ovulation and then decreases during menstruation (Doty 1986). However, this is also observed with women on the contraceptive pill, which suggests that the variations in sensitivity are not hormone dependent. Therefore, the mechanisms underlying the correlations between odour perception and hormonal status still have to be clarified. With regards to verbal skills, it is known that women perform better than men in verbal tasks and that there is sex differences in the functional organization of the brain for language (Shaywitz et al 1995). Thus, the superiority of women in olfaction could reflect a type of cognitive advantage that is also found in the other senses or situations. A strong similarity between odour and language perception has been advanced by Lorig (1999). For this author, odour information processing shares some of the cortical resources used in processing language. In this way, it would not be surprising if an advantage in verbal tasks is correlated with an advantage in olfactory perception (Larsson et al 2004).

3.7.5. Smoking and Sense of Smell

One in five adults (20%) aged 16 and over and one in 7.7 (13%) adults aged 60 and over were smokers in the UK in 2012 (Office for National Statistics 2013). In this PhD study, there are 4 current smokers (see Table 3.1), this represents one in 28 (4%) of the PD population which is significantly lower than that of the general population, even if we only compare it to patients over 60 years of age (which is when PD is most likely to be diagnosed). Although smokers appear to be poorly represented in this study sample this is also mirrored in Checkoway et al (2002) study who had 7 smokers out of the 210 PD patients which is one in 29.4 adults (3%) which is lower than national figures again. Therefore, this may well represent the general percentage of smokers in the PD population (For a systematic review further confirming low incidence rates of smokers in PD see Hernan et al 2002).

Within this study group, in addition to the 4 current smokers there are also 61 non-smokers and 47 ex-smokers (see Table 3.1). The mean UPSIT of present smokers is less than ex-smokers and non-smokers (figure 3.10). This is in support of Katotomichelakis et al (2007) who reported smokers to be nearly six times as likely to evidence an olfactory deficit as non-smokers, depending on the duration and the number of cigarettes smoked. On the other hand, findings of this present PhD study are in contrast with the findings of Lucassen et al (2014) who also used UPSIT 40 and examined 76 PD subjects (22 with a history of smoking (smokers), 54 who never smoked (non-smokers), and 70 Controls (17 smokers, 53 non-smokers) who in fact found a history of smoking is associated with better olfaction among PD. However, in this current study, results need to be interpreted with caution as there may be a sample size effect, as only 4 patients smoke. It could therefore be argued that a larger sample size incorporating an even distribution of smokers compared to non-smokers would be required to confirm or refute the findings in this present study.

There was a weak negative correlation (which was non statistically significant) between number of years since stopping smoking and the degree of smell loss (r_s=-0.107, n=47, p=0.472.). Indirectly, some results are supported by Murphy et al (2002) study who found that only current smoking was associated with impaired olfaction. They did not find any significant difference between persons who had never smoked and past smokers. In contrast, a recent study testing odour identification in a Japanese adult population (Ishimaru and Fujii 2007), demonstrated a decreased odour identification to both current and past smokers, thereby concluding that cessation of smoking may not provide recovery of olfactory function.

3.7.6. Taste Perception and Sense of Smell

Despite the key role of taste function in nutrition and health, little is known about changes in taste perception caused by PD, particularly as Cecchini et al (2014) suggest that taste dysfunction should be included in the list of non-motor symptoms of PD.

In this PhD study group, 82 patients (72%) self-reported no taste problems and 30 patients (27%) self-reported taste problems. This was mirrored by Shan et al (2009) study who also found impaired taste appreciation in about 27% of PD patients. However, in Shan et al (2009) study although they used the UPSIT to test loss of sense of smell they used a more robust way of measuring taste threshold using the Rion electrogustometer in 75 non-demented PD patients and 74 controls.

Although median UPSIT score is lower in patients with self-reported taste problems compared to those who self-reported no taste problems (figure 3.17) this difference was not statistically significant (p=0.111). These results suggest that the perceived ability to be aware of loss or change in ability to taste was not affected by the patient's sense of smell. This was mirrored in Kim et al (2011) study who also tested the taste function of 31 PD patients and 29 healthy controls using filter paper taste strip tests (TSTs). Although the mean TST score was significantly lower in female (rather than male), once again TST scores in PD patients did not correlate with olfactory function.

Further analysis of the degree of taste loss (mild, moderate or severe) self-reported by 30 PD patients in this study group and the degree of loss of sense of smell did not reach statistical significance (p=0.570). However, this might not have reached statistical significance due to a small sample size as only 30 PD patients (27%) self-reported taste problems.

3.7.7. Duration of PD and Sense of Smell

The duration of PD in the study group ranged from 6 months to 19 years. This is identical to Herting et al (2008) study who conducted a longitudinal study over 4.4 years rather than an open cross-sectional study. However, the duration of PD in other studies does vary considerably. For example, duration of PD ranged from 3 months to 55 years in Doty et al (1988) study and 3-10 years in the Cavaco et al (2015) study.

Further analysis shows that most patients participating in this study (61=54%) have PD for five years or less, with the next group of patients having PD between 6-10 years (35= 31%). The group least representative in this study are patients with PD for 16 years or more and accounts for less than 2% (2 patients) of the overall sample size (see table 3.1). There is slight difference noted in the mean and median in each 5-year duration group (table 3.2) and the overall mean duration of PD in this PhD study group is 5.5 years. This is similar to Cavaco et al (2015) study with a mean duration of 6 years but much lower than that of Doty et al (1988) study with a mean duration of 12.4 years.

Regardless of the duration of PD, this PhD study highlights that duration of PD alone is not that relevant when correlated with the loss of sense of smell as loss of sense of smell was present to a relatively high degree even in initial stages of the disease process (see figure 3.12). This suggests that there is no relationship between the duration of PD and loss of sense of smell. This is consistent with several studies suggesting that olfactory deficits in PD are unrelated to factors such as disease duration. For example, Doty et al (1988) (who examined 81 PD patients), Double et al (2003) (who examined 49 PD patients) and Haehner et al (2009) (who examined 400 PD patients from a large multicentre study) all concluded there was no association between loss of sense of smell and duration of disease.

However, as loss of sense of smell can be profound even in the early stages of disease these findings may not apply to all patients in the earliest stages of the disease or indeed all patients (Berendse et al 2011; Herting et al 2008; Siderowf et al 2005; Tissingh et al 2001). Therefore, to establish whether this PhD study confirms or refutes whether duration of disease does or does not correlate with loss of sense of smell, the 10 patients who had mild/moderate loss of sense of smell would need to be re-tested in several years' time. This would be simple to perform and warrants further study.

3.7.8. Cognitive Function and Sense of Smell

Results of this PhD study showed there is a trend for MoCA scores to decrease alongside the reduction in sense of smell (figure 3.18). Spearman's correlation showed there was a positive correlation between cognition and UPSIT (r_s=0.213) which is statistically significant (p=0.024). Although the link between cognitive impairment and olfactory loss remains poorly explored in PD, these findings agree with the findings of Postuma and Gagnon (2010) and Bohnen et al (2010). Bohnen et al (2010) implicated limbic cholinergic denervation and suggests that this cholinergic denervation may be more pronounced in a subset of PD patients with early emerging cognitive deficits and that greater deficits in odour identification may identify patients at risk of clinically significant cognitive impairment (Bohnen et al 2010, Bohnen and Albin 2010).

Further sub-group analysis demonstrates that the median UPSIT score was slightly less in patients with mild impaired cognition compared to those with normal cognitive function (figure 3.18) which was statistically significant (p=0.049). This agrees with Parrao et al (2012) who suggested there is a significant association between olfactory deficits and impairments of executive functions in PD.

There is evidence to suggest that patients with more pronounced olfactory loss are at increased risk of developing dementia (Baba et al 2012**,** Stephenson et al 2010). However, as shown in this PhD study profound olfactory dysfunction is found in PD patients whom are cognitively intact. This suggests that the dementia may not be the primary basis of the olfactory problem (Doty et al 1989). Therefore, it is not clear in this PhD study whether those patients with anosmia will eventually develop dementia.

3.8 SUMMARY

- Results of this study showed that 100% of PD patients participating in this study had an abnormal sense of smell.
- The most common UPSIT scores are 13 and 16 which are both in the anosmic group.
- Male to female ratio appears to be slightly higher (1.8:1) than that considered representative of the general PD population (1.5:1).
- There is a trend in reduction in the sense of smell as PD patients get older which is statistically significant.
- Females have an overall higher median UPSIT score than males in this study which was statistically significant.
- The mean UPSIT of present smokers is less than ex-smokers and non-smokers however, results need to be interpreted with caution as there may be due to a small sample size, as only 4 PD patients smoked in this study sample.
- The number of years since stopping smoking did not correlates with an improvement in sense of smell.
- Perceived ability to be aware of loss or change in ability to taste was not affected by the patient's sense of smell.
- The duration of PD in the study group has no effect on degree of smell loss and olfactory dysfunction was present to a relatively high degree even in initial stages of the disease process.
- Median UPSIT scores are slightly less in patients with mild impaired cognition compared to those with normal cognitive function which was statistically significant.

CHAPTER 4

SENSE OF SMELL AND MOTOR SYMPTOMS IN PARKINSON'S DISEASE

4.1. OVERVIEW

Motor symptoms of Parkinson's disease vary from person to person and change over time. For example, fluctuations in the symptoms of Parkinson's disease (PD), such as wearing-off and on-off effects, dyskinesias, dystonia and tremor are common and are related to a variety of factors, including duration and dosage of levodopa, age at onset, stress, sleep, food intake, and other pharmacokinetic and pharmacodynamic mechanisms (Weiner 2006, Jankovic 2005). These progressive fluctuating symptoms cause difficulty with walking and balance and have a significantly negative effect on quality of life (Dowding et al 2006). This chapter will address the link between the sense of smell (as measured by UPSIT 40) and the disease severity and motor symptoms associated with patients with Parkinson's disease. This is to confirm or refute whether there is any link between degree of loss of sense of smell and any of the motor symptoms in these PD patients.

4.1.1. Disease Severity of PD and Sense of Smell

The question of whether olfactory deficits in PD are related (or unrelated) to disease severity has been of considerable debate over the last 40 years. Some researchers report no associations (Haehner et al 2009, Hawkes et al 1997, Doty et al 1992, Doty et al 1988, Quinn et al 1987, Ward et al 1983), whilst others note positive associations (Cavaco et al 2015, Berendse et al 2011, Debb et al 2010, Tissingh et al 2001, Stern et al 1994, Ansari and Johnson 1975). However, as previously stated, these inconsistent findings may be related to procedural differences in measuring olfactory dysfunction (see tables 1.1 and 1.2; section 1.2.1). Interestingly, Hummell et al (2005)

noted that odour discrimination performance in PD patients rather than odour detection (as examined in this study) improves concurrent with clinical motor improvement after stereotactic neurosurgical treatment using deep brain stimulation. Boesveldt et al (2008) and Tissingh et al (2001) also noted that it was odour discrimination that was associated with disease severity. This possibly indicates that -at least- some aspects of olfactory dysfunction in PD may be secondary to on-going degenerative processes in PD.

However, none of the above studies divided PD patients according to the degree of their smell loss and therefore the correlation with disease severity of PD (measured by means of the Hoehn and Yahr scale and the UPDRS) and degree of smell loss appear to have never been analysed. This chapter will address these issues.

4.1.2. Motor Symptoms and Sense of Smell

There is a plethora of research trying to establish a link between the well-known motor domains aspects of PD and the loss of sense of smell (Casjens et al 2013, Litvan et al 2003, Ramaker et al 2002, Hawkes et al 1999, Hawkes and Shephard 1998, Mesholam et al 1998, Hawkes et al 1997, Doty et al 1988, Quinn et al 1987). These motor domains using the UPDRS motor III examination consists of 14 domains each measured on a 5-point scale (0-4) (see section 2.4.1). The higher the score the more severe is the disability (see Appendix 7). However, none of the above studies divided PD patients according to the degree of their smell loss and therefore the correlation with motor aspects and degree of smell loss appear to have never been analysed. This chapter will address these issues.

4.1.3. Rapid Eye Movement Behaviour Disorder (RBD) and Sense of Smell

RBD associated with Parkinson's disease (PD-RBD) is a common secondary form of RBD. The frequency of RBD in PD patients has been estimated to range from 15 to 59% (Yoritaka et al 2009, Gjerstad et al 2008, De Cock et al

2007) depending on method of diagnosis. PD patients with RBD are older, more likely to be male (Yoritaka et al 2009, Gjerstad et al 2008), sleepier (Yoritaka et al 2009), more likely to experience orthostatic hypotension (Postuma et al 2009) and less likely to have tremor-predominant PD (Kumeru et al 2008) than PD patients without RBD. Importantly, RBD could be an early feature of neurodegenerative disease especially PD (Claassen et al 2010, Postuma et al 2009, Scaglione et al 2005, Eisensehr et al 2003). Both RBD and PD are characterized by reduced striatal dopaminergic mediation (Poryazova and Zachariev 2005).

Olfactory loss is also an early biomarker of PD (Casjens et al 2013, Litvan et al 2003, Ramaker et al 2002, Hawkes et al 1999, Hawkes and Shephard 1998, Mesholam et al 1998, Hawkes et al 1997, Doty et al 1988, Quinn et al 1987). Therefore, one objective of this chapter is to establish whether there is a correlation between RBD and sense of smell in PD.

4.2 AIM

The main aim of this chapter is to establish whether any of the motor symptoms associated with Parkinson's disease, disease severity or RBD correlate with the degree of loss of sense of smell.

4.3. OBJECTIVES

(i) To establish whether there is a link between motor function, (as measured by UPDRS III) and the degree of loss of sense of smell (mild/moderate microsmia, severe microsmia or anosmia) in this study group.

(ii) To establish whether there is a link between disease severity (using Hoehn and Yahr Staging) and the degree of loss of sense of smell in this study group.

(iii) To establish whether there is a correlation between RBD and loss of sense of smell in PD.

(iv) To establish whether there is a correlation between tremor dominant PD compared to akinetic-rigid type PD (which presents with little or no tremor but increased bradykinesia and rigidity) in this study group.

4.4 OUTLINE OF THE METHODS

(i) The sense of smell was evaluated using the 40 items University of Pennsylvania Smell Identification Test (UPSIT) (as detailed in section 2.4.6).

(ii) Motor function was evaluated using part III of the Unified Parkinson's Disease Rating Scale, (see appendix 7), (as detailed in section 2.4.1).

(iii) Assessment of severity of PD based on clinical features and functional disability was measured using Hoehn and Yahr Staging (0-5), (see appendix 10), (as detailed in section 2.4.4).

(iv) Rapid Eye Movement Behaviour Disorder was evaluated using the Rapid Eye Movement Behaviour Disorder Questionnaire (See appendix 11), (as detailed in Chapter 2.4.5).

(v) Assessment of tremor was evaluated by assessing resting tremor in the UPDRS III motor section (see appendix 7).

4.5 RESULTS

4.5.1. Unified Parkinson's Disease Rating Scale (UPDRS) Motor Section III Scores and Sense of Smell

The Link between the total score of the UPDRS motor section III and the sense of smell UPSIT score will now be analysed using; (i) a whole group analysis approach and (ii) a sub-group analysis.

(i) Whole group analysis

Figure 4.1 shows a very weak negative correlation r=-0.1192 which is not statistically significant (p= 0.203) between the motor function (as measured by the UPDRS III) score and sense of smell score.

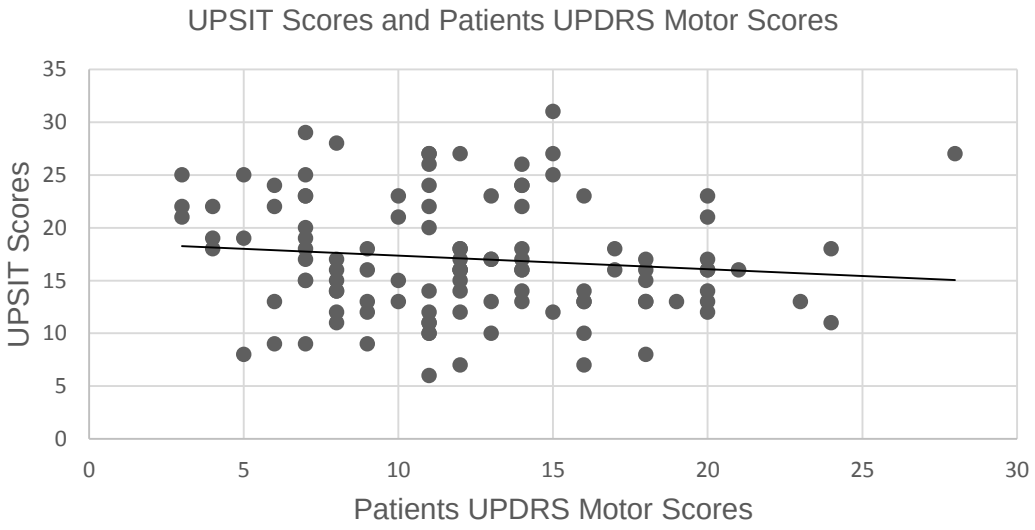


Figure 4.1: Patients UPSIT and Motor Unified Parkinson's Disease Rating Scale Scores. *There is a very weak negative correlation r/s=-0.1192 which was not statistically significant (p=0.203) between UPDRS motor scores and UPSIT scores.*

Further analysis of the 14 individual domains of the UPDRS motor scores shows a pattern indicative of decline in the sense of smell in association with an increase in the severity of certain motor disabilities, mainly in relation to speech (figure 4.2), facial expression (Figure 4.3), hand movement (figure 4.4), arising from a chair (figure 4.5) and posture domains (figures 4.6).

These findings were also confirmed by further statistical analysis (see table 4.1).

However, the results did not show any association between decline of sense of smell and the increase in certain other motor disabilities; these are (i) tremor at rest, (ii) action/postural tremor, (iii) rigidity, (iv) finger tapping, (v) rapid hand movements, (vi) leg agility,(vii) gait, (viii) postural stability, (ix) body bradykinesia and hypokinesia (see figures 4.7-4-11). (For UPDRS III motor domains, correlation and level of significance see table 4.1.).

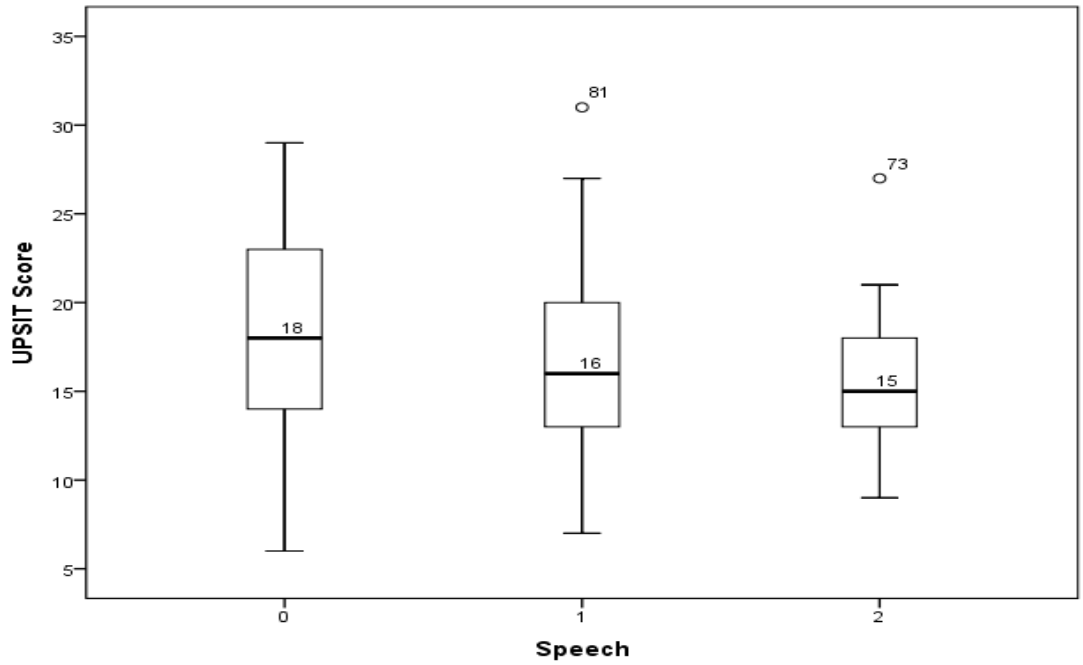


Figure 4.2: UPSIT Scores and Speech.
Median UPSIT scores decrease alongside the degree of speech disability. Further statistical analysis showed that it was close to being statistically significant (T_s= -0.163, p=0.085).

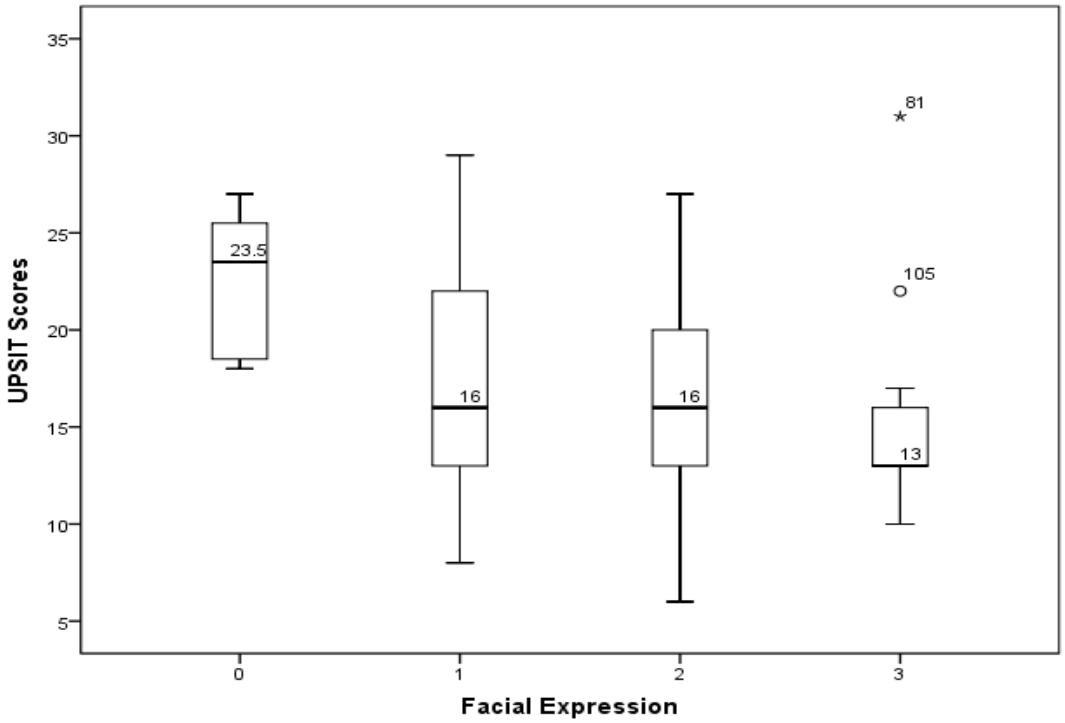


Figure 4.3: UPSIT Scores and Facial Expression.
Median UPSIT scores decrease alongside the degree of facial expression disability. Further statistical analysis showed that it was statistically significant (r_s= -0.207, p=0.029).

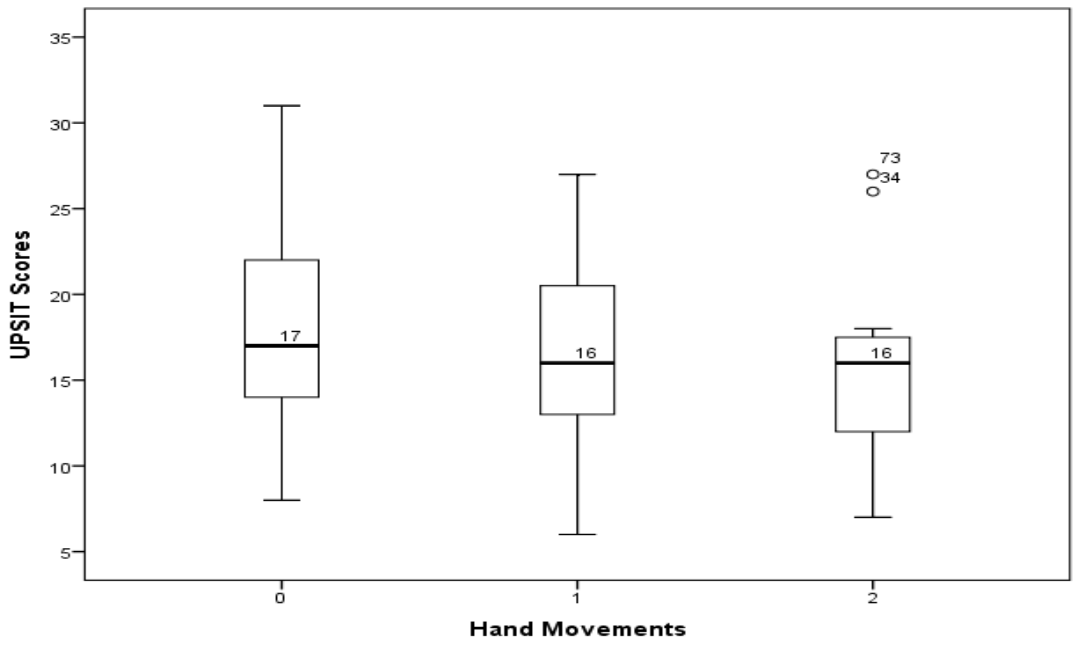


Figure 4.4: UPSIT Scores and Hand Movements.
Median UPSIT scores decrease alongside the degree of hand movement disability. Further statistical analysis showed that it was close to being statistically significant (r_s= -0.166, p=0.080).

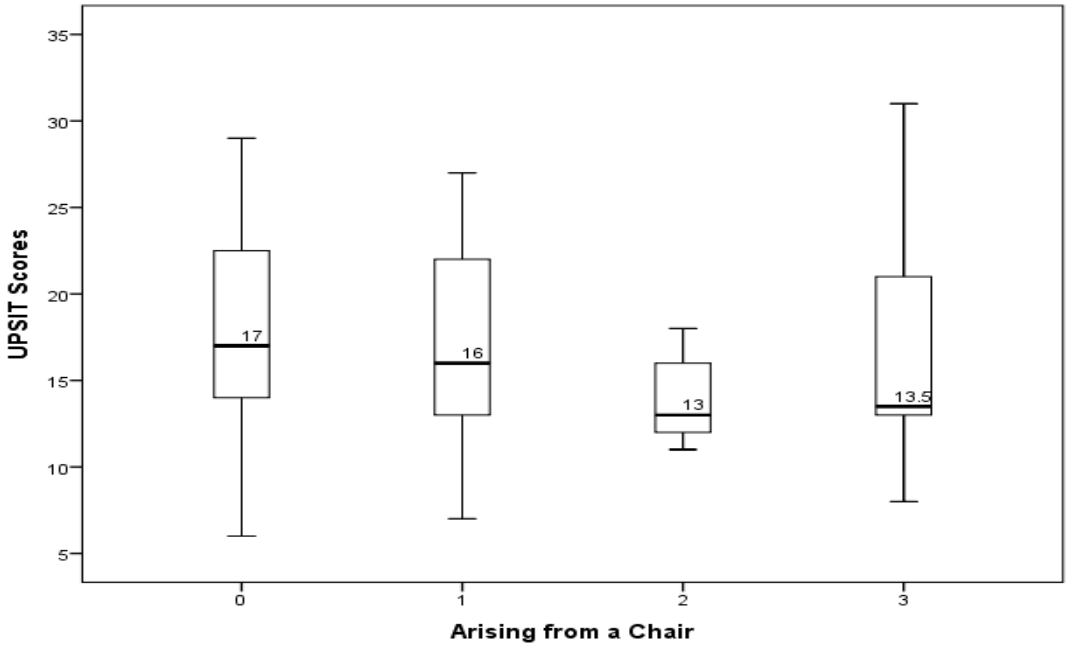


Figure 4.5: UPSIT Scores and Arising from a Chair.
Median UPSIT scores decrease alongside the degree of speech disability. Further statistical analysis showed that it was statistically significant (r_s= -0.190, p=0.045).

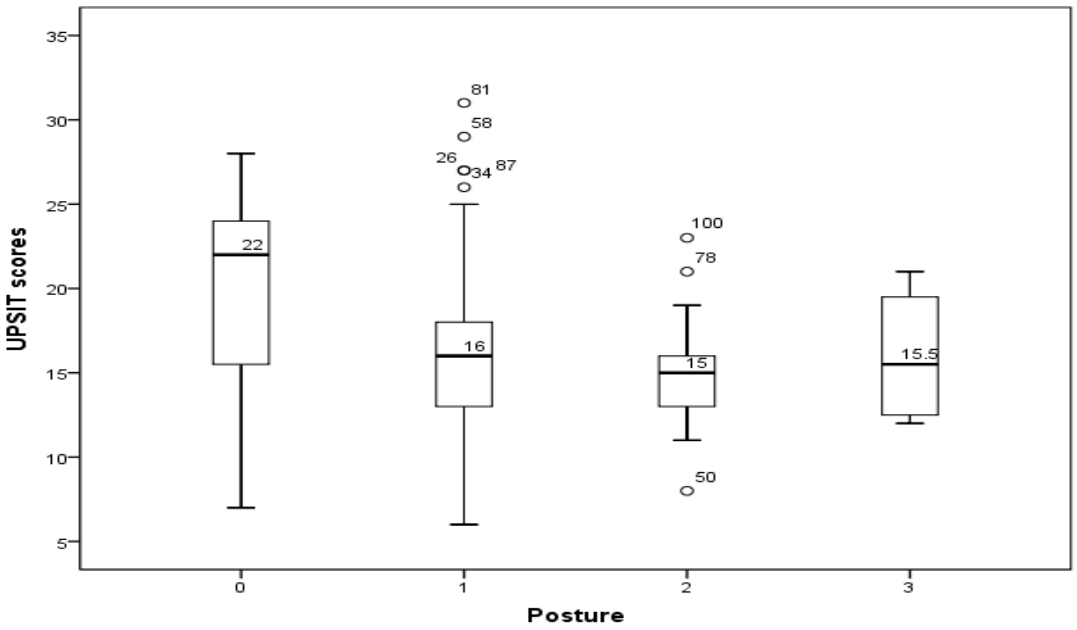


Figure 4.6: UPSIT Scores and Posture.
Median UPSIT scores decrease alongside the degree of speech disability. Further statistical analysis showed that it was statistically significant (r_s=-0.231, p=0.014).

Table 4.1 UPDRS III Motor Domains, Correlation and Level of Significance

UPDRS III Motor Domains	Correlation (r_s)	Level of Significance (P Value)
Posture	-0.231	0.014
Facial Expression	-0.207	0.029.
Arising from a Chair	-0.190	0.045
Hand Movements	-0.166	0.080
Speech	-0.163	0.085
Postural Stability	0.213	0.197
Gait	-0.119	0.212
Finger Taps	-0.072	0.451
Body Bradykinesia and Hypokinesia	-0.066	0.490
Action/Postural Tremor	-0.57	0.553
Leg Agility	0.035	0.711
Rapid Alternating Movements of Hands	-0.035	0.714
Tremor at rest	-0.010	0.920
Rigidity	-0.010	0.920

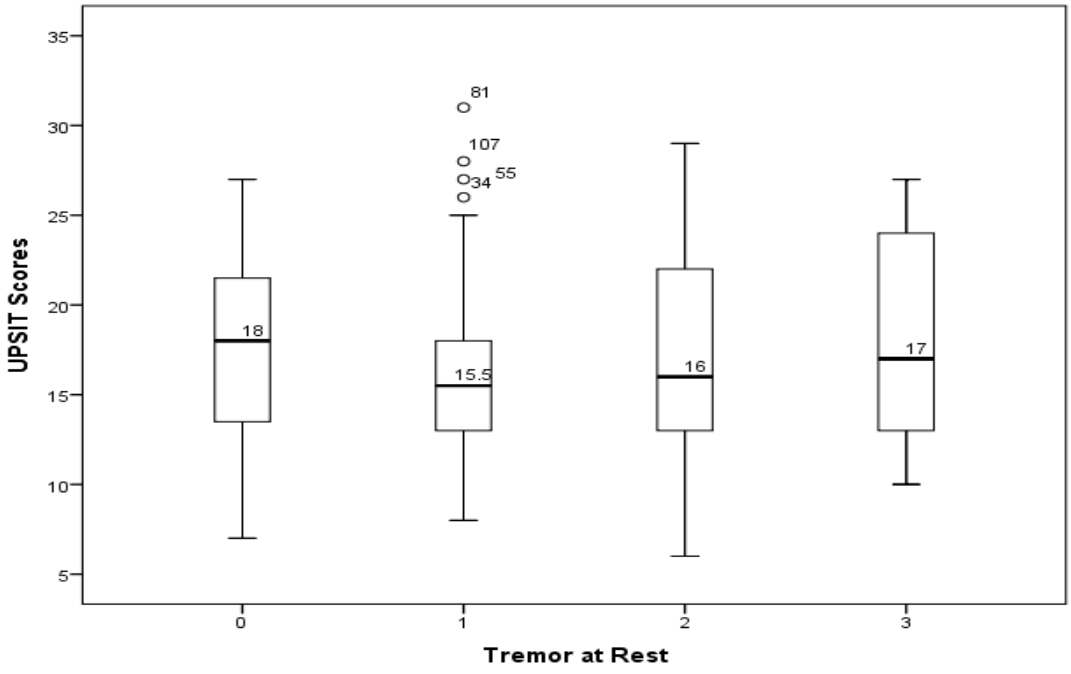


Figure 4.7: UPSIT Scores and Tremor at Rest.
Median UPSIT scores do not decrease alongside the degree of disability.

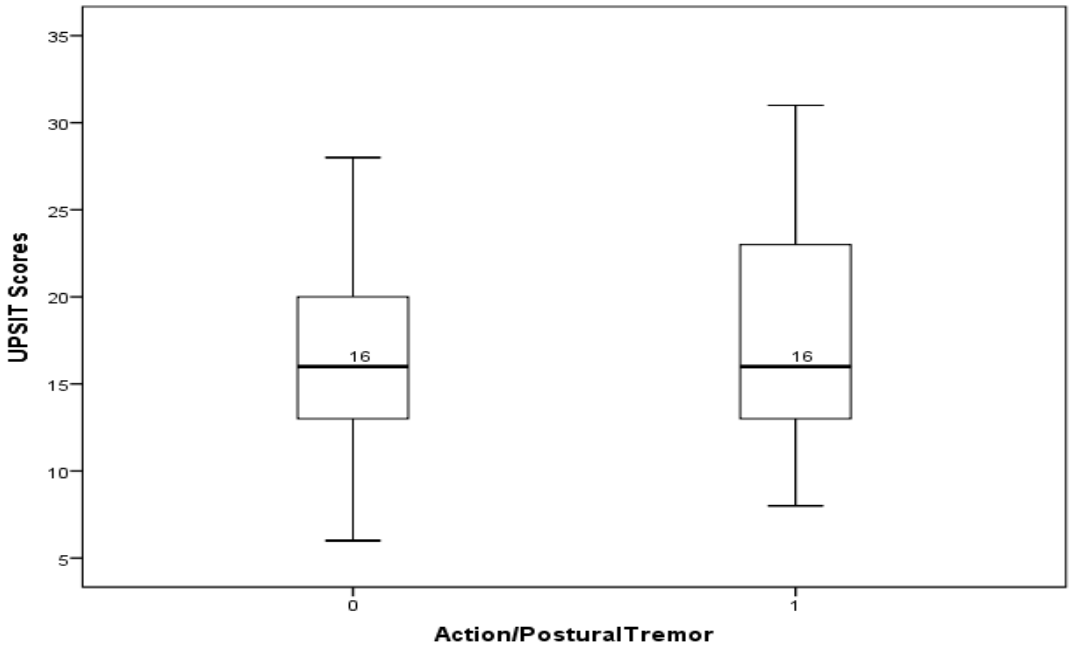


Figure 4.8: UPSIT Scores and Action/Postural Tremor.

Median UPSIT Scores are equal to those PD patients with no or mild disability.

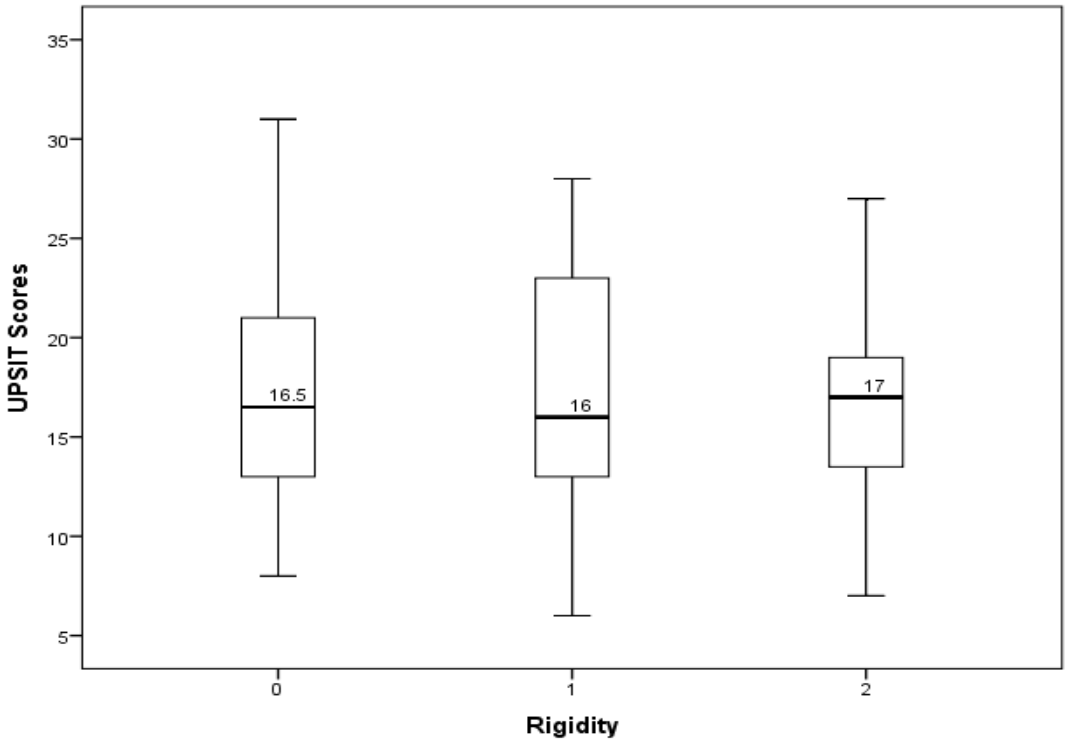


Figure 4.9: UPSIT Scores and Rigidity.

Median UPSIT scores do not decrease alongside the degree of smell loss.

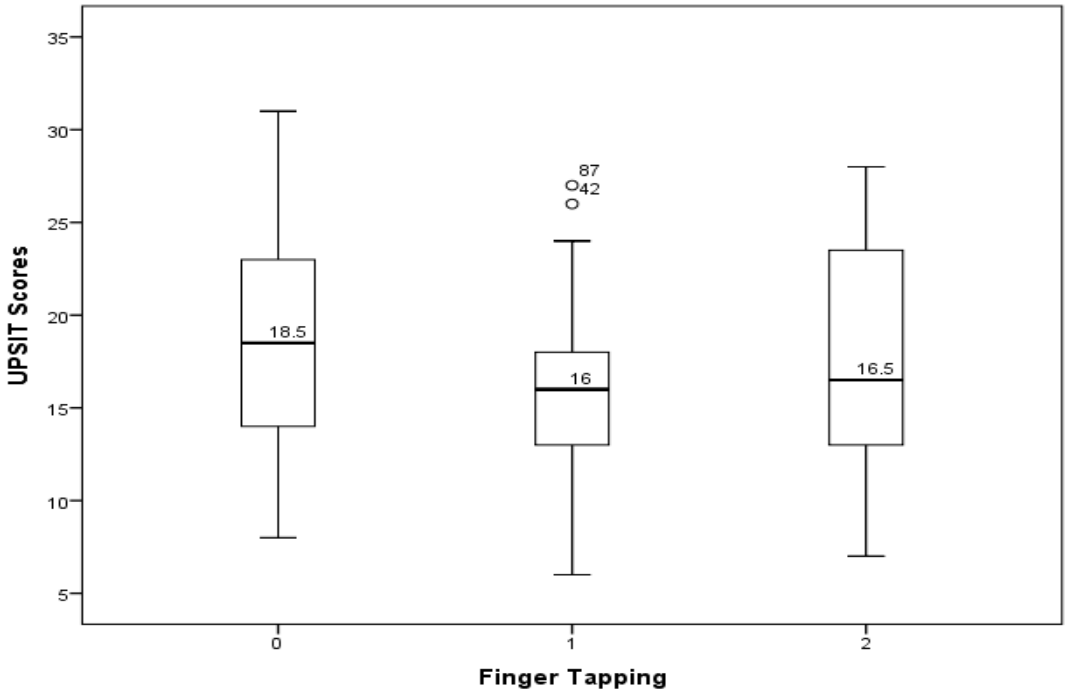


Figure 4.10: UPSIT Scores and Finger Tapping.

Median UPSIT scores do not decrease alongside the degree of smell loss.

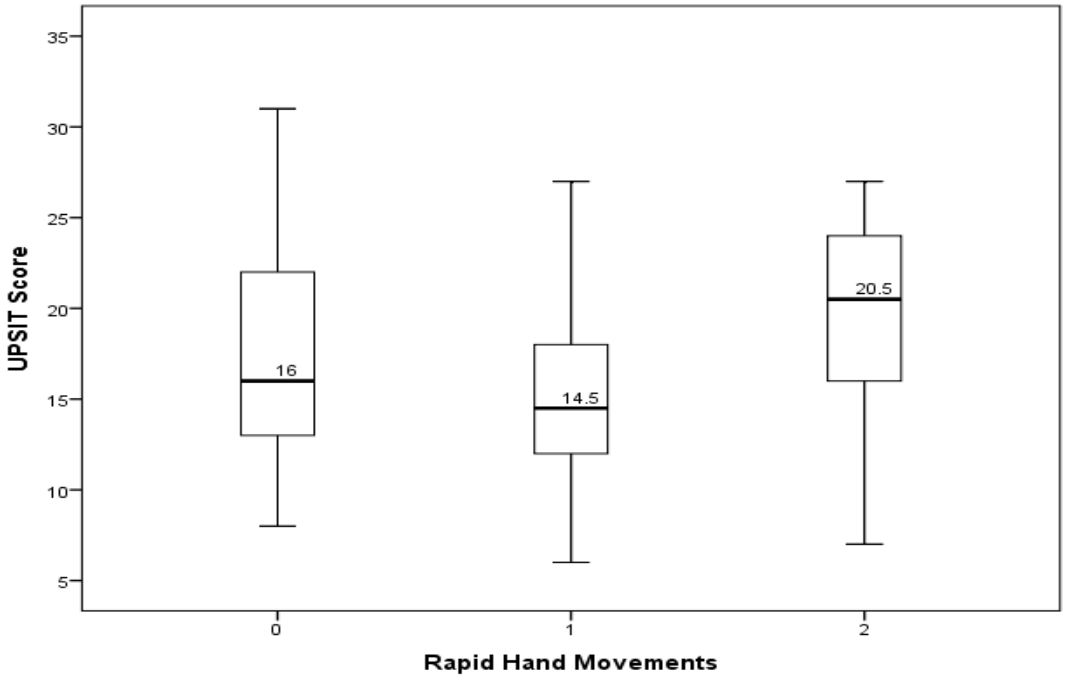


Figure 4.11: UPSIT Scores and Rapid Hand Movements.

Median UPSIT scores do not decrease alongside the degree of smell loss. In fact, sense of smell is more preserved in those patients with worsening ability to do rapid hand movements.

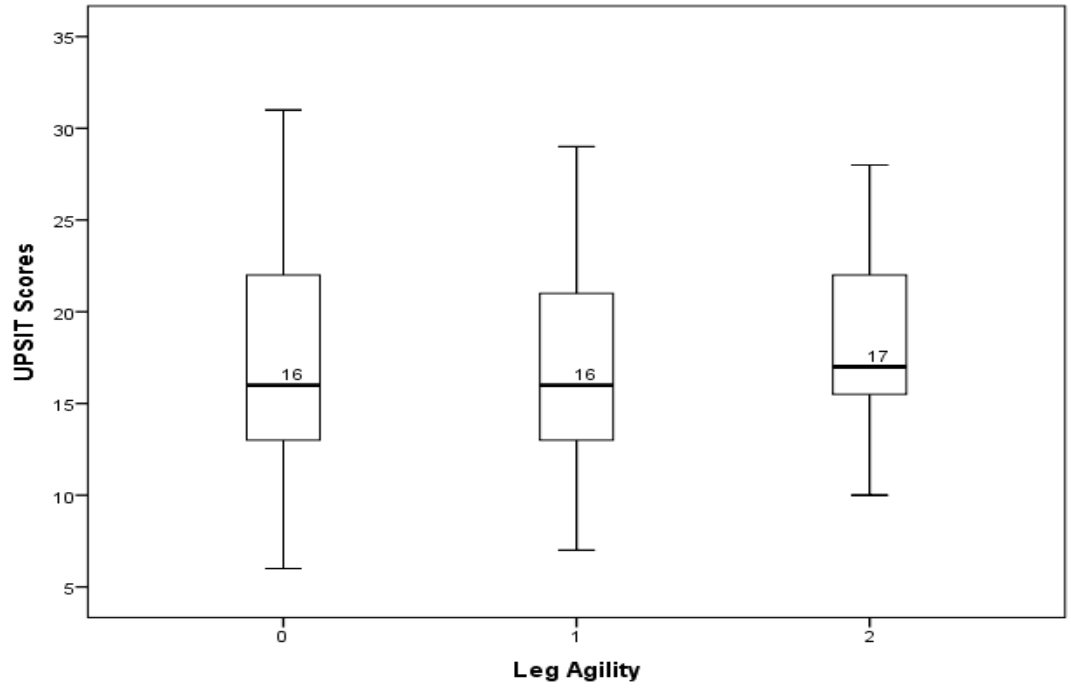


Figure 4.12: UPSIT Scores and Leg Agility.

Median UPSIT scores do not decrease alongside the degree of smell loss in fact the loss of sense of smell appears stable across the degree of leg agility.

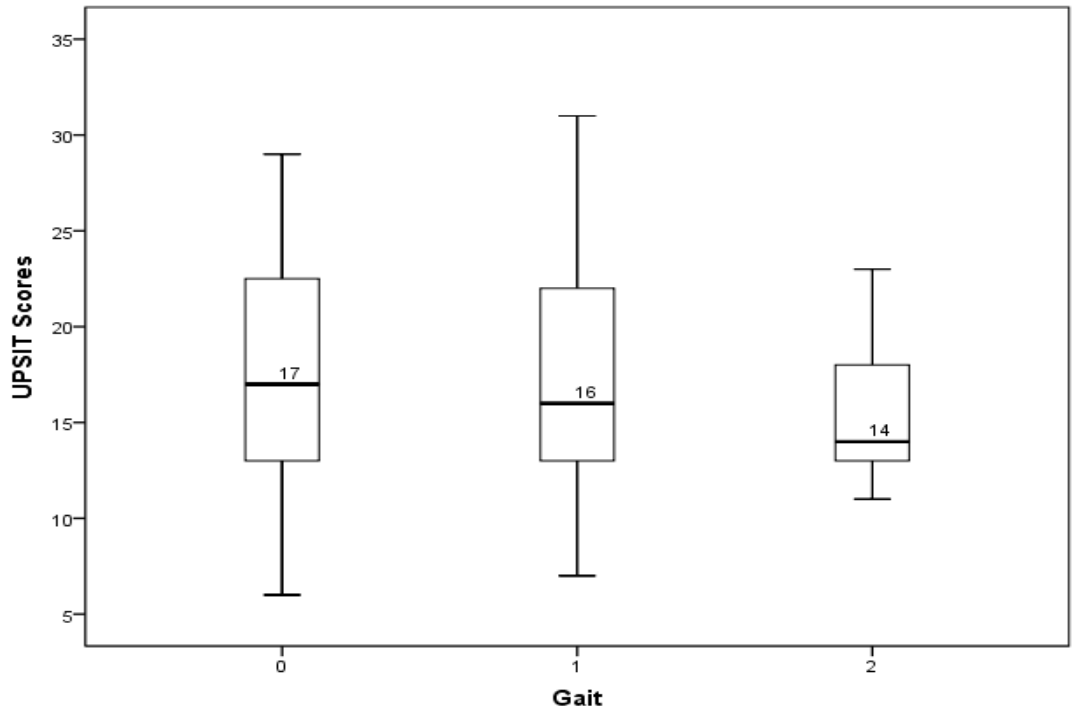


Figure 4.13: UPSIT Scores and Gait.

Median UPSIT Scores appear to worsen alongside the degree of disability although this was not Further statistical analysis showed that it was not statistically significant (r_s= -0.119, p=0.212).

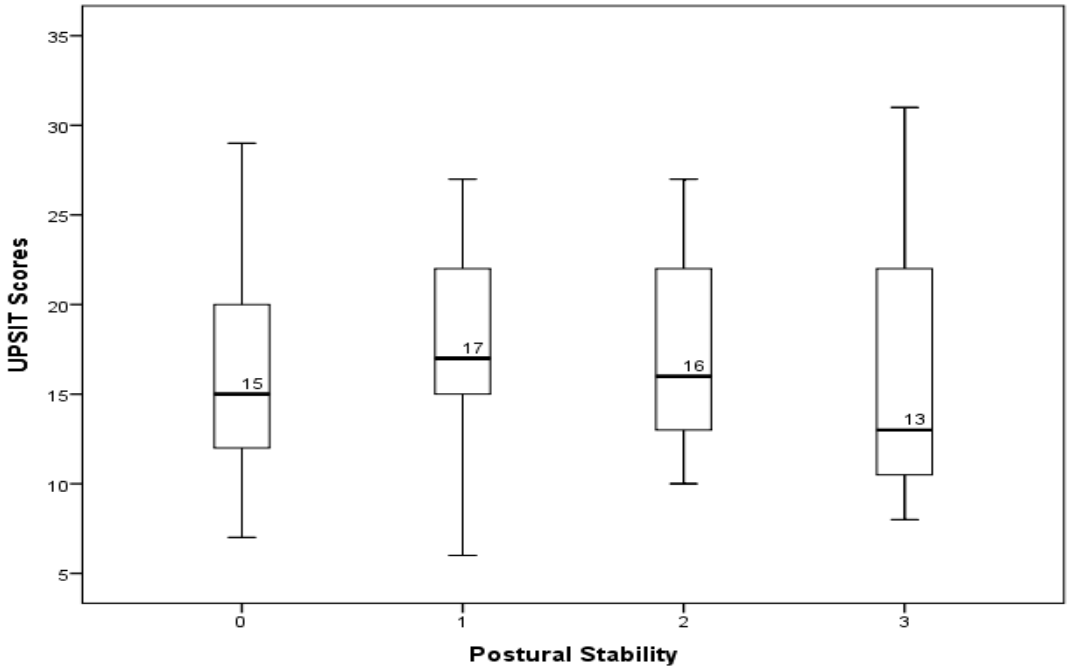


Figure 4.14: UPSIT Scores and Postural Stability.

Median UPSIT Scores appear to worsen in more advanced postural instability. Further statistical analysis showed that it was not statistically significant (r_s= -0.213, p=0.197).

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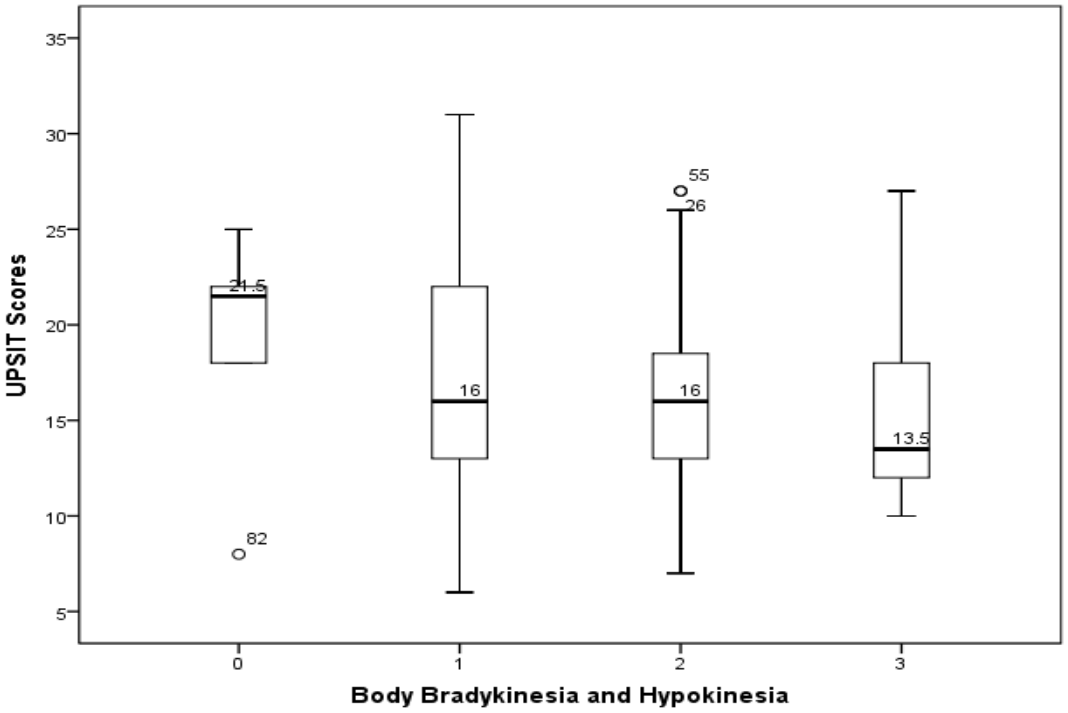


Figure 4.15: UPSIT Scores and Body Bradykinesia and Hypokinesia.

Median UPSIT appears to decrease alongside the degree of smell loss but due to the small number of patients in Hohen and Yahr stage 0. However, this did not reach statistical (r_s= -0.066, p=0.490).

Further statistical analysis between the UPDRS 14 motor domains and sense of smell scores showed all of them have a weak negative correlation although some reached statistical significance. As shown, correlation is significant on posture, facial expression and arising from a chair (see table 4.1). This agrees with figures 4.6, 4.3 and 4.5 and is close to being significant in motor domains; hand movements and speech (see figures 4.4 and 4.2).

4.5.2 Tremor and Loss of Sense of Smell

Table 4.2 breaks down those patients with either no, slight and infrequent, mild and persistent and moderate and present most of the time tremor, (assessed by the UPDRS III 'tremor at rest' domain), the number of patients in each group and their range, mean and median scores to establish whether patients with a more tremor dominant PD, rather than those patients with akinetic rigid PD had a better sense of smell. Although it appears those with more severe tremor have a better sense of smell a chi-square test was conducted and showed that there were no statistically significant differences between the groups (p=0.366), concluding there is no association between the degree of tremor and UPSIT scores in this study group.

Table 4.2. PD Patients Degree of Tremor, Range, Mean and Median Scores.

Tremor	Number of PD Patients	UPSIT (Range)	UPSIT (Mean)	UPSIT (Median)
Absent	39	7-27	17	17.5
Slight and infrequent	34	8-31	16	17.5
Mild and persistent	26	6-29	17	16
Moderate and present most of the time.	13	10-27	18	17.5

4.5.3 Hoehn and Yahr Staging and Sense of Smell

(i) Whole Group analysis

Categorisation of patients in each of the Hoehn and Yahr stages, together with their UPSIT scores, can be seen in table 4.3. Most patients are at stage 1 with little or no functional impairment, followed by stage 2 and then stage 3 (table 4.3). Only 2 patients are categorised as stage 4.

Table 4.3: Hoehn and Yahr Staging, Number of Patients in Each Stage, UPSIT Range and Mean.

Hoehn and Yahr Staging	Number of Patients in each Hoehn and Yahr Stage and Overall	UPSIT (Range)	UPSIT (Mean)
1	53 = 47%	6-29	18
2	33 = 30%	7-26	17
3	24 = 21%	8-31	17
4	2= 2%	13-16	14.5

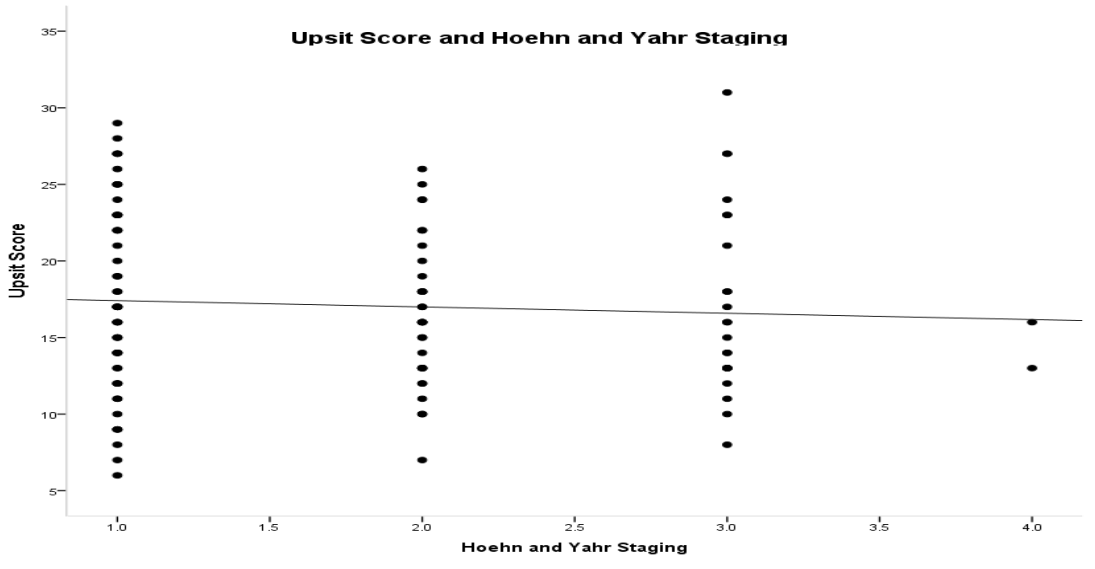


Figure 4.16 UPSIT score and Hoehn and Yahr Staging

Most patients are at stage 1 with little or no functional impairment, followed by stage 2 and then stage 3 (table 4.6). Only 2 patients are categorised as stage 4. On further analysis, there was a negative correlation between the severity/stage of PD and the degree of smell loss (r_s=-0.062, n=112, p=0.514) which did not reach statistical significance.

(ii)Sub-group analysis

To answer the research question whether there is a link between degree of loss of sense of smell and the severity of PD (measured by Hoehn and Yahrr staging), further sub-group analysis was carried out;

- Table 4.4 shows most patients (n= 53) are at stage 1. The overall percentage of patients represented decreases alongside the degree of olfactory loss.
- Stage 2 represents the next highest group (n=33) showing bilateral disease without impairment of balance. In this group, the opposite occurs, and percentage of patients represented increases alongside the degree of olfactory loss.
- In stage 3, which is mild to moderate disease with impairment of balance, most have mild/moderate microsmia or anosmia. Severe microsmia represents a lower overall percentage of patients.
- Finally stage 4 which signify severe disability, only patients with anosmia are represented.

Table 4.4: Sense of Smell and Hoehn and Yahr Staging and Percentage of Patients in Each UPSIT Group.

Sense of Smell	Stage 1 47% (n=53) (((n=53)	Stage 2 30% (n=33)	Stage 3 21% (n=24)	Stage 4 2% (n=2)	Total 100% (n=112)
Mild/Moderate Microsmia	(n=6)	(n=1)	(n=3)	-	10
Severe Microsmia	(n=15)	(n=8)	(n=4)	-	27
Anosmia	(n=32)	(n=24)	(n=17)	(n=2)	75

4.5.4 Rapid Eye Movement Behaviour Disorder Scores and Sense of Smell

(i) Whole Group Analysis

Analysis of RBD in PD patients showed that 55 patients (37 males 18 females) had RBD and 57 patients (35 males and 22 females) did not. (table 4.5). There was no difference in mean or median UPSIT scores comparing both groups suggesting there is no relationship between loss of sense of smell and RBD (figure 4.17).

Table 4.5 PD patients with or without RBD, gender in each group, UPSIT median, mean range and mean duration of PD.

PD Patients with or without RBD	Gender	UPSIT (median)	UPSIT (Mean)	Range	Mean duration of disease
With RBD (N= 55)	37 males 18 females	16	17	7-29	5.93
Without RBD (N=57)	35 males 22 females	16	17	6-31	5.28

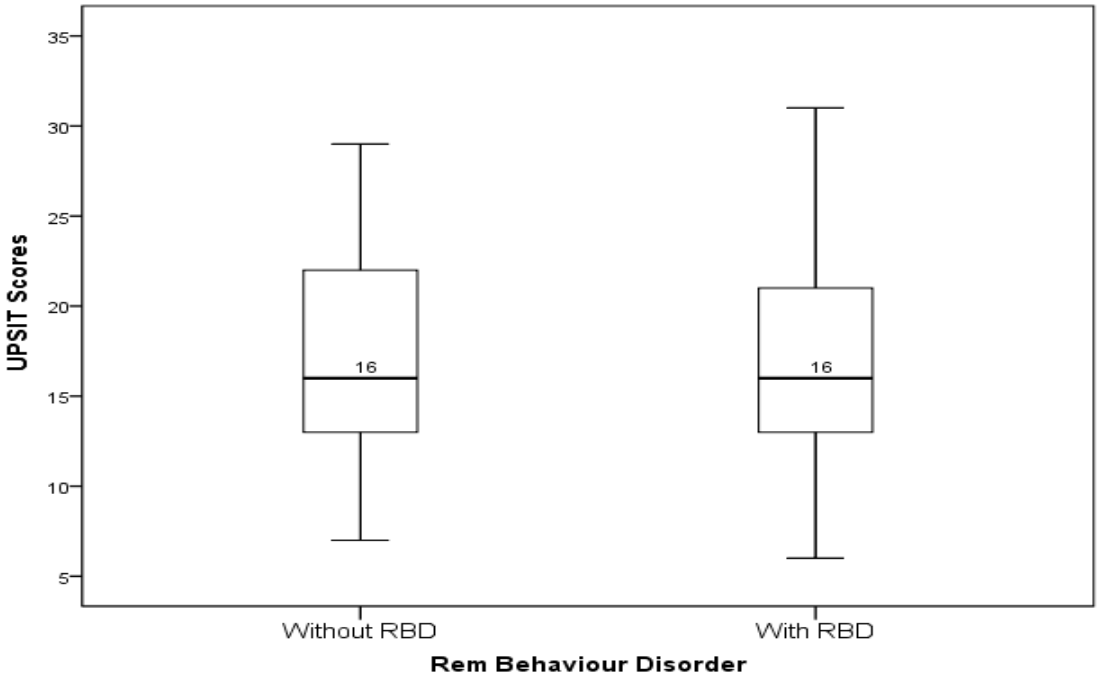


Figure 4.17: Patients without or with RBD and UPSIT Scores

57 patients did not have RBD compared to 55 patients who did have RBD (see figure 4.17). Results show there is no difference in the mean and median UPSIT scores with both groups having an UPSIT mean of 17 and median of 16 of patients without or with RBD.

Figure 4.18 shows no correlation between UPSIT scores and their RBD scores.

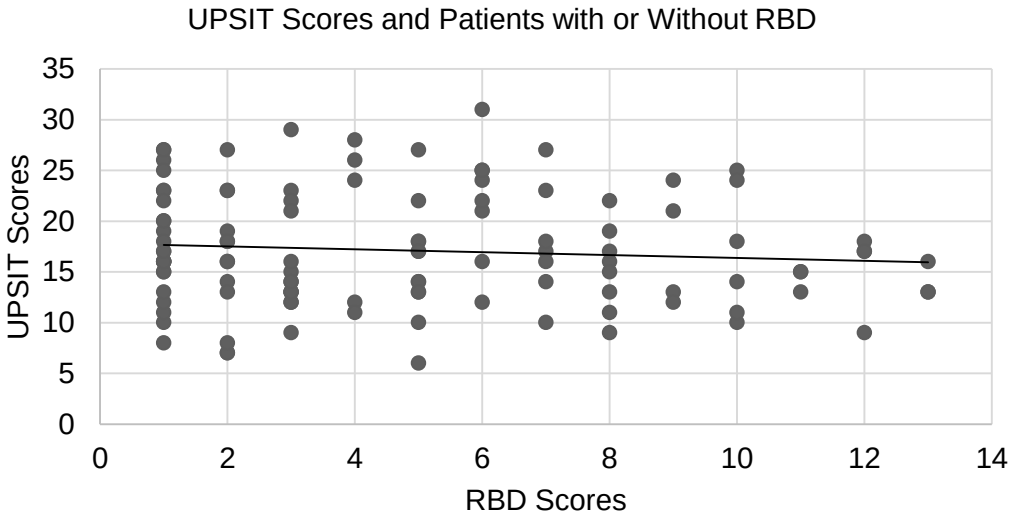


Figure 4.18: UPSIT Scores and Patients with or Without RBD

Correlation between UPSIT sores and all patients with or without RBD was not significant (r_s =-0.021, p=0.823.).

(ii) Sub-Group Description

Table 4.6 shows symptoms experienced by all PD patients who either do or do not meet the criteria for a diagnosis of RBD, and the number of PD patients with RBD who have mild/moderate microsmia, severe microsmia or anosmia. From table 4.6, (excluding question 10 as all patients have PD), the most reported symptom was having 'vivid dreams' in patients who either met the criteria for a diagnosis of RBD or not (63 patients of which 47 patients met the criteria for a diagnosis of RBD). The symptom least reported by all patients was 'things that fell down around the bed' (17 patients), although all these patients met the criteria for a diagnosis of RBD. Interestingly the symptom 'the dream content mostly match my nocturnal behaviour' (25 patients) was also only experienced by patients who met the criteria for a diagnosis of RBD.

Table 4.6: Symptoms Experienced by PD Patients Who Meet the Criteria for a Diagnosis of RBD and Number of PD patients with RBD who have mild/moderate microsmia, severe microsmia or anosmia.

Question	Symptom	Mild/Moderate Microsmia N=3	Severe Microsmia N=13	Anosmia N=39	Patients with RBD N=55
1	I sometimes have very vivid dreams.	1	12	34	47
2	My dreams frequently have an aggressive or action-packed content.	0	7	23	30
3	The dream contents mostly match my nocturnal behaviour.	0	5	20	25
4	I know that my arms or legs move when I sleep.	3	9	28	40
5	It thereby happened that I (almost) hurt my bed partner or myself.	2	5	20	27
6	I have or had the following phenomena during my dreams				
6.1	speaking, shouting, swearing, laughing loudly	1	9	30	40
6.2	sudden limb movements, "fights"	2	9	31	42
6.3	gestures, complex movements, that are useless during sleep, e.g., to wave, to salute, to frighten mosquitoes, falls off the bed.	1	3	17	21
6.4	things that fell down around the bed, e.g., bedside lamp, book, glasses	1	0	16	17
7	It happens that my movements awake me	2	8	19	29
8	After awakening I mostly remember the content of my dreams well.	0	8	28	36
9	My sleep is frequently disturbed	2	8	18	28
10	I have/had a disease of the nervous system (e.g., stroke, head trauma, parkinsonism) which?	3	13	39	55

4.6 DISCUSSION

4.6.1 The Link Between the Sense of Smell and Unified Parkinson's Disease Rating Scale (UPDRS) Motor III Scores

Results of the whole group analysis showed a non-significant very weak negative correlation between the severity of motor function (as measured by the UPDRS motor section III) score (see appendix 7) and sense of smell score (UPSIT) r_s =-0.012 (see figure 4.1). This finding is in keeping with previous research. For example; Haehner et al (2009), in a multicentre study using a comprehensive testing method in a large sample of PD patients (*n* = 400) from 3 independent populations failed to find a correlation between olfactory loss and clinical severity as measured by means of the Hoehn and Yahr scale and the UPDRS. Doty et al (1988), who tested 81 PD patients and 81 controls through the results of the factor analysis also unequivocally indicate that the olfactory dysfunction of PD is independent of disease stage, and motor function and finally, Hawkes et al (1997) who tested 96 PD patients and 96 controls using a standardised odour identification test, together with an evoked potential assessment with hydrogen sulphide also failed to find a correlation between olfactory loss and motor severity.

However, other studies, which are particularly comparable to this present study, have reported significant associations between severity of motor symptoms, using the UPDRS lll motor scores and olfactory testing (using B-SIT and UPSIT respectively) in PD (Cavaco et al 2015, Deeb et al 2010). However, it is worth highlighting, Deeb et al (2010) did not differentiate normal from abnormal odour identification and Cavaco et al (2015) study PD patients were consistently evaluated in "off" state (i.e., overnight without antiparkinsonian mediation), to reduce the confounding effect of medication. Therefore, we could argue that, in this present PhD study, evaluation of PD patients in the ''on'' state (i.e., taking PD medication as prescribed to optimise control of symptoms) is more representative of a typical PD patient. However, most studies on the topic lack information regarding motor

symptom assessment circumstances of treated patients (i.e., “on” versus “off” medication) which raises an important point that motor assessment circumstances are an important methodological aspect that has somewhat been neglected by the literature, which may partially explain the variability of findings. However, this depends also on whether medication has an effect on sense of smell.

On further sub-group analysis of the individual 14 UPDRS motor III domains, the results show there is a decline in smell ability alongside an increase in motor disability in the speech, facial expression, hand movement, arising from a chair and posture domains. (See figures 4.2-4.6). When each individual domain of the 14 UPDRS motor domains was further analysed within each sense of smell sub-group and showed correlation is significant in posture (r_s = -0.231 p=0.014), facial expression (r_s=-0.207 p=0.029) and arising from a chair (r_s =-0.190 p=0.045) (See table 4.1). This agrees with figures 4.6, 4.3, and 4.5 and table 4.1 and is close to being significant in motor domains, hand movements (r_s=-0.166 p=0.080) and speech (r_s = -0.166 p=0.085). (See figures 4.4 and 4.2 and table 4.1). Comparison between other studies cannot be made as this study appears to be the first to address the link between individual domains of motor symptoms and sense of smell loss.

4.6.1.1 The Link Between the Sense of Smell and Tremor Identified by the Unified Parkinson’s Disease Rating Scale (UPDRS) Motor III Scores

This study also highlights that people with tremor dominant PD did not have a superior sense of smell. (See table 4.4). This reflects previous observations in a small sample size of 37 patients (Muller et al 2002) and a larger study (400 patients) conducted by Haehner et al (2009) (who used sniff sticks). However, this PhD study findings are contradicting the findings of Lijima et al (2011), (using odour identification sticks), Ondo and Lai (2005), (using UPSIT 40) and Stern et al (1994) (using UPSIT), who all reported superior odour identification scores in patients with tremor dominant compared to akinetic-rigid type PD.

Despite this, the findings in this present study highlight that individual motor domains may be linked to the degree of smell loss rather than the total UPDRS III motor domains.

4.6.2. The Significance of The Outliers in UPDRS III Motor Scores

As it is well known, outliers should be investigated carefully. To understand why they appeared, each outlier was examined for any unusual traits that might be the cause of higher UPSIT 40 scores in this present study. The most significant finding was that the PD patient who scored the highest UPSIT score (patient number 81 with an UPSIT score of 31) was the only patient in this study group to have mild olfactory loss and is, in fact, the only patient in this study since initial testing (May 2013) who has had their diagnosis reviewed by another expert and has now been diagnosed with PSP-P (June 2015). This is a significant finding as previous studies have suggested that either microsmia is not present or is better preserved in PSP-P (Silveria-Moriyama et al 2010, Wenning et al 1995, Doty et al 1993). (See section 1.4.1.3.). Indeed, Silveria-Moriyama et al (2010) suggests smell tests might differentiate PSP-P from PD, particularly when UPSIT scores are lower than 14/40 (a cut-off that provides a sensitivity of 97.3%). This result supports that theory.

4.6.3. The Stages of PD Severity and Sense of Smell

The results of this study suggest that olfactory deficits (using smell identification) in PD are unrelated to disease severity (using Hoehn and Yahr staging) (r_s=-0.062, n=112, p=0.514) (see figure 4.16). This has been observed by previous studies (Haehner et al 2009, Hawkes et al 1997, Doty et al 1988, Quinn et al 1987, Ward et al 1983). However, a study by Tissingh et al (2001), who administered odour detection, discrimination, and identification tests to a partly de novo group of forty-one non-demented PD patients, (24 of whom had untreated early PD, and 18 healthy controls), highlighted that odour discrimination scores, (using 'sniffin sticks' whereby the patient needs to identifying the sample that has a different odour) , (not

seen in detection or identification scores) were related to disease severity. This was consistent with other findings from neuropathological and electrophysiological studies on PD patients (Potagas et al 1998, Barz et al 1997, Pearce et al 1995) and suggests that at least some aspects of olfactory dysfunction in PD (e.g., odour discrimination, which is considered to involve the more central olfactory structures, unlike odour detection that may be a consequence of peripheral defects in the olfactory pathway), may be secondary to on-going degenerative processes in PD. This study is unable to support or refute this work as smell identification, rather than discrimination, was the method used for analysing smell loss in this study group (detailed in chapter 2.4.6).

However, it is worth noting that, in this present PhD study, most patients are at stage 1 and stage 2 with poor representation of disease stage particularly at stage 4 (2 patients are categorised as stage 4) (see table 4.6).

Therefore, there may be a sampling bias influencing median UPSIT scores due to poor representation of PD patients in certain Hoehn and Yahr stages. To address this there would need to be an even distribution of patients in each stages of Hoehn and Yahr which requires recruiting more PD patients. Ethical approval would need to be sought to address this (discussed in limitations of this study (see section 9.6) and therefore subsequent studies could further prove or disprove these findings.

4.6.4. Rapid Eye Movement Behaviour Disorder Scores and Sense of Smell

Idiopathic RBD is strongly linked to PD (Postuma 2014, Iranzo et al 2011, Postuma et al 2009, Plazzi et al 1998). In fact, there is growing evidence to suggest that RBD precedes PD by years or even decades (Gao et al 2011, Claassen et al 2010, Postuma et al 2009, Monderer and Thorpy 2009, Iranzo et al 2006, Olson et al 2000).

Initial analysis of this present study shows 57 patients did not have RBD and 55 patients did (see figure 4.17). This highlights that approximately 50% of PD patients in this study have a clinical diagnosis of RBD, using the RBD screening questionnaire (see appendix 11). Generally, RBD is said to affect 15 - 65% of patients with PD (Postuma et al 2009, De Cock et al 2007, Scaglione et al 2005, Olson et al 2000) but is rare in tauopathies such as Progressive Supra Nuclear Palsy (Boeve et al 2001). Reasons for the variation in percentages of patients noted in individual studies could be due to the tools used to diagnose RBD. For example, one theory is that, unlike the diagnosis of idiopathic RBD which can easily be made by conducting only a structured clinical interview, more than half of the RBD cases in patients with Parkinson's disease would be omitted using this technique (the sensitivity was poor at 33% with a specificity of 90%, in patients with PD) (Poryazova and Zachareive 2005). Also, although the RBD screening questionnaire shows good internal consistency and a high sensitivity (96%) compared to the clinical interview, it has a low specificity (56%) (Stiasny-Kolster et al 2007*)* and therefore patients with PD should ideally be examined by polysomnography (Schenck and Mahowald 2002). This is particularly since there are mild forms of RBD in Parkinson's disease while the idiopathic forms always present with markedly severe clinical manifestations. This may suggest that patients who have RBD in PD may be unaware of it (similar to patients not realising they have a reduced sense of smell).

Therefore, polysomnography is the gold standard assessment for RBD in PD. However, on a practical note, polysomnography requires monitoring equipment, including time synchronized video recordings, specially trained technologists, bed availability in a sleep laboratory and clinicians who can interpret the data. For a patient with PD they have an additional burden of possibly being too physically impaired to tolerate and undergo an adequate study. Also, since the background EEG is often so abnormal in those with moderate to severe dementia, which can be a late symptom of PD, determining which periods represent REM sleep on polysomnography can be difficult if not impossible. It is also worth noting, in some PD patients, the dream enactment behaviour is so infrequent and mild that a clinical

polysomnography is difficult to justify. Therefore, although not ideal, a questionnaire such as the Rapid Eye Movement Behavior Disorder Screening Questionnaire was the only useful tool to measure this in this study. Boeve (2010a) states that a diagnosis of probable RBD would be justified.

As seen in table 4.7 and figure 4.17 there are no differences in the mean and median UPSIT scores with both groups of PD patients regardless if they had RBD or not (mean 17 and median 16). Further analysis between UPSIT and RBD scores confirmed this was not statistically significant (r_s = -0.021 p=0.823) (see figure 4.18). This is surprising as pathogenically, PD shares many similar features with RBD. Both conditions are characterized by reduced striatal dopaminergic mediation (Poryazova and Zachareive 2005). This raises the question why do not all PD patients in this study have RBD, particularly as stage 2 in the Braak classification (Braak et al 2003) affects the key areas for sleep control and eye movement (Trotti 2010, Benedito and Camarini 2001). There appears to be no definitive answer to the question and this warrants further future analysis. Finally, table 4.8 highlights that (excluding question 10 in which all patients have PD) the two most common symptoms reported in patients with RBD are vivid dreams and sudden limb movements and the two least common symptoms are things falling down around the bed and complex movements.

4.7 SUMMARY

- Whole group analysis in this study showed a non-significant negative correlation between the severity of motor function and sense of smell scores.
- Examining the individual 14 UPDRS motor III domains, the results show there is a decline in smell ability alongside an increase in motor disability in the facial expression, arising from a chair and posture domains and is close to being significant in hand movements and speech domains.
- Tremor dominant PD patients did not have a superior sense of smell compared to PD patients with akinetic-rigid type PD.
- The PD patient who scored the highest UPSIT score (patient number 81 with an UPSIT score of 31) was the only patient in this study group to have mild olfactory loss and is, in fact, the only patient in this study since initial testing (May 2013) who has had their diagnosis reviewed and has now been diagnosed with PSP (June 2015).
- Olfactory deficits (using smell identification) in PD are unrelated to disease severity.
- Loss of sense of smell is unrelated to RBD.

CHAPTER 5

SENSE OF SMELL, NON-MOTOR SYMPTOMS AND QUALITY OF LIFE IN PARKINSON'S DISEASE

5.1 OVERVIEW

The non-motor symptoms of PD are an important aspect of nursing assessment and have a direct negative impact on health-related and perceived quality of life in PD (Santos-Garcia and de la Fuente-Fernández 2013). The main research question that will be addressed in this chapter is whether any other non-motor symptoms, highlighted in the non-motor symptom questionnaire, or any of the quality of life issues, raised in the PDQ39 questionnaire, correlate with loss of sense of smell.

5.1.1. Non-Motor Symptoms Questionnaire and Sense of Smell

James Parkinson recognised the implications and importance of key non-motor symptoms, such as sleep dysfunction, cognitive and neuropsychiatric issues in 1817 (Parkinson 2002, Parkinson 1817). However, it was almost 150 years before the importance of the burden of non-motor symptoms on the lives of the people with Parkinson's and the carers became apparent (Chaudhuri et al 2006). In clinical practice, most of these non-motor symptoms are not usually volunteered by patients. Indeed, a recent study has shown that most of the non-motor symptoms remain undeclared to health care professionals, probably because patients are either embarrassed or unaware that such non-motor symptoms are due to PD (Bostantjopoulou et al 2013). Therefore, it is important that there is systematic questioning by health care professionals.

Non-motor symptoms are found in a substantial proportion of patients with PD (Bostantjopoulou et al 2013). These symptoms consist of autonomic dysfunction, sensory complaints, neuropsychiatric disturbances, sleep disorders, fatigue, and many others (Chaudhuri et al 2011). The use of the

validated non-motor symptoms screening questionnaire (Martinez-Martin et al 2007) to assess the non-motor symptoms of Parkinson's disease can assist in the ability to recognise and manage these symptoms in clinical practice.

There appears to be no research papers examining the link between the degree of loss of sense of smell and other non-motor symptom in PD patients. Therefore, one of the aims of this chapter is to establish whether the degree of loss of sense of smell correlates with any other non-motor symptoms.

5.1.2. PDQ39 Quality of Life Scores and Sense of Smell

There appears to be a lack of research generally around reduced sense of smell and diminished quality of life, with only a few studies demonstrating the impact on reproductive behaviour (Stevenson 2010), decreased sexual arousal and testosterone levels in men (Gelstein et al 2011) and depression in those patients who develop anosmia (Hede'n Blomqvist et al 2004, Temmel et al 2002). There are also a few studies on some disease specific conditions (Politis et al 2010, Deems et al 1991) of which PD is one such condition (Politis et al 2010). In the Politis et al (2010) study, they found olfactory loss belongs to the top-five most prevalent motor and non-motor symptoms in early stage PD patients that have affected their quality of life. Furthermore, Miwa et al (2001) also highlighted in their research that patients' overall satisfaction with life correlated positively with smell scores.

One of the aims of this chapter is to establish whether there is a correlation between the loss of sense of smell and any of the other quality of life scores.

5.2 AIM

The aim of this chapter is to investigate whether the loss of sense of smell correlates with any non-motor symptoms or quality of life scores in PD patients.

5.3 OBJECTIVES

(i) To establish whether the loss of sense of smell correlates with any of the non-motor symptoms highlighted in the non-motor symptoms questionnaire.

(ii) To establish whether the loss of sense of smell correlates with any of the quality of life scores highlighted in the PDQ39 quality of life questionnaire.

5.4. OUTLINE OF METHODS

(i) The sense of smell was evaluated using the University of Pennsylvania Smell Identification Test (UPSIT) (as detailed in section 2.4.6).

(ii) Non-motor symptoms were measured by the non-motor symptoms questionnaire, which provides a measure of 30 key non-motor symptoms seen in PD (as detailed in section 2.4.2).

(iii) Quality of life was measured using the PDQ39 quality of life questionnaire (PDQ39) which provides an overall assessment of PD patients 39 quality of life issues (as detailed in section 2.4.3).

5.5. RESULTS

5.5.1. Profile of Non-Motor Symptoms in the PD Study Group

The most prevalent non-motor symptoms and percentage of patients reporting them are shown in table 5.1. A sense of urgency to pass urine (63%), getting up regularly at night to pass urine (61%) and constipation (54%) are the most prevalent top three non-motor symptoms experienced by PD patients in this study, irrespective of their sense of smell status. Table 5.2 shows the most prevalent top five non-motor symptoms and number of males and females experiencing that symptom.

Table 5.1: Non-Motor Symptoms Questionnaire Results and Percentage of Each Symptom Reported.

Symptom	Percentage Patients Reporting Symptoms
8 A sense of urgency to pass urine makes you rush to the toilet	63%
9 Getting up regularly at night to pass urine	61%
5 Constipation (less than three bowel movements a week) or having to strain to pass a stool	54%
26 Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	52%
12 Problems remembering things that have happened recently or forgetting to do things	51%
16 Feeling sad, 'low' or 'blue'	48%
20 Feeling light-headed, dizzy or weak standing from sitting or lying	46%
1 Dribbling of saliva during the daytime	44%
23 Difficulty getting to sleep at night or staying asleep at night	44%
15 Difficulty concentrating or staying focused	40%
7 Feeling that your bowel emptying is incomplete after having been to the toilet	38%
25 Talking or moving about in your sleep, as if you are 'acting out' a dream	38%
17 Feeling anxious, frightened or panicky	36%
19 Finding it difficult to have sex when you try	35%
24 Intense, vivid or frightening dreams	34%
2 Loss or change in your ability to taste or smell	33%
3 Difficulty swallowing food or drink or problems with choking	32%
18 Feeling less interested in sex or more interested in sex	32%
10 Unexplained pains (not due to known conditions such as arthritis)	29%
27 Swelling of the legs	29%
21 Falling	27%
13 Loss of interest in what is happening around you or in doing things	23%
28 Excessive sweating	20%
29 Double vision	20%
4 Vomiting or feelings of sickness (nausea)	17%
14 Seeing or hearing things that you know, or are told, are not there	16%
22 Finding it difficult to stay awake during activities such as working, driving or eating	16%
6 Bowel (faecal) incontinence	7%
11 Unexplained change in weight (not due to change in diet)	7%
30 Believing things are happening to you that other people say are not	2%

Table 5.2: Top Five Non-Motor Symptoms Questionnaire Results and Number of Males or Females Reporting that Symptom.

Symptom	Percentage Patients Reporting Symptoms	Males	Females
8 A sense of urgency to pass urine makes you rush to the toilet	63%	47	24
9 Getting up regularly at night to pass urine	61%	43	25
5 Constipation (less than three bowel movements a week) or having to strain to pass a stool	54%	39	22
26 Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	52%	34	24
12 Problems remembering things that have happened recently or forgetting to do things	51%	44	13

(I) Sub-group analysis

Further sub-group analysis was carried out to investigate the frequency of these non-motor symptoms in the three sub-groups of patients (according to the severity of loss of sense of smell), (i.e., mild/moderate, severe, anosmia) and link them with the percentage of PD patients (See table 5.3 A, B, C, D).

Table 5.3 (A) highlights an increase in frequency of non-motor symptoms alongside the degree of smell loss and is reported in 12 out of the 30 non-motor symptoms overall. This is in support of the research hypothesis. However, when conducting a chi-square test of independence to examine the relation between the degrees of smell loss and each individual non-motor symptom, the only symptom to reach statistical significance is dribbling of saliva during the day ($p=0.003$).

Furthermore, with the exception of the mild/moderate sense of smell group, (which only has a small number of the overall sample size), table 5.3 (B) also shows an increase in frequency of non-motor symptoms alongside the degree of smell loss. This pattern is reported in 15 out of the 30 non-motor symptoms overall. However, none of these symptoms reached statistical significance.

Table 5.3 (C) highlights only two symptoms which are more prevalent in those patients with severe microsmia than those with mild to moderate

microsmia or anosmia. However, they were not statistically significant. Finally, Table 5.3 (D) highlights that only one symptom appears to be reported least by patients, despite the degree of olfactory deficit being worse, and this is unexplained pains. This was also not statistically significant (p=0.159).

Interestingly, if we exclude the mild/moderate sense of smell group (due to small sample size, *n*=10), 27 out of the 30 non-motor symptoms are more prevalent in patients with anosmia.

(ii) Sense of Smell in Each Sub-group and Percentage of Patients Reporting Symptoms in Each Non-Motor Symptom

Table 5.3(A): Non-Motor Symptoms that Increase Alongside the Degree of Smell Loss

Non-Motor Symptom	Mild/Moderate Microsmia (N=10)	Severe Microsmia (N=27)	Anosmia (N=75)	Chi Square (P value)
1 Dribbling of saliva during the daytime	20%	22%	55%	0.003
2 Loss or change in your ability to taste or smell	20%	33%	35%	0.628
3 Difficulty swallowing food or drink or problems with choking	30%	30%	34%	0.928
12 Problems remembering things that have happened recently or forgetting to do things	30%	52%	53%	0.371
14 Seeing or hearing things that you know or are told are not there	10%	15%	15%	0.809
16 Feeling sad, 'low' or 'blue'	40%	44%	51%	0.856
17 Feeling anxious, frightened or panicky	30%	30%	41%	0.645
19 Finding it difficult to have sex when you try	10%	26%	43%	0.059
20 Feeling light-headed, dizzy or weak standing from sitting or lying	40%	48%	49%	0.904
24 Intense, vivid or frightening dreams	10%	22%	41%	0.141
25 Talking or moving about in your sleep, as if you are 'acting out' a dream	20%	33%	43%	0.295
28 Excessive sweating	10%	11%	24%	0.226

Table 5.3 (B): Non-Motor Symptoms that Improve in Patients with Severe Microsmia

Non-Motor Symptom	Mild/Moderate Microsmia (10)	Severe Microsmia (27)	Anosmia (75)	Chi Square P value
4 Vomiting or feelings of sickness (nausea)	40%	11%	16%	0.154
5 Constipation (less than three bowel movements a week) or having to strain to pass a stool	60%	37%	59%	0.113
6 Bowel (faecal) incontinence	10%	4%	8%	0.681
7 Feeling that your bowel emptying is incomplete after having been to the toilet	40%	26%	43%	0.293
8 A sense of urgency to pass urine makes you rush to the toilet	70%	52%	68%	0.360
9 Getting up regularly at night to pass urine	50%	44%	69%	0.078
11 Unexplained change in weight (not due to change in diet)	10%	4%	8%	0.681
13 Loss of interest in what is happening around you or in doing things	30%	15%	24%	0.447
15 Difficulty concentrating or staying focused	30%	19%	42%	0.722
21 Falling	20%	15%	32%	0.176
22 Finding it difficult to stay awake during activities such as working, driving or eating	30%	7%	18%	0.212
23 Difficulty getting to sleep at night or staying asleep at night	50%	37%	46%	0.692
26 Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move	80%	44%	51%	0.131
27 Swelling of the legs	40%	19%	32%	0.296
29 Double vision	20%	15%	22%	0.755

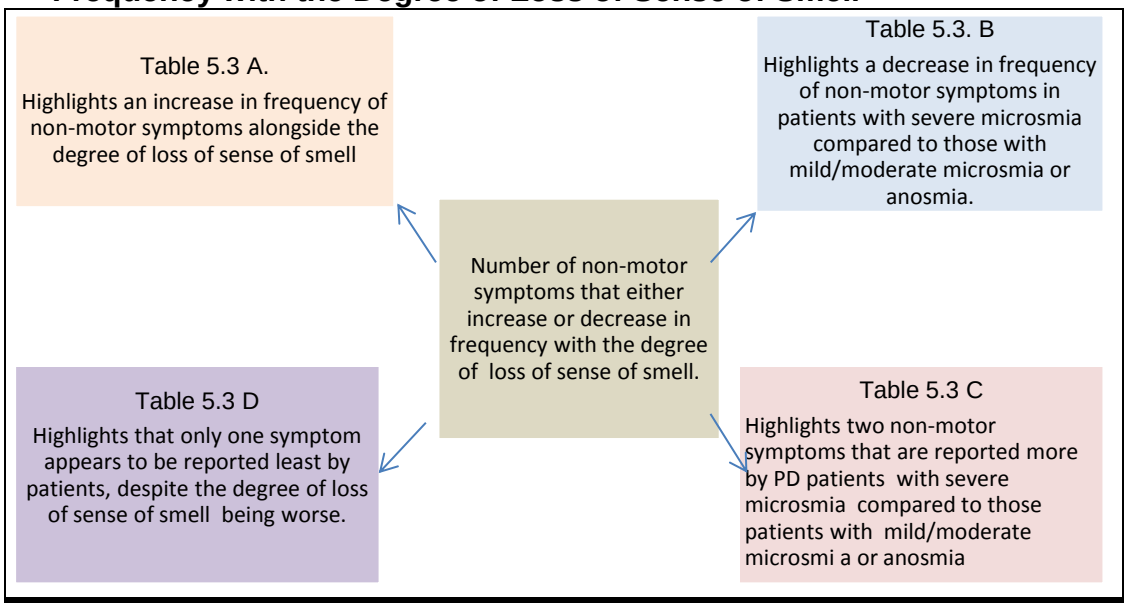
Table 5.3 (C): Non-Motor Symptoms that are More Prevalent in Patients with Severe Microsmia

Non-Motor Symptom	Mild/Moderate Microsmia (10) (10)	Severe Microsmia (27)	Anosmia (75)	Chi Square P Value
18 Feeling less interested in sex or more interested in sex	30%	37%	32%	0.824
30 Believing things are happening to you that other people say are not	0%	4%	1%	0.641

Table 5.3 (D): Non-Motor Symptom that are More Prevalent in Patients with Mild/Moderate Microsmia

Non-Motor Symptom	Mild/Moderate Microsmia (10)	Severe Microsmia (27)	Anosmia (75)	Chi Square P Value
10 Unexplained pains (not due to known conditions such as arthritis)	50%	37%	24%	0.159

Figure 5.1 Non-Motor Symptoms that either Increase or Decrease in Frequency with the Degree of Loss of Sense of Smell



5.5.2. PDQ39 Quality of Life Scores and Sense of Smell

(i) Analysis of the Overall Scores

Initial analysis of quality of life overall scores showed that most of the scores are particularly clustered around the 5-40 scores; with few PD patients scoring over 40 (see figures 5.2 and 5.3). This may suggest that this group of PD patients have, on average, a reasonable quality of life. However, looking at the sense of smell (UPSIT score) and its relationship with PDQ39 it does appear to worsen slightly alongside worsening quality of life. Figure 5.2 shows a negative correlation, (r_s=-0.120), between quality of life (as measured by the PDQ39 quality of life questionnaire) and sense of smell score which is not statistically significant, (p=0.350).

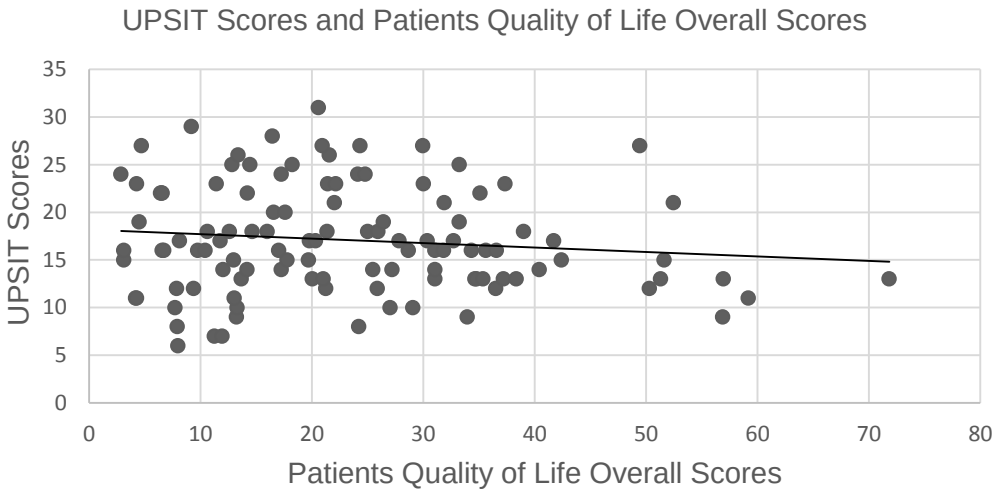


Figure 5.2: UPSIT scores and Patients' Quality of Life (PDQ39) Scores.
Most of the scores are clustered around the 5-40 scores, with few PD patients scoring over 40. The trend line appears to show worsening quality of life scores alongside the degree of loss of sense of smell, however this was not statistically significant (r_s=-0.120 p=0.350).

(ii) Frequency of PDQ 39 Scores

Figure 5.3 shows the distribution of PDQ39 scores within this study group The mean score is 23.26 and SD =14.254, median 21.025 and IQ range 19.622.

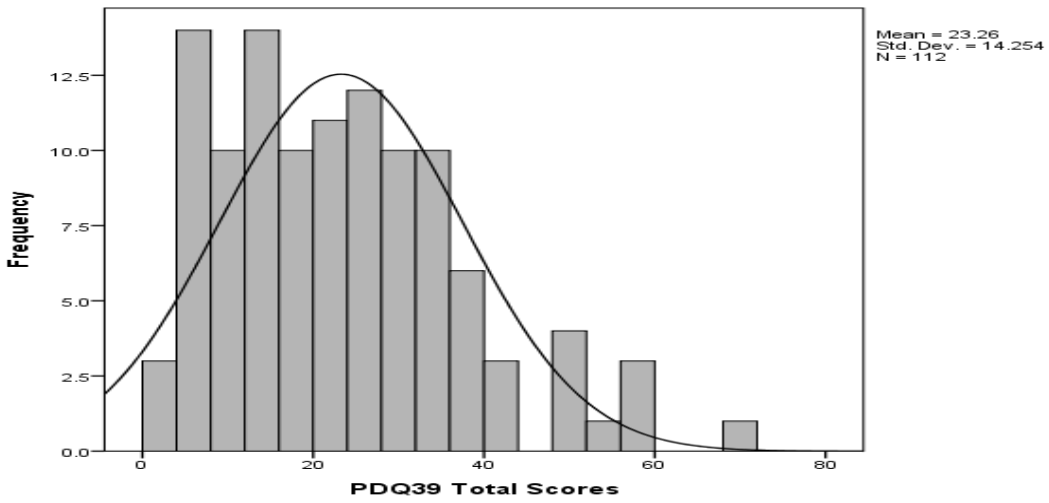


Figure 5.3: Frequency of Patients' Quality of Life (PDQ39) Scores.
Distribution of PDQ39 scores within this study group is positively skewed with one outlier. The mean score is 23.26 and SD =14.254, IQ range 19.622.

By examining the correlation between the individual PDQ39 themes and UPSIT score using Pearson's correlation it was noted all (except bodily

discomfort) have a weak or very weak negative correlation except cognition which is statistically significant (r_s= -0.198 p=0.036), (see table 5.4).

Table 5.4: PDQ39 Themes and Correlation of UPSIT

PDQ39 Themes	Correlation between UPSIT and Theme (r_s)	P value
(i) Activities of Daily Living	-0.110	0.250
(ii) Emotional Wellbeing	-0.087	0.360
(iii) Stigma	-0.048	0.618
(iv) Communication	-0.147	0.123
(v) Bodily Discomfort	0.033	0.730
(vi) Mobility	-0.046	0.633
(vii) Cognition	-0.198	0.036
(viii) Social Support	-0.030	0.750

(iii) Sub-Group Analysis

To answer the research question as to whether PD patient's PDQ39 quality of life themes, are clinically distinct depending on their degree of smell loss, further sub-group analysis has been carried out (see tables 5.5). Although initially from table 5.5 quality of life seems to worsen alongside the degree of smell loss in the, (i) activities of daily living, (ii) emotional well-being, (iii) stigma, and (iv) communication themes (highlighted in purple), which implies that the degree of olfactory loss may well be associated with worsening of these themes, on further statistical analysis, using a Kruskal Wallis test showed there is no statistically significant differences between the three sense of smell sub-groups and their quality of life themes scores.

Table 5.5: Sense of Smell and PDQ 39 Quality of Life Themes and Mean Scores in Each Sub-group

PDQ39 Themes	Mild/Moderate Microsmia. Mean PDQ39 Score	Severe Microsmia. Mean PDQ39 Score	Anosmia. Mean PDQ39 Score	Kruskal Wallis Test P value
(i) Activities of Daily Living	19.56	27.29	32.16	0.497
(ii) Emotional Wellbeing	17.47	20.51	22.64	0.741
(iii) Stigma	11.82	13.19	13.61	0.687
(iv) Communication	14.14	16.64	23.08	0.546
(v) Bodily Discomfort	38.31	30.83	34.86	0.825
(vi) Mobility	32.75	26.85	32.93	0.546
(vii) Cognition	23.12	21.29	29.75	0.206
(viii) Social Support	11.65	7.08	7.09	0.311
(ix) Total score for All Themes	168.82	163.68	196.12	

- Purple supports the research question that the degree of smell loss worsens alongside the degree of quality of life issues.
- Red neither supports nor refutes the research question that the degree of smell loss worsens alongside the degree of quality of life issues.
- Green refutes the research question that the degree of smell loss worsens alongside the degree of quality of life issues.

Once again, if we exclude the mild/moderate sense of smell group (due to small sample size, *n*=10), all the PDQ39 themes worsen alongside the degree of loss of sense of smell.

5.6. DISCUSSION

5.6.1. Non-Motor Symptoms Questionnaire and Sense of Smell

The most frequent non-motor symptoms reported by PD patients in this study were a sense of urgency to pass urine (63%), getting up regularly at night to pass urine (61%) and constipation (54%), irrespective of their sense of smell status (see table 5.1). These results are consistent with an International study by Martinez-Martin et al (2007) who examined 545 PD patients and found nocturia (61.9%), urinary urgency (55.81%) and constipation (52.48%) as the top three most prevalent non-motor symptoms and Bostantjopoulou et al (2013), who enrolled one hundred sixty six PD patients and sixty six matched controls and also found that in the PD patients urinary urgency (54.3%), nocturia (51.8%) and constipation (45.7%) were the top three non-motor symptoms. Similarly, nocturia and urinary urgency were the most frequent non-motor symptoms reported by Gallagher et al (2010).

However, these findings were not mirrored in other studies, for example; Barone et al (2009) who performed a multicentre survey using a semi-structured interview in 1,072 consecutive patients with PD found the most frequent non-motor symptoms were fatigue (58%), anxiety (56%) and leg pain (38%) and in the study of Cheon et al (2008) who evaluated 74 parkinsonian patients and 54 family members. the most frequent non-motor symptoms were getting up regularly at night to pass urine (nocturia) in men and feeling sad, low or blue in women, followed by restless legs and constipation.

Although the three most frequent non-motor symptoms highlighted in this study can be troublesome to the PD patient, and indeed are, the non-motor symptoms that appear to have a major impact on quality of life to the patients themselves, noted through many years of clinical observation in the clinical area of work, are feeling anxious, frightened or panicky (36%) and falling (27%) which are less prevalent in this study group than those reported by others (see table 5.1). However, it is worth noting that all the above studies, including this PhD study did not look at PD patients with advanced disease

and therefore, in this subset of PD patients, non-motor symptoms may play an even greater role and may be more prevalent.

Therefore, it is important to note that; (i) the most frequent symptoms experienced by PD patients are not necessarily the most significant symptoms that affect their quality of life (ii) the effect of these symptoms is very individual to each patient (one symptom not considered troublesome to one patient could be significantly troublesome to another) and (iii) the most frequently cited problems in this study may have other causes rather than PD. For example, a sense of urgency to pass urine (63%) and getting up regularly at night to pass urine (61%) could well be associated with prostate problems in men, such as benign prostatic hyperplasia (BPH), which is a common progressive clinical disease of ageing men (Shrivastava and Gupta 2012). Indeed, a multicenter study showed 34% of men in the USA and 29% of European men aged 50–80 years had BPH (Nordling 2005). Equally, an overactive bladder is another common cause of frequent urination affecting an estimated 50 to 100 million people worldwide (Miller and Sand 2005). The prevalence of an overactive bladder is known to increase with age and is a major problem particularly for women (Robinson and Cardoz 2002). Epidemiological studies have implicated oestrogen deficiency in the aetiology of lower urinary tract symptoms, although the role of oestrogen replacement therapy remains controversial (Robinson and Cardoz 2002).

Also, table 5.1 highlights the loss (or change) in ability to smell or taste was only reported by 33% of the study group. This further supports that self-reporting of smell dysfunction is regarded as too unreliable (Muller et al 2002, Doty et al 1988, Doty et al 1992, Hawkes and Doty 2009) as 100% of PD patients recruited for this study have varying degrees of smell loss. This also contradicts the work of Hawkes and Doty (2009) who commented that those who are unaware of their olfactory dysfunction, probably have mild impairment, as in this study over 90% of the PD patients have either anosmia or severe microsmia (see figure 3.4).

Regarding unexplained pains, there appears to be a significant amount of research on pain in PD, looking at a broad range of pain such as burning,

tingling, dystonic pain and central pain, although underlying mechanisms are not yet fully understood (for a comprehensive review of the literature see Fil et al 2013). However, for the first-time Hara et al (2013) examined the link between impaired pain processing and its association with the sense of smell. They examined forty-two patients (18 males and 24 females) with PD and 17 healthy control subjects (8 males and 9 females). A thin needle electrode was used to stimulate epidermal Aδ fibers, and somatosensory evoked potentials (SEPs) recorded at the vertex. Olfactory function was evaluated using the Odour Stick Identification Test. They concluded that pain processing in PD patients was impaired under specific nociceptive stimulation of Aδ fibers and significant correlation with smell dysfunction was detected and suggest that this mechanism may involve the limbic system during PD pathology. This present PhD study highlights that 29% of PD patients experience unexplained pains of which 50% of those patients had – infact- mild to moderate microsmia, which does not support Hara et al (2013) findings. The conclusion therefore is that this PhD study neither confirms nor refutes Hara et al (2013) findings; this is mainly because this study was not designed specifically to test the link between sense of smell and pain. However, this warrants further analysis.

With regards to falling, around 70% of people with PD who fall do so recurrently. Recurrent fallers reported 4.7 to 67.6 falls per year confirming that recurrent falling is a substantial problem for PD patients (Allen et al 2013).

In this PhD study 27% of the PD patients had fallen (see table 5.1), although the researcher did not examine the frequency of falls. The link between falls and olfactory dysfunction however has not been studied in PD, although, Sakamoto et al (2012) did find that the odour lavender reduced the risk of falls in elderly nursing home residents. However, it is beyond the scope of this study to analyse this in depth and give justification for this finding. Although this PhD study does highlight those patients who did fall, it neither supports nor refutes the research question that the degree of smell loss worsens alongside falling (see table 5.2 B).

When analysing the link between degree of smell loss with individual non-motor symptoms, table 5.3(A) highlights an increase in the reported frequency of non-motor symptoms alongside the degree of smell loss. This is in support of the research hypothesis. Furthermore, with exception of the mild/moderate sense of smell group, (which only has a small number of the overall sample size), table 5.3 (B) also shows an increase in frequency of non-motor symptoms alongside the degree of smell loss. Meanwhile table 5.3 (C) highlights only two symptoms which are more prevalent in those patients with severe microsmia than those with mild to moderate microsmia or anosmia. Finally, Table 5.3 (D) highlights that only one symptom appears to be reported least by patients, despite the degree of olfactory deficit being worse, and this is unexplained pains. Interestingly, if we exclude the mild/moderate sense of smell group (due to small sample size, *n*=10), 27 out of the 30 non-motor symptoms are more prevalent in patients with anosmia. Nonetheless, when conducting a chi-square test of independence to examine the relation between the degrees of smell loss and individual non-motor symptom, the only symptom to reach statistical significance is dribbling of saliva during the day (p=0.003).

Due to the lack of a standard definition and criteria for diagnosing dribbling in PD patients, estimates of prevalence vary. Previous studies showed that prevalence ranged from 84% (Ozdilek et al 2012) to 10% (Nicaretta et al 2008). This study's prevalence rate is 44% (see table 5.1), which is sitting between the high and the low prevalence rates quoted by others.

Factors possibly associated with dribbling of saliva in other studies were; (i) Severity of PD; For example, Rana et al (2012) conducted a retrospective chart analysis on 314 PD patients from six ethnic categories and concluded that PD patients at Hoehn and Yahr stage 4 were the most at risk. This is not surprising as these patients have severely disabling PD (see appendix 10) and dribbling is often seen in patients at this stage in clinical practice. (ii) Male gender (Rana et al 2013, Cheon et al 2008, Scott et al 2000). Indeed, Rana et al (2013) states males are twice more likely to have dribbling of saliva than females, and highlights in his study that there is a clinically

significant link in males between the prevalence of drooling and dementia. (iii) Ageing; For example, Kalf et al (2007) examined 63 PD patient's questionnaires relating specifically to drooling and found mild and severe dribbling of saliva in patients differed significantly in age ($p = 0.03$), the severe dribbling of saliva patients being on average 5.8 years older. Although this is not mirrored in all research with Rana et al (2012) finding no correlation between age and dribbling of saliva and (iv) Disease duration of PD (Rana et al 2012). Although this is not mirrored in other research (Kalf et al 2007).

Several factors may cause or increase dribbling of saliva in PD. Mounting evidence suggests that hypersalivation is unlikely to induce dribbling of saliva (Proulx et al 2005). In fact, the researcher recognises and observes this in clinical practice and it is more likely to result from pooling of saliva in the mouth, due to decreased frequency of swallowing and antecollis in PD patients (Pehlivan et al 1996).

Although not previously considered, there may be a link between facial expression, dribbling of saliva and sense of smell (facial expression was statistically significant when examining the UPDRS 14 motor scores ($p=0.029$) (see figures 4.3 section 4.3.1). The reason for this is that the muscles of the face in PD patients become more rigid and less animated (masklike facies) and the key to these movements is dopamine. Therefore, there may be a direct link between dribbling, sniff vigour and reduced sense of smell as the muscles of the face are required and therefore the link can be proposed. However, this study is not designed to test this hypothesis further.

Regarding dribbling of saliva and posture, there may also be a link with loss of sense of smell (posture was significantly associated with sense of smell loss and UPDRS 14 motor scores ($p=0.014$) (see figures 4.6 section 4.3.1), because PD patients do not have the ability to use the muscles in the face adequately, (masklike facies), and therefore have poor lip seal. Consequently, if the patient is stooped forward this will cause dribbling and

therefore may have been a contributing factor. Once again, this study was not designed to examine this hypothesis further.

5.6.2. PDQ39 Quality of Life Scores and Sense of Smell

The results of this present study showed a non-significant negative correlation between quality of life (as measured by the PDQ39 questionnaire) and UPSIT sense of smell scores. Summary scores as well as the themes of the PDQ-39 were calculated according to the scoring algorithm (Jenkinson et al 1998) (see Appendix 9 and section 2.4.3) and sense of smell score (UPSIT) r_s =-0.120 (see figure 5.2). When examining other research regarding quality of life and sense of smell this appears to be poorly explored in PD and this PhD study appears to be the first study to examine this.

Examining the link between PDQ39 themes and sense of smell in the whole group, using Pearson's correlation revealed all, (except bodily discomfort), have weak or very weak non-significant negative correlations except cognition which is statistically significant (r_s= -0.198 p=0.036). Interestingly, Doty et al (1989) tested 58 Parkinson's disease patients using UPSIT and modified Randt memory test and concluded that the olfactory disorder of parkinsonism is independent of the cognitive manifestations of the disease. However, this disagrees with section 3.6.6. (Cognitive Function and Sense of Smell) which used a spearman correlation on all MoCA and UPSIT scores of whole group which showed a positive correlation between cognition and UPSIT (r_s=0.213), which is statistically significant (p=0.024), (see figure 3.17 section 3.6.6). This supports the findings of Postuma and Gagnon (2010), Bohnen et al (2010) and Schrag et al (2000) who all found a positive correlation between odour identification scores and verbal memory in patients with PD who have olfactory loss (see section 1.2.6). Indeed, Schrag et al (2000) conducted a population-based study on quality of life on 92 PD patients from 15 GP practices in London and found that cognition has in fact one of the greatest influences on quality of life in Parkinson's disease.

A sub-group analysis of PD patients (using (i) mild/moderate microsmia, (ii) severe microsmia or (iii) anosmia categorisations) showed that quality of life seems to worsen alongside the degree of smell loss in the (i) activities of daily living, (ii) emotional well-being, (iii) stigma and (iv) communication themes (highlighted in purple). (Table 5.4) and therefore implies that the degree of olfactory loss may well be associated with these themes.

However, further statistical analysis, using Kruskal Wallis test, highlights there is no statistically significant difference between all the quality of life themes and sense of smell in each sub-group. It is important to note that the overall total scores are higher overall in the anosmia group and lower in the severe group (see table 5.5). This might be due to a sample size effect due to the small number of PD patients within the severe microsmia sub-group (27 PD patients in severe microsmia group compared to 75 patients in anosmia group).

5.7. SUMMARY

- The most frequent non-motor symptoms reported were a sense of urgency to pass urine (63%), getting up regularly at night to pass urine (61%) and constipation (54%).
- The loss or change in ability to smell was only reported by 33% of the study group.
- When examining the relation between the degrees of smell loss and individual non-motor symptoms, the only symptom to reach statistical significance is dribbling of saliva during the day (p=0.003).
- A non-significant negative correlation between quality of life (as measured by the PDQ39 questionnaire) and loss of sense of smell was found in this study, suggesting quality of life does not correlate with the degree of sense of smell loss. This appears to be the first study to examine this.

CHAPTER 6

ADDITIONAL CONFOUNDING FACTORS AFFECTING THE SENSE OF SMELL IN PD PATIENTS

6.1. OVERVIEW

Several confounding factors have been reported to affect the sense of smell in patients with PD. Deliberations are particularly noted around the effects of medication, sniff vigour, environmental settings and handedness. This chapter will address whether medication, sniff vigour, environment and handedness may affect the sense of smell in PD patients in this study.

6.1.1. Anti-Parkinsonian Medication and Sense of Smell

Several studies have explored whether Parkinson's disease medications have any effect on the sense of smell (Doty et al 1992, Quinn et al 1987, Ward et al 1983, Ansari and Johnson 1975), including the potent dopamine agonist Apomorphine (Roth et al 1998). Conclusions from these studies reported that olfactory function remains unaffected by anti-parkinsonian medication. One of the aims of this chapter is to establish whether any PD medications worsen or improve PD patients' ability of sense of smell in this study group.

6.1.2. Sniff Vigour and Sense of Smell

Sobel et al (2001) reported that suboptimal sniffing may contribute to the loss of sense of smell seen in PD. This might be linked to fatigue. Practically, this is said to equate to a mean reduction of around two to three points on the 40-odour University of Pennsylvania smell Identification (UPSIT-40) test (Doty et al 1984). To test this, each of the four booklets was examined regarding overall scores. The theory is that if sniff vigour fatigues, like other motor symptoms of PD, then we would expect the scores on each

subsequent smell test booklet to worsen. Patients were not encouraged to increase sniff vigour during the examination as this can improve scores (Sobel et al 2001).

6.1.3. Environmental Setting and Sense of Smell

The setting (environment) in which data is collected is one of the most important factors in conducting research. Bloor et al (2001) comment that the venue is important and should, ideally, be accessible, comfortable, private, quiet and free from distractions. However, while a central location, such as clinical setting within a Trust might be ideal for some patients, other patients may be affected by any anxieties that affect them when they attend in a patient role and therefore, would much prefer their home environment (Bloor et al 2001). For this reason, patients were offered the choice of attending a research room at a local Trust or to have their assessments completed at home. This was firstly to establish whether this may have a direct effect on odour detection scores (UPSIT 40) and, secondly to ensure the researcher could capture enough PD patients to complete this study. Ultimately, the aim is to compare results in the two environments to establish whether this may have a direct effect on sense of smell (UPSIT 40). This appears to have not been studied before in PD patients.

6.1.4. Handedness and Sense of Smell

Handedness may be a confounding factor affecting the sense of smell (Gottschlich and Hummel 2015). This present PhD study re-investigates this subject as; (i) handedness is also said to play a large part in memory (Prichard et al 2013) and (ii) the memory part of the brain shares parts with the olfactory part of the brain, resulting in a connection between memory and olfactory sense (Witze 2006). Investigating handedness, research showed that each hand is controlled by opposite hemispheres, so the left hand is controlled by the right hemisphere and the right hand by the left (Annett 2006). Handedness also determines which hemisphere of the person will be dominant. Although over simplified right-handed people have dominant left

brains, so they can encode memories easier; the left brain enforces encoding. Left-handed people have dominant right brains, so they can retrieve memories better because retrieval is enforced by the right brain. Ambidextrous people tend to have the best memory, because both sides of their brain are strong, and therefore they can retrieve and encode well (Propper et al 2005, Annett, 1970), followed by PD patients who are left-handed (Annett 1970).

6.2 AIM

To investigate whether PD medications, sniff vigour, handedness and environment affect the sense of smell in patients with PD in this PhD study.

6.3 OBJECTIVES

(i) To confirm or refute whether different classes of PD medication and the timing of medication has an impact on the sense of smell.

(ii) To establish whether sniff vigour fatigues during the UPSIT 40 smell test which may contribute to lower UPSIT scores seen in patients with PD in this study group.

(iii) To establish whether the environment (in which the smell test was conducted) has an impact on sense of smell.

(iv) To establish whether handedness has an impact on sense of smell.

6.4. OUTLINE OF METHODS

(i) Prescribing practice of the anti-parkinsonian medication was assessed by looking at the type of medication, duration of disease and timing of medication and whether there is a correlation with UPSIT scores.

(ii) Sniff vigour was analysed by comparing the four 40 UPSIT smell test booklets to see if there is a significant reduction in the number of correct answers as the PD patient goes through each smell booklet. This is to establish if there is fatigability of sniff vigour.

(iii) The effects of the environment in which the PD patient was tested (either in the patient's own home or in hospital to test the sense of smell) was analysed to see if this affects mean UPSIT scores.

(iv) Handedness was captured on the Odour Detection in Parkinson's Disease Participants Questionnaire (see Appendix 14) and analysed to see if this might have influenced a PD patient's ability to smell.

6.5. RESULTS

6.5.1. Type of Anti-Parkinsonian Medication and Sense of Smell

Table 6.1 shows that the most prescribed medication is levodopa (87.5%). The UPSIT range is similar in each group. The mean UPSIT is higher in those patients not taking a particular anti-parkinsonian medication compared to those that are except dopamine agonists. This shows PD patients either taking or not taking dopamine agonists both have a mean UPSIT score of 17. UPSIT median remains comparable with the mean by one-mark lower except in patients not taking a COMT inhibitor in which sense of smell score is two marks lower. Standard deviation is spread more in PD patients not taking medication in all anti-parkinsonian medications. None of the medications with regards to the sense of smell reached statistical significance between those taking certain anti-parkinsonian medication and those not taking it. (Table 6.1).

Table 6.1: Anti-Parkinsonian Medication and Sense of Smell in PD Patients.

Variable	Medication	Percentage	UPSIT Range	UPSIT Mean	UPSIT Median	Standard deviation	P value
Patients either taking or not taking medication (N=112)	Yes= 107 No= 5	95.5 4	6-31 7-28	17 18	17 18	5.494 7.918	0.334
Levodopa	Yes =98 No=14	87.5 12.5,	6-31 7-28	17 19	16 18	5.450 6.359	0.279
COMT Inhibitor	Yes=31 No=81	28 72	7-27 6-31	16 18	15 16	4.633 5.867	0.315
Dopamine Agonist	Yes=55 No=57	49 51	7-27 6-31	17 17	16 16	5.334 5.851	0.750
MAO-B Inhibitor	Yes=8 No=104	7 93	6-31 10-27	17 19	18 18	4.794 5.739	0.875

The table shows name of anti-parkinsonian medication taken, number of Individual patients taking It, the overall percentage and UPSIT range, mean and median, standard deviation and P value.

6.5.2. Duration of Disease

PD disease duration (as a reflection of duration of taking PD medication) may be a confounding factor alongside the type of anti-parkinsonian medication taken. Table 6.2 analyses this possibility. Initial analysis of table 6.2 suggests that disease duration combined with the use of anti-parkinsonian medication might affect olfaction as UPSIT scores are lower in patients taking medication than those who are not (except dopamine agonists) and are lower in patients with a longer duration of PD. However, correlation between duration of disease and UPSIT showed a very weak negative correlation (r_s =-0.04344, n=112), which did not reach statistical significance (p=0.535).

Table 6.2: Anti-Parkinsonian Medication Taken and Number of Individual Patients taking it, Mean Duration of Disease and Standard Deviation.

Variable	Mean Duration of disease on medication	Standard Deviation
Patients either taking or not taking medication		
Yes = 107	6	3.850
No = 5	1	0.593
Levodopa		
Yes = 98	6	3.929
No = 14	3	2.450
COMT Inhibitor		
Yes = 31	9	3.922
No = 81	4	3.152
Dopamine Agonist		
Yes = 55	7	3.580
No =57	4	3.777
MAO-B Inhibitor		
Yes = 8	6	2.386
No = 104	5	3.974

6.5.3. Timing of Medication

The degree of sense of smell loss may also be affected by the timing of the medication. Figure 6.1 displays minutes since last PD medication taken and UPSIT scores. Initial analysis of figure 6.1 highlights that most medication was taken between 60 to 120 minutes before testing a patient's sense of smell. Correlation between timing of the doses and UPSIT showed a weak negative correlation (r_s=-0.247) between the two which is statistically significant (p=0.010). (N=107).

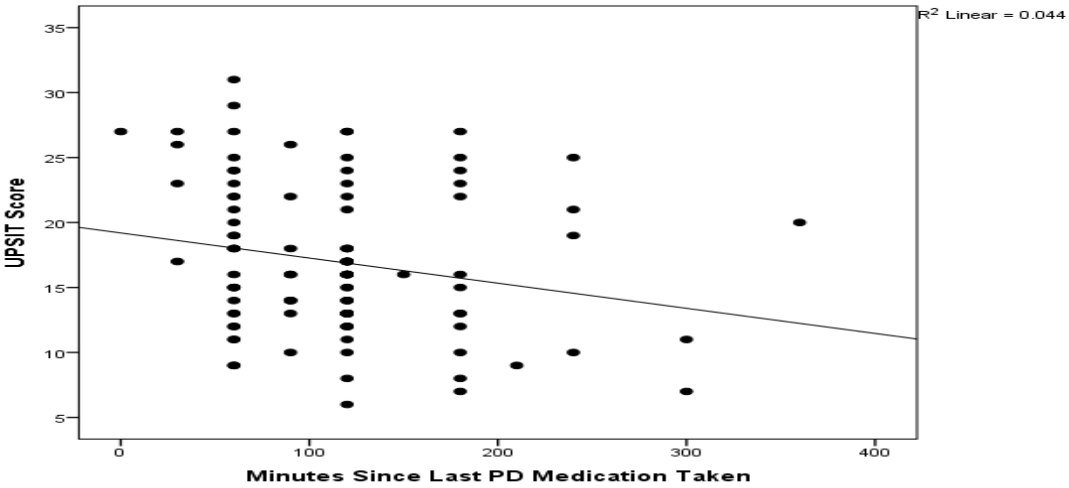


Figure 6.1: UPSIT Scores and Minutes Since Last PD Medication Taken.
Correlation between timing of the doses and UPSIT showed a weak negative correlation (r_s=-0.247) between the two which is statistically significant (p=0.010), (n=107).

6.5.4. Levodopa vs Non-Levodopa Treatment

As levodopa is the most prescribed medication in this study, dividing the study group into (i) patients taking levodopa and (ii) patients not on levodopa will now be analysed.

Figure 6.2 illustrates ninety-eight patients' UPSIT scores taking levodopa and minutes since last levodopa dose taken. Correlation between timing of levodopa dose and UPSIT score showed a weak negative correlation between the two (r_s=-0.1875) which is statistically significant (p=0.015) (n=98).

Figure 6.2: UPSIT Scores of Patients on Levodopa and Minutes Since it was Last Taken. Correlation between timing of levodopa dose and UPSIT score showed a weak negative correlation between the two (r_s=-0.1875) which is statistically significant (p=0.015) (n=98).

Further analysis of patients on a dopamine agonist and/or a MAO-B inhibitor (9 patients) appears to suggest that patients' UPSIT scores worsen alongside the time since taking PD medication. However, correlation between minutes since last PD medication taken and UPSIT was not statistically significant (r_s =-0.462 n=9, p=0.461).

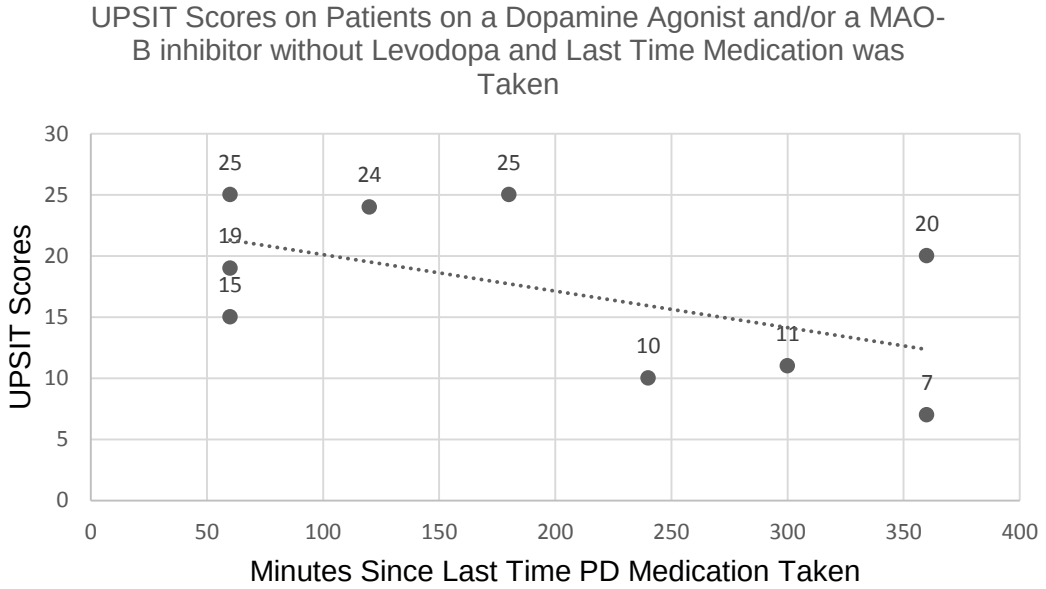


Figure 6.3: UPSIT Scores on Patients on a Dopamine Agonist and/or a MAO-B inhibitor without Levodopa and Last Time Medication was Taken, *Correlation between minutes since last PD medication taken and UPSIT using one-way anova was not statistically significant (r_s=-0.462, n=9, p=0.461).*

6.5.5. Sniff Vigour and Sense of Smell

Figure 6.4 divides patients smell (UPSIT) scores according to the total scores for each booklet to establish whether PD patients' sniff vigour fatigues during the UPSIT 40 smell test (the overall total score for each booklet is 1,120). Each booklet has 10 different odours and is assessed continually until 40 odours are sniffed. Initial analysis suggests sniff vigour does not fatigue during the 40 UPSIT smell test. On further statistical analysis using one-way ANOVA there was no statistically significant difference between each book (p =0.212).

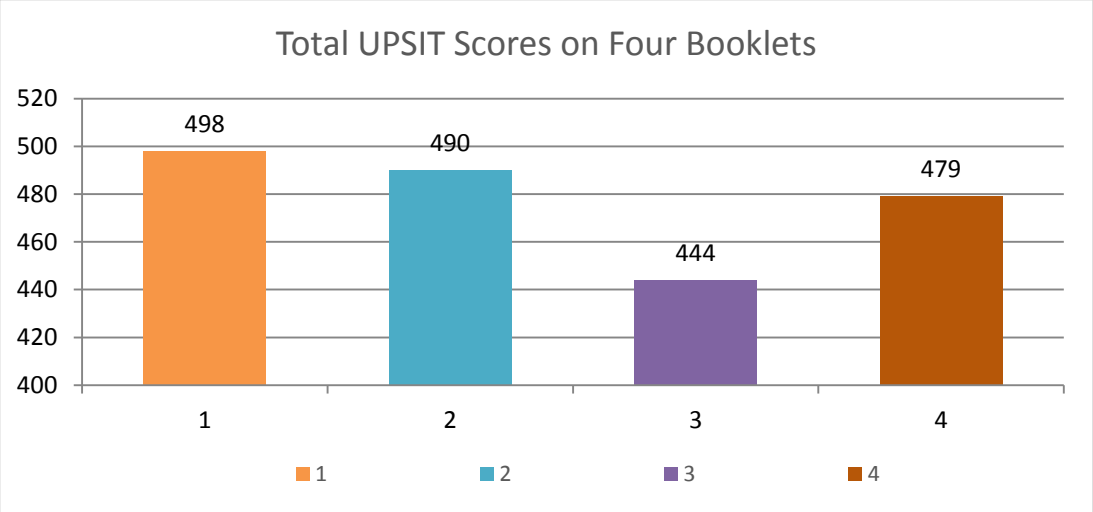


Figure 6.4: UPSIT Scores and Total Scores for Each Booklet. (Booklet one=498 points, booklet two=490 points, booklet three=444 points and booklet four=479 points). (N=112*). On further analysis, there was no statistical significance between each book (p =0.212).*

This is further analysed by dividing patients into (i) anosmia, (ii) severe microsmia or (iii) mild to moderate microsmia (see figures 6.5-6.7). Figures 6.5 (PD patients with anosmia) and figure 6.7 (PD patients with mild to moderate microsmia) give the impression that sniff vigour does not worsen. On further statistical analysis this was confirmed using one-way ANOVA. (anosmic booklets p=0.693, mild to moderate microsmia booklet P=0.866). However, figure 6.6 (PD patients with severe microsmia) do have mild worsening of their sniff vigour, (as shown by the reduction in their sense of smell UPSIT scores). However, on further statistical analysis using one-way ANOVA this again did not reach statistical significance (p= 0.546).

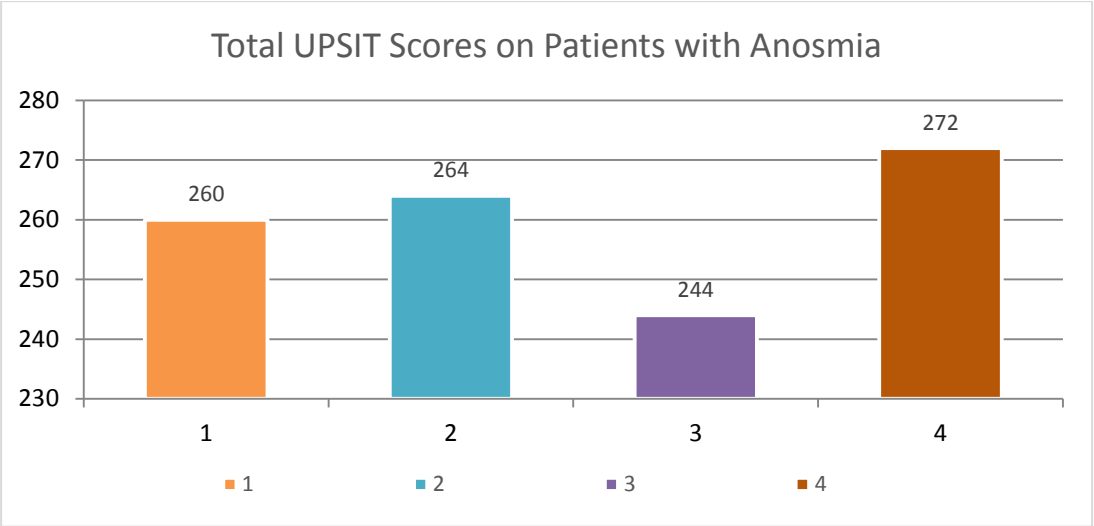


Figure 6.5: Total UPSIT Scores on Patients with Anosmia. (N= 75).

On further analysis, there was no statistical significance between each book (p =0.693).

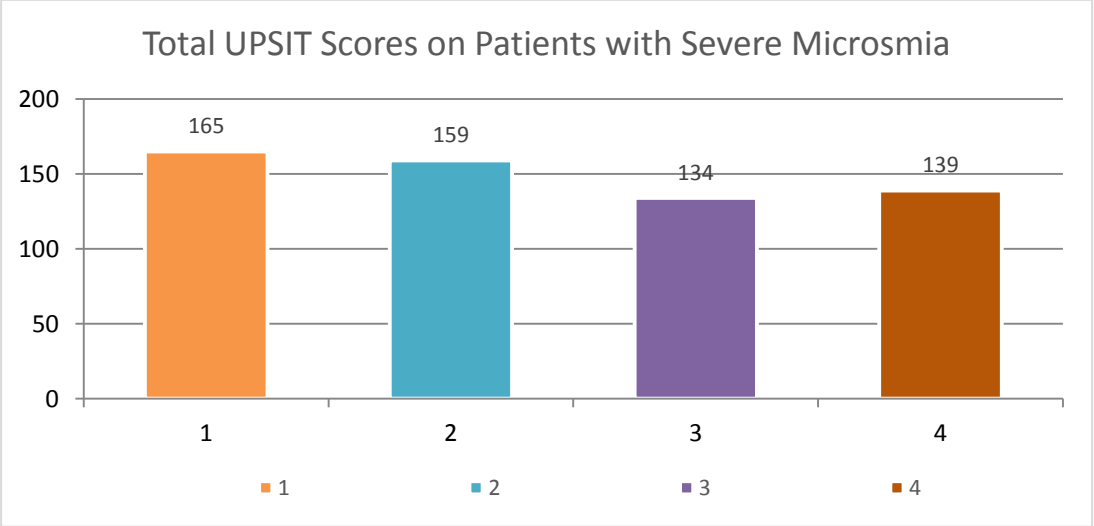


Figure 6.6: Total UPSIT Scores on Patients with Severe Microsmia (N= 27).

On further analysis, there was no statistical significance between each book (p =0.546).

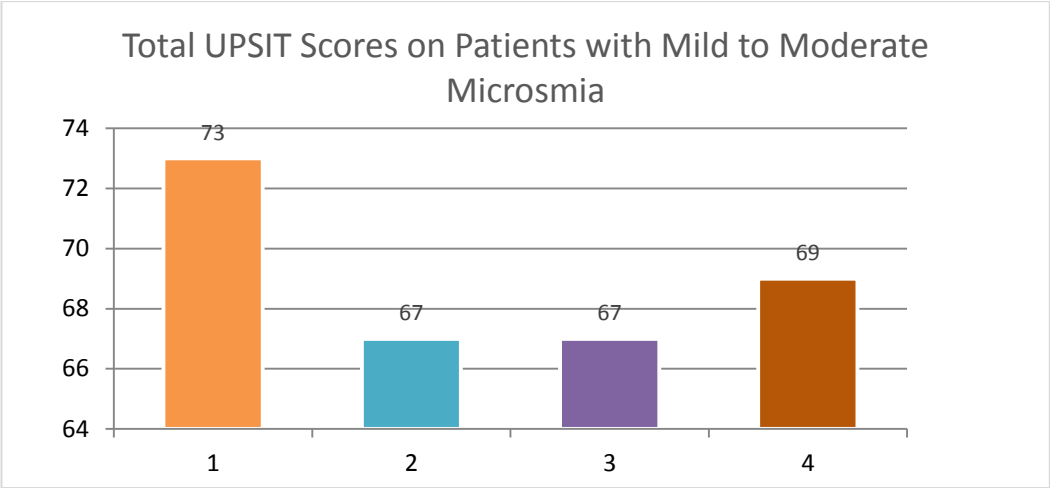


Figure 6.7: Total UPSIT Scores on Patients with Mild to Moderate Microsmia. (N=10). *On further analysis, there was no statistical significance between each book (p =0.866).*

6.5.6. Environmental Setting and Sense of Smell

Sixty patients (54%) were tested in clinic and 52 patients (46%) were tested at home. Figure 6.8 shows that the median is slightly higher in patients tested in clinic (17) compared to those tested at home (16). A Mann-Whitney U test was performed to provide further statistical analysis on the effects of the environment on the sense of smell; however, this did not reach statistical significance (p=0.746).

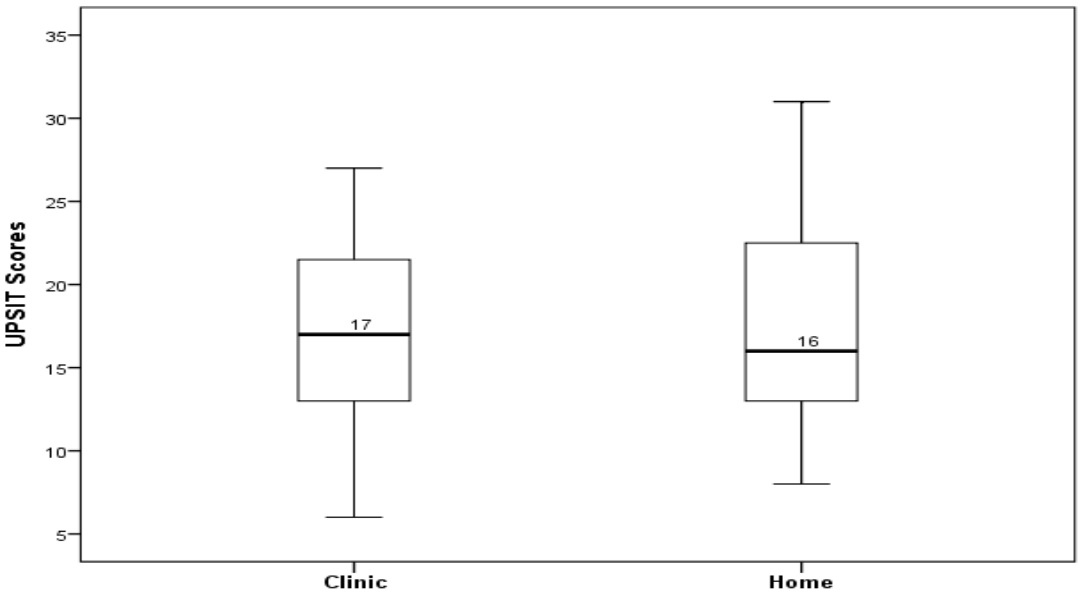


Figure 6.8: UPSIT Scores and Environment in Which Patients Were Tested.

Whether these two groups differ in gender or age, which may affect the sense of smell, is further analysed in table 6.3. Table 6.3 highlights that mean and median UPSIT is lower in patients tested at home. The mean age is comparable. However, gender differences are more marked in patients tested in clinic, with fewer women being tested. This is not surprising as more men are recruited to this study.

Table 6.3: Environment, UPSIT Mean, Median and Range, Mean Age, Gender and Mean UPSIT and Age of Each Gender.

Environment	UPSIT (Mean)	UPSIT (Median)	UPSIT (Range)	Age (Mean)	Gender	UPSIT (Mean)	Age (Mean)
Clinic (60 patients) +/- SD=	17 5.430	17	6-27	70	Female=15 Male=45	19 16	70 72
Home (52 Patients) +/- SD=	15 5.781	16	8-31	71	Female=25 Male=27	19 16	69 71

6.5.7. Handedness and Sense of Smell

Figure 6.9 shows the number of patients either being (i) ambidextrous, (ii) left handed or (iii) right handed and total number in each group. Most PD patients in this study are right handed and account for 84% of the whole study group.

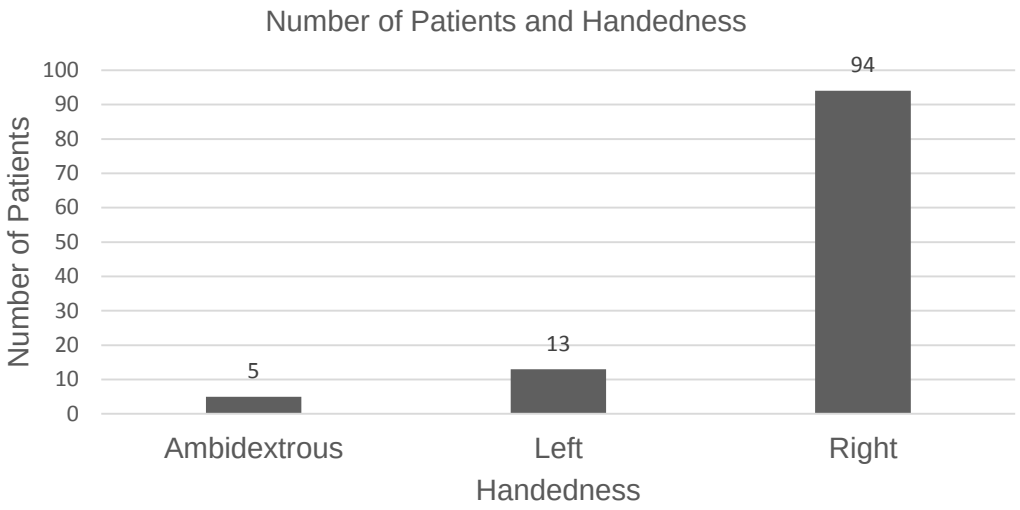


Figure 6.9: Number of Patients Reporting Either being Ambidextrous, Left or Right Handed.

To establish whether the handedness of a patient influences their olfactory loss, both figure 6.10 and table 6.6 show the mean, median and range of UPSIT scores for each group. As shown in figure 6.10 and table 6.6 the range and median of patients who are right or left handed are similar. However, those PD patients who are ambidextrous have a much higher median and mean score although this result needs to be interpreted with caution due to the small sample size of ambidextrous patients (only 5) in this study.

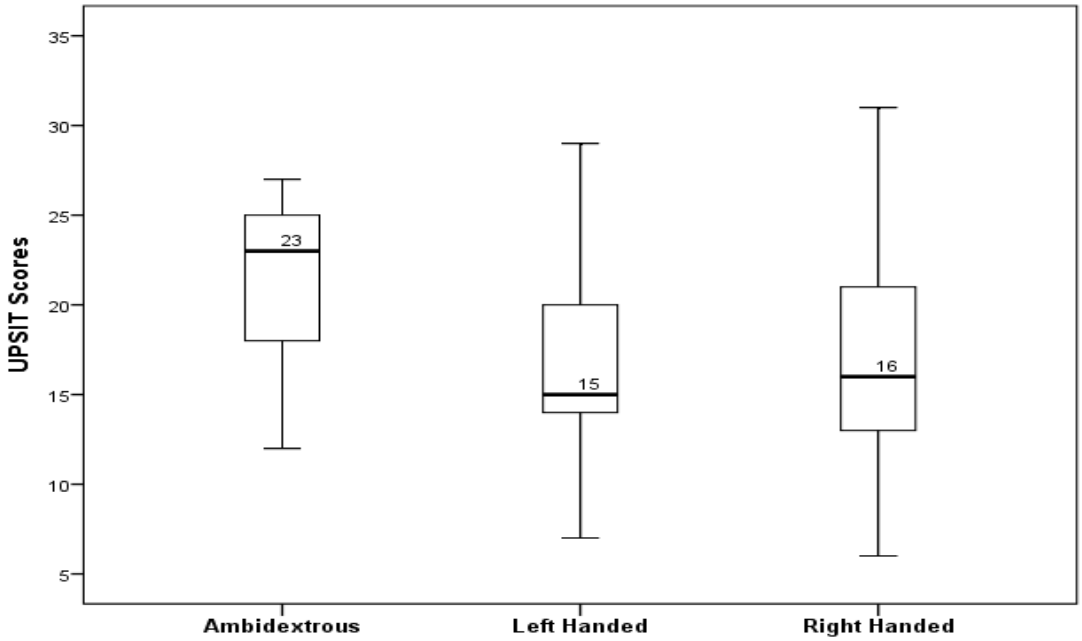


Figure 6.10: UPSIT Scores and Handedness on All Patients Recruited to This Study.

Table 6.4: Handedness, Number of Patients in Each Group, Range Mean and Median of UPSIT Scores.

Handedness	Number of Patients	UPSIT (Range)	UPSIT (Mean)	UPSIT (Median)
Ambidextrous	5	12-27	21	23
Left	13	7-28	17	15
Right	94	6-31	17	16

6.6 DISCUSSION

6.6.1. Medication and Sense of Smell

Type of Medication

The most important class of medication, which may influence the sense of smell, could be levodopa. This is because levodopa is a precursor of dopamine (the neurotransmitter significantly reduced in PD) and remains the most effective drug for treating PD for 5 decades (LeWitt and and Fahn 2016, Tomlinson et al 2010, Katzenschlager and Lees 2002).

Table 6.1 shows that Levodopa is the most prescribed medication in this study group (n=98, 87.5%). This is mirrored when examining olfaction and medication in PD research in general (Rosser et al 2008, Doty et al 1992, Quinn et al 1987, Ward et al 1983, Ansari and Johnson 1975), unless the study is specifically designed to look at another class of drug, such as the potent dopamine agonist Apomorphine (Roth et al 1998). The next class of drug prescribed is dopamine agonists (n=55, 49%), followed by COMT inhibitors (n=31, 28%) then MAO-B inhibitors (n=8, 7%).

From table 6.1 the mean and median UPSIT is similar in all patients taking levodopa, COMT Inhibitor, dopamine agonist and MAO-B inhibitors. This might suggest that anti-parkinsonian medication does not improve olfaction. This has been frequently found in other studies (Rosser et al 2008, Huisman et al 2004, Hsia et al 1999, Koster et al 1999, Duchamp-Viret 1997, Wilson and Sullivan 1995, Doty et al 1992). The rationale for this can be found in section 1.2.5. as dopamine is known to inhibit olfactory transmission in the olfactory bulb (Huisman et al 2004). Indeed, correlation showed that regardless of the class of drug and whether (or not) PD patients were taking that class of drug; none reached statistical significance (see figure 6.1). This PhD study therefore supports previous research that PD medication does not improve olfaction. This has been confirmed by others in both clinical practice and in the research laboratory. For example, Rosser et al

(2008) tested olfaction in 19 older patients without a diagnosis of PD before and after administration of levodopa in a double-blind, placebo-controlled, randomized cross-over study. They concluded that in contrast to what had been demonstrated in rats, levodopa did not improve olfaction, with even a trend for the reverse. It is also important to acknowledge from Rosser et al (2008) study that the results of animal studies cannot be directly transferrable to the human situation. Also, Ward et al (1983) in a comparison study of PD patients with closely matched controls found patients with PD had not only reduced scores in odour detection but olfactory impairment was not related to treatment. Furthermore, Quinn et al (1987) examined 78 patients with PD and 40 age-matched controls also highlighted there was no significant correlation between olfactory threshold and current therapy with levodopa or anti-cholinergic drugs. At a molecular level, both Huisman et al (2004) and Hsia et al (1999), noted that PD patients have a marked increase in dopaminergic neurons (which inhibit olfaction) in the olfactory bulbs which makes it understandable why olfaction is not improved in PD patients treated with L-dopa (see figure 1.3 section 1.2.5). Therefore, loss of sense of smell may involve mechanisms that are not influenced by pharmacological manipulation of dopaminergic or cholinergic status.

6.6.2. Disease Duration, Medication and Sense of Smell

The duration of disease is similar in each group (see table 4.2), and disease duration is not a significant predictor of the degree of smell loss in this study. This has been shown by others (Hakymenze et al 2013, Haehner et al 2009, Hawkes et al 1997, Doty et al 1988, Quinn et al 1987, Ward et al 1983). However, this is not universal with other studies reporting disease duration is a predictor of the degree of smell loss (Cavaco et al 2015, Deeb et al 2010).

When examining disease duration combined with the use of anti-parkinsonian medication, UPSIT scores are lower in patients taking medication than those who are not, (except dopamine agonists) and is lower in patients with a longer duration of PD (see table 6.2). However, interestingly patients who are on no medication had significantly higher

UPSIT score (UPSIT 22); the rationale for this is unclear but could be due to a sample size effect as only 5 patients out of the 112 were on no medication. This warrants future research to establish whether UPSIT scores worsen as the disease progresses in individual patients.

However, correlation between duration of disease and UPSIT (r_s=-0.04344, n=112), did not reach statistical significance (p=0.535). This is in support of previous research (Haehner et al 2009, Hawkes et al 1997, Doty et al 1988, Quinn et al 1987, Ward et al 1983).

Nevertheless, these data must be viewed with caution as almost all patients will eventually end up on levodopa (plus or minus a COMT inhibitor). Therefore, the reason for a difference in mean duration of disease can simply be attributed to prescribing practice. For example, levodopa traditionally has been prescribed later in the disease progression to avoid long-term side effects, such as levodopa induced dyskinesia.

6.6.3 Timing of Medication and Sense of Smell

Initial analysis of the degree of loss of sense of smell and the minutes since last or no PD medication taken suggests that UPSIT scores worsen alongside the increase in minutes since last or no PD medications taken (see figure 6.1). Further analysis shows the correlation between minutes since last PD medication taken and UPSIT scores (r_s=-0.2634, n=112, p= 0.008) was significant at the 0.01 level (2-tailed).

As levodopa is the most prescribed medication in this study figure 6.2 illustrates that the UPSIT score of the ninety-eight patients taking levodopa is also worsening. Further analysis shows the correlation between timing of levodopa dose and UPSIT scores (r_s=-0.1875, n=112, p= .015) again was significant at the 0.05 level (2-tailed). Therefore, UPSIT scores worsen alongside the minutes since PD medication taken. Whether this is due to the wearing off effect of the medication (when dopamine levels are reducing) as levodopa tends to be given every 240 minutes and takes approximately 45

minutes to be absorbed (when dopamine levels are at their peak) suggesting that PD medications might improve sense of smell. This is beyond this present study to investigate further but warrants further analysis. However, as dopamine is known to inhibit olfactory transmission in the olfactory bulb, (Hsia et al 1999, Koster et al 1999, Duchamp-Viret 1997, Wilson and Sullivan 1995, Doty et al 1992) it would not be unreasonable to suspect that levodopa would worsen sense of smell loss. Therefore, this PhD study does not support this finding.

Finally, further analysis of patients on a dopamine agonist and/or a MAO-B inhibitor suggests that patients UPSIT scores worsen alongside the time since taking PD medication (figure 6.3). However, correlation between minutes since last PD medication taken and UPSIT was not statistically significant at the 0.05 level (2-tailed) (r_s=-0.462 n=9, p= 0.211). This may be a sample size effect as only 8% (9 patients) of patients in our study are on a dopamine agonist with or without a MAO-B inhibitor.

6.6.4 Sniff Vigour and Sense of Smell

This study suggests sniff vigour does not fatigue during the 40 UPSIT smell test (see figure 6.4). Further analysis by dividing patients into (i) mild to moderate microsmia, (ii) severe microsmia or (iii) anosmia found initially that PD patients with severe microsmia have worsening UPSIT scores and therefore possible sniff vigour on booklet 3 but then improves on booklet 4 (see figure 6.6). It however, must be considered that the UPSIT scores on each booklet may well be influenced by the familiarity of smells presented in each booklet (see appendix 23). Therefore, both (whole group and sub-group) analysis showed that sniff vigour does not fatigue which was supported on further statistical analysis. Therefore, this PhD study findings did not support Sobel et al (2001) research which suggests that suboptimal sniffing may contribute to the olfactory problems seen in PD. However, Sobel et al (2001) does state that sniff impairment is not the sole cause of the olfactory impairment in PD and increasing sniff volume only helped the worst of the performers and did not bring them to normal performance.

Interestingly, in our study olfactory function was significantly correlated with a subset of measures on the Unified Parkinson's Disease Rating Scale (UPDRS) related to axial function, such as gait and postural instability, (see appendix 22), prompting speculation that impaired sniffing may be another motor symptom of PD. However, the study was not designed to test this hypothesis, but it warrants further analysis.

6.6.5. Environmental Setting and Sense of Smell

The results of this PhD study suggest that the environment in which the smell test is conducted does not affect the sense of smell (see figure 6.8).

When taking into consideration the difference in gender or age, which may affect the sense of smell, it appears mean UPSIT difference is insignificant in patients tested at home (see table 6.3). The mean age is comparable, between the two groups. However, gender differences are more marked in patients tested in clinic, with fewer women being tested. This is not surprising as more men are recruited to our study. However, mean gender UPSIT is consistently higher in females and may reflect the lower mean age of women tested in both clinic and at home or due to the ability of women understood to have a greater sense of smell (Lundstrom et al 2006, Dalton et al 2002, Brand and Millot 2001, Liu et al 1995, Cain 1982).

6.6.6. Handedness and Sense of Smell

Handedness is defined as the preferred hand used for a motor activity (manual preference) or the hand most skillful at performing a task (manual proficiency) (Henninger, 1992). Approximately 90-95% of the population is right-handed (dextral) (Annett, 1970). The remainder are left-handed (sinistral) or ambidextrous. Most PD patients in this PhD study are right handed and account for 84% of the whole study group (see figure 6.9).
To establish whether the handedness of a patient influences their olfactory loss, figure 6.10 and table 6.6 show the range and the median of patients (who are right or left handed) are similar. This supports Lubke et al (2012)

research who suggested that left or right handedness does not seem to play a substantial role in the processing of olfactory information (by using functional MRI to assess olfactory activation whilst sniffing the rose-like odour phenyl ethyl alcohol and the smell of rotten eggs).

However, those PD patients who are ambidextrous have much higher median and mean UPSIT scores. This suggests PD patients who are ambidextrous may have a more preserved sense of smell although; this might be due to a sample size effect as only 5 patients were ambidextrous in our study. There appears to be no other research to substantiate this.

6.7 SUMMARY

- Levodopa is the most prescribed medication in this study group.
- The association between duration of disease and degree of loss of sense of smell did not reach statistical significance.
- Olfactory function may be affected by anti-parkinsonian medication or a confounder for disease stage.
- None of the medications with regards to the sense of smell reached statistical significance between those taking certain anti-parkinsonian medication and those not taking it.
- The environment in which the smell test is conducted does not affect the sense of smell. This appears to have not been studied before in PD patients.
- UPSIT score of patients taking levodopa decreased the further away from the time the medication was taken.
- Correlation between minutes since last PD medication taken and UPSIT was statistically significant.
- Correlation between sniff vigour (fatigue) and UPSIT was not statistically significant.
- PD patients who are ambidextrous have higher median and mean UPSIT scores. However, this might be due to a sample size effect as only 5 patients were ambidextrous in our study.

CHAPTER 7

THE PROFILE OF PERCEIVED SENSE OF SMELL AND PHANTOSMIA IN PD PATIENTS.

7.1 OVERVIEW

This chapter will address whether PD patients in this study group are aware of any impairment of their sense of smell (i.e. perceived sense of smell), or of any recovery/ fluctuation of their sense of smell. It will also establish if any PD patients in this study group have phantosmia (persistent pleasant or disgusting smell) and whether any of the above affects UPSIT scores. Finally, the profile of the UPSIT 40 odours will be presented and number/percentage of patients answering correctly will be shown.

7.1.2 Perceived Sense of Smell

As previously stated (section 1.2.2.), PD patients frequently complain of impaired sense of smell years prior to the appearance of motor impairments (Wolters et al 2000, Hawkes et al 1999, Mesholam et al 1998, Hawkes et al 1997). However, although there have been few systematic studies, self-reporting of smell dysfunction in PD patients is regarded as too unreliable as between 40% and up to 76% (Muller et al 2002, Doty et al 1988, Doty et al 1992, Hawkes and Doty 2009) of PD patients with smell deficits on formal testing have failed to notice it. This is certainly evident in the researcher's clinical working area. Although, according to Hawkes and Doty (2009) those patients who are unaware of their olfactory dysfunction, probably have mild impairment. Regardless of this, the evidence so far highlights that simply asking a patient about their sense of smell is too unreliable and it must be properly measured. Part of this chapter is designed to confirm or refute previous studies as to whether PD patients are aware of, or can with some accuracy, detect any impairment in their sense of smell and to what degree.

7.1.3 Recovery/Fluctuations of Sense of Smell

James Parkinson (1817) reported autonomic dysfunction in PD. Since then, a variety of fluctuating non-motor symptoms have been described. These include changes in blood pressure (Fereshtehnejad and Lokk 2013), dyspnea (Wang et al 2014), and drenching sweats (Sage and Mark 1995). These fluctuations are mainly associated with the "off" state but also with peak-of-dose dyskinesia (Goetz et al 1986). However, no study has mentioned either fluctuating or recovery sense of smell in PD. Seiden and Duncan (2001) suggest that if the olfactory loss fluctuates (for example, in response to a variety of physical or environmental activities), this would suggest an obstructive or conductive loss secondary to nasal inflammation, such as allergic rhinitis. On the other hand, it must be noted that less than 50% of patients with a conductive olfactory loss will report a history of fluctuation (Sieden and Duncan 2001). Part of this chapter is designed to establish whether patients perceive their sense of smell recovers or fluctuates and whether this correlates with the degree of loss of sense of smell.

7.1.4 Phantosmia

Phantosmia is the perception of a smell in the complete absence of any physical odour. The perceived odour can range from pleasant to disgusting (Sandyk 1981). Several types of phantosmia include: unirhinal (single nostril), episodic, and recurrent, where the activation of brain's GABAergic system seems to play a role in the inhibition of the unirhinal phantosmia (Levy and Henkin 2004). Although the causes of phantosmia are uncertain, it often occurs with psychological and neurological disorders such as PD (Landis et al 2008).

Phantosmia has not been extensively reported in PD and the first report appears to be briefly mentioned over 30 years ago, (Sandyk 1981). However, several more recent case reports showed that some patients have experienced phantosmia at the early stage of PD (Hirsch 2009, Singh and Schwankhaus 2009, Landis et al 2008). Indeed, Landis et al (2008) proposed phantosmia as a new premotor manifestation of PD, but interestingly the disappearance of phantosmia in both patients within Landis

et al (2008) study coincided with the development of typical PD. Also, a follow up study (Landis et al 2010) of 44 patients with idiopathic phantosmia concluded that idiopathic phantosmia improves or disappears in almost two thirds of patients after 5 years and it seems it is more likely a harmless symptom rather than a reliable predictor of early PD (Landis et al 2010). Part of this chapter is designed to establish how many PD patients report phantosmia in this study group and whether this correlates with the degree of loss of sense of smell.

7.1.5 UPSIT 40 Scores

The UPSIT 40 test was administered in a designated research room at a local hospital Trust or at the patient's own home. On average the test took only 5 minutes to complete. Part of this chapter is designed to establish which of the 40 odours are best detected by the 112 PD patients in this PhD study.

7.2 AIM

To investigate whether PD patients in this study group are aware of any impairment of their sense of smell (i.e. perceived sense of smell), or of any recovery/fluctuation of their sense of smell. Also, to investigate the prevalence of phantosmia (persistent pleasant or disgusting smell) and whether any of the above affects UPSIT scores.

7.3 OBJECTIVES

Objectives of this chapter is to establish whether;

(i) PD patients in this study group are aware of any impairment of their sense of smell (i.e. perceived sense of smell).

(ii) Any evidence of phantosmia and whether phantosmia impacts on UPSIT scores.

(iii) Patients reporting a recovery or fluctuation of their sense of smell affects UPSIT scores.

(iv) Finally, the profile of the 40 odours presented and number/percentage of patients correctly identifying each individual odour will be shown.

7.4 OUTLINE OF THE METHODS

(i) Perceived sense of smell, whether phantosmia is present and whether a patient reports a recovery in their sense of smell were all recorded on the Odour Detection in Parkinson's Disease Participants Questionnaire (see appendix 14).

(ii) The sense of smell was evaluated using the 40 items University of Pennsylvania Smell Identification Test (UPSIT) (as detailed in section 2.4.6).

7.5. RESULTS

7.5.1. Patients Self Reporting Perceived Sense of Smell

Figure 7.1 shows patient's perceived (self-reported) sense of smell. Thirty-three patients reported a normal sense of smell.

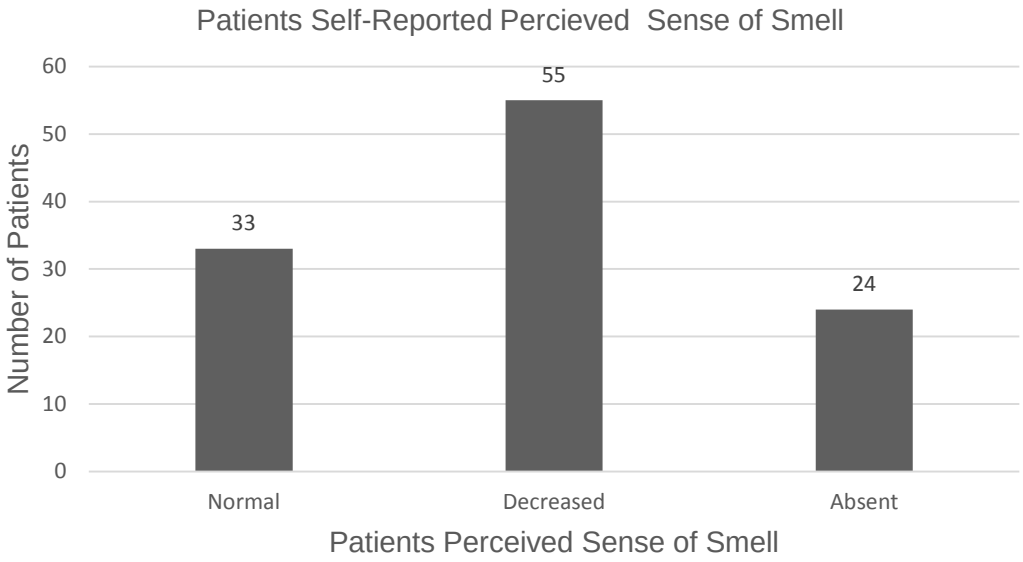


Figure 7.1: Patients Self-Reported Perceived Sense of Smell.

Figure 7.2 shows median UPSIT scores for patients self-reporting sense of smell. Interestingly, the median UPSIT for those patients self-reporting a normal sense of smell is 18 (figure 7.2) which is higher than the median of patients self-reporting an absent (median =12.5) or decreased (median=16) sense of smell.

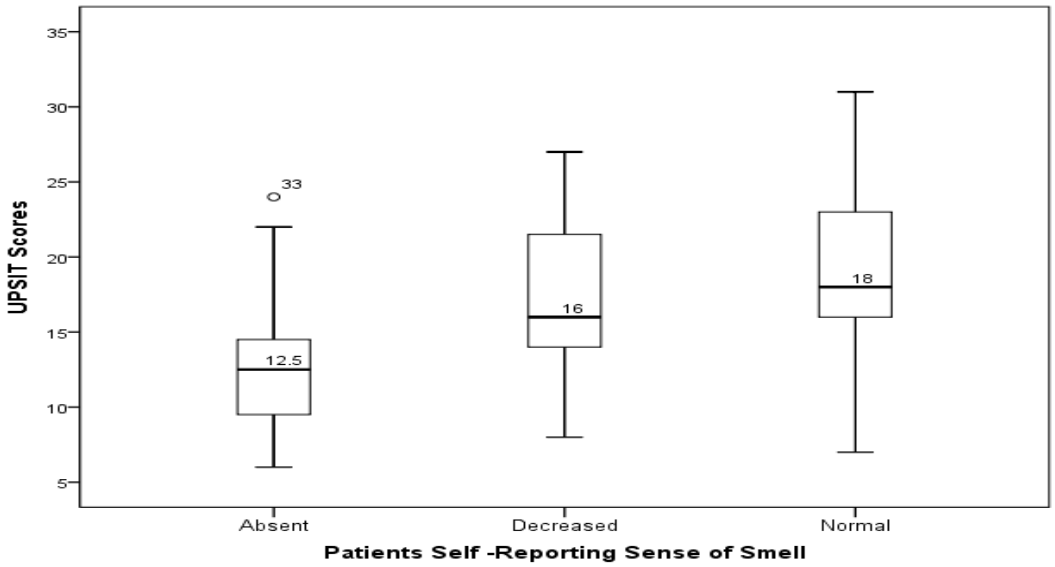


Figure 7.2: Patients Self-Reporting Sense of Smell and their UPSIT Scores.

Further analysis of patients self-reporting normal sense of smell and their individual UPSIT scores can be seen in figure 7.3 which shows that 29 out of the 33 PD patients (self-reporting a normal sense of smell) had, in fact, a severe degree of sense of smell loss (UPSIT range 7-25, mean 16) without recognising it. This highlights the need to test the sense of smell formally, using more objective means.

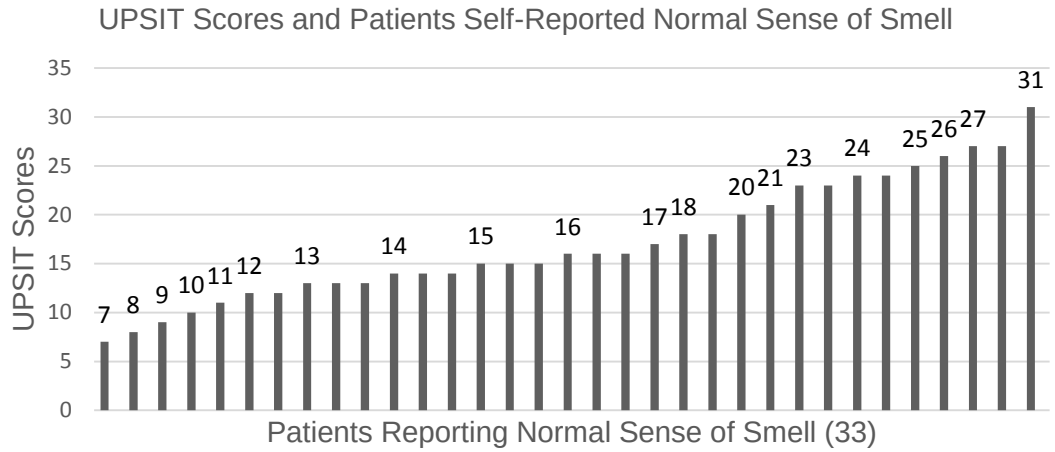


Figure 7.3: Patients Self-Reported Normal Sense of Smell and UPSIT Scores.

Further analysis of the PD patients self-reporting number of years during which they experienced either a decreased or absent sense of smell is shown in table 7.1 (which breaks down years of smell loss into 5 yearly intervals).

The tables 7.1 and 7.2 also highlights that self-reported decreased sense of smell was recognised by the patient from approximately I month to 60 years before and after diagnosis. Table 7.1 also highlights that the longest record of loss of sense of smell (60 years) in a PD patient has only been diagnosed for 5 years. Therefore, this person had sense of smell loss for 55 years prior to a diagnosis and had an UPSIT score of 18 (anosmic).
The eight PD patients reporting smell loss for a significant amount of years prior to a diagnosis of PD (26-60 years) had a mean diagnosis of PD for 7 years and all had anosmia.

Thirty-three PD patients reporting normal sense of smell had a diagnosis of PD ranging from 1-13 years and did have a slightly better UPSIT mean (20). However, a mean of 20 is still considered severe microsmia.

Table 7.1 PD Patients Reporting Years of Smell Loss, Years Since Diagnosis of PD and Number of PD Patients and UPSIT Mean in each 5 Yearly Intervals.

Smell Loss (years involved)	PD Years	Number of Patients	UPSIT (Mean)
0	1-13	33	20
0.1-5	1-14	34	16
6-10	1-12	20	17
11-15	2-12	6	14
16-20	1-19	11	16
21-25	0	0	0
26-30	3-7	5	13
31-35	0	0	0
36-40	4-6	2	13
60	5	1	18

A Spearman's correlation was run to determine the relationship between the perceived number of years since sense of smell reported as

normal/decreased or absent and the UPSIT mean. This did not reach statistical significance (r_s=0.093, n=112, p= 0.328).

Further analysis of these sub-groups per their age, gender, Hoehn and Yahr score, PD Years and whether they suffer from RBD is also shown in table 7.2. Table 7.2 highlights that age range appears comparable in each self-reported perceived sense of smell group. However, mean age is higher (73 years) in patients self-reporting perceived absent sense of smell than the other two groups. Female representation is also less in those patients reporting an absent sense of smell (20%) compared to those in the normal (39%) and decreased (42%) group.

Hoehn and Yahr stage 1 appears to be represented more in patients self-reporting perceived decreased sense of smell (25 patients). This accounts for 22% of the 112 patients enrolled in this PhD study. Fifty-five patients in total reported decreased sense of smell accounting for 49% of the whole study group.

Analysing the mean duration for disease showed that mean years is slightly higher in those patients self-reporting perceived decreased sense of smell (6 years). This is in comparison to mean age of 5 years in those patients self-reporting perceived normal or absent sense of smell.

Analysing RBD, patients self-reporting perceived decreased sense of smell appear to represent more patients meeting the criteria for a diagnosis of RBD (30 out of 55) (55%) and represents 27% of the overall PD study group. However, when grouping patients with decreased or absent sense of smell (n=79) there appears to be a slight difference in those with or without RBD (with RBD 42=53%, patients without RBD 37=47%) which possibly concludes decreased or absent perceived sense of smell does not direct the clinician to the fact the patient may have RBD. Equally of those reporting normal sense of smell (33), 20 patients did not have RBD (61%) and 13 (40%) did, further confirming that the sense of smell may not be correlated with RBD.

Further analysis using a chi-square test highlighted there is no association between RBD and perceived decreased sense of smell in this study group, (p=0.670).

Table 7.2. Demographics and Clinical Characteristics of PD Patients Self-Reporting Sense of Smell.

Variable	Normal (N=33)	Decreased (N=55)	Absent (N=24)
Self reported sense of smell (before or after a diagnosis of PD).	-	1 month-60 years	1-40 years
Years involved	-	10 years	13 years
Mean duration	-	7 years	7 years
Median duration	29%	49%	22%
Overall percentage of patients in this study			
Gender			
Males	(N=20) (18%)	(N=32) (28%)	(N=20) (18%)
Females	(N=13) (11%)	(N=23) (21%)	(N=4) (4%)
Age (years)			
Range	49-86	51-84	62-83
Mean	71	70	73
Median	71	70	73
IQ	7	7.5	4.5
Duration of Disease	6months-13 years	1-16 years	1-19 years
Mean	5	6	5
Median	**3**	6	4
IQ	**5**	5.5	3
Hoehn and Yahr Stage			
1	(N=14) (12.5%)	(N=26) (22%)	(N=12) (11%)
2	(N=9 (8%)	(N=16 (14%)	(N=8) (7%)
3	(N=9 (8%)	(N=12) (11%)	(N=4) (4%)
4	(N=1) (.8%)	(N=1) (.8%)	(N=0)
RBD			
No	(N=20)	(N=25)	(N=12)
Yes	(N=13)	(N=30)	(N=12)

Data are presented on means, medians, IQ ranges.

7.5.2. Patients Reporting Phantosmia (persistent pleasant or disgusting smell) and their UPSIT Scores

Figure 7.4 shows that 102 (91%) PD patients reported no phantosmia and 10 (9%) patients did. The length of time since diagnosis with those patients who reported phantosmia ranged from 0.5-8 years with a mean of 4.85 years (see table 7.3); their median UPSIT score is 19.5, with a range of 13-25 (see figure 7.5). The length of time involved in PD patients reporting phantosmia ranged from 1-20 years with a mean of 5.25 years. The median UPSIT score of 102 patients reporting no phantosmia is 16, with a range of 6-31 (see figure 7.5). Initial analysis suggests that patients with phantosmia have a higher median UPSIT score and generally higher overall range of UPSIT scores, compared to those patients reporting no phantosmia. However, a Mann-Whitney U test was performed which did not reach statistical significance (P=0.095).

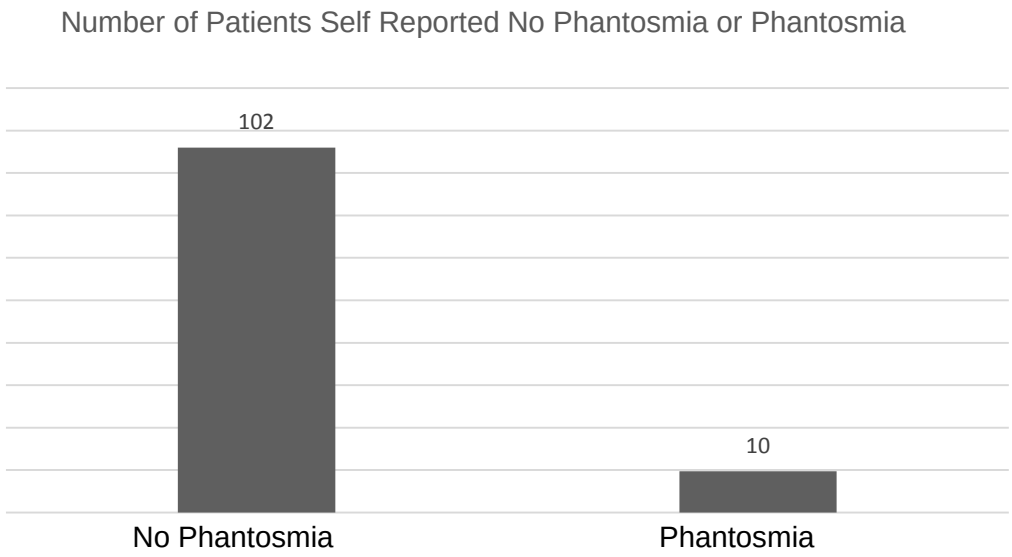


Figure 7.4: Number of Patients Self-Reporting No Phantosmia or Phantosmia.

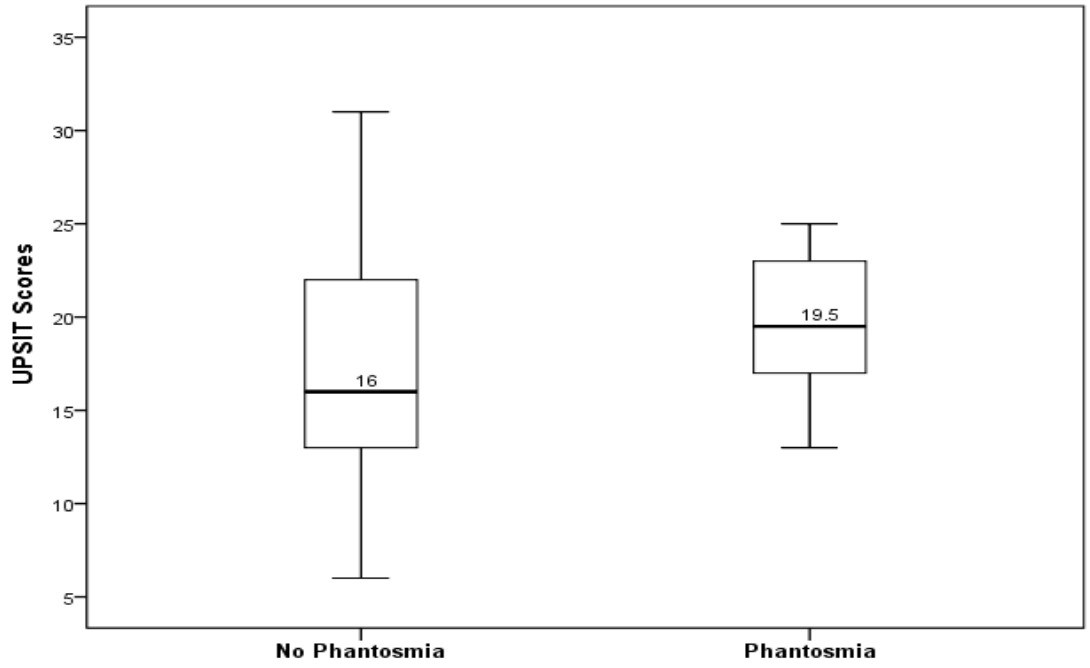


Figure 7.5: Patients Reporting No Phantosmia or Phantosmia and their UPSIT Scores.

Table 7.3 PD Patients Phantosmia and the Year's Prior to or Post Diagnosis of PD

PD Years	Years since Phantosmia noted
5	5
8	8
7	1
3	1
7	20
1	5
0.5	2
6	4
4	1.5
7	5

7.5.3 Patients Reporting Recovery of their Sense of Smell and their UPSIT Scores

Eighty-three patients (74%) self-reported their sense of smell did not recover and 29 patients (26%) reported it did. Initial analysis suggests that patients self-reporting, that their sense of smell recovers, do not have increased sense of smell when tested using UPSIT. The median UPSIT score is 16 in both groups (see figure 7.6). A Mann-Whitney U test was conducted which did not reach statistical significance (P=0.973).

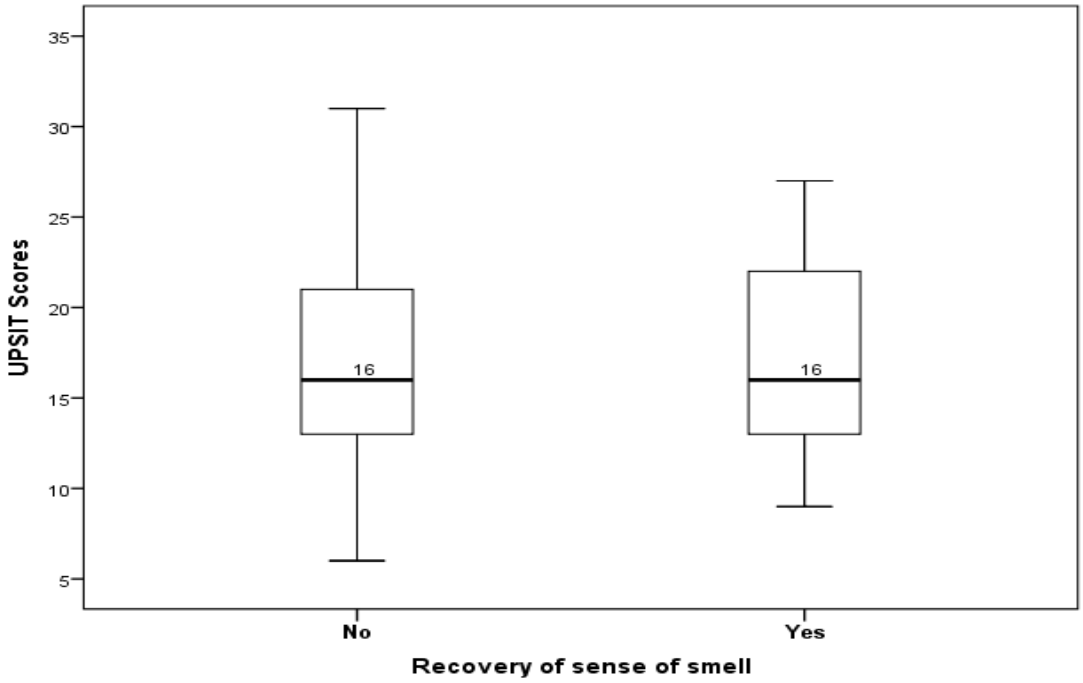


Figure 7.6: Patients Reporting Recovery of their Sense of Smell or not and Their UPSIT Scores.

7.5.4 Individual Odours Presented and Number/Percentage of Patients Identifying Them

Table 7.4 shows the odour presented, the number of patients who correctly identified the individual odour and the overall percentage. As it can be seen, onion (71%) and leather (65%) were the two odours PD patients could identify the most and lemon (13%) and root beer (21%) were the two odours PD patients had difficulty identifying the most.

Table 7.4: Correct Odour Presented in UPSIT 40 and Number/Percentage of Patients Answering Correctly.

Correct odour presented	Number of patients who answered correctly.	Percentage of patients who answered correctly.
Pizza	27	24%
Bubble gum	45	40%
Menthol	68	61%
Cherry	46	41%
Motor oil	47	42%
Mint	45	40%
Banana	40	36%
Clove	56	50%
Leather	73	65%
Coconut	51	46%
Onion	80	71%
Fruit punch	32	29%
Liquorice	36	32%
Cheddar cheese	40	36%
Cinnamon	53	47%
Gasoline	28	25%
Strawberry	46	41%
Cedar	48	43%
Chocolate	71	63%
Gingerbread	56	50%
Lilac	60	54%
Soap	27	24%
Peach	63	56%
Root Beer	24	21%
Dill Pickle	27	24%
Pineapple	50	45%
Lime	36	32%
Orange	55	49%
Wintergreen	45	40%
Watermelon	57	51%
Paint thinner	52	46%
Grass	34	30%
Smoke	72	64%
Pine	53	47%
Grape	45	40%
Lemon	15	13%
Soap	48	43%
Natural Gas	50	45%
Rose	51	46%
Peanut	59	53%

7.6 DISCUSSION

7.6.1 Patients Self Reporting Perceived Sense of Smell

There has been an interest in analysing perceived sense of smell in PD as research suggests PD patients are unable to detect, with some clarity, their degree of smell loss (Muller et al 2002, Doty et al 1988, Doty et al 1992, Hawkes and Doty 2009). In this present study, thirty-three patients (29%) reported a normal sense of smell but on formal testing had, in fact, anosmia or severe microsmia (see figure 7.1). This is in support of previous research which highlights self-reporting of smell dysfunction are regarded as too unreliable as between 40% and up to 76% (Muller et al 2002, Doty et al 1988, Doty et al 1992, Hawkes and Doty 2009) of PD patients with smell deficits on formal testing have failed to notice it. Although, Hawkes and Doty (2009) commented that those who are unaware of their olfactory dysfunction probably have mild impairment, this study did not support this as only one out of the 33 patients had mild microsmia. However, the evidence in this PhD study and that of others (Muller et al 2002, Doty et al 1988, Doty et al 1992, Hawkes and Doty 2009) highlights that simply asking a patient about their sense of smell is unreliable and it must be properly measured.

Another important question was to discover how long this group of PD patients noticed either a decreased or absent sense of smell. This was to establish if there was a clear prodromal stage of PD, as some PD patients complain of impaired sense of smell years prior to the appearance of motor impairments (Wolters et al 2000, Hawkes et al 1999, Mesholam et al 1998, Hawkes et al 1997). Of those patients who were aware of a decreased sense of smell this ranged from I month to 60 years (see table 7.1). This is in support of previous research in that estimates of prodromal phase duration vary considerably from 2 to 50 years (Hawkes 2008). In addition, those PD patients reporting complete absent sense of smell (anosmia) ranged from 1 year to 40 years (see table 7.2). Mean duration was 7 years in both groups (see table 7.2). Most researchers agree the pre-diagnosis period probably covers 4-6 years (7 years in this study). This period fits the proposed

duration of 4.7 years from the onset of neuronal loss until the classic PD symptoms, as calculated from post mortem neuronal counts in the substantia nigra (Greffard et al 2006, Gonera et al 1997).

Further analysis of these self-reported sub-groups per their age, gender, Hoehn and Yahr stage, PD years and whether they suffer from RBD highlighted that age range appears comparable in each self-reported perceived sense of smell group (see table 7.2). Female representation appeared less in patients reporting an absent sense of smell which could support the theory that women have a better sense of smell than men (Silveria-Moriyama et al 2008, Lundstrom et al 2006 Schaal et al 2004, Dalton et al 2002, Brand and Millot 2001, Cain 1982), (as briefly described in section 1.2.7).

Hoehn and Yahr stage 1 appears to represent more in patients self-reporting perceived decreased sense of smell (25 patients). This accounts for 22% of the 112 patients enrolled in this PhD study. Fifty-five patients in total reported decreased sense of smell accounting for 49% of the whole study group (see section 4.5.2). The researcher could find no studies examining Hoehn and Yahr stage and patients self-reported smell loss.

When analysing PD duration in years and PD patients self-reporting sense of smell, it appears that mean duration of disease is slightly higher in those patients self-reporting perceived decreased sense of smell (6 years) (see table 7.1) comparable to mean duration of 5 years in those patients self-reporting perceived normal or absent sense of smell.

Analysing RBD, patients self-reporting perceived decreased sense of smell (which did not reach statistical significance (r_s=0.093, n=112, p= 0.328)). appear to represent more patients meeting the criteria for a diagnosis of RBD (27% compared to 22%) but less in normal sense of smell (39% compared to 61%), and equal to in anosmic patients (50% each) (see table 7.2). The rationale for this is difficult to establish as the researcher was unable to confirm or refute these findings in any other research papers.

7.6.2 Patients Reporting Phantosmia (persistent pleasant or disgusting smell) and their UPSIT Scores

In this PhD study 10 patients reported phantosmia (see figure 7.4, table 7.3), which equates to 9% of the study group. Phantosmia has been reported as an uncommon form of smell disturbances in a variety of conditions involving the peripheral and central olfactory system, including, head trauma, temporal lobe epilepsy and stroke (Frasnelli et al 2004 Leopold 2002). It appears from this PhD study results and available research that phantosmia is also uncommon in PD. For example; despite a detailed report of phantosmia mentioned nearly 35 years ago, (Sandyk 1981), only a small number of case reports show that some PD patients have experienced phantosmia very early during the disease (Hirsch 2009, Singh and Schwankhaus 2009, Landis and Burkhard 2008). Indeed, according to Landis and Burkhard (2008) idiopathic phantosmia, as an early sign of PD, remains probably a rather exceptional presentation, whereas most people with idiopathic phantosmia will not develop PD. Therefore, due to limited research, the prevelence of phantosmia in PD is probably rare but this may be due to lack of research in this area.

The length of time involved with those patients who reported phantosmia before or after a diagnosis of PD ranged from 1-20 years with a mean of 5.25 years overall and and an average of 6.1 years prior to a diagnosis of PD and 2.9 years post diagnosis. This neither supports nor refutes the findings of Hirsch (2009), Singh and Schwankhaus (2009) and Landis (2008) who report that some patients have experienced phantosmia very early (within the first couple of years) during the disease.

Initial analysis suggests that patients with phantosmia have a higher median UPSIT score and generally higher overall range of UPSIT scores, compared to those patients reporting no phantosmia. No study on PD, sense of smell and phantosmia could be found. However, this is consistent with the published work of Smith and Seiden (1991) (which relates to head trauma and not PD). This warrants further analysis, to exclude sample size effect, as

only 9% of patients in our study reported phantosmia. However, this appears to be the first time this has been reported in PD patients, but a more evenly distributed percentage of patients reporting phantosmia would be required to substantiate this.

7.6.3. Patients Reporting Recovery/Fluctuations of their Sense of Smell and their UPSIT Scores

Eighty-three patients (74%) self-reported their sense of smell did not return and 29 patients (26%) reported it did (see figure 7.6). Further examination of figure 7.6 suggests that patients self-reporting that their sense of smell returns do not have increased sense of smell when tested using UPSIT. Further statistical analysis by means of the Mann Whitney test showed no statistical significance (P=0.973). However, due to the small sample size (30 PD patients) and that this PhD study is a cross sectional study rather than a longitudinal study this must be interpreted with caution). Despite extensive research no papers could be found to support or refute these findings. To the best of the researcher's knowledge it appears that this is the first time this has been reported in PD patients. Although Sandyk (1999) found treatment with AC pulsed electromagnetic fields on two PD patients improves olfactory function in conjunction with recurrent episodes of yawning, the rational behind this was difficult to establish.

7.6.4. UPSIT 40 Odours Presented and Number/Percentage of Patients Answering Correctly

Table 7.3 shows that onion (71%) and leather (65%) were the two odours PD patients could identify the most and lemon (13%) and root beer (21%) were the two odours PD patients had difficulty identifying the most. Interestingly, lemon was also an odour most readily misidentified by PD patients on the UPSIT test in a much earlier study (Hawkes et al 1999).

Interestingly, most odourant's also stimulate the trigeminal nerve (Fraznelli et al 2007, Doty et al 1978). Therefore, even anosmic patients can distinguish

between odorants based on their trigeminally mediated sensitivity. However, despite this, anosmic patients show reduced trigeminal sensitivity when compared with healthy controls (Fraznelli et al 2007, Hummel et al. 2003, Walker et al 2001). This suggests that, in addition to the known mutual interactions between the olfactory and the trigeminal chemosensory systems in healthy subjects (Livermore and Hummel 2004), even the absence or presence of a functioning olfactory system influences trigeminal perception. Anatomical and functional characteristics of the underlying mechanisms are largely unknown. This study did not test patient's trigeminal impact on odours and therefore this cannot be examined.

Also, this study did not address whether certain odours are more difficult to detect in PD patients rather than controls. However, interestingly in one study banana, licorice and dill pickle could distinguish PD subjects from controls with the greatest accuracy (Bohnen et al 2007). These 3 odours also had stronger correlations with nigrostriatal dopamine denervation than the total UPSIT. Another study found that the UPSIT odours pizza and wintergreen were best able to distinguish PD patients from controls (Hawkes and Shephard 1993), while pizza, mint, and licorice were optimal in another study (Silveira-Moriyama 2005). Double et al (2003) reported that gasoline, banana, pineapple, smoke, and cinnamon were the odours most affected in Australians with PD using the 12-odour Brief Smell Identification Test (BSIT) Daum et al (2000) using the 12-odour Sniffin' Sticks test reported that licorice, followed by aniseed, pineapple, apple, turpentine, and banana, best separated PD patients from controls.

This seems to highlight that olfactory impairment in PD is not confined to a subset of odours and therefore, at this present time, there is no convincing evidence for the concept of selective hyposmia in PD (Doty et al 1988, Boesveldt et al 1984).

7.7 SUMMARY

The most significant findings from this chapter are;

- PD patients need to be formally tested to establish their loss of sense of smell.
- Self-reported decreased sense of smell was recognised by the patients from approximately one month to sixty years pre-and post diagnosis.
- The mean self-reported loss of sense of smell pre-diagnosis period was 7 years in this study.
- Female representation is less in those patients reporting an absent sense of smell which could support the theory that women have a better sense of smell than men, (within the limits of reliability of self-reporting).
- Decreased or absent perceived sense of smell does not suggest that the PD patient may have RBD.
- The difference in UPSIT Scores between PD patients who self-reported their sense of smell did or did not recover, did not reach statistical significance. This PhD study appears to be the first study to examine this.
- Ten (9%) of the PD patients reported phantosmia, which highlights phantosmia is uncommon in PD and that the prevalence of Phantosmia in PD is unknown.
- The difference in UPSIT scores between PD patients reporting phantosmia or not did not reach statistical significance.
- Onion and leather were the two odours PD patients could identify the most and lemon and root beer were the two odours PD patients had difficulty identifying the most.

CHAPTER 8 BIOMARKERS IN PARKINSONS DISEASE

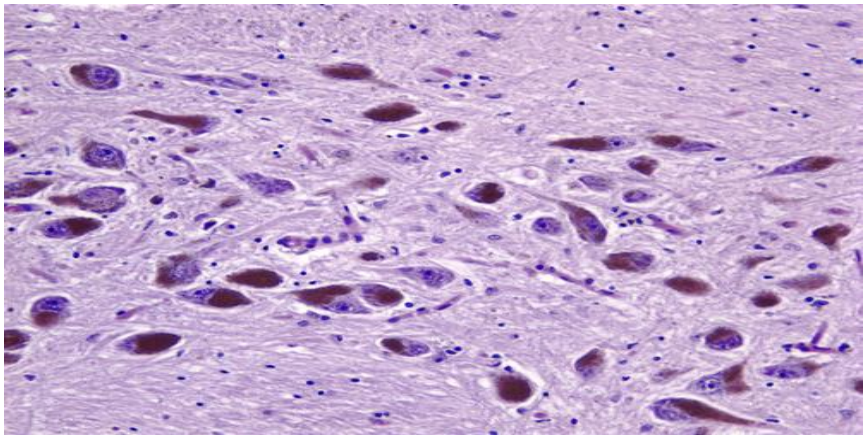
8.1. THE USE OF BIOMARKERS IN PD

Biomarkers are biological characteristics used to indicate or measure disease risk, presence of disease and disease progression (Atkinson et al 2001). It is believed that the development of reliable biomarkers for PD would accelerate advances in research on the aetiology, pathophysiology, early diagnosis, disease progression and therapeutics of PD.

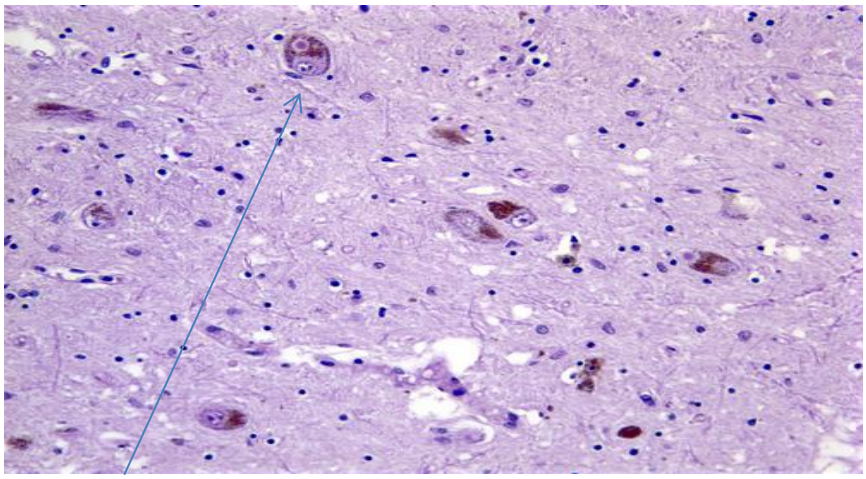
PD pathology is now known to be much more widespread and includes Lewy bodies, not only in dopamine neurons but also cholinergic neurons of the nucleus basalis of meynert, norepinephrine neurons of the locus coeruleus, and serotonin neurons of the raphe as well as neurons of the olfactory system, cerebral hemisphere, spinal cord and peripheral autonomic system (Del Tredici and Braak 2012, Jellinger 2012). Lewy bodies are insoluble intraneuronal inclusions that contain the misfolded protein alpha-synuclein in aggregated form (Dickson et al 2009, Norris et al 2004, Dickson 2001, Spillantini et al 1997). They ultimately cause neuronal degeneration and death.

Figure 8.1 shows (i) normal substantia nigra zona compacta which is involved earliest and most severely in PD (ii) substantia nigra in PD-in the same location and (iii) Lewy body inclusion (Agamanolis 2011).

(i) Normal Substantia Nigra Zona Compacta

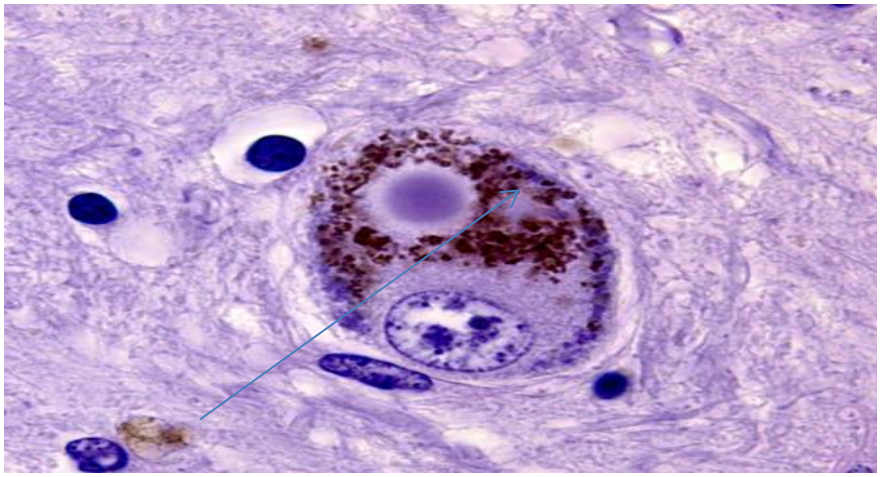


(ii) Substantia Nigra Zona Compacta in PD- same location



Lewy Body

(iii) Lewy Body inclusion



Lewy Body

Figure 8.1: Substantia Nigra and PD Pathology (source Agamanolis, 2011). Pathological staging of PD proposed initially by Braak et al (2003), observed by others (Duda et al 2007, Muller et al 2005) and recently revised by

Halliday and McCann (2010) and Beach et al (2009) has suggested that the neuropathological changes in PD may begin in extranigral structures. This includes the olfactory bulb or brainstem nuclei or even extra central nervous system structures (Halliday and McCann 2010, Beach et al 2009, Braak et al 2003). The non-dopaminergic pathology is associated with a variety of clinical features such as autonomic dysfunction, olfactory loss and sleep disorders. These clinical features are said to precede the development of classical dopaminergic pathology (Braak et al 2003). This has led to research targeting these areas as possible biomarkers (Del Tredici and Braak 2012, Jellinger 2012). Figure 8.2 highlights the stylized representation of the Braak et al (2003) staging for Parkinson's disease.

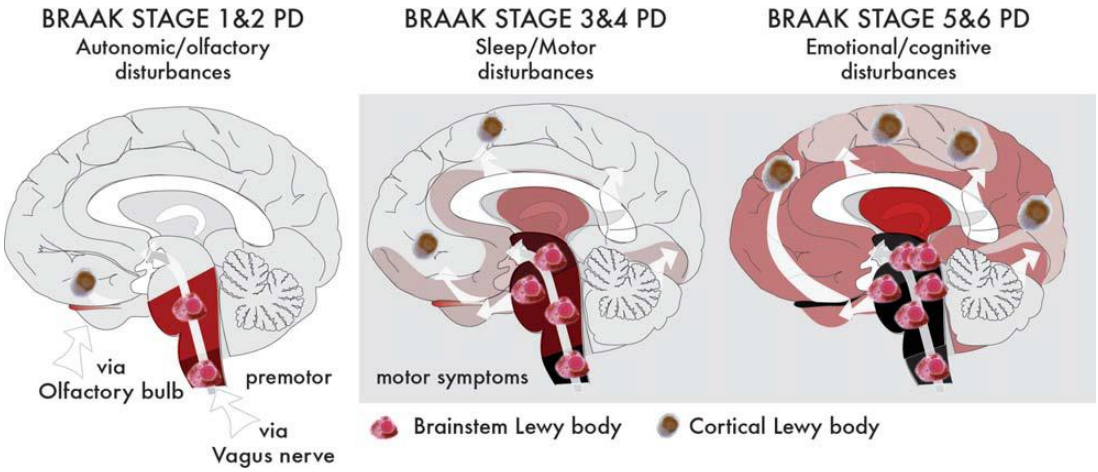


Figure 8.2: Stylized Representation of the Staging for Parkinson's Disease (with permission from Braak et al (2003).

Braak et al (2003) through this neuropathological staging system suggests a characteristic spread of Lewy body pathology as the features of PD evolve. The initial sites are in the medulla oblongata and olfactory bulb with later infiltration of Lewy pathology, and finally in the cortical regions.

Although there are clearly deviations from this design (Jellinger 2009, Halliday et al 2008, Zaccai et al 2008) and reasonable debate around Braak et al (2003) staging (Lim et al 2009, Lees 2009, Burke et al 2008, Kalaitzakis et al 2008, Dickson et al 2008, Parkkinen et al 2008, Attems and Jellinger

2008), predictable development of pathology does occur in many patients. It would therefore be reasonable to propose that clinical features associated with different brain regions would also develop in an orderly fashion. If this was the case in PD, understanding the order of onset of clinical and observable physiological features could guide screening strategies for pre-motor PD.

There are several potential biomarkers which can aid diagnosis and can be used as a biomarker for PD. For example,

1. Non-motor features of PD (such as olfactory deficits, constipation, rapid eye movement sleep behaviour disorder (RBD) (Chaudhuri and Naidu 2008) as well as excessive daytime sleepiness (Gao et al 2011).

2. The most widely used test is neuroimaging using DAT SPECT and [18F]-fluorodopa PET scans (Piccini et al 1999, Marek et al 1996, Holthoff et al 1994) which assesses the integrity of the nigrostriatal system with ligands specific for dopamine (DA) metabolism or transport.

3. Other examples of biochemical biomarkers include measuring alpha-synuclein levels in blood or spinal fluid (El Agnaf et al 2006, Abdi et al 2006), evidence of cardiac sympathetic denervation demonstrated by metaiodobenzylguanidine (MIBG) SPECT imaging of postganglionic sympathetic neurons (Fujishiro et al 2008, Orimo et al 2008, Courbon et al 2003, Braune et al 1999, Braune et al 1998, Yoshita 1998) and alpha-synuclein accumulation in colonic neurons following colonic biopsy (Shannon et al 2012, Lebouvier et al 2010).

4. Genetic biomarkers that confer a considerable risk of developing PD in the future (Healy et al 2008, Adams et al 2005, Lucking et al 2000, Polymeropoulos et al 1997) such as testing for mutations in the Parkin and LRRK2 genes are now commercially available.

8.2 PARKINSONS DISEASE STAGES

Current research appears to have divided the natural history of PD into stages based on the presence of clinical, physiological, or risk markers of disease and a conceptual model known as the 'Parkinson's At-Risk Syndrome' (PARS) pyramid has been devised which describes a hierarchical classification pyramid for patients who do not yet have clinical PD (Siderowf and Stern 2006, Stern 2004). See Figure 8.3.

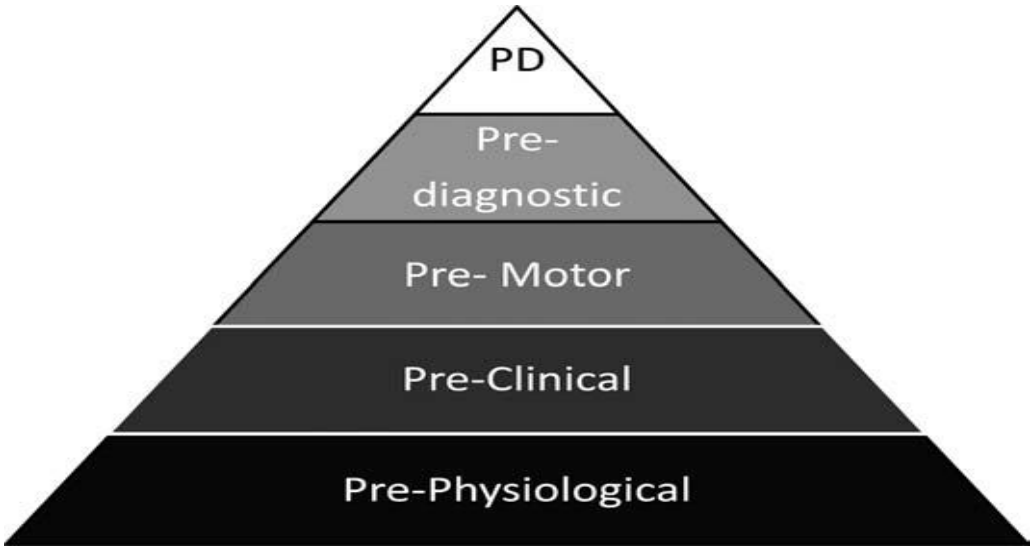


Figure 8.3: The PARS Pyramid**.** (With permission from Stern 2004).

In this conceptual model, there are 4 stages that precede clinically manifest PD: pre-physiological, pre-clinical, pre-motor and pre-diagnostic.

8.2.1. Pre-Diagnostic Phase

At the pre-diagnostic phase, patients have subtle parkinsonian features which may represent very early Parkinson's disease, but these features can be seen, to a certain degree, in normal ageing as well (Louis and Bennett 2007). There is a potential role for imaging in the pre-diagnostic stage of PD, using dopamine transporter (DAT), single-photon emission computerized tomography (SPECT) imaging and glucose metabolism positron emission tomography (PET). (see appendix 24)

Appendix 24 highlights potential imaging biomarkers which are based on preliminary data in PD patients. However, these do not serve as a stand-alone definitive diagnosis as dopamine deficiency can occur in other diseases (Ravina et al 2005). It is also worth highlighting that not all patients who meet the criteria for PD at this stage go on to develop Parkinson's disease. This is evident in clinical practice and recognised by others (Stern et al 2012).

8.2.2. Pre-Motor Phase

There is a developing consensus on the clinical features that make up the pre-motor phase of PD. Although these pre-motor features are nonspecific with limited sensitivity/specificity for their clinical utility, it appears that pre-motor biomarkers can be identified based on the known non-motor features of PD (such as olfactory deficits, constipation, rapid eye movement sleep behaviour disorder (Chaudhuri and Naidu 2008) as well as excessive daytime sleepiness (Gao et al 2011). These are discussed below.

8.2.3. Pre-Clinical Phase

Pre-clinical PD refers to physiological changes that can be detected using biomarker techniques in the absence of any clinical features. The most widely used test is neuroimaging using DAT SPECT and [18F]-fluorodopa PET scans (Piccini et al 1999, Marek et al 1996, Holthoff et al 1994) which assesses the integrity of the nigrostriatal system with ligands specific for dopamine (DA) metabolism or transport.

The feasibility of neuroimaging with DATSPECT, [18F] dopa PET, [11C] dihydrotetrabenazine PET, and [18F] fluorodeoxyglucose PET to monitoring disease progression in PD has been extensively discussed (Ravina et al 2005, Brooks et al 2003, Marek et al 2003, Brooks 2003, Morrish 2003). However, it is not within the scope of this thesis to discuss these techniques and equipment.

Appendix 25 shows a range of biomarkers highlighted in the literature for PD. However, all these biomarkers, as well as genetic testing, raises important ethical, professional and financial issues and concerns about the effects of such screening on the well-being of individual persons and groups and the ways in which it could harm people. For example, to deny them access to health insurance, employment and education. In fact, people cite fear of losing insurance as a major reason to avoid genetic testing (Lapham et al 1996).

8.2.4. Pre-Physiological Phase

Finally, pre-physiological patients have no evidence suggestive of PD but possess traits, such as a genetic mutation that confer a high risk of developing PD in the future (Healy et al 2008, Adams et al 2005, Lucking et al 2000, Polymeropoulos et al 1997). Genetic testing for mutations in the Parkin and LRRK2 genes is now commercially available. These gene tests have the potential to make the diagnosis of preclinical PD at the time of birth because they identify a lifelong trait rather than an evolving pathological state. The risk imparted by genetic factors varies depending on the gene involved. (See appendix 26).

Healy et al (2008) suggest, over all, the two strongest risk factors for PD are having a family member who has a known genetic mutation and having a diagnosis of idiopathic rapid eye movement behaviour disorder .

8.3 IMPLICATIONS OF THE FINDINGS OF THIS PhD STUDY ON THE USE OF BIOMARKERS IN PD

This study highlights that loss of sense of smell is common and profound in PD patients. Testing for sense of smell is thus considered as a candidate biomarker for PD because of its high prevalence in PD patients. This study also highlights that loss of sense of smell precedes the motor features of PD by a mean of 7 years and therefore testing sense of smell could be a useful biomarker to predict PD.

The Odour identification testing using UPSIT 40 is the gold standard of smell identification tests for its reliability (reliability = 94%) (Doty et al 1989). However, the relatively low specificity (83.5%) (Silveira-Moriyama et al 2008) discovered during the literature review limits the diagnostic application of loss of sense of smell because loss of sense of smell exists not only in PD, but also in other neurological diseases (Silveria-Moriyama et al 2010) as well as other medical conditions (Rombaux et al 2012, Jafek et al 1990, Douek et al 1975) (see appendix 20) and related to medications (Doty et al 2008, Seiberling and Conley 2004, Schiffman and Graham 2000) (see appendix 21).

However, this study does highlight that once loss of sense of smell has developed it might help distinguish patients with idiopathic PD from other parkinsonian syndromes (Doty *et al*., 1993; Hawkes, 2003) as it was discovered that the only PD patient to have mild microsmia was later diagnosed with PSP. However, although loss of sense of smell has the potential to distinguish PD from other parkinsonian syndromes, it is not being used as a formal testing guideline because there are not enough large-scale studies to show that it is accurate enough and even if this was the case, from the patient's perspective there is no known treatment to improve the sense of smell. Although, it could indirectly improve mortality rates by raising awareness of the profound loss of sense of smell in PD patients and the dangers that might face that person which could in turn reduce mortality rates caused by accidental food poisoning or fire.

In conclusion by combining sense of smell testing with other non-motor symptoms in PD such as autonomic dysfunction, depression, visual symptoms, and RBD, the specificity of loss of sense of smell as a biomarker for PD may be enhanced (Berg 2012). Currently, a large-scale multicentre prospective longitudinal epidemiological and biomarker study of PD is underway looking specifically at the use of biomarkers in PD (Tracking Parkinson's ProBand Study) (Grosset et al 2013). It is the world's largest ever in-depth study of people with PD. This study may help to establish an effective screening protocol for the early diagnosis of PD at the population level.

CHAPTER 9
Conclusion

9.1 THE BURDEN OF PARKINSONS DISEASE

Approximately 127,000 people in the UK have been diagnosed with PD in 2009 (Parkinson's UK 2009) with a diagnosed projected prevalence of 162,000 in 2020 (Parkinson's prevalence in the UK 2012). Such projections give impetus to the need for innovative early diagnosis and new treatments to prevent, delay onset, or alleviate symptoms of PD and other similar diseases (Kowal et al 2013). However, a lack of treatment options for changing the trajectory of disease progression, in combination with an increasing elderly population, indicate a rising economic burden.

The burden of illness associated with PD is related not only to the disease itself, but also to the progressive disability that patients experience as their disease advances. Impairments in motor function cause problems with mobility and interfere with activities of daily living. Problems with balance and gait can lead to falls and injuries, and the inability to perform everyday tasks. Non-motor complications also increase over time and dementia, depression and other neuropsychiatric disorders are commonly reported comorbidities (Korczyn 2001, Huse et al 2005, Guttman et al 2003). Currently, over 500 people with a diagnosis of PD are registered on the PD local Trust database for which the researcher has shared responsibility for alongside the local consultant physician. These patients have complex and progressive needs. Home visits are often required for the more advanced cases and are costly in terms of time and expenses incurred. Also, despite having reasonable rehabilitation facilities, such as a local day hospital and a dedicated neurology physiotherapist, demand far outweighs the capacity of these services.

However, most services focus on motor symptoms of PD and the non-motor symptoms of PD have received little attention in clinical settings, particularly

when planning care, even though they can lead to greater disability, restrict the patient's independence, limit social and recreational activities and lead to increased reliance on carers and the healthcare system (Lohle et al 2009, Wolters 2009, Global Parkinson's Disease Survey Steering Committee 2002, Whetten-Goldstein et al 1997).

With increases in life expectancy, finding ways of controlling the costs associated with PD is a major societal challenge. It has been shown that costs increase as a patient's condition becomes more severe, so slowing down PD progression is a major unmet need.

In this present study, olfactory loss, on formal testing, was the most prevalent non-motor symptom seen in PD patients (100%). Indeed, a recent study by Politis et al (2010) found that olfactory loss belongs to the top-five most prevalent motor and non-motor symptoms in early stage PD patients that have affected their quality of life. Only pain is referred to as a more prevalent troublesome non-motor problem in their study. Therefore, if it can be established that the loss of sense of smell correlates with any of the motor or non-motor symptoms, the potential benefits to PD patients will include a better understanding of the natural history of one of the non-motor features of PD, namely the sense of smell.

Depending on the clinical features associated with the sense of smell, health care workers, particularly nurses, are in an excellent position to view PD patients holistically and interface with the specific disciplines, for example, physiotherapists, occupational therapists, speech and language therapists and dietitians, which may be needed over the disease course. Nurses are also in an ideal position to monitor responses to medication and symptoms that arise such as motor fluctuations, constipation and speech problems (van Laar 2003, Fahn and Parkinson's Study Group 2005). Such evaluation skills, along with provision of appropriate therapy, are critical in minimizing the development of complications of PD and preventing undue loss of quality of life, not only for patients, but also for caregivers as well.

9.2. RESEARCH QUESTIONS

The purpose of this study was to investigate whether patients with PD who have mild/moderate microsmia, severe microsmia or anosmia (as measured by the University of Pennsylvania Smell Identification Test (UPSIT)) were clinically different when comparing their natural history of PD in terms of motor, non-motor and quality of life symptoms. These questions were prompted as little is known about PD patients with mild to moderate microsmia and whether they are clinically distinct from those with severe microsmia or anosmia.

9.3 METHODOLOGICAL ASPECTS AND USE OF TOOLS IN THIS STUDY.

Having now completed this PhD study, the researcher considers the choice of an open cross-sectional observational study to test whether varying degrees of the sense of smell worsen alongside motor and other non-motor symptoms seen in PD to be appropriate. This is because the researcher was able to recruit a reasonable number of PD patients to study, thereby allowing the results to be generalisable It was also relatively cheap to conduct such a study which is a major concern in today's financial climate within the NHS. The researcher also felt the data collected did, in the majority of cases, answer the specific question around sense of smell. However, the researcher is keen now to re-test PD patients who presented with mild/moderate sense of smell loss (total number =9), to establish if their sense of smell loss deteriorates alongside the disease progression, as the motor domains do, to complete the one element that the researcher felt was missing from this study.

Generally, the tools and scales used for this study were easy to use, but most were very subjective and for a more robust study more formal testing would be needed for example; polysomnography to test for RBD as the researcher felt it would be difficult for a PD patient to know if they had RBD if they slept alone, even accounting for bed clothes movement. The researcher

also felt the PDQ39 required reasonable mathematical skills to complete the scoring system and was personally statistically difficult to calculate.

9.3.1 Correlation between the Demographic Features of PD Patients in the study group and their Sense of Smell.

Although there is a trend in reduction in the sense of smell as PD patients get older, which is mirrored in this study (p=0.026), the actual loss of sense of smell in this sample of PD patients is consistently reduced and in most cases profound. This indicates that loss of sense of smell seen in PD patients is unlikely to be due to simple ageing and supports Hawkes (2008) research. This obviously has implications for this group of patients and indeed the disease itself , such as quality of life issues and safety. This obviously needs careful consideration when planning care for PD patients.

The majority of PD patients in this study were males (72) but this is not surprising as males are 1.5:1 more likely to get PD than females; although, the ratio is slightly higher at 1.8:1 in this study. The reason behind this could purely be due to a convenient sample of PD patients on the local Trust database, although, the researcher doubts this is a significant source of bias, as prevalence and incidence rates agreed with the local PD population and the local Trust database. However, it could be due to the concept of age-increasing male to female ratios due to etiological changes with age in PD (Moisan et al 2016), as the mean age for this study population was 71 years. Therefore, sex-related risk/ protective factors may play a different role across the continuum of age at onset in PD (Moisan et al 2016). However, a genetic linkage study has localised a PD susceptibility gene (autosomal dominant) to the X chromosome (2q36-37), a finding that could, potentially, explain the higher incidence of PD among men (Pankratz et al 2002). Therefore, until more genome-wide association studies are preformed, it remains to be seen whether X linked factors play a role in PD and whether their effect is age dependent. Despite this, whatever the cause of increased risk of PD among men, a search for its basis may provide new evidence as to the pathology of this condition.

Females outperformed men on the UPSIT smell test which was significant (p=0.024). Many studies reports this finding regardless if they have investigated PD or not (Fusari et al 2008, Doty et al 1984, Cain 1982). Also, female representation is less in those patients reporting an absent sense of smell which could further support the theory that women have a better sense of smell than men.

Therefore, having grounds to believe gender differences exist here; this needs to be considered when recruiting PD patients into smell studies and could be why there is sometimes a variation in loss of sense of smell between studies. Although it is beyond this study, further research into gender differences and motor, non-motor and quality of life issues may produce some interesting results.

There were only four current smokers in this study sample and although mean UPSIT of present smokers is less than ex-smokers and non-smokers, results need to be interpreted with caution as there may be a sample size effect. Therefore, this finding is difficult to generalise. Also, the number of years since stopping smoking did not correlates with an improvement in sense of smell in the forty-seven ex-smokers which may suggest that smoking causes long-term irreversible effects on the sense of smell. However, due to the fact this study is an open cross-sectional observational study and not a longitudinal study this would again be difficult to justify. It would also be difficult to measure due to the profound smell loss seen in most PD patients in this study sample. However, as smokers are reported to have lower risk of developing PD and there are only 4 current smokers in this study this could support the theory that smokers have a lower risk for developing PD (Burton et al 2013, Huang et al 2010, Hawkes et al 2007, Hawkes et al 2009, Allam et al 2004). The potential mechanisms underlying this association remain debated and it is unknown whether it is truly causal or a consequence of preclinical disease (Ritz and Rhodes 2010).

Perceived ability to be aware of loss or change in ability to taste was not affected by the patient's sense of smell (p=0.111), which highlights that taste

problems do not co-exist with loss of sense of smell. However, it is worth highlighting that most PD patients cannot detect loss of sense of smell and it needs to be formally tested. This may also be true of taste which needs consideration when examining these results. Also, when examining when taste problems occurred and when PD was diagnosed, 20 out of the 30 patients reported taste loss 1-18 years (mean 9 years) before a diagnosis of PD. This finding does not support Fernando et al (2005) research who suggested that if loss or change in ability of taste does occur it is probably a late feature of PD.

Duration of PD in this study ranged from 6 months to 19 years and it was particularly interesting to discover that loss of sense of smell was present to a relatively high degree, and in some cases profound, even in initial stages of the disease process, suggesting that loss of sense of smell is or can be affected before any motor manifestations.

This study showed there was a positive correlation between loss of sense of smell and cognition during whole group analysis ($p=0.024$) and when comparing PD patients with mild impaired cognitive function or normal cognitive function ($p=0.049$). The reasons for this are not fully understood and the implications to the individual PD patients are not transparent. However, what is evident in clinical practice (and in the research) is most PD patients do go on to develop dementia. Overall, the incidence rate of dementia in patients with PD is consistently estimated at approximately 100 per 100,00 patient years, a rate almost five- to six-fold higher than controls without PD (Hobson and Meara 2004) and a cumulative incidence of dementia in PD is reported to be as high as 80 percent (Aarsland et al 2003). The prevalence rate amongst the PD patients at a local Trusts database is approximately 43%. However, most importantly, in practice, dementia is a key part of survival in PD and must be planned for in services for this condition (Buter et al 2008). However, it would be unwise to assume those patients with anosmia will eventually develop dementia from this study as this warrants further in-depth research.

9.3.2 Correlation Between Traditional (Cardinal) PD Motor Symptoms and Sense of Smell; Implications for Clinical Practice

No correlation between the motor function (as measured by the UPDRS III) score (whole group analysis) and sense of smell in PD was found in this study. However, interestingly individual domain analysis revealed that a negative correlation was significant in posture, (p=0.014) facial expression (p=0.029) and arising from a chair (p=0.045). This is an interesting finding, but the association is difficult to validate. It appears no previous studies have linked posture, facial expression or arising from a chair to loss of sense of smell and the only reasonable theory is that due to poor posture and reduced facial expression, sniff vigour might be compromised. Arising from a chair may also be linked to posture and this is often seen in clinical practice and is therefore not an unreasonable assumption. However, at this stage, the implications that directly help a PD patient is to be mindful that these motor domains may highlight a PD patient has a more profound loss of sense of smell. This however, warrants further investigation.

Also, PD patients with tremor dominant PD did not have a superior sense of smell, compared to patients with akinetic –rigid type PD. (Whole group analysis p=.920; Individual sub-group analysis p=-0.366). This mirrors previous observations by Haehner et al (2009) who tested 400 patients by means of 'Sniffin Sticks', and Ondo and Lai (2004) Who tested patients sense of smell using UPSIT 40. Although Ondo and Lai (2004) found the subgroup of tremor-dominant PD with a family history of tremor had less loss of sense of smell loss than those without a family history (p=0.0007) or those with regular PD (p=0.0350). However, the research findings of Lijima et al (2011) who tested 90 patients with PD using a 12 odour stick identification test specifically for the Japanese population noted that people with tremor dominant PD had a better sense of smell (p=0.05). The reason behind this could not be explained as tremor is still poorly understood from a pathophysiological basis and in practice PD tremor treatment is a clinical challenge. It appears only surgery (lesion or high frequency stimulation) of

discrete deep brain targets consistently provides symptomatic long-lasting alleviation. This is a procedure not often seen in practice. However, it did highlight that olfactory dysfunction in this PhD study is more prevalent than the cardinal sign of a resting tremor (approximately 70%) of PD patients (Alves et al 2008), and similar to rigidity and bradykinesia (approximately 90% and 100% respectively) (Alves et al 2008, Hawkes et al 1999. Hoehn and Yahr 1967).

The results of this study also suggest that olfactory deficits (using smell identification) in PD are unrelated to factors such as disease stage (Hoehn and Yahr) and therefore disease severity. This is supported by others using DatSPECT scans (Marek and Jennings 2009, Panzacchi et al 2008). Also, in this PhD study, the loss of sense of smell can be profound even in the initial stages of PD. This suggests therefore, that loss of sense of smell is helpful in diagnosis at pre-clinical stage; however, it is not clear if it changes with disease progression.

Finally, RBD in this study does not correlate with the degree of smell loss. This is surprising as RBD and PD are both alpha-synuclein pathologies and both loss of sense of smell and RBD are both pre-motor biomarkers of PD (Chaudhuri and Naidu 2008). Also, it is known that RBD arises in the Pons, which is stage two of Braak staging in PD (Braak et al 2003).

9.3.3 Correlation Between PD Non-Motor Symptoms and Sense of Smell; Implications for Clinical Practice

An important finding is that despite all the PD patients in this study having varying degrees of loss of sense of smell, change in ability to smell or taste was only reported by 33% of the study group on the NMS questionnaire even though on the screening questionnaire 70.5% reported a loss of sense of smell. Although it is difficult for patients to retrospectively recognise a reduction in their sense of smell, it does highlight that self-reporting of smell dysfunction is too unreliable even from one questionnaire to another in the

same study. It also re-enforces the fact that sense of smell must be formally tested.

The link between pain and its association with the sense of smell in this study does not support the work of Hara et al (2013) who found a significant correlation with smell dysfunction. What is evident in clinical practice however, is patients' rarely volunteer pain as a symptom of their PD. To establish if there is a link between pain and PD a more specific questionnaire would need to be administered rather than a general question as shown in the NMS questionnaire.

Of all the 30 non-motor questions asked dribbling of saliva during the day showed a negative correlation (r_s= -0.256) with loss of sense of smell which was statistically significant (p=0.003). The rationale as to the cause of this has been discussed in chapter 5. However, it is important to mention that drooling is a major non-motor complaint in many patients suffering from PD, 44% of patients reporting it in this study and it is not uncommon for it to be a disabling social problem for many PD patients. Drooling also increases the risk of aspiration pneumonia, skin maceration, and infection, (Meningaud et al 2006).

Whole group analysis highlighted that quality of life did not deteriorate alongside the loss of sense of smell. However, when examining the individual themes there was a negative correlation between cognition and UPSIT scores (p=0.036).

9.3.4 Additional Confounding Factors and their Impact on Sense of Smell testing in PD Patients: Implications for Clinical Practice

This study supports previous research that PD medication does not improve loss of sense of smell regardless of how long a person was diagnosed and what class of medication they were taking. This has been found in other

studies (Hsia et al 1999, Koster et al 1999, Duchamp-Viret 1997, Wilson and Sullivan 1995, Doty et al 1992).

Interestingly, correlation between duration of disease and UPSIT did not reach statistical significance (p=0.535). This is in support of previous research which also suggested that there is no correlation between disease duration and loss of sense of smell (Haehner et al 2009, Hawkes et al 1997, Doty et al 1988, Quinn et al 1987, Ward et al 1983). This is an interesting finding as other known symptoms of PD in particular motor symptoms, such as bradykinesia and rigidity, progressively worsen. Therefore, these findings may suggest that olfactory loss is not a motor symptom of PD but it is beyond the scope of this study to give this theory any justice. Also, this study did not confirm or refute whether impaired sniffing may be another motor symptom of PD.

The effects of the environment on the sense of smell did not reach statistical significance (p=0.746). This appears to have not been studied before in PD patients.

PD patients who are ambidextrous have a much higher median and mean UPSIT scores. However, due to the small sample size in the ambidextrous group (5 patients) statistical analysis was not possible.

9.3.5 Perceived Recovery or Fluctuations in Sense of Smell. Phantosmia and UPSIT 40 Odours Presented

Self-reported decreased sense of smell was recognised by the patients from approximately I month to 60 years pre-and post-diagnosis. This highlights that the loss of sense of smell is often recognised before the onset of the motor symptoms of PD as evidenced by the fact that seventy-nine PD patients correctly detected a reduced sense of smell before being formally tested.

Comparison of UPSIT scores between PD patients reporting phantosmia or not did not reach statistical significance. Equally, UPSIT scores between PD patients self-reporting their sense of smell did or did not return, did not reach statistical significance. Despite extensive research no papers could be found to support or refute these findings. However, this study demonstrates that only ten (9%) of the PD patients reported phantosmia, which confirms phantosmia as an uncommon symptom in PD.

This PhD study further highlights that most PD patients cannot smell common food substances. For example, 87% of PD patients could not smell lemon, 76% could not smell pizza and 64% could not smell cheddar cheese (see section 3.6.4 table 3.30).

Appropriate counselling with patients and their family members is important in the management of olfactory deficits. This may be particularly crucial in the elderly patient that lives alone.

9.3.6 Loss of Sense of Smell in PD and Risk and Safety Implications

There are two major risk and safety concerns particularly relevant in PD patients associated with the reduced or absent sense of smell findings in this study, these are; increased risk of hazards (such as fire) and food poisoning.

(i) Fire Risk

In this study, 36% of PD patients were unable to detect smoke and 55% of PD patients were unable to detect gas leaks (which is potentially a significant fire risk). The inability to smell smoke and therefore detect fires and the fact that people over the age of 65 (Taylor et al 2004), which most PD patients are (Rao et al 2006, Simuni 2007) puts this client group as having one of the greatest risk of being involved in a fire. Undoubtedly, when exploring older decades and fire risks this has been documented over several centuries. For example, a study of fire casualties (Hall 1997) highlighted that elderly people are involved in a disproportionate number of house fires and gas poisonings and the fire statistics of Great Britain (2012-2013), highlight the risk of dying

in a fire for elderly people (65 and over) is over twice as high as the average for all ages. Given the well-documented increase in olfactory dysfunction with increasing age, this may be a factor in the increased risk of fire-related deaths in this population. Obviously, many other factors may also apply, and further research is needed to conclusively identify a contributory role of olfactory dysfunction.

Risk is also said to be further impacted by the patient's gender, with women being at higher risk (Taylor et al 2004, Santos et al 2004). However, this is seen in the very old (80 and over) (National Statistics Online 2012-2013). This is not surprising as women tend to out-live men (National Statistics Online 2011-2013).

It is important for the nurse to educate and advise the patient with an olfactory disorder regarding safety issues (e.g. use of smoke and carbon monoxide detectors in the home). Home fire and safety visits are a free service via the fire service in the United Kingdom and fire detectors are also installed free of charge.

(ii) Food Poisoning

The findings in this PhD study highlight that most PD patients cannot detect food substances. For example, 76% of PD patients could not detect pizza and 87% of PD patients could not detect lemon (see table 7.3). This means that the nurse should teach PD patients to focus on checking visually for spoilt food, being more vigilant with regards to expiry dates on food items and being more vigilant when cooking food particularly ensuring that heat sources are off.

9.4 LIMITATIONS OF THE PRESENT PhD STUDY

There were several limitations to the present PhD study:

- Although sample size calculations have been carried out and simple statistical analysis has been conducted, the researcher believes this study does not represent the whole spectrum of PD patients because the mean age for this study group is 71 years. This is predominately due to demographics of the area (as discussed in section 3.1.2). Therefore, this study does not represent younger onset PD patients. Second, those patients with mild/moderate microsmia represent only 9% of PD patients in this study. This was due to the sub-group analysis of the UPSIT scores as suggested by Doty (2003) which ultimately led to comparing three sub-groups of unequal distribution.

- Although initial analysis of some of the variables that might affect the sense of smell suggests evidence of interesting and original findings, these may be due to a sample size effect. To address this issue, a larger percentage of patients with mild/moderate microsmia would need to be recruited into this study. This would require ethical and trust research and development approval and assessment of over 200 more Parkinson's disease patients to increase the mild/moderate group to 30 patients, if our study is to have a more even distribution.

- As an open cross-sectional study, it does not capture whether odour detection progresses alongside the natural history of PD and this warrants further longitudinal analysis to measure changes in the sense of smell over time.

- For more credibility, patients would need to have a battery of tests such as a polysomnography to confirm RBD, a full ear, nose and throat examination to exclude any other pathology which might be causing their reduced sense of smell, autonomic tests to highlight any dysfunction and further psychophysical tests to assess olfactory

function. However, it is beyond this thesis to complete these assessments from both a resource and time constraint perspective. This would also increase the burden on the patients recruited for this study and may cause significant issues with ethical and trust research approval.

- Some aspects of our study relied on self-reported data in the form of questionnaires. The researcher had to take what patients said at face value. The researcher is aware self-reported data contain potential sources of bias. For example, remembering or not remembering experiences or events that occurred at some point in the past, such as, how long they had noticed their sense of smell had been compromised or overstating or understating effects of PD on their quality of life. The researcher, on occasions, had to seek further clarity on these issues.

- With regards to literature review, access to online journal articles was denied or otherwise limited. This caused some frustration and was time consuming for the researcher. Also, some of the odours were culturally bias as the booklets used were American (root beer and dill pickle). If the PD patient volunteered that they had not smelt any odour before such as root beer the researcher explained it smelt like germolene, black liquorice or even celery. However, the researcher is further reassured in the fact that both these odours had a distinct smell unlike other odour possibilities presented on that particular page.

- The PD patients in this study were not in the 'off state' when they were examined. It could be argued that addressing and reducing any 'off periods' is more representative of a typical PD patient and therefore data collected in this present study is more realistic (particularly when examining the motor state). However, most studies on the topic lack information regarding motor symptom assessment conditions of treated patients (i.e., "on" versus "off" medication) which raises an

important methodological aspect that has somewhat been neglected by the literature, which may partially explain the variability of findings.

- Due to the small sample size of those PD patients with mild/moderate microsmia, and the concern that data presented could be due to sample size effect (rather than an original finding); in hind sight, it could be suggested that two sub-groups [which are those PD patients with anosmia (UPSIT scores 6-18) and those PD patients with varying degrees of microsmia (mild/moderate/severe) (UPSIT scores 19-31)] may have addressed this issue and added better clarity to the overall results and add better understanding of the relationship between sense of smell and the motor and non-motor symptoms of PD.

- Finally, from a practical point of view, seeking ethical approval has been mentioned in previous reports and this was particularly challenging. Also, data collection was time consuming, but keeping to a strict time-table enabled this to be done in a timely manner. The researcher has also managed to continue to stay focused on completing the study although, at times, this has been personally challenging.

9.5 IMPLICATIONS FOR PROFESSIONAL AND PERSONAL DEVELOPMENT

From a more professional nursing development perspective, so far, this study has, as well as enriching the researcher's knowledge and understanding of Parkinson's disease, the non-motor symptoms, biomarkers and clinical stages, enabled the researcher to have a greater understanding of the use of Microsoft office, including excel and sky drive and the ability to work with software such as IBM SPSS Statistics.

This study has also enabled the researcher to look more critically and analytically at other aspects of her professional role and to have the confidence to be more proactive due to increased knowledge.

9.6 SUMMARY

This study has enabled the researcher to explore how prevalent loss of sense of smell is in PD and how it might be a predictor of clinical features, in particular its association with the motor, non-motor and quality of life symptoms in PD patients.

Testing a patient's sense of smell is an easily applied assessment tool capable of evaluation during PD patient reviews. The outcomes that this study may generate will allow the application of new knowledge to practice through publicising and disseminating (raising awareness) how the sense of smell impacts on the motor, non-motor and quality of life of PD patients; the aim is to improve the overall care of the PD patient.

Therefore, the importance of assessing loss of sense of smell PD is that by determining a PD patient's sense of smell with a simple test at the outset may help to provide important information, such as; (i) the range of clinical features that are likely to be encountered in this patient, (ii) providing very important prognostic information for this person (iii) provide a supportive diagnostic tool for PD (iv) planning nursing goals and (v) highlight dangers or hazzards the individual PD patient might not be aware of and (vi) improve safety and quality of lifeThis can only help in our understanding of PD.

Potential benefits to nursing are, by raising awareness of the prevalence and implications of smell loss in PD, nurses can ensure coping mechanisms have been employed to improve safety and well-being and, where appropriate, refer to other members of the multi-disciplinary team. It may also help to provide very important prognostic information about the sense of smell in PD. This is particularly relevant to specialist nurses working with patients and their carers. This can only help in our understanding of PD. This may then support the need to review the Parkinson's Disease National Institute for

Health and Clinical Excellence Guideline (2006) on treatment and management for Parkinson's disease.

9.7 FUTURE DIRECTIONS

Olfactory loss at clinical level shows profound impairment of smell function, which means that this symptom may improve the diagnostic error rate and may need to be considered as part of the brain bank criteria. Hawkes et al (1999) pointed out that there needs to be evidence that the olfactory system is consistently and severely involved to a degree of equalling or exceeding that of the classical motor symptoms of tremor, rigidity and bradykinesia. Evidence to support this is presented in this research. However, there is a need for further research to:

- represent younger onset PD patients to cover the whole spectrum of PD symptoms which can vary according to age of onset.
- have a larger sample size of patients with mild/moderate loss of sense of smell recruited into a new study to establish whether those patients are clinically distinct.
- perform a further longitudinal study in order to measure changes in the sense of smell over time.
- establish whether PD patients are tested during the 'on' or 'off' (particularly when examining the motor state) and sense of smell.
- In hindsight, a two rather than 3 sub-groups [i.e., those with anosmia (UPSIT scores 6-18) and those with varying degrees of microsmia (mild/moderate/severe) (UPSIT scores 19-31)] would added better clarity to the overall results and add better understanding of the relationship between sense of smell and the motor and non-motor symptoms of PD.
- finally, the researcher intends to publish the results of this PhD in nursing, neurological and movement disorder journals.

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APPENDIX 1

Holland & Rees: Nursing: Evidence-Based Practice Skills

A framework for critiquing qualitative research articles

Aspect	Questions
Focus	What topic is the concern of this article? Is this an important topic? The focus here will be broader than that of quantitative research and may emphasise experience of a condition or situation.
Background	How does the researcher argue that the topic is worthwhile? How widespread or big a problem is it? Is the seriousness of the topic reinforced by the previous studies? Is there a thorough review of the literature outlining current knowledge on this topic? The background may make the qualitative approach a logical choice.
Aim	What is the statement of the aim of the data collection? This usually begins with the word 'to' and may concentrate on an exploration of a situation, e.g. 'The aim of this study is to explore the lived experience of chronic illness.
Methodology or Broad approach	Within a broad qualitative approach is it phenomenological, ethnographic, grounded theory, or broad qualitative design? Does this match the statement of the aim?
Tool of data collection	What was the method used to collect the data? Had this tool been used in previous studies of this type? A qualitative tool will not be piloted to check accuracy but may be used firstly on a small scale to give the researcher experience of its use in this situation. There may be mention of credibility where the researcher attempts to give clear details on the circumstances and environment in which data gathering took place. The descriptions of such things as individual interviews may be extensive to allow you to feel almost as though you were there. Do you feel this tool worked well or might an alternative have been more effective?
Method of data analysis and presentation	This is one of the most important steps in qualitative approach where the researcher's understanding emerges inductively from the data and their interpretation of what is going on with those involved. To make sense of large amounts of text the researcher may mention specific systems for analysing the data either in the form of computer programs such as NUDIST and NVivo, or systems designed by other qualitative analysts such as Colaizzi or Van

	Manon. There may be reference to immersion in the data where the researcher reads over and over the details of what people have said or done. Codes to categorised themes may be mentioned and illustrations of the way this was done may be presented to form an 'audit trial' to allow you to follow the way the researcher managed the data from transcript to coded themes. The data will be in the form of observed descriptions or verbal comments and statements from those involved. These may be quite powerful in their description of feelings and emotions where the researcher is attempting to provide evidence of 'credibility' so we can believe in the accuracy of the findings and the interpretation of them.
Sample	Here the numbers of participants will be low, perhaps under 10 and often not more than 20. Data collection may have stopped once 'saturation' was reached, that is, where no new categories emerged from the findings. Were there inclusion and exclusion criteria stated? Were these reasonable given the research question and the nature of the sample? Do the selection criteria limit to whom the results may apply? What method was used to select who got into the study (the sampling strategy)? Is this appropriate for this research question and approach? Does the sample suffer from any kind of bias?
Ethical considerations	Did an ethics committee (LREC, or in US an Institutional Review Board 'IRB') approve the study? Was informed consent gained and mention made of confidentiality? Could the study be said to be ethically rigorous?

APPENDIX 2

Holland & Rees: Nursing: Evidence-Based Practice Skills

A framework for critiquing quantitative research articles

Aspect	Questions
Focus	What topic is the concern of this article? Can you identify measurable 'variables' in the title or researcher's statement concerning their main interest? Is this an important topic for research?
Background	How does the researcher argue that the topic is worthwhile? How widespread or big a problem is it? Is the seriousness of the topic reinforced by the previous studies? Is there a thorough review of the literature outlining current knowledge on this topic? Are the key variables defined and an attempt made to consider how they can be measured? E.g. definitions of 'pain' or 'anxiety' and descriptions of scales frequently used to measure them.
Aim	What is the statement of the aim of the data collection? This usually begins with the word 'to', e.g. 'The aim of this study is 'to examine/determine/ establish/compare/etc'. If it is a randomised control trial there may be a hypothesis.
Methodology or Broad approach	Within a quantitative approach, is it a survey, experimental (RCT), or correlation study? Does seem suitable given the aim of the study?
Tool of data collection	What was the method used to collect the data? Had this been used in previous studies and so may be regarded as reliable or accurate? If not, was it piloted? Is there any mention of reliability or validity? Is there a rationale given for the choice of tool? Could an alternative tool have been considered?
Method of data analysis and presentation	Is the method of processing and analysing the results described in the methods section, such as statistical process through SPSS computer analysis, and are the results clearly presented in the results/findings section? Does the researcher clearly explain any statistical techniques or methods of presentation such as tables, graphs, pie charts?
Sample	On how many people, events, or things are the results based? If questionnaires were used, what was the response rate? If it was a randomised control trial, what was the dropout rate? Is either of these likely to have an impact on the results? Were there inclusion and exclusion criteria stated?

	Were these reasonable given the research question and the nature of the sample? Do they limit to whom the results may apply? What method was used to select who were included in the study (the sampling strategy)? Does the sample suffer from any kind of bias?
Ethical considerations	Did an ethics committee (LREC, or in US an Institutional Review Board 'IRB') approve the study? Was informed consent gained and mention made of confidentiality? Could the study be said to be ethically rigorous?
Main Findings	What did they find in answer to their aim? What were the large results that relate to the aim of the study?
Conclusion and Recommendations	Did they give a clear answer to their aim? If they stated a hypothesis, did they say if this was supported or rejected? Were clear recommendations made (who should do what, how, now)?
Overall strengths and limitations	What would you say were the aspects of the study they did well? What aspects were less successful? Did they acknowledge any limitations to the study?
Application to practice	How do the results relate to practice? Should any changes be considered?

APPENDIX 3

LIST OF PRESENT UK DRUGS USED TO TREAT PD

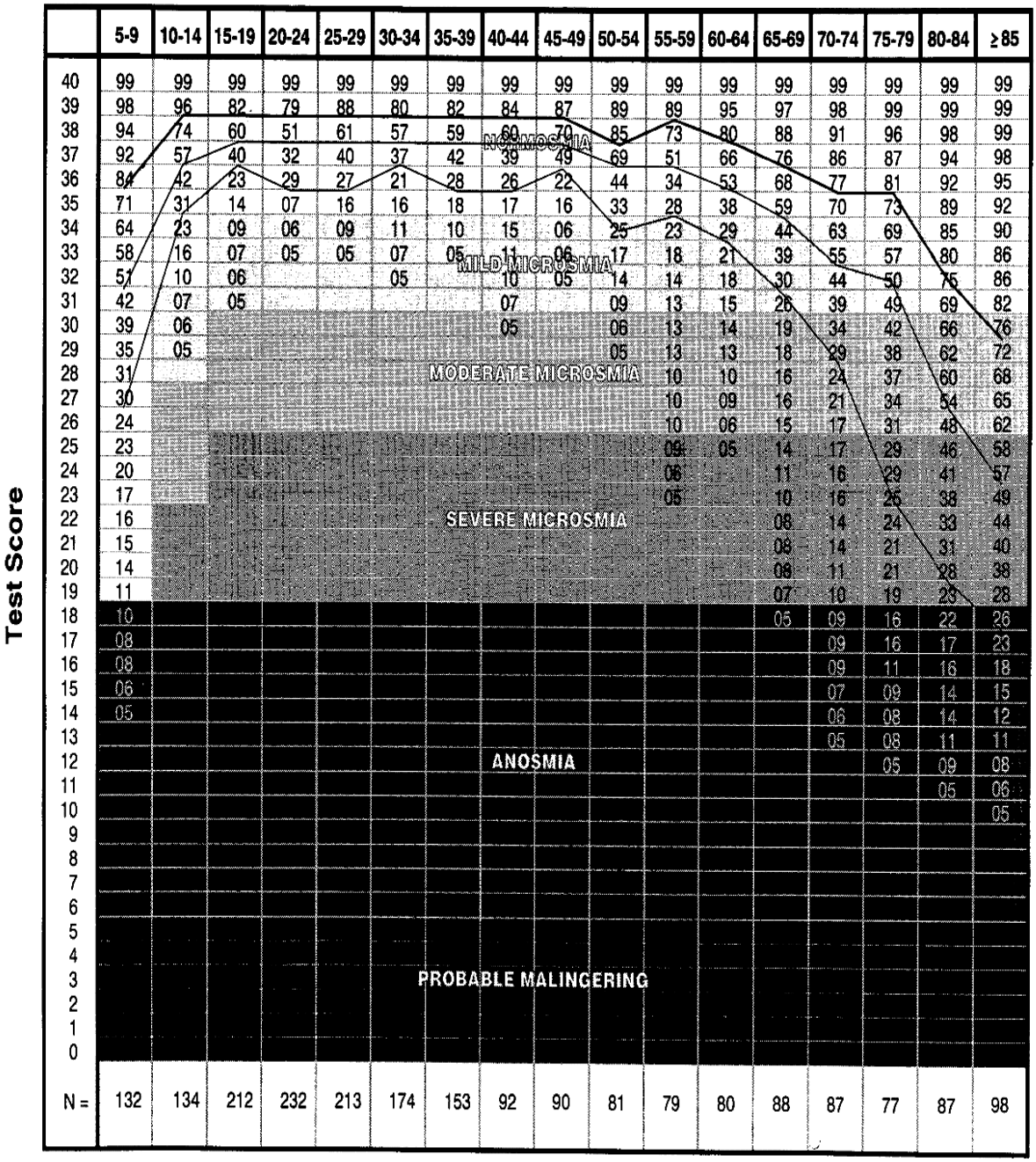
The major classes of drugs currently available for the treatment of Parkinson's disease in the UK		
Levodopa preparations	Standard release Slow release Rapid release	Levodopa/benserazide Levodopa/carbidopa Levodopa/benserazide Levodopa/carbidopa Levodopa/benserazide
Dopamine agonists	Non-ergot	Pramipexole Ropinirole Rotigotine Apomorphine
Catechol-O-methyltransferase inhibitors		Entacapone
Monoamine oxidase B inhibitors		Selegiline Rasagiline
Other	NMDA antagonist Anticholinergics	Amantadine Benzhexol Benztropine Biperiden Orphenedrine Procyclidine

Drugs for Parkinson's disease (Fung et al 2001)

APPENDIX 4

FEMALE AND MALE PERCENTILES

FEMALE NORMS: PERCENTILE VALUES



	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	≥85
40	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99	99
39	98	96	82	79	88	80	82	84	87	89	89	95	97	98	99	99	99
38	94	74	60	51	61	57	59	69	70	85	73	80	88	91	96	98	99
37	92	57	40	32	40	37	42	39	49	69	51	66	76	86	87	94	98
36	84	42	23	29	27	21	28	26	22	44	34	53	68	77	81	92	95
35	71	31	14	07	16	16	18	17	16	33	28	38	59	70	73	89	92
34	64	23	09	06	09	11	10	15	06	25	23	29	44	63	69	85	90
33	58	16	07	05	05	07	05	11	06	17	18	21	39	55	57	80	86
32	51	10	06			05		10	05	14	14	18	30	44	50	75	86
31	42	07	05					07		09	13	15	26	39	49	69	82
30	39	06						05		06	13	14	19	34	42	66	76
29	35	05								05	13	13	18	29	38	62	72
28	31										10	10	16	24	37	60	68
27	30										10	09	16	21	34	54	65
26	24										10	06	15	17	31	48	62
25	23										09	05	14	17	29	46	58
24	20										06		11	16	29	41	57
23	17										05		10	16	26	38	49
22	16												08	14	24	33	44
21	15												08	14	21	31	40
20	14												08	11	21	28	38
19	11												07	10	19	28	28
18	10												05	09	16	22	26
17	08													09	16	17	23
16	08													09	11	16	18
15	06													07	09	14	15
14	05													06	08	14	12
13														05	08	11	11
12															05	09	08
11																05	06
10																	05
9																	
8																	
7																	
6																	
5																	
4																	
3																	
2																	
1																	
0																	
N =	132	134	212	232	213	174	153	92	90	81	79	80	88	87	77	87	98

MALE NORMS: PERCENTILE VALUES

Age of Examinee

Test Score

	5-9	10-14	15-19	20-24	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74	75-79	80-84	≥85
40	99	99	89	99	99	99	99	99	99	99	99	99	99	99	99	99	99
39	98	94	77	90	89	85	87	91	90	95	93	97	97	99	99	99	99
38	94	81	59	68	73	70	64	75	70	89	82	92	93	95	98	99	99
37	93	71	44	50	54	53	50	53	58	73	70	78	83	90	95	99	99
36	90	59	35	31	37	37	36	43	49	60	56	66	71	83	87	99	95
35	83	52	26	22	23	25	27	26	31	41	42	56	64	77	74	97	95
34	80	44	17	16	15	18	19	21	22	33	33	47	54	74	65	93	89
33	76	32	11	14	10	11	12	17	15	30	27	34	44	66	53	85	86
32	69	28	08	11	07	10	09	13	11	21	23	26	44	62	44	78	84
31	63	19	06	07	05	08	06	11	10	19	23	22	41	58	35	71	81
30	59	15	05	06		07	05	08	10	18	23	21	36	52	35	65	81
29	49	12		05		05		06	07	14	19	15	31	48	34	63	75
28	45	10						06	06	14	18	15	31	42	32	63	74
27	36	05						06	05	10	18	13	27	36	31	56	68
26	34							05		08	12	13	24	34	29	50	63
25	29									08	12	13	20	30	27	47	60
24	25									08	11	13	20	25	27	46	54
23	23									06	11	13	17	23	24	43	47
22	21									05	11	11	15	23	25	40	44
21	17										07	11	10	18	23	40	44
20	17										05	11	08	16	21	34	44
19	15											11	07	14	18	31	42
18	10											11	07	13	15	28	40
17	06											09	07	13	11	25	40
16	05											05	05	10	11	24	37
15														08	10	19	32
14														08	06	18	32
13														08	05	16	28
12														06		10	25
11														05		06	21
10																05	12
9																	07
8																	05
7																	
6																	
5																	
4																	
3																	
2																	
1																	
0																	
N =	126	145	197	148	186	160	129	103	81	80	73	68	59	77	62	68	57

NORMOSMIA

MILD MICROSMIA

MODERATE MICROSMIA

SEVERE MICROSMIA

ANOSMIA

PROBABLE MALINGERING

APPENDIX 5

LIST OF SOME SUSPECTED DRUGS CAUSING PARKINSONISM

List of neuroleptic drugs available in the UK	
Generic name	**Trade name**
Amisulpride	Solian
Chlorpromazine hydrocloride	Chloractil/Largactil
Clozapine	Clozaril, Denzapine
Flupenthixol	Depixol
Fluphenazine hydrochloride	Modecate/Moditen/Motival (includes nortriptyline)
Haloperidol	Dozic/Haldol/Serenace
Methotrimeprazine/Levomepromazine	Nozinan
Olanzapine	Zyprexa
Oxypertine	Oxypertine
Pericyazine	Neulactil
Perphenazine	Fentazin, Triptafen (Perphenazine+amitriptyline)
Pimozide	Orap
Pipotiazine	Piportil
Prochlorperazine	Stemetil
Promazine hydrochloride	Promazine
Quetiapine	Seroquel
Risperidone	Risperdal
Sulpiride	Domatil/Sulpitil/Sulpor (Sulparex is discontinued)
Thioridazine	Melleril
Trifluoperazine	Stelazine
Zuclopenthixol acetate	Clopixol
Zotepine	Zoleptil

Other drugs that can cause drug-induced parkinsonism		
Generic name	**Trade name**	**Used to treat**
Amiodarone	Cordarone X	Heart problems
Cinnarizine	Stugeron	Nausea and vomiting, motion sickness, vertigo, dizziness, tinnitus, vascular disease and Raynaud's syndrome, high blood pressure, abnormal heart rhythm, angina pectoris, panic attacks, manic depression and migraine
Fluphenazine	Motival, Motipress	A combination of antidepressant and with nortriptyline antipsychotic drug
Lithium	Camcolit, Li-Liquid, Liskonum, Priadel	Depression
Methyldopa	Aldomet	High blood pressure
Metoclopramide	Maxolon	For sickness and indigestion. Also included in some medicines used migraine such as Paramax (with paracetamol) and Migramax (with aspirin)
Prochlorperazine	Stemetil	Dizziness and nausea
Tranylcypromine	Parnate	Depression

APPENDIX 6

LONE WORKERS POLICY

Points for Managers

• Make informal inspections to make sure the workplace is safe and the lone worker is working safely

• Ask yourself if you would feel safe in that situation

• Check that all equipment is properly maintained and appropriate records are kept

• Make sure all relevant risk assessments and safe working procedures are produced and readily at hand

• If hazardous substances are in use, make sure the relevant Manufacturers Safety Data Sheet(s) is/are easily available (e.g. in a laboratory) and ensure a COSHH assessment has been completed and is up to date

• Make sure that lone workers are fully aware of all of the relevant Trust guidance/policies

• Check the signing in book for out of hours to make sure that the workers are signing in and out

• Make sure that you have a reliable system for contacting the lone worker and checking that the individual is safe e.g. calling a pre-determined telephone extension at agreed times. Additionally, if a worker is using radio or mobile phone, then a prior check on reception in the area of work is essential. In areas of poor mobile phone reception, a satellite phone may be required instead

• Consider what emergency situations could arise and ensure that you have the
procedures in place to cater for them

• Talk informally with the lone workers to find out whether they have any health and/or safety concerns about working alone

Points for Staff

Out-of-Hours

• Make sure someone knows when you leave for the workplace and when you arrive e.g. on Trust site(s), patient's home etc. the location and when you anticipate leaving

• Do not do anything that you feel may put you in danger. If you are at all unsure what to do, or feel that the work requires more than one person to be done safely contact your Manager and request advice/assistance
• Report any adverse incident, including ‘no harm events’, to your Manager using the
Trust’s AIR form
• Make sure you know and follow the relevant risk assessments, safe working procedures and guidelines for the work, including those relating specifically to the lone working situation
• Make sure you know the appropriate accident and emergency procedures and that you know where the nearest telephone extension is
• If you are injured or become ill try to stay calm, remember your training and contact the emergency services
• Check any equipment you will be using to ensure that it is in safe working order
• Check the workplace on arrival to make sure that it is safe to work there. You should do this, even if you have been there before, since there may be changes [e.g. different chemicals in use, a new/additional domestic animal at a patient’s home/phone reception etc.] which alter the level of risk
• Check reception for your mobile phone or radio before starting work and regularly during it.

Visit to a home

Together with the Manager the lone worker must:
• Undertake a risk assessment of the work activity to be carried out
• Make contact with subject to arrange suitable visit time and to explain the purpose and content of the visit and answer any initial queries they may have
• Establish transport and routes to ensure there is adequate information on safe routes/parking and, if using public transport, have information on timetables etc. Be aware of any social tensions in the area to be visited
• Ensure that there is communication with the Manager e.g. mobile phone/pager
• Have a clear itinerary of the visit including appointment times and the names, addresses and contact numbers of the individual(s) being visited and

that arrangements are in place for communicating with the Manager. This must include an agreed procedure for making contact following the procedure to ensure the Manager knows the lone worker is safe.

• Become familiar with procedures for what to do in the event of an emergency

• Ensure that the Trust identification badge is shown to the patient on arrival at their home

• At the home note where the door(s) potentially allowing for a rapid exit, should this become necessary

• Leave the house if at any point if you feel uncomfortable or threatened

• When appropriate, arrange a debriefing session with the Manager following the visit to discuss if the control measures in place were adequate.

 Transport

Personal vehicle

Staff have responsibility for their own vehicle and for producing MOT, insurance and driving licence documents to the relevant manager. **Staff should:**

• Make sure the vehicle being driven is regularly serviced, tyres/oil/fuel checked and filled

• Consider access to a national breakdown service

• Plan route in advance

• Inform colleagues of destination and expected time of arrival and departure

• Carry change/phone card/mobile ‘phone/pager

• Keep possessions out of site

• Keep a map handy in case you have to stop for directions

• If returning to the vehicle after dark ensure parked in a well - lit area

• Have your key ready on returning to the vehicle

• Reverse into a parking space, ensuring easy exit from the space on your return

• ‘De-personalise’ the vehicle e.g. do not make it obvious a female drives/rides the vehicle, or you are a supporter of a particular football team etc

Car/van etc –

• Keep doors locked and windows closed wherever possible

• Do not pick up hitchhikers

• Always lock the car/van etc and keep everything in the boot

Taxis

• Avoid all unlicensed taxi cabs. In case a licensed cab is unavailable carry the number of a reputable company. Where possible book taxis in advance, do not get into a cab that you have not asked for.

Train

• Wait on the platform where it is well lit and there are plenty of people

• Stand well back from the platform edge

• Avoid compartments and try to sit with other people

• If you feel threatened or there is an incident act immediately, alert guard or driver, pull emergency alarm

APPENDIX 7

Unified Parkinson's Disease Rating Scale (UPDRS)

Ref No. [/] Date: [/ /20_]

The information you give will be treated in complete confidence.

111 MOTOR EXAMINATION

18. Speech

0 = Normal.

1 = Slight loss of expression, diction and/or volume.

2 = Monotone, slurred but understandable; moderately impaired.

3 = Marked impairment, difficult to understand.

4 = Unintelligible.

19. Facial Expression

0 = Normal.

1 = Minimal hypomimia, could be normal "Poker Face".

2 = Slight but definitely abnormal diminution of facial expression

3 = Moderate hypomimia; lips parted some of the time.

4 = Masked or fixed facies with severe or complete loss of facial expression; lips parted 1/4 inch or more.

20. Tremor at rest (head, upper and lower extremities)

0 = Absent.

1 = Slight and infrequently present.

2 = Mild in amplitude and persistent. Or moderate in amplitude, but only intermittently present.

3 = Moderate in amplitude and present most of the time.

4 = Marked in amplitude and present most of the time.

21. Action or Postural Tremor of hands

0 = Absent.

1 = Slight; present with action.

2 = Moderate in amplitude, present with action.

3 = Moderate in amplitude with posture holding as well as action.

4 = Marked in amplitude; interferes with feeding.

22. Rigidity (Judged on passive movement of major joints with patient relaxed in sitting position. Cogwheeling to be ignored.)

0 = Absent.

1 = Slight or detectable only when activated by mirror or other movements.

2 = Mild to moderate.

3 = Marked, but full range of motion easily achieved.

4 = Severe, range of motion achieved with difficulty.

23. Finger Taps (Patient taps thumb with index finger in rapid succession.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

24. Hand Movements (Patient opens and closes hands in rapid succession.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

25. Rapid Alternating Movements of Hands (Pronation-supination movements of hands, vertically and horizontally, with as large an amplitude as possible, both hands simultaneously.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests

in ongoing movement.

4 = Can barely perform the task.

26. Leg Agility (Patient taps heel on the ground in rapid succession picking up entire leg. Amplitude should be at least 3 inches.)

0 = Normal.

1 = Mild slowing and/or reduction in amplitude.

2 = Moderately impaired. Definite and early fatiguing. May have occasional arrests in movement.

3 = Severely impaired. Frequent hesitation in initiating movements or arrests in ongoing movement.

4 = Can barely perform the task.

27. Arising from Chair (Patient attempts to rise from a straight-backed chair, with arms folded across chest.)

0 = Normal.

1 = Slow; or may need more than one attempt.

2 = Pushes self up from arms of seat.

3 = Tends to fall back and may have to try more than one time, but can get up without help.

4 = Unable to arise without help.

28. Posture

0 = Normal erect.

1 = Not quite erect, slightly stooped posture; could be normal for older person.

2 = Moderately stooped posture, definitely abnormal; can be slightly leaning to one side.

3 = Severely stooped posture with kyphosis; can be moderately leaning to one side.

4 = Marked flexion with extreme abnormality of posture.

29. Gait

0 = Normal.

1 = Walks slowly, may shuffle with short steps, but no festination (hastening steps) or propulsion.

2 = Walks with difficulty, but requires little or no assistance; may have some festination, short steps, or propulsion.

3 = Severe disturbance of gait, requiring assistance.

4 = Cannot walk at all, even with assistance.

30. Postural Stability (Response to sudden, strong posterior displacement produced by pull on shoulders while patient erect with eyes open and feet slightly apart. Patient is prepared.)

0 = Normal.

1 = Retropulsion, but recovers unaided.

2 = Absence of postural response; would fall if not caught by examiner.

3 = Very unstable, tends to lose balance spontaneously.

4 = Unable to stand without assistance.

31. Body Bradykinesia and Hypokinesia (Combining slowness, hesitancy, decreased arm swing, small amplitude, and poverty of movement in general.)

0 = None.

1 = Minimal slowness, giving movement a deliberate character; could be normal for some persons. Possibly reduced amplitude.

2 = Mild degree of slowness and poverty of movement which is definitely abnormal. Alternatively, some reduced amplitude.

3 = Moderate slowness, poverty or small amplitude of movement.

4 = Marked slowness, poverty or small amplitude of movement.

APPENDIX 8

Date 8th January 2013. Version 2

Non-motor symptoms questionnaire

Reference..... Date: .....

Have you experienced any of the following in the last month?

All the information you supply through this form will be treated with confidence and will only be used for the purpose for which it has been collected. Information supplied will be used for monitoring purposes. Your personal data will be processed and held in accordance with the Data Protection Act 1998. Developed and validated by the International PDnon-motorGroup.

Non-movement problems in Parkinson's

The movement symptoms of Parkinson's are well known. However, other problems can sometimes occur as part of the condition or its treatment. It is important that the doctor knows about these, particularly if they are troublesome for you.

A range of problems is listed below. Please tick the box 'Yes' if you have experienced it during the past month. The doctor or nurse may ask you some questions to help decide. If you have not experienced the problem in the past month tick the 'No' box. You should answer 'No' even if you have had the problem in the past but not in the past month.

	Yes	No
1 Dribbling of saliva during the daytime.	☐	☐
2 Loss or change in your ability to taste or smell.	☐	☐
3 Difficulty swallowing food or drink or problems with choking.	☐	☐
4 Vomiting or feelings of sickness (nausea).	☐	☐
5 Constipation (less than three bowel movements a week) or having to strain to pass a stool	☐	☐
6 Bowel (faecal) incontinence.	☐	☐

	Yes	No
7 Feeling that your bowel emptying is incomplete after having been to the toilet.	☐	☐
8 A sense of urgency to pass urine makes you rush to the toilet.	☐	☐
9 Getting up regularly at night to pass urine.	☐	☐
10 Unexplained pains (not due to known conditions such as arthritis).	☐	☐
11 Unexplained change in weight (not due to change in diet).	☐	☐
12 Problems remembering things that have happened recently or forgetting to do things.	☐	☐
13 Loss of interest in what is happening around you or in doing things.	☐	☐

	Yes	No
14 Seeing or hearing things that you know or are told are not there.	☐	☐
15 Difficulty concentrating or staying focused.	☐	☐
16 Feeling sad, ‘low’ or ‘blue’.	☐	☐
17 Feeling anxious, frightened or panicky.	☐	☐
18 Feeling less interested in sex or more interested in sex.	☐	☐
19 Finding it difficult to have sex when you try.	☐	☐
20 Feeling light-headed, dizzy or weak standing from sitting or lying.	☐	☐
21 Falling.	☐	☐
22 Finding it difficult to stay awake during activities such as working, driving or eating.	☐	☐

	Yes	No
23 Difficulty getting to sleep at night or staying asleep at night.	☐	☐
24 Intense, vivid or frightening dreams.	☐	☐
25 Talking or moving about in your sleep, as if you are 'acting out' a dream.	☐	☐
26 Unpleasant sensations in your legs at night or while resting, and a feeling that you need to move.	☐	☐
27 Swelling of the legs.	☐	☐
28 Excessive sweating.	☐	☐
29 Double vision.	☐	☐
30 Believing things are happening to you that other people say are not.	☐	☐

Chaudhuri KR, Martinez-Martin P, Schapira AHV, Stocchi F,
Sethi K, Odin P et al (2006) 'An international multicentre pilot study of the first comprehensive self-completednon-motorsymptoms questionnaire for Parkinson's disease: The NMSQuest study' *Mov Disord*; 21(7):916-923.

All the information you supply through this form will be treated with confidence and will only be used for the purpose for which it has been collected. Information supplied will be used for monitoring purposes. Your personal data will be processed and held in accordance with the Data Protection Act 1998. Developed and validated by the International PDnon-motorGroup.

APPENDIX 9

Ref No. / Date: / /20_

The information you give will be treated in complete confidence.

HEALTH SERVICES RESEARCH UNIT

DEPARTMENT OF PUBLIC HEALTH AND PRIMARY CARE

UNIVERSITY OF OXFORD

PDQ-39

Parkinson's Disease Quality of Life Questionnaire

DUE TO HAVING PARKINSON'S DISEASE, how often have you experienced the following, during the last month? *Please tick **one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
1.	**Had difficulty doing the leisure activities which you would like to do?**	☐	☐	☐	☐	☐
2.	**Had difficulty looking after your home, e.g. DIY, housework, cooking?**	☐	☐	☐	☐	☐
3.	**Had difficulty carrying bags of shopping?**	☐	☐	☐	☐	☐
4.	**Had problems walking half a mile?**	☐	☐	☐	☐	☐
5.	**Had problems walking 100 yards?**	☐	☐	☐	☐	☐
6.	**Had problems getting around the house as easily as you would like?**	☐	☐	☐	☐	☐
7.	**Had difficulty getting around in public?**	☐	☐	☐	☐	☐
8.	**Needed someone else to accompany you when you went out?**	☐	☐	☐	☐	☐
9.	**Felt frightened or worried about falling over in public?**	☐	☐	☐	☐	☐

Please check that you have ticked one box for each question before going on to the next page

Due to having Parkinson's disease, how often <u>during the last month</u> have you ….

*Please tick **one box** for each question*

	Never	Occasionally	Sometimes	Often	Always
10. Been confined to the house more than you would like?	☐	☐	☐	☐	☐
11. Had difficulty washing yourself?	☐	☐	☐	☐	☐
12. Had difficulty dressing yourself?	☐	☐	☐	☐	☐
13. Had problems doing up buttons or shoe laces?	☐	☐	☐	☐	☐
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?	☐	☐	☐	☐	☐

Please check that you have ticked <u>one box for each question</u> before going on to the next page

Due to having Parkinson's disease, how often during the last month have you ….

*Please tick **one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
20.	**Felt angry or bitter?**	☐	☐	☐	☐	☐
21.	**Felt anxious?**	☐	☐	☐	☐	☐
22.	**Felt worried about your future?**	☐	☐	☐	☐	☐
23.	**Felt you had to conceal your Parkinson's from people?**	☐	☐	☐	☐	☐
24.	**Avoided situations which involve eating or drinking in public?**	☐	☐	☐	☐	☐
25.	**Felt embarrassed in public due to having Parkinson's disease?**	☐	☐	☐	☐	☐
26.	**Felt worried by other people's reaction to you?**	☐	☐	☐	☐	☐
27.	**Had problems with your close personal relationships?**	☐	☐	☐	☐	☐
28.	**Lacked support in the ways you need from your spouse or partner?** ***If you do not have a spouse or partner, please tick here***	☐	☐	☐	☐	☐
29.	**Lacked support in the ways you need from your family or close friends?**	☐	☐	☐	☐	☐

Please check that you have ticked one box for each question before going on to the next page

Due to having Parkinson's disease, how often <u>during the last month</u> have you ….

*Please tick **one box** for each question*

		Never	Occasionally	Sometimes	Often	Always
30.	**Unexpectedly fallen asleep during the day?**	☐	☐	☐	☐	☐
31.	**Had problems with your concentration, e.g. when reading or watching TV?**	☐	☐	☐	☐	☐
32.	**Felt your memory was bad?**	☐	☐	☐	☐	☐
33.	**Had distressing dreams or hallucinations?**	☐	☐	☐	☐	☐
34.	**Had difficulty with your speech?**	☐	☐	☐	☐	☐
35.	**Felt unable to communicate with people properly?**	☐	☐	☐	☐	☐
36.	**Felt ignored by people?**	☐	☐	☐	☐	☐
37.	**Had painful muscle cramps or spasms?**	☐	☐	☐	☐	☐
38.	**Had aches and pains in your joints or body?**	☐	☐	☐	☐	☐
39.	**Felt unpleasantly hot or cold?**	☐	☐	☐	☐	☐

Please check that you have ticked <u>one box for each question</u>

APPENDIX 10

HOEHN AND YAHR STAGING

Ref No. [/] Date: [/ /20]

STAGE 0 = No signs of disease.

STAGE 1 = Unilateral disease.

STAGE 2 = Bilateral disease, without impairment of balance.

STAGE 3 = Mild to moderate bilateral disease; some postural instability; physically independent.

STAGE 4 = Severe disability; still able to walk or stand unassisted.

STAGE 5 = Wheelchair bound or bedridden unless aided.
Key stage 0= No signs of disease.

Further Explanation

Stage 1. Unilateral involvement only, usually with minimal or no functional impairment.
Stage 2. Bilateral or midline involvement, without impairment of balance.
Stage 3. First sign of impaired righting reflexes. This is evident by unsteadiness as the patient turns or is demonstrated when he is pushed from standing equilibrium with the feet together and eyes closed. Functionally the patient is somewhat restricted in his activities but may have some work potential depending upon the type of employment. Patients are physically capable of leading independent lives, and their disability is mild to moderate.
Stage 4 Fully developed, severely disabling disease; the patient is still able to walk and stand unassisted but is markedly incapacitated.
Stage 5 Confinement to bed or wheelchair unless aided.

APPENDIX 11

Ref No. / Date: / /20_

The information you give will be treated in complete confidence.

RBD Screening Questionnaire

	Question	Answer
English		
1.	I sometimes have very vivid dreams.	yes/no
2.	My dreams frequently have an aggressive or action-packed content.	yes/no
3.	The dream contents mostly match my nocturnal behaviour.	yes/no
4.	I know that my arms or legs move when I sleep.	yes/no
5.	It thereby happened that I (almost) hurt my bed partner or myself.	yes/no
6.	I have or had the following phenomena during my dreams:	
6.1.	speaking, shouting, swearing, laughing loudly	yes/no
6.2.	sudden limb movements, “fights”	yes/no
6.3.	gestures, complex movements, that are useless during sleep, e.g., to wave, to salute, to frighten mosquitoes, falls off the bed	yes/no
6.4.	things that fell down around the bed, e.g., bedside lamp, book, glasses	yes/no
7.	It happens that my movements awake me.	yes/no
8.	After awakening I mostly remember the content of my dreams well.	yes/no

Ref No. [/] Date: [/ /20_]

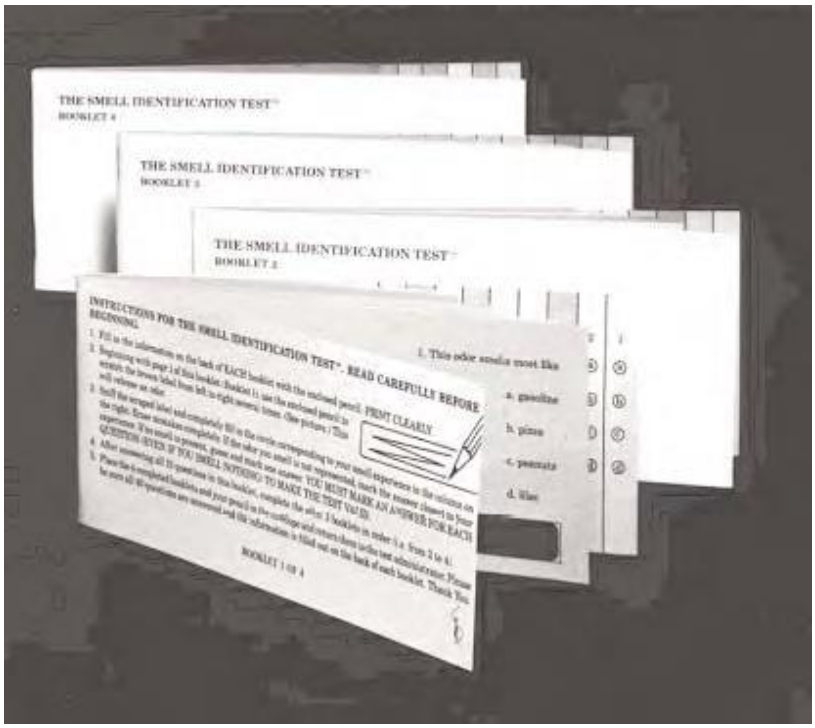
The information you give will be treated in complete confidence.

RBD Screening Questionnaire

	Question	Answer
9.	My sleep is frequently disturbed.	yes/no
10.	I have/had a disease of the nervous system (e.g., stroke, head trauma, parkinsonism, RLS, narcolepsy, depression, epilepsy, inflammatory disease of the brain), which?	yes/no

APPENDIX 12

The University of Pennsylvania Smell Identification Test, a 40-odorant forced-choice self-administered "scratch and sniff" test of olfactory function. This test is the most widely used test of olfactory function in the world, being available commercially as "The Smell Identification Tests."

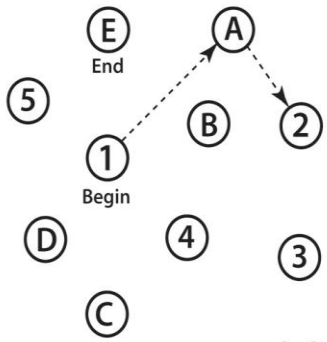


APPENDIX 13

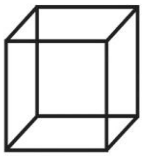
MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

NAME :
Education : Date of birth :
Sex : DATE :

VISUOSPATIAL / EXECUTIVE — POINTS



Copy cube

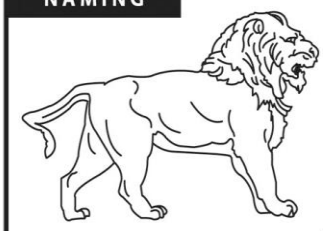
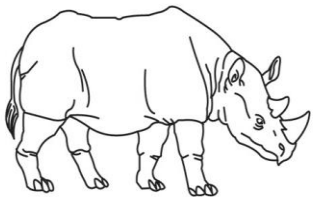
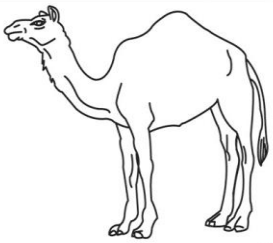


[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

[ ] Contour [ ] Numbers [ ] Hands __/5

NAMING

[ ] [ ] [ ] __/3

MEMORY Read list of words, subject must repeat them. Do 2 trials, even if 1st trial is successful. Do a recall after 5 minutes.

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 __/2

Read list of letters. The subject must tap with his hand at each letter A. No points if ≥ 2 errors
[ ] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B __/1

Serial 7 subtraction starting at 100 [ ] 93 [ ] 86 [ ] 79 [ ] 72 [ ] 65
4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** __/3

LANGUAGE Repeat : I only know that John is the one to help today. [ ]
The cat always hid under the couch when dogs were in the room. [ ] __/2

Fluency / Name maximum number of words in one minute that begin with the letter F [ ] _____ (N ≥ 11 words) __/1

ABSTRACTION Similarity between e.g. banana - orange = fruit [ ] train – bicycle [ ] watch - ruler __/2

DELAYED RECALL

	Has to recall words **WITH NO CUE**	FACE [ ]	VELVET [ ]	CHURCH [ ]	DAISY [ ]	RED [ ]	Points for UNCUED recall only
Optional	Category cue						
	Multiple choice cue						

__/5

ORIENTATION [ ] Date [ ] Month [ ] Year [ ] Day [ ] Place [ ] City __/6

www.mocatest.org
Normal ≥ 26 / 30

TOTAL __/30
Add 1 point if ≤ 12 yr edu

Administered by: _____

APPENDIX 14

Date 8th January 2013. Version 2

Odour detection in Parkinson's disease.

Participant Questionnaire

Ref No. [/] Date : [/ /20_]

The information you give will be treated in complete confidence.

Q1. Age: [years]

Q2. Are you? Male ☐ Female ☐

Q3. Describe your sense of smell

Normal ☐ Decreased ☐ Absent ☐ Other ☐ please specify

(If you answer normal please move on to Q7)

……..…….

……

Q4 If you have a smell problem when did it begin?

……

Q5 Does your sense of smell ever return? Yes ☐ No ☐

Q6 Have you ever been bothered by a persistent smell? Yes ☐ No ☐

If yes when did it begin …….

Please describe the odour……

……..

Q7 Do you have a problem with your sense of taste? Yes ☐ No ☐

(If you answer no please move on to Q9**).**

If yes when did it begin ……. ……..

Q8 If you do have a problem with your sense of taste would you consider it to be?

Mild ☐ Moderate ☐ Severe ☐

Q9 Have you ever smoked? Yes ☐ No ☐ (If you answer no please move on to Q11)

Q10 Do you currently smoke Yes ☐ No ☐

How many years? …… How many packs per day? …….

Q11. Do you have any sinus conditions (sinusitis, sinus infection, prior sinus surgery)?

Yes ☐ No ☐

1. Q12. Have you ever had serious or severe trauma for example resulting in loss of consciousness, a fracture or hospitalisation to your nose or sinuses

   Yes ☐ No ☐

If yes please specify

……

……

.

Q13. Are you: right handed? ☐ left handed? ☐ ambidextrous? ☐

Q14. Do you currently have a cold? Yes ☐ No ☐

Q15. Do you have any other recognised causes for loss of sense of smell?

Yes ☐

Details

……..…

……

…

No ☐

Q16. Do you have any history of neurological disease other than Parkinson's disease?

Stroke ☐ Dementia ☐ Other ☐ details:

……

……

……

THANK YOU FOR YOUR TIME IN COMPLETING THIS QUESTIONNAIRE

Q17. UPDRS Score (Motor):

……

Q18. Non-motor PD Score:

……

Q19. MOCA Score :

……

Q20. UPSIT Score :

……

.

……

……

……

Q21. PDQ 39 Score :

……

……

……

Q22. RBD Score:

……

……

……

Q23. Hoehn and Yahr Score:

……

……

Q24. Parkinson's Disease Duration:

……

……

Q25. Current PD Medications:

……

……

……

……

……

……

Other medications

……

……

……

……

Q 26. Timing of last PD medication dose:

……

..

……

……

……

……

…..

APPENDIX 15

Ethical Approval

The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust

The Royal Bournemouth Hospital
Castle Lane East
Bournemouth
Dorset
United Kingdom
BH7 7DW

Tel: 01202 303626
www.rbch.nhs.uk

Ms Cindy Thompson
Parkinsons Office
Christchurch Day Hospital
Christchurch Hospital
Fairmile Road
Dorset
BH23 2JX

13/03/2013

Dear Ms. Thompson,

Reference:	**An observational study investigating the link between sense of smell and motor and non-motor features of Parkinson's disease.**
REC reference:	**12/SC/0705**
IRAS Project ID:	**87288**

I am pleased to inform you that this project has now received approvals from all parties and that you now have formal permission to start.

Please see the Terms and Conditions for undertaking research at the Trust at:
http://dorsetresearch.org/docs/drc/TC_for_research_within_DRC.pdf.

Please let me know when you officially start and I would be grateful for a progress report annually.

Good luck with the study,

R.M. Chapman

Dr. R. M. Chapman
Head of Research

APPENDIX 16

Date 8thJanuary 2013. Version 2

Invitation letter

LETTER TO PARKINSON'S PATIENTS.

Dear ……..

I am writing to ask if you are willing to take part in a research study. This will only take about an hour of your time. The research study will give us information on whether the degree of loss of smell function is related to Parkinson's disease severity and progression. The findings of this research study could lead to better management of the condition. The information sheet enclosed with this letter gives an explanation of the study.

If you are willing to take part you can either attend Christchurch outpatients' clinic to have a smell test and a memory test or I can arrange to see you in your own home. This can be done entirely at your convenience. Several other questionnaires mentioned in the information sheet can be done in the comfort of your own home. There are no drugs or other treatments involved. Further information can be obtained from me, as indicated in the information sheet.

If you have Parkinson's disease, and you are willing to take part, please complete the form below and return it to me in the pre-paid envelope. I will contact you within two weeks of receiving your reply. You can change your mind later if you so wish. Not taking part in the study, or a later change of mind will not affect your medical care or legal rights.

Thank you for taking the trouble to consider this request.

Yours sincerely,

Ms C Thompson
Consultant Nurse. Parkinson's disease
Royal Bournemouth and Christchurch NHS Foundation Trust
CUT……

I am willing to take part in the smell test research

NAME……...

CONTACTNUMBER…….

ADDRESS……..

APPENDIX 17

Date 8th January 2013 Version 2

PARTICIPANTS INFORMATION SHEET

Plain English Title

Do people with Parkinson's disease "who have either normal sense of smell, or a reduced sense of smell or no sense of smell" differ clinically from each other?

Full Title

An observational study to investigate whether individuals with PD who have either normosmia, hyposmia or anosmia are clinically different when comparing them to the natural history of PD in the motor, quality of life, disease stage and non-motor domains.

Invitation Paragraph

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask if there is anything that is not clear or if you would like more information. Take time to decide whether you want to participate or not.

Thank you for reading this.

What is the purpose of the study?

Sense of smell is commonly reduced or even absent in patients with Parkinson's disease I am conducting the study as part of an educational project to find out whether people with Parkinson's disease who have either normal, reduced or no sense of smell are clinically different either from the motor (slowness of movement tremor rigidity) or non-motor (e.g. dribbling of

saliva, speech or swallowing problems, depression sleepiness etc) symptoms. This could help us formulate guidelines for the long-term management of Parkinson's disease.

Why have I been chosen?

You have been asked to take part in the study because you have Parkinson's disease.

Do I have to take part?

Your participation in this research is entirely voluntary. It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw from the study at any time or not to take part will not affect the standard of care you receive or have any adverse effects on your treatment.

What will happen to me if I take part?

If you agree to take part in our study we will only require about an hour of your time. After a few preliminary questions, I will explain what to expect. You will be asked to complete a participant's questionnaire to see if you fulfil the criteria to be included in the study. You will then sign a consent form and I will complete a short memory test. A simple smell test will then be performed consisting of 40 different smells via a scratch and sniff booklet. You will not be given any drugs or other treatments for the purpose of this research. If you are taking any medications I will not ask you to change these in any way. The testing can either be performed at Christchurch Hospital out patient's department or in the comfort of your own home. Four other short questionnaires will then be given to you to complete at your convenience and one we complete together. These are simple questionnaires presently used in clinical practice to measure your motor and non-motor symptoms. However, I can assist with completing them all with you if required.

What do I have to do?

Your participation in the research will be very brief (about an hour). Therefore, this research will have very little impact on your time and no impact on your lifestyle. I will explain the simple procedures to you before performing the tests, as described in the paragraph above.

What are the possible risks and disadvantages of taking part?

There is a potential risk of nausea and headaches during the smell test. If you are sensitive to any smells that may cause these side effects please inform me prior to the test. If during the test you feel nauseated or develop a headache please let me know and the test will be abandoned and side effects dealt with appropriately. The only disadvantage to you would be the donation of an hour of your time.

What are the possible benefits of taking part?

You are not likely to benefit personally from taking part in the research. However because the research will give us a better understanding as to whether the sense of smell and the progression of Parkinson's disease may be linked this could influence our understanding and treatment of individual Parkinson's disease patients.

Will my taking part in the study be kept confidential?

Your participation in the study will be entirely confidential. Once I have taken the necessary measurements from all your results they will be stored anonymously.

What will happen to the results of the research study?

The results will be analysed and published, if accepted, in movement disorders and neurology journals. If you wish to see a copy of any publications you can obtain one from Cindy Thompson Consultant nurse in Parkinson's disease. It is likely that the publications will take place one year after the study is completed. Because all the information is anonymous your name will not appear in any form of publication.

Who is conducting, organising and funding the research?

This research is being conducted as part of an educational project undertaken by Cindy Thompson Consultant nurse in Parkinson's disease. It is being jointly organised and supported by Bournemouth University and the Royal Bournemouth and Christchurch Hospitals NHS Trust. The resources to support the research are coming from the professional development and education budgets at the Royal Bournemouth and Christchurch Hospitals NHS Trust. The student involved in this research and the supervisors will receive no additional payments for conducting the tests or performing the analysis.

Will my General Practitioner (GP) be informed?

Yes. Your GP will be informed that you will be participating in the study. If any results impact on you Parkinson's control or condition they will be notified.

Who has reviewed the study?

The proposed research has been reviewed by South Central. Southampton B REC

Contact information

Further information can be obtained from Cindy Thompson at Christchurch Hospital, Fairmile Road, Christchurch, BH23 2JX. Telephone No: 01202 705320, Fax number 01202 705320, E-mail address: cindy.thompson@rbch.nhs.uk

Thank you for taking the trouble to read this information sheet.

APPENDIX 18

Date 8th January 2013. Version 2

CONSENT FORM

Title of Project

Plain English Title

Do people with Parkinson's disease who have either normal sense of smell, a reduced sense of smell or no sense of smell clinically different?

Full Title

An observational study to investigate whether individuals with PD who have either normosmia, hyposmia or anosmia are clinically different when comparing them to the natural history of PD in the motor, quality of life, disease stage and non-motor domains.

Name of Researcher: Cindy Thompson

Please initial box

1. I confirm that I have read and understood the information sheet dated …….for the above study and have had the opportunity to ask questions ☐

2. I understand my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that sections of any medical notes may be looked at by responsible individuals from the research team or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records ☐

4. I agree for my GP to be informed that I am participating in our study ☐

5. I agree to take part in the above study ☐

_____ _____ _____

Name of patient/participant Date Signature

_____ _____ _____

Name of researcher taking consent Date Signature

One copy for patient, one copy for researcher and one copy to be kept with hospital notes.

APPENDIX 19

Date 8th January 2013. Version 2

Letter to GP

Ms C M Thompson
Consultant Nurse Parkinson's Disease
Christchurch Day Hospital
Fairmile Road
Christchurch
Dorset BH23 2JX

An observational study to investigate whether individuals with PD who have either normosmia, hyposmia or anosmia are clinically different when comparing them to the natural history of PD in the motor, quality of life, disease stage and non-motor domains.

Patients Name……

Address……

Date of birth……

Hospital Number……

Dear Doctor ……

This patient is participating in the above study on whether patients with Parkinson's disease who have either normosmia, hyposmia or anosmia clinically different? The study will involve several questionnaires and assessment tools designed to record both motor and non-motor symptoms in Parkinson's disease as well as a 40 scratch and sniff test. None of these tests are invasive and are used in clinical practice.

It does not involve any changes in standard treatment. A copy of the patient's information sheet is enclosed.

With kind regards

Yours sincerely

Cindy Thompson

APPENDIX 20

Representative Medical Conditions that Affect the Senses of Smell or Taste.

Parkinson’s disease
Alzheimer's disease
Bell's palsy
Epilepsy
Head trauma
Korsakoff's syndrome
Multiple sclerosis
Tumors and lesions
Cancer
Chronic renal failure
Liver disease including cirrhosis
Niacin (vitamin B3). B12 and zinc deficiency
Sjogren syndrome
Zinc deficiency
Adrenal cortical insufficiency
Cushing's syndrome
Diabetes mellitus
Hypothyroidism
Turner's syndrome
Allergic rhinitis
Bronchial asthma
Influenza infections

Adapted and updated from Mann (2002) and Nordin and Bramerson (2008)

APPENDIX 21

Common Drugs that can affect the Sense of Smell or Taste.

Class of Drugs	Examples
Drugs to Treat Cancer	Cisplatin Doxorubicin Methotrexate
Antihistamines	Chlorpheniramine maleate Loratadine Terfenadine
Drugs to Treat Infections	Ampicillin Trimethoprim, Tetracycline
Drugs to Treat Arthritis and Pain	Colchicine Dexamethasone Hydrocortisone
Muscle Relaxants and Drugs to Treat PD	Levodopa Baclofen
Drugs to Improve Mood or Treat Epilepsy	Amitriptyline Carbamazepine Clozapine Fluoxetine Phenytoin
Cardiac medications	Acetazolamide Adenosine Captopril Clonidine Diltiazem Propranolol Spironolactone
Drugs to Lower Cholesterol or Lipids in blood	Cholestyramine Fluvastatin sodium Lovastatin Pravastatin sodium
Drugs for Asthma and Breathing Problems	Albuterol sulfate Flunisolide Metaproterenol sulfate Terbutaline sulphate
Other	Antifungals, smoking cessation aids, radiotherapy to head, vasodilators

Adapted from Doty et al (2008) and Schiffman and Graham (2000)

APPENDIX 22

UPSIT scores associated with the 14-motor examination

UPDRS Motor examination

Speech	Number of Patients	UPSIT Range	UPSIT Mean
0	46	6-28	18
1	52	7-31	16
2	13	11-27	16
3	1	23	23
4	0	0	0
Facial Expression	Number of Patients	UPSIT Range	UPSIT Mean
0	8	18-27	22.5
1	48	7-28	17
2	41	6-27	16
3	13	10-13	15
4	2	17-27	22
Tremor at Rest	Number of Patients	UPSIT Range	UPSIT Mean
0	39	7-27	17
1	34	8-31	16
2	26	6-29	17
3	13	10-27	18
4	0	0	0
Action/Postural Tremor	Number of Patients	UPSIT Range	UPSIT Mean
0	70	6-28	17
1	40	8-31	17
2	1	27	27
3	1	23	23
4	0	0	0
Rigidity	Number of Patients	UPSIT Range	UPSIT Mean

0	32	7-27	18
1	55	7-31	17
2	24	6-28	16
3	1	27	27
4	0	0	0

Finger Taps	Number of Patients	UPSIT Range	UPSIT Mean
0	34	8-31	19
1	53	6-27	16
2	24	7-27	18
3	1	27	27
4	0	0	0
Hand Movements	Number of Patients	UPSIT Range	UPSIT Mean
0	59	8-31	18
1	40	6-27	16
2	12	7-27	16
3	1	12	12
4	0	0	0
Rapid Hand Movements	Number of Patients	UPSIT Range	UPSIT Mean
0	68	8-31	18
1	34	6-27	15
2	10	7-27	20
3	0	0	0
4	0	0	0
Leg Agility	Number of Patients	UPSIT Range	UPSIT Mean
0	45	6-31	17
1	55	7-29	17
2	11	10-28	19
3	1	11	11

4	0	0	0
Arising from Chair	Number of Patients	UPSIT Range	UPSIT Mean
0	64	6-29	18
1	29	7-27	17
2	13	11-18	14
3	6	8-31	17
4	0	0	0

Posture	Number of Patients	UPSIT Range	UPSIT Mean
0	31	7-27	20
1	62	6-31	16
2	14	8-23	15
3	4	12-21	16
4	1	27	27
Gait	Number of Patients	UPSIT Range	UPSIT Mean
0	48	6-29	18
1	50	7-31	17
2	13	13-23	15
3	1	16	16
4	0	0	0
Postural Stability	Number of Patients	UPSIT Range	UPSIT Mean
0	45	7-29	16
1	48	6-27	18
2	16	10-27	17
3	3	13-31	17
4	0	0	0

Body Bradykinesia and Hypokinesia	Number of Patients	UPSIT Range	UPSIT Mean
0	6	8-25	19
1	45	6-31	17
2	52	7-27	17
3	8	11-27	15.5
4	1	27	27

The higher the score the higher the disability. So generally 0= abcent or normal and 4= severe, marked or unable.

APPENDIX 23

Smells presented in each booklet

Booklet 1
Pizza
Bubble Gum
Menthol
Cherry
Motor oil
Mint
Banana
Clove
Leather
Coconut

Booklet 3
Lilac
Soap
Peach
Root Beer
Dill Pickle
Pineapple
Lime
Orange
Wintergreen
Watermelon

Booklet 2
Onion
Fruit punch
Liquorice
Cheddar cheese
Cinnamon
Gasoline
Strawberry
Cedar
Chocolate
Gingerbread

Booklet 4
Paint thinner
Grass
Smoke
Pine
Grape
Lemon
Soap
Natural Gas
Rose
Peanut

APPENDIX 24

Neuroimaging Markers for PD.

Imaging Modality	Ligand and Target	Changes in PD patients	Value	References
SPECT	DaTSCAN, B-CIT Dopamine transporter	Reduced binding in striatum of PD patients	Helpful in diagnosis at preclinical stage but not clear if it changes with disease progresses.	Booij et al 1997 Marek and Jennings 2009 Panzacchi et al 2008
PET	DTBZ, AV133 Vesicular monoamine transporter	Reduced in striatum of PD patients	Showing encouraging results. Less sensitive to drugs but warrants further study.	Hsiao et al 2014 Okamura et al 2010
PET	F-DOPA Aromatic L-amino acid decarboxylase	Reduced in striatum of PD Patients	Helpful at preclinical stage but expensive and could be affected by levodopa	Brooks et al 2003 Morrish et al 1998
PET	Flurodeoxyglucose Glucose metabolism	PD-specific network pattern	Not disease specific but may prove useful. Alternative to SPECT.	Boehm et al. 2011
PET	Raclopride D2 receptors	Altered receptor numbers	Has potential implications for models of basal ganglia function in PD. More studies needed.	Strafella et al 2005
PET	PK11195 Peripheral benzodiazepine receptors/activated microglia	Increased brain inflammation in PD-patients	Possible early biomarker. Remains stable after two years. Longitudinal and pre-diagnostic studies needed.	Gerhard et al 2006
SPECT	MIBG Sympathetic terminals in the myocardium	Reduced cardiac innervation in PD patients	Helpful in preclinical stage but needs more studies	Fujishiro et al 2008 Orimo et al 2008
Optical coherence tomography	Retinal morphology	Reduced innervation of retina in PD patients	Could be used for evaluating progression.	Inzelberg et al 2004
Magnetic resonance imaging/ diffusion tensor imaging	Fractional anisotropy	Nigral-specific pattern in PD patients	Could be used as a biomarker but lacks standardization and validation. More studies needed.	Peran et al 2010
Nigral ultrasound	Unknown (nigral iron?)	Nigral-specific pattern in PD patients	Reliability still a matter of debate. More studies needed.	Walter et al 2003 Belaidi and Bush 2016

APPENDIX 25

Biomarkers in PD

	Study	Number of cases	Years follow-up	Assessment	Results	Years noted prior to a diagnosis of PD
Olfaction	HAAS (men only) Ross et al 2008	35	8	BSIT e	Relationship of olfactory loss not seen before 4 years	Within 4 years
	Haehner et al 2007. (follow-up study from Sommer et al 2004)	30	4	Sniff sticks and SPECT	7% developed PD compared to 1.6% general population	Within 4 years
	Stiasny-Kolster et al 2005	30	_	Sniff sticks and SPECT	4 diagnosed with PD	7-6 years but hard to verify as bed partners assessment
	Ponsen et al 2004	hyposmic = 40 normosmic = 38 asymptomatic relatives	2	A combination of olfactory detection, identification, and discrimination tasks. Plus, SPECT scan	10% hyposmic patients developed PD. No normosmic patients did.	? 2 years
	Berendse et al 2001	25 hyposmic 23 normosmic relatives of PD patients	_	SPECT Scan B SIT	4 /25 developed IPD 0/23 no signs of PD	Possibly 3
	Montgomery et al 1999	80 first degree relatives 100 controls	-		22.5% relatives had abnormal sense of smell compared to 9% controls	? asymptomatic carrier state or risk of PD
Daytime Sleepiness	HAAS Abbot et al 2005	43	8	Self-reporting	Risk of PD in men with EDS vs men without EDS (p = 0.004).	0.5-4.9 years
	Gao et al 2011	770	4-10	Self-reporting hours of daytime napping		4-10 years
RBD	Classen et al 2010	27 RBD	15	Clinical Diagnosis	9 Developed PD	15-50 years
	Iranzo et al 2006	44 RBD	2	Clinical diagnosis	7 Developed PD	6-18 years
	Postuma et al 2009	93 RBD	_	Clinical diagnosis	19 Developed PD	Mean = 11 years
	Olson et al 2000	93 RBD	5	Clinical diagnosis. Medical records	25 had parkinsonism	3 years in PD
Constipation	HAAS Abbot et al 2001	96	24	Self-reported bowel movements	Infrequent bowel movements increase risk of PD	Mean = 12 years
	Savica et al 2010	196	_	Medical records review	Constipation and laxative use	Could be greater than 20 years
	HPFS men only Gao et al 2011	156	6	Self-reported bowel movements	Infrequent bowel movements increase risk of PD. Risk 4.88	6 years plus

	NHS women only Gao et al 2011	402	24	Self-reported bowel movements	Infrequent bowel movements increase risk of PD. Risk 2.15	No association beyond 6 years
Depresion	Shiba et al 2000	196	8-87	Medical records review	1.9 (1.1–3.2)	Within 5 years
	Gonera et al 1997	60PD 58 controls	10 years preceding diagnosis	Medical notes	29 PD 15 controls	4-6 years
Neurological Imaging	Hiker et al 2005	31	Mean 64 months	(18f) dopa PET	These data suggest that the neurodegenerative process in PD follows a negative exponential course and slows down with increasing symptom duration, contradicting the long-latency hypothesis of PD.	5.6 years
	Morrish et al 1998	32	39 months	(18f) dopa PET and UPDRS x2 occasions	Estimation of mean rate of progression varies according to the sensitivity of a functional imaging method to clinical severity.	7 years
Alpha synuclein levels in blood or spinal fluid	El Agnaf et al 2006	34 PD 27 Controls	_	Blood samples	52% of PD and 14.8% showed dramatic increase in oligomeric alpha-synuclein	_
	Abdi et al 2006	10PD 10AD 5DLB 10 Controls	_	Changes in spinal fluid 1,090 new proteins identified	Three confirmed candidate markers found for PD but not decreased in all patients. No single marker could detect difference in conditions but increases when two dimensions used.	_
Cardiac sympathetic denervation	Fujishiro et al 2008	4 controls 11 DLB 14 PD	-	Biopsy anterior left ventricle	Cardiac sympathetic innervation significantly less in PD ($P < 0.01$) and increases with disease duration.	-
Cardiac sympathetic denervation	Orimo et al 2008	20 patients with incidental Lewy body disease (ILBD), 10withPD, 20withmultiple system atrophy (MSA) and10 control subjects	-	Both cardiac tissues and paravertebral sympathetic ganglia were obtained	May represent the pathological mechanism underlying a common degenerative process in PD.	-
	Courbon et al 2003	8PD 10 PD with Autonomic Failure 10 MSA	-	(1231) MIBG	Sensitive test in diagnosis autonomic failure in PD but not differentiating PD and MSA.	-
	Braune et al 1998	10 PD 10 autonomic failure		(1231) MIBG	Cardiac uptake of MIBG significantly lower in PD.	-

	Yoshita 1998	25 with PD 24 other parkinsonian disorders 20 controls		(1231) MIBG	Cardiac uptake of MIBG significantly lower in PD.	-
Colonic Biopsy	Shannon et al 2012	3	2.5 years before –	Colonic biopsy	Alpha synuclein pathology	-
	Lebouvier et al 2010	29PD 10 Controls	–	UPDRS III ROMEIII Colonic biopsy's x4	Lewy body pathology 21/29 of PD Patients. 0/10 in controls. Useful pre-mortem to demonstrate the presence of Lewy pathology in the colon at initial stages of disease.	-

APPENDIX 26

Genes Invoved so far in PD

LOCUS NAME	GENE SYMBOL	PROTEIN PRODUCT	MODE OF INHERITANCE	% OF AFFECTED INDIVIDUALS	REFERENCES
PARK2	PRKN	Parkin	Recessive	50% early onset PD	Kitada et al (1998). Lucking et al (2000).
PARK6	PINK1	PTEN-induced putative kinase1i	Recessive	1-7% early onset PD	Valente et al (2004).
PARK7	DJ-1	Protein DJ-1	Recessive	Rare. Early onset PD	Bonifati et al (2003).
PARK8	LRRK2	Leucine-rich repeat kinase 2	Dominant	2%*	Funajama et al (2002). Paisan-Ruiz et al (2004). Zimprich et al (2004).
PARK1/4	SNCA	Alpha-synuclein	Dominant	Rare. Late PD and early onset PD, dementia	Polymeropoulos et al (1997). Farrer (2006).

In white populations, the frequency of LRRK2 mutations is 5% in those with a family history of PD and in 1.5% in those with sporadic PD. Other populations can vary widely.

For a review of all other genes involved in the pathogenesis of PD which are autosomal recessive, causing atypical features of parkinsonism, autosomal dominant with unclear pathology or those found to be an important risk factor, can be seen in Schulte and Gasser (2011) review.