Voice tremor in Parkinson's disease (PD)

Identification, characterisation and relationship with speech, voice, and disease variables

By

Patricia Gillivan-Murphy

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Abstract

Voice tremor is associated with Parkinson's disease (PD), however little is known about the precise characteristics of PD voice tremor, optimum methods of evaluation or possible relationships with other speech, voice, and disease variables. The question of possible differences between voice tremor in people with PD (pwPD) and neurologically healthy ageing people has not been addressed.

Thirty pwPD 'off-medication' and twenty eight age-sex matched neurologically healthy controls were evaluated for voice tremor features using acoustic measurement, auditory perceptual voice rating, and nasendoscopic vocal tract examination. Speech intelligibility, severity of voice impairment, voice disability and disease variables (duration, disability, motor symptom severity, phenotype) were measured and examined for relationship with acoustic voice tremor measures.

Results showed that pwPD were more likely to show greater auditory perceived voice instability and a greater magnitude of frequency and amplitude tremor in comparison to controls, however without statistical significance. PwPD had a higher rate of amplitude tremor than controls ($p<0.05$). Judged from 'silent' video recordings of nasendoscopic examination, pwPD had a greater amount of tremor in the palate, tongue, and global larynx (vertical dimension) than controls during rest breathing, sustained /s/, /a/ and /i/ ($p<0.05$). Acoustic voice tremor did not relate significantly to other speech and voice variables. PwPD had a significantly higher voice disability than controls ($p<0.05$), though this was independent of voice tremor. The magnitude of frequency tremor was positively associated with disease duration ($p<0.05$). A lower rate of amplitude tremor was associated with an increase in motor symptoms severity ($p<0.05$). Acoustic voice tremor did not relate in any significant way to PD disability or phenotype.

PD voice tremor is characterised by auditory perceived instability and tremor, a mean amplitude tremor of 4.94 Hz, and tremor in vocal tract structures. Acoustic analysis and nasendoscopy proved valuable adjunctive tools for characterising voice tremor. Voice tremor is not present in all people with PD, but does appear to increase with disease duration. However pwPD examined here represent a relatively mild group with relatively short disease duration. Further work will look at people with more severe disease symptomatology and longer duration.

Dedication & Acknowledgements

Dedication

I dedicate this thesis to Michael my ever supportive husband, and to my children, Saerlaith, Tighernach, and Caelan.

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Abbreviations

ADSD	Adductor Spasmodic Dysphonia
ALS	Amyotrophic Lateral Sclerosis
ANOVA	Analysis of variance
BG	Basal Ganglia
BG-TH-CTX	Basal Ganglia-thalamic-cortical
CAPE-V	Consensus Auditory Perceptual Evaluation of Voice
CRS's	Clinical Rating Scales
CSL	Computerised Speech Laboratory
DBS	Deep Brain Stimulation
EGG	Electroglottography
EMG	Electromyography
ET	Essential Tremor
ETV	Voice tremor in Essential Tremor
FEV_1	Forced Expiratory Volume in 1 second
Fo	Fundamental frequency
FOG	Freezing of gait
Gpi	Globus pallidus internal segment
HADS	Hospital Anxiety & Depression Scale
HNR	Harmonic to Noise Ratio

ICC	Intraclass correlation coefficient
IPA	International Phonetic Alphabet
L-dopa	Levodopa
LEMG	Laryngeal electromyography
Matr	Magnitude of amplitude tremor
MDS	Movement Disorder Society
MDVP	Multi-dimensional Voice Programme
MMSE	Mini-Mental State Examination
MS	Multiple Sclerosis
MSA	Multiple Systems Atrophy
MSP	Motor Speech Profile
PD	Parkinson’s Disease
PDS	Parkinson’s Disease Society
PET	Positron Emission Topography
PIGD	Postural Instability Gait Disorder
PPND	Pallido-ponto nigral degeneration
PwPD	People with PD
SD	Spasmodic Dysphonia
SDFo	Variability of fundamental frequency
SLT’s	Speech & Language Therapists
SNpc	Substantia Nigra pars compacta
SPL	Sound Pressure Level

UPDRS	Unified Parkinson’s Disease Rating Scale
VAS	Visual Analogue Scale
VHI	Voice Handicap Index
VTE	Vocal Tract Examination
VTP	Voice and Tremor Protocol
VTSS	Vocal Tremor Scoring System

Introduction

There are four salient aspects to this thesis, Parkinson's disease (PD), tremor, speech and voice changes in PD and voice tremor. Chapters 1 and 2 cover the disease and speech and voice changes associated with PD, chapters 3 and 4 address the tremor and voice tremor aspects.Chapter 4 leads into the research questions and study aims.

Chapter 5 describes the methods used in the study. Chapter 6 delineates the main research question results and the supplementary results. Chapter 7 discusses general points emerging from the study, the findings from the four research questions, some additional findings, clinical implications and pointers for further research. The appendices, glossary and references follow chapter 7.

Chapter 1. Understanding Parkinson's disease (PD)

Chapter 1 begins with a definition of idiopathic Parkinson's disease or PD as it is commonly referred, with further information given on its prevalence and incidence. This is necessary in order to place the current PhD study in context. The neuropathology underlying the cardinal motor symptoms is described, leading to a delineation of myriad of motor and non-motor symptoms associated with PD. In order to complete the background knowledge, the chapter also includes a description of the clinical diagnosis and evaluation of PD, different phenotypes, and medical management of PD. Underlined words in chapter 1 and subsequent chapters are explained in the glossary section.

1.1. Definition

Idiopathic Parkinson's disease (PD), the most common parkinsonian disorder is a progressive neuro-degenerative, multi-system disorder with both motor and non motor symptoms[1 2]. PD differs from parkinsonism, a condition which refers to any symptom profile similar to that of PD, but with a known aetiology including vascular Parkinson's, Wilson's disease, iatrogenic Parkinson's, exposure to dopaminergic neurotoxins as in 1-methyl- 4 phenyl-1,2,3,6-tetrahydropyridine (MPTP)[3] or encephalitis[4].

Traditionally, PD has been described in relation to the four cardinal motor signs of rigidity, bradykinesia, postural instability, and rest tremor [5]. *Rigidity* is detected as a resistance to passive movement of the limbs. It is often characterised as uniform in directions of flexion and extension resulting in ''lead pipe rigidity'', and there may also be a superimposed ratcheting most likely associated with accompanying tremor referred to as ''cogwheel rigidity'' [6]. *Bradykinesia* defined as slowing of motion and a decrease in automatic movements is considered the most characteristic finding of PD and is manifested by the loss of facial expression, and loss of other associated movements such as arm swinging when walking[6]. *Postural Instability* relates to the loss of postural reflexes and is associated with advanced PD, occurring

after the onset of other clinical symptoms[6]. *Tremor*, in particular a 4 Hz "pill rolling" *rest tremor* is considered the hallmark symptom of PD[6]. Tremor, with particular reference to tremor in PD will be elaborated on in chapter 3. In addition to the classical motor symptoms, the disease process is associated with involvement of the limbic, autonomic and non-motor symptoms[7-9]. The non-motor symptoms will be outlined in section 1.4. PD is associated with a reduced life span[10], increased disability[11], reduced quality of life[12], and ageing[13].

1.2. Prevalence and incidence

PD, the second most common degenerative disease of the ageing brain after the dementia of Alzheimer's disease[1], is twice as frequent in men as it is in age-matched women[14]. Prevalence varies worldwide from 7 to 450 per 100,000 with lower rates associated with the developing world[15], possibly reflecting the association of PD with age and its nonappearance in countries with low life expectancy. The estimated incidence is 13/100,000 population, with incidence increasing with age[14]. PD is associated with the loss of the chemical neurotransmitter dopamine in the substantia nigra pars compacta (SNpc) of the basal ganglia, and ageing is closely linked with progressive decline in dopamine levels[16]. Although there are close links between PD and the ageing process[16], PD is not due to ageing alone[17]. The exact cause of PD is unknown however several mechanisms are thought to be involved with interaction between toxic environmental factors, genetic susceptibility, and ageing[4,1].

1.3. Neuropathology

There is consensus that the neuropathophysiology resulting in the motor symptoms of PD relates to the progressive loss of melanin-containing dopaminergic neurons in the substantia nigra pars compacta (SNPc) of the basal ganglia and the resultant depletion of dopamine in the striatum[18]. This depletion in turn leads to changes in thalamic and cortical activity[19]. The basal ganglia (BG) are large subcortical interconnecting nuclei involved in the regulation and control of movement, through a complex circuitry, which also involves the cerebral cortex and the thalamus[20 21]. The primary role of the BG is to synergistically effect and coordinate the initiation and direction of volitional movement. Disorders of the BG result in paucity of movement, or 'hypokinesia'

as well as some degree of involuntary movement, including tremor[22].The standard account of this basal ganglia-thalamic-cortical (BG-TH-CTX) circuitry is that the striatum (the primary input structure in the BG) receives messages primarily from the motor cortex and then through *direct* and *indirect* activation output pathway sends messages to the globus pallidus internal segment (GPi) (output structure) which in turn feeds back to the cortex[21]. The neurotransmitter dopamine which is produced in the substantia nigra pars compacta (SNpc) has a differential effect on the pathways. In the direct pathway it increases or has a facilitatory effect, whilst in the indirect pathway it has a suppressive effect on movement. In PD, the increased rate of the GPi neuronal discharges (GPi rate theory) is posited to suppress neuronal activity in the thalamus and motor cortex, thus suppressing movement[23], and resulting in the cardinal PD symptom of hypokinesia (reduced movement). More recently the 'systems oscillator theory' has been put forward as an explanation for PD. The BG-TH-CTX system is thought to be made up of dynamically coupled polysynaptic oscillators representing a wide range of frequencies. Dopamine loss could affect synaptic efficiency within the BG-TH-CTX system changing the oscillatory dynamics and thus affecting behaviour[23].

It is argued that PD progresses sequentially and topographically in 6 stages beginning in the dorsal motor nucleus of the vagus in the brain stem, and the olfactory bulb[24] and finishing in the cerebral cortex with the full range of PD symptoms including dementia [2 9]. The early stages (stage 1 and 2) are considered pre-symptomatic in that the disease is not clinically evident. In advance of the clinical diagnosis being made, a significant amount (60-70%) of dopaminergic neuronal degeneration occurs [25]. Lowered volume of voice, changes in rate of speech, flat facial expression, and changes in fundamental frequency variability (monotone voice) have been reported in patients in advance of the clinical diagnosis of PD[26 4].

1.4. Symptomatology

The depletion of dopaminergic neurons results in the characteristic motor symptoms, described in section 1.1. In addition to the 'cardinal' motor symptoms, other clinical features termed secondary motor symptoms are also

associated with PD and can be equally or more disabling than the cardinal features[6]. They include: micrographia (abnormally small handwriting)[27]; festination (increase of speed with reduced amplitude during fast repetitive movements, which may affect gait, tapping, and movement of the articulators during speech)[28]; freezing of gait or FOG (sudden and transient difficulty in moving forward)[29]; dystonia[6]; bradyphrenia (slowness of thought)[17]; hypomimia (reduced facial expression)[6]; sialorrhea (poor saliva control)[30]; dysarthria (neuromuscular speech disorder)[31];dysphagia (swallowing disorder)[32]. Speech and voice symptoms, described in chapter 2 have been linked to orofacial-laryngeal bradykinesia and rigidity[33 34].

The neuropathology underlying PD extends beyond the nigrostriatal pathways and into other areas not directly involved in motor control (non dopaminergic), including the peripheral autonomic nervous system[35]. These wider effects of change are reflected in the non-motor symptoms which feature strongly in PD[36]. They include: cognitive impairment[37 38 39 40], dementia[37 41], depression[42, 43], anxiety[43], sleep disorders[44],visual hallucinations[45], autonomic changes (postural hypotension, bladder dysfunction) hyposmia (loss of sense of smell)[46], and apathy[43]. Cognitively, bradyphrenia, reduced attention span and alertness, slowness in processing information, and difficulty in switching sets may occur[17]. A substantial number of patients will develop dementia during the course of their PD (PD-D)[40]. Although dementia is associated with advanced PD[47], cognitive executive dysfunction has been identified in the early stages of PD[48]. Depression is a frequent co-occurring symptom in PD[49 50 43 51], with prevalence rates of 40% reported[52-54]. Anxiety, which has received much less attention in the literature is also prevalent with rates reported from 28% to 49%[54]. Anxiety and depression impact negatively on quality of life in pwPD.

The myriad of motor and non-motor symptoms just described create a complex clinical picture, resulting in wide ranging effects on the life of a pwPD including loss of independence, difficulty communicating, withdrawal from socialisation, and early retirement, leading to reduced quality of life[11].

1.5. Diagnosis and evaluation

There is no specific diagnostic test available to identify PD[17]. Diagnosis is made on the basis of clinical symptoms which must fulfil the UK Parkinson's Disease Society (PDS) Brain Bank criteria for PD[55]. For a diagnosis of PD to be made, bradykinesia must be present and at least one of the following symptoms; muscular rigidity; a 4-6 Hz rest tremor; disorders of posture, balance or gait[56]. The two most widely used clinical scales for rating clinical symptoms in PD[57 58] are the Hoehn & Yahr [59] staging system and the Unified Parkinson's Disease Rating Scale (UPDRS)[55].

The Hoehn & Yahr scale[59] is the most commonly used instrument for evaluating overall severity of PD, using a simple staging approach, ranging from stage 0 (no sign of disease) to stage 5 (wheelchair bound)[6 57]. Patients are usually classified into 'early' or 'late' stage PD on the basis of the severity of motor symptoms[7], with postural instability being the primary index of severity[60]. In this study, the disability resulting from PD will be measured using UPDRS section II (APPENDIX A), and the overall severity of motor symptoms and disease stage will be measured using UPDRS section III (APPENDIX B), and Hoehn & Yahr (APPENDIX D) staging respectively.

Unified Parkinson's Disease Rating Scale (UPDRS)

The UPDRS [55] is made up of four subsections: Part 1 (Mentation, Behaviour, and Mood), Part II [(activities of daily living (ADL)], Part III (motor examination), Part 1V (complications of treatment). Part II and III are widely used clinically and include patient's self-rating of activities of daily living and a clinician rating of motor signs respectively. Each item is scored from 0 (normal) to 4 (severe disability). There are thirteen items in the UPDRS II, which can yield an overall score between 0 (normal) and 52 (severe disability). In UPDRS III (motor) there are fourteen items with a range of scores from 0 (normal) to 108 (severely impaired).

There are three tremor items for scoring in the UPDRS II and III combined. Item 16 in part II is a self-report measure of tremor. Items 20 and 21 in part III are clinician ratings of tremor at rest, and action tremor respectively. Two items only

in the UPDRS cover speech: item 5 in part II and item 18 in part III. Item 5 addresses how intelligible a person considers he or she is, based on the frequency with which he/she needs to repeat him or herself. Item 18 is rated by the examiner and could be described as a' global' measure of speech, voice and communication rating. It encompasses diction, volume, intelligibility and expression, with a score of 0 = normal and 4 = unintelligible speech. It is evident from the range of parameters included that item 18 is an insensitive measure of the speech and voice symptomatology associated with PD. Therefore, in this study, item 18 (UPDRS III) will not be utilised as an index of speech or voice symptom severity. However, UPDRS II and III will be utilised to obtain an overall rating of motor disability and impairment in pwPD, and to determine PD sub-type or phenotype (section 1.6.3).

1.6 Disease variables

1.6.1 Onset of disease

The mean age of onset of PD, defined as when the first PD symptom is reported to appear[61] was 59.0 (9.6) years in a large study of 800 patients[61]. Age of onset of the disease is an important factor in terms of the rate of disease progression and clinical manifestations. For example, patients with early-onset, (defined as patients who had their first symptom at or before the age of 40)[62], have a greater tendency to develop fluctuations of response to medication and abnormal involuntary movements[17]. Older age at onset, termed 'late-onset' (greater than 70 years old) is associated with a more rapid disease progression, greater cognitive decline[17] and, greater likelihood of freezing than at younger age at onset[62]. The rate of deterioration of the disease process and of different functions affected (e.g. speech, gait, mood) is variable[6]. But whatever the relative pattern, as the disease process advances, the motor and non-motor symptoms become more prominent.[63]

1.6.2 Disease duration

The length of time that a person has the disease, i.e duration of disease, may be calculated from the time of clinical diagnosis, or based on patient reporting of first PD symptom. Regardless of the method used, it is accepted that significant

neuronal degeneration, in the region of 60-70% has occurred in the substantia nigra[46], at the time that a patient fulfils the clinical diagnostic criteria of PD[56]. Non-motor symptoms[46] including low mood, and olfactory dysfunction, subtle motor impairment[46] and voice changes may be apparent in this 'pre-clinical' phase[64]. Efforts are being made to identify 'markers' of early signs of PD, to assist in the development of neuroprotection and thus avoid the relentless course of neuronal degeneration[46].

1.6.3 Phenotypes

PD is not a single clinical entity. There is considerable heterogeneity in the clinical symptomatology and disease progression, to the extent that the existence of distinct clinical subtypes or phenotypes with different clinical profiles and different pathophysiological systems is recognised[5 18 61 62 65].

People with PD (pwPD) are broadly classified into tremor- dominant and non-tremor subtypes[18 61 66], for example, postural instability gait disorder (PIGD). Some people with PD (pwPD) do not fit neatly into tremor-dominant or PIGD subtypes and are described as indeterminate. The particular phenotype is determined from the UPDRS by calculating the ratio of the average global tremor score to the overall postural instability gait disturbance score[61]. A ratio of mean tremor score/mean PIGD score greater than or equal to 1.5 constitute the tremor-dominant phenotype, those with a ratio of less than or equal to 1.0 constitute the PIGD group.[61] The indeterminate phenotype does not fit into either category, with scores falling between the extremes.

Tremor dominant PD is associated with early symptomatic tremor in the upper and lower limbs, and is contrasted with a different form of PD in which postural instability and gait problems (axial symptoms) are dominant (PIGD). Tremor dominant PD is also contrasted with a phenotype in which bradykinesia and rigidity are the dominant features[18]. There are different rates of progression for each phenotype[62], with the tremor-dominant form associated with a slower rate [61,18 67], and PIGD associated with a more rapid disease progression[68 64].

1.7 Treatment with dopaminergic medication

The mainstay treatment of the cardinal motor symptoms in PD is through medication using dopamine replacement, levodopa (L-dopa), which is converted to dopamine in the brain and, dopamine agonists which directly stimulate dopamine receptors in the brain[69]. The positive effect of L-dopa on the limb symptoms of tremor, rigidity and limb akinesia is strongly established in the literature[63]. The reported effect of dopaminergic medication on 'axial' signs, including neck rigidity, rising from a chair, posture, gait postural instability, and speech, are less positive[69 70]. Patients taking dopaminergic medication often experience cyclic fluctuations of their symptoms, with the term "on" used when motor symptoms are relieved and "off", when motor symptoms are present[71].

Long-term side effects of dopaminergic medications include motor complications, neuropsychiatric complications, and lowered blood pressure[63]. The motor complications include fluctuations (shortening of the response to individual L-dopa doses) and dyskinesias or involuntary movements[63 69]. Sometimes, it can be difficult to discern which motor symptoms are disease and which are medication related. This issue is frequently addressed during clinical evaluation and/or research by evaluating pwPD when they are in a "practically defined off" state, which is considered to be at least twelve hours after the last medication dose[72]. This topic will be discussed further in section 2

Summary

- PD is a common, multi-system, degenerative, neurological disease, resulting in motor and non-motor symptoms.
- The depletion of dopamine in the substantia nigra pars compacta (SNpc) is considered pathognomic of the disease, but the underlying cause of the neuronal degeneration is unknown.
- PD is twice as frequent in males as females. It is associated with ageing; however it is not caused by increasing age.
- The clinical diagnosis of PD is made primarily on the basis of the cardinal motor symptoms of rest tremor, muscle rigidity, bradykinesia and postural instability.
- Clinical heterogeneity is extensive and is reflected in the emergence of PD sub-types or phenotypes.
- Dopaminergic medication is the mainstay treatment for PD.

Chapter 2 explains the terminology used in speech-voice studies, describes the varied PD speech and voice symptoms with special focus on voice symptoms, outlines evaluation approaches used to identify speech and voice symptomatology, gives consideration to possible influencing factors in speech and voice analysis, and finally describes findings from studies exploring relationships with disease variables.

Chapter 2. Speech and Voice changes in PD

The focus of this thesis is voice tremor in PD. Chapter 2 addresses speech and voice changes in PD, in order to place voice tremor in the context of the wider changes in the speech-voice system. The relevant technical terms frequently used in the literature are explained in section 2.1. Sections 2.2 and 2.3 delineate the overall speech and voice symptomatology respectively. Evaluation approaches and relevant studies applying these measures are discussed in section 2.4. Potential confounders associated with PD are explored in section 2.5. The final section 2.6 relates PD speech and voice symptom to the underlying disease process which was the focus of chapter 1.

2.1 Terminology

Speech generally refers to the production or articulation of sounds in words and sentences used to communicate a message verbally and involves the tongue, lips, soft palate and mandible. *Voice* refers to the sound that is generated through the combined action of the expiratory breath and muscular properties of the vocal cords and modified by the resonating cavities above the vocal cords. Voice relates to the function of the larynx. The term *phonation* is frequently used interchangeably with *voice.* *Prosody* incorporates loudness, pitch and rate of speech and refers to the stress, intonation and rhythmic patterns of a language. *Fluency* refers to the smooth flow of words and sentences. *Dysfluency* refers to presence of (unexpected) pauses, hesitations, false starts, repetitions of sounds and syllables. *Intelligibility* of speech refers to the degree to which a listener/s can understand a person's speech. *Dysarthria* is a neuromuscular speech disorder, potentially involving the four speech sub-systems: respiratory; phonatory, resonatory; articulatory. Respiratory refers to the lungs and breathing; phonatory refers to the vocal cords and voice; resonatory refers to balance of sound between oral and nasal cavities which in turn relates to nasal and non-nasal resonance; articulatory refers to articulators used in the production of different sounds. *Communication* refers to a speaker conveying a message to a listener/s using either, a verbal and/or a non-verbal medium or both. *Non-verbal communication* relates to facial expression and arm gestures that may accompany speech.

2.2 Symptomatology

Motor speech, voice and communication disorders are strongly associated with PD [73] [31] [74]. Reported prevalence rates are high with varied speech and voice symptomatology reported across studies[75] [76] [77] [78]. For example, in a study of 178 patients with parkinsonism, [idiopathic PD and post-encephalitic etiologies (mixed)], 89% were reported to have impaired function of the larynx, lip and tongue, on perceptual voice analysis[75]. Logemann et al.,[76] in a different study of 200 patients (mixed etiologies) reported mis-articulations in 45 % of their sample. Miller et al.,[77] in a study of 125 pwPD reported that 69% had reduced intelligibility of speech. Sapir et al.,[78] found that 85% of their group of 42 pwPD had voice changes, some of whom had additional deficits in articulation, prosody, and fluency.

In addition to the varied speech and voice symptoms just described, non-verbal communication is also impaired as a result of a masked-like facies, reduced blinking, smiling, arm gestures, and deterioration in writing[79] [31]. PwPD are perceived negatively and less likeable by their listeners, as a result of reduced fundamental frequency variability (monopitch), increased use of pauses, and lack of facial expression[80] [81]. Speech and voice problems in pwPD are associated with increasing disability and may be an equal or more disabling feature than the cardinal motor signs[82] [83], with poor awareness of symptoms reported[84].

The term 'hypokinetic dysarthria' coined initially by Darley et al.,[85] in a seminal piece of work, is frequently used as a global descriptor of the varied perceptual speech and voice symptoms in PD. 'Hypokinetic' refers to reduced movement extent [86] and, 'dysarthria' relates to the neuromuscular speech disorder (section 2.1). However, it is clear that the term 'hypokinetic dysarthria' does not capture the clinical heterogeneity that is associated with the PD profile[87] [88] [89].

2.3 Voice symptomatology

Among the heterogeneity, there is consensus that the voice-related features are central among the diverse symptomatology in pwPD, with voice impaired more

frequently than the other symptoms and featuring early in the disease process. [31 88 75 89 77 90 64] Darley et al.,[31] considered that monopitch, monoloudness and reduced stress were the most salient features evident when they evaluated thirty eight speech dimensions in a group of 32 pwPD. Stewart et al.,[88] in their study of twelve 'early' stage (mild disease severity) pwPD reported that changes in voice quality (breathiness, roughness), reduced loudness, and monopitch were the most common voice features on a dysarthria evaluation. Logemann et al.,[75] reported that 89% of a group of 200 patients had abnormal vocal features (breathiness, hoarseness, roughness,tremulousness), in contrast to 45% with articulation and 20% with rate disorders. Chenery et al.,[89] in their study of nineteen pwPD reported that from a total of thirty - two respiratory, speech, and voice symptoms, the voice symptoms (hoarseness, breathiness, strained-strangled phonation) occurred more frequently than the other symptoms. Miller et al.,[77] in a survey of one hundred and twenty-five patients reported that 76% of the group felt that their voice was not as good it used to be prior to PD. Ho et al.,[90] found that 73.5 % of a group of two hundred PD patients showed a gradual deterioration of speech features, with voice quality being the first parameter to change. Finally, Harel et al.,[64] in a retrospective speech analysis identified reduced fundamental frequency variability (a measure of pitch variability) during free speech in two pwPD prior to the clinical diagnosis of PD.[64] The fact that voice symptoms frequently occur early in the PD clinical presentation and even more importantly in the 'pre-clinical' [46] (section 1.5) stage of the disease warrants their focussed attention.

Although there is agreement regarding the salience and early presentation of voice problems in PD, there is less clarity regarding the presence and nature of voice tremor. Duffy et al.,[84] consider that 'true voice tremor' is uncommon in PD, but consider that the voice may be 'unsteady' or 'tremor like'. The authors did not elaborate on what they meant by 'true voice tremor and how it is different to 'tremor like' or 'unsteady'. Darley et al.,[79] state that the tremor of parkinsonism is not reflected in speech. However they did not state how they came to this conclusion. Conversely, other authors have described tremulousness,[75 91] 'vocal tremor'[88] and shakiness in pwPD. The issue of varied tremor descriptors will be revisited in chapter 4.

2.4 Evaluation approaches

A major goal of this thesis is to find ways to evaluate and measure PD voice tremor, so that methods of identification can be improved upon. The purpose of section 2.4 is to assist in this goal with an explanation of the terms used in the evaluation of speech and voice symptoms in general, to highlight some of the strengths and weaknesses of the different evaluation approaches, and finally to focus on evaluation methods and findings that have been used in PD studies.

A review of the literature highlights that a range of evaluation approaches have been used in the study of PD speech and voice symptomatology, These include auditory perceptual, visual perceptual, instrumental, and patient self-report measures. Table 2.1 provides a summary of studies with respect to the evaluation methods used, together with key study findings.

2.4.1 Auditory Perceptual evaluation

Auditory perceptual evaluation is a central component in the measurement of speech and voice disorders by speech and language therapists (SLT's)[92 93]. It is the process whereby an expert listener/s listens to a live or recorded speech sample, and rates intelligibility of speech and/or the overall (global) severity of voice quality on a rating scale[94]. In relation to voice, ratings are carried out using pre-determined features, e.g. roughness, breathiness, weakness, tremor. The person carrying out the rating ('rater/s') may be required to indicate the presence/absence of a feature or to rate its severity. The voice quality can be rated during different tasks; for example during sustained vowels, during reading, and/or speaking. The rating of voice quality during a speaking task is more functional than that during sustained vowels. However a sustained 'steady state' vowel task[95], allows the rater to focus on the target voice quality without the extraneous influence of different articulatory configurations.

The key strengths of perceptual evaluation are that: it has the most functional significance relative to the other approaches, in that a person's voice is judged to be normal or abnormal through the ear of the listener; it is convenient; does not require expensive instrumentation; is non-invasive; and findings are easily

communicable between clinicians[110 94].However, perceptual evaluation is susceptible to a variety of sources of error and bias[110] . Listeners vary widely in their levels of reliability and agreement sometimes failing to reach even chance levels in the mid-range of the rating scale[96]. Suggested solutions to the 'unreliable rater problem' include: averaging the scores across raters to achieve a reliable mean (based on the assumption that rating variability within and across raters is mostly random),[97] and training listeners to increase the extent to which they share common standards for different voice qualities[98]. In designing the protocol for perceptual rating in the current study, cognisance was given to these recommendations.

There are a variety of formal perceptual rating tools available for rating voice quality features[94], including the GRBAS[99] scale, and the Consensus Auditory Perceptual Evaluation of Voice (CAPE-V)[100]. There are a number of similarities and differences between the GRBAS and CAPE-V, which are important to mention in the context of the current study. Both measures are reported to have a similar mild level of difficulty regarding the application of the scale[101]. They use different measurement scales, GRBAS an ordinal measurement scale and the CAPE-V a continuous visual analogue scale (VAS). The VAS in CAPE-V is considered to have greater sensitivity in detecting small differences in voice quality than has the ordinal scale in GRBAS[101]. Finally, CAPE-V offers the possibility of including additional parameters for rating in additional to the standard pre-determined measures in GRBAS.

In PD studies, perceptual rating has been the cornerstone of speech and voice analysis studies and has frequently been used as the sole method of evaluation [31 75 76 89 102 78 90 103]. A striking feature of perceptual based PD studies is their generic focus on a wide range of different sub-systems (voice, respiration, articulation, prosody), in the same study. PD studies carried out by Darley et al.,[31] Logemann et al.,[75] Chenery et al.,[89] Stewart et al.,[88] Murdoch et al.,[104] and Plowman-Prine[103] all exemplify generic perceptual approaches (Table 2.1).These studies reflect the extent, complexity and variability of perceptual changes in pwPD, and thus are valuable. However, a weakness of this approach in relation to PD symptomatology is that varied descriptors are used

extensively, with the result that there is little detailed knowledge on any one specific feature. This certaintly has been the case with PD voice tremor, and this issue will be elaborated on further in Chapter 4. In addition, an overreliance on perceptual evaluation, relative to visual perceptual (section 2.4.2) and instrumental evaluation (2.4.3) leads to poor characterisation of the underlying pathophysiology. To counteract this weakness, the additional use of physiological and acoustic evaluation is recommended[89].

2.4.2 Visual Perceptual evaluation

Another evaluation approach used in the evaluation of speech and voice symptoms is that of visual perceptual evaluation, which is the process whereby a rater or raters makes a judgment about the presence and/or severity of a pre-determined behaviour based on what the person perceives visually. Appearance and/or movement of facial features[55], the jaw[105], tongue[105], palate[106] and larynx[107] may be rated clinically using visual perceptual evaluation. Clearly, identifying structures in the vocal tract is an important component in the evaluation of speech and voice symptoms.

However, obtaining an adequate view of internal bodily structures, for example, the palate, the tongue base, and the larynx for the purpose of diagnostics is challenging. Specialised 'invasive' procedures and expertise is required. Laryngoscopy is a broad term used to describe the procedure whereby the larynx and associated structures in the vocal tract are examined using a flexible endoscope and/or a rigid endoscope. The flexible endoscope is passed transnasally ('nasendoscopic' examination) and permits the examiner to view a number of different structures in the vocal tract including the soft palate, tongue base and larynx during speech and voicing. The term 'nasendoscopy' or 'nasendoscopic' examination will be used by this author when referring to the aforementioned procedure in the remainder of the thesis. A key strength of the flexible endoscope in voice evaluation is that different structures in the vocal tract can be visualised and imaged during a range of speech and voice tasks. In contrast, the rigid endoscope is introduced transorally, and affords a view of the larynx and vocal cords during a sustained /i/ [i] vowel [(International Phonetic

Alphabet (IPA)]. The vowel /i/ is pronounced 'e' as in the word 'eel'. In this thesis, the 'vocal tract' is an all encompassing term referring to the vocal cords, the larynx and the structures above the larynx (tongue base, palate), involved in speech and voice production. This researcher is aware that other texts may also include the respiratory structures (lungs, diaphragm) in their definition of the vocal tract. However, for the purpose of this thesis, the respiratory structures are not included in the definition of vocal tract[108]. The examination of the vocal tract for the purpose of identifying and measuring voice tremor will be addressed in Chapter 4.

In addition to the inherent difficulty in visualising dynamic vocal tract structures, a further challenge is in quantifying the observations, since one is required to extract objective information from observations which are subjective,[109] and prone to variability between individuals[110]. It is important to note that visual perceptual rating of laryngeal examinations is plagued with the same reliability issues as perceptual rating. There are also issues around rater experience and training, quality of video recordings, and the method of rating the target behaviour[111]. Rating involuntary movement in the vocal tract from video recordings has been shown to have poor reliability in a study of patients with 'normal' voices[111].

Despite the possibility afforded by nasendoscopy of gaining increased understanding of the underlying PD vocal tract physiology, few PD studies have adopted this approach. Those studies that have used laryngeal examination, report closure defects (incomplete closure of the vocal cords), bowing of the vocal cords, contraction of the supra-glottic (above the vocal cords) muscles, and tremor in the strap muscles, tongue and larynx in pwPD[34 107 112 113 114].

2.4.3 Instrumental evaluation

The term instrumental evaluation encompasses a range of computer-based equipment methods used to measure the acoustic properties of the speech output signal (acoustics), the movement of structures (kinematics), and the physiological properties of speech and voice related structures. Instrumental evaluation is considered to add objectivity to findings, since the ensuing

measures are quantifiable and are not subject to the same variability as is the case with listener ratings. The different instrumental approaches and the PD studies that have applied them in voice analysis are outlined in the following sub-sections. The studies reported in this section are also summarised in Table 2.1.

Acoustic measures

Acoustic measures provide a non-invasive measure of the voice output pressure signal and provide indirect quantifiable information about the physical properties of sound[115]. For example, the acoustic measure fundamental frequency relates to the rate of vibration of the vocal cords, amplitude relates to the extent of vocal cord excursion. Jitter and shimmer relate to the amount of perturbation (instability) in the frequency and amplitude of the voice respectively [116].Acoustic measurement of phonatory function is widespread and popular in voice quality measurement, aided by the proliferation of cheaper computers systems, the availability of automated analysis algorithms, the non-invasive nature of the equipment, and the quantifiable findings[117 118].

Acoustic material for the evaluation of voice is frequently drawn from maximally stable or 'steady state' vowel prolongations [94], to avoid the confounding effects of interaction between the vocal tract and larynx. Understandably therefore, the clinical utility of many acoustic measurements based on sustained vowels is questionable in relation to their significance for voice quality and speech. The relationship between the majority of acoustic measures and perceptual features has not been established[117]. The authors of the Motor Speech Profile (MSP) programme from the Computerised Speech Laboratory (CSL) advised that since many of the parameters were new it would take some time before efficacy was established[119].

In PD studies, acoustic measures have been applied for a range of purposes, including some of the following: differentiating pwPD from healthy controls[120 121]; identifying acoustic markers in patient who have not received a clinical PD diagnosis (pre-clinical)[4]; chart disease progression[64]; identifying gender differences[122 123]; examining the effects of dopaminergic medication on

phonatory function[121]; and examining relationships with non-speech PD variables [124]

An array of acoustic measures have emanated from these studies as highlighted in the following brief review of some of the literature. Jimenez-Jimenez et al.,[120] compared a group of pwPD and controls on selected acoustic measures, fundamental frequency (Fo), jitter, shimmer, harmonic - noise ratio (HNR), using the CSL and differentiated the groups, with findings of higher Fo in female PD and higher jitter in male PwPD. Goberman et al.,[121] identified higher mean Fo, higher fundamental frequency variability (SDFo), and lower intensity range in nine pwPD versus controls.

Jitter and shimmer measures which are widely used for clinical and research diagnostic purposes in voice studies require mention here[125]. Also referred to as 'short-term' measures of perturbation, they contrast with 'long-term' fluctuation measures which are associated with tremor and will be discussed in a later section. The 'short-term' aspect refers to the fact that variation (perturbation) occurs between glottal cycles in less than 10 msec. Although jitter and shimmer measures have been used widely in PD studies, they are considered to be more informative in relation to laryngeal pathology than to the study of neurological disorders[125]. This study on voice tremor will not include short-term measures of instability.

Harel at al.,[4] in a retrospective longitudinal single case review examined long-term variation of fundamental frequency (vFo) in speaking using the multi-speech programme from the CSL and found reduced speech variability, years in advance of the PD diagnosis. They carried out the speech analysis from archived video recordings from a national television news service which were available to them. The authors argued for using acoustic voice measures to identify patients in pre-clinical (symptoms appearing before clinical diagnosis is made) stages of PD[4]. Stewart et al.,[64] used narrow band spectrogram to chart disease progression in a study of twelve patients and identified visually, frequency and amplitude tremor in the spectrogram in four patients with early stage PD.

Acoustic measures have also been used to look at gender differences in a comparison study of pwPD and age-matched neurologically healthy controls[122]. Using tremor measures, frequency tremor intensity index (FTRI %), amplitude tremor intensity index (ATRI %), frequency tremor frequency (Fftr Hz), and amplitude tremor frequency (Fatr Hz) from the Multi Dimensional Voice Programme (MDVP) of CSL, Tanaka et al.,[122] reported that tremor measures FTRI% and Fftr Hz were significantly higher for male PD patients than for male controls.

Goberman et al.,[121] looked at the effects of dopaminergic medication on phonatory function in nine pwPD using acoustic measurement. Although they found no group effect from medication, they described an increase in fundamental frequency (Fo) in vowels and reading in some individuals.

Finally, there is evidence of acoustic measures being used to understand ways in which speech and non-speech symptoms in PD relate. In a study of nine pwPD, Goberman et al.,[124] selected Fo and FoSD as measures of laryngeal rigidity and stability respectively. They reported that increased voice instability (FoSD) correlated significantly with the total score and the axial (gait, facial expression, posture) score from the UPDRS.

This review highlights the varied ways in which acoustic measures have been applied to study PD voice symptomatology. However it is not always clear what the acoustic measures are in fact measuring. There is a need to utilise additional auditory and visual perceptual measures to give clinical meaning to the measures. The application of acoustic measures to the study of voice tremor will be addressed further in section 4.4.

Kinematic

Another instrumental approach that has been used albeit with less frequency than acoustics is that of kinematics, which measures the amplitude and range of movement. Kinematic evaluation involves the placing of markers on target muscles and structures for the purpose of measurement [108]. In PD studies, kinematic movement of the rib cage, lip, and the jaw have been measured with mixed findings[126] [127]. Murdoch et al.,[126] studied respiratory function in nineteen

pwPD, all of whom had some features of hypokinetic dysarthria, and a matched control group. They recorded the circumference of the rib cage and abdomen by means of strain-gauge belt pneumographs, and reported that kinematic measurement during conversation and reading showed normal results in their group of PD patients. They concluded therefore that reduced range and amplitude of abdominal and rib cage movement during speaking was not a contributory factor to the discernible dysarthria in this group of pwPD. Walsh et al.,[127] also using kinematics studied lip and jaw movements in sixteen pwPD and sixteen age-and sex-matched neurologically healthy controls. The authors [127] reported decreased amplitude and velocity of lower lip and jaw movements in pwPD in comparison to controls. However, when it comes to measuring the movement of the more 'internal' vocal tract structures, for example the soft palate and/or the laryngeal structures during speaking, kinematic measurements are not indicated.

Spirometry

Continuing with instrumental approaches, spirometry measures a range of indices of pulmonary function including respiratory rate, tidal volume, vital capacity, residual volume, forced expiratory volume 1 sec (FEV_1) and total lung capacity. Murdoch et al.,[126] in a study combining spirometry and kinematic evaluation, found that only a minority of pwPD had lung volumes and capacities outside normal limits. However, they reported irregularities in chest wall movements of some pwPD on sustained vowels and considered that it may have been suggestive of tremor in the respiratory muscles[126]. The potential role of spirometry and other respiratory measures in the evaluation of PD voice tremor is acknowledged by this author however respiratory evaluation is outside the remit of this thesis.

Auditory perceptual, visual perceptual and instrumental approaches are clearly clinician led and although offering considerable insight into PD speech and voice symptomatology, they do not address the effect of the impairment on the pwPD. The next sub-section which looks at the patient's perspective of speech and voice dysfunction, together with the impact on his/her life completes section 2.4.

2.4.4 Patient self-report measures

Self-report measures help to identify the disability associated with the impairment which in turn helps to inform the clinical management of the problem, and may assist in decision making in relation to planning and allocation of therapy resources.

Disability, a multi-dimensional concept relates to the relationship between a person with a health condition, and a person's context (environmental, personal issues). Voice disorders can impact significantly on a person's overall health and quality of life[128], with problems related to psychological, emotional, social and work-related issues[129]. Evaluating the patient's perception (self-report) of voice impairment and the resultant functional and emotional sequelae is an important component of voice studies[130].

Studies have clearly shown that pwPD have greater self-reported voice disability than people who do not have PD[131], and that voice related disability is associated with both mild[131 132] and severe disease severity[113](*Table* 2.1). Midi et al.,[131] studied twenty patients with a less than 5 year diagnosis of PD and found that mean total scores on the Voice Handicap Index (VHI) for male and female patients were higher (meaning increased voice disability) than sex-matched controls. The mean (SD) total VHI scores for male pwPD was 34.4 (3.45) in comparison to 0.60 (1.9) for male controls and 15.5 (2.86) for female pwPD in comparison to 0.9 (1.85) for female controls. It is interesting to note the higher VHI score (greater disability) in male pwPD than in female pwPD[131]. This is a surprising result when one considers that voice problems in general are more prevalent in females than males. Blumin et al.,[113] studied fifteen patients with advanced PD, and reported that 50% of the patients had VHI scores greater than 60 points, suggesting significant self-perceived voice handicap.

Knowing which aspect of voice-related impairment relates to voice disability is an important issue, since it helps to inform treatment decisions, and thus minimise voice disability. Carmichael et al.,[132] in a study of respiratory function and voice disability in nine pwPD found that $\underline{FEV_1}$ was negatively correlated with the emotional sub-section of the VHI. The findings imply that negative emotions related to voice increase (worsen) as respiratory function decreases.

Reduced respiratory function may have a negative effect on voice quality and volume. However the authors[132] did not include a control group, therefore, the study findings are inconclusive regarding reduced respiratory function and voice disability in pwPD. Frost et al.,[71] also using the VHI, reported a significant negative correlation between speech intelligibility and voice disability, meaning that the more intelligible the speaker the lower the voice disability. However, similar to Carmichael et al's[132] study, Frost et al's [71]findings are inconclusive regarding relationship between speech intelligibility and voice disability in PD, since they did not study people without PD.

In relation to voice tremor, the nature of the relationship with voice disability is unknown and warrants investigation. However, based on the aforementioned study findings, it would be important to control for the confounding effect of ageing on voice disability, by studying age matched controls also.

This review has highlighted the varied evaluation approaches that have been applied in PD speech and voice studies. It is evident that each approach has value and can potentially increase understanding of PD symptomatology, including voice tremor which is the subject of this thesis. Chapter 4 will address specifically voice tremor in PD in the context of ways in which it has and has not been evaluated, giving direction to the research questions in this study. The next section 2.5 addresses the potential confounding effect of ageing, depression, anxiety and medication on PD speech and voice symptoms.

Guide to Abbreviations Table 2.1

CSL	Computerised Speech Laboratory
DBS:	Deep Brain Stimulation
EGG:	Electroglottography
FEV_1	Forced expiratory volume 1 second
FRC:	Functional residual capacity
Fo:	Fundamental frequency
FTRI:	Frequency Tremor Intensity Index (FTRI) (MDVP parameter)
HNR:	Harmonic to Noise Ratio
IC:	Inspiratory capacity
Med:	Medication (dopaminergic**)**
MDVP	Multi-dimensional voice programme from (CSL)
NHR:	Noise to Harmonic Ratio
NR	Not reported
RV:	Residual volume
SPI:	Soft phonation Index (MDVP parameter)
SLT	Speech & Language Therapist
Sx:	Surgery
TLC:	Total lung capacity
vFo:	Variation in Fo
Vis-P:	Visual Perceptual evaluation
VC:	Vital capacity

Table 2.1.Overview of PD studies, evaluation approaches, voice and speech findings

Reference	*n*	Method	Speech and Voice areas	Findings	Rating variables
Darley et al.[31] 1969 Parkinsonism Control: No Med: unknown	32	Perceptual	38 speech dimensions 7 categories [(pitch,loudness, vocal quality, respiration, prosody, articulation, overall (general impression)]	Monopitch, monoloudness & reduced stress most striking characteristic.	Task: varied between reading, conversational speech, sentence repetition 7 point scale of severity 3 raters
Logemann et al.[75]1978 (PD & post-encephalitic) Control: No Med: Off	178	Perceptual	Voice, speech, rate, resonance, articulation	89% vocal tract features (larynx, lip tongue) 45% laryngeal as the sole symptom 13.5% tremulous voice	Task: read & speak Present/absent 2 raters
Logemann et al.[76]1981 PD & post-encephalitic) Med: unknown Control: No	200	Perceptual	Articulation	45% misarticulations Spirantisation: weakened plosives, affricates and fricatives	Task: Reading sentences 2 raters

Hanson et al.[34] 1984 Med: On Control: No	32	Vis-P (Laryngeal exam)	Cine-laryngoscopy	Bowing Contraction of supra-glottic musculature Tremor in strap muscles, tongue	Examiner rated
Chenery et al. [89]1988 Med: NR Control: Yes (age & sex matched)	19	Perceptual	32 dimensions 5 aspects (Voice, respiration, prosody, articulation, intelligibility)	100% Voice (hoarseness, strain-strangled, breathiness), prosodic, respiratory, articulatory	Task: Dysarthria ax Reading 9 judges Interval scale
Murdoch et al. [126]1989 Med: On Control: Yes (age/ sex matched)	19	Instrument (Spirometry) Kinematic	Respiration rate, tidal volume;VC; $FEV_{1,;}$ FRC; IC; TLC; expiratory/ inspiratory reserve volumes; volume/flow relationships Changes in circumference of rib cage and abdomen	Spirometry: minority pwPD had lung volumes outside normal Kinematic: normal findings 'Motion jerks' in rib cage suggestive of tremor in respiratory muscles of some pwPD	Task: conversation & reading

Hartelius et al.[133]1994 Med: NR Control: No	460	Self-report	Frequency, type & severity of speech and swallowing symptoms	70 % experience speech & voice problems after PD Voice (weak, hoarse, monotonous) Articulation (imprecise)	Survey
Hertrich et al.,[123] 1995 Med: On Control: Yes, (not age/sex matched)	24	Instrument [134] [(Acoustic) (CSL)]	Spectograms of EGG recordings Fo; jitter; shimmer, HNR	Increased Fo in males pwPD	Task: Sustained /ah/: 1 second interval
Stewart et al. [88]1995 Med: None Control: No	12	Perceptual Instrument (Acoustic) (DSP Sonagraph)	Speech, voice, rate, prosody, Tremor	100% 2 features dysarthria Voice (roughness, reduced loudness, breathy, monopitch) 'Vocal Tremor' on narrow band spectrogram (amplitude & frequency) in 4/12pwPD	Task: dysarthria Assessment (Scale 1-7) Sustained vowel

Perez et al.,[107]1996 Med: NR Control: no	n=29 (22 PD; 7 PPS)	Vis-P (Laryngeal exam)	Compare tremor in pwPD and PPS patients Describe vocal fold vibratory characteristics	Laryngeal tremor evident in 55% Kinetic i.e. phonation tremor /i/ in 71% pwPD Vertical laryngeal tremor predominant Predominant open phase configuration. High incidence of phase asymmetry (timing of opening and closing of vocal cords)	Task:' rest'; phonation /i/ vowel at normal pitch & loudness; loud phonation
Coates et al. [102]1997 Med: On (excepting 2 pwPD) Control: No	48 (20males; 28 females) 46 on med 2 no meds	Perceptual	Speech intelligibility (Intelligibility of Dysarthric Speech Assessment Scale)	Reduced speech intelligibility in 64% of group. Mean % score for sentences was 91.1%	Task: word/ sentences
Murdoch et al[104]1997 Med: On Control: Yes	20	Perceptual Instrument	9 laryngeal dysfunction parameters incuding, pitch steadiness, excessive pitch fluctuations 1.EGG 2.Computer airflow system (Aerophone II)	89.5% showed deviant laryngeal features (hoarseness,glottal fry, pitch unsteadiness, breathiness) No difference between PD & control on EGG measures 4/5 aerophone parameters differentiated the groups	Task: reading Raters: 2 judges (SLT's) – descriptive 4 point rating scale

Jimenez-Jimenez et al.[112]1997 Med: Untreated Control: Yes	22(12M; 10 F)	Instrumental [(Acoustic (CSL)] Vis-P [(Laryngeal exam) (indirect and/or nasendoscopy)] Self-report	Fo, Jitter, shimmer, Harmonic/Noise ratio Presence of laryngeal tremor, degree of glottal closure, presence of hyperphonation. Voice normal/ altered/ very altered. Tone: low/normal/high Presence/absence: monopitch, harshness, voice arrests, pitch breaks, tremor, struggle	Significant differences between PD & control jitter & shimmer and Fo females 45% PD Laryngeal tremor versus 0% controls Glottal closure 'good ' in most pwPD	Task: sustained /ah/ vowel (2 seconds); sentence Rater: 1 (not blinded)
Gamboa et al.[135]*1997* Med: On Control: Yes (age-sex-matched)	41 (24M, 17 F)	Instrumental [(Acoustic)(CSL)] Vis-P [(Laryngeal exam) (indirect and/or nasendo)] Self- report	Fo, Jitter, shimmer, Harmonic/Noise ratio Presence of laryngeal tremor, degree of glottal closure, presence of hyperphonation. Voice: normal/ altered/ very altered. Tone: low/normal/high Presence/absence: monopitch, harshness, voice arrests, pitch breaks, tremor, struggle	PD significantly higher Fo, jitter, lower H/N noise; lower intensity & frequency SD in sentence microphone signal, lower phonational range Tremor in 14.6%; hyperphonation signs in 20%; 2pwPD showed slight lack of glottal closure Most outstanding features: monopitch; tremulousness; strain/struggle. 14/27 reported tremulousness	Task: sustained /ah/ vowel (2 seconds); sentence Rater: 1 (not blinded)

Ackermann et al.,[136]1997 Med: On Control: Yes (not age/sex matched)	12	Instrumental Perceptual (speech)	Kinematic - lower lip gestures during speech) (Optoelectric movement analysis system) Intelligibility		 Task: word
Ho et al.[90] 1998 Med: On Control: No	200	Perceptual	Voice, articulation, fluency (conversational speech) (communication profile)	73%-Voice (change in quality, volume reduction); Articulation; Fluency	2 trained-listeners Quantitative and qualitative, presence and severity of abnormal features.
Sapir et al. [78] 2001 Med:	42	Perceptual	Voice, articulation, fluency, prosody	85% voice changes +- articulation, prosody, fluency	Task: reading Raters:2 SLT Presence/absence
Sanabria et al.[137] 2001 Med: Off & On Control: No	20	Instrument (Acoustic) (MDVP)	Effects of dopamine on vocal function (tremor, noise, frequency and amplitude parameters)	Fo increased with med. Jitter, SPI, FTRI decreased with med	Task: sustained /ah/ vowel x 2 seconds
Blumin et al., [113] 2004 Med: NR Controls: No	15	Vis-P [(Laryngeal exam(Rigid endoscopy)] Self-report (VHI)	Baseline of laryngeal findings pre DBS (vocal tremor, glottal configuration, bowing, other lesions) Voice disability	87% significant vocal fold bowing 53% vocal tremor (tremulous movement of laryngopharynx during phonation) 50% significant voice handicap (VHI scores > 60)	Task: phonate /i/

Gobermann et al. [124] 2005 Med: On Control: No	9	Instrument (Acoustic CSL)	Articulatory Prosodic Phonatory	7/16 speech acoustic measures correlated with non-speech measures. Phonatory: FoSD	Tasks: sustained vowel reading, monologue
Miller et al. [74] 2006 Meds: On Control: No	37	Self-report	Perception of speech changes	Perceived changes to communication. (changes to voice, making oneself, understood, managing conversations, reactions of others)	Interview (qualitative)
Miller et al. [77] 2007 Med: Off Control: Yes (age matched)	125	Perceptual (speech) (Self-rating)	Speech intelligibility Test Speech & voice	Reduced intelligibility (69%) PwPD felt not as good as pre PD (76%)	Task: single words
Miller et al.,[82] 2008 Meds: off Control: Yes (40 unaffected speakers)	104	Self-rating	Perceived impact of PD on self-perception of communication	PD- a significant perception of deterioration in communication after onset of PD	Survey

Midi et al. [114] 2008 Med: On Control: Yes	20	Perceptual Vis-P [(Laryngeal exam) (rigid scope)] Instrument [(Acoustic), MDVP)] Self-report (VHI)	Voice quality (GRBAS) Degree of glottis closure Jitter, shimmer, NHR, vFo, Fo Voice disability	Compared to controls: Male PD: voice more hoarse, breathy, weak Female PD: more breathy, weak Nonclosure glottic pattern (posterior chink or spindle shape) more common in PD Mean jitter & shimmer higher (not significant) Higher Fo in female PD than controls Higher vFo in male PD NHR differences not significant Greater voice disability in PD than controls (male & female)	Task: reading Raters: 4 (blinded)` NR Sustained /ah/ 5 seconds Questionnaire
Carmichael et al [132] 2009 Med: On Control: No		Instrument Spirometry Self-report (VHI)	Respiratory function & muscle strength Voice disability	Weakness & dysfunction of respiratory muscles Mean total VHI score 39.22	 Questionnaire
Plowman-Prine [103] 2009 Med: on & off Control: No	16	Perceptual	35 speech dimensions grouped under 6 speech sign-clusters (articulation, respiration, resonance, phonation, prosody, rate)	Prosody most affected of speech sub-systems Voice tremor: Overall mean score 1.85 (12^{th} highest score out of 35 speech dimensions)	Task: reading Raters:3 blinded SLT's using 7 point scale

Frost et al. [71] 2010 (23 post DBS 28 non DBS) Med: Control: Yes (non-surgical PD)	51	Perceptual (speech) Self-report (VHI)	Speech Intelligibility (reading sentences) (for sx patients only) Voice disability	79% intelligibility pre-sx 72% intelligibility post-sx Disability increased over time in both DBS & non DBS group Significant relationship between VHI and speech intelligibility	Task: Reading sentences (for surgery patients only) Rater: 1 (SLT)
Tanaka et al. [122] 2011 Med: On Control : yes (age-matched)	39	Instrument [Acoustic (MDVP*)]	Tremor measures (FTRI, ATRI, Fftr, Fatr)	Higher F0 in PD males versus controls	Task :Reading
Walsh et al., 2012 [127] Med: On Control: yes (age ±3 years, sex)	16	Instrument (Kinematic) [(Acoustic) (Praat software)]	Lip & jaw movements Intensity, speech rate, F2 slope	Decreased amplitude & velocity of lower lip and jaw movements Decreased vocal intensity Reduced 2nd formant slops	Kinematic system (Northern digital Optotrak 3020) Task: 2 sentences

2.5 Speech and voice symptoms and confounders (ageing, depression, anxiety, medication)

An evaluation of PD speech and voice symptomatology would be incomplete without considering potential confounding variables (ageing, depression and anxiety, and dopaminergic medication) that exist in PD and require consideration.

2.5.1 Ageing

The ageing process has an impact on voice and laryngeal characteristics secondary to changes in skeletal and muscular systems of the body [3 138 139 140 141]. There are alterations in respiratory support, atrophy of neural and muscle tissues, and calcification of laryngeal cartilages. Further, the vocal folds lose their elastic and collagenous fibres which makes them stiffer and thinner[140]. These physiological changes are reflected in the acoustic voice signal. Elderly speakers (over 70 years) have been found to have significantly different (poorer) acoustic measurements on fifteen selected parameters from the MDVP, when compared with young and middle aged adults[141]. Measured parameters included fundamental frequency, jitter, shimmer, harmonic to noise ratio, and soft phonation index. Tremor measures were not included in the study.

An increase in fundamental frequency (Fo) has been associated with male pwPD[121 123 22 122] and with ageing males[140]. A bowing appearance of the vocal cords has been described in relation to the ageing larynx [142] and to the PD larynx [113 142]. Voice tremor has been documented in relation to PD and is also a positive predictor of increasing age[143]. A challenge therefore is to determine which voice symptoms are secondary to the ageing process, which stem from PD[144] and which may stem from both processes[145]. An important and necessary step therefore is to study neurologically healthy age-sex matched controls alongside pwPD. The issue of controls will be addressed in the current study.

2.5.2 Depression and anxiety

There is a strong association between anxiety and depression, and PD (section1.4) A depressed mood impacts negatively on speech and voice manifested in symptoms of reduced stress, monopitch and monoloudness[146]. A salient and prevalent feature of PD voice is reduced variability of pitch and loudness, resulting in a monotone voice[147]. When a person feels anxious or nervous, their voice may sound somewhat tremulous and 'shaky', a feature which is also associated with PD. It is difficult to discern if a perceived monotone tremulous voice in pwPD is secondary to disease-related physiological changes or to additive anxiety and depression or to both processes. Consideration therefore will be given in this study to the possible confounding effects of depression, and anxiety by measuring and identifying these variables[43].

2.5.3 Dopaminergic medication

The positive effect of dopaminergic medication on limb motor signs of tremor, rigidity and bradykinesia is widely acknowledged [70]. However its effect on speech and voice is less conclusive [69] [148]. For example, positive effects have been reported in relation to improvement in word intelligibility[149], and in reduction of voice tremor using acoustic measures [137]. Other studies show that there has been no significant improvement in acoustic[121] [150], perceptual[103] [148] [151], or glottographic measures[134] [152] [153] following dopaminergic medication.

However, when one looks at individual data, rather than group data, it appears that dopamine may differentially affect speech and voice symptoms[121] [152]. In Goberman's [121] study, six out of nine patients showed increased fundamental frequency (Fo), three patients showed decreased pitch variability and two showed increased intensity with dopamine medication. Conversely, Jiang et al.,[152] using a combination of acoustic, airflow, and electroglottography (EGG) found no change in Fo, jitter (pitch perturbation) or mean flow rate, with patients on medication. However they found that speed quotient (an EGG measure), shimmer (amplitude perturbation) and the extent of tremor measured through spectral analysis of the acoustic signal was decreased. It appears therefore, that dopamine may have a differential effect on different components of the

speech-voice mechanism, and may potentially increase or decrease voice tremor. Therefore, it is necessary for the current study to control for the possible confounding effects of medication on voice tremor and other speech/voice related variables. Following the practice in other studies, the proposal here would be to assess individuals in a practically defined 'off medication' state, which is considered to be at least twelve hours after the last medication dose [72]. The specific procedure followed in this study is outlined in methods section 5.4.

Further understanding of PD speech and voice symptomatology can be gained from exploring possible relationships with disease variables.

2.6 Relationship between speech and voice changes, and disease variables

Examining the relationship between speech and non-speech variables is worthwhile for a number of reasons. The practice increases understanding of the neurological mechanisms underlying dysarthria in PD, and in the PD disease process, which in turn contributes to diagnostics and treatment[78]. In addition, there may be greater prediction of which speech/voice variables are likely to show more change across dopaminergic medication cycles; greater understanding of why levodopa has a stronger and more consistent effect on non-speech than speech symptoms; better prediction of the likely effect (positive or negative) of deep brain stimulation (DBS) on speech/voice parameters[124].

In general, the assumption is that speech/voice symptoms deteriorate with an increase in disease severity and/or duration of PD [69]. The literature however shows mixed findings in relation to this subject. Some studies report a poor correlation[102, 77 135] others report a moderate correlation[78], and others report strong correlations[124]. Coates et al.,[102] in a study of forty eight pwPD found a poor correlation between reduced intelligibility of speech using a shortened version of the standardized Yorkston and Beukleman assessment scale, disease severity (UPDRS III), and disease duration. Miller et al.,[77] in a larger study of one hundred and twenty five speakers found no significant correlations and only weak correlations between speech intelligibility and disease duration and severity respectively. Gamboa et al.,[135] found that disease severity and/or

duration did not influence their findings using a combination of measures: acoustic (fundamental frequency, perturbation measures, harmonic/noise ratio); frequency and loudness range; maximum phonation time; s/z ratio.

Sapir et al., [78] in a study of forty two patients, using auditory perceptual rating reported a positive moderate correlation for the number of speech and voice abnormalities and the global UPDRS motor score, meaning that as disease severity increased a person had a greater number of speech and voice symptoms. Finally, Goberman et al.,[124] showed that some acoustic measures were significantly correlated with non-speech or motor symptoms when motor symptoms were measured with the UPDRS III scale. The acoustic measures used in the study [124] were variability of fundamental frequency (FoSD) in vowels/reading, F2 slope (rate of tongue movement) for /u/ and /ae/, articulation rate in monologue, and percent pause in reading and monologue.

Analysis of PD speech and voice symptomalogy in the context of the overlying disease process enhances understanding of the variability of symptoms across patients, intra-subect variability, and the differential effect of treatment on speech and voice variables.The relationship between voice tremor and disease variables will be discussed in section 4.6.

Summary:

- Speech and voice problems, subsumed under the umbrella term of ‘hypokinetic dysarthria, are pervasive in PD.
- The ‘hypokinetic dysarthria classification term does not adequately capture the heterogeneity of speech and voice symptoms in PD.
- Voice-related symptoms are central in the disease process and may even be evident in advance of the clinical diagnosis of PD.
- There is less clarity around the nomenclature and defining characteristics of voice tremor in PD than the other voice-related symptoms.

- A range of evaluation approaches including perceptual, instrumental and self-report have been applied to the study of PD speech and voice changes.
- Cognisance should be given to the confounding effects of age, depression, anxiety and medication on speech and voice symptoms.
- Evaluating the relationship between speech and voice symptoms, and disease variables offers opportunity to increase knowledge of disease pathophysiology.

The focus of Chapter 3 is tremor and its manifestation in PD.

Chapter 3. Tremor

Chapter 3 introduces the phenomena of tremor and more importantly gives an overview of PD tremor. In Section 3.1 tremor is defined, and the distinction between 'normal' and 'pathological' tremor explained. This is an important distinction, and has implications for the identification of voice tremor in PD. The system of classifying tremors is outlined in section 3.2, the different ways in which tremor can be measured are elucidated in section 3.3, and the final section 3.4 describes the characteristics of tremor in PD.

3.1 Definition of tremor

Tremor is defined as a rhythmical involuntary, periodic, sinusoidal oscillation of a body part[154 155]. It is differentially diagnosed on the basis of three aspects: the topography (the specific body part with tremor); the conditions under which the tremor is activated; the frequency of the tremor. In relation to the topography, the oscillatory behaviour may occur in one or a number of body parts including the limbs, trunk, head, vocal folds or facial structures[105 156 157]. Activating conditions for tremor include 'rest' and 'action' .The frequency or rate of tremor is measured in cycles or hertz (Hz) and different rates have been associated with different neurological conditions (section 3.2). In addition to the topography, activating conditions and tremor rate, tremor can also be described in relation to its amplitude and the shape of its waveform. The frequency is relatively fixed, whereas the amplitude and waveform shape are variable[154]. A tremor may be considered 'normal' or 'abnormal', although the distinction between the two types is not always clear.

Normal tremor

Normal tremor, also referred to as 'physiological tremor[158], is mostly invisible to the naked eye and is associated with the frequency band 8 -12 Hz (i.e. 8-12 cycles per second)[159 160]. An important feature of 'normal tremor is that it typically has a small amplitude and a high frequency[161]. The term 'enhanced physiological tremor' is applied to physiological tremor when its rate becomes irregular as a result of factors like anxiety, fatigue and hyperthyroidism[159]. In contrast, a tremor is considered to be abnormal or pathological when either the

movement is visible to the naked eye or if any frequencies occur that are lower than normal tremor, i.e., lower than 8 -12 Hz. However the distinction between normal and pathological tremor is not always clear since pathological tremors[159] can occur within the frequency band of physiological tremors.

Pathological tremor

Tremor is pervasive in neurological disease[162]. Pathological tremor is associated with a variety of neurological conditions including PD[163], pallido-ponto nigral degeneration (PPND)[164], amyotrophic lateral sclerosis (ALS)[165], essential tremor (ET), dystonia, multiple sclerosis(MS), and cerebellar ataxia[166]. It is also associated with metabolic diseases, peripheral neuropathies, toxins, certain medications (including neuroleptics, lithium) and, emotional states of anxiety and stress[160].

3.2 Classification of tremors

The pathological tremors may be differentiated from each other on the basis of different frequency bands and whether they are 'fast' or 'slow' tremors. For example, a tremor with a frequency band of 4-6 Hz associated with PD is a 'slow' tremor. Other 'slow' tremors are associated with cerebellar disease (3-5 Hz), and ET (4-9 Hz). In contrast, the 7-10 Hz tremor associated with ALS[116] [162], PPND [164], and multiple system atrophy (MSA)[167], is termed a 'fast' tremor or 'flutter'. However, there are problems differentiating pathological tremors solely on the basis of frequency bands, since the frequency bands can overlap as in the case of ET and PD with a frequency band of 4-9 Hz and 4-6 Hz respectively[159].

The Movement Disorder Society (MDS) have proposed a clinical classification for limb tremor based on the distinction between different tremor 'types', which are broadly sub-divided into 'rest' and 'action' tremor, on the basis of the conditions under which they are activated[155]. Action tremor is further subdivided into postural, isometric, kinetic,and task-specific kinetic-tremor[155].These tremor terms are delineated in Table 3.2. In addition to the physical characteristics of tremor, the medical history and neurological examination are also considered in tremor classification[155] [160].

Tremor is not confined to the limbs, and may occur in the head, face, jaw, and tongue, termed 'orolingual tremors'. Orolingual tremors[105],or tremors in the palate and/or larynx do not fit neatly into a limb classification system[105]. Silverdale et al.,[105] has proposed a different classification system for orolingual tremors to that for limb tremor with tremors described as being predominantly "rest" or predominantly activation-induced. However, the authors stress the importance of describing in detail the 'features' of the tremors, so that classification is less related to knowing the neurological diagnosis and more to the discernible features[105]. Tremor features in the PD vocal tract have not been comprehensively described (section 4.5.3). Identification of tremor features is achieved through different measurement approaches outlined in section 3.3.

Table 3.2. Tremor types based on conditions under which the tremor is activated

Tremor type	Activation Condition
Rest Tremor	Body part is not voluntarily activated and is completely supported against gravity
Action Tremor	Voluntary contraction of a muscle (postural, isometric and kinetic)
Postural Tremor	Voluntarily maintaining a position against gravity (hands outstretched)
Isometric Tremor	Muscle contraction against a rigid stationary object
Kinetic Tremor	Voluntary goal-directed or non-goal directed movement
Task-specific kinetic-tremor	Goal –directed activities (e.g. speaking and hand-writing)

3.3. Measurement of Tremor

The measurement of tremor is complicated by the fact that tremors behave in different and complex ways with natural variations in amplitude and frequency [168]. Notwithstanding the inherent problems, a variety of measurement

approaches have been used to measure tremor including clinical rating scales, and physiological (instrumental) techniques[163 168].

3.3.1 Clinical Measurement

Clinical rating scales

Clinical rating scales (CRS's) involve rating the presence and/or severity of specific tremor features, generally using an ordinal rating scale. CRS's are used extensively in the measurement of tremor across a range of neurological conditions, and include the Fahn-Tolosa Marin Tremor Rating Scale for ET[169], and the UPDRS [55] for PD. CRS's have a number of advantages over physiological methods: instrumentation is not required; they are low cost and easily accessible; the results are more meaningful to professionals and patients[168].Their disadvantages include subjectivity, poor quantification, and issues in relation to reliability[170 171],and sensitivity[172].

Reliability between (inter-rater) and within (intra-rater) raters varies with the type of tremor and the task. For example, studies have reported good inter- and intra-rater reliability for rating postural tremor of the upper limb in patients with MS [171], and a mixed group with ET and dystonia[170]. Inter-rater reliability was reported to be better when rating tremor in body parts than it was in a writing and drawing task in patients with essential tremor[169].However, reliability was poorer rating kinetic than postural tremor in the MS group [171]. The studies indicate, not surprisingly, that tremor is more difficult to rate in structures that are in motion in contrast to structures that are 'at rest' or 'holding a posture'.

3.3.2 Instrumental methods

The rhythmic nature of tremor lends itself to the objective measurement of its frequency and amplitude components using physiological or instrumental methods[168 173]. Instrumentation used to quantify tremor includes digitizing tablets [174 175], accelerometry [176 154]and electromyography (EMG)[177].

In PD, instrumental measurements have been used to compare tremor rate in PD patients and in healthy controls, and to evaluate tremor simultaneously across different sites[178 177]. Aly et al.,[178] found that a spectral peak between 5Hz and 6 Hz differentiated the PD group from the control group in a shape-tracing

task using a graphic (digitizing) tablet. Using EMG, Hunker et al.,[177] found uniform rest tremor frequencies across the lips, jaw, tongue and index finger in a group of three PD patients. When structures from limb and speech systems have a similar rate of tremor, it points towards a central oscillator as a cause of tremor [179]. Measuring the rate of voice tremor offers exciting opportunities to understand more about the complexities of tremor pathophysiology.

However there are limitations with objective instrumental measures, including their unavailability, expense, and the time required in using them[168]. A further problem is the difficulty in obtaining an appropriate sample of tremor for measuring, especially in the case of PD which can show great variability and even switch on and off during a 30-second recording[168]. The validity of instrumental measures is also an issue. Validity relates to whether an instrument measures what it purports to measure [94]. One study reported poor correlation between an objective measure of limb postural tremor using accelerometry and self-reported tremor disability using an Activities of Daily Living questionnaire[170]. In explaining the poor relationship between the measures, it may have been that the accelerometer was not sensitive enough in detecting the tremor or that the tremor was accurately detected but did not result in disability as perceived by the patient. The issue of relationships between different measures will be revisited in the context of voice tremor in section 4.5.4.

It is evident that tremor can be measured using a variety of techniques and no single evaluation method will comprehensively capture its complexity and variability. The type of evaluation method used to measure the oscillatory movement affects the results of the measurement.Thus multi-dimensional evaluation of tremor is recommended for assessment of tremor severity in clinical trials[168]. The issues highlighted in this section relating to measuring tremor will re-emerge in chapter 4 when discussing evaluation of voice tremor in PD. The final section of chapter 3 describes neurophysiological aspects together with the different types of tremor associated with PD.

3.4 Tremor in PD

Although the precise pathophysiology of PD tremor is unclear, dopaminergic deficit in the striatum is accepted as contributory to the development of PD tremor[5]. Tremor severity however, does not correlate with the severity of dopaminergic depletion in the striatum, confirmed with positron emission tomography (PET)[5]. Further, the clinical severity rating of tremor does not correlate with clinical disease progression, in contrast to rigidity and akinesia. Therefore, it is argued that other transmitter systems, i.e non-dopaminergic, for example the serotenergic system, or other neural circuits (non basal ganglia) may also contribute to PD tremor[5]. Therefore the relationship between PD tremor and disease is not a straightforward one. It would be very informative on many fronts to explore PD voice tremor in the context of disease severity, to see if a similar 'tenuous' relationship exists.

The presence of a 4-6 Hz 'rest tremor' is central to the PD diagnosis, and is often an early symptom of the disease. However other types of tremor including tremor during action (kinetic) or postural tremor may also occur in PD[18] [158],singly and in combination complicating differential diagnosis[180]. In the literature, variable estimates of postural tremor and under-appreciation of kinetic tremor occur, due to inconsistencies in the definitions of the different tremor types and assessment tasks employed[180].To add further to the complexity of presentation, tremor does not occur in all pwPD, with reports of up to 30% of patients not showing any form of tremor, including rest and postural[180] [181]. PD tremor may be difficult to differentiate from normal tremor for a number of reasons including, the variable characteristics of PD tremor[182], the differing physical, emotional and mental state of the individual, and the tremors own natural cycle[168]. A further issue of particular relevance to voice tremor in PD is the challenge in differentiating PD voice tremor from 'normal' tremor due to the association of ageing with PD and with tremor (section 2.5.1).

In addition to tremor in the limbs, rest tremor is reported to involve the lips, chin, and the jaw[105]. However, Jankovic[6] states that rest tremor rarely involves the neck/head or the voice. The phenomenon of 'rest tremor' cannot easily be applied to the 'voice', since during voicing the structures in the vocal tract are

moving and not ‘at rest’. Jankovic[6] did not explain what he meant by the term ‘voice’. Perhaps he was referring to vocal tract structures associated with the production of voice, thereby implying that tremor does not occur in the vocal tract during ‘rest’ breathing (non-voicing). Tremor has also been reported in the tongue and the larynx in pwPD [34 107 112 113]. However, similar to orolingual tremors, the classification system used for limb tremor cannot easily be applied to the palate, tongue, and larynx, leading to poor characterisation of oral, pharyngeal and laryngeal tremor in PD. This core subject of tremor in vocal tract structures in PD will be explored in detail in section 4.5.3.

Summary:

- Tremor is defined as the rhythmical involuntary periodic oscillatory movement of a body part.
- It is pervasive in neurological conditions where it is termed pathological tremor; however normal tremor also exists.
- Tremor is generally classified on the basis of: the body part that has tremor; the conditions under which the tremor is activated (‘at rest’ or during a held posture or movement); and the frequency of the tremor.
- A limb tremor classification system cannot easily be applied to tremors in the oral structures, the pharynx, and the larynx.
- Tremor is complex and variable in its presentation, and precise measurement can be problematic. Clinical rating scales and instrumentation are used, and both have value in tremor evaluation.
- Multi-dimensional evaluation is recommended for assessment of tremor severity in clinical trials.
- Rest tremor is the most common and easily recognised symptom of PD, however other types of tremor also occur, and a sizeable number of pwPD do not develop tremor.

- Although the pathophysiology of PD tremor is related to loss of dopamine in the striatum, the non linear relationship between tremor and disease severity suggests adjunctive etiological factors.

Chapter 4 follows with a change in focus, moving closer to the central issue of voice tremor in PD.

Chapter 4. Voice tremor, and Voice Tremor in PD

Chapter 4, the final chapter leading to the formulation of the research aims of the thesis has two themes. The first theme addressed in sections 4.1 to 4.3 defines voice tremor, examines voice tremor in neurological disorders, and outlines ways in which voice tremor has been evaluated in non-PD conditions. The second theme, voice tremor in PD covered by sections 4.4 to 4.7 addresses the following areas: evaluation approaches in PD voice tremor; relationships between voice tremor and PD speech/voice variables, and disease specific variables.

4.1 Voice tremor defined

Tremor may occur in normal phonation[183], and when it does it is termed 'normal' or 'physiological' tremor. Voice tremor is associated with ageing (section 2.5.1), and with pathological voice disorders (section 4.2).The difference between 'normal' and 'abnormal' voice tremor is not clear cut. 'Phonatory instability' is a useful term to apply to understand the phenomenon of voice tremor and to explore the difference between tremor in 'normal' voice and 'pathological' voice[184 185]. The human voice is inherently unstable [186 187] as a result of normal oscillatory behaviour that occurs in the respiratory, laryngeal, and articulatory muscles of the vocal tract. The oscillatory movements give rise to fluctuations or modulations in the fundamental frequency (Fo) and/or amplitude of the voice [188 189]. These modulations are generally not perceptually prominent but contribute to the natural quality of the voice [187 190]. Singers exploit this normal oscillatory behaviour through technique and practice to produce perceptually salient frequency modulations, which is termed 'singers' vibrato [191 190].

Abnormal (pathological) voice tremor

In contrast, when oscillatory movement in the vocal tract is involuntary and rhythmical, and causes rhythmic fluctuations in the fundamental frequency and amplitude of the voice, perceived as rhythmic (quasi-rhythmic) fluctuations in pitch and loudness, it is considered 'pathological' voice tremor [187]. The term 'voice tremor' will be used generically in this study to denote abnormal or pathological voice tremor. Voice tremor related to PD will be termed 'PD voice

tremor'. Regarding the source of the oscillatory tremor movement, the muscles of the vocal cords, the larynx, and the respiratory muscles are possible causes of voice tremor [166] [183]. In addition, changes in articulatory configurations may result in alterations of fundamental frequency, through the coupling of the larynx and tongue by the extrinsic laryngeal muscles [166]. In effect, therefore, voice tremor may relate to fluctuations in any one or all of the following muscle groups: respiratory; vocal cords; laryngeal; articulatory (jaw, tongue, soft palate), also referred to to as the vocal tract.

Voice tremor has been described as a 'long-term phonatory instability' and contrasts with 'short-term phonatory instability'.The 'long-term' part of the descriptor refers to the fact that the variations in frequency and amplitude, which can be (quasi-cyclical) or non-cyclical are slower than the 'quasi-periodic' glottis vibration (vocal cords) itself [184] [185]. Conversely, short-term phonatory instability relates to variations in frequency and amplitude from one cycle to the next, also referred to as jitter and shimmer respectively (section 2.4.3).The 'phonatory instability' part relates to fluctuations in the frequency and amplitude of the voice[185]. An important point to highlight here, in advance of acoustic measures of voice tremor (section 4.3.3) is that phonatory instability can be 'cyclic' or 'non- cyclic'. 'Cyclic' refers to the fact that the tremor is of sufficient regularity and periodicity for a tremor rate to be detected. Voice tremor has been referred to as a 'cyclic phonatory instability'[184].

4.2 Voice tremor and neurological disease

Voice tremor is pervasive in neurological disease and has been reported in association with the following conditions: spasmodic dysphonia (SD)[109]; ET[192] [193]; MS [185]; parkinsonism [164] [75] [194]; ALS [165] [162]; and cerebellar ataxia[166]. Additionally, voice tremor has also been reported as an early feature of some neurological diseases including ALS, [162] PPND [164] and PD [88].Notwithstanding its pervasiveness and early presentation in neurological disease, the classification of voice tremors has not developed to the same degree as has the neurological understanding of tremor in general [173] or of PD tremor (section 3.4).

Little is known about the different ways in which voice tremor is manifested in different neurological conditions and the possible basis for those differences [159]. For example, does PD voice tremor and voice tremor in ET (ETV) sound the same or different and if there is a difference, what is the nature of the difference? A fundamental problem is that voice tremor in PD has not been characterised, and ways in which it can be measured have not been elucidated. Studies that have explored voice tremor in other neurological conditions provide direction for improved methods of PD voice tremor evaluation (section 4.3).

4.3 Voice tremor evaluation in the neurological (non-PD) literature

In a previous section 2.4, the different approaches used in the evaluation of speech and voice symptoms were described as background information to the measurement of voice tremor. The current section focuses on the most clinically applicable measures to the study of voice tremor, highlighting issues with each approach. The auditory perceptual rating of tremor will be presented first, followed by visual perceptual rating and finally, acoustic measurement. Non-PD studies will be used to highlight some of the issues. Section 4.4 will then focus on voice tremor in PD with particular reference to issues and possible solutions related to different voice tremor evaluation approaches.

4.3.1 Auditory Perceptual Rating

The centrality of auditory perceptual rating of voice in the analysis of voice quality was highlighted in section 2.4.1. Voice tremor is clinically identified in sustained vowels [(/a/ and /i/], and during speaking tasks.However voice tremor is best perceived auditorily during sustained vowel production of /a/ or /i/[195 196]. The reason being, that a sustained vowel task allows the rater to focus specifically on the voice quality without the additional sound artefacts that are associated with connected speech, and avoids variability in the signal from alternating voiced-voiceless sounds[196].

Not dissimilar to rating limb tremor (section 3.3), the reliability of perceptual rating of voice tremor is an issue. For example, Bain et al.,[170] carried out a study of twenty patients with postural tremor of their upper limbs, twelve of whom had a diagnosis of essential tremor and eight had tremor related to dystonia. ‘Vocal

tremor' was detected in six participants. Four raters (doctors) graded the severity of perceived voice tremor using an interval scale of 0-10, during a speaking and a sustained singing /a/ task', in addition to rating tremor in the head, leg and hands. The authors reported that there was poor reliability for rating 'vocal tremor', with the raters not able to agree on which patients had 'vocal tremor'. In contrast, the rating of tremor in the head and upper limbs was rated as 'good'. Lack of clarity around the terminology may have negatively impacted on reliability of ratings, since it is not clear from the study if 'vocal tremor' was defined for the raters in advance of the rating experiment. A further confounding factor impacting on poor agreement/reliability may be the type of speaking task used in the rating experiment. The raters were asked to rate vocal tremor during a speaking task and a sustained 'singing /a/'. A sustained vowel task, resulting in a more perceptually salient tremor, might have improved reliability[195]. Further, it may have been difficult for the raters to perceive the tremor during the singing task, since the magnitude of tremor is reduced with high-pitched voicing[197].

Barkmeier et al.,[197] in their study addressed some of the aforementioned problems. They set out to ascertain if inexperienced raters could match experienced raters in rating perceived symptoms of SD and 'vocal tremor'. The outcome of the study was that expert judges (at least 5 years specialised clinical/research experience with SD and vocal tremor) showed high reliability between themselves rating voice and tremor features, with inexperienced voice clinicians achieving similar levels of reliability as the expert judges[197]. The following factors contributed to the high reliability. At the outset, they defined 'vocal tremor' as 'periodic fluctuations in pitch and/or loudness'. They used a sustained /a/ vowel task for tremor rating. Finally, the raters were required to decide if tremor was intermittent or continuously present and then rate its severity on a scale of 0 (normal) to 3 (interferes with intelligibility).

4.3.2 Vocal tract examination and sources of tremor

Voice tremor is inextricably linked to involuntary oscillatory movement in vocal tract structures. The term 'oscillation' in general refers to regular periodic variations of a measured value about a mean[19]. Applying this explanation of

oscillatory movement to the vocal tract implies that the movement is rhythmic or quasi-rhythmic at least. Methods of examination of the vocal tract were previously discussed in section 2.4.2. In relation to assessing tremor in the vocal tract, the preferred method is using nasendoscopic examination[198]. The examiner can potentially identify rhythmic movements in a number of different anatomic sites, including the soft palate, base of tongue, larynx, and pharynx during non-phonatory (breathing, voiceless sounds) and phonatory tasks (sustained vowels) [192 193 199].

There is evidence of characterisation of voice tremor in ET[192 200]. Warrick et al.,[192] using nasendoscopy in a botulinum toxin treatment study of ten patients with ETV evaluated tremor in the larynx and the palate during 'rest breathing', during sustained /i/ and /a/ vowels, and fricatives. They[192] reported that most of the patients had three to four anatomical sites of tremor, with the vocal cords being the most frequent tremor site followed by the soft palate. In a further study of patients with ETV, Sulicia et al.,[193] also using nasendoscopy applied the Vocal Tremor Scoring System (VTSS)[200] to their analysis of thirty four patients with ET. They [193] identified and graded tremor across six different tremor sites [soft palate; base of tongue; pharyngeal wall; global larynx (larynx as a unit); vocal folds; supra glottis (above vocal cords)]; using different tasks including tongue protrusion, and a sustained /i/ vowel. The authors[193] found that the highest rating (most severe) was for tremor in the global larynx, the supraglottis, and the vocal folds, and the lowest rating was for the 'extra-laryngeal' (outside the larynx) sites (palate, tongue, pharyngeal walls). Examining different sites in the vocal tract, and rating tremor features during different speech-related tasks moves closer to a classification type approach for voice tremor, similar to the approach used in limb tremor classification which was outlined in section 3.2.

4.3.3 Acoustic measurement of tremor

The contribution of acoustic measurement to voice analysis was previously outlined in section 2.4.3. This section focuses specifically on the contribution that acoustic measurement makes to the identification and characterisation of voice tremor.

Rhythmical (quasi-rhythmic) oscillatory movement of muscles in the vocal tract is manifested in the acoustic wave form.Tremor may be manifested in variations in the length of the vibratory cycle when it is termed 'frequency tremor' and/or in the amplitude of the cycle, termed amplitude tremor[183].The rhythmic or quasi-rhythmic fluctuations in frequency and amplitude secondary to oscillatory movement in the vocal tract, lend themselves to acoustic measurement[183] . Ludlow et al.,[183] in a study of nine patients, five of whom had ET and four had a variety of neurological diagnoses measured 'slow systematic changes' in frequency and amplitude of the signal over blocks of 50 cycles and found that both frequency and amplitude aspects of tremor were affected in their group.They related the frequency and amplitude tremor to the nasendoscopically observed vocal fold tremor. However no formal correlations of this suggested relationship were carried out by the authors. The identification of frequency and amplitude tremor in neurological disorders is welcome, however conclusions are limited without studying a neurologically healthy control group.

An ongoing challenge is to find appropriate acoustic measures that will differentiate between pathological tremor and normal tremor[116] . Ramig et al.,[116] compared a heterogenous neurological group including PD, ALS, ETV, adductor spasmodic dysphonia (ADSD), spinal muscular atrophy, and a group of normal healthy controls. They found that there was greater extent of amplitude tremor in the neurological group than in the control group, but the difference between the groups was not significant. An even more challenging exercise is to differentiate voice tremor in different neurological conditions[116 201]. Lundy et al.,[201] wished to differentiate between three groups of participants with ADSD, ALS and ETV. (PwPD were excluded from the study). Using MSP from the CSL[119], they found that the magnitude (extent) of amplitude tremor (Matr %) [119] differentiated the ETV group from the ALS and ADSD group, on a sustained /a/ vowel task. In addition, they found that all three groups had increased values of Matr %[119] over available CSL normative data. However a word of caution when interpreting these study findings, consideration needs to be given to the fact that the CSL norms [119] are based on a younger age group for males and females than the participants in Lundy et al's., study[201].

The role that short-term phonatory instability (section 4.1) measures have in identifying and measuring voice tremor is a moot one. Jiang et al.,[157] considered that jitter (frequency perturbation) in addition to long-term frequency and amplitude modulation should be useful for the detection and quantification of 'vocal tremor'. However, other authors have not found the short -term perturbation (jitter and shimmer) measures to be as useful as the long-term measures[202]. Zwirner et al.,[202] examined three groups of patients: PD, Huntington's disease, and cerebellar ataxia. They reported that the 'long-term measure' of variability of fundamental frequency (SDFo) differentiated the three groups, however fundamental frequency (Fo), jitter, shimmer, and signal to noise ratio (SNR) did not differentiate them.

When selecting acoustic voice tremor measures, it is important to consider their clinical utility[117](meaning the way in which a specific tremor measure relates to a clinical measure of voice tremor). Hertegard et al.,[203] found that measures of SDFo as a tremor measure did not correlate with a perceptual tremor rating in a group of fifteen patients with ETV. The authors surmised that SDFo is probably sensitive to parameters other than tremor and highlighted the need for further studies to clarify the acoustic parameters that are most useful for measuring tremor. Another explanation might relate to the artefact of trying to compare perceptual and instrumental measures.

Acoustic measurement has an important contribution to make in quantifying the rate of voice tremor, in an effort to see if measuring the rate of voice tremor assists in understanding the underlying pathophysiology (section 3.3.2). Drawing from the classification approach used for limb tremor (section 1.5), some studies have applied tremor rates (Hz) to differentially diagnose voice tremor in different neurological conditions, and to differentiate patients with neurological conditions and normal controls[159 183]. For example, Boutsen et al.,[159] compared a group of four patients with ALS and one female pwPD and found a high frequency tremor, i.e. flutter (7-10 Hz) in the ALS group and the pwPD. Flutter has been associated with ALS [162] and not with PD. Ludlow et al.,[183] in a study of eight patients with different neurological diseases and twenty controls found that mean frequency and/or amplitude tremor rates did not

differentiate between patients with ETV, dystonia with tremor, myoclonus, SD with tremor, and normal controls. The rate of frequency tremor was 5.45 Hz in the neurological group and 6.64 Hz in the control group. For amplitude tremor, the rate in the neurological group was 6.27 Hz and 7.48 Hz in the control group.

Acoustic measurement offers the opportunity to move closer to a classification approach for voice tremor with opportunities to measure the rate, and the magnitude of the tremor. A shortcoming of acoustic measurement when used for voice tremor analysis is that it does not throw light on the physiological correlates of unsteadiness in the vocal tract[204]. Cannito et al.,[205] writing about vocal tract steadiness in SD, suggested that more direct observation of specific muscles in the vocal tract was necessary to understand the relationship between the instability measured acoustically and oscillatory behaviour of a related structure. The topic of acoustic tremor measurement will be re-visited in the context of PD voice tremor in section 4.5.2.

The key points from section 4.3 pertaining to measurement approaches that have been used in non-PD studies follows. Voice tremor can be perceived more easily in sustained phonation than in connected speech. A clear explanation of voice tremor facilitates improved reliability of ratings. Nasendoscopy is the preferred examination approach for characterising possible sources of voice tremor, since it permits the identification of tremor in different vocal tract sites and during different tasks. Frequency and amplitude fluctuations secondary to involuntary oscillatory movement, together with the rate of tremor can be measured acoustically. Long-term instability measures are more appropriate for measuring voice tremor than are jitter and shimmer (short-term) measures. An increase in the magnitude of amplitude tremor has been associated with neurological disease. An ongoing challenge however is to find acoustic measures that will differentiate voice tremor in neurological conditions from healthy controls. These findings emanating primarily from the non-PD literature are brought forward into the final sections on PD voice. The outstanding issues driving the main aims of this study will complete chapter 4.

4.4. Voice Tremor in PD

In this section the diversity of voice tremor terminology extant in the PD literature and the variable prevalence rates are reported. Section 4.5 reviews studies which have reported on voice tremor in PD, highlighting the evaluation approach used with subsequent findings. The literature relating to PD voice tremor in association with other voice and speech variables will be reviewed in section 4.6. The final section (4.7) of the chapter looks at ways in which PD voice tremor relates to disease variables. A short summary will complete the chapter with particular reference to the gaps in our knowledge of PD voice tremor, leading to the research questions.

Descriptors

Voice tremor has been variously described as a feature of the PD speech-voice complex. These descriptors include 'tremorous voice' [116], 'tremulousness'[75] , tremulous pitch (deficit in pitch steadiness)'[89], 'pitch unsteadiness'[104], 'perceptible vocal tremor'[116], 'flutter' [159], 'vertical laryngeal tremor [107],'laryngeal tremor' [120], 'rhythmic amplitude tremor'[116].The two main reasons for the diversity of terminology are: the majority of studies do not have voice tremor as a main focus[206] and different evaluation approaches with different types of measures are used across studies (Table 2.1). It is difficult to know if the descriptors refer to the same or a different phenomenon. For example, it is not clear if the perceived 'tremulousness' in Logemann et al's.,[75] study is the same phenomenon as the 'tremulous pitch' and 'deficit in pitch steadiness' perceived and described in Chenery et al's.,[89] study. It is also unclear if the 'laryngeal tremor' cited in Schulz's[207] study is the same as the 'vertical laryngeal tremor' described in Perez's study [107]. Therefore lack of clear nomenclature is problematic and confusing.

Prevalence

Variable prevalence rates of voice tremor in PD are reported regardless of the evaluation approach used. *Perceptual-based* voice studies report prevalence rates which vary from a low 13.5% [75] to a high 68%[89]. In Logemann et al's.,[75] study of two hundred patients with parkinsonism (PD and post-encephalitic PD), two raters identified the presence of perceived tremulousness in 13.5% of the

sample in a sentence and connected speech task. In a reading aloud task, Chenery et al.,[89] identified 68% of a group of nineteen mild-moderate PD patients with 'tremulous pitch' which they also termed a 'deficit in pitch steadiness'. Based on what is known about the variability of PD tremor, it is possible that such widely varying prevalence rates exist. However, it is also possible that methodological differences may account for much of the disparity in prevalence figures, between the two studies. The studies differed in relation to: tremor 'descriptor'; homogeneity of the study group; the number of raters; and the type of rating scale.

PD studies using laryngeal examination report similar varying prevalence rates of tremor. Gamboa et al.,[135] identified 'laryngeal' tremor in 14.6% of their group of forty one pwPD, using either indirect laryngoscopy or nasendoscopy. In a different study, the same group of authors also using indirect laryngoscopy or nasendoscopy identified 'laryngeal' tremor in 45.5% of a group of twenty two PD patients[120]. The contrasting findings in relation to 'laryngeal tremor' findings is difficult to explain since the methodologies were similar excepting difference in medication schedules and severity of PD symptoms as measured with the UPDRS (APPENDIX A). The pwPD in Jimenez-Jimenez et al,'s[120] study were un-medicated, had a shorter disease duration and milder disease severity than the pwPD in Gamoba et al's study[135]. Midi et al.,[131] used rigid laryngoscopy in their study of voice abnormalities in twenty male pwPD and reported that three out of twelve patients (15%) had 'laryngeal tremor'. They did not describe the speech-voice tasks used to elicit the tremor behaviour, or the characteristics of the tremor in the larynx. Blumin et al., [113] identified tremor of the 'laryngopharynx' (tremulous movement of the laryngopharynx during phonation) in 53% of a group of fifteen patients with advanced PD, undergoing DBS on a sustained /i/ vowel task using rigid laryngoscopy. Finally, Perez et al.,[107] identified 'vertical laryngeal tremor', using nasendoscopy in 55% of their group of twenty- two PD patients. Based on the these studies, the exact prevalence of 'laryngeal' tremor is unclear due to the varied evaluation approaches used coupled with the lack of detailed information regarding the characteristics of the tremor findings.

Therefore, studies using auditory perceptual and visual perceptual evaluation report varying prevalence rates of voice tremor. It appears that voice tremor (similar to PD limb tremor) is not a feature of all pwPD.

4.5. Voice Tremor Evaluation approaches in PD

This section outlines the PD studies that have reported voice-tremor features with particular attention given to the evaluation method applied. This is necessary to give direction to the current study methodology.

4.5.1. Auditory Perceptual Evaluation

The varied non specific tremor descriptors emanating from auditory perceptual based studies frequently relate to incidental findings. As a result, important details are not explicit. For example, Ramig et al.,[116] reported that four out of eight patients (50%) had perceptible 'vocal tremor', in a study whose main focus was acoustic voice analysis and not perceptual evaluation. The specific speech/voice task used to elicit the tremor and the rating procedures used were not described, rendering replication of the study difficult [116]. Sataloff et al.,[208] in a single case study of a pwPD undergoing DBS, described perceived tremor with a rating of 3 on a scale of 0-5 However, they did not describe the rating methodology as in the number of rater/s involved, or indicate whether the rater/s were blind to the diagnosis.

A further issue is that perceptual based PD studies describing voice tremor features based their findings on natural speaking and reading tasks [75 89], and did not include a sustained /a/ vowel task, which is considered the most sensitive method for identifying tremor (section 4.3.1).The result is that studies may underestimate the presence and severity of tremor, since contextual speaking tasks (reading, speaking) may mask the underlying tremor. In addition, studies describing perceived PD voice tremor have not included neurologically healthy participants[75 103]. Therefore it is not possible to be definite that PD is the cause of the perceived voice tremor. This is a very important issue to address particularly in the context of the association of ageing and voice tremor (section 2.5.1).

The issue of poor reliability in rating voice tremor in non-PD voice studies was highlighted in section 4.3.1. Few PD studies have reported on the reliability of auditory perceived tremor. Solomon et al. [209] looked at the effects of DBS on speech in three men with severe PD. They reported that the highest intra-class correlation coefficient (ICC) (a measure of inter-rater reliability) was achieved for ratings of tremulousness relative to the reliability for monopitch. Ratings of tremulousness were carried out by six SLT's, using a four point scale in a reading and monologue task. Based on the author's reporting in the study, it appears that tremulousness achieved an ICC of 0.754 for the reading task and 0.768 for the monologue[209]. It is not clear from the study if the authors addressed reliability by defining the descriptor 'tremulousness' at the outset. Definite conclusions cannot be drawn regarding reliability of tremor ratings from this small study.

To summarise, consideration has not been given to optimum ways of evaluating PD voice tremor perceptually, in relation to the consistency in terminology used, the type of task used to elicit tremor, the type of rating scale best suited for the purpose, or ways to improve reliability. To begin to address these issues, this study on PD voice tremor will include a clear definition of perceptual voice tremor; include a sustained vowel task for rating purposes; rate the severity of perceived tremor; and have rating carried out in a blinded fashion. Section 4.5.2 reviews PD studies reporting voice tremor features using instrumental evaluation.

4.5.2. Instrumental evaluation

In addition to describing PD voice tremor on the basis of auditory perceptual evaluation, studies have also described voice tremor features using non-invasive instrumental methods including: acoustic; aerodynamic; EGG [134]; and laryngeal electromyography (LEMG).

Acoustic evaluation

In section 4.3.3, the use of acoustic voice measurement for the purpose of identifying frequency and amplitude tremor in neurological conditions was introduced. A smaller number of PD studies have also tried to address this question. Some studies have identified amplitude tremor[116 208], and others

have identified frequency and amplitude tremor features in pwPD[88 173]. Ramig et al.,[116] described a 'rhythmic amplitude tremor imposed upon cycle-to cycle deviancies', visually evident in the waveform of one of nine PD patients, which differed from the waveform of the patients with Myotonic Dystrophy, and Huntington's disease. In a single case study of a man with PD undergoing DBS, Sataloff et al.,[208] reported that there was greater variation in amplitude tremor than in frequency tremor, with a 'vibrator intensity variation' of 16% in intensity and 1.50% in frequency variation. It appears from the cursory description in the methods section of Sataloff et al's study [208] that the MDVP from the CSL was used in the voice analysis. Information was not provided on the type of task used or the number of trials elicited for analysis.

In a larger group, Stewart et al.,[88] visually identified (using narrow band spectrographic analysis), fluctuations in both amplitude and frequency tremor aspects in 33% of a group of twelve 'early' pwPD, (mean disease duration less than 3.2 years), on a sustained vowel task. They did not quantify the amplitude and/or frequency tremor, and did not include a control group, therefore we do not know if their findings were specific to PD. In contrast, Jiang et al.,[173] in their study, set out to quantify the frequency and amplitude of voice tremor in a mixed group of ten neurological patients, using spectral analysis of the acoustic intensity contour. Seven of the group had PD, one had cerebellar atrophy, one upper motor neuron dysfunction and one had idiopathic tremor. They also studied ten gender and age-matched controls. They reported that the pathological tremor group was distinguishable from the normal control group by the magnitude of amplitude modulation of the acoustic intensity, and surmised that the findings point towards greater fluctuations in the respiratory system, vocal fold tension, and/or articulatory configurations in pathological tremor. What is not clear from these studies however is the contribution that acoustic tremor measures make to the differentiation of pwPD from neurologically healthy controls, and the specific measures that might be helpful in differentiating between the groups.

Acoustic measures have been used in PD studies for varying purposes, including the monitoring of treatment effects of dopaminergic medication

(section 1.7) and DBS [210] [211] (section 2.4.3). D'Alatri et al.,[210] applied tremor measures [(magnitude of frequency tremor Mftr%**);(**magnitude of amplitude tremor Matr%)] from MSP in CSL, to evaluate the differential effect of medication and DBS in a group of twelve pwPD[12]. The authors reported baseline mean Mftr and Matr values of 0.63 and 4.72 respectively, when patients were off-medication and without stimulation[210]. They reported improvement in acoustic voice tremor with significantly reduced Mftr and Matr values of 0.38 and 2.87 respectively, when patients were 'on-medication' and 'on-stimulation'. Xie et al.,[211] in their study of eleven patients also undergoing DBS reported significant changes in Mftr values (females) between the pre-surgical 'on medication' state and the post-surgical states. However, the authors did not indicate if Mftr values had increased or decreased. De letter et al.,[212] also applied tremor measures of Mftr and Matr from MSP to investigate the sequential changes in respiratory, speech, and voice variables across a medication cycle in seven pwPD. Using analysis of variance (ANOVA), they found significant differences between subjects across the cycle in eighteen out of twenty measures including Mftr and Matr. The authors did not report the individual or the mean Mftr or Matr values for their group, so it is not possible to compare the tremor values with those from D'Alatri et al's.,[210] study. Although the findings from these studies suggest that Mftr and Matr may be useful indices for charting changes in tremor behaviour secondary to medication and/or neurosurgical treatment, their potential role in differentiating pwPD from neurological healthy controls has not been established to date.

A review of the PD studies using acoustic evaluation highlights the value in quantifying frequency and amplitude tremor for the purpose of: determining differences between pwPD and healthy controls; for measuring pharmacological and surgical (DBS) treatment outcomes. However, the findings to date are somewhat mixed with no clear conclusions regarding the presence of frequency and amplitude tremor in PD due to a combination of: small sample size, the lack of a control group; a heterogenous grouping of patients; the paucity of detailed information relating to the methods used. Therefore a major step in this direction is to evaluate a group of pwPD and neurologically age and sex

matched controls, with clear documentation of the evaluation approaches used to identify tremor in the acoustic voice signal.

Aerodynamic measures

Another instrumental evaluation approach that has been used in PD studies, albeit with limited application to PD voice tremor to date, is aerodynamic evaluation. Aerodynamic measures include non invasive measures of the flow of air through the glottis (area between the vocal folds), air pressure, and the extent to which the larynx offers opposition to the flow of air through the glottis (laryngeal airway resistance) [104]. Murdoch at al.,[104] examined laryngeal and phonatory dysfunction in a study of twenty PwPD and twenty non-neurologically impaired subjects, using aerodynamic measures, in addition to EGG [134], and perceptual measures. They found significant differences between pwPD and controls with reduced sub-glottal pressure and phonatory sound pressure level (SPL), and increased laryngeal resistance in the pwPD group in comparison to the control group. They considered that incomplete closure of the vocal folds causing inadequate valving of the air stream, and rigidity in the laryngeal muscles to be related factors in the aerodynamic findings. Interestingly, they raised the issue of compromised velopharyngeal function as an additional cause of the lowering of intra-oral pressure. However they did not go as far as suggesting tremor in the palate could be an underlying cause of reduced velo-pharyngeal control. It is reasonable therefore to argue that aerodynamic measures, in addition to spirometry (section 2.4.3) could potentially increase understanding of PD vocal tract tremor. However, it is not possible to address this question in the present study.

Electroglottography

Another instrumental tool used in voice studies, albeit with limited application to date to voice tremor evaluation is EGG, also referred to as laryngography. EGG indirectly measures vocal fold contact, and the opening/closing patterns of the vocal cords. Murdoch et al.,[104] in their study of twenty pwPD found that EGG measures of fundamental frequency (Fo), duty cycle (ratio of time that vocal cords are open during the vocal period compared to the duration of the total vibratory cycle), and closing time (duration of the closing phase from totally

open to totally closed) did not differentiate the pwPD from the healthy control group. They concluded that the EGG measures did not contribute to the understanding of the pathophysiology of the deviant perceptual characteristics including 'pitch unsteadiness' [104]. It is conceivable that EGG may not capture the long term instabilities of tremor in the vocal tract, since it is designed to assess cycle-by-cycle periodicity and contact of vocal cords ('microfunctions of the larynx') [104]. EGG has potential for use when tremor in the vocal folds is the main study focus, however its inclusion in the current study is not warranted since the focus is tremor in the vocal tract.

Laryngeal electromyography (LEMG)

The final instrumental approach described in this review is that of laryngeal electromyography (LEMG), which is the application of EMG to laryngeal muscles. The only available objective test of the electrical function of the intrinsic laryngeal musculature [213], LEMG has been used minimally in the measurement of voice tremor. The fact that it is a highly invasive technique and that the laryngeal muscles are difficult to access, has contributed to its lack of use. LEMG offers the opportunity of determining if tremor in the vocal cords is a feature of PD. However PD studies have been inconclusive with respect to pinpointing the exact location of tremor in the larynx or vocal tract [213 214]. Zarzur et al.,[213] looked at LEMG findings in twenty six patients with PD and twenty six controls with presbyphonia (voice change secondary to ageing). They carried out 'flexible videolaryngoscopy' (nasendoscopy) for diagnosis and documentation. Although a tremor was observed in three pwPD during 'clinical, vocal and videolaryngoscopic' examinations, they reported that no tremor was evident in the intrinsic laryngeal muscles based on the LEMG tracings in any of the patients, during a phonatory /i/ task. Zarzur et al.,[213] concluded therefore that the 'clinical tremor' observed during 'videolaryngoscopic' examination was likely to have originated in muscles other than those chosen for the LEMG.

Zazur et al.,[214] in a later study of twenty six pwPD reported similar findings regarding the non-detection of laryngeal tremor using EMG. This time they used acoustic voice analysis in addition to LEMG. The authors[214] reported that voice tremor was detected acoustically in the spectrogram tracings of 69.5% of

pwPD, and perceptually in 61% of the subjects. Of note in the context of this study, is that tremor was identified in the acoustic voice signal. Not surprisingly however in the context of Zarzur et al's., [213] previous study, there was no correlation found between LEMG and 'voice analysis'[214]. However, it is not clear from the paper [214] if 'voice analysis' included the perceptual *and* the acoustic measures. Further, no information was provided in the text on the perceptual rating of voice tremor or the cited acoustic measures of 'VOXMETRIA ® and GRAM 5.1.6. These issues weaken the findings from the study regarding the lack of correlation between the different measurement approaches. Finally, Kimaid et al.,[215] in contrast to the previous studies [213] [214]reported positive LEMG findings of the thyroarytenoid muscle in two pwPD in a mixed group of twenty patients with movement disorders. They identified rhythmic bursts of 5-6 Hz muscle activity at rest that disappeared with phonation.

Therefore, the findings to date in relation to the use of LEMG for measuring PD voice tremor suggest that it may have an adjunctive role to play in identifying tremor in the vocal cords, during 'rest breathing' and during phonation. However, considering its invasiveness coupled with its application only to tremor in the vocal cords, it will not used in the current study for the evaluation of voice tremor.

To conclude this section on instrumental evaluation of PD voice tremor, it is evident that acoustic measurement can increase understanding of ways in which tremor affects the frequency and amplitude aspects of the PD voice, and contribute to quantifying differences between pwPD and healthy neurological controls. The final evaluation approach for consideration is that of identifying tremor in structures in the vocal tract.

4.5.3. Visual Perceptual Evaluation and sources of voice tremor

In PD, there is speculation about the possible source of perceived voice tremor. For example, Solomon et al.,[209] in a study of three males with severe PD queried if limb tremor acting on the chest wall resulted in 'perceived vocal tremulousness'. However the authors did not consider that the perceived tremor might be related to tremulous structures in the vocal tract [209]. As discussed in section 4.5.2, tremor in the vocal cords is not considered to be a

main source of PD voice tremor [34 213 214]. An outstanding and important question therefore pertains to which 'tremulous' structure/s in the vocal tract are associated with PD voice tremor.

PD studies using laryngeal examination have described tremor in the larynx, the tongue and the strap muscles[120 131 216]. Jimenez-Jimenez et al.,[120] noted 'laryngeal tremor' in three patients out of a group of twenty-two pwPD, using stroboscopy. Midi et al.,[131] also using stroboscopy documented 'laryngeal tremor' in three patients out of a group of twelve male pwPD. There is no detail in either studies[120 131] regarding the specific location of the tremor. For example, was the tremor behaviour manifested in the entire larynx structure (global larynx), in the vocal cords, or the arytenoid cartilages. Further, the non-phonatory/phonatory tasks used to elicit the identified 'laryngeal' tremor are not described. Following the limb tremor classification approach (section 3.4), Perez et al.,[107] reported that 'resting laryngeal tremor' was a feature in 35% (n=22) of a group of pwPD. The author's[107] documentation of laryngeal tremor in an non-phonatory or 'resting' condition is a step towards improved classification of PD vocal tract tremor. However Perez et al.,[107] did not describe the characteristics of 'resting laryngeal tremor', making it difficult to relate their findings to other study findings or indeed to replicate their study.

Hanson et al's.,[216] study suggests that PD voice tremor is not confined to the larynx. The authors [216] described tremor in the tongue, and the 'strap muscles', in addition to the 'supraglottic' (above the vocal cords) muscles and 'arytenoids', in thirty two male PD patients. However, it is not clear how tremor in the strap muscles was identified during the laryngeal examination. Strap muscles are also referred to as the infra-hyoid muscles, and their function is to lower the larynx during speech and swallowing. Perhaps the authors [216] identified 'vertical laryngeal tremor' [107]during the examination and inferred tremor in the infrahyoid (strap) muscles. The reporting of tongue tremor in Hanson et al's[216] study is an important finding in relation to understanding more about the possible sources of voice tremor in PD, since other studies, have reported laryngeal tremor only[107]. However it is important to note that the 'rigid laryngopharyngoscope' (rigid laryngoscopy) used by Hanson et al.,[216] would

have resulted in a forward fixed tongue position. This is not a natural tongue posture during phonation and may have confounded the examination findings.

Perez et al.,[107] carried out the largest prospective laryngeal tremor study using 'flexible nasendoscopy' in twenty two pwPD. They wished to differentiate between pwPD (*n*=22) and patients with atypical Parkinsonism (*n*=7) (progressive supra-nuclear palsy; multiple systems atrophy), on the basis of the location of laryngeal tremor. They identified 'vertical laryngeal tremor' as being the prominent feature in the PD group versus tremor in the arytenoids in the atypical Parkinsonism group. The authors did not define what they meant by the term 'vertical laryngeal tremor'. It is understood by this author to refer to 'global laryngeal tremor' described by Bove et al.,[200] as 'motion in the vertical dimension of the larynx, as a unit, relative to the surrounding upper aerodigestive tract'. It is possible that the terms 'vertical laryngeal tremor' [107], 'tremor in the strap muscles' [34], and 'global laryngeal tremor' [200] are describing the same phenomenon. Clearly, greater clarity is required regarding the location of tremor sites to improve classification of PD voice tremor. Consistency in terminology and explanation of terms would be helpful. The focus of Perez et al's.,[107] study was laryngeal tremor. Thus, no information is available regarding other possible sources of voice tremor in the vocal tract, for example the tongue[216] or the soft palate.There was no control group in the study therefore it is not possible to say if their findings are pertinent only to the PD population. Finally, since the medication status is not reported in the study, the possible relationship between medication effects (section 2.5.3), and tremor findings cannot be discussed.

Other important aspects of characterising PD voice tremor include making explicit the condition/s under which the tremor was identified and the type of rating scale used. The following questions require answers: was the presence and/or the severity of tremor documented; what type of measurement scale was used (ordinal scale versus continuous scale); were the raters blinded to the diagnosis; did the raters hear the voice when they were rating the tremor visually; what was the reliability data.

The few studies that have described vocal tract tremor in pwPD have rated the presence and not the severity of tremor and have not reported reliability results[107 216]. Greater sensitivity in rating methods through the use of scales documenting the severity of tremor, together with information on rater reliability is important towards the identification and characterisation of PD voice tremor.

Based on studies to date therefore, it appears that for some pwPD, possible sources of tremor are the 'larynx', the arytenoid cartilages, and the tongue. Tremor may be observed as 'vertical movement of the larynx'. The documentation of tongue tremor in addition to 'laryngeal' tremor, suggests that PD voice tremor is a wider vocal tract phenomenon rather than a laryngeal one. Therefore it is argued by this researcher that tremor in pwPD is not confined to the vocal cords and 'vocal tract tremor' is thus an appropriate term to use in this study.

Interestingly, there are no reports in the PD studies to date of tremor findings in the velopharynx or soft palate, in contrast to reported finding of palatal tremor in ETV, on a sustained /i/ vowel task[193]. Hypernasality (excessive air coming through the nasal cavity) during speech has been identified in the PD dysarthria profile [217]. It is conceivable that tremor in the velopharynx may contribute to hypernasality due to the difficulty sustaining velopharyngeal closure. A notable omission is that no study to date has set out to determine if palatal tremor is a feature of PD. Therefore an important question pertains to whether palatal tremor is a feature of PD and the conditions under which it can be elicited. A further question relates to the amount of tremor evident in structures in the vocal tract and the way in which raters agree or disagree on rating tremor severity.

'Activating conditions' or speech 'tasks'

An important aspect of limb tremor classification is differentiating between 'rest tremor' and 'action tremor' (section 2.2). It is noted from a review of the studies that there is a lack of clarity around the specific tasks that were associated with the identification of laryngeal and tongue tremor in pwPD. For example, in relation to Hanson et al's.,[216] study, information is not provided on the specific

non-phonatory/phonatory tasks that gave rise to tremor in the ‘strap muscles’, and the tongue.

Drawing from the classification approach used in limb tremor, Perez et al.,[107] reported the presence of ‘resting tremor’ and ‘kinetic’ (phonation) tremor in their study group. The authors[107] did not define the term ‘resting tremor’, but it is understood by this author to relate to tremor behaviour identified during ‘quiet breathing’. The term ‘rest breathing’ will be used in this study to describe the vocal cords opening (abducting) and approximating (adducting) when a person is not phonating (vocal cords not involved in vibratory movement).

Important questions therefore remain unanswered in relation to the presence and severity of tremor in the vocal tract of pwPD, and the relationship with perceived voice tremor including: the likely source or sources of voice tremor; the activating conditions or tasks that elicit tremor in the vocal tract. Therefore to identify possible sources of PD voice tremor, it is important to examine laryngeal and extra-laryngeal sites, including the soft palate, the tongue, larynx/pharynx and vocal cords using nasendoscopy. To assist in the characterisation of voice tremor, it is important to evaluate tremor using non-phonatory and phonatory tasks. The following tasks should be included: rest breathing; sustained voiceless /s/; sustained /a/ and /i/ vowels. This author considers the sustained /s/ task to be an appropriate vocal tract ‘postural’ task in that during /s/ production the tongue is held against the teeth or gingival (gums), the soft palate is held in an elevated position and the vocal cords are held in an open albeit approximated (between fully closed and fully opened) position. The sustained vowel tasks (/a/, /i/) may be considered an appropriate vocal tract ‘kinetic’ task since the vocal cords are involved in sustained vibratory movement. The reason for including an /i/ vowel in addition to an /a/ vowel (considered the easiest for perceiving tremor), is because /i/ facilitates elevation of the larynx through the action of an elevated tongue position. This physiological adjustment in the vocal tract affords a view of the vocal cords and surrounding structures. Therefore, in pursuit of the goal of characterising PD voice tremor, the researcher considers it important to include non-phonatory

[(rest breathing, sustained /s/] tasks, in addition to phonatory tasks (sustained /a/, /i/) during vocal tract examination in this study.

The core aspects of voice tremor are: perceptually salient rhythmic or quasi-rhythmic modulations in the voice, involuntary oscillatory movement of muscles in the vocal tract; and fluctuations in the frequency and amplitude of the voice (section 4.1). Reviewing these defining tremor features highlights that multi-dimensional evaluation incorporating auditory perceptual, visual perceptual and acoustic evaluation is required to identify and fully characterise the complexities of PD voice tremor. The next sub-section 4.5.4 reviews the small number of studies that have alluded to relationships between different tremor measures.

4.5.4. Relationship between different tremor measures

Considering ways in which auditory perceptual, visual perceptual and acoustic evaluation measures relate to each other improves understanding of the effect of involuntary oscillatory movement on the acoustic voice signal and the perceived voice quality. Further, exploring the relationship between acoustic tremor measures for example and perceived tremor demonstrates the clinical relevance or utility of the acoustic measure. However the way in which the different tremor measures relate to each other has not been seriously addressed in the PD literature. Extending the review to include non-PD voice tremor, Ludlow et al.,[183] in their study of nine patients with ETV, reported that acoustic measures of frequency and amplitude tremor related to 'fiberoptically' observable vocal fold tremor. However, information was not provided in relation to the speech task or the rating procedures used in the nasendoscopic examination to identify 'vocal fold tremor'. Further they did not report the results of any correlational analyses between acoustic and visual-perceptual ratings. Therefore a further question that needs to be addressed in this PD voice tremor study pertains to the way in which different tremor measures relate to each other.

This review now moves away from the specifics of PD voice tremor to a broader view looking at PD voice tremor in the context of speech and voice symptomatology (section 4.7) and disease variables (section 4.8).

4.6. Voice tremor and PD speech-voice variables

This section places voice tremor in the context of other PD speech and voice variables that have been reported in the literature. In addition to voice tremor, changes in voice quality, voice disability and speech intelligibility have all been described in the context of PD However, little attention has been given to the way in which voice tremor might or might not relate to these variables.

Dysphonia-related parameters

Voice changes are inextricably linked with the PD speech-voice symptom complex (section 2.3). Although perceived 'breathiness' and 'roughness' are frequently reported in the PD literature there are no reported studies in which voice tremor has been explored in the context of the overall severity of dysphonia. A step in this direction is to measure the severity of dysphonia in addition to measuring tremor in a group of pwPD.

Speech Intelligibility

Speech intelligibility is a measure of communication efficiency [218], which reflects the level of functioning of the numerous sub-systems, including verbal and non-verbal aspects. A more balanced view of speech intelligibility is to be gained from consideration of dimensions other than articulation, considered to be a dominant factor in reduced intelligibility [219].

PwPD have been shown to have reduced intelligibility of speech in a number of studies [77 102]. Although sound imprecision and monopitch [103] have been found to be contributory factors to reduced intelligibility in pwPD, it is probable that other speech and voice systems are also involved. It is conceivable that voice tremor may impact negatively on speech intelligibility through its disruption of phonatory and articulatory configurations in the vocal tract. However, the relationship between PD voice tremor and speech intelligibility is unknown, since studies have not specifically addressed this question. D'Alatri et al.,[210] in a treatment study using DBS, stated that improvement in acoustic measures of tremor and glottal vibration was not associated with an improvement in intelligibility. It is not possible to draw firm conclusions from one study. Further, the authors based their intelligibility findings on item 18 from the UPDRS motor

section[55], which is a global measure of speech and voice function rather than an intelligibility scale. Therefore the issue of the effect of voice tremor on intelligibility rating is open to further exploration in this study.

Voice disability

The impact of voice-related problems on self-perceived voice handicap in pwPD was previously discussed in section 2.4.4. It is important to identify the phonatory features that are contributing to voice disability, so that they can be prioritised for treatment. Two studies which reported on greater voice disability in pwPD than in controls, reported the presence of 'laryngeal tremor' [131] [113]. However, neither study addressed the relationship between laryngeal tremor and voice disability.

Exploring the way in which voice tremor relates to other speech-voice variables helps to improve the understanding of the pathophysiology of voice tremor, assists in targeting specific areas for rehabilitation in an effort to improve intelligibility and ultimately communication. Therefore, consistent with the overall aim of this work to increase understanding of PD voice tremor, voice tremor features will be analysed in the context of overall severity of dysphonia, speech intelligibility, and voice disability.

4.7 Voice tremor and disease specific variables

This section presents a review of the studies that have reported in relation to voice tremor and disease specific variables.

Hanson et al.,[216] in their study of thirty two male pwPD stated that visually perceived tremor of the vocal tract, using rigid laryngoscopy correlated with 'general neurological symptoms'. However they did not describe the 'neurological symptoms' or clarify the nature of the relationship between neurological symptoms and vocal tract tremor. Two studies, both using laryngeal examination, related voice tremor to greater disease severity[135] [113]. Gamboa et al.,[135] reported that the presence of laryngeal tremor was significantly more frequent in the PD patients with a higher score on the total UPDRS i.e. greater disease severity. They identified tremor in 60% (6/10) of patients with total UPDRS scores greater than 24.3, which was the mean score

for the group. Tremor was not identified in any of the patients with scores less than 24.3. However, there were methodological variations across patients in relation to the equipment used to examine the larynx, with an indirect laryngeal examination used for some patients and nasendoscopy with others. It is possible that mild or subtle laryngeal tremor was not visually perceptible in patients with milder disease severity. Using acoustic tremor measures in addition to or in lieu of vocal tract examination may have helped to identify voice tremor in these patients with mild PD symptoms. Finally, the ratings were carried out by the same person who carried out the examination, resulting in rater bias. Blumin et al., [113] reported the presence of tremulous movement of the laryngopharynx in 53% (n=8) of a group of fifteen patients with advanced PD (stage III) identified using the Hoehn & Yahr Scale [59]. However the authors did not include a comparison group with milder disease severity, therefore the relationship between laryngeal tremor and disease severity is inconclusive based on the study findings.

Two further studies have linked voice tremor with 'early stage', and with 'early' and 'later stage' or more severe PD symptomatology, using acoustic[88] and perceptual measures[220]. Stewart et al.,[88] identified 'vocal tremor', using narrow band spectrogram in four out of twelve 'early stage' PD patients. The group had average disease duration of 3.2 years, and a mild disease severity with a mean score of 1.2 on the H & Y scale. Holmes et al.,[220] examined voice characteristics using eleven auditory perceptual measures and a range of acoustic measures in thirty 'early' stage and thirty 'later' stage (severe disease) PwPD and compared data with thirty normal control subjects. They used a combination of the Webster motor disability scale, disease duration, and presence/absence of motor fluctuations to classify patients into early or later stages of PD. They reported that perceived 'vocal tremor', rated in a monologue task was only associated with later stage disease and was not apparent in patients with early stage PD. The authors considered therefore that vocal tremor was related to advanced stage PD only. Based on the findings from these studies, it is difficult to draw strong conclusions regarding a definite relationship between voice tremor, disease duration, and disease severity.

PD phenotypes

The relationship between voice tremor and PD phenotype (sub-type) is unknown (section 1.6.3). In fact, there is little evidence in the PD clinical research literature of pwPD being classified into tremor-dominant or postural instability gait disorder (PIGD) phenotypes[65].

A logical conclusion would be that voice tremor is more likely to be associated with tremor dominant PD, rather than PIGD phenotype. However, dysarthria in PD has been linked to the PIGD phenotype[68 70]. Studies that have linked dysarthria to PIGD have based the dysarthria diagnosis and severity rating on item 18 from the UPDRS section III, which is non-specific regarding the nature of the dysarthria symptomatology[55]. The tenuous link between dysarthria and PIGD phenotype appears to be based on the findings of a limited effect of dopaminergic medication on speech symptoms, rather than any relevant research on the topic.

Exploration of the relationship between voice tremor and phenotype may increase understanding of the pathophysiology of PD voice tremor. For example, if voice tremor was considered to be related to tremor dominant PD, this would suggest a more benign disease course than if voice tremor was associated with PIGD phenotype (section 1.6.3).

From a review of studies carried out to date, it is not possible to determine how voice tremor fits into the overall disease profile. Further exploration of voice tremor in the context of disease duration and disease severity and PD phenotype is warranted, and could potentially contribute to the important discussion on the relationship between speech-motor and limb motor symptoms.

In summary of chapter 4

- Instability of the voice is a feature of normal voice however the oscillations in the vocal tract muscles are so small that they are not perceived visually or auditorily.

- In neurological disease, involuntary oscillatory movements may result in frequency and amplitude tremor with perceptually prominent voice tremor.
- A range of evaluation methods including auditory perceptual, visual perceptual (vocal tract examination) and acoustic are available for the measurement of voice tremor.
- In PD, there is lack of clarity surrounding the presence and characteristics of voice tremor, and how pwPD differ from neurologically healthy age-sex matched controls.
- The varied voice tremor descriptors used in PD studies emanate from generic rather than tremor specific studies, contributing to the overall confusion.
- A tremor specific study, using a sustained vowel task, nasendoscopic examination of the vocal tract and long-term phonatory instability measures is necessary to document and characterise voice tremor in PD.
- The important relationship between PD voice tremor and (a) speech and voice variables and (b) disease specific variables has not been properly addressed previously in the literature.

Research Questions

It is clear from this literature review that there is a lack of clarity about voice tremor in PD on a number of fronts. From this researcher's perspective, there are three fundamental issues which need addressing in order to move towards the identification and characterisation of PD voice tremor; determining if voice tremor is a feature of PD; using a multi-dimensional approach to measurement; understanding where PD voice tremor fits into the greater scheme of the speech-voice disorder and the overall disease process. These issues may be addressed in the following research questions.

1. Is there a difference between pwPD and neurologically healthy age-sex matched controls in relation to voice tremor, when voice tremor is measured using (a) acoustic tremor measures (b) auditory perceived tremor and (c) visually perceived tremor in the vocal tract? If there is a difference between pwPD and healthy controls, is the difference statistically significant?

2. What is the nature and degree of the relationship between acoustic voice tremor measures and perceptual measures, and visual perceptual measures in pwPD?

3. What is the nature and the degree of the relationship between acoustic voice tremor measures and (a) severity of dysphonia (b) voice disability (c) speech intelligibility?

4. What is the nature and degree of the relationship between acoustic voice tremor measures and disease variables: (a) disease duration (b) disability (c) motor symptom severity (d) phenotype?

Aims of Study

Given the above questions, the aims of my study are as follows:

1. To determine if voice tremor is a feature of PD in comparison to a group of age and sex matched neurologically healthy controls and if the difference is statistically significant, using a multi-dimensional approach of (a) acoustic evaluation (b) auditory perceptual (c) visual perceptual evaluation.
2. To evaluate the relationship between acoustic voice tremor, auditory perceptual and, visual perceptual tremor measures.
3. To examine acoustic voice tremor in the context of other voice and speech variables for analysis of relationships with: (a) dysphonia severity (b) self-reported voice disability (c) speech intelligibility.
4. To identify a relationship if any between acoustic voice tremor measures and PD disease measures: (a) disease duration (b) activities of daily living (disability) (c) motor symptoms (d) PD phenotype.

Methods of tremor evaluation

The adoption of a multi-dimensional approach poses a challenge when examining relationships between voice tremor measures and other variables (research questions 2, 3 and 4). This author considered it prudent to select acoustic measures over perceptual measures as the key tremor measure when examining voice tremor relationships. This is not to say that acoustic measures are the gold standard for measuring voice tremor. The main reason for selecting acoustic measures as the lead measure is to minimise issues that arise from reliability rating of voice tremor.

Chapter 5 covers the methodology designed to address the main research questions.

Chapter 5. Methods

5.1 Ethical approval and consent

Ethical approval for the study was granted by the Ethics committee of the Mater Misericordiae University Hospital (MMUH) on the 19th May 2009. Written informed consent was obtained from all participants prior to taking part in the study. There were two main ethical-related issues which required consideration by the researcher in conducting the study. (a) Asking pwPD to refrain from taking their dopaminergic medication on the morning of testing, in addition to fasting for food and liquids excepting water. (b) For pwPD and controls, carrying out the vocal tract examination which is an 'invasive' procedure. The way in which these issues were addressed is outlined in section 5.6.

5.2 Participants

Two groups were recruited for the study: a group comprised patients with idiopathic Parkinson's disease (PD) termed the 'PD group'; a group comprised neurologically healthy controls called the 'control group'.

PD group

In order to be eligible for inclusion in the study, every patient had to have a diagnosis of PD made by a consultant neurologist specialist in PD, based on the UK Brain Bank criteria[55]. The presence of a speech and/or voice disorder, or voice tremor as rated by a clinician or as self-rated by a patient was not an inclusion criteria for entry into the study. The rationale for this decision was based on the fact that the primary aim of the study was to determine if voice tremor is a feature of PD and to determine ways in which it should be measured. Setting down strict inclusion criteria at the outset in relation to speech and voice symptomatology would have biased the study towards pwPD with more severe symptomatology. As a result, patients with subtle or very mild perceptual changes in voice and/or voice tremor would have being excluded from the study. In addition, the researcher hypothesised that acoustic tremor measures might identify tremor features in pwPD, before tremor was

perceptually salient and thus wanted to ensure that pwPD were not excluded from the study because of difficulties identifying tremor using auditory perceptual methods.

The researcher identified potential participants for the PD group, during their scheduled appointment at the neurology out-patient Movement Disorder Clinic, a specialised clinic held three times per month at the Dublin Neurological Institute, Mater Misericordiae University Hospital, in Dublin. Patients with a documented diagnosis of PD were 'screened' for eligibility to take part in the study. The following exclusion criteria were applied for entry into the study.

Exclusion criteria

Patients were excluded from the study if they:

- Reported a diagnosis of a concomitant neurological disease
- Had a dementia [identified in this study as a score of 23 or less on the Mini-Mental State Examination (MMSE)] [221]
- Had received a diagnosis from, or were under the care of a psychiatrist/pschologist for a psychological disorder
- Were taking any medication that is known to cause tremor, including lithium, anticonvulsant medication, immune-suppressants, or bronchodilators
- Were currently a 'smoker' or were an ex-smoker for less than five years (Smoking is a known cause of laryngeal and voice-related dysfunction)
- Had a history of cancer of the head and neck region, including laryngeal cancer
- Had a history of speech or voice problems unrelated to and prior to the onset of PD, and/or reported receiving speech/voice treatment or received Lee Silverman Voice Treatment (LSVT) for PD in the previous two years. The effect of speech and/or voice treatment on

voice tremor is unknown. Therefore it was important to control for the confounding effects of speech/voice treatment on tremor features, so that tremor findings could be related to the disease process and not treatment effects

- Reported inadequate hearing (defined as being unable to hear conversational speech comfortably), and/or wore hearing aids. The researcher wished to ensure that any speech and voice problems identified were related to PD only and not hearing deficits

- Were not agreeable to postponing their dopaminergic medication for twelve hours in advance of study testing, and to fasting for food and liquids (excepting water) on the morning that testing was taking place [(termed 'off-medication' state) (5.3)]

- Reported any significant dyskinesias. The reason for this exclusion was that one of the tests involved a fiberoptic nasendoscopic examination which is contraindicated in patients who have excessive extraneous/involuntary movements (dyskinesias)

- Were not a native English speaker. Difficulty in comprehending and/or producing the english language would affect the participants ability to follow instructions and pronounce sounds/words, and therefore confound the results

Control group

A healthy neurological age-and-sex matched group i.e., without PD and other neurological disease was recruited as the 'control' group. In order to be eligible to enter the control group, the participants had to be without PD. Otherwise, the same inclusion and exclusion criteria that applied to the PD group applied to the control group. Participants for the control group were recruited by inviting family members of PD participants, staff at the hospital, and parents of colleagues to get involved in the study.

5.3 Screening procedure

PD group

Potential participants for the PD group were 'screened' for the purpose of evaluating their eligibility for the study. The researcher attended the out-patient movement disorder clinic over a period of fourteen months, and reviewed the charts of attending patients to identify the patients with a PD diagnosis. If the diagnosis was unclear from the chart, the opinion of the consultant neurologist was sought to confirm the diagnosis. Once the PD diagnosis was confirmed, patients were invited to take part in a screening evaluation, which took approximately ten minutes to complete. The screening form outlined in APPENDIX E was applied to all potential participants. They were interviewed using standard questions in a questionnaire format, which covered all the areas outlined under exclusion criteria in section 5.2. If a pwPD satisfied the inclusion/exclusion criteria, the Mini-Mental State Examination (MMSE) [221] was then administered by the researcher to out-rule cognitive impairment. Cognisance was not given to whether patients were 'on-medication' or 'off-medication', during the screening of cognition.

Control group

Potential participants for the control group were recruited by: inviting relatives of pwPD to take part; asking staff at the hospital to get involved if age and gender appropriate, and/or to seek out appropriate family members. Control participants were screened using the same protocol that was used with the PD group *(*APPENDIX E*).* None of the control participants recruited for the study were involved in voice therapy, or in voice and/or singing training at the time of recruitment.

Participant expenses

Participants were not paid for taking part in the study. However, every effort was made to reimburse participants from both groups who incurred expenses due to travelling to the hospital, or through parking charges. A book token in the amount of €20.00 was offered to the participants in the control group.

Participant expenses were covered by a research grant from the Mater Hospital post-graduate college.

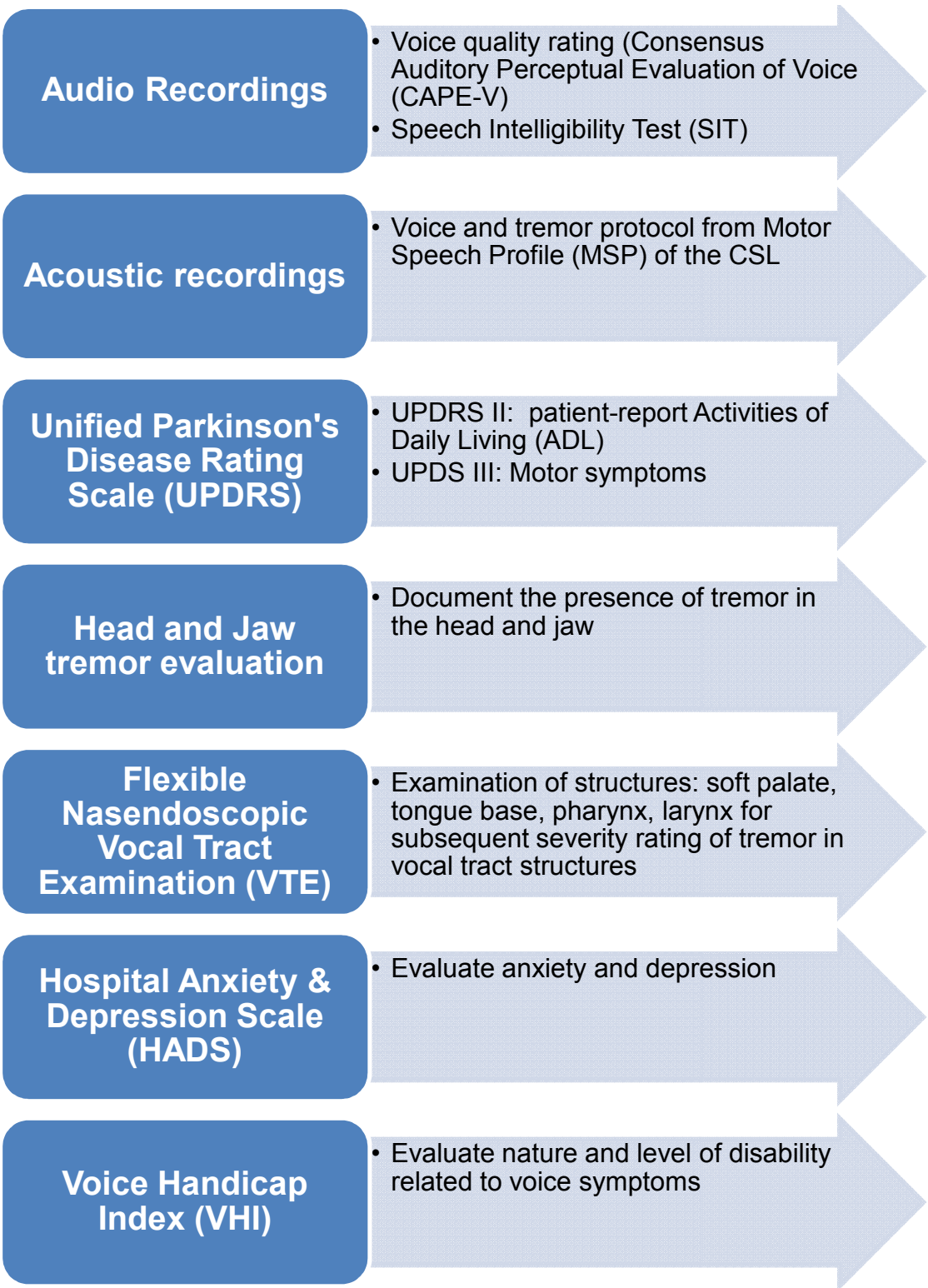
5.4 General procedures

PwPD on a dopaminergic medication regime were tested in a practically defined "off" medication state, i.e., after a 12-hour overnight withdrawal of anti-parkinsonian medication[72].They had been instructed not to take dopaminergic medication after 8pm the evening prior to the scheduled assessment date, and not to eat or drink excepting water during that time. They were evaluated in the morning between 08.00am and 10.00am. This advice was similar to other studies that tested patients in an off-medication state[22 77]. The rationale for testing patients 'off-medication' was outlined in section 2.5.3.

All assessments for PD and control participants were carried out in a single visit to the Speech and Language Therapy (SLT) department of the Mater Hospital. It took approximately eighty minutes to carry out the battery of assessments for each participant in the PD group. For the control group, testing duration was shorter because an evaluation of PD symptoms was not required. All participants were given a glass of water during the testing period.

The speech and voice recordings were carried out in a sound-treated audiology room, with ambient noise levels measured at 50 dB sound pressure level (SPL). The remainder of the assessments were carried out in the adjacent researcher's clinical office. In relation to the ordering of tasks, the researcher decided that the nasendoscopic exam should follow the audio recordings, and in the case of the PD group, the Activities of Daily Living and motor symptom exam, to reduce participant anxiety relating to the nasendoscopic examination. The same protocol and order of testing was carried out for the study and control group participants.The only exception was that the UPDRS was not administered to the control group. The flow chart outlines the assessments used in the study and the order in which they were carried out (Figure 5.1).

Figure 5.1. Flow chart showing order of assessments



5.5 Assessments

Section 5.5 describes the assessments employed to acquire the data for the study, section 5.6 addresses problem solving related to ethical issues. Management of data and preparation for analyses is covered in section 5.7, rating procedures in section 5.8 and finally, section 5.9 describes the data analyses.

5.5.1 Auditory perceptual evaluation

Firstly, the audio recording set up is described, followed by a description and rationale for using (a) the Consensus Auditory Perceptual Evaluation of Voice (CAPE-V)[100] and (b) the Speech Intelligibility Test (SIT) [222].

Audio-recording set-up

A Sony digital mini-disc coupled with an AKG 520 headset microphone was used to obtain the recordings. The microphone was positioned at the side of the mouth, approximately 5 cm and at the same level as the oral angle. All recordings were carried out with the participants seated. Volume of speech was not measured in this study. However every effort was made to optimise the signal capture by setting the recording gain on the mini-disc. The following procedure was followed in advance of the recording.

- The microphone was placed on the participant's head
- While listening on a head set, the researcher put the mini-disc into 'record' mode
- The microphone position was adjusted, so that there were no microphone popping sounds when the participant produced /puh/ and /buh/ sounds
- The record gain was set so that the average level was in the upper half of the recording meter and that the loudest speech was at least one bar below the maximum position of the meter.

(a) Consensus Auditory Perceptual Evaluation of Voice (CAPE-V)

The researcher selected the CAPE-V[100] for perceptual rating of voice quality,considering it to have advantages over the GRBAS for the purpose of the current study. The strengths of the CAPE-V are: the inclusion of different speech tasks, i.e sustained vowels and sentences; the option of including additional perceptual parameters in addition to the standard roughness, breathiness, strain features; detailed guidelines for the administration and scoring of the instrument. In addition, the CAPE-V[100] uses interval scale measures by incorporating millimeter measures on a visual analogue scale (VAS), which has been shown to a more sensitive method of voice analysis than an ordinal scale[223]. The CAPE-V protocol was followed as outlined by the authors in their published work[100], and is outlined in APPENDIX F. The rating procedures followed for the CAPE-V are outlined in a later separate section 5.8.1.

Auditory perceptual parameters

Tremor features and overall severity of dysphonia specifically, were the auditory perceptual parameters of interest in this study. The researcher wished to determine if there were features of *tremor* and/or *instability* in the voice of pwPD. *Tremor* was defined as rhythmic or nearly rhythmic fluctuations in pitch and/or loudness of the voice. *Instability* or unsteadiness was defined as irregular fluctuations in pitch and/or loudness. Perceptual descriptions of voice features in pwPD include tremor and unsteadiness (section 4.4). Since, it is unclear from the literature if different phenomena are encapsulated by the descriptors *tremor* and *instability,* this researcher decided to include both paramers for perceptual rating. The researcher was cognisant of the fact that asking raters to differentiate between two conceptually similar features,i.e. *tremor* and *instability* was challenging and potentially confusing, with the potential to affect the ratings applied to both features. However, notwithstanding these issues, she felt that it was important to include both parameters for reasons highlighted above. Tremor and instability were therefore additional

auditory perceptual parameters included on the CAPE-V form for rating (APPENDIX K).

The parameter 'overall severity' from CAPE-V[100], defined as 'a global integrated impression of voice deviance' was maintained in this study for the purpose of quantifying the extent or overall severity of voice deviance in pwPD. The parameters roughness and breathiness from the CAPE-V rating protocol were also maintained for this study (APPENDIX K).

(b) The Speech Intelligibility Test (SIT)

The SIT [222] is a computerised windows application for evaluating speech intelligibility, and is similar to the sentence portion of the Assessment of Intelligibility of Dysarthria Speech (AIDS)[224]. The SIT generates eleven sentences at random from the computer programme. The random generation of the sentences coupled with the computer scoring of the transcribed sentences was considered an advantage over the AIDS, for this study. In the SIT, the sentences may be presented to the speaker directly from the computer or the examiner may print the eleven sentences and the participant reads aloud the text. In this study, the latter option was chosen.

In the sound-treated room, the participants read aloud eleven sentences which had been generated a priori by the examiner from the SIT. As per the SIT protocol, the examiner read aloud a sentence with the participant following the text. This was followed by the participant reading the sentence. The researcher and the participants sentence reading was recorded onto the Sony mini- disc recorder. A new tape was inserted for each participant and labelled with patient's ID number. The rating procedures for the SIT are outlined in section 5.8.2.

5.5.2 Acoustic recordings

The recordings for the acoustic analysis were carried out in the sound treated audiology room, immediately following the audio recordings for the CAPE-V and SIT. The Voice and Tremor Protocol (VTP) from the Motor Speech Profile Advanced (MSP Advanced), which is a module of the Computerised Speech

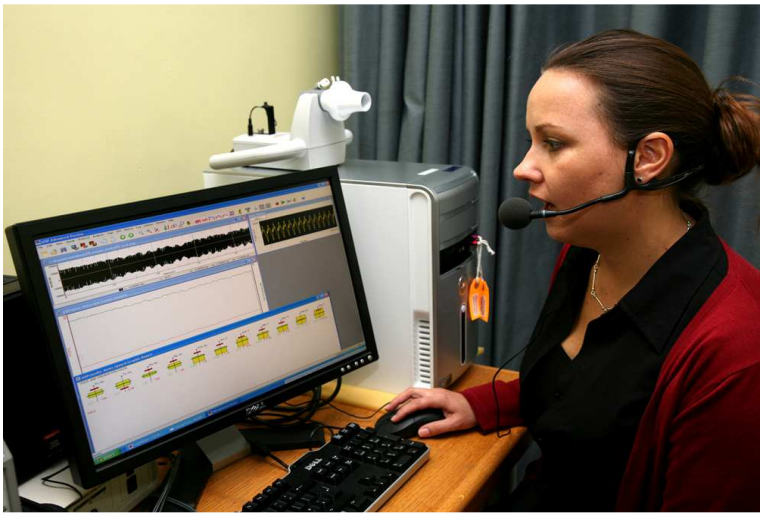
Laboratory (CSL), Model 5141 from Kay Pentax (Lincoln Park, NJ), was used for the analysis. The VTP was specifically developed to analyse voice problems associated with cycle-to-cycle variations and to assess tremor characteristics commonly associated with motor speech disorders[119]. The built-in protocols are designed to perform the procedures necessary to acquire the speech signals, analyse the signals and present numerical and graphical results for screen display and for printed reports[119]. The VTP yields a range of nine to thirteen voice and tremor related parameters, based on a sustained /a/ vowel task.

Recording set up; practice and test trials

The participants were seated beside the computer desk and the CSL. An AKG-C420 head-mounted microphone connected to the CSL was placed on the participant's head and placed 10 cms from the angle of the mouth. The authors of the MSP recommend a microphone distance of 10-15 cms[119]. In the VTP, a sustained /a/ vowel of 4.5 second duration is recorded directly on to the CSL, at a sampling rate of 50,000 Hz.

The VTP in CSL provides an example of a sustained /a/ vowel audio signal from a male voice (5 second duration), records the input from the participant, and analyses the data. Firstly, the participants were asked to listen to the registered voice from CSL, and then repeat the task. However, they were advised that they should not strive to imitate the male voice recording, but rather to produce their own natural voice. A range of one to three training trials was carried out by each participant, prior to the test trials. The reason for the practice trials was to ensure that the participant understood the task and that any technical problems that might arise could be rectified in advance of the test trials. For example, the input level was lowered if the red section of the VU meter lit up, since this signified that the input signal was overloaded. For the test, each participant sustained the vowel /a/ three times and each recording was saved to the Kay data file for later analysis (Figure 5.2).

Figure 5.2. Volunteer wearing AKG head set microphone and recording sustained /a/ directly onto the Voice and Tremor Protocol of the CSL



5.5.3 Parkinson's disease symptoms

For the PD group only, the symptoms pertaining to Parkinson's disease were evaluated with the Unified Parkinson's Disease Rating Scale (UPDRS). Two sections of the UPDRS were used: the patient-derived questionnaire of Activities of Daily Living (ADL, part II) (APPENDIX A) and the clinician-derived test of motor function (UPDRS-motor, part III) (APPENDIX B). The UPDRS II and UPDRS III contain thirteen and fourteen items respectively, with a range of possible scores from 0 to 52 for UPDRS II and from 0 to108 for UPDRS III. Some items have two components for example upper and lower limb tremor are both rated under tremor component. The assigned scores range from 0 (absent behaviour) to 4 (severe behaviour) with each item recorded in rank order (mild, moderate, severe), but without uniform intervals. For example a tremor score of 4 is not twice as bad as 2.

It was not possible to have a neurologist or a doctor with experience in using the UPDRS involved in the administration and/or rating of the UPDRS items. The researcher administered and rated UPDRS II and UPDRS III, having received training through observation of a specialist neurologist conducting the exam, and through following the MDS training video[225] .The researcher used the UPDRS data collection form used by the doctors in the Movement Disorder Clinic, for rating and recording the scores from the different items. A speech and language therapy (SLT) assistant was present for the motor examination. This was especially important for the postural instability task, which required the researcher to pull the pwPD backwards and catch the person if he or she was going to fall.

5.5.4 Head and jaw tremor clinical evaluation

A clinical rating of the presence/absence of head and jaw tremor was carried out in pwPD and controls, immediately prior to the nasendoscopic vocal tract examination (VTE). Tremor was defined as 'any observable involuntary tremulous movement of a structure'. The researcher carried out the rating with the participant seated upright. The participant was instructed to look straight ahead and not to speak. The head and then the jaw were observed for signs of

tremor, for a period of 5 seconds approximately. Any observable movement of the head in any direction (up and down; left to right) considered to be involuntary and abnormal was documented as tremor present. The jaw was evaluated with the mouth closed for five seconds, and then with the mouth open for five seconds. Both postures were used since the jaw opens and closes during speaking. Following the rating of head and jaw tremor, the participants were asked to sustain the voiceless sound /s/ and the vowels /a/ and /i/. This gave the researcher the opportunity to trial the speech tasks with the participants in advance of the nasendoscopic VTE examination.

5.5.5 Nasendoscopic Vocal Tract Examination (VTE)

One of the primary aims of this study is to characterise vocal tract tremor in PD. Nasendoscopy was the examination tool used to evaluate tremor behaviour in anatomical structures in the vocal tract. The advantages of nasendoscopy over rigid laryngoscopy for the purpose of this study were detailed in section 2.4.2.

Exam set up

The researcher, trained and highly experienced in the use of nasendoscopy for voice and swallowing evaluation, carried out the VTE. An SLT assistant was present during all examinations to assist with recording and supporting the participants.

The examination set up was as follows: both examiner and participant were seated; the participant faced the examiner; the stack holding the computer, monitor, and camera processor was behind the participant. Therefore the participants were unable to view the monitor during the examination. However the researcher offered all participants the opportunity to view the video recording of the nasendoscopy exam after all the tests were completed. In advance of the examination, the researcher inquired regarding history of nose bleeds and previous injury to the nose. The current or recent use of anti-coagulants was noted. Neither a topical anaesthesia nor a vasoconstrictor was used for the exam however a surgical lubricant ‘surgilube’ was applied to the distal end of the endoscope to assist passage through the nasal cavity. To ascertain the side of the nose that was likely to be most comfortable, the

participant was instructed to sniff whilst closing off one nostril and then the other nostril.

Equipment

A flexible video endoscope, Olympus ENF type V2 with an external diameter of 3.2mm diameter and an Olympus constant xenon light bulb was used for all the examinations for pwPD and controls (Figure 5.3).The camera system was coupled to a digital archiving system which permitted the researcher to view the exam on the monitor, and enabled video and audio recording of the exams onto the computer hard drive (Figure 5.4).

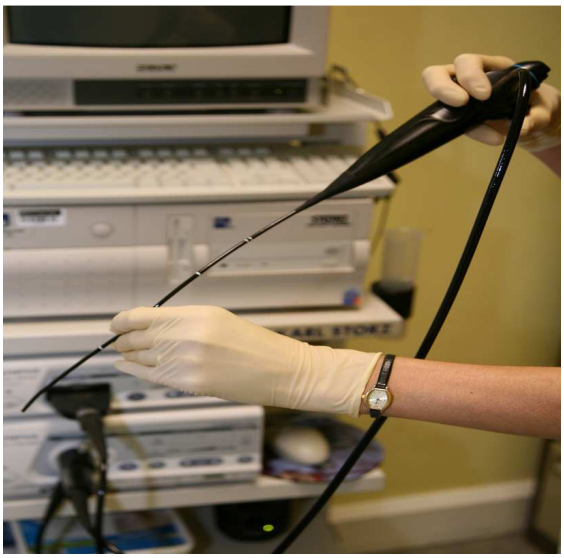


Figure 5.3. Videoendoscope used in vocal tract examination

Figure 5.4. Camera control unit, monitor and digital archiving system

Exam protocol

The same protocol for passing the scope and for eliciting the different tasks was followed for the PD and controls participants. For the purpose of this study, the researcher applied a modified version of the 'Vocal Tremor Scoring System (VTSS) [200] protocol. The VTSS was developed by Bove et al.,[200] specifically for the purpose of identifying anatomical sources of tremor in essential tremor of the voice. The protocol [200] involves the evaluation of tremor at six anatomical sites: palate; base of tongue; pharyngeal walls; larynx (global); supraglottis; and true vocal cords, using the sustained /i/ vowel for all sites excluding base of tongue which is evaluated with sustained tongue protrusion.

For this study, the VTSS protocol was modified in relation to the anatomical sites and the activating tasks used to identify tremor (APPENDIX G). For example, tremor was not specifically evaluated in the pharyngeal walls like in the VTSS. Further, tremor was evaluated using additional tasks to that used in the VTSS protocol [200], including 'rest breathing', sustained /s/ voiceless sound, and sustained /a/ vowel [(International Phonetic Alphabet (IPA)].

Anatomic sites & tasks

The flexible scope was introduced into the nares and advanced through the nasal cavity along the floor of the nose to the nasopharynx. The scope was held in position with the soft palate and pharyngeal walls in view to observe the *soft palate* during the tasks 'rest breathing', sustained /s/, and sustained /a/. The scope was then advanced to the oropharynx to view the *tongue base* during the tasks 'rest breathing', sustained /s/, and sustained /a/. Finally, the scope was advanced to the laryngopharynx (also referred to as the oropharynx) to view the *larynx* during the following tasks: 'rest breathing'; sustained /s/; sustained /a/; and the vocal cords during sustained /i/ [(International Phonetic Alphabet (IPA)] (APPENDIX G). The position of the scope in the laryngopharynx affords a view of the entire larynx and the posterior and lateral pharyngeal walls, necessary for the identification of tremor in the 'global' larynx also referred to as 'vertical laryngeal tremor'[226].Tremor in the global larynx is described as 'motion in the vertical dimension of the larynx, as a unit, relative to the surrounding upper aerodigestive tract' [200].During endoscopy, the entire larynx structure (vocal

cords,arytenoid cartilages, aryepiglottic folds,laryngeal surface of epiglottis) engages in movement in a vertical dimension relative to the lateral and posterior pharyngeal walls. Figure 5.5 shows a screen shot of the larynogopharynx during endoscopy with a participant sustaining an /a/ vowel.

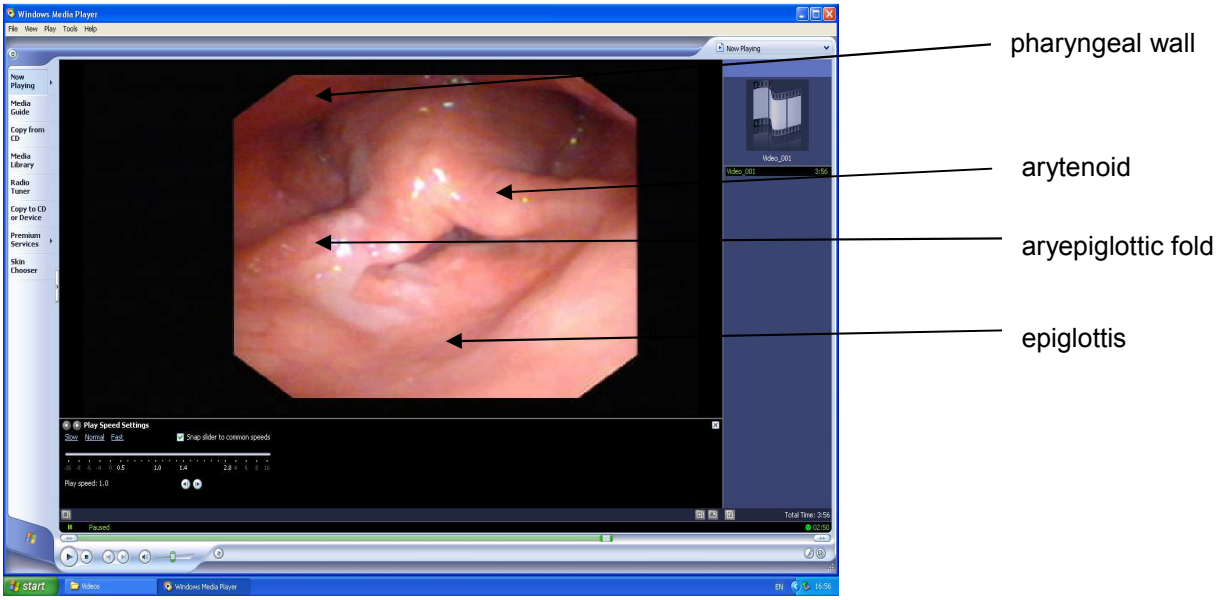


Figure 5.5. Screen shot of 'global larynx' during production of sustained /a/ vowel

Additional laryngeal sites for tremor identification were the vocal cords (oscillation of the vocal folds in the lateral dimension), and the arytenoid cartilages (oscillation of the arytenoid cartilages in the lateral dimension[200].

The sustained vowel /i/ was selected specifically to evaluate tremor in the vocal cords. The production of the /i/ vowel involves the elevation of the tongue towards the roof of the mouth (referred to as a high vowel). During production of /i/, the tongue connected to the hyoid bone in the laryx pulls the larynx forward permitting an unobstructed view of the vocal cords. The voiceless sound /s/ was selected to evaluate tremor in a non-phonatory task, in the palate, tongue base, and arytenoid cartilages. During a sustained /s/ sound: the soft palate is elevated and contacts the posterior pharyngeal wall; the arytenoid cartilages move towards the midline, but do not contact. The position of the soft palate and the arytenoid cartilages is 'held' in position during sustained /s/, therefore a sustained /s/ task could be considered a 'postural' non-phonatory tremor task.

For all tasks, the researcher aimed to view each anatomic site for duration of five seconds. All exams were video and audio recorded. On completion of each examination, the exam file was saved into either a 'PD' folder, or a 'control' folder on the computer hard drive.

At this juncture in the testing schedule with the completion of the tremor measures, and in advance of administering the Hospital Anxiety and Depression Scale (HADS) and the Voice Handicap Index (VHI), the PD participants were invited to take their medication.

5.5.6 Hospital Anxiety and Depression Scale (HADS)

In consideration of the known prevalence of anxiety and depression in pwPD, together with the association between anxiety and a 'shaky' voice, the author considered that it was prudent to collect data on emotional status as background information. The Hospital Anxiety and Depression Scale (HADS), [227] a short self-rated scale yielding a global measure of mood disorder, with separate sub-scores for anxiety and depression was selected since it has been found to be valid, consistent, precise and a potentially responsive scale for use with the PD population [228]. An advantage of the HADS over other measures is that it does not include somatic items, therefore the test findings are not confounded by PD physical problems, which can also relate to depression and anxiety [54]. A score in the range of 0-7 is considered normal. Scores in the range of 8 -10, 11-14, and 15-21 are considered a mild, moderate and severe effect respectively[227]. The authors recommend that the distinction between the two scales is retained, lest a 'nebulous' estimate of emotional distress is given. [229] The HADS was administered as per the protocol in the manual, with the participants instructed to rate their responses on the basis of the previous seven days[229].

5.5.7 Voice Handicap Index (VHI)

Finally, the Voice Handicap Index (VHI)[165] was used to measure voice handicap/disability in the PD and the control group. The VHI is a 30 - item scale with thirty different questions in three different categories, functional, physical

and emotional and yields a total score between the ranges of 0-120 (APPENDIX H). Scores that fall between 0 and 14 are considered to be within the normal range, and the higher the score the greater the voice disability. In this study, the participants were instructed to give a rating to the questions in the questionnaire based on their own perception of their voice in the previous four weeks.

On completion of the assessments, the pwPD were strongly encouraged to have breakfast before leaving the hospital. In a number of cases, the researcher accompanied the pwPD to the café for breakfast.

5.6 Ethical issues and problem solving

The way in which the two main ethical issues highlighted in section 5.1 were addressed is described below.

(1) Asking pwPD to refrain from taking their dopaminergic medication on the morning of testing, in addition to fasting for food and liquids excepting water.

This issue was addressed in the following ways: discussing it at length with pwPD during the screening process; carrying out the testing in the morning once it was twelve hours after the last medication dose; advising the patients to bring their medication with them to the testing session so that they could take it immediately after the vocal tract examination; ensuring that patients had water during the test session; inviting patients to the hospital café for ‘breakfast’ so that they could eat before leaving the hospital; The cost of breakfast was covered by a research grant obtained from the post-graduate college of the Mater Hospital.

(2) For pwPD and controls, carrying out the vocal tract examination which is an ‘invasive’ examination.

This issue was addressed by scheduling the exam towards the end of the session, giving participants the chance to become familiar with the testing process and thus encouraging relaxation. All participants were reassured that the researcher (the endoscopist) was experienced in the

procedure, and that it would be discontinued if the participant found it too uncomfortable.

An Ear Nose and Throat consultant (ENT) working in the same hospital as the researcher agreed to provide clinical support, in the event of the researcher identifying any abnormal anatomical findings that may require an ENT opinion.

5.7 Data management and preparation for analysis

The management of the scores from the following measures: Mini Mental State Examination (MMSE), UPDRS II, UPDRS III, head/jaw tremor rating, HADS) and Voice Handicap Index (VHI) is outlined in section 5.7.1.

5.7.1 MMSE, UPDRS II & III, Head/jaw tremor rating, HADS, VHI scores

The raw scores from the following measures: MMSE; UPDRS II; UPDRS III; head/ jaw rating; HADS; and VHI, were inputted into excel sheets from the raw data score sheets, with a research assistant's help. Once entered into excel, the researcher and the assistant cross-checked the scores for accuracy. The researcher subsequently imported the individual scores into a file on SPSS v.17, excepting the head/jaw tremor ratings since they did not require statistical analyses. Further preparation of data was required for some measures as outlined below.

- *UPDRS II*: the scores for items 5 to 17 were summed yielding an UPDRS II score.
- *UPDRS III*: the scores for items 18 to 31 were summed yielding an UPDRS III score.

UPDRS II & UPDRS III: scores from specific items from both measures were combined to obtain: [206] a mean tremor score (items included tremor from UPDRS II, tremor at rest of either face, lips or chin, all four limbs, and action or postural tremor in both arms from UPDRS III; (2) a mean score for the complex of postural instability and gait difficulty (PIGD), [(items included falling, freezing, walking difficulty (UPDRS II), and gait and postural instability (UPDRS III)] [61].

The ratio of the mean tremor score to the PIGD mean score was calculated for pwPD to determine the PD phenotype. Disease subtype was classified as PIGD when the ratio of total tremor score/total PIGD score was equal to or less than 1.0, whereas pwPD with a ratio of 1.5 or more were defined to have tremor-dominant subtype. When the tremor/PIGD ratio was more than 1.0 and less than 1.5, patients were classified to be in the indeterminate class.

- *Head & Jaw tremor:* for the head and the jaw, a score of 1 was assigned if tremor was present and a score of 0 if tremor was absent. For scoring tremor in the jaw, no differentiation was made between jaw closed and jaw opened position. A score of 1 was assigned if tremor was evident in either position.The scores for the head and jaw were entered into the participant's score row on excel.

- *HADS:* For the PD and control group, the individual scores for the Anxiety and Depression items were summed to yield a separate total Anxiety and total Depression score.

- *Voice Handicap Index (VHI):* In addition to obtaining a summed total VHI score, the scores from the physical, emotional and functional items were also summed yielding three different subscale scores. The excel scores were then imported into SPSS v. 17 for later descriptive statistics and statistical analyses.

5.7.2 Acoustic recordings

From a sustained /a/ vowel, the voice and tremor protocol (VTP) analysis in MSP from CSL generates a minimum of nine and a maximum of thirteen voice measures, their respective values, and corresponding mean values. The reason for the variation in the number of measures is that the values for rate of frequency tremor (Rftr) and rate of amplitude tremor (Ratr) and the corresponding periodicity measures are produced by MSP only when the detected tremor is somewhat regular.

For this study, the rate, periodicity, and magnitude of frequency and amplitude tremor were selected from the VTP as the key tremor measures for further analyses. The rate of tremor refers to the rate of modulation of fundamental

frequency and/or amplitude in the voice signal, measured in cycles per second (Hz). In order for the rate of tremor to be determined the voice tremor has to have a certain level of regularity. Periodicity is a measure (%) of the regularity of the tremor. The higher the periodicity the more regular is the tremor. The magnitude (%) of tremor (frequency and amplitude) is a measure of the extent of variation in frequency and/or amplitude secondary to the effect of involuntary movement in the muscles of the vocal tract.

Adjunctive measures of unsteadiness were also included. The selected VTP measures for the study are outlined below and for the purpose of completeness, descriptions of all the measures[119] generated from the VTP are outlined in APPENDIX I.

Key tremor measures

- Rate of frequency tremor [Rftr (Hz)]
- Rate of amplitude tremor [Ratr (Hz)]
- Periodicity of frequency tremor [Patr (%)]
- Periodicity of amplitude tremor [Patr (%)]
- Magnitude of frequency tremor [Mftr (%)]
- Magnitude of amplitude tremor [Matr (%)]

. Adjunctive measures of unsteadiness

- Coefficient of variations in the Fundamental Frequency [vFo)(%)]
- Coefficient of variations in amplitude [vFo) (%)]

The acoustic recordings for each participant were trimmed and re-digitised. Trimming (excluding) the initial and final segment of the signal is standard practice in voice analysis to avoid the confounding effects of phonatory-onset and phonatory-offset[230 231].The researcher opened the saved trials, i.e. trial 1, trial 2, trial 3 on the CSL, with the acoustic waveform visible on the screen, and

then trimmed each waveform, placing the first blue cursor (left side) on the 1.0 second mark and the second blue cursor (right side) on the 4.0 second mark, leaving the middle 3 seconds for analysis (Figure 6.5). Consistent with other studies, the value of 3 seconds was chosen since it was considered to be sufficiently long to afford reliable analysis[230 231].

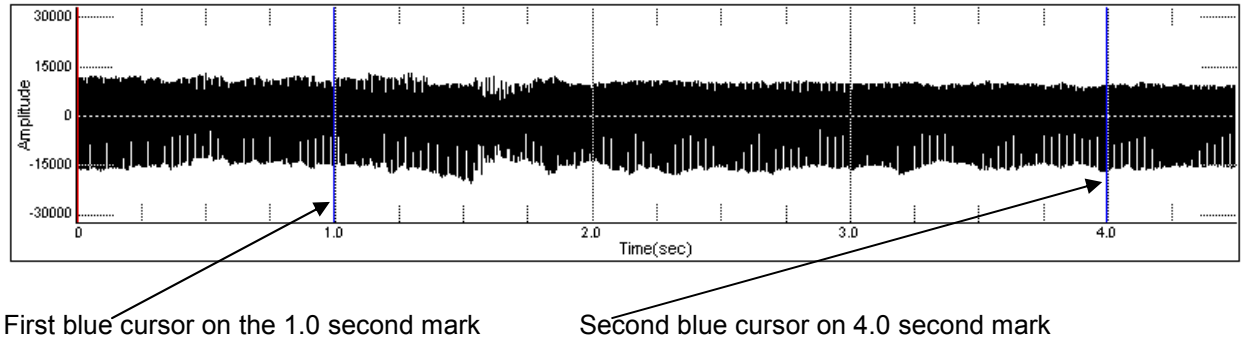


Figure 6.5. The waveform (VTP) trimmed to middle 3 seconds showing placing of blue markers

The trimmed voice signals for the PD and control group were then re-analysed using the Voice and Tremor Protocol (VTP), with the trimmed voice signal and associated measures saved in a sub-folder on the Kay data file. The values for the selected acoustic measures (trimmed signals) for the three trials for pwPD and controls were entered into an excel spread sheet. Due to technical difficulties with the re-digitisation, seven of the pwPD group had data on two trials instead of three trials. For controls, three participants had data on two trials and one participant had data on one trial. The mean value across three trials was calculated for each acoustic measure. For pwPD and control participants with two trials, the mean value of the two trials was calculated.

5.7.3 Audio recordings

The Speech Intelligibility Test and Consensus Auditory Perceptual Evaluation of Voice (CAPE-V) recordings from the Sony Mini disc recorder were imported into a MAC book Pro laptop, using the Audacity 2.0.1 software sound editing programme (http:// audacity.sourceforge.net). The researcher was instructed in the use of Audacity software by a staff member in the department of clinical photography. The imported audio files were cleaned, anonymised, and exported

as MP3 recordings using the MAC book. The term 'cleaning' refers to deleting the researcher's voice when it was present in the recording and extraneous sounds (coughs, restarts, hums).

Speech Intelligibility Test (SIT)

There were no SIT audio files for two PD participants (PD 13, PD 27) and three controls (C30, C31, C32) due to technical problems with the recording procedure, leaving a total of fifty-three files. Five (10%) audio SIT files (3 pwPD, 2 controls) from the total sample were randomly selected for duplication. This was necessary for intra-rater reliability ratings. The final total was 58 SIT files. The order of the anonymised MP3 recordings from the PD and control group was randomised. Subsequently, the entire file containing the randomised audio files was burnt to CD for subsequent independent rating of speech intelligibility. The rating procedure is described in section 5.8.2.

Consensus Auditory Perceptual Evaluation of Voice (CAPE-V)

There were technical problems with the original audio recordings of three participants (PD 7, PD 14, control 22), leaving fifty-five recordings (twenty eight in the PD group, twenty seven in the control group). In preparing the audio recordings for independent perceptual rating of tremor features and overall voice deviance, the sustained vowel and sentence tasks were exported as MP3 recordings. The 'spontaneous' speech task was not exported since the researcher considered that the sustained vowels and connected speech captured in the reading task were sufficient. Ten percent [(n=6) (three PD and three controls] of the total number of recordings were randomly selected for duplication for reliability rating, resulting in sixty one recordings. The order of the recordings was then randomised, saved to a folder and all the CAPE-V recordings were copied to a CD for independent rating at a later stage (section 5.8.1).

5.7.4 Vocal tract exam video recordings

There were fifty six video exams (thirty PD and twenty six controls) and the average length of each recording was five minutes. The preparation of the video recordings for independent visual perceptual rating was time consuming and

technically challenging. A clinical photographer from the clinical photography department agreed to help with the editing of the videos in preparation for independent rating of the video recordings.

(1) Firstly, the researcher systematically viewed each video recording of the vocal tract examination (VTE) and decided which parts needed to be 'cleaned'. The first trial of the sustained /s/ and vowel tasks was deleted in all samples, except in the case when there was only one trial recorded. Using the time indicator on windows media player, the researcher played the video with the accompanying sound and recorded in writing the starting time of a task and the completion time. For example, at the start of a task, the video recording was paused, the time on the display was noted, the play button was activated again and the video stopped at the completion of the task, with the time on the display noted. The same protocol was followed for all the anatomical sites and tasks in the VTE. The video file in CD format with the edits in writing using start and finish times was given to the clinical photographer for editing.

(2) The clinical photographer's first task was to import the mpeg files from the individual participant's CD into Final Cut Pro, a Mac software video editing programme. She then edited the clips in Final Cut Pro as detailed by the researcher. The researcher then reviewed the edited video file of each participant with the clinical photographer to ensure that the recordings had been edited correctly. When all the mpegs (n=56) were imported and edited, she exported the work using a compressor and then made a DVD of the work.

All sound was removed from the video recordings ('silent') requiring the raters to rate tremor on the basis of visually perceived involuntary movement solely, without contribution from perceived auditory tremor in the voice signal. The researcher considered that it was important for this study to remove the potential confounding effect of perceived voice tremor on ratings of tremor behaviour in vocal tract structures. However one could question the clinical utility of such an approach considering that tremor in the vocal tract is identified clinically endoscopically when a

person is phonating. However, a key aspect of this study is to identify PD tremor using different evaluation approaches, therefore rating tremor from 'silent' video recordings was chosen by the researcher.

A particular challenge in preparing the video exams for subsequent rating was how best to indicate for the rater the particular task that was being trialled at a particular time on the video, since the video recordings were silent. The decision was made to label the task with text, so for example when the video was showing the soft palate as the participant was sustaining /s/, the text on the screen was 'palate /s/. The text was placed at the bottom of the screen so as not to obscure the view of the anatomical structures.This protocol was followed for all tasks of the examination. The end product was an anonymised silent video file showing the vocal tract during different tasks, differentiated by text prompts. The video moved from one task to the other with text prompts demarcating the video into different tasks. A blank screen (black) was inserted between the anatomic areas to assist the rater in moving from one site to the next. The average length of each edited video file was one to two minutes.

(3) The entire sample, comprising sixty-two exams including four repeats for reliability analysis was then randomised by the researcher. The clinical photographer then copied the files to CD in the randomised order. The final video file CD with the anonymised randomised recordings was copied four times to CD by clinical photography, for the purpose of later independent rating (section 5.8.3).

5.7.5 Preparation for reliability rating

In order to evaluate reliability of acoustic, auditory-perceptual and visual perceptual ratings it was necessary to carry out the following steps as described below.

Acoustic data

The saved acoustic signal files from ten PD and ten control participants were randomly selected by the researcher for independent re-analysis. Three trials

had been saved for each participant. The first trial only was selected for re-analysis. The decision to choose the 1st over the 2nd and 3rd trial was not based on any scientific reasoning. However, the researcher considered that it was important to be consistent in the selected trial across the twenty files, i.e. choosing the first trial for all the participants selected. An SLT colleague opened the trimmed acoustic signal file, and re-digitised the signal, saving the measurements to a separate folder.

Auditory perceptual ratings

Ten percent (10%) of the audio recordings of the Consensus Auditory Perceptual Evaluation of Voice (CAPE-V), and the Speech Intelligibility Test (SIT) were repeated for the purpose of determining intra- rater reliability.

Visual perceptual ratings

Ten percent (10%) of the vocal tract tremor exam recordings were repeated for the purpose of intra-rater reliability. Four PD (PD1, PD4, PD13, PD16) and two control participants (C13, C28), were selected resulting in sixty-two exams for rating. The researcher selected the exams for repeating with the aim to capture a range of tremor severities.

5.8 Rating procedures

An important component of auditory perceptual and visual perceptual evaluation is the degree to which a particular rating or score assigned to a particular feature is considered to be a valid and reliable measurement. In clinical evaluation, it is important that different clinicians agree on the presence/absence and severity of a particular feature. For example, if one clinician gives a rating of 1 (mild/intermittent tremulous movement) for tremor in the soft palate on a sustained /a/ vowel, it is important that a different clinician or clinicians assigns the same rating. This indicates that the rating scale is clinically useful and can be used across different clinicians and settings. To address this issue of reliability, a number of raters were recruited for each rating experiment. In this study three different rating experiments were required for evaluation of the perceptual data from the following assessments:

- Consensus Auditory Perceptual Evaluation of Voice (CAPE-V)

- Speech Intelligibility Test (SIT)
- Vocal Tract Tremor (VTE) evaluation

It is important to highlight at this juncture that three completely different group of raters were recruited for each rating experiment. The researcher considered that having different raters for the three rating experiments was important, particularly in the case of the auditory perceptual rating tasks, since a rater might recognise a participant's voice from CAPE-V tasks and SIT tasks for example, which would introduce a possible source of bias. The rating procedures for the three rating experiments are described in the following sub-sections.

5.8.1 Consensus Auditory Perceptual Evaluation of Voice (CAPE-V)

Raters

For CAPE-V ratings, four SLT's experienced in working with voice disorders were recruited by the researcher The SLT's experience in assessment and treatment of patient with voice disorders ranged from ten to twenty years. One of the raters was unable to attend on the designated day of the rating session, due to an injury leaving three raters to carry out the rating task. The raters were not given any information about the speakers, other than their gender.

Rating protocol

The rating experiment was carried out in a quiet room in the SLT department at the National Univeristy of Galway (NUIG), Ireland. All ratings were completed on the same day, over a period of five hours, with breaks given for coffee and lunch.

The raters had theoretical but not experiental knowledge of the CAPE-V, therefore a short training session was given at the beginning of the experiment to explain the CAPE-V protocol (APPENDIX J). In addition the inclusion of two perceptual tremor measures (instability, tremor) on the CAPE-V form was highlighted. *Instability* also referred to as unsteadiness, was defined as irregular fluctuations in pitch and/or loudness. *Tremor* was defined as rhythmic or nearly rhythmic fluctuations in pitch and/or loudness of the voice.

The rating session started with an introduction and explanation of the task followed by a rating of twenty samples, a refreshment break, a further 20 samples, lunch and the final 32 samples. The recordings were played through a Mac book Pro lap top with a Logitech Speaker System Z320. The Mac book and speakers were placed on a table. The three raters sat at individual student desks which were positioned equidistant from the speakers. They were instructed not to confer regarding any of the ratings. The researcher was present in the room for the duration of the rating session.

Each rater had a 'rating booklet' containing all the CAPE-V rating forms needed for each participant (APPENDIX K*)*. The researcher announced the identification number, for example 'ID 1' and played the recording twice. The raters rated voice quality features (overall severity; roughness; breathiness) on the sustained vowels and sentences tasks. They rated tremor features (instability, tremor) on the sustained /a/ vowels only. The parameters 'roughness' and 'breathiness' were maintained in the CAPE-V protocol for rating, even though they were not required for the purposes of the current study. In keeping with the CAPE-V protocol, the raters placed a perpendicular mark on the 100 mm visual analogue continuous scale. The extreme left of the 100m line corresponds to a score of 0 and the extreme right to a score of 100. Using a ruler, placed directly under the continuous 100mm line, the researcher determined the number (score) corresponding to the location of the perpendicular mark. The number relating to the point on the ruler was written above the perpindicular line. This method was applied for the three perceptual parameters: overall severity, instability and tremor. The scores were later recorded in the excel score sheet for each PD and control participant. The raters were unable to rate two ratings from the PD group (PD03, PD04) due to low volume of voice on the recording. This resulted in twenty six PD participant ratings going forward for data analysis (section 5.9).

5.8.2 Speech Intelligibility Test (SIT)

Raters

Four female students who were in the third year of a four year degree in SLT were recruited as independent raters for the SIT. All students were on clinical

placement in the Mater Hospital, when they carried out the rating task. They all reported normal hearing at the time of the experiment. Some of the students reported that they had used the Assessment of Intelligibility of Dysarthria Speech (AIDS),[224] (non-computerised version), however none of the students had prior experience of the computerised SIT. Therefore some time was allocated pre-rating tasks to explain the protocol as laid out in the SIT manual[222]. The raters were blinded to the target sentences, the client groupings, and gender.

Rating protocol

The SIT software was installed on two desktop computers in the researcher's office. This set-up facilitated one rater to use one computer and another rater to use a different computer simultaneously, however conferring between raters was not allowed. The SIT software allows for ratings by multiple 'judges'. Therefore each rater was assigned to be either 'rater 1', 'rater 2', 'rater 3', 'rater 4', and inputted the respective rater number into the SIT software programme. The raters listened to the recordings using sennheiser headphones, which were connected to the computer for the rating task. They were instructed that they should listen to each sentence twice only, before transcribing (typing) the perceived words. In the SIT programme, misspelled words and/or typing errors reduce intelligibility scores, therefore the raters were advised to check the typed sentence for spelling errors and correct accordingly before saving and moving on to the next sentence.

The audio CD containing the sixty-two participant's files of twelve sentence recordings was saved to the desktop on each computer. A shortcut for the SIT software programme was also placed on the desktop. This set-up was to facilitate the raters switching from the audio file to the computer software programme, when listening to and then transcribing the sentences. The following steps were followed: The rater opened an anonymised audio recording (file 01) from the CD, which contained the twelve recorded sentences for the participant. Using the SIT software programme, the rater opened file 01. Sentence 1 was listened to and then transcribed (typed) by the rater using the SIT programme continuing until all twelve sentences were transcribed, and then

saving the file. Regarding volume level, the raters were advised to regulate the volume from the volume control on windows media player. The computer programme automatically scores the sample and computes the intelligibility score.

It took an average of five minutes for a rater to transcribe twelve sentences, and approximately six hours to transcribe the complete data set. The raters controlled the rate at which they worked through the recordings however, they were encouraged to take a ten minute break after a one hour listening period. Following a break, rater 1, for example could re-open the SIT file and continue transcribing from where she had stopped before the break. Since the four raters were carrying out the rating task in addition to their student placement work, it took five days for them to work through the sixty-two participant recordings.

There was a technical problem with four of the SIT computer files, and the raters could not upload them on the computer. In these four cases, the raters transcribed sentences into a word document and the intelligibility score was computed manually.

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5.8.3 Vocal Tract Tremor Video Recordings

Raters

The researcher found it difficult to recruit SLT's to act as raters for the visual perceptual rating of tremor, primarily because there are only a small number of SLT's in Ireland who routinely view and evaluate laryngeal images. Four SLT's were recruited, all of whom had clinical experience in voice disorders, ranging from three to sixteen years. Three of the four raters had some experience in viewing dynamic images of the larynx and pharynx. Exposure to rating soft palate movement was limited for all raters.

Training protocol

Time was given before the rating task for the raters to view video clips of participants not included in the research experiment, for the purposes of orientating them to the different vocal tract structures and to discuss possible ratings of video clips. The researcher explained the terms on the rating forms and the manner in which the forms were to be completed *(*APPENDIX L*).* For example, the term global laryngeal tremor was described as 'motion in the vertical dimension of the larynx as a unit, relative to the surrounding upper aerodigestive tract', and an example was shown with an endoscopy clip.

Rating protocol

The rating task using four different computers was carried out in one room in the SLT department at the Mater Hospital. The DVD containing the complete data set of video files was saved in advance, to the desk top of each computer. The recordings were silent hence there was no need for sound equipment.

Each rater sat at the computer with a folder containing all the anonymised rating sheets required for the task. There was one rating form for each participant labelled ID 1, ID 2, etc. The raters were required to rate the presence and severity of 'tremor' movement on a scale of 0-3, where 0=absent, 1=mild/intermittent tremulous movement, 2=moderate tremulous movement, 3=severe tremulous movement *(*APPENDIX L*).*

In total, the raters were required to rate ten different tasks, across the palate, tongue and larynx. A text prompt at the bottom of the screen indicated to the rater the task that was being carried out on the video recording. They were asked to indicate on the form reasons for not giving a rating using the symbols (UR) for 'unable to rate' and (PV) for 'poor view'. They were allowed to view the recording twice and encouraged to use the first viewing to get an overall impression of the vocal tract and to score the ten tasks on the second viewing.

The raters were blinded to group and to repeats. They were not informed that some of the recordings were from pwPD and some from neurologically healthy controls, or that some of the exams were repeated. The order of the recordings was the same for the four DVD's, however the raters worked through them at their own pace. The raters completed the ratings on the same day, excepting one rater who had to go home before the session was complete. She took the DVD with her, completed the ratings at her home on a desk top computer and posted the rating forms to the researcher.

After the rating sheets were completed, and in preparation for analysis of the data, the individual scores for the tasks were inputted by the research assistant into the appropriate score row on the excel sheet. The individual scores for the ten tasks, for the four raters were cross checked with the researcher and then imported into SPSS v. 17.

5.9 Data Analysis

Statistical analysis was carried out using the SPSS programme version 17.0 for windows. Differences were considered significant at alpha level < 0.05. Prior to statistical analysis, the ordinal data (UPDRS II and UPDRS III, visual-perceptual ratings of vocal tract tremor, VHI), and continuous data (acoustic measures, auditory-perceptual ratings) scores for the PD and control groups were analysed for normality of distribution using the Kolmogorov - Smirnov test from SPSS v.17.

Descriptive statistics

Central tendency measures of mean and median, and distribution measures of standard deviation (SD), range and interquartile range were computed to describe the data for the PD group and for controls where appropriate. The data included were: demographical (age, disease duration), PD status (UPDRS II, UPDRS III, Hoehn & Yahr stage); MMSE and HADS scores; acoustic measures previously outlined in section 5.5,; Consensus Auditory Perceptual Evaluation-Voice (CAPE-V) measures outlined in section 5.5,visual-perceptual ratings of tremor in the vocal tract previously outlined in section 5.5, Speech Intelligibility Test % scores; Voice Handicap Index (VHI) total and subscale scores.

Reliability measures

Inter-rater and intra-rater reliability measures were carried out for auditory- and visual perceptual ratings using a two-way mixed effects model (consistency definition) intra classcorrelation coefficient (ICC) based on a single rater, using SPSS (v.17).

Intra-rater reliability for visual perceptual rating of tremor severity was measured in the following ways: percentage (%) exact agreement [the percentage of times that a rater assigned exactly the same score (range 0-3)]; [206] percentage % agreement within one point (the number of times a rater assigned a score within one point of the previous score).

Twelve (20%) acoustic signal wave forms were independently re-digitised by an SLT colleague of the researcher. Identicial values were found for repeated analyses of the same segments, therefore no further measures of agreement were calculated.

Differences between groups

To determine whether statistically significant differences existed between median scores of the PD and control group, a Mann-Whitney U test was applied to the following data: acoustic measures; auditory perceived dysphonia severity; visually perceived ratings for ten vocal tract tremor tasks, VHI scores; HADS scores; sentence intelligibility scores. A *t test* was applied to auditory perceived ratings for *instability* and *tremor.*

Question 2

For question 2, spearman's rho correlation was carried out to examine the relationship between acoustic tremor measures (Rftr, Ratr, Mftr, Matr, vFo, vAm), and auditory perceptual tremor measures (*instability, tremor),* and the relationship between acoustic tremor measures and visual perceptual tremor measures. The visual perceptual tremor measures selected for the correlational analysis are outlined below.

- Palate /a/: (tremor in the palate on a sustained /a/ vowel)
- Tongue /a/ (tremor in the tongue on a sustained /a/ vowel)
- Larynx /a/ (vertical laryngeal tremor on a sustained /a/ vowel)
- Larynx /i/ (tremor in the vocal cords on a sustained /i/ vowel)

The visual perceptual vowel based tasks only were selected over 'rest breathing' and voiceless /s/ tasks for inclusion in the correlational analysis across measures. The reason for this selection was that the acoustic measures ('gold standard' for this study) are based on a sustained /a/ vowel.Therefore,in order to examine the relationship between acoustic and visual perceptual measures, without the confounding effect of task, it was necessary to keep the task constant across measures and use a sustained /a/ vowel. A further reason is that voice tremor is best identified on a sustained vowel and not on a voiceless and/or breathing task.

Question 3

For question 3, which looks at the relationship between acoustic voice tremor measures and voice and speech variables, Spearman's (rho) was applied. The acoustic tremor measures included in the correlation were Rftr (Hz), Ratr (Hz), Mftr (%), Matr (%), vFo (%) and vAm (%). The voice variables were: mean values (3 raters combined) of auditory perceived *instability* and *tremor* from CAPE-V; VHI total and subscale scores and mean values. The speech variables were mean values (4 raters) for % scores speech intelligibility.

Question 4

For question 4, which examines the relationship between acoustic voice tremor measures and disease variables, [disease duration, activities of daily living (UPDRS II), motor symptoms (UPDRS III)], spearman's rho was calculated.

PD phenotype calculation

To explore the relationship between acoustic measures and PD phenotype, the following steps were carried out. The phenotype [(tremor-dominant, posture and gait instability (PIGD) or indeterminate)] was derived from the UPDRS score as follows.

The mean of the following nine tremor items was calculated to give an overall global tremor score: right and left arm tremor determined from history (UPDRS II), tremor at rest (face, lips or chin, four limbs), and action or postural tremor based on researcher's rating (UPDRS III).The mean of the following five items was calculated to give a postural instability and gait difficulty (PIGD) score: falling; freezing; walking difficulty (UPDRS II), and gait and postural instability by examination (UPDRS III).

The ratio of tremor score to PIGD score was calculated. Participants with a ratio of mean tremor /mean PIGD score greater than or equal to 1.5 were considered tremor-dominant. Those with a ratio less than or equal to 1.0 were considered PIGD. Indeterminate did not fall into either category.Three of the pwPD were identified as 'indeterminate' on the basis of the above formula and were not entered into any further analysis. Tremor-dominant and PIGD pwPD were coded as 1 and 2, respectively on SPSS v. 17.

A series of Mann Whitney U tests were carried out to examine differences between tremor- dominant and PIGD pwPD on the basis of the six acoustic measures (Rftr, Ratr, Mftr, Matr, vFo, Vam). Further analyses followed of differences between tremor dominant and PIGD phenotypes on the basis of auditory perceptual (*instability*; *tremor*) measures and visual perceptual (palate /a/, tongue /a/,larynx /a/, larynx /i/) measures, using Mann Whitney U tests.

Chapter 6. Results

The findings from the screening protocol for eligibility of the study for the PD and control group will be presented in section 6.1, followed by the participant characteristics in section 6.2. The main and supplementary results for the four research questions are presented in section 6.3.

6.1 Screening

PD group

A total of seventy six pwPD (50 males; 26 females) were screened for eligibility to join the study. Thirty-five pwPD (21 males; 14 females) were not eligible for inclusion and were therefore excluded from the study. Forty one pwPD (29 males: 12 females) were therefore deemed to be eligible but a further nine subjects (5 males; 4 females) declined to participate in the study. Consequently, thirty-two (24 males; 8 females) pwPD proceeded to assessment (Figure 6.7).

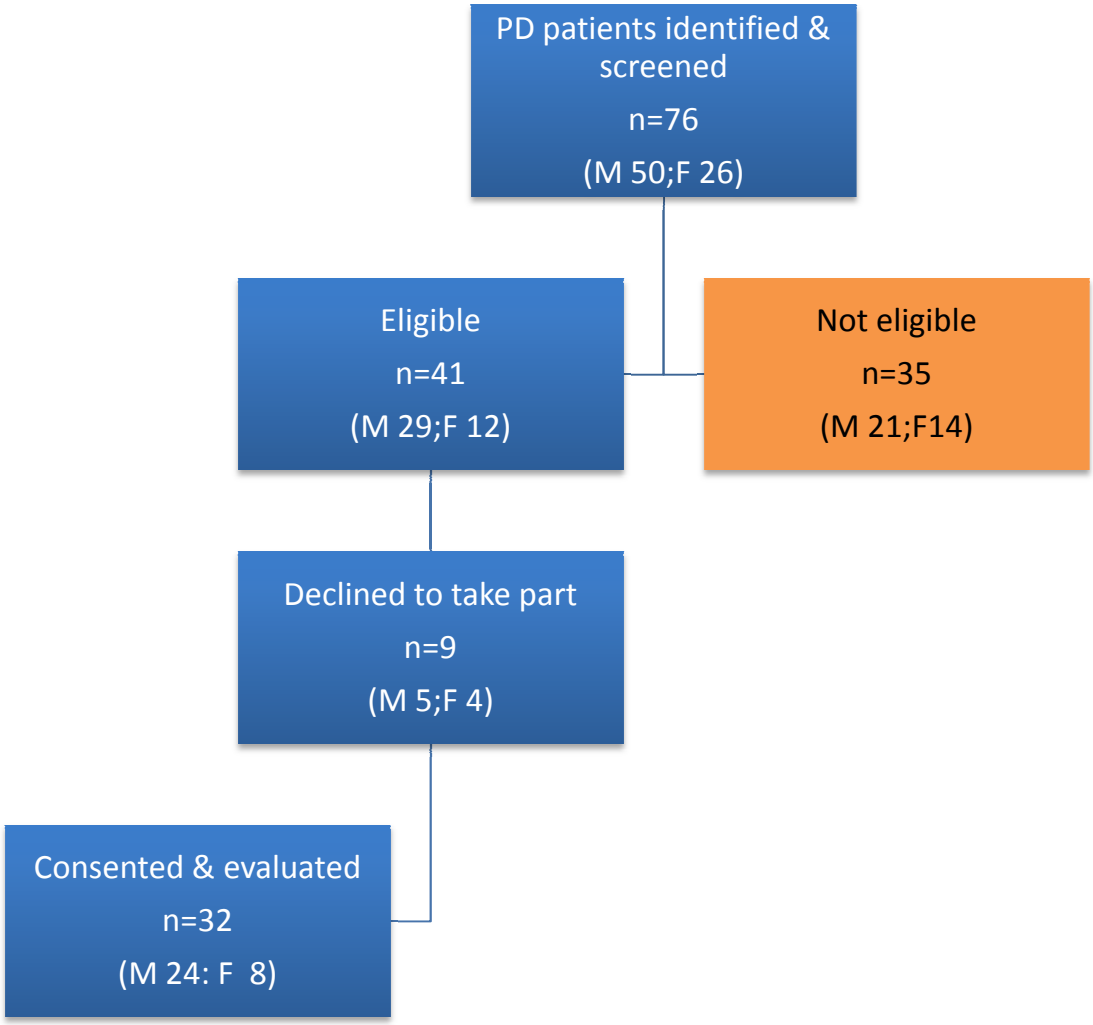


Figure 6.7. PD group flow diagram from screening to entry into study

Exclusions

Table 6.3 shows the number of participants and the reason for their exclusion from the study.The most frequent reason for exclusion was smoking, followed by cognitive impairment. The mean age of the group excluded from the study was 66.26 years.

Table 6.3. PD participants excluded from study: number (n) and reason for exclusion

Reason for exclusion	*n**
Smoker in past five years	6
Cognitive impairment	5
Depression	4
Head trauma	4
Previous surgery to neck or spinal region	4
Dyskinesias	3
Voice treatment in past year (Lee Silverman Voice Treatment)	2
History of CVA	2
Bell's Palsy	1
Lesion to basal ganglia	1
Lewy Body disease	1
Hearing difficulties	1
Dysarthria & hypotonia related to non-PD medication	1
Radiotherapy	1

*n = 35 (21 males, 14 females). Mean age: 66.26 years

Control group

Twenty eight participants (20 males; 8 females) were recruited for the study by the cut off date. Recruiting controls proved more difficult than initially anticipated by the researcher. Some controls were reluctant to have a nasendoscopic examination, and this was the main contributory factor to the lower number of healthy controls than pwPD in the study.

6.2 Participant characteristics

Following assessment for the study, two further participants from the PD group were excluded since they were identified with neurological co-morbidities. This knowledge was not available to the researcher prior to testing. One participant had an occipital lesion (PD 22, male), and the other (PD 8, female) had a lacunar infarct, leaving thirty pwPD participants for data analysis.

Gender distribution, mean (SD), range, median and interquartile range (IQR) for chronological age, Mini Mental State Examination (MMSE) and anxiety and depression scores from the Hospital Anxiety and Depression Scale (HADS) are shown in Table 6.4, together with *p* values for the comparison of the PD and control group. The raw data for demographical, MMSE, HADS, and disease variable data for the PD group are shown in APPENDIX M. The raw data for demographical, MMSE, HADS and VHI scores for the control group are shown in APPENDIX N.

Table 6.4. Mean (SD), range, median, (IQR) values for age, MMSE, HADS scores, and p values for PD and control group

	PD group (n=30)	Control group (n=28)		*p*
Gender [n (%)]				
Males	22 (73)	20 (71)		
Females	8 (27)	8 (29)		
Age (years)				
Group				
Mean (SD)	61.40 (10.31)	60.11 (9.54)	0.495 [1]	0.623
Range	(34 - 76)	(36 - 74)		
Median (IQR)	61.00 (54.75 -70.25)	60.50 (53.25 -68.50)		
Males	60.95 (10.82)	59.55 (10.24)		
Females	62.63 (9.29)	61.50 (7.96)		
MMSE				
Mean (SD)	28.87 (1.00)	28.82 (1.21)		
Range	(26 -30)	(25 -30)		
Median (IQR)	29.00 (28.00 -30.00)	29.00 (28.00 -30.00)	412.000 [2]	0.895
HADS	*n=30*	*n=27*		
Anxiety				
Mean (SD)	4.47 (3.46)	2.63 (2.27)		
Range	(0 -14)	(0 -8)		
Median (IQR)	4.00 (1.75 - 7.00)	2.00 (1.00-4.00)	275.500 [2]	**0.037 ***
Depression				
Mean (SD)	3.97 (3.33)	1.52 (1.69)		
Range	(0-18)	(0-7)		
Median (IQR	3.50 (2.00-5.25	1.00 (0.00-2.00)	176.00 [2]	**0.000 ***

[1]Independent *t*-test: [2]Mann Whitney U
MMSE:Mini-Mental State Examination
HADS: Hospital Anxiety & Depression Scale

As can be seen from Table 6.4, a total of fifty eight participants completed the study.There were more males than females in both groups, with a ratio of 2.75:1 and 2.50:1 respectively. There was no statistically significant difference between the two groups with respect to age (p >0.05), or MMSE (p>0.05) *(*Table 6.4).These findings confirm homogeneity of the PD and control group for age and cognitive functioning.

Hospital Anxiety and Depression Scale (HADS)

The PD participants had higher scores for anxiety and depression than the control group when measured on the Hospital Anxiety and Depression Scale (HADS) and this was statistically significant ($p<0.05$). The guidelines in the HADS manual were followed for interpretation of the individual pwPD and control total scores[232]. A score in the range of 0-7 is considered normal. Scores in the range of 8 -10, 11-14, and 15-21 are considered a mild, moderate and severe effect respectively. Six pwPD scored outside the normal range: 3 indicated mild anxiety; 2 indicated moderate anxiety and 1 indicated moderate depression. The HADS was not administered to one control participant due to researcher error, hence the reason for 27 participants in the control group.

Unified Parkinson's Disease Rating Scale (UPDRS), and Hoehn & Yahr (H & Y) Scale

Table 6.5 shows the mean (SD), range, median and interquartile (IQR) range for age at disease onset, years since disease onset, Unified Parkinson's Disease Rating Scale (UPDRS) part II, UPDRS part III, and Hoehn & Yahr Scale (H&Y) for the PD group.

Table 6.5. Mean (SD), range, median, (IQR) for age at disease onset (years), disease duration, UPDRS II, UPDRS III & Hoehn & Yahr for PD group

	PD group (n=30)				
	Age disease onset (years)	**Disease duration**	**UPDRS II**	**UPDRS III**	**Hoehn & Yahr**
Mean (SD)	56.17 (9.56)	5.23 (3.17)	10.20 (3.85)	25.00 (9.23)	2.17 (0.74)
Range	32 - 70	1 - 12	4-19	8-41	1-4
Median	56.00	5.00	9.50	24.50	2.00
(IQR)	(47.75 -65.25)	(2.75-7.25)	(7.00-13.25)	(17.75-33.00)	(2.00-3.00)

Disease duration= number of years post diagnosis

Head and jaw clinical tremor evaluation

The number (%) of pwPD and control participants rated with head and jaw tremor is shown in Table 6.6.

Table 6.6. Head and Jaw tremor [(n)(%)] in PD and control group

	PD group (n=31)	**Control group (n=23)**
	Tremor present *n (%)*	Tremor present *n* (%)
Head tremor	2 (6.4%)	0 (0%)
Jaw tremor	11 (35.4%)	1 (4.3%)

Head tremor was present in two pwPD. Jaw tremor was more frequent, and was present in eleven pwPD. For the control group, head tremor was not identified in any participant and jaw tremor was identified in just one participant.

6.3 Research questions

The findings for the four research questions are presented in section 6.3. A similar lay out is followed across all four questions. For example, the results relating directly to the research questions are presented first. When supplementary findings are reported, these will be presented under 'supplementary findings' and raw data when appropriate will be presented in the relevant appendix.

6.3.1 Question 1

The over-riding aim of Question 1 was to determine if there was a difference between pwPD and neurologically healthy controls in relation to voice tremor. There are three parts to question 1, and the results for each part will be reported separately as Part (a), Part (b) and Part (c). At the end of question 1, the salient findings from the three parts will be summarised.

6.3.1 Question 1. (Part A)

Is there a difference between pwPD and neurologically healthy age-sex matched controls in relation to voice tremor, when measured using acoustic tremor measures?

The key and ancillary acoustic voice tremor measures applied to question 1 are listed below to assist in interpretation of the results**.** The specific measures with brief explanations from the Motor Speech Profile (MSP) manual[119] are outlined in APPENDIX I. The raw data for the acoustic measures for the PD and control group are displayed in contained in APPENDIX O and APPENDIX P respectively.

Key voice tremor measures

- Rate of frequency tremor [Rftr(Hz)]:
- Rate of amplitude Tremor [(Ratr(Hz)]:
- Periodicity of the frequency tremor [Pftr (%)]:
- Periodicity of the amplitude tremor [Patr(%])*:*
- Magnitude of the frequency tremor [Mftr (%)]:
- Magnitude of the amplitude tremor [Matr (%)]*:*

Ancillary tremor measures

- Coefficient of variations in the fundamental frequency [vFo (%)]:
- Coefficient of variations in the amplitude [vAm (%)]*:*

Tremor detection, rate, periodicity and magnitude of tremor

Table 6.7 shows the descriptive statistics for the number (%) of participants in the PD and control group in which frequency tremor and amplitude tremor was detected by the voice and tremor protocol from the motor speech profile (MSP). The mean (SD), median, and inter quartile range (IQR) with p values are also shown in Table 6.7 for rate (Hz), periodicity, and magnitude of frequency and amplitude tremor for the PD and control group.

Table 6.7. Tremor detection rate [(n) (%)], & mean (SD), range, median, and IQR values for tremor rate, periodicity & magnitude of frequency and amplitude tremor for PD and control group

	Frequency Tremor		**Amplitude Tremor**	
Tremor detected	PD	Control	PD	Control
n (%)	13 (43.3)	10 (35.7)	16 (53.3)	17 (60.7)
Tremor rate (Hz)				
Mean (SD)	4.39 (2.59)	3.03 (1.33)	4.94 (2.25)	2.85 (0.72)
Median	3.25	2.66	4.44	2.66
IQR	2.43-6.54	2.29-3.03	3.40-5.69	2.30-3.35
	p = 0.19 [a]		p = **0.001** [b]	
Periodicity %				
Mean (SD)	30.22 (16.50)	24.09 (8.11)	45.07 (10.64)	37.12 (12.35)
Median	25.14	22.61	43.40	38.84
IQR	19.67-39.52	18.44-27.53	34.21-55.39	31.33-44.37
	p = 0.38 [a]		p = 0.057 [b]	
Magnitude %				
Mean (SD)	0.91 (0.73)	0.71 (0.12)	3.23 (2.08)	2.27 (0.91)
Median	0.69	0.68	2.50	2.10
IQR	0.40-0.69	0.37-0.63	1.49-3.11	1.59-2.22
	p = 0.71 [a]		p = 0.16 [a]	

[a] Mann Whitney U test
[b] Independent *t* test

Frequency tremor was detected in almost 50 % of the pwPD. The detection rate was lower in the control group. In the 13 pwPD in whom frequency tremor was detected, the mean rate of tremor (Hz) was higher than in the control group, however the difference between the groups was not statistically significant when a Mann Whitney U test was applied (Table 6.7).

Frequency tremor was more periodic and had greater magnitude in pwPD than in controls however the difference between the groups for Pftr and Mftr did not reach statistical significance.

Amplitude tremor was detected in more than 50% of pwPD. There was a marginally higher rate of detection of amplitude tremor in the control group. In pwPD in whom amplitude tremor was detected, the mean rate (Hz) of amplitude tremor was higher than in controls. The difference between the groups for rate of amplitude tremor was statistically significant ($p<0.001$), when an independent *t* test was applied. Amplitude tremor showed greater periodicity in pwPD than the control group, with the difference approaching significance ($p=0.057$), (Table 6.7). The pwPD had a greater magnitude of amplitude tremor than the controls had, however the difference between the groups did not reach statistical significance.

Magnitude of frequency tremor (Mftr), magnitude of amplitude tremor (Matr)

Table 6.8 reports the mean, standard deviation (SD), median, interquartile range (IQR) and *p* value for Mftr and Matr for the PD and control group.

Table 6.8. Mean (SD), median, interquartile range (IQR) & p values for Mftr, Matr, for PD & control group

	PD *(n=30)*	Control *(n=28)*	U	p
Mftr				
Mean(SD)	0.661(0.531)	0.510 (0.191)	***329.000***	***0.157***
Median	0.602	0.482		
IQR	0.404-0.695	0.377-0.638		
Matr				
Mean(SD)	2.496 (1.74)	2.059 (0.787)	***402.000***	***0.779***
Median	1.999	1.882		
IQR	1.496-3.115	1.594-2.228		

The PD group had a higher mean (SD) Mftr% value than the control group but this difference was not statistically significant ($p>0.05$). The mean (SD) Matr% value was higher for the PD group than the control group, but again the difference did not reach statistical significance ($p>0.05$). It is important to note that the Mftr% and Matr% mean values in Table 6.8 include periodic and non-periodic modulations in contrast to Table 6.7, which showed Mftr and Matr for periodic modulations only.

Co-efficient of variation of frequency (vFo), coefficient of variation of amplitude (vAm)

Table 6.9 reports the mean, standard deviation (SD), median, interquartile range (IQR) and *p* value for vFo and vAm for the PD and control group.

Table 6.9. Mean (SD), median, interquartile range (IQR) & p values for vFo, & vAm for PD & control group

	PD *(n=30)*	Control *(n=28)*	U	p
vFo				
Mean(SD)	1.577(2.499)	1.057 (0.482)	***330.500***	***0.164***
Median	1.060	0.930		
IQR	0.862-1.355	0.710-1.221		
vAm				
Mean(SD)	7.857(3.428)	8.259 (3.034)	***358.000***	***0.335***
Median	6.852	7.929		
IQR	5.981-8.491	6.116-9.269		

p≤ 0.05: Mann Whitney U test

Similar to the other measures, the mean (SD) vFo value for the PD group was higher than the control group but the difference between the groups was not statistically significant (p>0.05). For vAm, the mean (SD) value for the PD group was lower than the mean value of the control group, however the difference between the groups was not statistically significant (p>0.05) (Table 6.9). The finding of higher vAm values for the control group in comparison to pwPD was not anticipated and will be discussed in section 7.1.

6.3.1 Question 1 (Part B)

Is there a difference between pwPD and neurologically healthy age-sex matched controls in relation to voice tremor measured auditory perceptually?

To answer this question, two different perceptual measures of voice tremor, *instability* and *tremor*, were rated independently by three experienced listeners using a 100mm visual analogue scale. The inter-rater and intra-rater reliability findings for instability and tremor are presented first, followed by the main research question findings.

Inter-rater reliability for perceived instability and tremor

The intraclass correlation coefficients (ICC) and confidence intervals for inter-rater reliability for *instability* and *tremor* are outlined for the PD and control group in

APPENDIX Q. Applying the guidelines for Kappa coefficients[233], a kappa of 0.01 indicates poor agreement and a kappa of 0.81 to 1.00 indicates almost perfect agreement. The raters achieved 'substantial' agreement when rating *instability* in the PD (ICC 0.780) and control group (ICC 0.717). However, agreement for rating *tremor* was lower with ICC values of 0.306 for pwPD and 0.481 for controls, suggestive of only 'fair agreement'.

Intra-rater reliability for perceived instability and tremor

The intraclass correlation coefficients (ICC) and confidence intervals for intra-rater reliability of instability and tremor are outlined in APPENDIX R. The ICC's relate to the rating of repeat recordings from six participants (3 pwPD and 3 controls). For rating perceived *instability,* Rater A achieved a moderate level of agreement. Rater B, showed no consistency in ratings, and rater C achieved almost 'perfect agreement' within herself (Kappa guidelines[233]). For perceived *tremor* ratings, Rater A showed poor agreement within herself. In contrast Rater B and rater C achieved moderate agreement. The confidence intervals for *instability* and *tremor* show a wide range of values for each rater. Overall, Rater C was the most consistent of the three raters.

Research question findings

The mean (SD), median and interquartile range (IQR) values, and *t* test results for perceived *instability* and *tremor* are displayed in Table 6.10. The raw data for perceived *instability* for the PD and control group are shown in APPENDIX S. The raw data for perceived *tremor* for the PD and control group are displayed in APPENDIX T and APPENDIX U respectively.

Table 6.10. Mean (SD), range, median values for perceived instability and tremor and p values for PD and control group

	PD (n=26)	Control (n=27)	t	*p*
	Perceived Instability			
Mean (SD)	27.27 (14.92)	24.37 (12.73)	0.762	0.450 [a]
Median (Range)	24.00 (4.00-63.00)	23.00 (5.00-56.00)		
IQR	15.00-37.50	14.00-34.00		
	Perceived Tremor			
Mean (SD)	18.54 (11.63)	18.07 (12.08)	0.142	0.887 [a]
Median (Range)	16.50 (2.00-55.00)	18.00 (4.00-48.00)		
IQR	11.25-24.25	7.00-28.00		

a: *t-test*

For perceived *instability*, the PD group had a higher mean (SD) value than the control group, however the difference was not statistically significant . For perceived *tremor*, the PD group had a similar mean (SD) value to the control group, without statistical significance (Table 6.10).

Table 6.10 shows that the PD group had higher mean (SD) values for instability in comparison to tremor. Supplementary analyses showed that the difference between ratings for instability and tremor for the PD group was statistically significant using a paired samples *t* test ($p<0.01$) (Table 6.11).

The control group also showed a similar trend with higher ratings for instability than tremor and the difference was also found to be statistically significant ($p<0.01$) Table 6.11.

Supplementary analysis results

Instability and tremor mean value comparison, and p values for PD and control group

Table 6.11. Mean (SD) IQR and p values for perceived instability and tremor ratings and p values for pwPD and for control group

	PD (n=26)				**Control (n=27)**			
	Instability	Tremor	t	p	Instability	Tremor	t	p
Mean	27.27	18.54	4.760	**<0.01**	24.37	18.07	6.280	**<0.01**
SD	14.920	11.635			12.728	12.086		
IQR	15.00-37.50	11.25-24.25			14.00-34.00	7.00-28.00		

Relationship between perceived instability and tremor

Instability and tremor were positively and strongly correlated in the PD ($p< 0.01$) and control group ($p<0.01$) with pearson r values of 0.77 and 0.91 respectively (Table 6.12).

Table 6.12. Pearson r correlation between perceived instability and tremor for the PD & control group

	Perceived Tremor	
	PD (n=26)	Control (n=27)
Perceived Instability	0.779**	0.913**

**. Correlation is significant at the 0.01 level (2-tailed).

6.3.1 Question 1 (Part C)

Is there a difference between pwPD and neurologically healthy age-sex matched controls in relation to voice tremor measured visually perceptually?

The final part of question 1 relates to the visual perceptual rating of tremor in the vocal tract, using nasendoscopy. Four speech and language therapists (SLT's) independently rated tremor behaviour from silent video recordings of nasendoscopic examinations, using a four point interval rating scale (0=absent tremor, 1 = mild/intermittent tremulous movement, 2= moderate tremulous movement, 3 = severe tremulous movement). The inter- and intra-rater reliability findings will be presented first followed by the main research question findings.

Inter-rater reliability for visually perceived tremor in the vocal tract

The intraclass correlation coefficient (ICC) results for inter-rater reliability is shown in APPENDIX V. Kappa guidelines[233] were applied in interpreting the results (kappa of 0.01 indicates poor agreement and a kappa of 0.81 to 1.00 indicates almost perfect agreement). Overall, ICC's for inter-rater reliability were higher in the PD than the control group. The ICC results show a wide range of coefficients for rating tremor severity in the PD group. The highest ICC (0.7) was for rating tremor in the palate during 'rest breathing' and the lowest was for rating tremor in the vocal cords on a sustained /i/ vowel (ICC of 0.2). For the control group, the highest ICC (0.5) was for rating tremor in the palate on a sustained /a/ vowel and the lowest was for rating tremor in the tongue on a sustained /a/ vowel (ICC of 0.07).

Intra-rater reliability for visually perceived tremor in the vocal tract

Intra-rater reliability based on the percentage of times that the raters assigned exactly the same score (exact agreement) on a scale of 0-3, on repeat viewing of the exams shown in (*APPENDIX W)* for pwPD and controls. The results for tremor severity ratings show that agreement is generally higher for pwPD ratings than it is for controls.

Exact agreement scores for pwPD range from a high 94% (tongue tremor rest breathing) to a lower 43% (tongue tremor sustained /s/). For controls, exact agreement scores ranged from 75% (four different tasks) to 38% (palate tremor rest breathing).

Agreement within one point (%) is also shown in *APPENDIX W* for pwPD and controls. Overall, percent agreement within one point is higher than it is for exact agreement, with 100% agreement for 9/10 tasks, for pwPD and controls.

The percentage of time that the raters agreed within themselves regarding the *presence /absence* of tremor in pwPD and controls is shown in *APPENDIX X.* For pwPD, the highest agreement (100%) was achieved for rating tremor in the palate on a sustained /s/, /a/, and in the larynx on sustained /a/, and the lowest (62.5%) for rating tremor in the larynx on a sustained /i/. Again, raters show much higher agreement within themselves when rating the presence/absence of tremor in pwPD than in controls. The percent agreement for rating presence/absence of tremor in controls ranged from 87.5 % to 50%.

Research question findings

The mean (SD), median, range, p values and effect sizes for severity ratings of visually perceived tremor in the palate, tongue and larynx (vocal tract) during different tasks, for the PD and the control group are displayed in Table 6.13. Figure 6.8 graphically displays the mean and p values for the ten tasks across the palate, tongue and larynx. Figure 6.9 graphically shows the mean vocal tract tremor score (mean of scores for ten tasks) for thirty individual pwPD.

Table 6.13. Mean (SD) median, range, p values and effect sizes for rating tremor in vocal tract structures, for PD and control group

	PD		Control				
	Mean (SD) n=30	Median (Range)	Mean (SD) n=24	Median (Range)	U/Z	*p*	Effect size
Palate Breathe	1.19 (0.88)	1.12 (0.00-3.00)	0.70 (0.42)	0.62 (0.00-1.50)	254.00/ -1.861	0.063 [a]	N/A
Palate /s/	n=29 1.43 (0.68)	1.25 (0.00-2.75)	n=25 0.72 (0.51)	0.50 (0.00-1.75)	152.00/- 3.665	**p<0.001*** [a]	0.49 [c]
Palate /a/	n=28 1.60 (0.81)	1.50 (0.00-3.00)	n=25 1.04 (0.57)	1.00 (0.00-2.00)		**0.006*** [b]	0.37 [c]
Tongue Breathe	n=30 0.74 (0.81)	0.50 (0.00-3.00)	n=24 0.32 (0.43)	0.25 (0.00-2.00)	226.500/ -2.384	**0.017 *** [a]	0.32 [c]
Tongue /s/	n=29 0.81 (0.72)	0.50 (0.00-3.00)	n=24 0.36 (0.32)	0.25 (0.00-1.25)	208.00/ -2.552	**0.011 *** [a]	0.35 [c]
Tongue /a/	n=30 0.78 (0.65)	0.50 (0.00-3.00)	n= 25 0.40 (0.26)	0.50 (0.00-1.00)	237.500/- 2.379	**0.017 *** [a]	0.32 [c]
Larynx Breathe	n=30 0.95 (0.69)	1.00 (0.00 -2.50)	n=26 0.43 (0.38)	0.25 (0.00-1.33)	230.00/- 2.654	**0.008 *** [a]	0.35 [c]
Larynx /s/	n=29 1.27 (0.82)	1.25 (0.00-3.00)	n=26 0.51 (0.44)	0.41 (0.00-1.50)	167.00/- 3.556	**p<0.001 *** [a]	0.47 [c]
Larynx /a/	n=30 1.04 (0.63)	1.00 (0.00-2.25)	n=26 0.35 (0.30)	0.25 (0.00-1.00)	131.00/- 4.309	**p<0.001 *** [a]	0.57 [c]
Larynx /i/	n=30 0.68 (0.45)	0.62 (0.00-1.75)	n=26 0.30 (0.30)	0.25 (0.00-1.25)	185.00/- 3.439	**0.001 *** [a]	0.45 [c]

a: Mann Whitney U test:
b*: t-test*
c: r effect size [(Cohen (1988)]

Palate

For tremor in the *palate,* the mean (SD) values were higher (indicating greater severity) in the PD group than the control group for the three tremor conditions: breathing, sustained /s/, and /a/ vowel (Table 6.13). For rating of palatal tremor on a sustained /s/ and on a sustained /a/ vowel, the difference between the groups was statistically significant ($p<0.05$). For rating palatal tremor during rest breathing, the difference between the groups was not statistically significant. The sustained /a/ vowel task achieved the highest tremor rating in the palate in comparison to rest breathing and sustained /s/ with a mean (SD) of 1.60 (0.81).

Tongue

For *tongue* tremor, the PD group had higher mean (SD) values than the control group for rest breathing, sustained /s/ and /a/ vowel (Table 6.13).The difference between the groups for all three tasks was statistically significant ($p<0.05$). The sustained /s/ task achieved the highest mean tremor rating in comparison to rest breathing and sustained /a/ tasks with a mean value of 0.81 (0.72).

Larynx

For rating tremor in the larynx for all tasks, rest breathing, sustained /s/, /a/ and /i/ vowels, the PD group had higher mean (SD) values than the control group (Table 6.13*).* The difference between the groups was statistically significant ($p<0.05$) for all tasks. The sustained /s/ task achieved the highest mean tremor rating in comparison to rest breathing, sustained /a/ and sustained /i/,with a mean value of 1.27 (0.82).

Figure 6.8 graphically displays the mean and p values for the ten tasks across the palate, tongue and larynx for PD and control group.

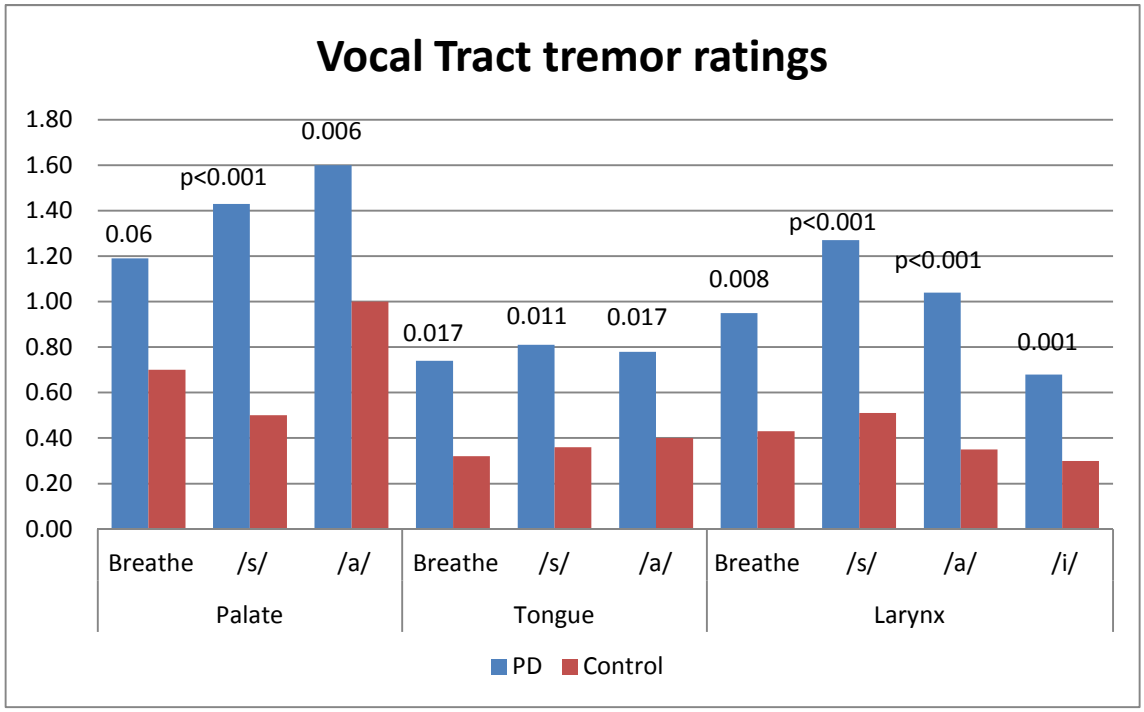


Figure 6.8. Mean ratings across 4 raters for different tasks across the palate, tongue, and larynx, for PD and control group

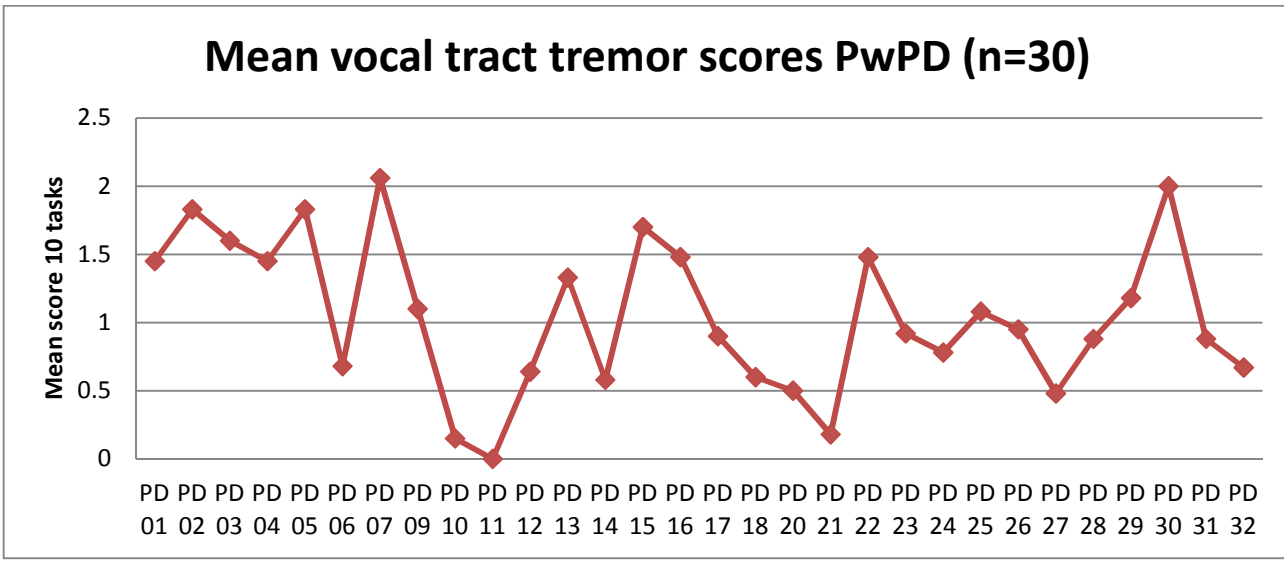
Supplementary findings

Effect sizes for rating ten vocal tract tasks

Analysis of effect sizes using Cohen's r [234] shows that the majority of the tasks achieved a medium to large effect size (Table 6.13).The 'larynx /a/ task (tremor in the global larynx /vertical laryngeal tremor) had the highest effect size at 0.57.

Individual pwPD mean vocal tract tremor scores

Figure 6.9 shows the dispersion of mean vocal tract tremor scores (3 anatomic sites and four tasks combined) for individual pwPD across thirty pwPD.



Rating scale: 0 = no visually perceived tremor, 1= mild/intermittent, 2= moderate, 3= severe

Figure 6.9. Individual mean scores for vocal tract tremor ratings (10 tasks combined) for 30 pwPD

Fourteen pwPD obtained mean scores between 1 and 2 (1=intermittent/ mild tremor, 2 = moderate tremor), whilst 16 pwPD achieved a mean tremor score of 1 or less. Therefore close to 50% pwPD could be considered to have definite evidence of tremor in the vocal tract and 55% to have minimal or no tremor on visual perceptual analysis (Figure 6.9).

Patient 'experience of nasendoscopy exam

Thirty pwPD (n=30) tolerated the nasendoscopy exam. The findings from a short questionnaire completed by pwPD post examination showed that the experience of the examination was 'acceptable' with low levels of discomfort and anxiety associated with it. The findings from the self-report questionnaire for rating of 'experience', 'pain', and 'anxiety' are graphically shown in APPENDIX CC.

Summary main results for question 1

Evaluating voice tremor using different approaches yielded varied findings with differences between pwPD and controls identified with some measures and not with others. The salient findings were:

- For *acoustic* measures, the rate of amplitude tremor differentiated the PD from the control group. The periodicity of amplitude tremor, the extent (magnitude) of frequency and amplitude tremor, and overall variation in frequency was greater in the PD than in the control group, but the difference was not statistically significant

- PwPD were rated as having more perceived *instability* in their voice than the control group. However, this difference did not reach statistical significance. For *tremor* ratings, the PD and control groups were closely matched in severity. Comparing *tremor* and *instability* mean values within the PD group, the PD group were rated as having more instability than tremor with statistical significance. A similar trend for higher ratings of instability than tremor occurred in the control group with statistical significance achieved

- In relation to *visually perceived* tremor in the vocal tract, the PD group were rated as having higher levels (greater severity) of tremor in the palate, tongue and larynx than the control group when evaluated on ten different tasks. Statistical significance was achieved for all sites and tasks with the exception of the task 'palate breathe'

    - There were medium to large effect sizes for the visually perceived tremor ratings. Almost 50% of pwPD were considered to have definite evidence of tremor in the vocal tract, 55% were rated as having less than mild/intermittent tremor

    - Inter-and intra-rater agreement tended to be higher for ratings of vocal tract tremor in pwPD than in the control group

- The majority of pwPD considered the nasendoscopy procedure to be an ‘acceptable’ experience with a small number experiencing mild pain/discomfort and anticipatory anxiety

6.3.2 Question 2

Question 2 explores the nature of the relationship between acoustic and auditory perceptual tremor measures, and between acoustic and visual perceptual tremor measures. The following ten measures were entered into the correlational analysis to answer question 2.

- *Acoustic measures*: rate of frequency tremor (Rftr Hz); rate of amplitude tremor (Ratr Hz); magnitude of frequency tremor (Mftr %); magnitude of amplitude tremor (Matr %); variation in frequency (vFo %); variation in amplitude (vAm %)
- *Auditory perceptual measures*: instability; tremor
- *Visual perceptual measures of tremor in the vocal tract:* palate /a/; tongue /a/; larynx /a/; larynx /i/

To gain further insight into the relationship between different measurement approaches, a further supplementary corrrelational analysis was carried out. The relationship between auditory perceptual (*instability, tremor*) and visual perceptual (palate /a/; tongue /a/; larynx /a/; larynx /i/) measures was explored for the PD and control group separately.The research question results will be presented first, followed by the results for the supplementary analysis.

Question 2: What is the nature and degree of the relationship between acoustic and auditory perceptual voice tremor measures, and visual-perceptual measures?

PD group

The relationship between the acoustic measures and auditory perceptual measures, and between the acoustic and visual perceptual tremor measures, for pwPD are displayed in the correlation matrix in Table 6.14, with significant associations in bold and with asterisk to denote significance.

Table 6.14.Spearman correlations (rho) for acoustic voice tremor measures and auditory perceived instability and tremor, and visual perceptual ratings for PD group

	Auditory perceptual measures		Visual-perceptual measures			
Acoustic measures	Instability	Tremor	Palate /a/	Tongue /a/	Larynx /a/	Larynx /i/
Rftr (Hz)	-0.471 n=12	-0.212 n=12	0.281 n=12	0.118 n=13	0.063 n=13	-0.120 n=13
Ratr (Hz)	0.221 n=15	0.106 n=15	-0.126 n=16	-0.173 n=16	-0.147 n=16	0.118 n=16
Mftr (%)	**0.454*** n=26	**0.515**** n=26	0.196 n=28	0.347 n=30	0.182 n=30	**0.472**** n=30
Matr (%)	0.309 n=26	0.349 n=26	0.359 n=28	0.068 n=30	0.358 n=30	0.271 n=30
vFo (%)	**0.518**** n=26	**0.565**** n=26	0.198 n=28	0.244 n=30	0.021 n=30	**0.401*** n=30
vAm (%)	0.341 n=26	0.110 n=26	0.256 n=28	0.221 n=30	0.251 n=26	0.145 n=30

** correlation is significant at the 0.01level (2-tailed)
*correlation significant at 0.05 level (2-tailed)

Relationship between acoustic measures and auditory perceptual measures

Two out of six acoustic tremor measures showed significant positive correlations with auditory perceived *instability* and *tremor* (Table 6.14). Specifically, an increase in Mftr% was associated with an increase in auditory perceived *instability* and *tremor*.This means that as the magnitude of tremor in the frequency domain increased the amount of instability and tremor perceived in the voice increased also. Similarly an increase in vFo% was associated with an increase in *instability* and *tremor.* As the overall variation in frequency of the voice increased, there was an increase in the amount of instability and tremor perceived auditorily in the voice (Table 6.14).

Relationship between acoustic measures and visual perceptual measures

There were significant correlations for two of the acoustic measures with visually perceived tremor in the vocal tract. Mftr and vFo showed significant positive correlations with tremor in the vocal cords, identified on a sustained /i/ vowel (Table 6.14).

Combining the acoustic, auditory perceived and visually perceived tremor findings for the PD group, the results show the following: As the magnitude of frequency tremor and /or the overall variation in the frequency of the voice increase, there is an increase in auditory perceived tremor and instability, and an increase in tremor in the vocal cords on a sustained /i/ vowel.

Control group

The correlational matrix in Table 6.15 displays rho values for relationships between acoustic tremor measures and perceived *instability* and *tremor* and, visually perceived tremor in the vocal tract.

Table 6.15. Spearman correlations (rho) for acoustic voice tremor measures and auditory perceived instability and tremor, and visual perceptual ratings, for control group

	Auditory perceptual Measures		**Visual-Perceptual Measures**			
Acoustic measures	Instability	Tremor	Palate /a/	Tongue /a/	Larynx /a/	Larynx /i/
Rftr (Hz)	-0.503 n=10	**-0.661*** n=10	**0.807*** n=8	0.504 n=9	-0.196 n=9	**-0.936 **** n=9
Ratr (Hz)	0.041 n=17	0.098 n=17	0.394 n=16	0.029 n=17	0.114 n=17	0.423 n=17
Mftr (%)	**0.429*** n=27	0.340 n=27	0.136 n=25	0.141 n=25	-0.118 n=26	-0.151 n=26
Matr (%)	**0.569**** n=27	**0.500**** n=27	0.152 n=25	0.072 n=25	-0.156 n=25	-0.097 n=25
vFo (%)	**0.632**** n=27	**0.488**** n=27	0.081 n=25	-0.014 n=25	-0.240 n=26	-0.188 n=26
vAm (%)	0.203 n=27	0.048 n=27	0.046 n=25	0.365 n=25	0.001 n=27	0.029 n=27

** correlation is significant at the 0.01level (2-tailed
*correlation significant at 0.05 level (2-tailed)

Relationship between acoustic measures and auditory perceptual measures

The control group shows a different correlational pattern to the PD group, for the acoustic measures.Table 6.15 shows that, three acoustic tremor measures (Mftr%, Matr%, vFo%) correlated positively and significantly with auditory perceived *instability*, and *tremor*. In contrast, RftrHz had a significant negative correlation with auditory perceived *tremor.* This suggests that an increase in the rate of tremor (frequency component) is associated with a decrease in auditory perceived *tremor.*

Relationship between acoustic measures and visual perceptual measures

For relationships with visually perceived tremor in the vocal tract, the rate of frequency tremor (RftrHz) showed a significant positive correlation with tremor in the palate and a negative correlation with tremor in the vocal cords, on a sustained /i/ vowel (Table 6.15).

Supplementary results

The relationship between auditory perceptual (*instability, tremor*) and visual perceptual tremor measures for the PD group is shown in the correlation matrix in Table 6.16. For the control group, the correlational matrix for auditory perceptual (instability, tremor), and visual perceptual measures is shown in Table 6.17. Significant associations are denoted in bold, with an asterisk to denote significance.

Table 6.16. Spearman correlations (rho) for auditory perceptual and visual perceptual ratings for the PD group

	PD group			
	Visual-perceptual measures			
Auditory perceptual measures	Palate /a/	Tongue /a/	Larynx/a/	Larynx /i/
Instability	0.226	0.183	0.372	0.344
	n=25	n=26	n=26	n=26
Tremor	0.347	0.098	**0.399***	**0.436***
	n=25	n=26	n=26	n=26

** correlation is significant at the 0.01level (2-tailed
*correlation significant at 0.05 level (2-tailed)

Table 6.17. Spearman correlations (rho) for auditory perceptual and visual perceptual ratings for the control group

	Control group			
	Visual-perceptual Measures			
Perceptual Measures	Palate /a/	Tongue /a/	Larynx/a/	Larynx /i/
Instability	0.374	0.081	0.068	0.194
	n=24	n=24	n=25	n=25
Tremor	**0.499***	-0.011	0.127	0.307
	n=24	n=24	n=25	n=25

** correlation is significant at the 0.01level (2-tailed
*correlation significant at 0.05 level (2-tailed)

PD group

The correlational matrix shows that there was a significant positive correlation between auditory perceived *tremor* and visually perceived tremor in the vocal tract for pwPD (Table 6.16). Specifically, with an increase in the perception of *tremor* in the voice on a sustained /a/ vowel there was a greater amount of tremor evident in the larynx (vertical laryngeal dimension) and the vocal cords on sustained vowels.

Control group

In contrast, a different relationship to that for pwPD is evident for the control group for auditory perceptual and visual perceptual measures (Table 6.17). There was a significant positive relationship between perceived *tremor* and visually perceived tremor in the palate on a sustained /a/ vowel.

Summary results for question 2

For pwPD:

- An increase in the magnitude of tremor (frequency aspect), and the overall variation in frequency is associated with a greater amount of auditory perceived *instability* and *tremor.*
- As the magnitude of frequency tremor, and the amount of overall variation in the frequency of the voice increases on a sustained /a/ vowel, there is an increase in the amount of tremor identified in the vocal cords on a sustained /i/ vowel.
- An increase in the amount of *tremor* perceived auditorily on a sustained /a/ vowel is associated with an increase in tremor in the larynx (vertical larynx dimension) on a sustained /a/ vowel, and with tremor in the vocal cords on a sustained /i/ vowel.

For controls:

- As the rate of frequency tremor increases, there is a lesser amount of *tremor* perceived auditorily in the voice.
- With greater magnitude of amplitude tremor and overall variation in frequency, there is a greater amount of perceived *instability* and *tremor* in the voice. With greater magnitude of frequency tremor, there is a greater amount of perceived *instability* in the voice.
- As the rate of frequency tremor increases there is an increase in tremor perceived in the palate on a sustained /a/ vowel. As the rate of frequency tremor increases there is a decrease in the amount of tremor perceived in the vocal cords on a sustained /i/ vowel.
- An increase in the amount of *tremor* perceived auditorily on a sustained /a/ is associated with a greater amount of tremor perceived in the palate on a sustained /a/ vowel.

6.3.3 Question 3

Question 3 explores the nature of the relationship between acoustic voice tremor measures and speech and voice variables. Measures of the rate (Hz) of frequency and amplitude tremor (Rftr, Ratr), the magnitude (%) of frequency and amplitude tremor (Mftr, Matr), together with overall variation (%) in frequency and amplitude (vFo, vAm) were selected for analysis. The computerised speech laboratory (CSL)[119] explanations of the acoustic measures are outlined in APPENDIX I.

There are three parts to question 3. Part (A) examines the relationship between acoustic tremor measures and overall severity of dysphonia, the results are presented in section 6.3.3 (A). Part (B) examines the relationship between acoustic voice tremor measures and voice disability, with the results outlined in section 6.3.3 (B). Finally, part (C) reports the relationship between acoustic tremor measures and speech intelligibility in section 6.3.3 (C). For each part, the main results will be presented first followed by the supplementary results. The tables showing reliability findings for dysphonia severity ratings (CAPE-V) are presented in the Appendices section.

6.3.3 Question 3 (Part A)

What is the nature and degree of the relationship between acoustic voice tremor measures and overall severity of dysphonia?

The results of the Spearman's Correlation Coefficient (rho) examination of the relationship between acoustic tremor measures and dysphonia severity ratings from the Consensus Auditory Perceptual Evaluation of Voice (CAPE-V) are displayed in Table 6.18*,* for the PD and the control group. The descriptive statistics for CAPE-V dysphonia severity scores and the inter- and intra-rater reliability results are outlined in the supplementary results sub-section.

Table 6.18. Spearman's (rho) for Rftr, Ratr, Mftr, Matr, vFo, Vam and severity of dysphonia, for PD and control group

	CAPE-V Dysphonia Severity	
Acoustic Measures	PD group (n=26)	Control group (n =27)
Rate frequency tremor [Rftr (Hz)]	-0.499 (n=12)	-0.297 (n=10)
Rate amplitude tremor [Ratr (Hz)]	0.138 (n= 15)	0.191 (n=17)
Magnitude frequency tremor [Mftr (%)]	0.358	**0.589 ****
Magnitude amplitude tremor [Matr (%)]	0.158	**0.429 ***
Variation in frequency [vFo (%)]	**0.454 ***	**0.764 ****
Variation in amplitude [vAm (%)]	0.387	0.230

**Correlation significant at the 0.01 level (2-tailed);*Correlation significant at the 0.05 level (2-tailed)

For pwPD, there was a statistically significant moderately weak positive correlation between vFo and severity of dysphonia ratings with CAPE-V ($p \leq 0.05$). In contrast, there was a moderate negative correlation between Rftr and severity of dysphonia, which failed to reach statistical significance, possibly because of the small sample size for Rftr measures. There were moderate to weak positive correlations between Mftr, vAm, Ratr, Matr and CAPE-V scores, without statistical significance (Table 6.18).

For the control group, there was a statistically significant, strong positive correlation between Mftr, vFO, and dysphonia severity ($p \leq 0.01$). For Matr, there was a statistically significant moderate positive correlation with severity of dysphonia ($p \leq 0.05$) (Table 6.18).

Supplementary results for Question 3 (Part A)

Descriptive statistics for CAPE-V ratings of dysphonia severity for PD and control group

The mean (SD), median and interquartile range (IQR) scores, and *p* values for CAPE-V severity ratings of dysphonia for the PD and control group are displayed in Table 6.19.

Table 6.19. Mean (SD), median IQR and *p* value for perceived severity of dysphonia for the PD and control group

	CAPE-V dysphonia severity			
	PD (n=26)	Control (n=27)	*U*	*p*
Mean (SD)	24.46 (10.63)	20.41 (11.37)		
Range	6-42	6-52		
Median	26.00	16.00	1.443	0.149
(IQR)	(15.25-34.00)	(12.00-31.00)		

Table 6.19 shows that the PD group achieved a higher mean rating for severity of dysphonia (greater severity) than the control group, however the difference between the groups was not statistically significant, when a Mann Whitney U test was applied.

Inter-rater reliability for dysphonia severity (CAPE-V) ratings of PD & control group

The inter-rater reliability results for three raters for rating severity of dysphonia (CAPE-V) in pwPD and controls are shown in APPENDIX AA.The guidelines for Kappa[233] coefficients were applied for interpretation of the intraclass correlation coefficients (ICC). The ICC's indicate moderate to moderately strong agreement for perceptual ratings of dysphonia severity in the PD and the control group.

Intra-rater reliability for CAPE-V dysphonia severity ratings of PD & control participants

The findings for intra-rater reliability of perceived severity of dysphonia for three raters, using CAPE-V are shown in APPENDIX BB.The intraclass correlation coefficients show 'moderate' to 'substantial' agreement within the three raters when rating dysphonia severity in six participants (three pwPD and three controls).

6.3.3 Question 3 (Part B)

What is the nature and the degree of the relationship between acoustic voice tremor measures and patient-reported voice disability, in pwPD?

The results of the Spearman's correlation (rho) for the examination of the relationship between acoustic tremor measures and Voice Handicap Index (VHI) total and subscale scores, for the PD and control group, are displayed in Table 6.20.The descriptive statistics together with *p* values for differences between pwPD and control groups for VHI total and subscale scores are displayed in Table 6.21, in the supplementary results section.

Table 6.20. Spearman's (rho) for Rftr, Ratr, Mftr, Matr, vFo, vAm and VHI total and subscale scores, for PD and control group

	VHI total and subscale scores							
	PD group (n=30)				Control group (n=27)			
Acoustic Measures	**Total**	**Functional**	**Physical**	**Emotional**	**Total**	**Functional**	**Physical**	**Emotional**
Rftr [a] (Hz)	0.280	0.265	0.188	0.170	-0.351	-0.436	-0.149	-0.114
Ratr [b] (Hz)	-0.096	0.034	-0.044	-0.299	-0.219	-0.173	-0.173	-0.364
Mftr (%)	0.007	-0.049	0.047	-0.061	0.333	0.312	0.269	0.107
Matr (%)	-0.107	-0.150	-0.011	-0.123	0.213	0.186	0.185	0.049
vF0 (%)	0.052	0.085	0.028	0.026	0.145	0.161	0.078	0.112
vAm (%)	-0.155	-0.212	-0.126	-0.129	0.264	0.354	-0.042	0.251

[a] :pwPD (n=13), Controls (n=9); [b] pwPD (n=16); Controls(n=16)

The findings show that there were no significant correlations (positive or negative) between any of the acoustic measures and the VHI total or subscale scores for the PD, or for the control group (Table 6.20).

Supplementary results for Question 3 (Part B)

Descriptive statistics with p value for VHI total and subscale scores for PD and control group

The mean, standard deviation (SD), range, median, interquartile range (IQR) and *p* values for Voice Handicap Index (VHI) total and subscale scores for the PD and control group are displayed in Table 6.21.

Table 6.21. Mean (SD), range, median, (IQR) and *p* values for total and subscale VHI scores for PD and control group

	PD (n=30) M22, F8	Control (n=27) M19, F8	*U*	*Z*	*p-value*
Total VHI					
Mean (SD)	19.50 (15.11)	4.00 (6.02)	156.000	-4.012	***<0.001*** [a]
Range	(0-49)	(0-24)			
Median (IQR)	19.00 (5.75-33.25)	1.00 (0.00-6.00)			
Subtests					
Functional					
Mean (SD)	6.53 (4.92)	2.00 (2.51)	185.500	-3.558	***<0.001*** [a]
Range	(0-16)	(0-9)			
Median (IQR)	6.50 (1.00-11.00)	1 (0.00-4.00)			
Emotional					
Mean (SD)	4.97 (5.16)	0.67 (2.13)	179.000	-4.025	***<0.001*** [a]
Range	(0-17)	(0-10)			
Median (IQR)	3.50 (0.00-9.00)	0.00 (0.00-0.00)			
Physical					
Mean (SD)	8.00 (6.16)	1.33 (2.34)	164.500	-3.964	***<0.001*** [a]
Range	(0-18)	(0-10)			
Median IQR	9.50 (0.75-13.00)	0.00 (0.00-2.00)			

[a] t-test

The mean total VHI and subscale (functional, emotional, physical) scores were higher (meaning greater severity), in the PD than the control group. The difference between the groups for the total and the three subscale VHI scores was statistically significant ($p<0.05$).

6.3.3 Question 3 (Part C)

What is the nature of the relationship between acoustic voice tremor measures and speech intelligibility?

The results of the correlational analysis with rho values for the relationship between acoustic voice tremor measures and the computerised Speech Intelligibility Test (SIT) percentage correct scores are displayed in Table 6.22. The descriptive statistics with *p* values for the SIT scores for pwPD and controls are outlined in the supplementary results section in Table 6.23. The inter- and intra-rater reliability findings for SIT ratings are also reported in the supplementary results section.

Table 6.22. Spearman's correlation coefficient (rho) showing values for strength of association of Rftr, Ratr, Mftr, Matr, vF0 & vAm with Speech IntelligibilityTest % scores

		Speech Intelligibility Test (SIT)	
Acoustic measures		**PD group (n=28)**	**Control group (n=25)**
Rate frequency tremor	Rftr (Hz)	0.469 (n=12)	0.492 (n=10)
Rate amplitude tremor	Ratr (Hz)	0.230 (n=16)	-0.253 (n=17)
Magnitude frequency tremor	Mftr (%)	0.122	-0.162
Magnitude amplitude tremor	Matr (%)	0.074	0.063
Variation in frequency	vFo (%)	0.078	-0.143
Variation in amplitude	vAm (%)	-0.005	-0.271

To interpret the rho values from the correlational analysis, Cohen's guidelines were applied[234]. For the PD group, Rftr showed a positive medium correlation and Ratr and Mftr showed a weak positive correlation with SIT scores. However, neither

correlation showed statistical significance. Matr, vFo, and vAm did not show any meaningful correlations with speech intelligibility ratings (Table 6.22).

For the control group, Rftr showed a moderate positive relationship with SIT scores without statistical significance. There were weak negative correlations with SIT scores for Ratr Mftr, vFo and vAm, without statistical significance (Table 6.22).

Supplementary Results for Question 3 (Part C)

Descriptive statistics with p values for Speech Intelligibility Test (SIT) % correct scores for PD and control group

The mean (SD), range, median, IQR and p value for the SIT scores, for the PD and control group are displayed in Table 6.23.

Table 6.23. Mean (SD), median, interquartile range (IQR) and *t*-test for SIT values for PD and control group

	Speech Intelligibility Test (%) scores			
	PD (n=28)	Control (n=28)	*t*	*p*
Mean (SD)	94.56 (2.82)	94.79 (2.56)	-.328	0.74
Range	87.73-98.92	86.14-98.41		
Median (IQR)	94.89 (93.07-96.14)	95.23 (93.35-96.70)		

The mean percentage intelligibility scores for the PD and control group were closely matched. The *t*-test results show that there was no statistically significant difference between the mean values for the PD and control group (Table 6.23).

Inter-rater reliability for SIT ratings of PD and control group

The findings from the Intraclass Correlation Coefficient (ICC) for inter-rater reliability rating for the PD and controls group are shown in *APPENDIX* Y. The results show moderate agreement between the raters for their ratings of sentence intelligibility for the PD and the control group.

Intrarater reliability for SIT ratings of PD and control group

The results for intra-rater reliability showing the intraclass correlation coefficient (ICC) values and confidence intervals for speech intelligibility ratings for three judges are shown in *APPENDIX Z*. The ratings from Judge A were excluded in the statistical analysis due to missing data related to technical problems. Overall, a moderate to almost perfect level of intra-rater agreement was reached by the raters for transcription of sentence recordings, with judge B and Judge D achieving identical (almost perfect) levels of agreement with ICC's of 0.968 each.

Summary results for question 3

- For pwPD, an increase in the long-term variation of fundamental frequency was significantly associated with an increase in perceived severity of dysphonia. For controls, an increase in the magnitude of frequency and amplitude tremor, and variation in frequency was significantly associated with an increase in dysphonia severity.

- PwPD were rated as having a greater severity of dysphonia than controls however the difference between the groups was not statistically significant.

- Inter-rater agreement showed moderate to moderately strong agreement between three raters for ratings of perceived dysphonia severity in pwPD and controls respectively. For intra-rater agreement, agreement was moderate to substantial across the three raters.

- Acoustic tremor measures did not relate in any significant way to self-reported voice handicap in pwPD or in controls.

- PwPD had a greater amount of voice handicap than controls and the difference was statistically significant.

- For pwPD, acoustic tremor measures did not relate in any significant way to percentage correct speech intelligibility for sentences. For controls there were no significant relationships between acoustic tremor measures and percentage correct speech intelligibility for sentences.

- PwPD and controls had the same level of speech intelligibility at the sentence level.

- Inter-rater reliability for sentence transcription was moderate for pwPD and controls. Intra-rater agreement was higher with moderate to almost perfect levels of agreement reached by two of the raters for pwPD and controls.

6.3.4 Question 4

Question 4 relates to the nature and the degree of the relationship between acoustic voice tremor measures and specific disease variables. There are four parts to question 4 and the results will be presented separately. Part (A) explores the relationship between acoustic tremor measures and disease duration. Part (B) and part (C) explore the relationship with activities of daily living and motor symptom severity from the Unified Parkinson's Disease Rating Scale (UPDRS), parts II and III respectively. Finally, part (D) looks at the relationship with PD phenotype. The main results relating to the specific research question are presented first, followed by supplementary findings where appropriate. The findings for question 4 are summarised at the end of the section.

Question 6.3.4 (Part A)

What is the nature of the relationship between acoustic voice tremor measures and disease duration?

The main study findings are presented first, followed by supplementary findings**.**

Spearman's rho values from the correlational analysis of the acoustic voice tremor measures (Rftr, Ratr, Mftr, Matr, vFo, vAm) and disease duration are displayed in Table 6.24. The descriptive statistics for disease duration are outlined in Table 6.25.

Table 6.24. Spearman's correlation coefficient (rho) for Rftr, Ratr, Mftr, Matr, vFo, vAm, and disease duration

		PD group (*n*=30)
Acoustic Measures	Abbreviations	**Disease duration**
Rate frequency tremor	Rftr (Hz)	-0.160 (n=13)
Rate amplitude tremor	Ratr (Hz)	0.336 (n=16)
Magnitude frequency tremor	Mftr (%)	**0.515****
Magnitude amplitude tremor	Matr (%)	**0.418***
Variation in frequency	vFo (%)	**0.408***
Variation in amplitude	vAm (%)	0.280

*<0.05 **<0.01:
Disease duration: years (n) since disease diagnosed

Table 6.25. Mean (SD), range, median and IQR values for disease duration (years) in PD group

	PD group (*n*=30)
	Disease duration
Mean (SD)	5.23 (3.17)
Range	1-12
Median	5.00
IQR	2.75-7.25

Table 6.24 shows that there was a highly significant positive relationship between Mftr and disease duration, and that there was a significant positive relationship between Matr, vFo, and disease duration. Figure 6.10, Figure 6.11, and Figure 6.12 show the relationship between Mftr, Matr, vFo, and disease duration respectively.

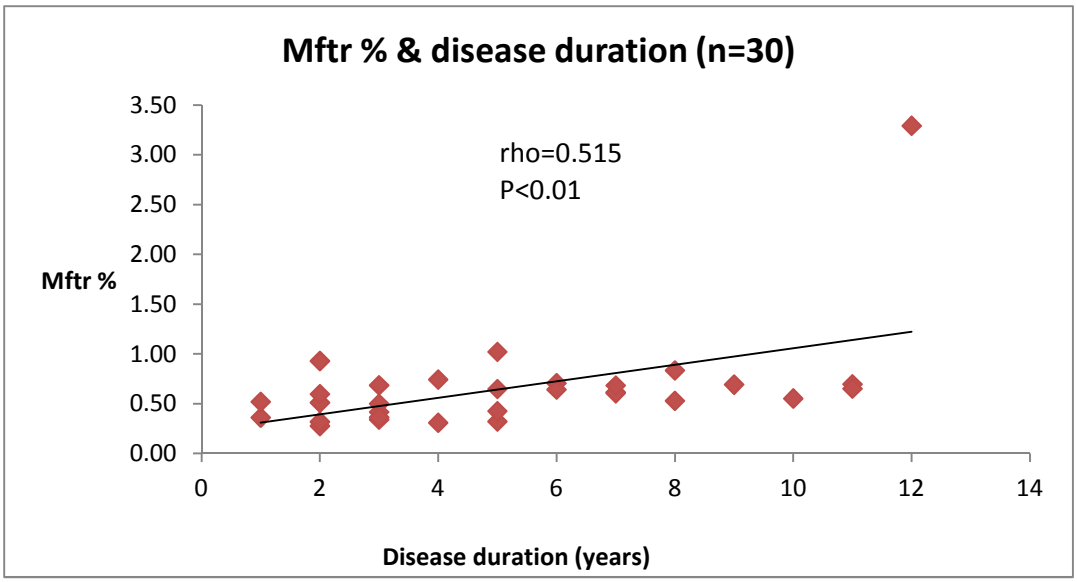


Figure 6.10. Correlation between Mftr and disease duration

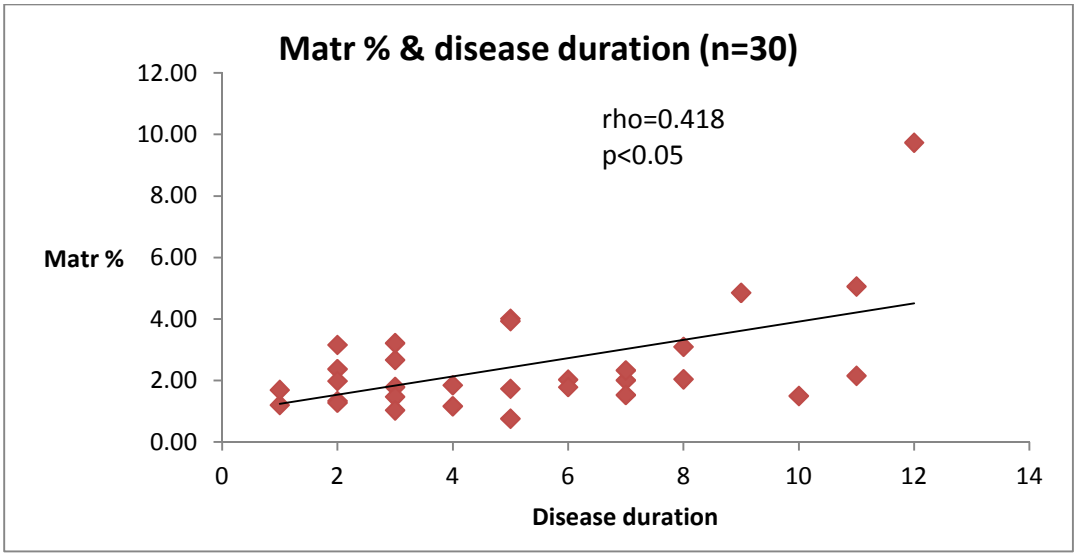


Figure 6.11. Correlation between Matr, and disease duration

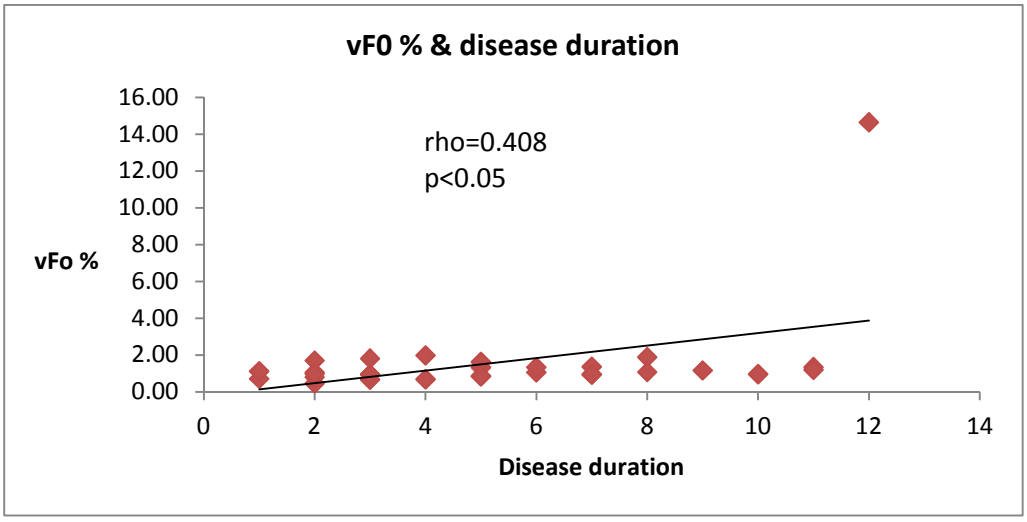


Figure 6.12. Correlation between vFo, and disease duration

There is one outlier (PD 5) evident in the data for Mftr, Matr and vFo as shown in figures 4-1, 4-2, and 4-3. A review of the acoustic raw data for PD 5 shows wide variability of values across the three /a/ trials for Mftr, Matr, vFo and vAm (APPENDIX O).

A further analysis was carried out with PD 5 data removed from the analysis to evaluate the effect of PD 5 on the correlational findings (Table 6.26).

Table 6.26. Spearman's correlation coefficient (rho) for Rftr, Ratr, Mftr, Matr, vFo, vAm, and disease duration with outlier (PD5) removed from the analysis

		PD group (*n*=29)
Acoustic Measures	Abbreviations	**Disease duration**
Rate frequency tremor	Rftr (Hz)	-0.147(n=12)
Rate amplitude tremor	Ratr (Hz)	0.192 (n=15)
Magnitude frequency tremor	Mftr (%)	**0.463***
Magnitude amplitude tremor	Matr (%)	0.355
Variation in frequency	vFo (%)	0.344
Variation in amplitude	vAm (%)	0.202

*<0.05 **<0.01:
Disease duration: years (n) since disease diagnosed

Table 6.26 shows that when PD 5 data was removed from the analysis, the magnitude of frequency tremor was positively and significantly correlated with disease duration. However, the magnitude of amplitude tremor and variation in frequency did not show significant association with disease duration when PD 5 was excluded. Figure 6.13 displays the relationship between Mftr and disease duration, with PD 5 (outlier) excluded from the analysis.

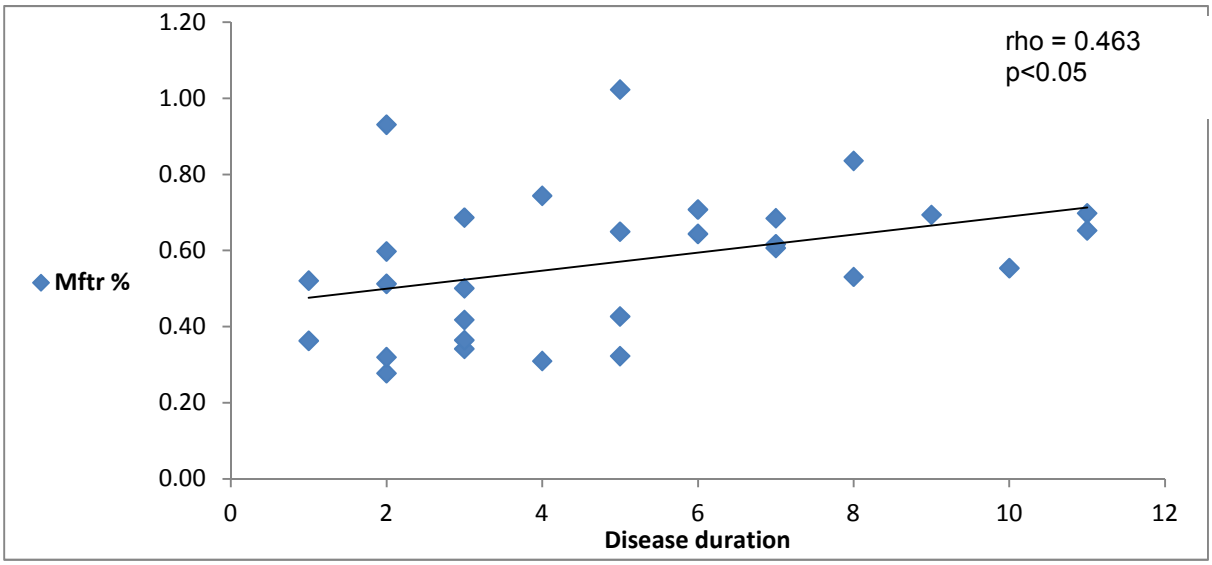


Figure 6.13. Correlation between Mftr and disease duration, with PD 5 removed from the analysis

A further analysis examining the relationship between acoustic tremor measures and age was carried out to determine if acoustic tremor measures related to age in any significant way. The findings are reported in supplementary results.

Supplementary results

Relationship between acoustic tremor measures and age (years)

The results showing Spearman's rho correlations for acoustic voice tremor measures and age are shown in Table 6.27.

Table 6.27. Spearman's correlation coefficient (rho) for Rftr, Ratr, Mftr, Matr, vFo, vAm, and age (years) for PD and control group

	PD group (n=30)	Control group (n=28)
Acoustic measures	**Age (years)**	
Rftr (Hz)	0.008 (n=13)	-0.401 (n=10)
Ratr (Hz)	-0.077 (n=16)	0.193 (n=17)
Mftr (%)	0.233	**0.509****
Matr (%)	0.009	**0.407***
vFo (%)	0.186	**0.528 ****
vAm (%)	0.239	0.340

*<0.05 **<0.01:

The significant relationship between selected acoustic measures and disease duration was upheld when age was factored into the equation. Table 6.27 shows that for pwPD there was no significant relationship between any of the selected acoustic measures and chronological age. In contrast, for the control group there were significant positive relationships between Mftr, Matr vFo and age (Table 6.27).

To ascertain the possible effect of outlier PD 5 on the findings in relation to acoustic measures and chronological age, the correlational analysis was repeated with PD 5 data excluded from the analysis. Spearman's rho analysis of the relationship between acoustic tremor measures and chronological age is shown in Table 6.28.

Table 6.28. Spearman's correlation coefficient (rho) for Rftr, Ratr, Mftr, Matr, vFo, vAm, and age (years) for PD and control group, with PD 5 excluded

	PD group (n=29)	Control group (n=28)
Acoustic measures	**Age (years)**	
Rftr (Hz)	0.014 (n=12)	-0.401 (n=10)
Ratr (Hz)	-0.284 (n=15)	0.193 (n=17)
Mftr (%)	0.1533	**0.509****
Matr (%)	-0.094	**0.407***
vFo (%)	0.103	**0.528 ****
vAm (%)	0.160	0.340

*<0.05 **<0.01:

Table 6.28 shows that there were no significant relationships between any of the acoustic tremor measures and chronological age for pwPD, when the outlier PD 5 was excluded from the analysis.

Question 6.3.4 (Part B)

What is the nature of the relationship between acoustic voice tremor measures and activities of daily living?

Table 6.29 presents the results of the Spearman Correlation Coefficient (rho) examination of the relationship between acoustic voice tremor measures (Rftr, Ratr, Mftr, Matr, vFo, vAm), and activities of daily living as measured on the Unified Parkinson's Disease Rating Scale (UPDRS) part II. The descriptive statistics for UPDRS II are shown in Table 6.30.

Table 6.29. Spearman's correlation coefficient (rho) for Rftr, Ratr, Mftr, Matr, vFo, vAm, and UPDRS II

		PD group (*n*=30)
Acoustic Measures	Abbreviations	**UPDRS II**
Rftr (Hz)	Rftr (Hz)	0.283 (*n*=13)
Ratr (Hz)	Ratr (Hz)	-0.425 (*n*=16)
Mftr (%)	Mftr (Hz)	-0.009
Matr (%)	Matr (Hz)	-0.018
vFo (%)	vFo (Hz)	-0.149
vAm (%)	vAm (Hz)	-0.126

UPDRS II: Activities of Daily Living

The results show that there were non-significant negative correlations between acoustic measures Ratr, Mftr, Matr vFo and vAM, and a non-significant positive correlation between Rftr, and activities of living when measured on the UPDRS II (Table 6.29).

Descriptive statistics for UPDRS II

The mean (SD), range, median, and IQR values for UPDRS II are shown in Table 6.30.

Table 6.30. Mean (SD) range, median and IQR values for UPDRS II scores

	PD group (n=30)
	UPDRS II
Mean (SD)	10.20 (3.85)
Range	4-19
Median	9.50
IQR	7.00-13.25

Supplementary results

UPDRS II- group mean scores for 13 items

The group mean scores and standard deviations for the individual items from the UPDRS II are displayed in Figure 6.14.

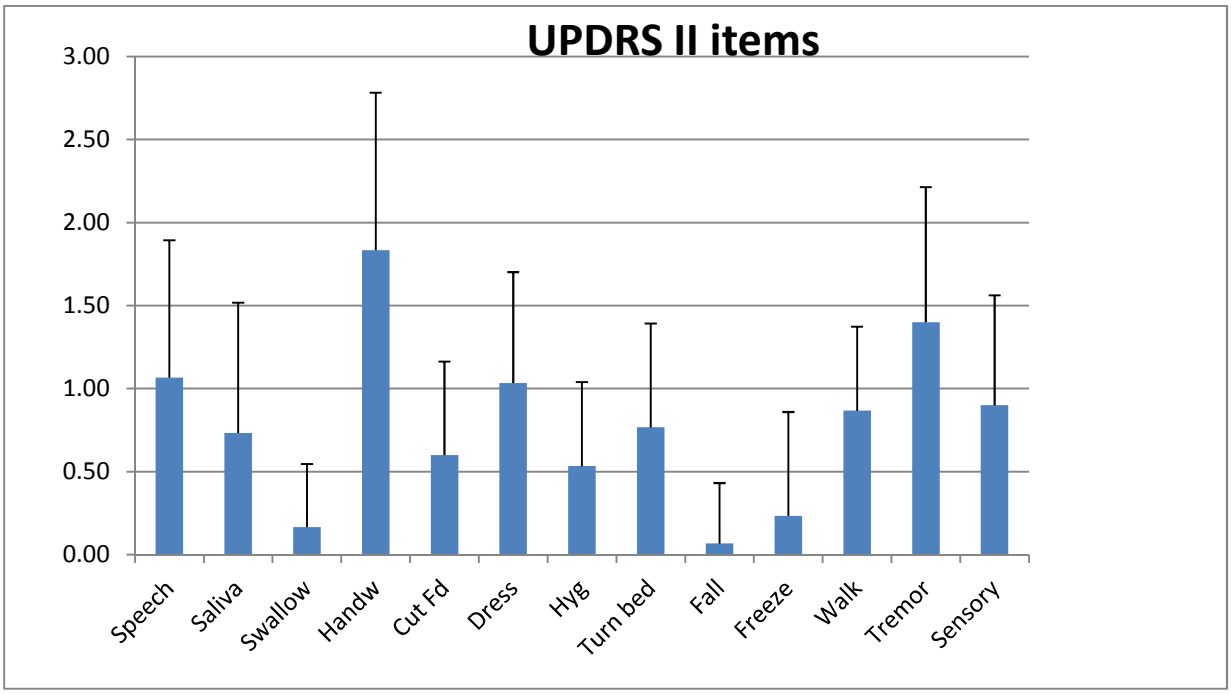


Figure 6.14. Group mean scores and standard deviations for UPDRS II items

Figure 6.14 shows that for this group of pwPD, tremor achieved the second highest severity rating, followed by speech. Handwriting achieved the highest severity rating.

Relationship between acoustic tremor measures and UPDRS item 16

A further analysis was carried out to determine the nature of the relationship between acoustic voice tremor measures and the self-report tremor item 16 from UPDRS II. Table 6.31 shows spearman's rho values for examination of the relationship between acoustic measures (Rftr, Ratr, Mftr, Matr, vFo, vAm) and self – report tremor item 16 from UPDRS II.

Table 6.31. Spearman's correlation co-efficient for Rftr, Ratr, Mftr, Matr, vFo, vAm and tremor item 16 from UPDRS II

		PD group (*n*=30)
Acoustic Measures	Abbreviations	**UPDRS II Tremor (item 16)**
Rate frequency tremor	Rftr (Hz)	0.303 (*n*=13)
Rate amplitude tremor	Ratr (Hz)	-0.120 (*n*=16)
Magnitude frequency tremor	Mftr (Hz)	0.210
Magnitude amplitude tremor	Matr (Hz)	0.092
Variation in frequency	vFo (Hz)	0.007
Variation in amplitude	vAm (Hz)	-0.185

Table 6.31 shows that there were no significant correlations between the acoustic measures and the self-reported tremor item 16 from UPDRS II.

Question 6.3.4 (Part C).

What is the nature and the degree of the relationship between acoustic voice tremor measures and PD motor symptom severity?

The results for the research question are presented first, followed by the supplementary results.

Table 6.32 presents results of the Spearman Correlation Coefficient (rho) examination of the relationship between acoustic tremor measures (Rftr, Ratr, Mftr, Matr, vFo, vAm) and motor symptom severity as measured on the motor part of the Unified Parkinson's Disease Rating Scale (UPDRS) part III.

The descriptive statistics for UPDRS III scores are shown in Table 6.33.

Table 6.32. Spearman's correlation coefficient (rho) values for Mftr, Matr, vFo, vAm and UPDRS III

	PD group (*n*=30)	
Acoustic Measures	Abbreviations	**UPDRS III**
Rate frequency tremor	Rftr (Hz)	0.168 (*n*=13)
Rate amplitude tremor	Ratr (Hz)	**-0.529*** (*n*=16)
Magnitude frequency tremor	Mftr	0.099
Magnitude amplitude tremor	Matr	0.299
Variation in frequency	vFo	0.110
Variation in amplitude	vAm	0.111

Significant at 0.05 level:

There was a significant negative correlation between the rate of amplitude tremor (Ratr Hz) and the severity of motor symptoms when measured on the UPDRS III. This means that an increase in motor symptom severity was associated with a lower rate of amplitude tremor. There were no other significant correlations, positive or negative for the acoustic tremor measures (Table 6.32). Figure 6.15 displays graphically the significant correlation between Ratr and UPDRS III.

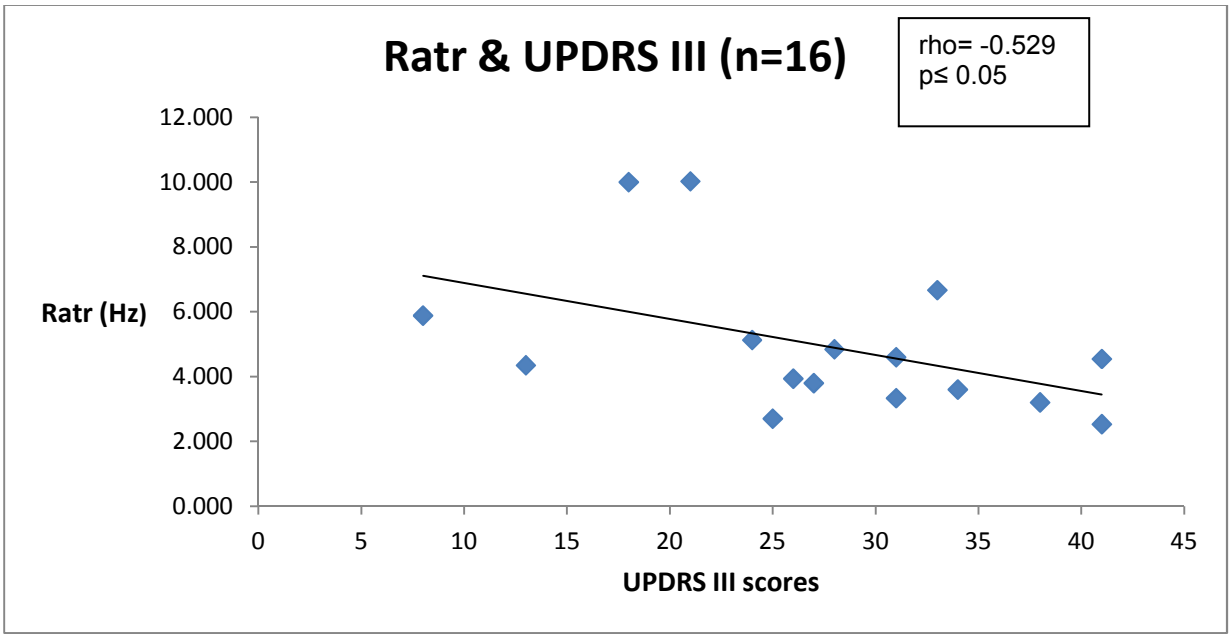


Figure 6.15. Correlation between Ratr (Hz), and UPDRS III

Descriptive statistics for UPDRS III

The mean (SD), range, median and IQR values for UPDRS III are shown in Table 6.33.

Table 6.33. Mean (SD), range, median and interquartile (IQR) values for UPDRS III for pwPD

	PD group (n=30)
	UPDRS III
Mean (SD)	25.00 (9.23)
Range	8-41
Median	24.50
IQR	17.75-33.0

Supplementary results

UPDRS III –group mean scores for individual items

The group mean scores and standard deviations for the individual items from the UPDRS III are displayed in Figure 6.16.

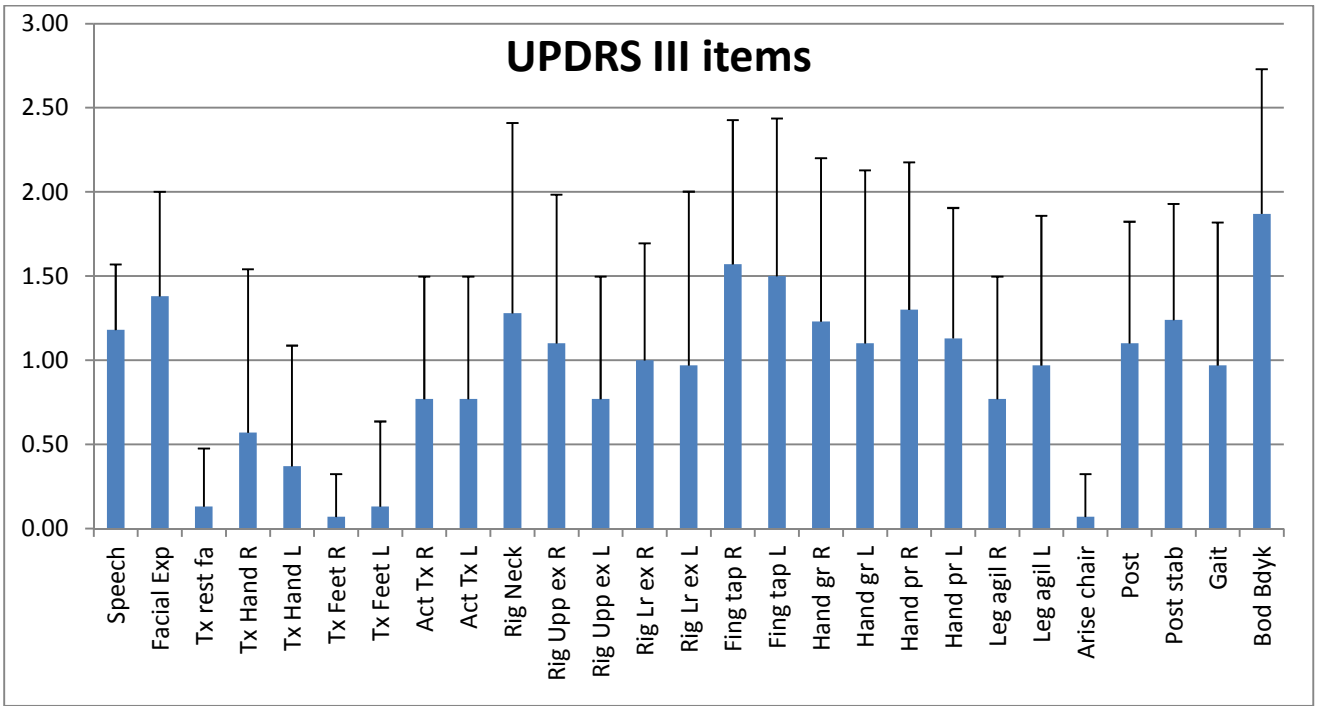


Figure 6.16. PD group mean scores and standard deviations for individual items in UPDRS III

Figure 6.16 highlights that body bradykinesia achieved the highest (most severe) rating and rest and action tremor scores were at the lower end of the score profile.

Relationship between acoustic measures and mean tremor score from UPDRS III

The rho values from the examination of the relationship between acoustic voice tremor measures and the mean tremor score from UPDRS III are displayed inTable 6.34. A mean tremor score was calculated from the scores of 5 tremor items in UPDRS III.

Table 6.34. Spearman's rho correlations for acoustic measures and mean tremor score from UPDRS III

	PD group (*n*=30)	
Acoustic Measures	Abbreviations	**UPDRS III Mean tremor score**
Rate frequency tremor	Rftr (Hz)	0.340(*n*=13)
Rate amplitude tremor	Ratr (Hz)	-0.012 (*n*=16)
Magnitude frequency tremor	Mftr	0.008
Magnitude amplitude tremor	Matr	0.070
Variation in frequency	vFo	-0.092
Variation in amplitude	vAm	-0.215

Table 6.34 shows that there were no significant correlations, positive or negative between acoustic tremor measures and the mean tremor scores from UPDRS III.

Relationship between disease severity (UPDRS II, UPDRS III) and disease duration

To establish the nature of the relationship between disease severity as measured with UPDRS II and UPDRS III, and disease duration, spearman's rho was calculated. Table 6.35 shows the correlational matrix for UPDRS II, UPDRS III and disease duration (years since diagnosis).

Table 6.35. Spearman's rho correlations for UPDRS II, UPDRS III and disease duration

	PD group (n=30)
	Disease duration
UPDRS II	0.031
UPDRS III	0.052

Table 6.35 shows that disease severity was independent of disease duration for this group of PwPD with no significant associations between UPDRS II and disease duration, or between UPDRS III and disease duration.

Question 6.3.4 (Part D)

What is the nature and degree of the relationship between acoustic voice tremor measures and PD phenotype?

The phenotype frequency data is presented first, followed by differences between phenotypes on the basis of acoustic measures, and finally supplementary findings showing frequency data for rate of tremor based on phenotype.

Phenotype data

Table 6.36 shows the categorisation and frequency (n %) of pwPD on the basis of phenotype.

Table 6.36. Frequencies [n (%)] of pwD with tremor dominant, PIGD and indeterminate PD phenotype

PD phenotype [n (%)]	PD (n=30)
Tremor dominant	7 (23.3%)
Postural Instability Gait Disorder (PIGD)	21 (70%)
Indeterminate	2 (6.7%)

Differences between tremor-dominant, PIGD, and indeterminate phenotypes in relation to acoustic measures

Table 6.37 presents the results for the analysis of variance (ANOVA) for rate of frequency tremor [Rftr (Hz)], rate of amplitude tremor [(Ratr (Hz)], magnitude of frequency tremor [Mftr (%)], magnitude of amplitude tremor [Matr (%)],variation in frequency [vFo (%)], and variation in amplitude [Vam (%)] in relation to PD phenotypes [tremor-dominant, postural instability gait disorder (PIGD), indeterminate].

Table 6.37. ANOVA for Rfrt, Ratr, Mftr, Matr, vFo & VAm, and PD phenotype (tremor-dominant, PIGD and indeterminate)

PD group (n=30)					
Acoustic					
	Sum of Squares	df	Mean Square	F	Sig.
Rftr					
Between Groups	1.572	2	0.786	0.099	0.907
Within Groups	79.457	10	7.946		
Total	81.028	12			
Ratr					
Between Groups	1.384	2	0.692	0.120	0.888
Within Groups	75.119	13	5.778		
Total	76.503	15			
Mftr					
Between Groups	.115	2	.057	0.192	0.826
Within Groups	8.062	27	.299		
Total	8.177	29			
Matr					
Between Groups	5.070	2	2.535	0.822	0.450
Within Groups	83.263	27	3.084		
Total	88.333	29			
vFo					
Between Groups	3.944	2	1.972	0.300	0.743
Within Groups	177.209	27	6.563		
Total	181.154	29			
vAm					
Between Groups	19.742	2	9.871	0.830	0.447
Within Groups	321.171	27	11.895		
Total	340.913	29			

ANOVA did not show a statistically significant difference in Rftr, Ratr Mftr, Matr, vFo, and vAm values for tremor-dominant, PIGD and indeterminate PD phenotypes ($p>0.05$) (Table 6.37).

A further analysis was carried out to look at differences between tremor-dominant and PIGD phenotypes for (a) acoustic (b) auditory perceptual and (c) visual perceptual measures, omitting the 'Indeterminate'phenotype from the analysis due to small sample size (n=2). Table 6.38 shows the mean (SD), median, range, and p values for all tremor measures on the basis of phenotype [tremor dominant; postural instability gait disorder (PIGD)].

Table 6.38 shows that for (a) acoustic tremor measures, mean values for Mftr, Matr, vFo and Vam were higher in the PIGD than in the tremor-dominant sub-group. However, the difference between the phenotypes was not statistically significant for any of the acoustic tremor measures. A further analysis was carried out with PD 5 (outlier previously identified in figure 4-1 to 4-3) omitted from the analysis to ascertain if this would make a difference to the statistical findings. However, the difference between the groups with PD omitted from the analysis was not significant.

In relation to (b) auditory perceptual measures, tremor dominant and PIGD had similar mean values for *instability*. For perceived *tremor,* tremor dominant PD showed a higher (greater severity) mean value than PIGD, however the difference was not statistically significant (Table 6.38).

For (c) visual perceptual measures, mean values were higher (a greater amount of tremor behaviour in the vocal tract) in the tremor dominant than the PIGD phenotype. However similar to the other measures, statistical significance was not found (Table 6.38).

Differences between tremor dominant and PIGD phenotypes in relation to (a) Acoustic (b) Auditory perceptual, (c) Visual perceptual measures

Table 6.38. Mean (SD), median, range and p values for (a) acoustic (b) auditory perceptual (c) visual perceptual tremor measures based on phenotype [(tremor-dominant; postural instability gait disorder (PIGD)]

	Tremor Dominant				PIGD						
(a) Acoustic	n	Mean (SD)	Median	Range	n	Mean (SD)	Median	Range	t	z	p
Mftr	7	0.58 (0.21)	0.55	0.34-1.02	21	0.69 (0.62)	0.60	0.27- 3.29		-0.292	0.796
Matr	7	2.25 (1.18)	1.73	1.28-4.01	21	2.43 (1.91)	2.01	0.76- 9.73		-0.239	0.836
vFo	7	1.09 (0.35)	0.97	0.66-1.63	21	1.81 (2.96)	1.06	0.68- 14.65		-0.663	0.533
vAm	7	6.41 (0.79)	6.48	4.97-7.56	21	8.23 (3.97)	7.48	3.40- 18.16		-0.822	0.435
(b) Auditory-P											
Instability	4	27.00 (7.25)	25.50	20.00-32.00	20	27.85 (16.45)	24.00	4.00-63.00		-0.233	0.852
Tremor	4	23.25 (6.70)	22.50	16.00-32.00	20	18.35 (12.51)	15.50	2.00-55.00		-0.115	0.273
(c) Visual-P											
Palate /ah/	7	1.61 (0.70)	1.50	1.00- 3.00	19	1.49 ((0.83)	1.50	0.00-3.00	0.328		0.746
Tongue /ah/	7	0.89 (0.93)	0.50	1.00-3.00	21	0.72 (0.55)	0.50	0.00-2.00		-0.299	0.796
Larynx /ah/	7	1.29 (0.58)	1.50	1.00- 2.00	21	0.90 (0.63)	0.75	0.00-2.00		-1.44	0.155
Larynx /ee/	7	0.71 (0.33)	0.75	0.00- 1.00	21	0.67 (0.50)	0.50	0.00-2.00	0.230		0.820

Supplementary results

Frequency of detection and descriptive statistics for Rftr and Ratr in tremor-dominant & PIGD phenotype

The frequency of detection [(n)%], and the mean (SD), median values of rate of frequency (Rftr) and amplitude tremor (Ratr) in tremor dominant & PIGD phenotypes is shown in Table 6.39.

Table 6.39. Frequency of detection [(n)%] and mean (SD), median values of Rftr and Ratr in tremor dominant and PIGD phenotypes

Acoustic	Tremor dominant			PIGD		
Rate of tremor	n (%)	Mean(SD)	Median	n (%)	Mean(SD)	Median
Rftr (Hz)	2 (28.6%)	4.50 (3.05)	4.50	10 (47.6%)	4.49 (2.79)	3.44
Ratr (Hz)	3 (42.9%)	4.88 (0.97)	4.84	11(52.4%)	5.09 (2.70)	4.34

Table 6.39 shows that frequency tremor (Rftr) was detected more frequently in the PIGD than the tremor-dominant phenotype. The rate of detection of amplitude tremor (Ratr) was closely matched in tremor dominant and PIGD groups.

Summary main results for question 4

- The magnitude of frequency tremor is positively associated with an increase in disease duration, when duration is defined as the number of years since diagnosis
- Acoustic voice tremor is not related in any way to the severity of PD disability (UPDRS II)
- The rate of amplitude tremor (Ratr %) lowers as the severity of PD motor symptoms increase, when motor symptom severity is measured with the UPDRS.
- There is no difference between people with tremor dominant PD sub-type and people with PIGD phenotype in relation to voice tremor measured acoustically.

Chapter 7. Discussion

Introduction

This is the first prospective study to be carried out on voice tremor in PD. This thesis set out to answer some fundamental questions about PD voice tremor. Is voice tremor a feature of PD? Is there a difference between pwPD on voice tremor measures and people without PD? How does voice tremor relate to pertinent voice and speech parameters, and disease variables? What are the characteristics of PD voice tremor?

This study took a multi-dimensional approach to evaluation, to highlight the different ways tremor can be evaluated and the varied findings which thus ensue. This approach gives greater clarity to the plethora of descriptors in the literature. A greater understanding of terminology, coupled with greater precision in measuring key variables leads towards improved characterisation of this complex phenomenon.

This is the first study to examine a number of different structures in the vocal tract using nasendoscopy, for the purpose of characterising 'vocal tract tremor' in PD. Based on this study findings, the term 'vocal tract tremor' is more apt than 'laryngeal tremor', when describing the source of auditory perceived PD tremor. This study moved beyond those studies that make claims about PD tremor in the absence of a matched comparator group, by including a neurologically healthy control group.

In this chapter, general findings relating to the experimental group regarding gender, age and disability will be discussed first, followed by some background general issues. The findings from the four research questions and their component parts will be discussed in sections 7.1 to 7.4. Additional findings considered to be of importance to the broader PD field, and not covered in the research questions section are addressed in section 7.5. Clinical implications arising from the study, together with pointers towards further research are

described in section 7.6, and the final section 7.7 outlines the study conclusions.

There were more males than females recruited into this study of thirty pwPD study, with a male to female ratio of 2.75:1. In comparison to other studies, the ratio of males to females in this study is both higher than the 1.5 male-to-female ratio reported by Midi et al.,[131] and lower than the 3.4 and 3.1 reported by Perez et al.,[107] and Goberman et al.,[124] respectively.

The age profile [(61 (10) 34-76 years)] of the pwPD in this study was very similar to D'Alatri et al.,[210] (60 years), Stewart et al.,[88] (59 years) and Perez et al's.,[107] study (65 years).

The experimental group represented the milder end of the disease spectrum in relation to disability. The pwPD were independently mobile, excepting one participant who required a wheelchair to mobilise when he was off-medication. Disease duration was relatively short with almost 40% receiving their PD diagnosis within the previous three years.

However whilst there are some important new findings from this study, there are several immediate issues against which background one has to view these results. The study findings indicate that voice tremor is associated with PD and with ageing. Comparing pwPD with neurologically healthy age-and-sex matched controls has highlighted the inherent challenges in identifying differences between the two groups. The fact that pwPD in the current study had short disease duration and a mild disease severity, contributed further to the challenge. However, the findings confirm that even though there are some similarities between pwPD and healthy controls, there are also some interesting differences which will be highlighted in sections 7.1-7.4.

There is debate in the investigatory literature on motor aspects of PD as to whether one should assess in an 'on' or 'off' medication state, the argument for the latter being that one may arrive at insights closer to the true effects of PD independent of medication effects (section 2.5.3). Accordingly, this study addressed the possible confounding effects of medication on voice and speech results by assessing pwPD in a practically defined 'off-medication' state.

However a possible negative effect of this approach was that there was a study bias towards pwPD who firstly were prepared to forego dopaminergic medication and secondly those pwPD who could mobilise independently or with help to a hospital clinic when in an ‘off’ medication phase. As a result, the participants tended to be younger and have a milder disease severity than other PD studies. Further studies should evaluate patients ‘off’ medication perhaps in the pwPD own home, a step which is likely to result in the inclusion of patients with more severe symptoms. However it would not be possible to carry out the nasendoscopic examination outside a medical setting, therefore the study could not be replicated in an exact fashion

Looking at voice tremor in the broader context of the disease is an important step towards greater understanding of the way in which speech/voice and limb symptomatology relate. The strong positive correlation between the magnitude of frequency tremor and disease duration, without the confounding effect of age points to a link between speech/voice system and the disease process. This is an important finding. However it would be important to test the relationship further, using auditory perceived tremor, and vocal tract tremor evaluation methods, in addition to acoustic measures as was used in the current study.

7.1 Research Question 1.

Given that tremor represents one of the claimed cardinal features of PD, a fundamental and over-riding question of this study was whether voice tremor is a distinguishing feature of PD. A further question was if pwPD differ from age-sex matched neurologically healthy controls when different instrumental and perceptual evaluation approaches are used. The findings in relation to acoustic, auditory perceptual and visual perceptual evaluation are discussed separately in the following three sections.

(A)Acoustic tremor measures

The current study represents the largest data set to report on acoustic voice tremor measures, in pwPD. Measures of the rate, periodicity and magnitude of frequency and amplitude tremor were selected as the key acoustic measures to differentiate pwPD from healthy controls. Variation in frequency and amplitude were selected as ancillary measures. In this section, I will discuss the findings for the key and ancillary acoustic tremor measures in the context of the literature, highlighting relevant issues relating to the methodology and study findings, before finally outlining the implications of the findings for further research.

When periodic tremor is detected in the voice signal, the Motor Speech Profile (MSP)[119] gives values for the rate, periodicity and magnitude of tremor. In the current study, frequency and amplitude tremor was detected by MSP in approximately 50% of pwPD. Amplitude tremor was detected in a slightly higher number of pwPD than frequency tremor (Table 6.7). Other studies have reported the presence of frequency and amplitude tremor in a small sample of pwPD[116 88], on the basis of visual perception of tremor in a waveform. However this study goes further with a larger sample size and quantification of the acoustic tremor measures.

An important finding is that frequency and amplitude tremor was also detected in controls, and that amplitude tremor was detected in a similar number of pwPD and controls. The study findings therefore indicate that frequency and amplitude tremor is a feature of this group of pwPD, and of neurologically

healthy controls. Therefore measures detecting the presence of frequency and/or amplitude tremor may not be useful indices for differentiating between pwPD and controls. Boutsen et al.,[184] also reported detection of frequency and amplitude tremor in their control group, using the same tremor protocol from MSP. However they reported lower rates of detection than the current study, and this is likely to be explained by the fact that control participants in the current study were older than those in Boutsen et al's.,[184] study. However in order to confirm this supposition, further studies would need to look at the effect of age on tremor measures in neurologically healthy controls. A further research development would be to look at the relationship between age and voice tremor in PD.

The rate of tremor is one of the parameters used in the classification of tremors (section 3.2) with a 4-6 Hz tremor rate associated with rest tremor in PD[180] (section 3.4). In this study, the rate of frequency tremor did not differentiate pwPD from controls. However, the rate of amplitude tremor did differentiate the groups. PwPD had a higher rate of amplitude tremor than controls (p value <0.05) (Table 6.7).The rate of voice tremor in the amplitude domain in this study, falls within the rest tremor frequency range associated with PD. Contrastively, Boutsen et al.,[184] also using the voice and tremor protocol from MSP found that frequency tremor rate and not amplitude rate differentiated a group of patients with ataxic dysarthria from a healthy neurological group. The frequency tremor rate of their patients with ataxic dysarthria was lower at 3.65 Hz than the frequency tremor rate of 4.39 Hz in pwPD in the present study. It appears therefore that the rate of amplitude tremor in the voice may be one useful diagnostic indicator in relation to PD voice symptomatology[184].

The measure of periodicity relates to the regularity of the detected tremor. The detected frequency and amplitude tremor was more periodic (closer to 100%) in pwPD than in controls. Periodicity of frequency tremor varied much more in pwPD than in controls, with a larger standard deviation evident. This variability coupled with the small sample size may have resulted in the lack of statistical significance between the groups. The difference between the groups for periodicity of amplitude tremor approached significance.

When tremor is not detected, MSP gives values for the magnitude of non periodic (irregular) modulations (frequency and amplitude) present in the voice signal. In the current study, the magnitude of 'non periodic' frequency tremor (Mftr%) and amplitude tremor (Matr%) was numerically greater in pwPD than the neurologically healthy age-sex matched control group, however these parameters did not differentiate the groups. It is reasonable to expect that Matr would have differentiated the groups, considering the differentiating qualities of rate of amplitude tremor and the near significance of periodicity of amplitude tremor. One possible reason for the non significant finding may have been the higher variability (higher SD) in pwPD than the control group. Limb tremor in PD is highly variable, both within and between patients [235]. Considering participant PD5 for example, the values for Mftr % for the 1st 2nd and 3rd consecutive trials were 6.567, 0.977, and 2.337. These are large differences between consecutive trials. There were no methodological changes relating to equipment to explain the variability. To minimise the effect of tremor variability on tremor measures, using one trial as carried out by other authors[184 210], instead of three as done in the present study may be indicated for further studies. An obvious disadvantage to this approach however, is that the variability of measures within patients is not evident. Recruiting a larger sample size and increasing the number of trials may help to offset the statistical issues arising from high variability between trials.

Since no other study has compared pwPD and neurologically healthy controls on acoustic measures of frequency and amplitude tremor it is not possible to compare study findings directly with the literature. However, there were important similarities and differences between the present study findings and other studies in relation to the magnitude of frequency and frequency tremor in the PD group. The magnitude of frequency tremor (0.66%), (non periodic), for pwPD in the current study was very similar to D'Alatri et al's [210] reported value (0.63%) in their study of twelve pwPD. In contrast the magnitude of amplitude tremor (2.49%) was lower in the present study than the value of 4.72% reported by D'Alatri et al.[210] Both studies were similar with respect to acoustic analysis software analysis, mean age of participants, and data collection in an off-medication state. However there were important differences also between the

studies which may explain the difference in findings. Firstly, D'Alatri et al's [210] reported mean values were based on one sustained /a/ trial, whereas the current study was based on the mean of three trials for each participant. Secondly, the pwPD had deep brain stimulation (DBS) carried out two to five years before the study evaluation was carried out. Finally, the participants in D'Alatri et al's.,[210] study had greater disease severity [higher scores on the Unified Parkinson's Disease Rating Scale (UPDRS) motor scale]. DBS is generally carried out on patients at the severe end of the disease spectrum, who are no longer benefitting from dopaminergic medication, and have significant tremor and/or dyskinesias. The mean disease duration for the present study was much lower at 5.23 years (range 1-12) versus 16.04 (10-32 years) in D'Alatri et al's study. It is conceivable that the magnitude of amplitude tremor would increase in tandem with greater disease severity and duration. This study has shown a significant positive relationship between magnitude of frequency tremor (Mftr%) and disease duration (Table 6.26).

In contrast to the present study findings, Jiang et al.,[173] reported that the 'magnitude of amplitude modulation' differentiated their 'pathological' tremor group (n=10) from the normal control group. However caution is required regarding interpretation of their findings in the context of the current study, for two reasons. Firstly, they had a heterogeneous study group, seven had PD and one had idiopathic tremor', (understood by this author to be an 'essential tremor'). Diagnostic information is not provided on the remaining two participants. Secondly, their method of quantifying the magnitude of amplitude tremor was different to the current study, and to D'Alatri et al's.,[210] study.

Ancillary tremor measures

Ancillary tremor measures of overall variation in frequency (vFo) and amplitude (vAm) were included in this study to broaden the scope of the analysis, and increase understanding of tremor measures. The findings show that pwPD had a greater amount of overall frequency variation (vFo) than controls, however the difference was not significant. An unexpected finding was the greater amount of vAm% in the control than the PD group (Table 6.9), albeit the difference was not significant. vAm (%) is a measure of the long-term variation in amplitude from

any variations in the amplitude of the voice (periodic modulations, non-periodic modulation, rising or falling amplitude)[119]. The findings from this study indicate that pwPD and age-sex matched controls have a similar amount of long-term frequency and amplitude variation. The study findings indicate that vFo and vAm do not differentiate pwPD from their matched controls, and suggest that pwPD and controls have similar levels of overall unsteadiness in the voice, using acoustic measurement.

Control group values versus CSL control values

An important ancillary finding in this study which has implications for clinicians and researchers using MSP is that the *control* group values for Mftr%, Matr % vFo% and vAm% were higher than the CSL published norms[119]. These differences may be explained by a number of factors. Firstly, the participants were older in the current study than they were in the CSL sample. The mean (SD) age of the male and female combined group in this study was 60.11 (9.54) however, the mean (SD) age of the combined group published in the CSL manual was lower at 37.9 (11.3) years. Therefore age positively influences measures of frequency and amplitude modulation and overall variation. Thirdly, the CSL norms are based on speakers from the US, who may have lower levels of tremor and instability than speakers from Ireland. Thirdly, there were methodological differences which may explain the different findings for controls. In the current study, the mean value of three trials was used in the analysis and the middle 3 seconds was selected for analysis. For CSL norms, two trials were obtained but it is not reported if the mean value of the trials was used and/or if the middle three seconds was included[119]. D'Alatri et al.,[210] used one trial from each participant after three training trials, however similar to the current study they selected the middle three seconds for analysis. Therefore, caution should be exercised when interpreting results generated from the MSP voice and tremor protocol for older patients. Clinicians will need to refer to norms gathered on subjects older than the CSL sample when interpreting their own patient's tremor values.

Implications of findings and further research

The findings in relation to acoustic measures of voice tremor and their role in differentiating pwPD from healthy controls underscores the challenge inherent in this task. The issue of ageing is a major confounder because of its effect on the neurologically healthy vocal tract and its relationship with PD. A necessary step towards greater clarity is that firstly there needs to be more research on the effect of ageing on voice tremor features in neurologically healthy controls, followed by the effect of age on voice tremor in PD.

Measures of the magnitude of tremor in addition to overall variation in frequency and amplitude may not be useful for differentiating pwPD from healthy controls at least when disease severity is mild. To confirm or reject this hypothesis, further studies need to use these measures across a range of PD disease severity levels.

The rate of amplitude tremor was the only acoustic measure that differentiated this group of pwPD from healthy controls. The clinical significance of this finding is not apparent from this study, especially since pwPD and controls did not differ significantly on auditory perceived tremor variables. However further insight into the implications of this finding may be obtained by looking at its relationship with visually perceived tremor in the vocal tract.

The paucity of norms for acoustic tremor measures has been highlighted in this study. Caution should be exercised when interpreting values for patients over the age of fifty years using the voice and tremor protocol from MSP. Researchers need to collate norms for neurologically healthy controls older than fifty, so that 'pathological' findings can be interpreted correctly.

(B) Auditory perceptual tremor measures

When listeners rated auditory perceived instability and tremor in pwPD and neurologically healthy controls, their ratings did not differentiate the groups on either instability or tremor. *Instability* (unsteadiness) was defined as *"irregular* fluctuations in pitch and/or loudness". *Tremor* was defined as "*rhythmic or nearly rhythmic* fluctuations in pitch and/or loudness of the voice." The issues relating to the findings for instability and tremor will be discussed separately in this section, followed by the supplementary study finding in relation to instability versus tremor, finishing with the implications of the findings for further research.

Instability rating

One reason for the lack of difference between the groups may have been the mild level of perceived instability in pwPD [(mean score of 27.27 (SD 14.92)] coupled with the mild level of instability in the healthy controls. The range of scores (4-63) across PD participants indicates that some patients had little or no perceptible voice instability and others had a significant degree. The low scores for instability may be explained by the fact that perceived instability and/or tremor was not a criterion for entry into the study. This requirement was important in order not to bias outcomes from the start and introduce the risk of circular argumentation. For example, two pwPD (PD 10, PD 21) achieved mean instability ratings of less than 10 /100 indicating little or no perceived voice instability. Of further relevance is that both of these pwPD had short disease duration (3 years and 1 year) respectively. In fact, over 60% of the group were diagnosed with PD in the last six years. This study has shown that there is a positive relationship between the magnitude of frequency tremor and disease duration (Table 6.26). It may be the case therefore that there is a similar positive relationship between perceived instability and tremor, and disease duration. If this were found to be the case, including pwPD with longer disease duration may be associated with increased perceived instability and tremor. Further studies are needed to explore this supposition.

The finding of mild instability in the neurologically healthy control group is worthy of comment especially since instability is associated with the ageing voice (section 2.5.1).The controls were mostly middle aged to elderly. None of

the controls had sought professional help in relation to their voice quality. Therefore one may conclude that the mild degree of voice instability did not impact on vocal function to a sufficient level to motivate them to seek professional help. Perhaps a mild degree of instability represents a 'normal feature' in the ageing voice.

Tremor rating

Similar issues relating to the instability findings apply to perceived tremor findings. Both pwPD and controls presented with a very mild degree of tremor. The individual ratings for pwPD show that six pwPD were rated with a mean score of ten or less indicating that tremor was barely perceptible. It is not possible from this work to say if tremor will be become more perceptible in time for this subgroup. However, this study has shown that the magnitude of frequency tremor increases in tandem with the number of years post diagnosis (Table 6.26).Therefore one would expect that perceived tremor would show a similar positive relationship. However, establishing the clinical utility of acoustic tremor measures (and acoustic measures in general) is an ongoing challenge. It may also be the case that voice tremor is never a feature for some pwPD in the same way that not all pwPD develop limb tremor (section 3.4). Longitudinal single case studies of pwPD using a multidimensional evaluation approach (similar to this study) would add to this study findings.

Controls

It appears from this study that pwPD with mild disease severity and neurologically healthy controls sound similar when rated on features of instability and tremor. Previous studies have not compared pwPD and neurologically healthy controls on auditory perceived tremor measures, therefore comparisons are not possible. However selected acoustic tremor measures have also shown similarities between pwPD and controls in this study (section 6.1.1).

Instability versus tremor

An important additional finding to the main research question was that *instability* on a sustained /a/ vowel was more of a feature than *tremor* for this group of pwPD (Table 6.11). This finding suggests one or both of the following

possibilities: this group of pwPD had in fact a greater amount of *irregular* than *rhythmica*l fluctuations in their voice; the listeners found it easier to hear and rate the irregular fluctuations than the rhythmical ones leading to higher (more severe) ratings for instability. The poor inter-rater reliability suggests that the raters experienced more difficulty perceiving tremor than they did instability, thus lending support to the second possibility outlined above.

The ratings for instability and tremor were found to be strongly and positively correlated in this group of pwPD. This is not surprising since both parameters pertain to fluctuations in the voice.

"Unsteadiness" (termed *instability* in this thesis) has been used by other authors to describe the speech and voice patterns of pwPD[89 104]. The fact that experienced SLT's considered pwPD to have a higher level of instability than tremor in their voice and were more reliable in their ratings between/within themselves, suggests perhaps the term 'instability' is a more appropriate descriptor than 'tremor' to use when describing fluctuations in pitch and/or loudness in the PD voice.

Implications of findings and further research

Perceived instability and tremor evident in pwPD with mild disease severity, is also a feature of neurologically healthy controls. Therefore caution should be exercised when attributing auditory perceptual voice analysis findings in pwPD to the disease process. Further research is indicated to see if pwPD differ from controls on perceived tremor measures when pwPD have more severe disease symptomatology.

(B) Visual perceptual measures

A key aspect of understanding and characterising PD voice tremor is identifying the anatomic sites in the vocal tract in which involuntary oscillatory movement occurs and the speech-related tasks which activate the tremor (4.3.2). Previous pronouncements on the topic have simply assumed that voice tremor must a priori be associated with laryngeal and/or vocal cord instability. There is though no a priori reason to assume this. The phonatory signal that forms the basis of acoustic and auditory perceptual analyses is open to influences from anywhere in the vocal tract. Visual analyses therefore represent important perspectives for understanding the source of perceived PD voice tremor.

This is the first study to use nasendoscopy for the purpose of identifying tremor in the vocal tract in pwPD. The results of this study show some promising results with the identification and characterisation of tremor in the palate, tongue base and larynx, during rest breathing, voiceless /s/ sound and vowel tasks. A novel finding was the identification of tremor in the palate in pwPD. Nevertheless, there were some issues arising from interpretation of findings. This section will firstly address the issue of reliability findings to assist the clinical interpretation of the vocal tract tremor findings which follow. Issues around nasendoscopic examination will be highlighted before discussing the findings from the clinical examination of head and jaw tremor. The final part of the section highlights clinical implications from the findings and direction for further research.

Inter-and intra-rater reliability

In this study, four experienced SLT's were required to make a judgement about the presence and severity of tremor behaviour, when viewing a silent video recording of a nasendoscopic examination of the vocal tract. The definition of tremor adopted for visual perceptual rating was that of an 'involuntary, rhythmical or quasi-rhythmical oscillatory movement of a body part'.

The raters showed poor to moderate *inter-rater* reliability when rating tremor severity in the PD group. This finding is not surprising considering that the raters were required to rate involuntary oscillatory movement from video recordings of silent nasendoscopic exams. Even though all the raters

considered they had experience in viewing endoscopic recordings, they would not have had extensive experience in rating involuntary movement. Visual perceptual judgements using 'nasendoscopy' have generally shown poor reliability in the literature [236] [237]. Rating tremor behaviour in structures in the vocal tract is even more challenging, since the palate, tongue base, and larynx are dynamic and rarely steady structures.

Reliability was poorer when rating tremor in the vocal tract in controls versus pwPD. The controls were rated with 'less tremor' in the vocal tract than pwPD therefore one might expect that the raters would show strong agreement regarding the fact that there was little or no involuntary movement evident. However raters may find it difficult to discern between 'normal' movement in structures and 'subtle tremulous' movement, thus leading to poorer agreement for the controls who have less involuntary movement. One issue therefore that arises for future work is the requirement for raters to have more training in interpreting and rating 'normal' movement of structures in the vocal tract.

The raters rated 10% (PD & control) of the exams a second time (intra-rater). The wide range of percent exact agreement scores across the different tasks for pwPD highlights differences in reliability between tasks (APPENDIX W). For example, the raters are much more consistent in themselves when rating palatal tremor on a sustained /a/ vowel (88% agreement) than when rating tremor in the tongue base on a sustained /s/ (43%). The exact reason is unclear.However there are two possibilities. Firstly, the raters have more experience in general in evaluating the palate, (albeit intra- orally as part of an oro-motor exam), than the tongue base. Therefore one would expect that greater familiarity with the structure would improve reliability. Secondly, there was more tremor evident in the palate on a sustained /a/ vowel (mean 1.60, range 0-3) than there was in the tongue on a sustained /s/ (mean 0.81, range 0-3). Raters are more consistent in repeat ratings when structures are showing a greater amount of involuntary movement than when the movement is barely evident.

When scores within one point were evaluated, agreement was 100% for all tasks excepting tongue /s/ (93%). Further analysis of agreement within raters for rating the presence and not the severity of tremor showed promising results

with 100% agreement reached for tremor in the palate (/s/, /a/) and tremor in the global larynx (vertical laryngeal tremor) on a sustained /a/ vowel. An increase in reliability as the specificity of the agreement is decreasing is not an unlikely finding.

Tremor findings in the vocal tract

This study differentiated pwPD from a neurologically health control group in relation to visually perceived tremor in the tongue, palate and larynx. The results clearly show that tremor goes beyond the larynx in PD. The term, 'vocal tract tremor' is therefore preferential (and more accurate) than the term 'larynx tremor' commonly used in the literature. This study went further than other studies by comparing pwPD with neurologically healthy controls using nasendoscopy, and by rating the severity and not just the presence of tremor.

Even though the PD group were rated with a greater amount of tremor than the control group, the mean values were low across all tasks. The palate /a/ task achieved the highest rating overall (1.60) indicating mild/intermittent to moderate tremor severity on a scale of 0-3. Effect size calculation however showed that the differences between the PD and control group were sizeable for a number of tasks (Table 6.13).The largest effect size (r =0.57) was achieved for tremor in the global larynx (vertical laryngeal tremor) on a sustained /a/ vowel. A previous study identified vertical laryngeal tremor in 55% of a group of 22 pwPD. However Perez et al.,[107] did not include a control group and rated only presence of tremor unlike this study which also addressed tremor severity. Vertical laryngeal tremor is emerging as an important source of tremor in pwPD and differentiates pwPD from controls. Further, raters gave it the same severity rating 75% of the time on repeat viewing which has important clinical implications, in terms of seeking variables that can be reliably identified and quantified. Vertical laryngeal tremor has also been reported in patients with essential tremor of the voice (ETV)[200].Therefore it appears that there are similarities between pwPD and patients with ETV in relation to vocal tract tremor.

Looking at individual pwPD profiles for overall vocal tract tremor, 97% (29/30) had some degree of tremor identified (Figure 6.9). This is higher than the 55%

reported by Perez et al.,[107] in their PD study. The difference in prevalence may be explained by the focus on the palate and tongue in addition to the larynx, as was the case with the current study. The vocal tract tremor profile for this group of pwPD clearly shows that tremor is more evident in the palate than in the larynx or the tongue (Figure 6.8). This is the first study to document palatal tremor on a sustained /s/ (voiceless) sound and a sustained /a/ vowel in pwPD. Interestingly tremor in the palate on a sustained /a/ vowel achieved the highest rating relative to the other sites/tasks. PwPD have been reported to have weakening of pressure consonants and nasal imbalance. Palatal tremor identified in this study may contribute to articulatory and resonance imbalance, though further studies would need to explore this issue further. Tremor in the tongue regardless of speech related task achieved the lowest ratings (mean score less than 1), relative to the palate or the larynx. Hanson et al.,[34] in their study of thirty two pwPD using a different examination approach considered that tremor mostly involved the 'tongue and strap muscles'. Their findings appear to be inconsistent with the current study, which showed multiple sites. However since they did not attempt to quantify or characterise tremor it is difficult to relate their findings directly to the present study.

An interesting and novel finding in the current study was that there was a greater amount of tremor behaviour identified in the larynx during a voiceless task [(larynx /s/; mean rating1.27)] than during sustained /a/ vowel (mean rating 1.04) and /i/ (mean rating 0.68). The specific structure that the raters were asked to focus on in the larynx for sustained /s/ was the arytenoid cartilages. Perez et al.,[107] in their laryngeal study of pwPD did not include a sustained /s/ task, but thought that it would be of interest to define a postural laryngeal task and examine tremor during the task[107]. During a sustained /s/, the arytenoids are 'held' in an open but slightly adducted position and therefore a sustained /s/ task with focus on the arytenoids cartilages could be considered a laryngeal 'postural' task. The relationship between tremor identified on a sustained /s/ and auditory perceived tremor is not addressed in this work. Further studies could progress this question by evaluating auditory perceived tremor in a speaking task, and looking at the relationship with tremor identified visually during sustained voiceless sound /s/, and voiced sounds.

Controls

Low levels of tremor were identified in the healthy neurological control group across the ten visual perceptual rating tasks. The mild rating of palatal tremor (/a/ in the control group is an interesting finding. Tremulousness has been associated with the ageing voice[238] and instability and tremor were identified in controls in the current study. Perhaps palatal tremor is a source of perceived instability and/or tremor in neurologically healthy controls. Further research is required to explore this topic further.

Nasendoscopy examination

Nasendoscopy permits the observation and evaluation of tremor behaviour in the palate, tongue, larynx, and vocal cords, thereby contributing important information on possible sources of PD voice tremor. The findings from PD vocal tract tremor evaluation are important for a number of reasons: they increase understanding of potential sources of perceived tremor; they contribute to a classification approach to PD voice tremor; they broaden discussion around PD voice tremor by including tremor sites outside the larynx together with breathing and speech tasks.

However, nasendoscopy is an invasive procedure, and is not routinely carried out on pwPD for voice analysis. In this study, all of the pwPD showed good tolerance of the nasendoscopic exam. The self-reported strong acceptability of the procedure coupled with a low level of reported discomfort in a minority of participants, and the valuable information obtained, implies that it is an acceptable procedure to use with pwPD for tremor analysis. Future studies should incorporate visual perceptual rating of vocal tract structures alongside routine auditory perceptual evaluation to improve understanding of pathophysiology of PD voice and speech disorders.

Head and jaw tremor

In this study the presence of head and jaw tremor was identified by this researcher prior to the nasendoscopic examination to give context to the voice tremor findings. Head tremor was identified in just two (6%) pwPD. This finding supports the literature which states that tremor rarely involves the head in PD[6]. The identified head tremor was considered subtle and mild in amplitude.

Conversely, jaw tremor was more prevalent than head tremor and was identified in eleven (35%) pwPD. The literature describes jaw tremor as being 'relatively common' in PD[105], however, no other study has quantified its prevalence in PD. It is not possible from this study to say if jaw tremor when present contributed any way to voice tremor identified acoustically, auditory perceptually or visually perceptually. Considering that jaw tremor is a feature of PD, further studies could incorporate jaw tremor evaluation, or control for it by using a bite block.

Implications of findings and further research

Focussing solely on the larynx gives an incomplete picture regarding possible sources of voice tremor in PD. Nasendoscopic examination, although invasive is well tolerated by pwPD and affords a view of tremor in laryngeal and extralaryngeal (outside larynx) sites. Therefore the term 'vocal tract tremor' is more meaningful when describing tremor behaviour in pwPD.

The salience of vertical laryngeal tremor in the vocal tract tremor profile coupled with the high intra-rater agreement supports its clinical use. Studies looking at the effect of dopaminergic medication, deep brain stimulation (DBS), and voice therapy on voice tremor could include vertical laryngeal tremor as an outcome measure. Note that vertical laryngeal tremor may be visually evident in a person's neck. It would be informative to explore the relationship between visually perceived tremor in the neck and in the vocal tract, since the former is non invasive and thus more accessible to all clinicians.

7.2. Research Question 2

Question 2 makes a logical progression from question 1, by examining acoustic tremor measures in the context of the more 'clinical' based measures. A major issue in the field of voice analysis relates to the clinical interpretation, and *clinical utility* of acoustic voice analysis (section 2.4.3). An issue of greater immediacy for this study is that of determining the clinical correlates of acoustic voice tremor measures, from an auditory perceptual, and visual perceptual perspective. This work is necessary to determine if acoustic tremor measures have a role in the clinical evaluation of PD voice tremor. The key findings emerging from question 2 will be discussed first, to be followed by consideration of the broader implications of the findings for the field of acoustic analysis.

The findings from this study showed that with an increase in the magnitude (extent) of frequency tremor (Mftr%), there was a greater amount of *instability* (unsteadiness) perceived in the voice. There was also a greater amount of *tremor* (rhythmic/quasi rhythmic fluctuations) perceived in the voice, with an increase in Mftr%. This finding suggests that what was perceived as 'tremor' or unsteadiness' in the voice was related to modulations in the frequency of the voice, in this group of pwPD.

Interestingly, but not altogether surprising, the overall variation in frequency (vFo %) was also associated with perceived *instability* and *tremor* in the voice. VFo is not strictly a measure of tremor. It is best to think of vFo as a generic measure of instability in the voice signal. It may reflect any of the following: rhythmic or quasi rhythmic oscillations (tremor), noncyclical or irregular oscillations (unsteadiness), or rising or falling fundamental frequency across the 3-5 second recorded segment[119].

This study goes further when it makes a link beween the magnitude of frequency tremor (Mftr %) and variation in frequency (vFo), and visually perceived tremor in the vocal cords. This makes an important link between frequency tremor and tremor in the vocal cords.

From a clinical perspective, the researcher considered it very important to look at the relationship between what a listener perceives as *tremor* (rhythmic/nearly rhythmic fluctuations in pitch/loudness of the voice), and the possible source of that *tremor* in the vocal tract. The supplementary analysis findings were very revealing and novel, in that they showed that when *tremor* was perceived it was positively associated with vertical laryngeal tremor, and with tremor in the vocal cords.

For controls, there were some similarities and some differences also, in the way that acoustic measures related to perceived *instability* and *tremor*, and to tremor in the vocal tract. The negative correlation between the rate of frequency tremor (Rftr Hz) and perceived *tremor* may be translated as, with an increase in the rate of tremor (more cycles per second), there is less perceived *tremor* in the voice. This is understandable since a faster tremor rate is harder to perceive. What is not clear though is why this relationship is evident in the control group and not the pwPD group. The study findings in general are confirming that tremor is a feature of the 'neurological' voice and the 'normal' voice. The challenge is to identify the way in which tremor is realised in PD, and in neurologically healthy controls.

From a methodological perspective, one might argue that a weakness of the study is the fact that the /a/ vowel on which the acoustic measures are based is not the same /a/ as which the auditory perceptual, and visual percpetual rating is based. This is a valid observation and therefore caution is required in the interpretation of the associations between the measures. However, it is also important to note that every effort was made by the researcher to minimise methodological variations by adhering to the following protocol: the same order of recording was followed for all pwPD and controls, i.e. audio-recordings were followed by acoustic recordings (maximum time interval of 5 minutes between audio and acoustic recording), followed by the nasendoscopic examination.

The acoustic tremor measures from the Motor Speech Profile (MSP) have had limited application in the clinical field. The findings from this thesis contribute to that knowledge base.

7.3 Research Question 3

This is the first study to evaluate PD voice tremor in the context of other pertinent voice and speech variables. The pupose of question 3 was to place PD voice tremor in the broader context of changes in voice quality, voice disability, and communication effectiveness, all of which are associated with PD. In the following sections, I will discuss the findings relating to the relationship between acoustic tremor measures and (a) severity of dysphonia (b) voice disability and (c) speech intelligibility.

(A) Acoustic tremor measures and overall severity of dysphonia

This is the first study to analyse PD voice tremor in the context of voice quality changes. Voice changes and PD are inextricably linked (section 2.3). The findings showed that for pwPD, acoustic tremor measures of rate (Rftr, Ratr) and magnitude of tremor (Mftr, Matr) did not relate to the perceived severity of dysphonia when dsyphonia was measured with the Consensus Auditory Perceptual Evaluation of voice (CAPE-V). However, a measure of overall instability, the overall variation in frequency (VFo %), did relate to severity of dysphonia. It is important to reiterate here that vFo is a measure of overall variation in frequency and may or may not reflect periodic tremor in the voice signal[119].

The positive relationship identified between vFo% and overall voice deviance (CAPE-V) cannot be considered unique to pwPD since a similar relationship was identified in the control group (Table 6.18). In addition, the positive relationship identified between magnitude of tremor (Mftr %) and auditory perceived voice deviance in the controls and not pwPD suggests that there may be differences between the groups in relation to tremor effects on voice quality. However, it is not possible to determine the nature of the difference based on the current study findings.

The pwPD group were rated as having a mild degree of dysphonia severity when rated independently by three experienced SLT's, using CAPE-V[100]. A mild severity rating is not surprising for a number of reasons. Participants were not

selected for the study on the basis of perceived dysphonia. As a group they had a relatively short disease duration and mild disease severity, which might suggest minimal dysphonia. The study findings relating to overall severity of dysphonia are novel. Other studies have described voice changes in pwPD, but have focussed on prevalence and qualitative voice changes rather than determining an overall rating of voice deviance as happened in this study. One exception is the study carried out by Midi et al.[131] who used the overall grade (G) parameter from GRBAS[99]. The grade (G) parameter from GRBAS and the severity grade from CAPE-V have been shown to correlate positively[101]. There were a number of similarities between the current study and Midi et al's[131]. Both pwPD groups were similar with respect to age and disease severity (mild), and both included a control group. However, disappointingly, it is not possible to compare the overall dysphonia severity CAPE-V findings with Midi et al's[131] (G) findings. Midi et al., [131] reported findings for overall grade of dysphonia (G) in graph format showing males to have a mean value of 6/10 and females a meanvalue of 3/10. Considering the GRBAS has a four point scale from 0-4, it is difficult to to interpret these scores.

In this study the pwPD group were rated with an overall mild degree of dysphonia. The highest score obtained in this group of pwPD was 34 (range 0-100). Severity of dysphonia was rated with the parameter 'overall severity', defined in CAPE-V as the 'global integrated impression of voice deviance'. A mild dysphonia rating is not surprising for this pwPD group considering that dysphonia was not a criterion for entry into the study, coupled with the fact that the group were at the milder end of the disease severity continuum.

A similar level of mild dysphonia was identified in the control group with a mean (SD) range value of 20.41(11.3). This finding may be explained by the fact that the majority of the control group were more than fifty years of age, with a mean age of 60 years. Changes in vocal tract structures are associated with ageing (section 2.5.1) and dysphonia in the aged population is relatively common[142]. It appears therefore that this group of pwPD with mild disease symptomatology and short disease duration were no different in terms of overall 'dysphonia severity' or 'voice deviance' when compared to a group of people without PD

who had a similar age profile. There is a need to look at pwPD across the whole time span of the disorder to truly appreciate voice changes and differences with healthy controls.

It is difficult to compare present study findings directly with other studies, since perceptual based studies have concentrated more on ratings of distinct perceptual parameters, for example 'hoarseness'[89] than on an overall severity level of dysphonia (Table 2.1). Nevertheless, there is some similarity between the current study findings and Chenery et al's[89], with the finding that even though hoarseness was present in 100% of their sample, it was 'just noticed' in 80% (n=19) of their group. Further, the difference between their PD and control group for hoarseness ratings was not significant. The fact that in both studies the pwPD were at the milder end of the disease spectrum may be relevant.

(B)Relationship between acoustic tremor measures and voice disability

The purpose of question 3 (part B) was to explore the nature of the relationship between acoustic voice tremor measures and voice disability as measured on the Voice Handicap Index (VHI).The results show that the selected acoustic tremor measures were not predictive of the total VHI, or the VHI subscale scores, for pwPD (Table 6.20). An important finding to highlight is that this group of pwPD were found to have a significantly greater voice disability than an age and sex-matched control group (Table 6.21).

The finding that there was no relationship identified between acoustic tremor measures, and voice disability is not surprising. It is difficult to relate objective acoustic measures to the self-perceived impact of a voice disorder which varies for each patient depending on their personality, social networks, family relationships and occupation[129]. Although a number of studies have used acoustic, and self-report measures[132 71 131 129] in voice evaluation of pwPD, no previous study has explored the relationship between acoustic voice tremor and self-report measures. Wheeler et al.,[129] looked at the relationship between acoustic measures (Fo, SDFo, jitter, shimmer) and the total and sub-scales of the VHI in a group of people (non PD) with mildly disordered voice quality, and also found that there was no significant relationship between acoustic and VHI

measures. The current findings highlight the non linear relationship that exists between disability and handicap[81]. Acoustic tremor measures and self-report voice disability measures are not interchangeable therefore, based on the current results.

VHI total and subscale scores

Self-perceived voice problems in pwPD have been reported in other studies, some of which have also used the Voice Handicap Index (VHI)[132 71 131]. The total VHI score for pwPD in the current study indicated a mild disability (Table 6.21) and was similar to the values reported by Frost et al.[71] Conversely, Carmichael et al.,[132] in their study reported higher mean VHI scores [(mean 39.99,(SD) 22.35)] than those in the current study which may be explained by the fact that their group had a greater disease severity profile (stages II to IV on the Hoehn & Yahr scale) than pwPD in the current study (Table 6.5).

Gender differences were not the focus of the current study. However it is of general interest to clinicians working with PD that male pwPD reported greater levels of voice disability than female pwPD. Midi et al's[131] results show a similar trend with mean (SD) scores of 34.42 (3.45) for males and 15.5 (2.86) for females. There were more males (n=22) than females (n=8) in the present study and this differential may have complicated the findings. However, the mean age of the male and female pwPD groupwas very similar (60 years vs.62 years) in the current study, therefore age difference cannot be seen as an influencing factor in the findings. In summary therefore, voice tremor when measured acoustically is not a predictor of increased voice disability in pwPD. Further studies should focus on different approaches to measuring tremor, in addition to other voice parameters for possible associations with voice disability. Gender differences in relation to voice disability in pwPD, is an area worthy of further exploration.

(C). Relationship between acoustic voice tremor measures and speech intelligibility

The final part of question 3 addresses the nature of the relationship between acoustic voice tremor measures and speech intelligibility for sentences, using

the Speech Intelligibility Test (SIT)[156]. In the current study, when the acoustic voice tremor scores were analysed with regard to associations with speech intelligibility, they were found not to relate in any significant way (Table 6.22). Previous studies have not addressed this specific question regarding voice tremor and speech intelligibility. However other studies have looked at other voice and speech variables with mixed findings reported.

The fact that the pwPD group had a very mild reduction in speech intelligibility (94%) for sentences may be influential in the findings reported in this study (Table 6.23). It is important to reiterate here that the pwPD in this study were not recruited on the basis of any perceptible speech and/or voice difficulty. A number of the participants had no reduction in speech intelligibility. In fact a matched neurologically healthy control group were found to have the same mean % intelligibility score as the pwPD with no difference found between the groups. Acoustic voice tremor findings did not relate to speech intelligibility scores for the control group (Table 6.22)).

An issue to consider is the fact that the sentences employed in SIT are not controlled for syntax or semantic cues to meaning [222]. Therefore high scores on the SIT may reflect overall understandability rather than signal speech intelligibility. Therefore the intelligibility task used might be contributory to the negative findings regarding acoustic voice tremor and speech intelligibility. Testing speech intelligibility in pwPD in a dual task condition, for example with background noise, or with a group of listeners, may give a different more realistic intelligibility index. Another area worthy of consideration would be to use an all-voiced sentence task, which one would expect would increase tremor and possibly impact reduce speech intelligibility. Studies could also use auditory perceptual tremor measures with a sustained vowel and sentence task to test the relationship further.

In this novel study, acoustic voice tremor measures did not contribute to sentence intelligibility scores, however further studies with a change in intelligibility task and/or a change in voice tremor measurement approach is indicated.

7.4 Research Question 4

The aim of the final question was to establish the nature of the relationship between acoustic voice tremor measures, and four specific disease variables: (a) duration of disease; (b) activities of daily living (disability) (c) motor symptom severity, and (d) PD phenotype. Exploring the relationship between PD voice symptomatology and disease variables is warranted to enhance understanding of voice and disease pathophysiology, which contributes to diagnostics and treatment approaches. Voice tremor is uniquely placed to explore the relationships between voice dysfunction and disease variables by virtue of the fact that phonatory changes are salient in PD and limb tremor is a cardinal symptom of PD. The findings from the four sub-questions within question 4 are discussed under the relevant headings.

(A) The relationship between acoustic voice tremor measures, and duration of PD disease?

This preliminary work exploring voice tremor in the context of PD disease duration raises some interesting findings and questions.This study has demonstrated that there is a significant positive correlation between acoustic voice tremor and disease duration in a group of thirty pwPD. The magnitude of frequency (Mftr %) and amplitude tremor (Matr %) in the voice signal together with the overall variation in frequency (vFo %) were found to relate positively and significantly to disease duration (number of years post diagnosis). This relationship was upheld when age was controlled (Table 6.27).Therefore as the length of time from diagnosis increased there was a corresponding increase in the magnitude of tremor and the overall variation in frequency of the voice. The findings reported here would be strengthened if auditory perceptual and visual perceptual tremor measures were found to show a similar positive relationship with disease duration.

Mftr % in the voice signal had the strongest correlation with disease duration. This may be revealing of the pathophysiology of PD voice tremor. For example, the fact that Mftr % showed a stronger correlation with disease duration relative to Matr %, might suggest changes in the physiology of tremor over time reflected more in Mftr % than Matr %. Conversely, it may be the case that in fact the 'magnitude' of frequency tremor is a more sensitive indicator of disease duration. This is a preliminary supposition based on a small sample of pwPD with a relatively short disease duration (mean 5.23 (3.17) (1-12 years). Further studies should replicate the methodology with a sample of pwPD who have had the disease for a longer period of time.

There was one outlier (participant PD 5) in the acoustic measures data, evident in the correlation graphs for Mftr, Matr, vFo, and disease duration (Figure 6.10, Figure 6.11, Figure 6.12).The values for Mftr, Matr and vFo were significantly higher for PD 5 than were the values for the other participants. PD 5 was a 76 year old female. She was the oldest participant in the group and had the longest disease duration (12 years) relative to the other participants. There was a wide range in values across the three trials for all the acoustic measures for this lady (APPENDIX O). The reason for the high variability across trials was not clear from re-analysis of the voice signals (3 trials) saved in the MSP data file. Limb tremor variability is a feature of PD (section 3.4) and voice tremor variability is also evident in acoustic voice tremor analysis shown in this study. It is important to note that the participant with the greatest magnitude (%) of acoustic voice tremor and the greatest variability between trials was also the oldest pwPD. A possible drawback of this study is the 'young' age profile of the pwPD group [(61.40 (10.31) years]. It is necessary to include older (i.e. aged 70 and over) participants in studies so that findings can be generalised to the clinical population[239].

Previous studies have not looked specifically at the relationship of acoustic or other voice tremor measures, and disease duration in pwPD. However, other studies have looked at other speech and voice variables and disease duration, and report contrasting findings to the present study[102 77 135].For example, Coates et al.,[102]and Miller et al.,[77] found that speech intelligibility did not

correlate significantly with disease duration. Gamboa et al.,[135] did not identify a relationship between self-report voice measures, a range of acoustic measures [fundamental frequency (Fo), jitter, shimmer, and harmonic-noise ratio (HNR)], 'phonetometric' (dynamic range, s/z ratio, maximum phonational time), and disease duration. All aforementioned studies defined disease duration in relation to the number of years since diagnosis, similar to the present study. However, apart from the important fact that different speech and voice variables were studied across the studies, there were also differences in relation to dopaminergic medication schedules [102] [77] [135].For example, in the current study pwPD were tested 'off medication', whilst in other studies pwPD were 'on medication'[135], 'off medication'[77], and on different medication regimes within the same study[102].

To firmly establish the relationship between voice tremor and disease duration, it is necessary to broaden the scope of the work by looking at the relationship between other evaluation approaches (auditory perceptual, visual perceptual measures), and disease duration. Additionally, including pwPD older than 70 years and with longer disease duration than the present study would be important methodologically. It would be informative also to establish if the same positive relationship between acoustic voice tremor and disease duration exists when pwPD are 'on medication'.

(B) The relationship between acoustic voice tremor measures, and activities of daily living?

The Unified Parkinson's Disease Rating Scale (UPDRS) II is used widely, clinically and in PD studies to document the impact of the disease on the person's activities of daily living. Understanding ways in which voice tremor relates to PD disability is important, particularly in the context of ameliorating symptoms and improving quality of life. Speech and voice studies do not generally report data on UPDRS II, therefore the findings here are novel and exploratory.

Acoustic voice tremor was found not to relate positively or negatively to activities of daily living measured with UPDRS part II. Possible reasons for the lack of a relationship between the two measures, together with some interesting findings from adjunctive analysis of the UPDRS II scores is discussed as follows.

The level of disability as measured with UPDRS II may have been too low for any meaningful relationships to emerge. Further studies encompassing pwPD with higher scores on UPDRS II may show different findings. Another reason may pertain to the way in which the different measurement tools are used. For example, computerised acoustic voice analysis was carried out at a discrete point in time. Conversely, global disability related to PD was measured on the basis of the pwPD self-perception of specific symptoms and activities (tremor, speech, handwriting etc.) over the preceding two week period. Item 5, which is the speech item in UPDRS II relates to pwPD self-perception of speech intelligibility only and not to voice tremor or other speech/voice variables. A final issue may relate to the fact that UPDRS II is a composite measure of pwPD self-reporting on different aspects of PD (walking, falling, tremor, handwriting etc) (APPENDIX A) and may not relate in any way to voice tremor. The researcher therefore tried to address this problem by looking specifically at the relationship between acoustic voice tremor measures and the self-report tremor item 16. However findings showed no significant relationship between acoustic voice tremor and self-report tremor measures (Table 6.31). It would be informative to broaden the scope of this question by including other voice

tremor measurement approaches (auditory perceptual, visual perceptual) in the analysis. In addition, looking at other voice variables, for example, hypophonia, dysphonia, speech intelligibility etc, to see how they relate to PD disability would also be valuable.

It is worth highlighting an interesting ancillary finding that emerged from a supplementary analysis of the UPDRS II scores, based on group scores for the individual items (Figure 6.14). Across the 13 UPDRS II items, handwriting achieved the highest mean rating (most severe), followed by tremor and then speech. Therefore, although the overall disability was mild for this group of pwPD, their self-rating of tremor and speech was at the higher end of range.However acoustic voice tremor did not appear to contribute to their overall disability.

(C) Relationship between acoustic voice tremor measures and PD motor symptom severity

The question of a relationship between voice tremor, motor symptoms, and limb tremor is not only interesting but also important because of the contribution the findings make to the motor/non motor debate. When the relationship between acoustic voice tremor and motor symptom severity (UPDRS III) were evaluated mixed findings emerged.

Rate of amplitude tremor (Ratr Hz)

As PD motor symptoms measured with the UPDRS III become more pronounced, there is a lowering of the rate of amplitude tremor (Ratr Hz) (Table 6.32). Neither the magnitude of tremor (frequency, amplitude) nor the overall variation of frequency or amplitude related in any way to UPDRS III scores. The findings suggest that as the disease process develops (increase in motor symptoms), the rate of tremor (amplitude) becomes slower. The rate of amplitude tremor [(mean 4.94(SD) 2.25 Hz)] differentiated pwPD from controls (Table 6.7) which strengthens the finding that Ratr and UPDRS are related at least in this group of pwPD. Pathological tremor is associated with a lower rate of tremor than normal 'physiological tremor' (section 4.1). One could speculate therefore, that the pathophysiology of voice tremor changes over the course of the disease leading to a lowering of the rate which translates into it being more noticeable clinically in more advanced stages of the disease.

Magnitude of tremor (frequency & amplitude)

It may be surprising that no relationship was found between the magnitude of frequency (Matr) or amplitude tremor (Matr) and the severity of motor symptoms, especially since Mftr and Matr were found to correlate positively with disease duration. One might expect a linear relationship between disease duration and motor symptom severity but supplementary analysis showed this not to be the case. Therefore although the rate of tremor (amplitude) was linked to motor symptom severity in this group of pwPD, the magnitude (frequency and amplitude) of tremor did not. It would be important to test this further with a group of pwPD who have greater disease severity than those pwPD in the current study.

Exploration of the relationship between acoustic voice tremor and limb tremor (UPDRS III tremor subscore) showed no significant associations for any of the acoustic measures (Table 6.34). Further analysis using auditory perceptual and visual perceptual measures would be helpful to support or refute the findings with acoustic tremor measures.

The profile of the UPDRS III items based on group mean scores is revealing (Figure 6.16). It shows that item 31 'body bradykinesia' achieved the highest (most severe) rating and the tremor items achieved some of the lowest scores. This finding reinforces the reports that PD tremor is highly variable. When pwPD self-rated limb tremor based on their observations over a two week period (UPDRS II), they rated limb tremor more severely than when the researcher rated limb tremor on the day of testing.

Previous studies have not specifically or systematically looked at the relationship between acoustic voice tremor measures and motor symptom severity. However other studies have reported on relationships between other voice and speech measures and disease severity with different findings to the current study. Gamboa et al.,[135] reported a higher incidence of 'laryngeal' tremor in 16 pwPD with a UPDRS total score greater than 24.3 (greater severity) when compared with 25 pwPD who had scores in the range of 0-24. There are a number of important differences between Gamboa et al's.,[135] study and the current one which makes interpretation difficult. For example, the authors[135] combined the UPDRS subsection II and III to yield a total UPDRS score, whereas the current question relates to the UPDRS III sub- section only. Testing was carried out with pwPD in an 'on-medication' state contrasting with the present study with testing carried out 'off medication'. In addition, there are also a number of methodological flaws in relation to the identification of 'laryngeal tremor' (section 4.4) in Gamboa et al's., study which makes it difficult to compare findings[135].

Goberman et al.,[124] found a significant relationship between laryngeal instability measured with SDFo and the UPDRS III and concluded that as motor function became more impaired, laryngeal instability increased. Their pwPD group had a similar mean UPDRS II score to the current study, However, the authors [124] did

not include tremor measures, and the pwPD were 'on medication' therefore the studies cannot be compared directly.

Extending the discussion from acoustic voice measurement to speech, Coates et al.,[102] did not show a significant correlation between speech intelligibility measures and disease severity. However, the authors cited a mean (SD) score of 1.4 SD (0.7) for the UPDRS motor subsection in their group of forty eight pwPD[102]. This score is difficult to interpret, considering the mean disease duration was 6.7 years.

Implications and further research

The novel and preliminary finding of a significant (negative) relationship between the rate of amplitude tremor and disease symptom severity is exciting since it suggests a tenuous relationship between voice tremor and PD pathophysiology. The fact that significant (positive) relationships were found between other tremor measures (Mftr, Matr), and disease duration adds further weight to the current question.

This study finding of a positive association between selected voice tremor measures and PD disease contributes to the motor symptom/ non-motor speech debate. However, it must be stressed that current findings are preliminary and what is needed is for other studies to replicate these findings in pwPD with varying levels of disease severity and age groups.

The lack of relationship between the magnitude of tremor measures (Matr, Mftr) and disease severity is somewhat surprising considering Mftr and Matr's positive association with disease duration. However, the fact that there is not a linear relationship between disease duration and disease severity (APPENDIX C) might help to explain the disparity of findings for Mftr and Matr. It would be interesting to see if non-acoustic tremor measures (auditory and visual perceptual) were included in the analysis would different findings emerge in relation to Mftr and Matr measures. If auditory and/or visual perceptual tremor measures were found to correlate with motor symptom severity, one could question the appropriateness of Mftr and Matr as useful indices of acoustic voice tremor.

(D) The relationship between acoustic voice tremor measures and PD phenotype?

The final part of question 4 sought to establish the nature of the relationship between acoustic tremor measures and PD phenotype. The results show that none of the acoustic measures differentiated tremor-dominant PD from postural instability gait disorder (PIGD) (Table 6.37). The small sample size of pwPD with tremor-dominant PD (n=7) relative to PIGD (n=21), may have influenced the significance findings.

It is important to note that Mftr%, Matr%, vFo%, and vAm% showed higher values in the PIGD group than the tremor dominant phenotype group. This finding suggests that pwPD who didn't have tremor as the dominant aspect of their PD symptomatology had higher levels of tremor in the acoustic voice signal than pwPD who were tremor dominant. However no definite conclusions can be made on this issue, since differences were non-significant between the groups.

The small number of pwPD classified as tremor dominant relative to PIGD was a surprising finding for this author, expecting limb tremor to be a more prominent feature in the disease profile. However 30% of pwPD do not present with tremor limb[180](section 3.4).

Auditory perceptual and visual perceptual tremor measures in tremor dominant and PIGD phenotypes

In addition to examining the relationship between acoustic tremor measures and tremor dominant and PIGD phenotypes, the analysis was extended to include perceptual and visual perceptual measures in the analysis. Neither auditory perceived *instability* and *tremor*, nor visually perceived tremor in the vocal tract differentiated the tremor dominant phenotype from the PIGD group. Therefore based on these study findings, pwPD with tremor dominant PD showed no difference to pwPD with a PIGD phenotype.

These study findings cannot be compared with other voice or speech studies since other studies have not addressed this question. In fact, in the PD literature in general, few clinical studies have incorporated PD sub-types[65] despite calls for their inclusion.

Clinical implications and further research

Surprisingly, voice tremor does not appear to be more of a feature of pwPD who fall into the tremor dominant category than pwPD of the postural instability gait disorder type (PIGD).

Speech and voice studies should incorporate data on pwPD phenotype to gain understanding of the how PD and speech-voice pathophysiology interact.

7.5 Additional study findings

An important finding from the study which does not come under the research question discussion section pertains to the Hospital Anxiety and Depression Scale (HADS) results.

Anxiety and depression

Anxiety and depression is associated with PD (section 1.4) and anxiety and/or depression may impact in general on speech and/or voice function (section 2.5.2). A known psychological disorder requiring treatment was one of the exclusion criteria for the study. The researcher considered it prudent also to obtain a baseline measure of the emotional status of pwPD, and used the Hospital Anxiety & Depression Scale (HADS) for that purpose (section 5.5.7). However no effort was made to relate the voice tremor findings to the HADS findings.

The study findings of significant differences between pwPD and controls in relation to anxiety and depression underscores findings in the literature reporting increased levels in pwPD [49 50 43 51 54]. Anxiety symptoms were more prominent than depression in this group of pwPD, with 23% (n=5) scoring outside the normal range (0-7) for anxiety, versus 12.5% (n=1) for depression. Of note is the fact that more male than female pwPD, scored outside the normal range for anxiety. The prevalence of reported anxiety based on HADS scoring was unexpectedly high (23%) in this group of pwPD, relative to the controls (3.7%). The effect of anxiety on voice tremor or other speech and voice findings cannot be ascertained from his study since it was not a study focus. However, an important point to highlight in this regard is that heightened anxiety did not prevent any of the pwPD having the nasendoscopy examination.

The prevalence of depression (12.5%) in the pwPD group is lower than other prevalence levels reported (section 1.4). It is probable that depression is a more overt condition than increased anxiety, with patients more likely to be referreed to mental health specialists and/or receiving treatment than is the case for anxiety. Four (11%) of patients were excluded from the study in relation to a known depression condition. However, none of the pwPD group had been

diagnosed with an anxiety related disorder and none were receiving professional help for anxiety.

PD speech and voice studies should not only control for anxiety levels in pwPD, but also look for evidence of a relationship between anxiety levels and speech and voice syptomatology. In addition, exploration of gender differences in anxiety levels in the context of communication disability in pwPD is warranted based on the current study findings.

7.6 Summary clinical Implications & further research

Based on the current study findings:

- Voice tremor analysis benefits from a multi-dimensional approach.
- Voice tremor is associated with PD and with 'normal voice'.
- PwPD with a mild disease severity and neurologically healthy controls may sound similar in relation to overall voice instability.
- The instability in the PD voice is probably related to tremor in the palate and tremor in the global larynx (vertical laryngeal tremor).
- There is a need to collect acoustic data on neurologically healthy controls (over 50 years) for comparison with pwPD data.
- More direction is needed regarding the optimum number of trials that should be used in acoustic voice analysis.
- Acoustic measurement detects tremor in the voice.
- The rate of amplitude tremor tremor appears to be a useful acoustic measure for differentiating pwPD from controls.
- Vocal tract tremor is a better descriptor than 'laryngeal tremor' to describe the source of PD voice tremor.
- Nasendoscopy is an acceptable procedure for use in voice analysis for pwPD.

- There are links between voice tremor and disease duration, and disease severity, but not between voice tremor and limb tremor.

Research ideas generated from the study are as follows:

The field of motor speech disorders would benefit from studies of the neurologically healthy person (over 50 years), for comparison with PD and other neurological disorders.

Speech-voice PD studies should include patients who have had the disease over a wide range of years (disease duration) and with varying levels of disease severity.

Gender differences in speech and voice symptomatology in pwPD should be explored further.

For the broader field, greater cognisance should be given to increased anxiety levels in pwPD.

Exploring contributory factors to increased voice disability in male versus female pwPD would guide treatment goals.

7.7. Conclusions

In this study I set out to determine if voice tremor was a feature of PD when pwPD were compared with neurologically healthy controls, and to determine ways in which voice tremor related to pertinent voice and speech variables and disease variables. I recruited thirty pwPd and twenty eight controls.I attempted to differentiate between the two groups by using a number of instrumental and perceptual analyses of voice tremor. The main findings of my work were: voice tremor is a feature of pwPD with mild disease severity and of neurologically healthy controls; voice tremor can be detected acoustically, and the rate of amplitude tremor appears to be a useful measure for differentiating pwPD from controls; tremor in the vertical laryngeal dimension and tremor in the palate are the main anatomic sources of voice tremor in pwPD; selected (acoustic) voice

tremor measures relate to duration of PD disease and disease severity; pwPD have significantly greater voice disability than controls.

These results have progressed our understanding of voice tremor in the following ways: voice tremor is a feature of pwPD however it is also a feature of people without PD. The rate of amplitude tremor may be an important acoustic tremor measure for identifying tremor particularly in pwPD with short disese duration. Selected acoustic tremor measures showed some association with disease variables. The main anatomic source of voice tremor in pwPD is the palate and the global larynx (vertical laryngeal dimension). There are a number of clear research priorities as a consequence of my work. These are to: study voice tremor in pwPD over a wider age span and duration of disease; determine acoustic norms for neurologically healthy controls over 50 years; explore gender differences in speech and voice symptoms in pwPD.

Appendices

APPENDIX A: Unified Parkinsons Disease Rating Scale II
(Activities of Daily Living)
5. Speech:

0 = Normal
1 = Mildly affected. No difficulty being understood
2 = Moderately affected. Sometimes asked to repeat statements.
3 = Severely affected. Frequently asked to repeat statements.
4 = Unintelligible most of the time.

6.Salivation:

0 = Normal.
1 = Slight but definite excess of saliva in mouth; may have nighttime drooling.
2 = Moderately excessive saliva; may have minimal drooling.
3 = Marked excess of saliva with some drooling.
4 = Marked drooling, requires constant tissue or handkerchief.

7.Swallowing:

0= Normal.
1= Rare choking.
2= Occasional choking.
3= Requires soft food.
4= Requires NG tube or gastrotomy feeding.

8. Handwriting:

0= Normal
1= Slightly slow or small
2= Moderately slow or small; all words are legible
3= Severely affected; not all words are legible
4= The majority of words are not legibl

9. Cutting food and handling utensils:

0= Normal
1= Somewhat slow and clumsy, but no help needed
2= Can cut most foods, although clumsy and slow; some help needed
3= Food must be cut by someone, but can still feed slowly
4= Needs to be fed

10.Dressing:

0= Normal
1= Somewhat slow, but no help needed
2= Occasional assistance with buttoning, getting arms in sleeves
3= Considerable help required, but can do some things alone
4 =Helpless

11.Hygiene:

0 = Normal.
1 =Somewhat slow, but no help needed.
2=Needs help to shower or bathe; or very slow in hygienic care.
3= Requires assistance for washing, brushing teeth, combing hair, going to bathroom.
4 =Foley catheter or other mechanical aids.

12. Turning in bed and adjusting bedclothes:

0 =Normal.
I =Somewhat slow and clumsy, but no help needed.
2 =Can turn alone or adjust sheets, but with great difficulty.
3 =Can initiate, but not turn or adjust sheets alone.
4 =Helpless.

13. Falling. (unrelated to freezing):

0 =None.
1 =Rare falling.
2 =Occasionally falls, less than once per day.
3 =Falls an average of once daily.
4 =Falls more than once daily.

14. Freezing when walking:

0 =None.
1 =Rare freezing when walking; may have start-hesitation.
2 =Occasional freezing when walking.
3= Frequent freezing. Occasionally falls from freezing.
4 =Frequent falls from freezing.

15. Walking:

0 = Normal.
I =Mild difficulty. May not swing arms or may tend to drag leg.
2= Moderate difficulty, but requires little or no assistance.
3=Severe disturbance of walking, requiring assistance.
4=Cannot walk at all, even with assistance.

16. Tremor:

0 =Absent.
1 =Slight and infrequently present.
2 =Moderate; bothersome to patient.
3 =Severe; interferes with many activities.
4 =Marked; interferes with most activities.

17. Sensory complaints related to parkinsonism:

0= None.
I = Occasionally has numbness, tingling, or mild aching.
2 = Frequently has numbness, tingling, or aching; not distressing.
3 = Frequent painful sensations.
4 = Excruciating pain.

APPENDIX B: Unified Parkinsons Disease Rating Scale III
(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:***

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 with widest amplitude possible, each hand separately.)

0= Normal.
I = 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 with widest amplitude possible, each hand separately.)*

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 or horizontally, with as large an amplitude as possible, both hands simultaneously.)

0 =Normal.
I =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 ground in rapid succession, picking up entire leg. Amplitude should be about 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 arise from a straight-back wood or metal chair with arms folded across chest.)

0 =Normal.
I = 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 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 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 armswing, 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 C: Table Spearman's (rho) correlation of disease duration, UPDRS II, and UPDRS III

	UPDRS II	UPDRS III
Disease duration*	0.031	0.052

*Years since onset of disease

APPENDIX D: Hoehn & Hahr Staging

Stage 0	No sign 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 unaided

APPENDIX E: Patient Data Screening Form- Eligibility Criteria

Inclusion criteria:

Patient must have a diagnosis of Idiopathic Parkinson's Disease (PD), given by Consultant Neurologist, fulfilling the criteria of the UK Parkinson's Disease Society Brain Bank.

Name _____ Date_____

DOB_____Age:_____

Year PD diagnosed_____ Number years since onset_____

PD Medications:

_____

Other Meds:_____

Exclusion criteria:

1. Does patient have a neurological condition in addition to PD? Yes / No

2. Has patient had neurosurgery including DBS? Yes / No

3. Has patient been a smoker in the past 5 years? Yes / No

4. Does patient have a history of:

    a. Laryngeal malignancy? Yes / No

    b. Surgery/Trauma to the Head/Neck region? Yes / No

    c. Radiotherapy and/or Chemotherapy to H/N? Yes / No

5. Does patient have a history of alcohol or chemical abuse? Yes / No

6. Does patient have a history of hyperthyroidism? Yes / No

7. Is patient taking any of the following medications?

    a. Mood stabilizers (lithium carbonate, solian, seroquel**)** Yes / No
    b. Bronchodilators (theophylline, Alupent) Yes / No
    c. Anticonvulsants (valproic acid, Depakote) Yes / No
    d. Immuno-suppresSants Yes / No

8. Does patient have speech/voice problems unrelated to PD? Yes / No

9. Does patient have a hearing problem that affects his/her ability to hear speech at a conversational level? Yes / No

10. Has patient had voice treatment including LSVT in the previous year? Yes / No

11. Does patient suffer from dyskinesias in the Off-Medication state that would preclude carrying out a fibreoptic examination of the vocal tract?

    Yes / No

12. Is patient immobile in an Off-Medication state to the extent that he/she would be unable to attend the SLT OPD clinic for study assessments?

    Yes / No

13. Is patient a non-english speaker?

    Yes / No

If patient satisfies the above criteria, i.e negative response to all questions, then proceed to carrying out the MMSE

MMSE score _____
(≤23/30 indicative of cognitive impairment)

14. Does patient have a cognitive impairment as assessed by the MMSE?

    Yes / No

If patient has a cognitive impairment (score of ≤23/30) then he/she is excluded from further involvement in the study

APPENDIX F: Consensus Auditory Perceptual Evaluation of Voice (CAPE-V) task protocol

Task 1: Sustained vowels

"The first task is to say the sound /a/. Hold it as steady as you can in your typical voice, until I ask you to stop" (The examiner gives a model of the task). The participant performs this task x 3 times for five seconds. "Next, say the sound /i/.Hold it as steady as you can, in your typical voice, until I ask you to stop". The participant performs this task x 3 times for five seconds.

Task 2: Sentences

The following sentences will be presented, one at a time to the participant on flash cards. The examiner says to the participant. "Please read the following sentences, as if you were speaking to somebody in real conversation". If the participant has difficulty reading, the examiner will ask the participant to repeat the sentence after the examiner.

a) The blue spot is on the key again

b) How hard did he hit him

c) We were away a year ago

d) We eat eggs every Easter

e) My mama makes lemon muffins

f) Peter will keep at the peak

Task 3: Spontaneous Speech

I want you to speak for 30 seconds on the topic of 'your early childhood, where you lived and the place you grew up'.

APPENDIX G: Flexible Endoscopic Vocal Tract Examination (VTE) protocol

Flexible Endoscopic Vocal Tract Examination protocol (VTE)		
Anatomic Site	**'Activating' condition**	**Instructions**
Soft Palate	At rest breathing	'I want you to breathe normally'
	Sustained /s/	'I want you to make a long S sound like this–SSSSSSSSSS for 5 seconds'
	Sustained /a/	'In a voice that feels comfortable in pitch & loudness, I want you to make a long /a/ sound like 'AHAHAHAHAHAH for 5 sec's'
Tongue Base	At rest breathing	'I want you to breathe normally'
	Sustained /s/	'I want you to make a long S sound like this–SSSSSSSSSS' for 5 seconds'
	Sustained /a/	'In a voice that feels comfortable in pitch & loudness, I want you to make a long /a/ sound like AHAHAHAHAHAH for 5 sec's'
Larynx/ Pharynx	At rest breathing	'I want you to breathe normally'
	Sustained /s/	'I want you to make a long S sound like this–SSSSSSSSSS for 5 seconds'
	Sustained /a/	'In a voice that feels comfortable in pitch & loudness, I want you to make a long /a/ sound like AHAHAHAHAHAH for 5 sec's'
	Sustained /i/	'In a voice that feels comfortable in pitch & loudness, I want you to make a long /i/ sound like eeeeee'

APPENDIX H: Voice Handicap Index (VHI)

Instructions: These are statements that many people have used to describe their voices and the effects of their voices on their lives. Check the response that indicates how frequently you have the same experience.

		Never	Almost Never	Sometimes	Almost Always	Always
F1	My voice makes it difficult for people to hear me					
P2	I run out of air when I talk					
F3	People have difficulty understanding me in a noisy room					
P4	The sound of my voice varies throughout the day					
F5	My family has difficulty hearing me when I call them throughout the house					
F6	I use the phone less often than I would like					
E7	I'm tense when talking with others because of my voice					
F8	I tend to avoid groups of people because of my voice					
E9	People seem irritated with my voice					
P10	People ask: "What's wrong with your voice?"					
F11	I speak with friends, neighbours or relatives less often because of my voice					
F12	People ask me to repeat myself when speaking face-to-face					
P13	My voice sounds creaky and dry					
P14	I feel as though I have to strain to produce voice					
E15	I find other people don't understand my voice problem					
F16	My voice difficulties restrict my personal and social life					
P17	The clarity of my voice is unpredictable					
P18	I try to change my voice to sound different					
F19	I feel left out of conversations because of my voice					
P20	I use a great deal of effort to speak					
P21	My voice is worse in the evening					
F22	My voice problem causes me to lose income					
E23	My voice problem upsets me					
E24	I am less out-going because of my voice problem					
E25	My voice problem makes me feel handicapped					
P26	My voice "gives out" on me in the middle of speaking					
E27	I feel annoyed when people ask me to repeat					
E28	I feel embarrassed when people ask me to repeat					
E29	My voice makes me feel incompetent					
E30	I'm ashamed of my voice problem					

APPENDIX I*: Voice and tremor parameters from the Motor Speech Profile (MSP) of Computerised Speech Laboratory (CSL)* [119]

1. *Fo (Fundamental Frequency) /Hz/*

   This is the average Fo of the client during the sustained /ah/

2. *To (Average Pitch Period)/ms/*

   This is the average value of all extracted using the pitch period values

3. *Fhi (Highest Fundamental Frequency)/Hz/*

   This is the greatest of all extracted period-to-period fundamental frequency values.

4. *Flo (Lowest Fundamental Frequency) /Hz/*

   This is the lowest of all extracted period-to-period fundamental frequency values

5. *STD (Standard deviation of Fo) /Hz/*

   This is the standard deviation of all extracted using the period-to-period fundamental frequency values.

6. *Rate of frequency tremor (Rftr) measured in Hz*

   The frequency of the most intensive low-frequency Fo-modulation component in the specified Fo-tremor analysis range

7. *Rate of amplitude tremor (Ratr) measured in Hz*

   The frequency of the most intensive low-frequency Fo-modulating component, in the specified amplitude-tremor analysis range

8. *Periodicity of the frequency tremor [Pftr (%)]*

   If rate of tremor is very consistent, then it is a periodic tremor

9. *Periodicity of the amplitude tremor [Patr(%])*

   If rate of tremor is very consistent, then it is a periodic tremor

10. *Magnitude of frequency tremor (Mftr), measured in %*

    The magnitude or extent of frequency tremor, can be from periodic or non-periodic modulation

11. *Magnitude of amplitude tremor (Matr), measured in %*

    The magnitude or the extent of amplitude tremor which can be from periodic or from non-periodic modulation

12. Coefficient of variations in the Fundamental Frequency (vFo), measured in %

vFo is the long-term variation in fundamental frequency (Fo) from any variations in the Fo of the voice. Fo variations include periodic modulations, non-periodic modulations, and rising or falling Fo across the recorded segment.

13. Coefficient of variations in the amplitude (vAm) measured in %

vAm is the long-term variation in amplitude from any variations in the amplitudes of the voice**.** Amplitude variations include periodic modulations, non-periodic modulations, and rising or falling amplitude.

APPENDIX J: Consensus Auditory Perceptual Evaluation of Voice (CAPE-V) Rating Protocol

Instructions to raters

This experiment is about rating voice quality and tremor features using the protocol of the Consensus Auditory Perception Evaluation of Voice, referred to as CAPE-V. I have made some minor modifications to the CAPE-V rating form for the purposes of this study.

There are 61 voice samples, each sample averages 1-1.5 minutes in length approximately. The only information that you will have is the gender which is stated on the rating sheet. All recordings follow the same format, you will hear the vowel /a/ sustained for 3-5 seconds 3 times, followed by a sustained vowel /i/, and then 6 short sentences from the CAPE-V.

Rating forms

In your folder you have 61 rating forms for the experiment and 4 extra forms for the practice session. You will note at the top of the sheet that there are two tasks: sustained vowels; sentence production (6 short sentences).

Parameters

There are 5 parameters to rate.

1. **Overall severity**: global, integrated impression of voice deviance
2. **Roughness:** perceived irregularity in the voicing source (voice is not smooth)
3. **Breathiness**: audible air escape in the voice
4. **Instability:** irregular fluctuations in pitch and/or loudness, also termed unsteadiness
5. **Tremor: (sustained /a/)** rhythmic or nearly rhythmic fluctuations in pitch and/or loudness of the voice

I will play each recording twice and then will repeat the sustained /a/ for you to focus specifically on the tremor aspects.

You should base your rating of the overall severity, roughness and breathiness on the sustained vowels and sentences, combining your ratings of each task to give one rating for each parameter. You will all hear the voice sample at the same time through the MAC and speakers, but will fill in the rating form independently, meaning without discussion between you.

How to rate a parameter

Each parameter is rated by placing a tick on the 100mm visual analogue scale. Your judgment may be assisted by referring to general regions indicated below each scale: “MI refers to “mildly deviant”; “MO” refers to moderately deviant; “SE” refers to severely deviant. The regions indicate

gradations in severity, rather than discrete points. You may notice that they are not placed in equal intervals because our perception of sound is usually not linear. You can place a tick mark at any location along the line.

Practice session

We will now have some practice with rating voices not related to the study and to help to familiarise you with the form. When rating parameters: overall severity, roughness, and breathiness, include the vowels and the sentences in your final rating. For the instability and tremor parameters, I want you to rate them on the basis of the sustained /a/ vowel.

After the 4 practice samples have been rated by you, we will discuss any issues that you might have before moving on to the study samples.

Study Samples

The next rating sheet should say ID 01 M. You will hear the sustained vowels, 6 sentences twice followed by the sustained /a/ once again to help with the tremor ratings. Remember that you rate the tremor feature only on the basis of a sustained /a/.

We will take a break after the first 20 samples.

APPENDIX K: Consensus Auditory-Perceptual Evaluation of Voice (CAPE- V) rating form (Modified Version)

Rater _____ **ID** _____

The following parameters of voice quality will be rated upon completion of the following tasks:

1. Sustained vowels, /a/ and /i/ for 3-5 seconds duration each
2. Sentence production:

a. The blue spot is on the key again.	a. We eat eggs every Easter.
b. How hard did he hit him?	b. My mama makes lemon muffins.
c. We were away a year ago	c. Peter will keep at the peak.

Legend: MI = Mildly Deviant; MO= Moderately Deviant;
SE= Severely Deviant

Overall Severity _____

MI MO SE

Roughness _____

MI MO SE

Breathiness _____

MI MO SE

Sustained /a/

Instability _____

MI MO SE

Tremor _____

MI MO SE

Tremulous Movement Rating Legend:
0= absent
1= mild/intermittent tremulous movement
2 = moderate tremulous movement
3= severe tremulous movement

APPENDIX L: Vocal Tract Tremor Rating Form
Reviewer Number _____

Video: **Start** _____ **Finish:** _____ Circle the number					Unable to rate (UR) Poor View (PV) (Place tick)
Palate					
Palate Breathe	0	1	2	3	
Palate 'SSSS'	0	1	2	3	
Palate 'AHAHAH'	0	1	2	3	
Base of Tongue (TB)					
TB Breathe	0	1	2	3	
TB 'SSSS'	0	1	2	3	
TB 'AHAHAH'	0	1	2	3	
Larynx (Lx)					
Lx Breathe (Arytenoid movement)	0	1	2	3	
Lx /S/ (Arytenoid movement)	0	1	2	3	
Lx 'AHAHAH' (global laryngeal tremor)	0	1	2	3	
Lx 'eeee' (vocal cords) (arytenoids)	0	1	2	3	

APPENDIX M: PD group-raw data for demographical, MMSE, HADS, & disease variables

Table. PD group: demographical, YSO, MMSE, HADS, H&Y, UPDRS II, III, mean tremor, PIGD score & phenotype

PD	Gender	Age	Age onset	YSO	MMSE	HADS Anxiety	HADS Depr	H&Y	UPDRS II	UPDRS III	Mean tremor	PIGD score	Phenotype
PD 1	M	69	62	7	29	2	6	2	14	25	0.25	0.80	PIGD
PD 2	M	55	46	9	29	0	3	2	15	31	0.88	0.80	Indet
PD 3	M	71	67	4	28	4	5	2	10	19	0.25	0.60	PIGD
PD 4	M	60	57	3	29	0	1	2	13	16	0.38	0.25	Tremor
PD 5	F	76	64	12	27	4	5	2	7	21	0.13	0.60	PIGD
PD 6	M	47	45	2	30	4	7	2	10	25	0.75	0.80	PIGD
PD 7	M	69	59	10	29	4	3	2	12	33	1.50	0.60	Tremor
PD 9	M	34	32	2	26	14	7	3	14	27	0.63	0.60	Indet
PD 10	F	58	55	3	29	8	18	1	7	11	0.50	0.60	PIGD
PD 11	F	60	55	5	29	1	1	1	16	19	0.00	0.60	PIGD
PD 12	M	71	67	4	30	7	6	2	9	16	0.38	0.40	PIGD
PD 13	M	54	52	2	29	11	6	2	11	21	1.25	0.20	Tremor
PD 14	M	60	55	5	29	6	2	2	7	28	1.13	0.20	Tremor
PD 15	M	54	46	8	29	7	5	3	17	38	0.50	1.00	PIGD
PD 16	F	76	65	11	28	3	2	2	12	18	0.13	1.20	PIGD
PD 17	M	73	66	7	30	1	1	1	9	17	0.63	0.20	Tremor
PD 18	F	49	44	5	30	7	0	1	7	8	0.75	0.20	Tremor
PD 20	M	44	41	3	30	7	3	2	8	24	0.25	0.40	PIGD
PD 21	F	57	56	1	30	0	3	1	4	13	0.25	0.40	PIGD
PD 22	M	76	70	6	29	0	2	3	13	31	0.50	0.80	PIGD
PD 23	M	70	67	3	29	5	6	3	9	37	0.25	0.80	PIGD
PD 24	F	62	56	6	30	3	1	1	7	13	0.25	0.40	PIGD
PD 25	M	51	48	3	28	3	2	3	10	33	0.75	0.80	PIGD
PD 26	M	67	66	1	29	2	4	3	8	41	0.25	0.80	PIGD
PD 27	M	65	63	2	30	4	4	2	8	24	0.50	0.80	PIGD
PD 28	F	63	52	11	29	6	4	2	4	22	0.00	0.80	PIGD
PD 29	M	71	66	5	28	3	4	2	7	26	1.13	0.60	Tremor
PD 30	M	67	65	2	29	8	3	3	19	34	0.50	1.80	PIGD
PD 31	M	58	51	7	27	9	5	3	14	41	0.88	0.60	PIGD
PD 32	M	55	47	8	28	1	0	3	5	38	0.25	1.40	PIGD

APPENDIX N: Control group-raw data for demographical, MMSE, HADS, and VHI data

*Table. Control group: demographical, MMSE, HADS and VHI scores (*missing data)*

	ID	Gender	Age	MMSE	HADS Anx	HADS Depr	VHI Total	VHI Funct	VHI Phys	VHI Emot
1	C 2	M	71	29	2	2	4	3	0	1
2	C 3	M	63	30	2	3	6	4	2	0
3	C 4	M	54	28	0	0	0	0	0	0
4	C 5	M	57	30	0	0	7	4	3	0
5	C 8	M	74	29	4	2	1	1	0	0
6	C 9	F	73	29	3	2	1	1	0	0
7	C 10	M	36	28	2	0	3	2	1	0
8	C 11	M	45	29	7	3	3	1	2	0
9	C 12	M	51	30	4	1	0	0	0	0
10	C 13	M	53	28	3	2	1	1	0	0
11	C 14	F	69	30	0	2	24	4	10	10
12	C 15	F	70	29	2	1	18	9	7	2
13	C 16	M	45	30	0	0	0	0	0	0
15	C 18	F	56	30	5	1	3	2	1	0
16	C 19	M	67	28	7	7	4	4	0	0
17	C 20	M	53	28	8	5	15	8	2	5
18	C 21	F	52	30	3	3	0	0	0	0
19	C 22	M	61	29	1	1	0	0	0	0
20	C 23	M	69	28	0	0	0	0	0	0
21	C 24	F	60	30	4	1	0	0	0	0
22	C 25	M	64	29	0	0	7	4	3	0
23	C 26	F	56	30	2	0	0	0	0	0
24	C 27	M	73	25	*	*	*	*	*	*
25	C28	F	56	29	1	0	0	0	0	0
26	C29	M	64	29	2	1	1	0	1	0
27	C30	M	67	28	2	1	1	1	0	0
28	C31	M	66	28	5	3	7	5	2	0
29	C32	M	58	29	2	0	2	0	2	0

APPENDIX O: PD group - Individual trial and mean trial values for acoustic measures from Motor Speech Profile (MSP)

	PD group	Fo Hz	STD F0	vFo%	vAm%	Rftr Hz	Pftr %	Mftr%	Ratr Hz	Patr %	Matr %
1	PD 1 M	118.119	1.228	1.039	6.465			0.562			1.579
		116.532	1.003	0.861	8.727			0.651	2.703	35.353	2.447
	PD 1 Mean	**117.326**	**1.116**	**0.950**	**7.596**			**0.607**	**2.703**	**35.353**	**2.013**
2	PD 2 M	119.270	1.441	1.209	8.579	1.835	24.591	0.682	4.545	33.085	3.982
		119.476	1.358	1.137	10.777	4.545	25.707	0.705	4.651	34.412	5.732
	PD 2 Mean	**119.373**	**1.400**	**1.173**	**9.678**	**3.190**	**25.149**	**0.694**	**4.598**	**33.749**	**4.857**
3	PD 3 M	131.267	2.606	1.985	19.46			0.818			1.772
		129.014	2.572	1.993	5.377	2.500	19.849	0.67			1.931
	PD 3 Mean	**130.141**	**2.589**	**1.989**	**12.419**	**2.500**	**19.849**	**0.744**			**1.852**
4	PD 4 M	120.021	0.77	0.641	8.391			0.337			1.754
		120.493	0.878	0.729	5.103			0.302			1.427
		120.853	0.759	0.628	5.968			0.388			2.196
	PD 4 Mean	**120.456**	**0.802**	**0.666**	**6.487**			**0.342**			**1.792**
5	PD 5 F	147.224	52.148	35.421	17.479	2.247	12.706	6.567	10.526	34.977	9.906
		111.739	2.399	2.147	15.064			0.977	9.524	46.928	8.151
		243.701	15.593	6.398	21.954	4.255	20.897	2.337			11.154
	PD 5 Mean	**167.555**	**23.380**	**14.655**	**18.166**	**3.251**	**16.802**	**3.294**	**10.025**	**40.953**	**9.737**
6	PD 6 M	201.832	1.222	0.606	8.849			0.249			1.621
		207.914	4.628	2.226	10.237			0.333			1.378
		210.148	0.709	0.337	4.837			0.252			1.024
	PD 6 Mean	**206.631**	**2.186**	**1.056**	**7.974**			**0.278**			**1.341**
7	PD 7 M	167.278	2.263	1.353	5.424			0.503			1.223
		163.860	1.365	0.834	6.129			0.657			1.658
		163.206	1.200	0.735	9.226			0.502			1.629
	PD 7 Mean	**164.781**	**1.609**	**0.974**	**6.926**			**0.554**			**1.503**
8	PD 9 M	120.649	0.735	0.609	9.725			0.400			3.405
		121.27	0.514	0.424	9.027			0.315	5.128	53.762	3.852
		121.356	0.436	0.36	5.537			0.245	2.469	37.933	2.233
	PD 9 Mean	**121.092**	**0.562**	**0.464**	**8.096**			**0.320**	**3.799**	**45.848**	**3.163**

	PD group	Fo Hz	STD F0	vFo%	vAm%	Rftr Hz	Pftr %	Mftr%	Ratr Hz	Patr %	Matr %
9	PD 10 F	175.117	1.207	0.689	7.513			0.445			1.807
		179.093	1.464	0.817	6.090			0.408			1.326
		196.872	1.070	0.543	6.730			0.402			1.291
	PD 10 Mean	**183.694**	**1.247**	**0.683**	**6.778**			**0.418**			**1.475**
10	PD 11 F	175.225	1.229	0.701	5.410			0.343			0.594
		180.314	1.690	0.937	8.283			0.294			0.882
		188.358	1.779	0.945	2.842			0.332			0.815
	PD 11 Mean	**181.299**	**1.566**	**0.861**	**5.512**			**0.323**			**0.764**
11	PD 12 M	121.048	0.878	0.725	3.198			0.334			1.059
		122.223	0.944	0.772	3.816			0.353			1.346
		122.556	0.700	0.571	3.186			0.242			1.108
	PD 12 Mean	**121.942**	**0.841**	**0.689**	**3.400**			**0.310**			**1.171**
12	PD 13 M	159.071	1.229	0.773	6.387			0.492			1.116
		166.939	1.292	0.774	4.699			0.498			1.168
		162.273	1.421	0.876	8.495			0.550			1.556
	PD 13 Mean	**162.761**	**1.314**	**0.808**	**6.527**			**0.513**			**1.280**
13	PD 14 M	148.313	2.087	1.407	4.800			0.567	4.651	47.087	3.708
		144.405	2.156	1.493	7.446			0.872	5.000	28.773	5.441
		142.271	1.584	1.114	5.991			0.511	4.878	25.315	2.894
	PD 14 Mean	**144.996**	**1.942**	**1.338**	**6.079**			**0.650**	**4.843**	**33.725**	**4.014**
14	PD 15 M	136.536	3.073	2.251	6.402			0.869	2.564	31.408	2.716
		128.554	2.066	1.607	3.550	2.174	30.515	0.810	2.500	30.099	1.693
		130.362	2.387	1.831	5.623	3.226	22.198	0.830	4.545	59.996	1.733
	PD 15 Mean	**131.817**	**2.509**	**1.896**	**5.192**	**2.700**	**26.357**	**0.836**	**3.203**	**40.501**	**2.047**

	PD group	Fo Hz	STD F0	vFo%	vAm%	Rftr Hz	Pftr %	Mftr%	Ratr Hz	Patr %	Matr %
15	PD 16 F	183.137	3.030	1.655	10.020	2.632	12.545	0.825			5.007
		177.395	1.854	1.045	13.934	2.105	26.466	0.670	10.000	53.802	5.950
		196.187	2.644	1.348	10.732			0.599	10.000	57.811	4.231
	PD 16 Mean	**185.573**	**2.509**	**1.349**	**11.562**	**2.3685**	**19.5055**	**0.698**	**10.000**	**55.8065**	**5.063**
16	PD 17 M	123.279	1.629	1.321	5.634			0.551			1.617
		123.028	1.463	1.189	3.917			0.588			1.479
		124.878	2.008	1.608	5.320	6.667	52.942	0.713			1.509
	PD 17 Mean	**123.728**	**1.700**	**1.373**	**4.957**	**6.667**	**52.942**	**0.617**			**1.535**
17	PD 18 F	184.317	2.218	1.203	3.812	2.105	16.502	0.682	5.882	34.067	1.472
		179.641	4.179	2.327	4.603	2.597	35.796	1.710			2.016
		180.412	2.463	1.365	10.694			0.677			1.723
	PD 18 Mean	**181.457**	**2.953**	**1.632**	**6.370**	**2.351**	**26.149**	**1.023**	**5.882**	**34.067**	**1.737**
18	PD 20 M	123.278	0.753	0.611	5.306			0.399			2.099
		126.368	1.649	1.305	6.820	3.636	51.334	0.603	5.128	53.194	3.245
	PD 20 Mean	**124.823**	**1.201**	**0.958**	**6.063**	**3.636**	**51.334**	**0.501**	**5.128**	**53.194**	**2.672**
19	PD 21 F	152.269	1.054	0.692	3.999			0.355	4.348	34.659	1.505
		159.335	1.277	0.801	4.880			0.447			1.186
		164.057	1.084	0.661	4.469			0.288			0.934
	PD 21 Mean	**158.554**	**1.138**	**0.718**	**4.449**			**0.363**	**4.348**	**34.659**	**1.208**
20	PD 22 M	143.561	1.493	1.040	4.756	4.167	28.439	0.764	3.333	55.835	2.207
		145.265	1.583	1.090	10.664	8.696	17.153	0.652			1.858
	PD 22 Mean	**144.413**	**1.538**	**1.065**	**7.710**	**6.432**	**22.796**	**0.708**	**3.333**	**55.835**	**2.033**
21	PD 23 M	149.354	1.739	1.164	6.892			0.442			0.779
		151.047	1.332	0.882	9.478			0.337			0.934
		156.130	1.261	0.808	6.090			0.316			1.399
	PD 23 Mean	**152.177**	**1.444**	**0.951**	**7.487**			**0.365**			**1.037**
22	PD 24 F	178.042	1.974	1.106	8.583			0.678			2.374
		181.025	3.449	1.906	5.337			0.700			1.664
		196.972	2.007	1.019	4.761			0.553			1.333
	PD 24 Mean	**185.346**	**2.477**	**1.344**	**6.227**			**0.644**			**1.790**

	PD group	Fo Hz	STD F0	vFo%	vAm%	Rftr Hz	Pftr %	Mftr%	Ratr Hz	Patr %	Matr %
23	PD 25M	107.077	2.190	2.045	2.045	10.000	71.015	0.702			3.485
		104.533	1.956	1.871	7.274	10.526	65.155	0.690	6.667	52.413	3.290
		105.427	1.623	1.540	6.589			0.669			2.882
	PD 25 Mean	**105.679**	**1.923**	**1.819**	**5.303**	**10.263**	**68.085**	**0.687**	**6.667**	**52.413**	**3.219**
24	PD 26 M	120.293	1.561	1.297	7.112			0.580			1.817
		120.057	1.489	1.240	8.008	1.980	23.928	0.621			1.455
		119.023	1.000	0.840	7.511			0.362	2.532	55.132	1.818
	PD 26 Mean	**119.791**	**1.350**	**1.126**	**7.544**	**1.980**	**23.928**	**0.521**	**2.532**	**55.132**	**1.697**
25	PD 27 M	122.819	1.394	1.135	6.959			0.701			2.061
		120.786	2.600	2.152	9.315	4.348	14.258	1.188			2.249
		121.780	2.247	1.845	13.401	3.226	41.162	0.905			2.825
	PD 27 Mean	**121.795**	**2.080**	**1.711**	**9.892**	**3.787**	**27.710**	**0.931**			**2.378**
26	PD28 F	163.818	1.894	1.156	19.627			0.716			1.716
		166.269	2.091	1.258	16.540			0.590			2.602
	PD 28 Mean	**165.044**	**1.993**	**1.207**	**18.084**			**0.653**			**2.159**
27	PD 29 M	86.749	0.716	0.825	8.299			0.466	4.167	50.186	4.298
		87.579	0.700	0.799	7.768			0.451	3.704	60.765	4.554
		87.137	0.842	0.966	6.624			0.364			2.959
	PD 29 Mean	**87.155**	**0.753**	**0.863**	**7.564**			**0.427**	**3.936**	**55.476**	**3.937**
28	PD 30 M	121.729	1.269	1.042	6.875	8.000	12.261	0.670	2.439	26.765	2.388
		130.379	1.423	1.091	6.159			0.542			1.442
		129.636	1.049	0.809	4.179			0.583	4.762	35.831	2.127
	PD 30 Mean	**127.248**	**1.247**	**0.981**	**5.738**	**8.000**	**12.261**	**0.598**	**3.601**	**31.298**	**1.986**
29	PD 31 M	118.983	1.301	1.094	5.825			0.697	4.545	61.955	1.937
		118.883	0.965	0.812	6.345			0.672	4.545	64.466	2.730
	PD 31 Mean	**118.933**	**1.133**	**0.953**	**6.085**			**0.685**	**4.545**	**63.211**	**2.334**
30	PD 32 M	120.979	1.474	1.219	8.837			0.586			2.691
		121.515	1.099	0.905	9.156			0.491			3.219
		120.954	1.369	1.132	11.578			0.516			3.387
	PD 32 mean	**121.149**	**1.314**	**1.085**	**9.857**			**0.531**			**3.099**

APPENDIX P: Control group: Individual trial and mean trial values for acoustic measures from Motor Speech Profile (MSP)

	CONTROLS	Fo Hz	STD F0	vFo%	vAm%	Rftr Hz	Pftr %	Mftr%	Ratr Hz	Patr %	Matr %
1	C02 M	102.530	1.168	1.139	5.886			0.493			2.107
		115.246	1.221	1.060	10.061			0.393			1.568
		115.410	1.208	1.046	11.024			0.545			1.809
	C 02 Mean	**111.062**	**1.199**	**1.082**	**8.990**			**0.477**			**1.828**
2	C03 M	97.151	0.852	0.877	7.360			0.486	2.941	53.594	2.084
		97.051	0.939	0.967	4.691			0.487	2.353	24.436	2.128
	C 03 Mean	**97.101**	**0.896**	**0.922**	**6.026**			**0.487**	**2.647**	**39.015**	**2.106**
3	C04 M	118.470	1.024	0.864	4.527			0.336			1.977
		121.032	1.047	0.865	5.028			0.432			2.699
		123.363	1.339	1.086	8.767			0.409	2.353	38.036	2.493
	C04 Mean	**120.955**	**1.137**	**0.938**	**6.107**			**0.392**	**2.353**	**38.036**	**2.390**
4	C05 M	131.116	1.506	1.149	9.846			0.588	2.410	46.556	2.470
		125.910	1.657	1.316	11.034	3.030	22.329	0.840	2.899	34.025	5.570
		127.513	1.666	1.307	10.367	2.041	17.672	0.646	2.439	17.388	3.708
	C 05 Mean	**128.180**	**1.610**	**1.257**	**10.416**	**2.536**	**20.001**	**0.691**	**2.583**	**32.656**	**3.916**
5	C08 M	122.753	1.013	0.825	9.572			0.438			2.112
		123.232	0.947	0.769	8.548			0.464			1.599
		123.271	2.048	1.661	9.743			0.774			2.520
	C08 Mean	**123.085**	**1.336**	**1.085**	**9.288**			**0.559**			**2.077**
6	C 09 F	186.100	3.097	1.664	12.285			0.589			3.163
		188.788	6.652	3.523	13.122			1.159			6.860
		89.706	2.485	2.770	13.563	2.817	25.085	0.931	2.899	39.321	4.671
	C09 Mean	**154.865**	**4.078**	**2.652**	**12.990**	**2.817**	**25.085**	**0.893**	**2.899**	**39.321**	**4.898**
7	C10 M	118.964	0.721	0.606	5.597			0.249			1.489
		119.145	0.674	0.566	5.392			0.208	2.247	32.911	1.576
		118.591	0.781	0.658	7.440			0.208			1.580
	C 10 Mean	**118.900**	**0.725**	**0.610**	**6.143**			**0.222**	**2.247**	**32.911**	**1.548**
8	C11 M	107.664	0.508	0.472	5.764			0.309			1.462
		97.944	0.628	0.641	3.806			0.399			1.186
		97.651	0.699	0.716	4.571			0.492			1.314
	C11 Mean	**101.086**	**0.612**	**0.610**	**4.714**			**0.400**			**1.321**

	CONTROLS	Fo Hz	STD F0	vFo%	vAm%	Rftr Hz	Pftr %	Mftr%	Ratr Hz	Patr %	Matr %
9	C12 M	120.236	1.753	1.458	10.023	2.817	28.726	0.786			1.236
		121.484	2.536	2.088	7.498	2.703	36.871	1.146	3.030	60.001	2.435
		123.241	2.121	1.721	8.254	3.226	11.078	0.696			1.838
	C 12 Mean	**121.654**	**2.137**	**1.756**	**8.592**	**2.915**	**25.558**	**0.876**	**3.030**	**60.001**	**1.836**
10	C13 M	145.600	0.864	0.593	7.705			0.298			1.064
		145.517	1.069	0.735	11.849			0.420			1.591
		150.408	1.326	0.881	8.092			0.383			1.207
	C 13 Mean	**147.175**	**1.086**	**0.736**	**9.215**			**0.367**			**1.287**
11	C14 F	166.929	2.174	1.303	7.693			0.488			1.870
		160.494	1.567	0.976	4.218			0.646	2.02	11.875	1.827
		164.404	1.649	1.003	6.965	2.632	16.792	0.711			1.203
	C 14 Mean	**163.942**	**1.797**	**1.094**	**6.292**	**2.632**	**16.792**	**0.615**	**2.02**	**11.875**	**1.633**
12	C 15 F	214.897	4.742	2.206	17.886	2.703	41.490	0.990			2.755
		222.563	2.295	1.031	20.936			0.574			1.746
	C 15 Mean	**218.730**	**3.519**	**1.619**	**19.411**	**2.703**	**41.490**	**0.782**			**2.251**
13	C16 M	120.306	0.675	0.561	3.382			0.331	6.667	35.799	1.644
		118.972	0.769	0.647	6.019			0.331			1.340
		121.050	1.335	1.103	10.131			0.465	2.273	33.029	2.175
	C 16 Mean	**120.109**	**0.926**	**0.770**	**6.511**			**0.376**	**4.470**	**34.414**	**1.720**
14	C 18 F	242.441	1.584	0.653	15.506			0.322			1.614
		250.331	1.803	0.720	7.795			0.526			1.959
		237.754	1.441	0.606	9.490			0.367			1.316
	C 18 Mean	**243.509**	**1.609**	**0.660**	**10.930**			**0.405**			**1.630**
15	C19 M	119.782	0.933	0.779	11.529			0.499			1.864
	C 19 Mean	**119.782**	**0.933**	**0.779**	**11.529**			**0.499**			**1.864**
16	C20 M	122.042	0.916	0.751	9.214			0.295			1.889
		121.539	0.710	0.584	11.756			0.337			2.915
		124.210	0.595	0.479	7.528			0.272			1.621
	C 20 Mean	**122.597**	**0.740**	**0.605**	**9.499**			**0.301**			**2.142**
17	C21 F	177.105	1.978	1.117	4.575	2.041	10.710	0.772			1.431
		170.734	1.434	0.840	3.749			0.539			1.390
		175.608	1.990	1.133	5.809	4.762	32.212	0.698	1.852	19.821	1.926
	C21 Mean	**174.482**	**1.801**	**1.030**	**4.711**	**3.402**	**21.461**	**0.670**	**1.852**	**19.821**	**1.582**

	CONTROLS	Fo Hz	STD F0	vFo%	vAm%	Rftr Hz	Pftr %	Mftr%	Ratr Hz	Patr %	Matr %
18	C22 M	117.766	0.960	0.815	7.797			0.450			1.535
		117.452	0.935	0.796	10.495			0.358			1.451
	C 22 Mean	**117.609**	**0.948**	**0.806**	**9.146**			**0.404**			**1.493**
19	C23 M	116.312	0.898	0.772	4.649			0.516			1.997
		117.478	0.947	0.806	8.272			0.306			1.970
		116.277	0.613	0.527	4.758			0.318	3.077	19.338	1.692
	C23 Mean	**116.689**	**0.819**	**0.702**	**5.893**			**0.380**	**3.077**	**19.338**	**1.886**
20	C 24 F	152.288	0.555	0.364	8.893			0.185			1.071
		161.130	1.372	0.851	9.444			0.362	2.667	53.751	1.537
		163.467	1.302	0.796	4.573			0.311			1.083
	C 24 Mean	**158.962**	**1.076**	**0.670**	**7.637**			**0.286**	**2.667**	**53.751**	**1.230**
21	C25 M	102.977	1.617	1.570	6.292			0.559	2.941	58.639	1.965
		101.195	1.227	1.212	4.331	11.111	40.324	0.686			1.684
		106.139	1.397	1.316	4.214	2.273	26.603	0.692			1.984
	C 25 Mean	**103.437**	**1.414**	**1.366**	**4.946**	**6.692**	**33.464**	**0.646**	**2.941**	**58.639**	**1.878**
22	C 26 F	149.904	0.977	0.652	5.815			0.240	1.942	26.011	2.137
		149.494	0.915	0.612	6.813			0.261	3.390	34.009	2.627
		150.002	3.119	2.080	10.392			0.481			2.429
	C 26 Mean	**149.800**	**1.670**	**1.115**	**7.673**			**0.327**	**2.666**	**30.010**	**2.398**
23	CM 27	189.887	3.994	2.103	8.166			0.912			2.352
		187.002	4.188	2.240	9.727			0.985	3.774	43.694	2.441
		193.440	3.033	1.568	6.661	2.273	18.942	0.724			1.693
	C 27 Mean	**190.110**	**3.738**	**1.970**	**8.185**	**2.273**	**18.942**	**0.874**	**3.774**		**2.162**
24	C 28 F	196.541	0.839	0.427	5.056			0.174			1.224
		201.394	0.903	0.448	7.611			0.188			1.051
		211.985	1.283	0.605	4.760			0.270			1.184
	C 28 Mean	**203.307**	**1.008**	**0.493**	**5.809**			**0.211**			**1.153**
25	CM 29	122.599	1.206	0.983	8.648			0.585			1.486
		121.295	1.052	0.867	5.014			0.439			2.141
		119.588	1.042	0.872	5.702			0.607	3.636	48.716	2.852
	C 29 Mean	**121.161**	**1.100**	**0.907**	**6.455**			**0.544**	**3.636**	**48.716**	**2.160**

	CONTROLS	Fo Hz	STD F0	vFo%	vAm%	Rftr Hz	Pftr %	Mftr%	Ratr Hz	Patr %	Matr %
26	CM 30	120.608	2.126	1.763	9.285	2.299	14.185	0.741			3.388
		121.342	1.566	1.291	9.444			0.394	2.151	38.449	3.133
		119.616	1.743	1.457	7.444			0.596	2.000	39.230	2.248
	C 30 Mean	**120.522**	**1.812**	**1.504**	**8.724**	**2.299**	**14.185**	**0.577**	**2.076**	**38.840**	**2.923**
27	CM 31	117.371	1.128	0.961	6.898			0.414	4.545	55.021	1.713
		117.725	0.892	0.757	8.613			0.494	2.500	45.133	2.150
		118.015	1.441	1.221	5.588	2.105	23.771	0.763	4.651	31.537	2.283
	C 31 Mean	**117.704**	**1.154**	**0.980**	**7.033**	**2.105**	**23.771**	**0.557**	**3.899**	**43.897**	**2.049**
28	CM 32	120.500	1.035	0.859	6.652			0.484	2.353	52.253	2.318
		119.592	0.899	0.751	9.378			0.372	2.778	37.470	2.518
		118.530	1.287	1.086	9.150			0.539			2.100
	C 32 Mean	**119.541**	**1.074**	**0.899**	**8.393**			**0.465**	**2.566**	**44.862**	**2.312**

APPENDIX Q: Intraclass correlation coefficient (ICC) & 95% confidence intervals (CI) for inter-rater reliability for auditory perceived instability and tremor (CAPE-V), for PD & control group

	Instability		Tremor	
	PD group *(n=26)*	Control *(n=27)*	PD group *(n=27)*	Control *(n=27)*
ICC	0.780	0.717	0.306	0.481
95% CI	0.628-0.885	0.541-0.847	0.065-0.560	0.249-0.692

ICC: two way mixed-effects model (consistency definition) based on a single rater

APPENDIX R: Intraclass correlation coefficient (ICC) and confidence intervals (CI's) for intra-rater reliability for auditory perceived tremor and instability (PD and controls combined)

	Instability (n=6)		**Tremor (n=6)**	
	Intraclass correlation coefficient *	95% confidence interval	Intraclass correlation coefficient *	95% confidence interval
Rater A	0.439	-0.472- 0.897	0.031	-0.741- 0.768
Rater B	-0.017	-0.762- 0.747	0.652	-0.202- 0.943
Rater C	0.846	0.253- 0.977	0.607	-0.272- 0.934

ICC: two way mixed-effects model (consistency definition) based on a single rater

APPENDIX S: Auditory perceived instability (CAPE-V), individual and mean ratings (Raters A, B, C) for PD group

		Instability Ratings			
n	PD group	Rater A	Rater B	Rater C	Mean
1	01	49	39	60	49
2	02	34	14	49	32
	03	*	*	*	*
	04	*	*	*	*
3	05	63	57	68	63
4	06	19	13	13	15
5	09	13	3	20	12
6	10	9	2	2	4
7	11	31	13	51	32
8	12	13	6	25	15
9	13	38	5	17	20
10	15	28	11	34	24
11	16	31	24	61	39
12	17	26	19	35	27
13	18	41	25	44	37
14	20	14	7	28	16
15	21	3	12	10	8
16	22	11	5	31	16
17	23	12	24	31	22
18	24	34	37	46	39
21	25	18	11	44	24
22	26	29	20	38	29
23	27	19	11	13	14
24	28	54	54	60	56
25	29	22	12	37	24
26	30	28	13	46	29
27	31	11	3	30	15
28	32	51	38	55	48

*Missing data

APPENDIX S*:* Auditory perceived instability (CAPE-V), individual and mean ratings (Raters A,B,C) for Control group

		Instability Ratings			
n	Controls	Rater A	Rater B	Rater C	Mean
1	02	40	36	43	40
2	03	20	14	32	22
3	04	25	25	38	29
4	05	30	12	50	31
5	08	39	27	37	34
6	09	37	37	32	35
7	10	22	4	10	12
8	11	12	12	24	16
9	12	23	13	33	23
10	13	15	5	17	12
11	14	24	37	37	33
12	15	15	15	14	15
13	16	43	24	37	35
14	18	10	5	2	6
15	19	23	12	28	21
16	20	14	14	22	17
17	21	10	4	27	14
18	23	9	11	21	14
19	24	0	4	11	5
20	25	12	28	47	29
21	26	35	25	39	33
22	27	41	56	70	56
23	28	20	4	19	14
24	29	13	4	5	7
25	30	40	39	57	45
26	31	16	11	47	25
27	32	40	29	37	35

APPENDIX T: Auditory perceived tremor (CAPE-V), individual and mean ratings (Raters A,B,C) for PD group

Auditory perceived tremor ratings (CAPE-V) for PD group					
n	PD group	Rater A	Rater B	Rater C	Mean
1	PD01	5	11	58	25
2	PD02	4	3	43	17
3	PD03	*	*	*	
4	PD04	*	*	*	
5	PD05	61	38	66	55
6	PD06	4	13	0	6
7	PD09	10	4	0	5
8	PD10	7	3	8	6
9	PD11	34	4	3	14
10	PD12	14	4	25	14
11	PD13	39	5	19	21
12	PD15	28	11	34	24
13	PD16	34	11	7	17
14	PD17	26	10	35	24
15	PD18	41	12	43	32
16	PD20	12	5	29	15
17	PD21	2	5	0	2
18	PD22	12	4	0	5
19	PD23	10	1	0	4
20	PD24	35	12	2	16
21	PD25	18	10	43	24
22	PD26	29	6	39	25
23	PD27	8	11	21	13
24	PD28	0	12	56	23
25	PD29	18	7	23	16
26	PD30	26	13	45	28
27	PD31	11	4	30	15
28	PD32	48	4	55	36

APPENDIX U: Auditory perceived tremor (CAPE-V) individual and mean ratings (raters A,B,C), for control group

Auditory perceived tremor ratings (CAPE-V) for control group					
n	Controls	Rater A	Rater B	Rater C	Mean
1	02	40	14	40	31
2	03	21	14	31	22
3	04	7	13	38	19
4	05	29	12	50	30
5	08	55	4	26	28
6	09	24	13	24	20
7	10	16	3	0	6
8	11	11	3	24	13
9	12	13	5	0	6
10	13	13	5	0	6
11	14	18	7	14	13
12	15	15	5	0	7
13	16	44	9	37	30
14	18	9	3	1	4
15	19	14	12	28	18
16	20	13	9	0	7
17	21	9	3	23	12
18	23	9	3	20	11
19	24	0	4	9	4
20	25	11	8	46	22
21	26	35	4	25	21
22	27	40	35	70	48
23	28	20	5	0	8
24	29	10	4	0	5
25	30	39	40	52	44
26	31	16	12	46	25
27	32	42	9	32	28

APPENDIX V: Intraclass correlation coefficient (ICC) (single measures) and 95% confidence intervals (CI) for inter-rater reliability (four raters), for tremor severity in ten vocal tract conditions, for PD and control group

	ICC	95% CI	ICC	95% CI
	PD *n*=27		Control *n*=22	
Palate breathe	0.754	0.614-0.864	0.315	0.107-0.564
	n=29		*n=24*	
Palate /s/	0.631	0.462-0.780	0.491	0.287-0.696
	n =25		*n=23*	
Palate /a/	0.686	0.518-0.827	0.577	0.377-0.762
	n=28		*n=22*	
Tongue breathe	0.672	0.509-0.810	0.461	0.246-0.683
	n=28		*n=23*	
Tongue /s/	0.524	0.338-0.707	0.211	0.023-0.460
	n=27		*n=22*	
Tongue /a/	0.574	0.390-0.746	0.071	-0.87-0.315
	n=28		*n=22*	
Larynx breathe	0.676	0.515-0.813	0.260	0.060-0.514
	n=27		*n=23*	
Larynx /s/	0.758	0.619-0.866	0.360	0.153-0.597
	n=30		*n=25*	
Larynx /a/	0.454	0.270-0.646	0.155	-0.14-0.391
	n=30		*n=24*	
Larynx /i/	0.225	0.056-0.439	0.244	0.054-0.487

APPENDIX W: Intra-rater agreement for vocal tract tremor ratings (scale 0-3) [(exact, and within 1 point agreement (%)], for PD and control group

	Intra-rater agreement %			
	PD group (n=4)		Control group(n=2)	
	Exact agreement	Within 1 point	Exact agreement	Within 1 point
Palate breathe	75	100	38	100
Palate /s/	63	100	50	100
Palate /a/	88	100	50	87
Tongue breathe	94	100	75	100
Tongue /s/	43	93	50	100
Tongue /a/	56	100	50	100
Larynx breathe	69	100	75	100
Larynx /s/	67	100	75	100
Larynx /a/	75	100	63	100
Larynx /i/	62	100	75	100

APPENDIX X: Intra-rater % agreement (4 raters) for vocal tract tremor ratings for presence & absence of tremor, for PD and control group

	% Agreement	
	Tremor present/absent PD (n=4) %	Tremor present/absent Control (n=2)
Palate breathe	87.5	50
Palate /s/	100	62.5
Palate /a/	100	87.5
T/B Breathe	93.75	75
T/B /s/	75	50
T/B /a/	75	50
Larynx Breathe	87.5	75
Larynx /s/	93.75	75
Larynx /a/	100	62.5
Larynx /i/	62.5	75

APPENDIX Y: Intraclass Correlation Coefficient (ICC) values for inter-rater reliability ratings (4 raters) of speech intelligibility, for PD and control group

	Speech IntelligibilityTest	
	PD (n=21)	Control (In=24)
Intra class correlation coefficient *	0.523	0.539
Confidence Intervals	0.307-0.733	0.338-0.731

*ICC two way mixed-effects model using a consistency definition for single measures

APPENDIX Z: Intraclass Correlation Coefficient (ICC) values for intra-rater reliability ratings (4 raters) of speech intelligibility, for PD and control group

	Intraclass correlation coefficient	95% confidence interval	
		Lower limit	Uppper limit
Judge A	*	*	*
Judge B	0.968	0.729	0.997
Judge C	0.599	-0.589	0.968
Judge D	0.968	0.730	0.997
Judge B,C,D	0.784	0.428	0.982

ICC: two-way random effects model, consistency definition

* Judge A not included for reliability since there was data missing for 3 out of 5 participants (PD1, PD 11, PD22, C2, C26)

APPENDIX AA: Intraclass correlation coefficients (ICC's) and confidence intervals (CI's) for inter-rater reliability of dysphonia severity rating (CAPE-V), for PD and control group

	CAPE-V Dysphonia Severity	
	PD group (n=26)	Control group (n=27)
ICC	0.564	0.726
CI	0.339-0.753	0.554-0.852

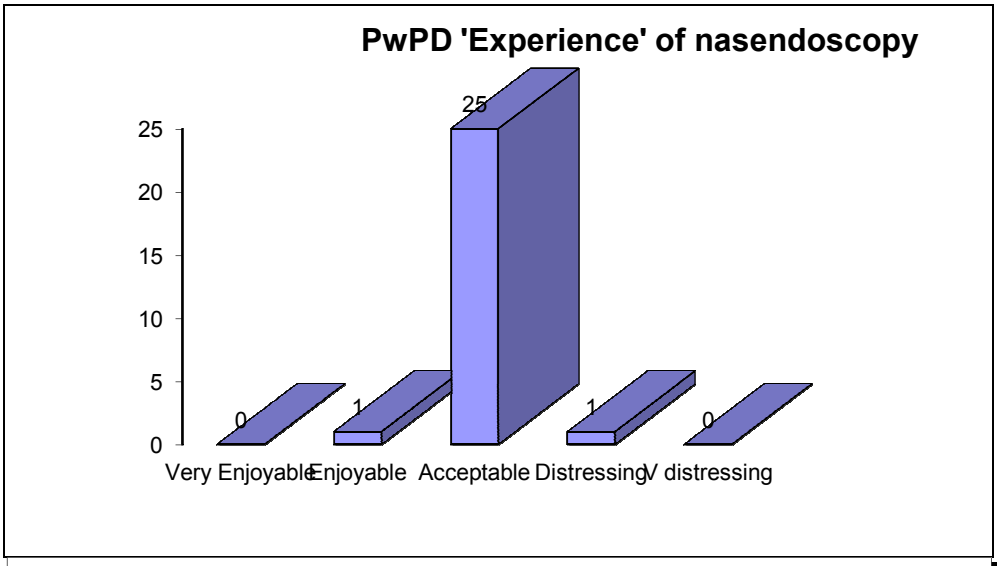
Two-way mixed effects model (single measures) using consistency definition

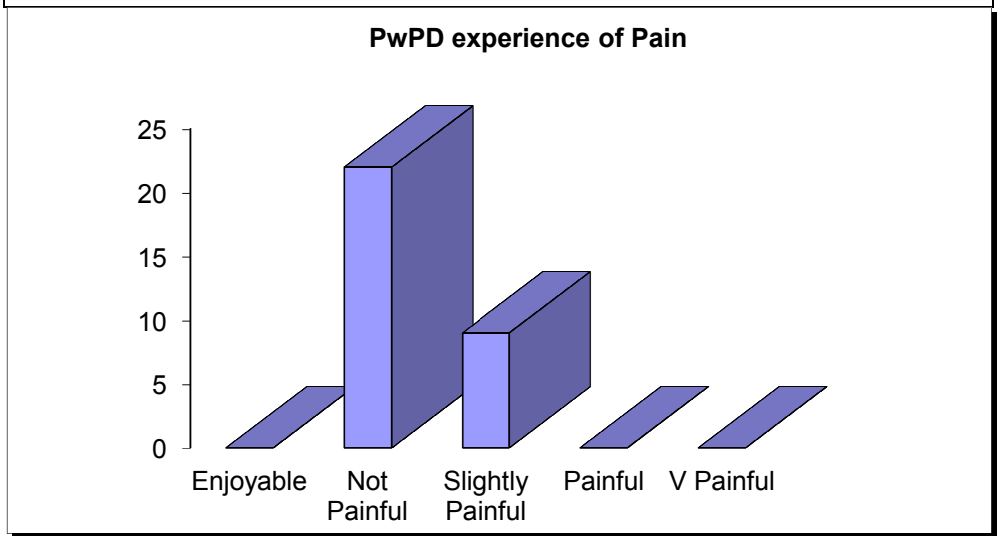
APPENDIX BB: Intraclass correlation coefficients (ICC's) and confidence intervals (CI's) for intra-rater reliability of dysphonia severity rating (CAPE-V), for PD and control group

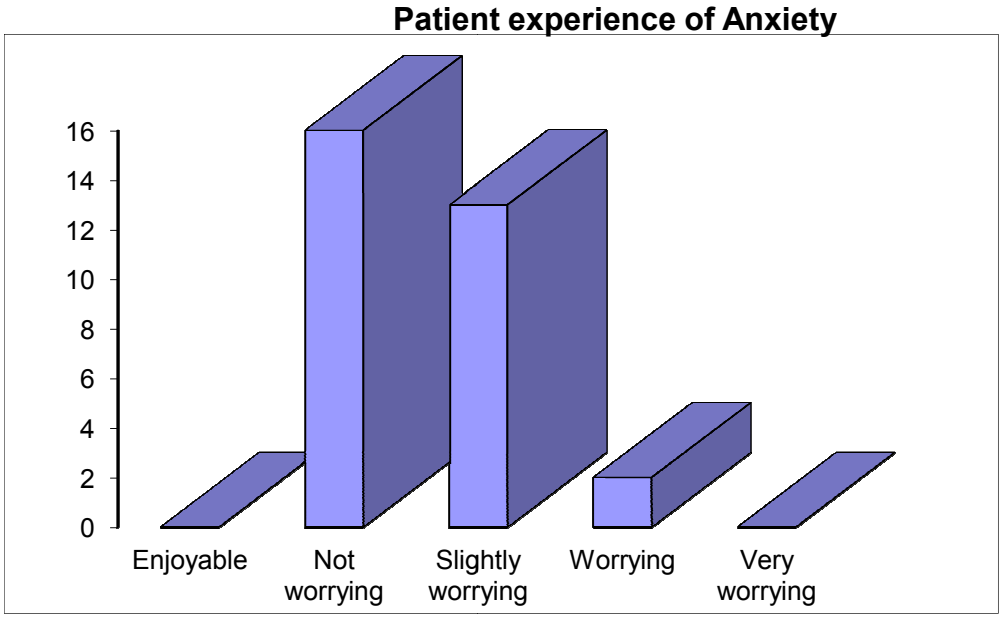
	Severity of Dysphonia (CAPE-V) (n=6)	
	Intraclass correlation coefficient *	95% confidence interval
		Lower limit
Rater A	0.418	-0.491-0.891
Rater B	0.777	0.056-0.966
Rater C	0.735	-0.043-0.958

Two-way mixed effects model (single measures) using consistency definition

APPENDIX CC: PwPD self-report of experience, pain and anxiety during nasendoscopy







Glossary

Accelerometry:
Means of measuring the motion of body segments through the use of small devices called accelerometers, which respond to the frequency and amplitude of movement.

Acoustic analysis:
Acoustic analysis is the process of extracting and quantifying precisely defined and salient features of the speech signal (e.g. intensity, duration, frequency) through objective instrumental means as opposed to subjective perceptual means.

Amplitude:
A property referring to the height of a (sound) wave. The bigger the wave, the more intense the sound pressure level, and the louder we perceive the signal to be.

Auditory-perceptual (perceptual):
Relates to rating sound with the naked ear (as opposed to using instrumentation)

Basal Ganglia (BG):
A set of nuclei situated subcortically in the brain and which act as a concerted unit. The BG comprises the striatum (caudate, putamen, nucleus accumbens), the sub-thalamic nucleus (STN), globus pallidus (internal and external segments, ventral pallidum), and substantia nigra (pars compacta, pars reticulate)

Bowing:
Bowing of the vocal cords refers to an effect of the physical changes associated with atrophy of the vocal cords which leads to loss of elasticity resulting in a bowed shape as opposed to parallel closure/vibratory pattern to the vocal cords.

Co-efficient of variation (COV):
Here, COV is a perturbation measure (frequency and amplitude), referred to as long-term (as opposed to cycle to cycle) and relies on a calculation over the entire set of cycles chosen for analysis. The COV for a sequence of numbers is the standard deviation divided by the mean times 100. COV would be large if periods or amplitude were to vary slowly around the mean, over the duration of the analysis (usually 100 consecutive cycles after vocal initiation). Relatively high values of COV for frequency may suggest uncontrolled low-frequency neuromuscular fluctuations of the cricothyroid or thyroarytenoid muscles or of the air pressure. Similarly high values of COV for amplitude may suggest relatively low-frequency (slow) neuro-muscular fluctuations in the thyroarytenoid muscles or sub-glottal air pressure fluctuations,

both of which may change the amplitude of glottal flow and the waveshape. The COV amplitude may be high if the laryngeal sound source is normal but the supra laryngeal vocal tract fluctuates.

Deep Brain Stimulation (DBS):
DBS involves the implantation of permanent electrodes into the brain and providing electrical stimulation.

Digitizing tablet:
A digitizing (graphic tablet) is a computer input device that allows one to hand draw images and graphics, and objectively quantify the amplitude and frequency of tremor.

Electroglottography:
Electroglottography [134] also referred to as laryngography is a non-invasive technique used to examine configuration of the glottis related to its opening and closing, using a high frequency electric signal (2-5 MHz typically) passed between two electrodes positioned at two different locations on the neck. As the vocal fold tissues make contact, the conductance increases, which is interpreted as glottal closing. Conversely, decrease in the conductance is interpreted as glottal opening. The speed quotient (contact index) measured by the EGG is the ratio of the durational difference between the contact closing and the contact opening phases, divided by the duration of the contact phase, and is intended to measure the symmetry of the EGG contact phase.

Electromyography (EMG)
EMG is a technique for evaluating and recording the electrical activity produced by skeletal muscles and is performed using an instrument called an electromyograph. An electromyography detects the electrical potential generated by muscles cells, when these cells are electrically or neurologically activated.

Fluctuation: (refer to Perturbation)

FEV_1:
Forced Expiratory Volume is the volume of air exhaled during the 1st second of a forced expiratory manoeuvre starting from the level of total lung capacity.

Flutter:
Flutter is a rapid vocal tremor of 7-10 hertz which is associated with the dysarthria of amyotrophic lateral sclerosis (ALS.) It is difficult to detect in conversational speech, and is usually measured acoustically.

Formant frequency
The second formant frequency (F2) slope is a measure of the rate of tongue movement from a consonant into a vowel and is measured by comparing the second formant (F2) value at the initiation of voicing (0msec) to the F2 value 50 msec into the vowel.

Freezing of gait:
Freezing of gait (FOG) described as a sudden and transient difficulty that can occur at the beginning or during the performance of rhythmic and repetitive movements. FOG has been positively associated with deterioration of speech and disease duration.

Fundamental frequency (Fo):
Fo is a measure of the rate at which the vocal cords open and close (vibrate) during phonation. One opening and closing movement is termed a cycle. Fo is measured in cycles per second (hertz), usually abbreviated as Hz.

Fundamental frequency variation (SDFo):
SD Fo is calculated as the square root of the variance around the mean Fo.

Global laryngeal tremor:
Here refers to tremor in the vertical dimension of the larynx as a unit, relative to the surrounding aero-digestive tract. [193]

Harmonics-to-noise ratio (HNR):
HNR reflects the relationship between the amount of periodic energy and noise in the voice signal per unit time.

Jitter:
An acoustic measure of 'perturbation' or variability of frequency between adjacent cycles (opening and closing movement of the vocal cords). It refers to the short-term (cycle-to-cycle) perturbation in the fundamental frequency of the voice and is therefore an evaluation of small cycle-to-cycle change in frequency. Typically, periods range from 1-10 ms and jitter deals with temporal changes down to a few microseconds. Since jitter involves changes that occur over adjacent cycles, the measure reflects short-term or high-frequency fluctuations.

Jitter is calculated as follows: For a sequence of *N* consecutive cycles, jitter is obtained by averaging the absolute values of adjacent-cycle frequency differences, dividing by the mean frequency for the *N* cycles and multiplying by 100.

Laryngoscopy (indirect, rigid, fiberoptic):
Indirect laryngoscopy: the examiner holds the tongue forward out of the mouth, the larynx is examined with a laryngeal mirror placed at the faucal arches, and the patient phonates and /i/ sound which elevates the larynx and permits visualization. The forward tongue position interferes with the normal physiological configuration of the larynx. This exam cannot be recorded and has been superseded by rigid laryngoscopy and fiberoptic endoscopy.

Rigid laryngoscopy: a rigid scope with a 70 or 90 degree angle lens at the distal end, introduced into the mouth and placed at the faucal arches, tongue is held forward and patient phonates /i/ sound (similar to indirect laryngoscopy. A camera can be attached to the scope which permits recording and playback of the procedure. Frequently strobe lighting is used with this technique which permits viewing of vocal cord vibration.

Fiberoptic laryngoscopy: also referred to as 'nasendoscopy', since the flexible fiberoptic scope is introduced into the larynx through the nasal cavity, permitting visualization of the nasopharynx, oropharynx and and laryngopharynx. A camera can be attached to the scope which permits recording and play backof the procedure. Strobe lighting may also be applied to examine vocal cord vibration.

Modulation:
The term modulation is used to quantify the systematic change of a cyclic parameter (usually the frequency or amplitude) of a periodic signal.

Nasendoscopy: (refer to Laryngoscopy)

Noise-to-harmonic ratio (NHR):
NHR is an average ratio of energy of the inharmonic components in the range of 1500 Hz to 4500 Hz to the harmonic components energy in the range of 70 Hz to 4500 Hz. It is a general evaluation of the noise presence in the analysed signal (e.g amplitude and frequency variations, turbulence noise, subharmonic components,and voice breaks)[138.]

Perturbation:
Perturbation represents a minor disturbance or a temporary change, from an expected behaviour. Perturbations do not alter the qualitative appearance/sound of a visual or temporal pattern. They are small irregularities that for the most part are overlooked. Perturbation analysis is based on the premise that small fluctuations in frequency, amplitude and wave shape are always present in a voice signal, reflecting the internal "noises" of the human body.

Whereas a perturbed system usually returns to normal, (it is attracted to a stable state), a fluctuating system is somewhat out of control. A *fluctuation* suggests a more severe deviation from a pattern. It reflects an inherent instability in the system. 'Vocal tremor' or 'vibrato' may be described as a fluctuation in fundamental frequency and amplitude. It is more than a perturbation since there is no ultimate stabilization of fundamental frequency or intensity toward some constant value. The tremor or vibrato is a pattern itself, rather than a small deviation from a pattern. [114]

Phonatory instability:
Phonatory instability relates to fluctuations in frequency and amplitude measures and has been described as short-term or long-term. *Short-term phonatory* instability refers to cycle-to cycle variations in frequency and amplitude. Measures include jitter and shimmer. *Long-term phonatory instability* refers to variations in frequency and amplitude that occur more slowly than the 'quasi-periodic' glottal vibration.

Physiological tremor: (refer to Tremor)

Pitch:
Pitch is the perceptual correlate of fundamental frequency. The inherent pitch of a voice is positively related to the size of the larynx and its structures (hence in general male voices are lower than female), but also to the anterior-posterior tension within the vocal cords.

Positron Emission Tomography (PET):
Positron Emission Tomography or PET as it is commonly called uses a special type of camera and a tracer (radioactive chemical) to look at organs in the body. The tracer usually is a spcial form of glucose which collects in cells that use a lot of energy.

Prosody:
Prosody is the rhythm, stress, and intonation of speech. It may reflect various features of the speaker or the utterance: the emotional state of the speaker; the form of the utterance (statement, question, or command); the presence of irony or sarcasm; emphasis, contrast and focus; or other elements of language that may not be encoded by grammar or choice of vocabulary.

Reliability:
Reliability refers to the likelihood that two individual raters will produce the same rating for a given speech or voice sample.

Shimmer:
Shimmer is a measure of the variability of amplitude between adjacent cycles, termed short-term (cycle-to-cycle) variability.

Soft Phonation Index (SPI)
An acoustic measure from the Multi-Dimensional Voice Programme (MDVP) from the Computerised Speech Laboratory (CSL), SPI is an average ratio of the lower frequency harmonic energy (1600Hz-4500Hz) harmonic energy. Increased SPI may be an indication of incomplete or loosely adducted vocal folds[138].

Spectogram:
Here a visual signal display of an acoustic signal from a voice sample.

Spectography:
Here the process of acquiring/displaying a graphic image of frequency and amplitude as a function of time from an acoustic signal.

Tremor:
Tremor is a low-frequency rhythmic involuntary fluctuation in amplitude or frequency or both.
Supraglottic tremor: tremor in the structures above (supra) the vocal folds (glottis), including the epiglottis, ventricular folds, aryepiglottic folds and supraglottic portion of the arytenoids.
Physiological tremor: normal physiological tremor that has an irregular rapid rate that ranges from 8 to 12 Hz.

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