Investigating reach and grasp in Parkinson's disease cognitive impairment

Dr Jeremy Cosgrove

MB ChB (Hons.), MRCP (UK)

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Abstract

Reach and grasp are evolutionary conserved motor actions controlled by highly specialised neural pathways that have major nodes in the posterior parietal and premotor frontal cortices. Mild cognitive impairment is an important non-motor symptom of Parkinson's disease (PD) and there is evidence that the risk of transition between PD mild cognitive impairment (PD-MCI) and Parkinson's disease dementia (PDD) is dependent on which neurotransmitter systems within the brain are most dysfunctional. Studies of reach and grasp in PD subjects with normal cognition (PD-NC) suggest a greater dependence on visual feedback to guide reach and grasp compared with controls.

The primary aim of this thesis is to explore how cognitive impairment influences reach and grasp in PD. Twenty two PD-NC, 23 PD-MCI, ten PDD and 19 controls reached and grasped for a target whilst wearing movement sensing equipment in four conditions: full vision, a darkened room with an illuminated target, with eyes closed at a natural speed and as quickly as possible in full vision. All PD subjects were tested whilst *on*. Kinematic parameters of reach and grasp were extracted from the movement data and analysed using standard statistical methods.

Our results show a spectrum of change to kinematic reach parameters when reaching and grasping with eyes closed: PD-NC are disproportionately affected compared to controls and PDD are disproportionately affected compared to PD-NC. Parameters of reach and grasp were similar between PD-NC and PD-MCI in all conditions. These results have been discussed in the context of abnormal integration of sensorimotor functions and impaired spatial working memory in PD. Reaction time when reaching and grasping as quickly as possible is significantly associated with global cognition in the PD subjects after controlling for age, motor signs and disease duration. This supports a role for reaction time as a potential biomarker for cognitive impairment in PD.

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Dedication

This thesis is dedicated to my Mum, with love.

Caroline Elizabeth Cosgrove

14th September 1954 – 17th July 2013

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Collaborations and roles in research

Dr Jane Alty, Dr Stuart Jamieson and Dr Stephen Smith

Devising the reach and grasp study protocol and gaining initial ethical approval. Reading all the chapters in this thesis and suggesting edits to the text.

Chiara Picardi

Extracting kinematic parameters from the movement data. Production of Figures 43, 44, 45, 46 and 62.

Dr Michael Lones and Stuart Lacy

Designing and programming the reach and grasp computer software.

Professor Martin Bland

Review of the statistical methods used in Chapters 6 and 7.

Author's declaration

"I confirm that this work is original and that if any passages or diagrams have been copied from academic papers, books, the Internet or any other sources these are clearly identified by the use of quotation marks and the references fully cited. I certify that other than where indicated, this is my own work and does not breach the regulations of HYMS, the University of Hull or the University of York regarding plagiarism or academic conduct in in examinations. I have read the HYMS Code of Practice on Academic Misconduct, and state that this piece of work is my own and does not contain any unacknowledged work from any other sources. I confirm that any patient information obtained to produce this piece of work has been appropriately anonymised."

Chapter 1

Abbreviations used in this chapter

α-syn	Alpha synuclein
ADL	Activities of daily living
AIP	Anterior intraparietal area in macaques/monkeys
aIPS	Anterior intraparietal area in humans
BA4	Brodmann area 4
BA6	Brodmann area 6
CSF	Cerebrospinal fluid
DLB	Dementia with Lewy bodies
FEF	Frontal eye field
fMRI	Functional magnetic resonance imaging
HC	Healthy controls
ICICLE-PD	Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation – Parkinson's Disease
IPL	Inferior parietal lobe
IPS	Intraparietal sulcus
ITC	Inferior temporal cortex
LIP	Lateral intraparietal area
M1	Primary motor cortex
MDS	International Parkinson and Movement Disorder Society
MIP	Medial intraparietal area
MRI	Magnetic resonance imaging
MSA	Multiple-system atrophy
MT	Movement time
PD	Parkinson's disease
PD-CI	Parkinson's disease cognitive impairment
PD-MCI	Parkinson's disease - mild cognitive impairment
PD-NC	Parkinson's disease - normal cognition
PDD	Parkinson's disease dementia
PIGD	Postural instability gait disorder
PMd	Dorsal premotor cortex
PMv	Ventral premotor cortex
PPC	Posterior parietal cortex
PRR	Parietal reach region
PwPD	People with Parkinson's disease
REM	Rapid eye movement
SMA	Supplementary motor area
SNpc	Substantia nigra pars compacta
SPL	Superior parietal lobe
TAP	Time to peak aperture
TD	Tremor dominant
TMS	Transmagnetic stimulation
TPA	Time to peak acceleration

TPD	Time to peak deceleration
TPV	Time to peak velocity
V3A	Visual area V3A
V6A	Visual area V6A
VIP	Ventral intraparietal area

Introduction

1.1 What is Parkinson's disease?

Parkinson's disease (PD) is a progressive and incurable neurodegenerative condition. It is common; the prevalence of PD in European adults is approximately 1.3%, rising to nearly three percent amongst people aged 80 or over (Pringsheim et al., 2014). The pathological hallmark of PD is early degeneration and death of dopaminergic neurons within the substantia nigra pars compacta (SNpc) of the basal ganglia. The resultant damage to basal ganglia function leads to the movement disorder first described by James Parkinson in 1817 and refined in 1877 by Jean-Martin Charcot (Kalia and Lang, 2015). The core features of the movement disorder are bradykinesia, rigidity, tremor and postural instability.

Another pathological hallmark of PD is the deposition of Lewy bodies (within the cell body) and Lewy neurites (within the axons of neurons) in the SNpc and elsewhere in the brain. Lewy pathology consist primarily of abnormal forms of a protein called alpha synuclein (α-syn), which is also found in dementia with Lewy bodies (DLB) and multiple-system atrophy (MSA) (sometimes collectively referred to as the 'alpha-synucleinopathies') (Halliday et al., 2014). An influential pathological staging system of PD proposes that Lewy pathology begins in the medulla and progressively spreads upwards through the brainstem, ultimately involving the neocortex (Braak et al., 2003).

PD is more than a movement disorder and comprises a number of non-motor symptoms, for example anxiety, depression and constipation. Some non-motor features can appear many years before the onset of motor problems and are part of the so-called 'pre-motor' or 'prodromal' phase of PD (Kalia and Lang, 2015). Braak et al.'s staging system offers a pathological explanation for this because the lower brainstem is affected by Lewy pathology before the SNpc in the midbrain. For example, anosmia

and rapid eye movement (REM) sleep behaviour disorder, two well known prodromal non-motor symptoms, can potentially be explained by infiltration of Lewy pathology into the olfactory bulb and pontine subcoeruleus nucleus, respectively (Braak et al., 2003).

1.2 Cognitive impairment and Parkinson's disease

Cognitive impairment is another non-motor feature of PD and will be reviewed in detail in Chapter 2. It is a common problem, highlighted by several longitudinal studies of incident cases of PD that demonstrated approximately half developed dementia ten years after diagnosis, rising to over 80% at 20 years (Williams-Gray et al., 2013, Perez et al., 2012, Auyeung et al., 2012, Hely et al., 2008). In addition to Parkinson's disease dementia (PDD), there has been increased interest over the last decade in a less severe cognitive disorder that may precede dementia and can be identified by formal cognitive testing, but does not dramatically interfere with a person's ability to manage activities of daily living (ADL). This has become known as PD mild cognitive impairment (PD-MCI) and was formally defined in 2012 by the International Parkinson and Movement Disorder Society (MDS) (Litvan et al., 2012). It has subsequently been shown that 35% to 42.5% of people meet the MDS criteria for PD-MCI at the time of PD diagnosis (Broeders et al., 2013, Yarnall et al., 2014).

PD-MCI is a risk factor for developing PDD (Janvin et al., 2006, Pedersen et al., 2013) but there is growing evidence to suggest that the progression of PD-MCI to PDD is dependent on which cognitive domains are affected, that is in turn dependent on which neurotransmitter systems in the brain are affected. PD-MCI characterised by executive dysfunction is thought to be primarily driven by catecholaminergic changes (including dopamine) and may not always progress to PDD, whereas PD-MCI characterised by memory, language or visuospatial dysfunction is thought to be primarily driven by acetylcholine deficiency and is a significant risk factor for developing PDD (Williams-Gray et al., 2007, Williams-Gray et al., 2009).

This idea forms the basis of the 'dual syndrome hypothesis' (Kehagia et al., 2010b, Kehagia et al., 2013) and is currently being explored in a UK-based longitudinal cohort study called Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation – Parkinson's Disease (ICICLE-PD) (Yarnall et al., 2014). From a pathological perspective, the Braak staging system of Lewy pathology has been correlated with cognitive function in some but not all studies (Kempster et al., 2010, Braak et al., 2005).

Drugs capable of disease modification and neuroprotection in PD remain an elusive but highly desirable goal. A number of potential therapeutic avenues exist including the prevention of accumulation and aggregation of abnormal α-syn (Kalia and Lang, 2015). It is very likely that if and when disease-modifying therapy becomes available it will be most effective if given before significant pathological damage has occurred, i.e. before the development of motor symptoms. The same is true in relation to the treatment of cognitive impairment in PD; earlier detection of those most at risk is likely to be necessary to maximise the benefit of any disease-modifying therapy.

If a biomarker, or panel of biomarkers, could accurately predict those with PD most at risk of developing PD-MCI or PDD this would allow tailored or targeted intervention with appropriate disease-modifying medication at an early stage. A range of potential biomarkers have been proposed and are currently under investigation, including different radiological modalities and blood and cerebrospinal fluid (CSF) constituents (Mollenhauer et al., 2014). Another avenue of research into potential biomarkers is to look for associations between motor function and cognition. This has been explored by analysing gait. There is evidence that velocity of gait and variability of stride length are both associated with deficits in executive function and attention in those with PD (Amboni et al., 2013). Furthermore, recent investigation of newly diagnosed people with PD (PwPD) has shown that the associations between cognition and gait are

greater for those with the postural instability gait disorder (PIGD) motor phenotype that the tremor dominant (TD) motor phenotype (Lord et al., 2014). This is exciting because PIGD is a risk factor for developing PDD (Williams-Gray et al., 2009).

Instead of using gait as the test of motor function, this thesis looks for links and associations between different parameters of reach and grasp and cognition in PwPD. This is done primarily by exploring and comparing reach and grasp in healthy controls (HC), those with PD and normal cognition (PD-NC), those with PD-MCI and those with PDD. The neural pathways that control reaching and grasping have been extensively studied in animals and humans. This allows any differences identified in the parameters of reach and grasp between the PD cognitive groups to be related back to the neural pathways.

1.3 What is reach and grasp?

Reach and grasp in humans derives from the ability to accurately orientate the arm and then flex, oppose and stabilise the thumb combined with independent movement of the fingers. This allows precise reach, grasp and manipulation of a seemingly endless number of objects. Reach and grasp is a motor behaviour performed many times every single day. Think about entering the kitchen to make a cup of tea; reach and grasp is required to pull the handle to open the kitchen door, to open the cupboard, to pick out a tea bag, to pick up the kettle, to turn on the tap. The list is endless. Each of these examples requires the reaching arm and grasping hand to precisely judge distance, orientation and grip force. All of this is achieved without conscious awareness and is generally done with consummate ease.

Reach and grasp is a highly conserved evolutionary function and can be traced back to animals such as mice and rats (Karl and Whishaw, 2013). Although there are well-defined stages of development of reaching and

grasping from birth until childhood in humans, a baby does not have to be taught how to reach and grasp; it is something that develops naturally and is an example of a 'non-learnt motor behaviour'.

1.4 How is reach and grasp analysed?

Prior to the early 1980's, the large number of degrees of freedom afforded to the human hand and arm prohibited detailed kinematic analysis of reach and grasp movements. This was overcome by video-recording at 50 frames per second as subjects reached and grasped an object and then manually analysing, frame by frame, three anatomical landmarks – the wrist, the tip of the finger and the tip of the thumb (Jeannerod, 2009, Jeannerod, 1984). In those pioneering experiments, movement time (MT) was defined as first movement of the wrist until detectable movement of the object to be grasped. Measuring the distance between anatomical landmarks during the trajectory of movement enabled calculation of velocity and acceleration. It became possible to determine the time to peak acceleration (TPA), time to peak velocity (TPV) and time to peak deceleration (TPD) of the wrist, as well as the size of the peak aperture between the index finger and thumb and the time to attain this (time to peak aperture - TAP) (Jeannerod, 2009). Although the equipment used has become more sophisticated, these parameters have formed the basis of kinematic analysis of reach and grasp up to the present day, and are also used in our study.

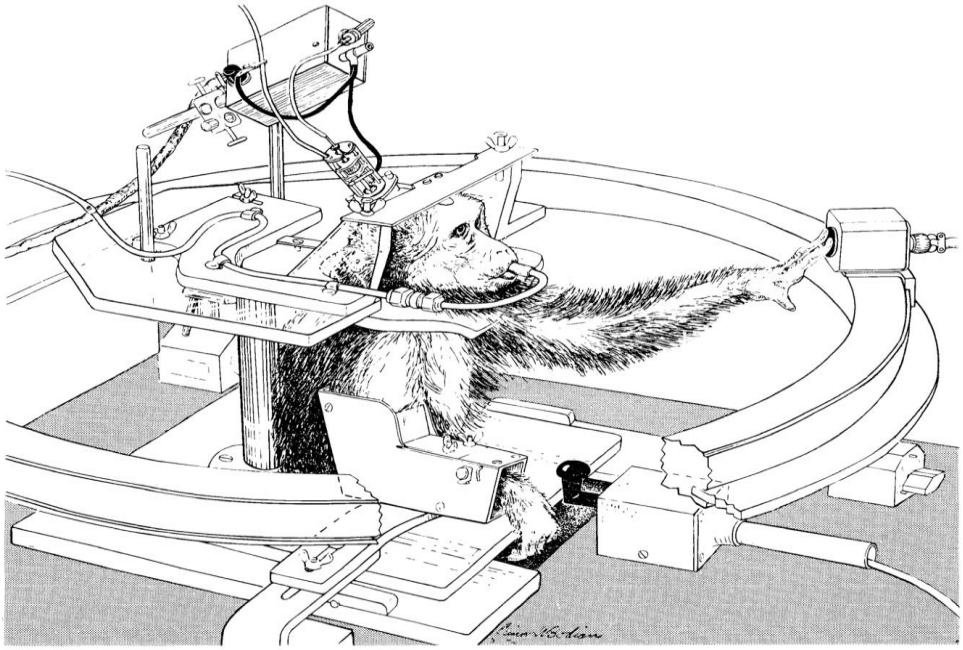
The literature relating to kinematic studies of reach and grasp is reviewed in Chapter 4. One key finding from previous research is the suggestion that PwPD are more affected than HC when reaching and grasping with less visual feedback, for example in complete darkness or when only the object to be grasped is illuminated in otherwise complete darkness (Schettino et al., 2006).

1.5 The anatomy of the reach and grasp circuits

1.5.1 Specialised neural networks

Parallel to the study of the kinematics of reach and grasp has been the study of the neural pathways that control this naturally acquired motor action. Single cell microelectrode studies have been used in animal models, most commonly the macaque monkey. Such experiments require precise insertion of microelectrodes into the relevant area of the macaque brain and allow electrical activity to be studied at single neuron resolution (Figure 1). This has led to the discovery of specialised neural circuits that control reaching and grasping (Karl and Whishaw, 2013, Castiello and Begliomini, 2008). Single cell microelectrode studies are impractical in humans and so identification of the reach and grasp pathways has instead involved radiological imaging techniques and inducing virtual lesions in specific brain areas using transmagnetic stimulation (TMS).

Figure 1: A single cell microelectrode study being performed on a monkey



Legend: This drawing provides an early example of the experimental design used in single cell microelectrode studies from a paper published in 1975. Although the technology has subsequently advanced the principle remains the same. The monkey (a macaque) is performing a reaching task with the left hand whilst neurons in the right parietal cortex are recorded using pre-implanted microelectrodes. In such studies the monkeys are trained to perform the task in question before relevant neurosurgery is performed. After study completion the monkeys are exterminated. Reproduced from Mountcastle et al., 1975 with permission (Mountcastle et al., 1975).

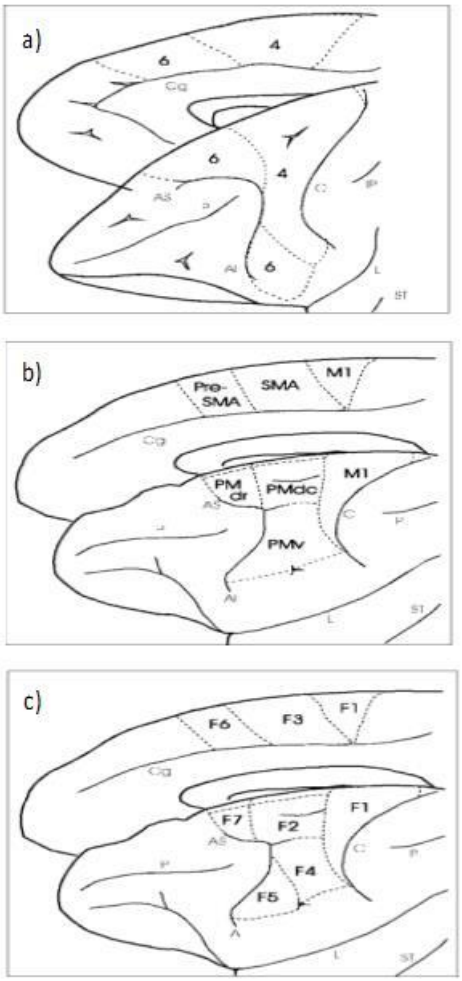
Modern neuroscientific understanding has moved away from the idea that a specific brain region controls a specific cognitive function and towards the current accepted view that different regions of the brain are linked together in highly specialised neural networks to mediate a cognitive function (Borra et al., 2015). Specific motor actions, including reaching and grasping, are thought to be mediated primarily by evolutionary conserved parieto-frontal networks, and it has been demonstrated in macaques and humans that the frontal premotor cortex and the posterior parietal cortex (PPC) contain an assortment of independent areas that deal with specific motor actions (Borra et al., 2015). Before proceeding further it is important to discuss the anatomy of the frontal premotor cortex and the PPC.

1.5.2 Anatomy of the frontal premotor cortex

Brodmann divided the cerebral cortex of human and primate brains into different regions based on cytoarchitectural appearance [1]. His analysis classified the frontal premotor cortex into two distinct areas, referred to as Brodmann area 4 (BA4) and Brodmann area 6 (BA6) (Figure 2a) (Brodmann, 1909). The primary motor cortex (M1) was traditionally believed to consist of BA4 and a significant portion of BA6 on the lateral convexity of the brain. The remainder of BA6, predominantly located on the mesial cortical surface, was considered to be the supplementary motor area (SMA) (Luppino and Rizzolatti, 2000). However, the study of neuronal function in macaques and other monkey species has led to further subdivision of the frontal premotor cortex in monkeys and humans into a number of different areas including M1, SMA, the dorsal premotor cortex (PMd) and the ventral premotor cortex (PMv) (Figure 2b) (Luppino and Rizzolatti, 2000). Based on a combination of cytoarchitectural and functional properties, Matelli et al. proposed a yet further subdivision of the macaque frontal premotor cortex into seven distinct areas, named areas F1 – F7 (Figure 2c) (Matelli et al., 1991). These areas are not clearly defined in the human frontal premotor cortex. In the macaque, PMd therefore contains areas F2 and F7 and PMv contains areas F4 and F5. The subdivision of the frontal premotor cortex proposed by Matelli et al. is important when considering the reach and grasp pathways of macaques in more detail, as will occur in Chapter 3.

[1] Cytoarchitecture – the microscopic study of the cellular makeup of the central nervous system.

Figure 2: Proposed subdivisions of the macaque frontal premotor cortex



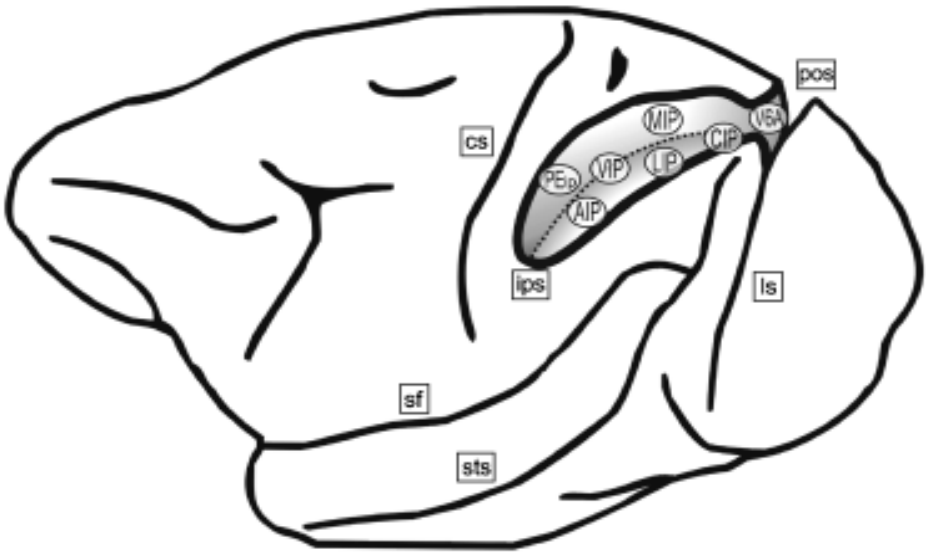
Legend: In all three figures the upper image represents the mesial cortical surface and the lower image represents the lateral cortical surface. BA4 and BA6 are shown in (a). Functional subdivisions are shown in (b) and the subdivisions proposed by Matelli et al. are shown in (c). Comparing figures (b) and (c) shows that in the macaque PMd is made up of areas F7 and F2 and PMv is made up of areas F4 and F5. Abbreviations: 6, Brodmann area 6; 4, Brodmann area 4; Pre-SMA, pre-supplementary motor area; SMA, supplementary motor area; M1, primary motor cortex; PMdr, dorsal premotor cortex, rostral; PMdc, dorsal premotor cortex, caudal; PMv, ventral premotor cortex; F1-F7, frontal subdivisions according to Matelli et al. (Matelli et al., 1991). Adapted from Luppino and Rizzolatti, 2000 with permission (Luppino and Rizzolatti, 2000).

1.5.3 Anatomy of the posterior parietal cortex

As with the frontal premotor cortex, the PPC of the macaque has been divided into different areas based on the results of single cell microelectrode studies and cytoarchitectural analysis. Other investigative

techniques have looked for homologues of these areas in human brains. In humans and macaques the intraparietal sulcus (IPS) divides the superior parietal lobe (SPL) and inferior parietal lobe (IPL). Specific areas located on the banks of the SPL and IPL form the parietal components of the parieto-frontal networks (Grefkes and Fink, 2005). The relevant areas in the macaque are shown in Figure 3, and include the anterior intraparietal area (AIP), the ventral intraparietal area (VIP), the medial intraparietal area (MIP) and the lateral intraparietal area (LIP).

Figure 3: The subdivisions of the posterior parietal cortex in the macaque



Legend: The lateral cortical surface of the macaque is shown and the intraparietal sulcus has been opened up. The dashed line represents the bottom of the intraparietal sulcus. Abbreviations: ips; intraparietal sulcus; cs, central sulcus; pos, parieto-occipital sulcus; ls, lunate sulcus; sf, Sylvian fissure (lateral sulcus); sts, superior temporal sulcus; V6A, visual area V6A; CIP, caudal intraparietal area; MIP, medial intraparietal area; LIP, lateral intraparietal area; VIP; ventral intraparietal area; AIP; anterior intraparietal area. Reproduced from Grefkes and Fink, 2005 with permission (Grefkes and Fink, 2005).

1.5.4 Parieto-frontal networks

Parieto-frontal networks are highly specialised neural networks that control specific motor actions. One example is the organisation of eye movements, which is controlled by a network that includes LIP and the

frontal eye field (FEF) (a specific population of neurons in the frontal premotor cortex located between BA4, BA6 and Brodmann area 8) (Luppino and Rizzolatti, 2000). Another example is the control of arm and mouth movements in the peripersonal[2] space, including defensive arm movements in response to a perceived threat. A specialised pathway involving VIP and F4 controls this in the macaque (Luppino and Rizzolatti, 2000). As discussed, one of the most important techniques used in the discovery of the parieto-frontal networks has been the ability to record the discharge of individual neurons within the macaque brain. This technique identified that F4 neurons of the PMv are responsive to visual, tactile and auditory stimuli, particularly when an object approaches a macaque or is in close proximity to it. A proportion of F4 neurons were also found to discharge during proximal reaching movements (Gentilucci et al., 1988). This combination of multimodal sensory function and activation during reaching movements led researchers to theorise that this part of the brain is activated when guiding defensive movements in response to nearby stimuli. This has subsequently been supported by demonstrating that macaques have exaggerated defensive limb movements when F4 neurons are stimulated and reduced defensive movements when they are inhibited (Cooke and Graziano, 2004). The degree to which parieto-frontal networks are conserved in humans compared to macaques is varied, and with the exception of the reach and grasp pathways is beyond the scope of this thesis.

1.6 The reach and grasp pathways

Reaching involves transporting the hand towards a target and utilises proximal rather than distal arm muscles. The parieto-frontal network controlling reach is often referred to as the 'dorsomedial circuit' (Prodoehl et al., 2009). It projects from visual area V3A (V3A) of the visual cortex through the parietal reach region (PRR) to PMd and then M1 (Prodoehl et

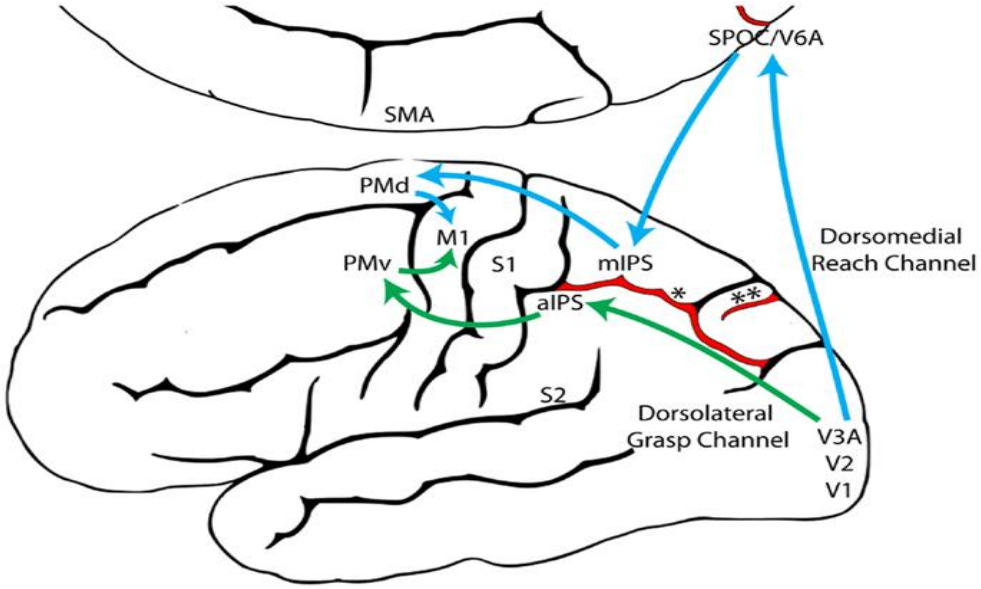
[2] Peripersonal space – the space within the reach of any limb of an individual.

al., 2009, Karl and Whishaw, 2013). PRR is a term used to describe neurons from visual area V6A (V6A) and MIP. In macaques, it is area F2 of PMd that is specifically involved in the dorsomedial circuit (Castiello and Begliomini, 2008, Raos et al., 2004), whereas the exact role of the PMd in the human reach pathway is uncertain.

Grasping involves opening the digits of the hand to a peak aperture greater than the size of the target object before closing them down around the object and is executed by the hand and finger muscles (Karl and Whishaw, 2013, Prodoehl et al., 2009). The parieto-frontal network that controls grasp can be referred to as the 'dorsolateral circuit' and projects from V3A through the AIS to PMv and finally M1. For the remainder of this thesis AIS will be the acronym used to describe the anterior intraparietal area in macaques and 'aIPS' will be used to describe the human homologue of the anterior intraparietal area.

Area F5 of the PMv is thought to be the major frontal premotor cortex area involved in the dorsolateral circuit in macaques (Rizzolatti et al., 1988), but less is known about the exact role of the PMv in the control of grasp in humans. The reach and grasp pathways are shown in Figure 4.

Figure 4: The reach and grasp pathways in humans and macaques



Legend: The dorsomedial reaching circuit is shown in blue. The dorsolateral grasping circuit is shown in green. The dorsomedial reaching circuit begins in V3A then passes through the PRR (including V6A and MIP) and then PMd before terminating in M1. The dorsolateral grasping circuit is shown in green. It also begins in V3A then passes through aIPS (AIP in macaques) then to PMv before terminating in M1. Abbreviations: **, parieto-occipital sulcus; *, intraparietal sulcus; V3A, visual area V3A; V6A, visual area V6A; SPOC, superior parieto-occipital cortex; mIPS, medial intraparietal sulcus (referred to as MIP in this thesis); aIPS, anterior intraparietal sulcus in humans (AIP is the abbreviation used to describe this region in the macaque in this thesis); PMd, dorsal premotor cortex; PMv, ventral premotor cortex; M1, primary motor cortex; S1, primary sensory cortex; S2; secondary somatosensory cortex; V1, primary visual cortex; V2, secondary visual cortex. Reproduced from Karl and Whishaw, 2013 with permission (Karl and Whishaw, 2013).

1.7 The visuomotor channel hypothesis

The 'visuomotor channel hypothesis' was originally proposed in the 1980's and theorised that the dorsomedial and dorsolateral circuits controlling reach and grasp are separate pathways but are temporally integrated under visual guidance (Jeannerod, 1986, Jeannerod, 1984). Furthermore, each of these pathways, or *visuomotor channels*, was theorised to have a specific mode of visuomotor transformation: reaching relates to the extrinsic characteristics of an object, i.e. the processing of the distance and direction of the object to determine where it is in space; grasping

processes the intrinsic properties of an object, such as size and shape (Jeannerod, 1999).

A source of support for the separation of reach and grasp pathways comes from the study of infants, in whom it has been demonstrated that reach and grasp follow independent profiles of development. Both pathways are initially guided by sensory feedback through touch, superseded by the use of vision to direct reach and grasp movements from approximately six months of age. Visually-based integration of reach and grasp, evidenced by accurate preshaping of the grasping hand during reach, occurs after approximately two years (Karl and Whishaw, 2013).

The study of animals such as mice and rats has led to an evolutionary theory about the origin of separate reach and grasp pathways. It is proposed that reach is derived from stepping movements of the forelimbs and grasp is derived from food handling (Karl and Whishaw, 2013). These somatosensory-based functions have subsequently developed to include the addition of visual input, allowing humans (and other primates including macaques) to integrate reach and grasp under visual guidance to produce appropriate reach and grasp movements to a seemingly infinite number of objects of different shapes, sizes and locations.

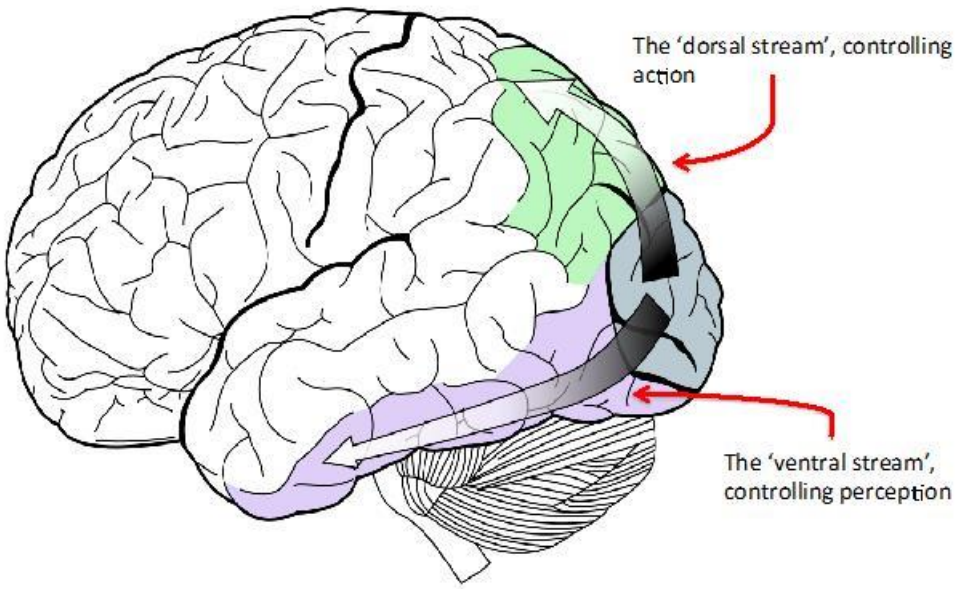
To summarise, the visuomotor channel hypothesis proposes that two distinct but integrated neural networks that pass through the parietal lobe control reaching and grasping. It is important to establish how this theory assimilates with the hypothesis that separate pathways govern visual perception and motor action.

1.8 The perception-action model of the visual system

Goodale and Milner expanded on the theory that the visual system could be divided in to two separate 'streams', one controlling localisation and the other identification (Schneider, 1969), when they proposed the

'perception-action model' in the early 1990's (Goodale and Milner, 1992) (Figure 5). A dorsal stream, projecting from the visual cortex to the parietal lobe, involves the real-time transformation of visual information into motor action. A ventral stream, projecting from the visual cortex to the temporal lobe, specifically the inferior temporal cortex (ITC), was proposed to be involved in object identification and the assignment of meaning and significance to such objects (Goodale, 2014).

Figure 5: The perception action model of the visual system



Legend: The dorsal stream transforms visual information into motor action, passing from the visual cortex (grey) to the parietal lobe (green). The ventral stream also arises from the visual cortex, terminating in the ITC (purple). This pathway identifies and assigns meaning to objects. Adapted from Wikipedia, open access (Wikipedia, 2007).

One major contributor to the development of the perception-action model was the interpretation of psychological studies from a patient who developed visual agnosia [3] after carbon monoxide poisoning but retained the ability to perform visually guided reach and grasp in the context of impaired object identification; i.e. she could perform the action of reaching

[3] Visual agnosia - an inability to recognise visually presented objects in the context of a normally functioning visual system.

and grasping without any perception of what she was reaching and grasping for (Goodale et al., 1994). Subsequent magnetic resonance imaging (MRI) of her brain revealed damage to the lateral occipital cortex, thought to be crucial for object recognition (James et al., 2003). Functional MRI (fMRI) has demonstrated that, in contrast to healthy subjects, her lateral occipital cortex does not show changes in activation levels when she is shown drawings of common objects compared to scrambled lines of no meaningful shape. Moreover, when performing visually guided grasping her fMRI scan shows the same activation pattern as healthy subjects, lending support to the concept of two distinct visual streams (James et al., 2003).

A number of psychological tests on healthy subjects have also supported a distinction between visual control of action and visual perception. For example, it has been demonstrated that when participants are exposed to optical illusion tests in which they perceive objects to be bigger or smaller than they actually are, the parameters of reach and grasp remain scaled to the correct object size, rather than that perceived (Aglioti et al., 1995).

However, there is also a body of evidence to suggest that extensive co-activation between the two visual streams occurs during any complex visual task (Schenk and McIntosh, 2010). Whether this is evidence of interaction between the visual streams or 'parallel-processing' of information by two distinct streams remains a matter of debate (Goodale, 2014), but the concept of a dorsal 'action' stream passing through the parietal lobe is fully compatible with the visuomotor channel hypothesis because both the dorsomedial reaching circuit and the dorsolateral grasping circuit pass through the PPC, and therefore are both considered part of the dorsal stream.

1.9 Summary of the cortical control of reach and grasp pathways and the visuomotor channel hypothesis

According to the visuomotor channel hypothesis, separate pathways that are temporally integrated under visual guidance control reaching and grasping. In macaques and in humans there is evidence that both pathways pass through neural circuits within the PPC to the frontal premotor cortex and then to M1 (Karl and Whishaw, 2013, Castiello and Begliomini, 2008). The distinguishing features of the dorsomedial and dorsolateral circuits are summarised in Table 1. The visuomotor channel hypothesis is compatible with the perception-action model of the visual system because both the dorsomedial and dorsolateral circuits have major nodes within the PPC and are considered part of the dorsal stream.

As with the perception-action model, there is evidence to suggest that the dorsomedial and dorsolateral circuits are more assimilated than proposed by the visuomotor channel hypothesis (Cavina-Pratesi et al., 2010b). However, the dorsomedial and dorsolateral circuits provide a framework to describe the major nodes of reaching and grasping in humans and macaques in more detail, and this forms the basis of Chapter 3.

Table 1: Distinguishing features of the reach and grasp pathways

	Dorsomedial circuit	**Dorsolateral circuit**
Function	Reach	Grasp
Major parietal node	Visual area V6A (V6A)	Anterior intraparietal area (AIP in macaques, aIPS in humans)
Major frontal premotor node	Dorsal premotor cortex (PMd)	Ventral premotor cortex (PMv)
Upper limb muscles	Proximal	Distal
Spatial properties	Location and orientation (extrinsic)	Size and shape (intrinsic)

1.10 Aims and objectives

The aim of this thesis is to explore how cognitive impairment influences reach and grasp in PD. Results will be discussed in the context of the current understanding of the pathological and neurochemical changes that drive cognitive impairment in PD and the neural pathways that are believed to control reach and grasp.

A study was conducted in Leeds, UK, using commercially available movement sensors and movement sensing gloves. Reach and grasp was recorded in HC and in PwPD categorised according to MDS level 1 diagnostic criteria into PD-NC, PD-MCI and PDD (Litvan et al., 2012, Emre et al., 2007). Kinematic parameters of movement were calculated from the data and analysed using standard statistical measures. Reach and grasp was performed under four different conditions: at a natural speed in full vision; as fast as possible in full vision; at a natural speed with target illumination in a darkened room; at a natural speed with eyes closed.

The objectives of this study are to:

- Evaluate whether PD-NC are more impaired than HC when reaching and grasping in conditions of reduced visual feedback.

- Test the hypothesis that those with PD-MCI and PDD will be more impaired when reaching and grasping in conditions of reduced visual feedback than those with PD-NC. Visuospatial function is mediated by the parietal lobes and is often affected in PD cognitive impairment (PD-CI). It is postulated that pathological and neurochemical changes to the parietal lobes will lead to greater impairment of visuospatial function in those categorised as PD-MCI and especially PDD, and therefore greater impairment when reaching and grasping under reduced levels of visual feedback.

- Evaluate how kinematic reach and grasp parameters are associated with global cognitive function in PwPD.

- Evaluate how kinematic reach and grasp parameters are associated with tests of visuospatial function and executive function in PwPD.

Chapter 2

Abbreviations used in this chapter

α-syn	Alpha synuclein
ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADL	Activities of daily living
APOE	Apolipoprotein E
Aβ	Amyloid beta plaques
CAMCOG	Cambridge Cognitive Examination
CamPaIGN	Cambridgeshire Parkinson's Incidence from GP to Neurologist study
CANTAB	Cambridge Neuropsychological Test Automated Battery
ChEI	Cholinesterase inhibitors
COMT	Catechol-O-methyltransferase
CSF	Cerebrospinal fluid
DLB	Dementia with Lewy bodies
DLPFC	Dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
fMRI	Functional magnetic resonance imaging
H&Y	Hoehn & Yahr
HC	Healthy controls
ICICLE-PD	Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation – Parkinson's Disease
ILBD	Incidental Lewy body disease
mAChR	Muscarinic acetylcholine receptor
MAPT	Microtubule associated protein tau
MCI	Mild cognitive impairment
MDS	International Parkinson and Movement Disorder Society
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
nAChR	Nicotinic acetylcholine receptor
nbM	Nucleus basalis of Meynert
NFT	Tau neurofibrillary tangles
NMDA	N-methyl-D-aspartate
PD	Parkinson's disease
PD-CI	Parkinson's disease cognitive impairment
PD-MCI	Parkinson's disease - mild cognitive impairment
PD-NC	Parkinson's disease - normal cognition
PDD	Parkinson's disease dementia
PET	Positron emission tomography
PIGD	Postural instability gait disorder
PPN	Pedunculopontine nucleus
PwPD	People with Parkinson's disease

RCT	Randomised controlled trial
REM	Rapid eye movement
ROC	Receiver operating characteristic
SCOPA-COG	Scales for Outcomes of Parkinson's disease–Cognition
SDs	Standard deviations
SNpc	Substantia nigra pars compacta
SPECT	Single-photon emission computed tomography
SWM	Spatial working memory
TD	Tremor dominant
TOL	Tower of London test
UKPDBBC	United Kingdom Parkinson's Disease Brain Bank Criteria
α-syn	Alpha synuclein

Cognitive impairment in Parkinson's disease

The last decade has seen a marked increase in appreciation of the importance of cognitive decline in PwPD. A key factor that has focused awareness is the recognition that a majority of PwPD will develop PDD if they survive long enough, as demonstrated by a number of large cohort studies (Williams-Gray et al., 2013, Perez et al., 2012, Auyeung et al., 2012, Hely et al., 2008). The construct of PD-MCI was formally defined in 2012 by the MDS (Litvan et al., 2012), and it has since been shown that approximately one-third of people have PD-MCI at the time they are diagnosed with PD (Broeders et al., 2013, Yarnall et al., 2014).

There is evidence that the risk of progression from PD-MCI to PDD is not uniform; rather, risk is linked to the type(s) of cognitive domain affected (Williams-Gray et al., 2007, Williams-Gray et al., 2009). A theory combining this finding with impairment of neurotransmitter systems within the brain is known as the 'dual syndrome hypothesis' (Kehagia et al., 2010b, Kehagia et al., 2013). Understanding the complex pathological and genetic factors governing transition between PD-NC, PD-MCI and PDD is an active area of research. One major aim is to identify biomarkers that can accurately predict those PwPD most at risk of developing dementia, because this would allow targeted study of such people and early delivery of disease modifying medication, if and when this becomes available. This chapter provides a review of current understanding of PD-CI.

2.1 Diagnosis

2.1.1 Diagnosing Parkinson's disease – Mild cognitive impairment

The 2012 MDS PD-MCI diagnostic criteria (Litvan et al., 2012) were published following a literature review by an MDS task force (Litvan et al., 2011). The aim was to create a unifying set of diagnostic measures in order to standardise practice across clinical trials and thereby improve understanding of PD-MCI. A core requirement when making a diagnosis of

PD-MCI is that PD has been diagnosed based on the United Kingdom Parkinson's Disease Brain Bank Criteria (UKPDBBC). The other diagnostic requirements are:

- *"Gradual decline, in the context of established PD, in cognitive ability reported by either the patient or informant, or observed by the clinician*
- *Cognitive deficits on either formal neuropsychological testing or a scale of global cognitive abilities*
- *Cognitive deficits are not sufficient to interfere significantly with functional independence, although subtle difficulties on complex functional tasks may be present"*

(Litvan et al., 2012)

In order to align with MDS PDD diagnostic criteria published in 2007 (Emre et al., 2007), the MDS PD-MCI criteria contain two diagnostic categories. A 'level 1' category diagnosis allows an approved test of global cognitive function to demonstrate deficits, and the Montreal Cognitive Assessment (MoCA) is one of the approved assessment tools. This is important because the MoCA was used in the study from which this thesis is derived (see Chapter 5). A 'level 2' category diagnosis requires neuropsychological testing of the five core cognitive domains most often affected in PD-MCI, which are essentially the same as the core domains affected in PDD (Emre et al., 2007). These are attention and working memory, executive function, language, memory, and visuospatial function (Litvan et al., 2012). Two neuropsychological tests specific to each of the five cognitive domains must be performed and deficits need to be identified in at least two tests in order to make a level 2 diagnosis. The abnormal tests can both be within the same cognitive domain or within different cognitive domains, therefore allowing subtyping of level 2 PD-MCI into single or multiple

cognitive domain types. The definition of impairment in cognitive tests is not precisely defined and can be demonstrated by:

- *"Performance approximately one to two standard deviations (SDs) below appropriate norms*
- *Significant decline demonstrated on serial cognitive testing*
- *Significant decline from estimated premorbid levels"*

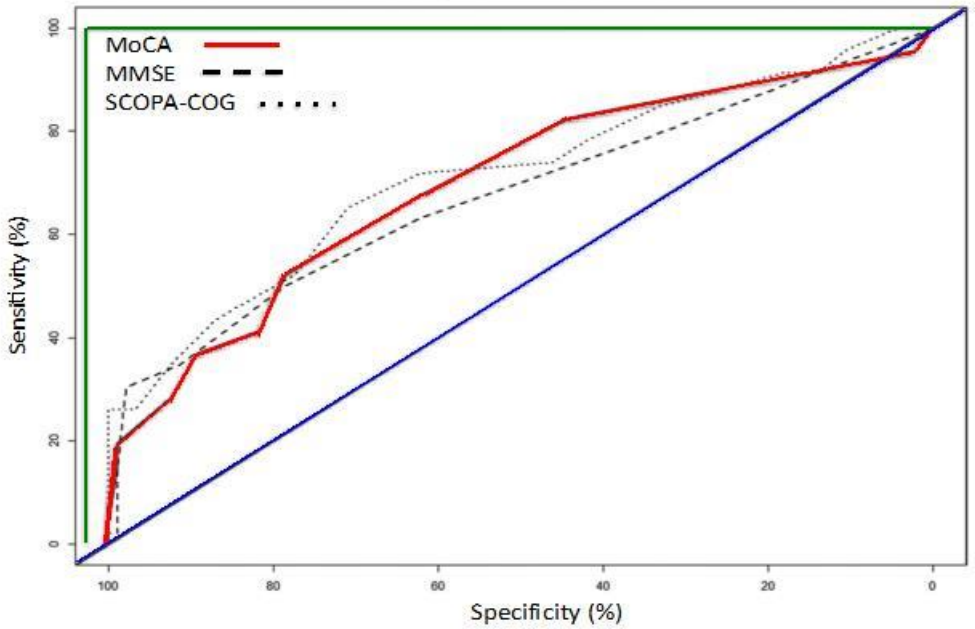
(Litvan et al., 2012)

Large-scale validation of the MDS diagnostic criteria is underway; the MDS PD-MCI Validation Study Group has applied level 1 and level 2 diagnostic criteria to over 5,500 PwPD – the vast majority of whom are already enrolled in existing longitudinal studies of PD – and 1,700 HC (Geurtsen et al., 2014). Results from this study will help resolve a number of problems identified with the MDS criteria. For example, as the formal definition of PD-MCI is a new construct there is a lack of a reference standard to validate against (Goldman et al., 2014). In an attempt to overcome this, a study of 76 PwPD from a clinic-based cohort had a diagnosis of PD-MCI based on the level 2 MDS criteria compared with a consensus diagnosis of a three person panel, consisting of a neurologist and two neuropsychologists, which served as the reference standard. Compared to the consensus diagnosis, the optimum sensitivity (85.4%) and specificity (78.6%) of level 2 MDS criteria was achieved when a performance of 2 SDs below normative means was used (Goldman et al., 2013).

This highlights another concern with the MDS diagnostic criteria; uncertainty regarding the optimum cut-off for impairment values when compared to normative means. In a study of 234 PwPD it was demonstrated that the number of people meeting the criteria for a level 1 diagnosis of PD-MCI was substantially different depending on SD cut-off; 109 (47%) were diagnosed as PD-MCI using 1 SD, 76 (32%) using 1.5 SDs

and 50 (21%) using 2 SDs below normative means (Szeto et al., 2015). In this study a level 1 diagnosis was via assessment of each of the core cognitive domains with one neuropsychological test (whereas two independent tests of each domain are required for a level 2 diagnosis according to MDS criteria (Litvan et al., 2012)). In another study, the validity of three global cognitive screening tests approved by the MDS to make a level 1 diagnosis was compared. One hundred and thirty nine PwPD initially performed the MoCA, Mini-Mental State Examination (MMSE) and the Scales for Outcomes of Parkinson's disease–Cognition (SCOPA-COG). One to three weeks later, participants undertook a battery of neuropsychological tests to enable a level 2 MDS diagnosis to be made. None of the global cognitive screening tests performed well when validated against the level 2 diagnoses. The MoCA was the best of the three but to achieve a sensitivity of 80% (a score of ≤26/30) resulted in a specificity of 44% and diagnostic accuracy of 57%. A specificity of 80% was achieved with a score of ≤23/30, resulting in a sensitivity of 41% and a diagnostic accuracy of 68% (Figure 6) (Marras et al., 2013).

Figure 6: Receiver-operator characteristic curves for MoCA, MMSE and SCOPA-COG



Legend: Receiver operating characteristic (ROC) curves are a graphical way to summarise trade-offs between sensitivity and specificity at different threshold levels. The blue line is a theoretical example of a test that has a sensitivity and specificity of 50%, i.e. is no better than chance. The green line is a theoretical example of a perfect test, i.e. sensitivity and specificity of 100%. The three cognitive tests perform similarly, although the MoCA was slightly superior. Adapted from Marras et al., 2013 with permission (Marras et al., 2013).

In addition, Marras et al. showed that defining PD-MCI as a decline from premorbid level of function, another means of making a level 1 diagnosis according to the MDS criteria, increased the diagnostic rate from 32% of the cohort using the global cognitive screening tests at a 1.5 SDs cut-off to 79% of the cohort. It was concluded that none of the three global cognitive tests would be adequate alone to screen for a research study to define PD-MCI, and more generally that MDS level 1 diagnostic criteria require reconsideration (Marras et al., 2013).

The MoCA performed better as a screening test in a study of 95 PwPD from a clinic-based cohort in Singapore, in which 34 patients were diagnosed with PD-MCI according to MDS level 2 diagnostic criteria (defined as neuropsychological test results 1.5 SDs below normative means). The

MoCA had a high discriminatory power in detecting PD-MCI with a score of ≤26/30 providing a sensitivity of 93%, specificity of 59% and a diagnostic accuracy of 91% (Kandiah et al., 2014). This study builds upon older studies pre-dating the MDS diagnostic criteria which demonstrated that the MoCA, at a score of ≤25/30 (Dalrymple-Alford et al., 2010) or ≤26/30 (Hoops et al., 2009) had a sensitivity and negative predictive value of >80% in detecting PD-MCI.

2.1.2 Diagnosing Parkinson's disease dementia

Prior to 2007 clinicians often relied upon PwPD meeting generic criteria for a dementia diagnosis in order to diagnose PDD, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) (Meireles and Massano, 2012). The 2007 MDS diagnostic criteria defined two core requirements in order to diagnose PDD (Emre et al., 2007). The first is the presence of PD according to UKPDBBC and the second is the development of a dementia syndrome in the context of established PD. The dementia syndrome is further defined as:

- *"Impairment in more than one cognitive domain*
- *Representing a decline from premorbid level*
- *Deficits severe enough to impair daily life (social, occupational, or personal care), independent of the impairment ascribable to motor or autonomic symptoms"*

(Emre et al., 2007)

An ante mortem diagnosis of PDD can be 'probable' or 'possible' according to MDS criteria. For a diagnosis of probable PDD, the dementia syndrome needs to affect two or more of the core cognitive domains (attention, executive function, visuospatial function, and memory). Behavioural symptoms including apathy, hallucinations and delusions support the diagnosis of probable PDD but are not an absolute requirement *(Emre et al.,*

2007). Exclusion criteria for a diagnosis of PDD include development of cognitive dysfunction before or within one year of typical motor symptoms of PD (in which case the a diagnosis of DLB should be considered (McKeith et al., 1996)), a delirium or features compatible with vascular dementia (Emre et al., 2007).

At the same time as publishing diagnostic criteria, the MDS task force produced recommendations about how to make the diagnosis (Dubois et al., 2007). These recommendations allow a level 1 and level 2-category diagnosis of PDD to be made. Testing for a level 1 diagnosis was designed to serve as a screening tool that could be performed quickly and does not require neuropsychological expertise. Level 2 testing requires detailed neuropsychological assessment and is designed for use in clinical trials and when level 1 testing produces ambiguous results (Dubois et al., 2007). An 'algorithm' for the diagnosis of PDD using level 1 testing was produced in addition to a 'diagnostic rating sheet' (Figures 7 and 8).

Figure 7: The MDS Parkinson's disease dementia level 1 diagnosis guidelines

1) A diagnosis of Parkinson's disease based on the Queen's Square Brain Bank criteria for PD 2) PD developed prior to the onset of dementia 3) MMSE <26 4) Cognitive deficits severe enough to impact daily living 5) Impairment in at least two of the following tests: Months reversed or Seven backward Lexical fluency or Clock drawing MMSE Pentagons 3-Word recall
The presence of one of the following behavioral symptoms: apathy or depressed mood or delusions or excessive daytime sleepiness may support the diagnosis of probable PDD. The presence of major depression or delirium or any other abnormality which may by itself cause significant cognitive impairment makes the diagnosis uncertain.

Abbreviations: MMSE, Mini-Mental State Examination. Adapted from Dubois et al., 2007 with permission (Dubois et al., 2007).

Figure 8: The MDS Parkinson's disease dementia diagnostic rating sheet

	YES	NO
1) Parkinson's disease	☐	☐
2) Parkinson's disease developed before dementia	☐	☐
3) MMSE <26	☐	☐
4) Dementia has Impact on ADLs	☐	☐
5) Impaired cognition (For yes, at least two of four tests below are abnormal) Mark which Tests are abnormal: ☐ Months reversed or sevens backwards ☐ Lexical fluency or clock drawing ☐ MMSE pentagons ☐ 3-word recall	☐	☐
6) Absence of major depression	☐	☐
7) Absence of delirium	☐	☐
8) Absence of other abnormalities that obscure diagnosis	☐	☐

Legend: In order to make a level 1 diagnosis of probable PDD all eight criteria from the diagnostic rating sheet must be fulfilled. **Abbreviations:** MMSE, Mini-Mental State Examination; ADLs; activities of daily living. Adapted from Dubois et al., 2007 with permission (Dubois et al., 2007).

Comparison of the MDS diagnostic criteria for PDD versus DSM-IV dementia diagnostic criteria (in which PDD would be classed as "a dementia due to other conditions") was performed in 299 PwPD who underwent a range of cognitive assessments (Martinez-Martin et al., 2011). One hundred and nine PwPD were diagnosed with probable PDD according to the level 2 MDS criteria whereas 99 PwPD were diagnosed according to the DSM-IV criteria, suggesting the MDS criteria are more sensitive. Agreement between the two diagnostic tools was 87.3%.

In a French study 188 PwPD were prospectively recruited from 16 movement disorder clinics (Dujardin et al., 2010). They initially underwent a clinical consultation during which information about their motor, cognitive and psychiatric symptoms was acquired – as would be expected in a routine outpatient consultation. At that stage the clinician was asked to decide whether or not each patient had dementia. Immediately afterward each patient undertook a series of short cognitive assessments as recommended by the MDS algorithm for a level 1 diagnosis of PDD. The same clinician was again asked to decide whether or not the patient had dementia. Finally, at a later date within three weeks, each patient underwent a full neuropsychological assessment allowing a diagnosis of PDD to be made using MDS level 2 criteria. A different staff member blinded to the previous diagnoses given interpreted the neuropsychological results, which served as a reference standard. It was shown that 13 of 188 patients were diagnosed with PDD after the clinic consultation, increasing to 35 after short cognitive tests were performed. Level 2 testing identified 41 patients. No sensitivity and specificity data were provided about the clinicians' initial impression but the sensitivity and specificity of level 1 testing in reference to level 2 testing was 65.9% and 94.6%, respectively (Dujardin et al., 2010).

Barton et al. compared a level 1 diagnosis of PDD using the MDS diagnostic rating sheet (Figure 8) with a level 2 diagnosis in 91 PwPD (Barton et al.,

2012). Level 1 testing identified seven patients with PDD, whereas a further eight patients were identified using level 2 testing, resulting in a 46.7% sensitivity and 100% specificity of the level 1 diagnostic rating sheet.

It therefore appears that MDS level 1 criteria for PDD are specific when applied to PwPD but lack sensitivity. Sensitivity can be improved by using different cut-offs, as has been determined via the use a logistic regression model by Dujardin et al. (Dujardin et al., 2010). Sensitivity of the MDS diagnostic rating sheet can be increased by removing 'MMSE <26' and 'Absence of major depression' to reduce the eight item checklist to six items (Barton et al., 2012). Otherwise it has been argued that the MDS PDD diagnostic rating sheet is only a useful diagnostic tool when all eight criteria are met; when this does not occur full cognitive assessment is required to differentiate PDD from PD-MCI (Barton et al., 2012).

2.1.3 Summary

The MDS has published diagnostic criteria for PD-MCI (Litvan et al., 2012) and PDD (Emre et al., 2007), both of which allow a diagnosis to be made without the need for detailed neuropsychological testing – referred to as a level 1 diagnosis in this thesis. A level 1 diagnosis lacks sensitivity in PDD (Dujardin et al., 2010, Barton et al., 2012). Large scale validation of the more recent PD-MCI diagnostic criteria are awaited (Geurtsen et al., 2014) but it has been shown that three of the global cognitive screening tests that allow a level 1 PD-MCI diagnosis to be made may lack the required diagnostic accuracy (Marras et al., 2013). In both PDD and PD-MCI, level 2 diagnoses require a neuropsychological assessment, which is a time consuming process that relies on availability of neuropsychological expertise.

2.2 Epidemiology

2.2.1 Epidemiology of Parkinson's disease – mild cognitive impairment

Studies looking at the incidence and prevalence of PD-MCI have been performed before and after the publication of the MDS diagnostic criteria (Litvan et al., 2012). The MDS task force review of PD-MCI, which ultimately led to the production of diagnostic criteria, summarised the literature in 2011 (Litvan et al., 2011). Six cross-sectional and two prospective studies met the inclusion criteria applied by the MDS task force, totalling 974 PwPD. A mean of 26.7% of non-demented PwPD were found to have PD-MCI (range 18.9- 38.2%) (Litvan et al., 2011). This figure is comparable to a multi-centre pooled analysis study by Aarsland et al. published in 2010, which included seven different cohorts of PwPD without dementia, totalling 1,346 patients (Aarsland et al., 2010). In that study, PD-MCI was diagnosed if a participant scored at least 1.5 SDs below a normative mean in any one of three cognitive domains (visuospatial, memory or attention/executive function), although the types of neuropsychological tests performed varied between cohorts. Using this definition, 25.8% of subjects were classified as having PD-MCI. Memory was the most common domain to be affected (13.3%), followed by visuospatial function (11%) and then attention/executive function (10.1%). In both the MDS review and Aarsland et al. study, PD-MCI was more commonly a dysfunction of cognitive domains other than memory, in contrast to MCI in Alzheimer's disease (AD), i.e. in single domain PD-MCI, non-amnestic MCI was more common than amnestic MCI (Aarsland et al., 2010, Litvan et al., 2012).

More recent longitudinal studies have investigated the prevalence of PD-MCI using the MDS criteria. Pedersen et al. published data from 182 of the original 212 participants in the Norwegian ParkWest Study cohort. Using level 1 diagnostic criteria, 37 (20.3%) of the 182 had PD-MCI (Pedersen et al., 2013). In a study of 123 newly diagnosed PwPD, 35% fulfilled MDS PD-MCI criteria for a level 2 diagnosis at baseline, increasing to 53% after three

years of follow-up (Broeders et al., 2013). The ICICLE-PD study found that 42.5% of newly diagnosed PwPD met the MDS level 2 criteria for a diagnosis of PD-MCI (Yarnall et al., 2014).

2.2.2 Epidemiology of Parkinson's disease dementia

In a systematic review, 24.5% of 1767 PwPD from 12 studies with substantial methodological variation were found to have PDD (Aarsland et al., 2005). The four studies that most closely matched pre-defined inclusion criteria yielded a point prevalence of 31.1%. The same authors found that 3.6% of 4711 cases of dementia of all types were PDD (Aarsland et al., 2005), a much smaller percentage than accounted for by AD (50-70%) or vascular dementia (15-25%) (Qiu et al., 2009).

Dementia becomes more prevalent in the later stages of PD and so studies prospectively following PD cohorts to see how many develop PDD are more relevant that those looking at point prevalence. Such studies have had a profound impact because they have highlighted that a large proportion of PwPD will develop dementia (Williams-Gray et al., 2013, Perez et al., 2012, Auyeung et al., 2012, Hely et al., 2008). Four longitudinal studies are discussed separately below and, of note, the diagnostic criteria for PDD are not uniform; only Perez et al. use the MDS PDD diagnostic criteria, applied retrospectively (Perez et al., 2012). Overall, ten years after PD diagnosis approximately 50% will progress to PDD:

- The study with longest follow-up is the Sydney Multicentre Study of Parkinson's Disease. This followed a cohort of 136 newly diagnosed PwPD over a 20-year period, by which time 83% of the 30 survivors had developed dementia. Overall, 75% of the total cohort developed dementia before death (Hely et al., 2008).

- The Cambridgeshire Parkinson's Incidence from GP to Neurologist (CamPaIGN) study attempted to follow all newly diagnosed cases of PD between 2000 and 2002 in Cambridgeshire, England, providing a population based cohort rather than clinical-trial or clinic-based cohort. Ten-year outcome of 142 patients showed that the cumulative proportion of PwPD who developed dementia, defined by an MMSE score of ≤24 and the DSM-IV criteria, was 46% (Williams-Gray et al., 2013).

- A French population based study that screened 3726 people over the age of 65 for 15 years identified 44 new cases of PD amongst the cohort. Of these, 20 (45%) developed PDD at a mean age of 82.9 years and a median follow-up time of 4.9 years since PD diagnosis. As a percentage of PD survivors, 50% had dementia at eight years of follow-up and 70% after 12 years (Perez et al., 2012).

- A similar risk of dementia was found in a Chinese clinic-based study of 171 newly diagnosed patients followed up for a mean of 11.3 years, at which point the cumulative proportion with dementia was 49% (Auyeung et al., 2012).

The relative risk of PwPD developing dementia compared to someone without PD varies across studies. In one prospective cohort of 140 PwPD and 572 HC a relative risk of 1.7 was found (Marder et al., 1995) but in a smaller UK study where 86 PwPD were compared with HC the relative risk was 5.1 (Hobson and Meara, 2004).

2.2.3 Summary

A literature review performed by an MDS task force and a multi-centre pooled analysis both report that approximately 25% of non-demented PwPD have PD-MCI (Litvan et al., 2011, Aarsland et al., 2010), but other

studies have shown that the incidence can be higher than this, even at the time of PD diagnosis (Yarnall et al., 2014, Broeders et al., 2013). The reported prevalence of PD-MCI varies depending on the definition used, for example whether or not studies use the MDS PD-MCI diagnostic criteria, whether a level 1 or level 2 diagnosis is made and the SD cut-off scores used to define abnormal results on neuropsychological tests. Prevalence is also dependent on the population studied, for example clinic cohorts versus community based studies (Yarnall et al., 2013). This highlights the need for further validation of the MDS PD-MCI guidelines and assessment of their usefulness as a tool to identify those most at risk of developing PDD (Yarnall et al., 2014). Furthermore, there is a need to directly compare clinical diagnosis of PD-MCI with pathological changes in the brain, something that has not been undertaken on a large scale at the time of writing.

Despite differences in the cohort type and diagnostic criteria for PDD, it seems that approximately half of PwPD will develop dementia within ten years of diagnosis. Compared to age matched HC, PwPD are at a greater risk of developing dementia. It may be that dementia is an inevitable consequence if a person with PD survives long enough, but 17% of survivors do not have dementia 20 years after a diagnosis of PD (Hely et al., 2008). Therefore, It is also possible that the dementia free survivors have a variant of PD, yet to be discovered, that is different at the pathological or biochemical level to those who develop PDD.

2.3. Risk factors for the development of cognitive impairment in Parkinson's disease

A number of studies have found risk factors for the development of both PD-MCI and PDD. Before looking at those in closer detail, it important to establish the current understanding regarding the conversion of PD-MCI to PDD. In AD, where the concept of mild cognitive impairment (MCI) was first introduced, the term has become synonymous with a one-way

transition state between normal cognition and dementia, although it is possible for those with AD related MCI to revert back to normal cognition (Goldman et al., 2014).

The literature looking at the outcome of PD-MCI in longitudinal studies is limited but clearly suggests that PD-MCI is a risk factor for the development of PDD. The oldest study classified 34 PwPD as having normal cognition and 38 as having PD-MCI (Janvin et al., 2006). Four years later, 59 of the original 72 participants were reviewed and 62% of those with PD-MCI at baseline had developed dementia compared to 20% of the cognitively intact group. A logistic regression model controlling for age, disease stage, education and gender demonstrated that PD-MCI was strongly associated with PDD development, with an odds ratio of 5.1 (Janvin et al., 2006).

More recently, a three-year follow-up of 182 participants in the Norwegian ParkWest Study cohort who were classified as having normal cognition (79.7%) or PD-MCI (20.3%) was published (Pedersen et al., 2013). Ten of the 37 (27%) with PD-MCI three years earlier had converted to PDD, compared to one of the 145 with normal cognition (0.7%), a relative risk of 39.2. This study also found that eight of the original 37 PwPD (22%) classified as PD-MCI had reverted to normal cognition at three-year follow-up (Pedersen et al., 2013), implying that MCI can be reversible in PwPD. More robust longitudinal studies using MDS PD-MCI level 2 diagnostic criteria are required to investigate the subjects who transition between PD-MCI and normal cognition.

The third longitudinal study to assess cognition at baseline and then conversion to dementia is the CamPaIGN cohort. Although PD-MCI was

not studied, it was shown that deficits in semantic fluency [4] and visuospatial function at baseline were risk factors in the development of cognitive decline at 3.5 and 5.2 years of follow-up (Williams-Gray et al., 2007, Williams-Gray et al., 2009). In contrast, deficits in executive function at baseline were not associated with cognitive decline. The significance of this finding is discussed in section 2.6.

If PD-MCI is a major risk factor for the development of PDD then one would expect that the two cognitive states, which form a spectrum of cognitive impairment, to share other risk factors. This appears to be the case with good evidence to suggest that both PD-MCI and PDD are associated with increased age and PIGD motor phenotype. This is discussed in more detail below. Other risk factors for developing cognitive impairment in PD are level of education (Elgh et al., 2009), severity of motor deficit (Williams-Gray et al., 2007, Williams-Gray et al., 2009) and male gender (Aarsland et al., 2010).

2.3.1 Age

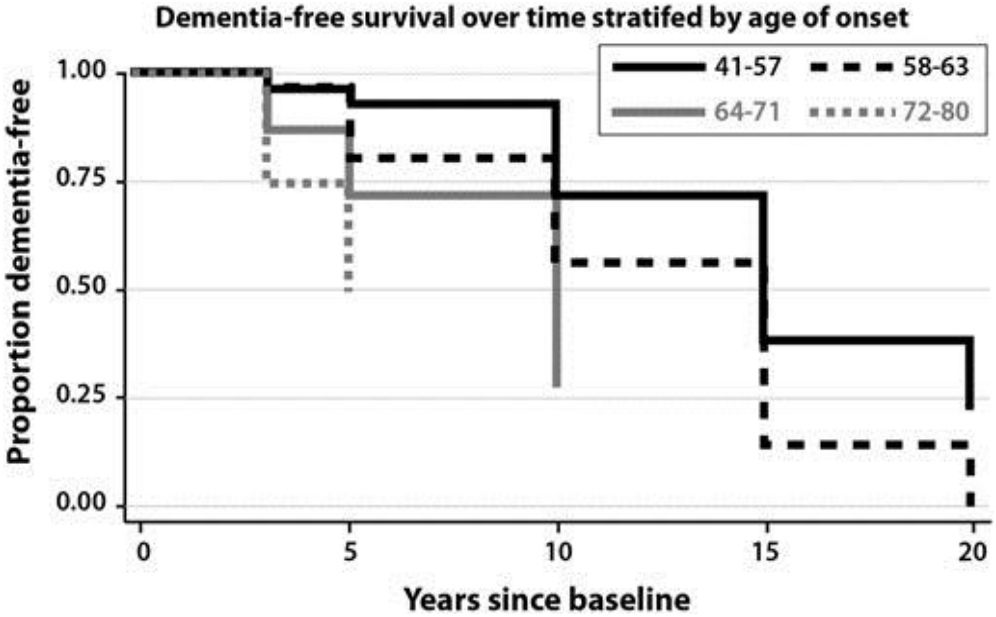
Age is the biggest risk factor for the development of PDD. Disentangling the effect of age, age at onset of PD, and duration of disease in cohort studies of PwPD is complex and there is a heterogeneous approach to this in the literature. Prospective analysis of two community-based cohorts incorporating 487 PwPD and over 2500 HC concluded that age at onset of disease did not have a significant effect on progression to PDD over and above age at baseline assessment, i.e. it is age, rather than age of onset of PD, that conveys an increased risk of developing PDD (Aarsland et al., 2007).

Findings from the Sydney Multicentre Study suggest a significantly longer dementia free survival in younger onset PD compared with later onset, such that *" a subject with a PD onset age of 75 years is 4.8 times as likely as*

[4] Semantic fluency – a type of verbal fluency test based on semantics, or categories. For example, naming as many animals as possible in a minute.

a subject with a PD onset age of 55 years to develop dementia" (Reid et al., 2011) (Figure 9).

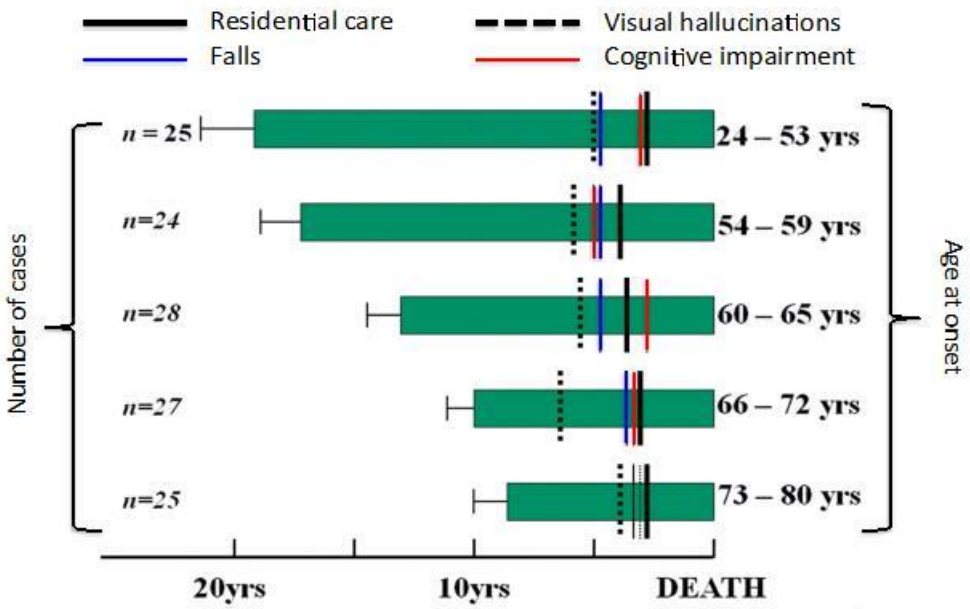
Figure 9: Dementia-free survival curves plotted for participants from the Sydney Multicentre Study



Legend: Those with dementia when the study started have been excluded and the groups are defined by age of onset of PD divided into quartiles. This figure illustrates that the younger the age of diagnosis of PD, the fewer cases of PDD will be present at any given time point from PD diagnosis. Reproduced from Reid et al., 2011 with permission (Reid et al., 2011).

A clinicopathological study of 129 proven cases of PD suggested that four clinical milestone – cognitive impairment, falls, visual hallucination and the need for residential care – are a common feature of advanced PD and mark a terminal phase of decline with death occurring approximately five years after onset of visual hallucinations (Kempster et al., 2010). However, those with early onset disease had significantly longer survival prior to the onset of the clinical milestones than those who developed PD later if life (Figure 10) (Kempster et al., 2010).

Figure 10: Disease course and disability of 129 Parkinson's disease subjects divided into five age-at-onset groups



Legend: The green bars represent the time from diagnosis of PD until death. The PD subjects have been divided into five groups based on age at onset. Those diagnosed with PD at a younger age have a longer interval until onset of the four clinical milestones heralding terminal phase of decline. Adapted from Kempster et al., 2010 with permission (Kempster et al., 2010).

2.3.2 Motor phenotype

There are two broad clinical motor phenotypes in PD, known as PIGD and TD. PIGD phenotype is associated with a more rapid cognitive decline than TD phenotype. After two years of follow up, a longitudinal study of 40 PwPD with normal cognition at baseline showed that four of 16 participants with PIGD phenotype had developed dementia but none of the TD group had. A linear regression model demonstrated that cognitive decline, as measured by changes in MMSE score, was associated with the presence or absence of PIGD phenotype (Burn et al., 2006).

In a larger population based observational study of 171 PwPD with normal cognition, a change in motor phenotype from TD to PIGD was associated with cognitive decline and development of PDD (Alves et al., 2006). At baseline, 92 of the 171 (54%) participants had PIGD phenotype, 43 TD and 36 indeterminate. At four and eight year review, the PIGD phenotype

became more common within the cohort, present in 93 of 128 (73%) at four years and 74 of 84 (88%) at eight years. Thirty-five of the TD phenotype participants at baseline were reclassified at PIGD at four years, and of those 16 (46%) had developed dementia compared to none of those who remained TD (Alves et al., 2006). At eight years of follow up, no further patients with TD or indeterminate phenotype had developed PDD, which was present in 48 of 74 (65%) of the PIGD group. Of the 20 participants who had changed phenotype from TD to PIGD between four and eight-year review, ten (50%) had demented. Therefore, in this study, dementia was almost exclusively a condition developing in PIGD phenotype. Additionally, transition of phenotype from TD to PIGD was irreversible and a logistic regression model showed that the odds ratio of developing dementia if a change in phenotype from TP to PIGD occurred was 56.7 when compared to those who remained TD (Alves et al., 2006).

The CamPaIGN study determined that the non-TD phenotype (i.e. those with PIGD or indeterminate phenotypes) is associated with a greater risk of cognitive impairment, as measured by annual decline in MMSE score, using bivariate correlation analysis although motor phenotype was non-significant in a multiple regression model (Williams-Gray et al., 2009). Poletti et al. demonstrated that 13 of 56 (23%) newly diagnosed PwPD with PIGD phenotype had MCI, defined on the basis of neuropsychological test scores 1.5 SD below normative means, compared to only 3 of 48 (6%) with TD phenotype (Poletti et al., 2012).

2.3.3 Genetic risk markers

The major genetic risk factors associated with PD-CI are briefly summarised in Table 2.

Table 2: Genetic risk factors linked to cognitive dysfunction in Parkinson's disease

Genetic risk factor	Risk of cognitive dysfunction
Catechol-O-methyltransferase (COMT) (see 2.6.1)	Single nucleotide polymorphism alters enzyme activity (Chen et al., 2004). Increased efficiency reduces dopamine availability which affects performance in some tasks of executive function (Williams-Gray et al., 2009)
Microtubule associated protein tau (MAPT)	H1 haplotype associated with 12-fold increase in dementia development compared to H2 haplotype in CamPaIGN cohort (Williams-Gray et al., 2009). Not replicated in some studies (Ezquerra et al., 2008).
Apolipoprotein E (APOE)	Meta-analysis suggests a 1.74 increase in dementia in those with PD who are APOE **ε**4 allele carriers (Huang et al., 2006).
Glucocerebrosidase	Heterozygous mutation may be associated with increased risk of developing dementia in those with PD (Chahine et al., 2013).

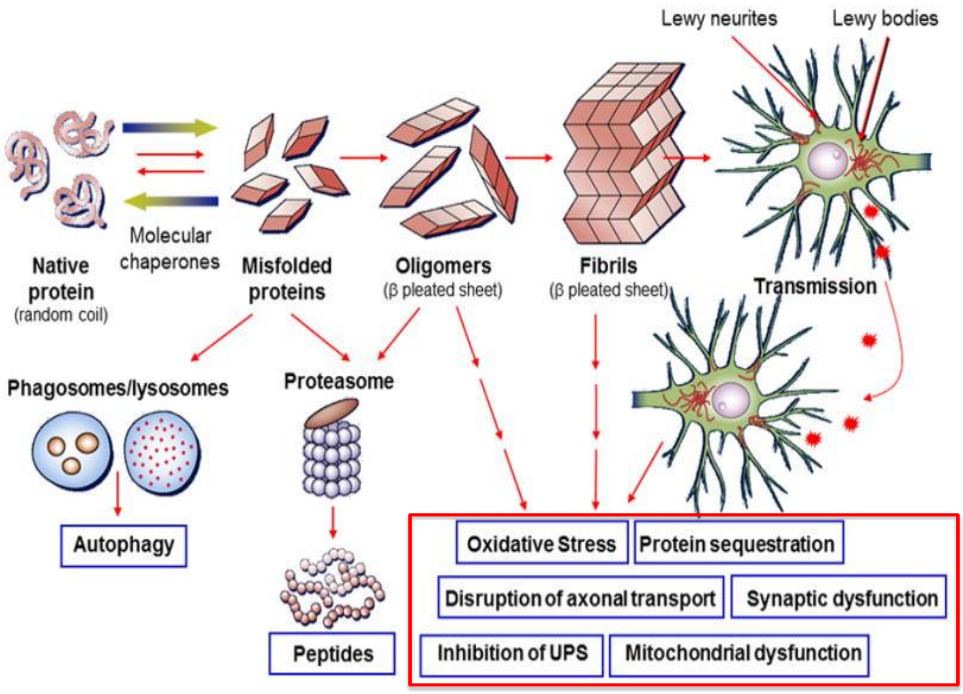
Abbreviations: APOE, apolipoprotein E; CamPaIGN, Cambridgeshire Parkinson's Incidence from GP to Neurologist cohort study. Adapted from Cosgrove et al., 2015 with permission (Cosgrove et al., 2015).

2.4 Pathological change in the development of cognitive decline in Parkinson's disease

Continued debate exists regarding the pathological correlates of PDD. The development of Lewy pathology in the limbic system and neocortex appears to be the major determinate in dementia development, but tau and amyloid deposition are also important (Svenningsson et al., 2012).

α-syn is the principle component of Lewy pathology. The pathogenicity of α -syn was established after identification of mutations in the α-syn gene – SNCA – in familial cases of PD (Polymeropoulos et al., 1997). α-syn is involved in vesicular transport and has an alpha-helical conformation. Misfolding of α-syn leads to conformational change from an alpha-helical to beta-pleated sheet structure, which further aggregates into higher-order structures such as amyloid fibrils (Irwin et al., 2013). The insoluble amyloid fibrils are thought to exert a neurotoxic effect via various mechanisms including oxidative stress, synaptic dysfunction and impaired axonal transport (Figure 11) (Irwin et al., 2013).

Figure 11: The processes involved in the pathogenesis of alpha-synuclein



Legend: The top part of the diagram shows the misfolding and then aggregation of abnormal forms of α-syn, the principle component of Lewy bodies and Lewy neurites. The mechanisms by which pathological species of α-syn causes neuronal toxicity are shown in the red box in the lower right of the diagram. This occurs because the abnormal forms of α-syn overwhelm phagosomes, lysosomes and proteases that naturally regulate α-syn quality. Abbreviations: UPS, ubiquitin proteasome system. Adapted from Irwin et al., 2013 with permission (Irwin et al., 2013).

Braak and colleagues proposed a staging system for the brain pathology in PD based on α-syn staining of 168 human brains (Braak et al., 2003). Using the assumption that non-symptomatic cases would have the mildest pathology and the most clinically severe cases have the most dramatic pathology, a caudo-rostral progression of Lewy pathology was proposed, beginning in the medulla and ascending to the neocortex (Braak et al., 2003). The proposed classification system was based on the consistent anatomical pattern of lesion distribution rather than the lesion load at each site, which was found to vary amongst cases. The six stages of the Braak PD classification are outlined in Table 3.

Table 3: The six stages of pathological spread of alpha-synuclein in Parkinson's disease

Braak stage	Distribution of α-syn
Stage 1: Medulla oblongata	Lesions in the dorsal IX/X motor nucleus and/or intermediate reticular zone
Stage 2: Medulla oblongata and pontine tegmentum	Pathology of stage 1 plus lesions in caudal raphe nuclei, gigantocellular reticular nucleus, and coeruleus–subcoeruleus complex
Stage 3: Midbrain	Pathology of stage 2 plus midbrain lesions, in particular in the substantia nigra pars compacta
Stage 4: Basal prosencephalon and mesocortex	Pathology of stage 3 plus prosencephalic lesions. Cortical involvement is confined to the temporal mesocortex (transentorhinal region) and allocortex (CA2-plexus). The neocortex is unaffected
Stage 5: Neocortex	Pathology of stage 4 plus lesions in high order sensory association areas of the neocortex and prefrontal neocortex
Stage 6: Neocortex	Pathology of stage 5 plus lesions in first order sensory association areas of the neocortex and premotor areas, occasionally mild changes in primary sensory areas and the primary motor field

Legend: The caudo-rostral propagation of Lewy pathology in PD divided into six stages. Involvement of the SNpc occurs at Stage 3. Adapted from Braak et al., 2003 with permission (Braak et al., 2003).

The stereotyped progression of α-syn in the majority of cases of PD is suggestive of transmission between cells, leading some authors to speculate that PD might be a prion disorder (Olanow and Brundin, 2013).

In support of that theory, a number of studies using mouse models have demonstrated that α-syn can transfer between host and graft (Hansen et al., 2011). In addition, a group of PwPD who died more than a decade after foetal mesencephalic brain tissue grafting had evidence of beta-pleated α-syn within the graft that was not present in graft recipients who died within 18 month of the procedure (Li et al., 2008). Accumulation of abnormal α-syn in the graft is suggestive of direct transmission from the striatum of affected recipients although no direct human-to-human transmission of PD has yet been demonstrated.

As discussed in Chapter 1, the caudo-rostral propagation of Lewy pathology is supported by the pre-motor phase of PD identified in some patients, characterised by impaired sense of smell (thought to be caused by Lewy pathology in the olfactory bulb, stage 1), autonomic dysfunction (raphe nuclei of the medulla and caudal pons, stage 2) and REM sleep behaviour disorder (subcoeruleus nuclei in the pons, stage 2). However, some pathological studies have identified cases where Lewy pathology did not follow the caudo-rostral propagation proposed by Braak, suggesting that neocortical Lewy pathology is not always dependent on the presence of subcortical pathology and that simultaneous cortical and subcortical Lewy body development is possible (Parkkinen et al., 2008).

Pathological stage has been linked to cognitive function in PwPD by some studies. For example, a correlation between MMSE and Braak pathological staging was found in a cohort of 88 cases of PD; stage 4 associated with MMSE score of 21-24, stage 5 with MMSE 11-20 and stage 6 MMSE 0-10 (Braak et al., 2005). Using the Consensus Guidelines for Pathological Diagnosis of Dementia with Lewy Bodies (McKeith et al., 1996) – where semi-quantitative Lewy body counts can be used to subdivide DLB into brainstem, limbic or neocortical subtypes – increasing Lewy pathology has been associated with dementia and visual hallucinations in a clinicopathological study (Kempster et al., 2010).

However, not all brains with evidence of Lewy pathology within the neocortex are associated with a history of cognitive dysfunction. Some authors have described this as 'incidental Lewy body disease' (ILBD) (Irwin et al., 2013). In a study of 226 autopsy cases of brains with α-syn positivity unrelated to ante-mortem diagnosis, only 25% (n = 6) of Braak stage 5 and 50% (n = 42) of Braak stage 6 had a diagnosis of dementia (Parkkinen et al., 2008). This suggests that the distribution of α-syn pathology cannot predict ante-mortem clinical status. ILBD has led some authors to speculate that α-syn may be a marker of neural protection rather than cause of neural death (Parkkinen et al., 2008), or alternatively people with ILBD may have died prior to development of cognitive dysfunction and parkinsonism (Irwin et al., 2013). Conversely it is possible, although rare, for people with a diagnosis of PDD to not have evidence of significant cortical Lewy pathology (Braak et al., 2003), implicating other factors in the development of cognitive dysfunction.

A number of studies have identified an association between the pathological changes associated with AD – namely tau neurofibrillary tangles (NFT) and amyloid beta plaques (Aβ) – and cognitive function in PDD. In one study of 56 pathologically confirmed cases of PD in which 29 had PDD, it was found that a combination of Lewy pathology, tau and Aβ pathology was a better neuropathological correlate of PDD than any of the pathologies in isolation (Compta et al., 2011). In the PD cases, tau pathology was confined to the entorhinal gyrus, but extended to other parts of the hippocampus and lateral temporal neocortex in cases of PDD. In 15 cases where MMSE had been performed in the year prior to death, a correlation between MMSE score and Braak staging for AD was found and a higher cortical Aβ score was associated with a quicker progression to dementia. However, the association was lost when age was combined with cortical Aβ score, implying that age and the development of abnormal amyloid plaques are closely related, as has been found in larger pathological brain studies (Matthews et al., 2009).

In another pathological study of 140 PwPD, 92 of which had an ante-mortem diagnosis of probable PDD, Lewy pathology was found to have a greater sensitivity for dementia (74%) than AD pathology (55%), although AD pathology had a greater specificity (Irwin et al., 2012). Thirty-eight percent of PDD cases had co-existing AD pathology in that series in keeping with other studies suggesting that 40-50% of pathologically proven cases of PDD have enough NFT and Aβ pathology to have an additional diagnosis of AD, i.e. co-exiting PDD and AD (Irwin et al., 2013). Amyloid plaque burden and NFT burden are higher in PDD than PD cases and work in mice models suggests that Lewy pathology, tau and Aβ might be synergistic. For example, introducing a mutant human α-syn transgene into mice with AD pathology leads to a more rapid cognitive decline and marked pathological change in contrast to mice with AD pathology alone (Clinton et al., 2010). Synergy of AD and Lewy pathology could explain the apparent shorter duration of disease in those with Lewy pathology and AD pathology versus those with just Lewy pathology (Irwin et al., 2012). Co-exiting PDD and AD pathology is more likely to be seen in elderly patients because of the association between increasing age and AD pathology (Matthews et al., 2009).

The role of vascular disease, cerebral amyloid angiopathy and hippocampal sclerosis in the development of cognitive decline in PwPD remains uncertain. The former two pathologies are common in the general population with increasing age and therefore present to variable degrees in autopsy studies of PwPD, where the average age is most often >75 years (Halliday et al., 2014).

Only a limited number of pathological studies have been performed on those with PD-MCI. As with PDD, it seems that a combination of Lewy pathology and AD pathology co-exist and the exact role of each is not yet determined (Halliday et al., 2014)

2.4.1 Summary

The pathological changes seen in those with PDD are complex and represent a variable combination of α-syn, tau, amyloid, age and other factors such as vascular disease. However, the caudo-rostral propagation of Lewy pathology is likely to be the major driver behind cognitive decline (Irwin et al., 2013, Halliday et al., 2014). Pathological damage results in changes to chemicals and neurotransmitter systems in the brain and the relationship between these and cognitive performance is discussed in section 2.6.

2.5. Biomarkers to detect cognitive decline in Parkinson's disease

Potential biomarkers for the detection of PD-CI include neuroimaging, CSF and blood constituents. Some examples are provided in in Table 4.

Table 4: Potential biomarkers for the detection of cognitive decline in Parkinson's disease

Potential biomarker	Example of evidence
MRI	Several regions of the limbic system are atrophied in PDD compared to PD (Duncan et al., 2013). Parietotemporal cortical thinning associated with cognitive scores in PD-MCI (Segura et al., 2014).
CSF	Aβ levels lower in PD-MCI than PD and Aβ-42 levels correlate with MoCA in PD-MCI group (Yarnall et al., 2014).
Blood	EGF levels able to discriminate between PD and PDD (Chen-Plotkin et al., 2011) and lower levels at baseline associated with poorer performance on executive function and semantic fluency tests at two years (Pellecchia et al., 2012).

Abbreviations: Aβ, amyloid beta; EGF, epidermal growth factor. Reproduced from Cosgrove et al., 2015 with permission (Cosgrove et al., 2015).

A combination of different investigative techniques to produce a panel of tests capable of predicting cognitive decline – as utilised in AD – may be more realistic than identifying a single predictive test, especially given the heterogeneous pathology and cognitive profile of PD-CI. In one prospective longitudinal study of 27 PwPD it was found that a combination of baseline reduction in CSF Aβ42, baseline cognitive assessment demonstrating posterior cortical dysfunction, and baseline MRI changes of cortical thinning focused around the anterior cingulate were 100% sensitive in predicting development of dementia at 18 month follow-up (Compta et al., 2013). However, the small sample size, single time-endpoint, short follow-up time and failure to sub-divide cases into normal cognition and MCI at baseline are limitations of this study.

2.6 Linking pathological change with cognitive deficit

The cognitive deficits in PwPD can vary from person to person but the core cognitive domains affected are attention and working memory, executive function, language, memory, and visuospatial function (Litvan et al., 2012, Emre et al., 2007). As has been discussed in section 2.4, the neuropathological processes occurring in PD are complex and the degree of involvement of α-syn, tau and vascular disease differs between each person affected over time. This causes variable change to neurotransmitter systems within the brain of each individual with PD, making analysis of cognitive impairment particularly challenging. In addition, other factors such as age, cognitive reserve and genetics are all likely to contribute to the cognitive dysfunction seen in each individual with PD. This section of the chapter reviews some of the important findings and hypotheses that link cognitive impairment with pathological and chemical changes in the brain.

2.6.1 Executive function deficits and dopaminergic depletion

A unifying definition of executive function does not exist but two examples are provided below:

"The cognitive process that regulates an individual's ability to organise thoughts and activities, prioritise tasks, manage time efficiently, and make decisions"

(thefreedictionary.com, 2014)

"A product of the coordinated operation of various processes to accomplish a particular goal in a flexible manner"

(Funahashi, 2001)

In other words, executive function allows an individual to problem solve, to sequence and to modify behaviour in response to a changing situation. Formal tests of executive function include set-shifting, planning, or tests of fluency (Elliott, 2003). It has long been accepted that the frontal cortex, more specifically the pre-frontal cortex, is the area of the brain where executive functions are governed and in neuropsychological literature the terms 'executive function' and 'frontal lobe function' have become synonymous (Elliott, 2003).

It has been demonstrated that PwPD show evidence of deficits in executive function and some studies have found that the severity of deficit is linked to the severity of motor symptoms. For example, 44 PwPD were compared with 44 HC matched for age and IQ as they performed a battery of tests of executive function, including a modified version of the Tower of London test (TOL) [5], performed on a computer as part of an assessment known as the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Owen et al., 1992). The PwPD were divided into three groups; non-medicated, 'medicated mild' (Hoehn & Yahr stage (H&Y) I-II) and 'medicated severe' (H&Y III-IV). All three groups were impaired at

[5] The Tower of London test requires participants to move different coloured beads on a pegboard, adhering to certain rules. Predominantly it is a test of planning ability, which is an executive function.

attentional shift [6] but other deficits of executive function (for example spatial working memory (SWM) and initial thinking time when planning movement solutions on the TOL) were only present in the PwPD with more advanced disease, i.e. were normal in the non-medicated group. The profile of deficits in executive function in PwPD is similar to that of young adults with frontal lobe damage, supporting the theory that reduced dopaminergic stimulation of frontostriatal cortical loops is responsible for deficits in executive function in PD (Owen et al., 1992).

Another source of support for this theory are studies that have shown deterioration in executive functions when PwPD are tested whilst *off* compared to *on*. For example, Lange et al. demonstrated that SWM and aspects of planning (initial thinking time on the TOL) deteriorated when *off* in ten PwPD (Lange et al., 1992), whilst others have established that facets of executive function such as flexibility of attention are improved when PwPD are *on* compared to *off* (Cools et al., 2003). However, despite the improvement in some aspects of executive function with dopaminergic stimulation, no improvement was found in cognitive features such as visual recognition memory (Lange et al., 1992), a complex cognitive process thought to involve the hippocampus and entorhinal cortex (Fahy et al., 1993).

The notion that levodopa either has a beneficial effect (on aspects of executive function) or makes no difference (visual memory and learning tasks) to cognition was challenged by the discovery that reversal learning [7]

[6] Attentional shift is the ability to direct attention towards a particular stimulus in order to increase efficiency of action, whilst simultaneously inhibiting attention towards other stimuli.

[7] Reversal learning – a learnt discrimination, for example choosing one colour in a two colour task, is reversed such that the individual is required to learn to reverse the original choice, i.e. choose the different colour.

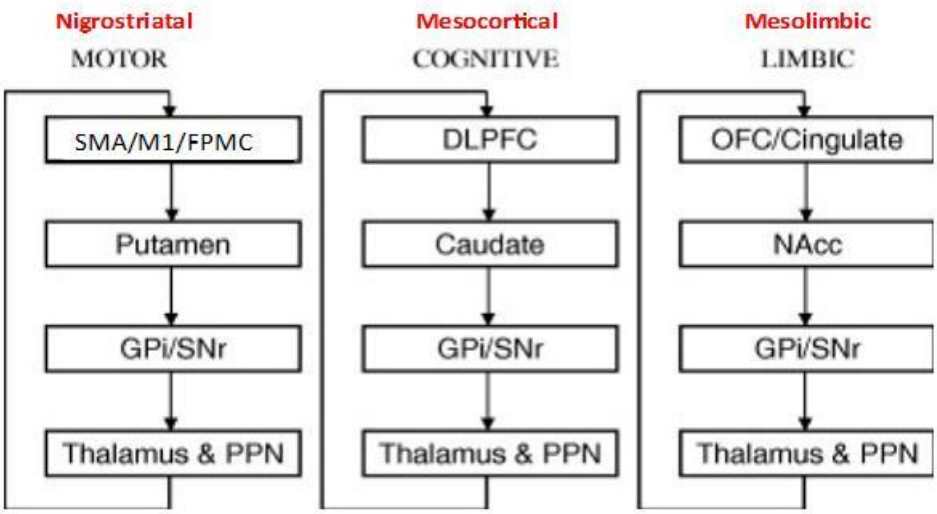
and motor sequence learning [8] can be impaired when PwPD are tested whilst *on* compared to *off* (Vaillancourt et al., 2013). For example, Swainson et al. demonstrated that medicated PwPD with moderate (H&Y I - II) or severe (H&Y III - IV) disease were slower to adapt to reversal of two-colour pattern test than non-medicated patients (Swainson et al., 2000). Another group showed that 14 PwPD were slower to learn a finger sequencing task than age-matched HC when *on*, but learnt at levels comparable to HC when tested whilst *off* (Kwak et al., 2010).

The theory proposed to explain why executive functions such working memory, flexibility and response inhibition improve in PwPD when taking medication, whereas reversal learning and motor sequence learning deteriorate is known as the 'dopamine overdose hypothesis' (Gotham et al., 1988). It is based around the fact that degeneration of dopaminergic neurons within the SNpc occurs in sequence in PwPD; the ventral lateral tier, whose dopaminergic projections primarily connect to the dorsal putamen, is most severely affected (Fearnley and Lees, 1991). Cognitive functions mediated by the dorsal putamen (executive functions such as flexibility and response inhibition as well as working memory) are improved by dopaminergic stimulation early in the disease course. However, the dorsal tier, whose dopaminergic projections primarily connect to the ventral striatum, is less affected early in the disease course and cognitive functions medicated by this pathway (probabilistic reversal learning and motor sequence learning), involving the nucleus accumbens and caudate nucleus, are effectively 'overdosed' by dopaminergic stimulation at this stage (Kehagia et al., 2010a). Longitudinal positron emission tomography (PET) studies have demonstrated the dorsal-ventral gradient of reduced dopamine storing within the putamen persists as disease progresses but reduces in prominence over time (Nandhagopal et al., 2009).

[8] Motor sequence learning – the ability to combine distinct components of action into an interconnected, cohesive movement.

In a seminal paper published in 1986 it was proposed that the basal ganglia contain a series of parallel neural networks that link different parts of the cerebral cortex with the basal ganglia, thalamus and brainstem (Alexander et al., 1986). Processing of diverse inputs within each individual circuit was suggested to occur whereas processing between circuits was not (Lewis and Barker, 2009). A basic version of this theory is that three core pathways exist; motor (nigrostriatal), cognitive (mesocortical) and limbic (mesolimbic) (Figure 12). Although the concept of distinct neural networks is a simplification – single cell labelling studies on rodents and monkeys have shown extensive collateralisation throughout the basal ganglia (Parent et al., 2000) – the model proposed by Alexander et al. (Alexander et al., 1986) provides a basis for understanding and it remains likely that dopamine plays a key role in the *"complex spatiotemporal sequence of neural events that ensures the flow of cortical information through the basal ganglia" (Lewis and Barker, 2009).*

Figure 12: A schematic representation of the motor, cognitive and limbic neural networks of the basal ganglia



Legend: Thalamic output of the motor loop is to the SMA, primary motor cortex (M1) and frontal premotor cortex (FPMC) (Galvan et al., 2015). Thalamic output of the cognitive loop is to the DLPFC. Abbreviations: SMA, supplementary motor area; M1, primary motor cortex; FPMC, frontal premotor cortex; DLPFC, dorsolateral prefrontal cortex; Cingulate, cingulate cortex; OFC, orbitofrontal cortex; NAcc, nucleus accumbens; GPi, globus pallidus interna; SNr, substantia nigra pars reticulata; PPN, pedunculopontine nucleus. Adapted from Lewis and Barker, 2009 with permission (Lewis and Barker, 2009).

A basic knowledge of the different neural networks within the basal ganglia is important because the mesocortical dopaminergic projections have also been implicated in the cognitive profile of PwPD. Like the nigrostriatal projections, excessive dopaminergic stimulation can have deleterious consequences on the mesocortical pathway (Kehagia et al., 2013), which receives dopaminergic stimulation from neurons located in the ventral tegmental area and innervates the dorsolateral prefrontal cortex (DLPFC) (Vaillancourt et al., 2013, Lewis and Barker, 2009). Establishing the effect of dopamine levels on the functioning of the DLPFC has occurred indirectly, by studying cohorts of PwPD who have been stratified according to COMT gene polymorphism (Williams-Gray et al., 2009). A methionine to valine polymorphism at residue 158 of the COMT gene exists and each valine substitution is associated with a fourfold increase in the efficiency of COMT and therefore a more rapid removal of dopamine (Chen et al., 2004).

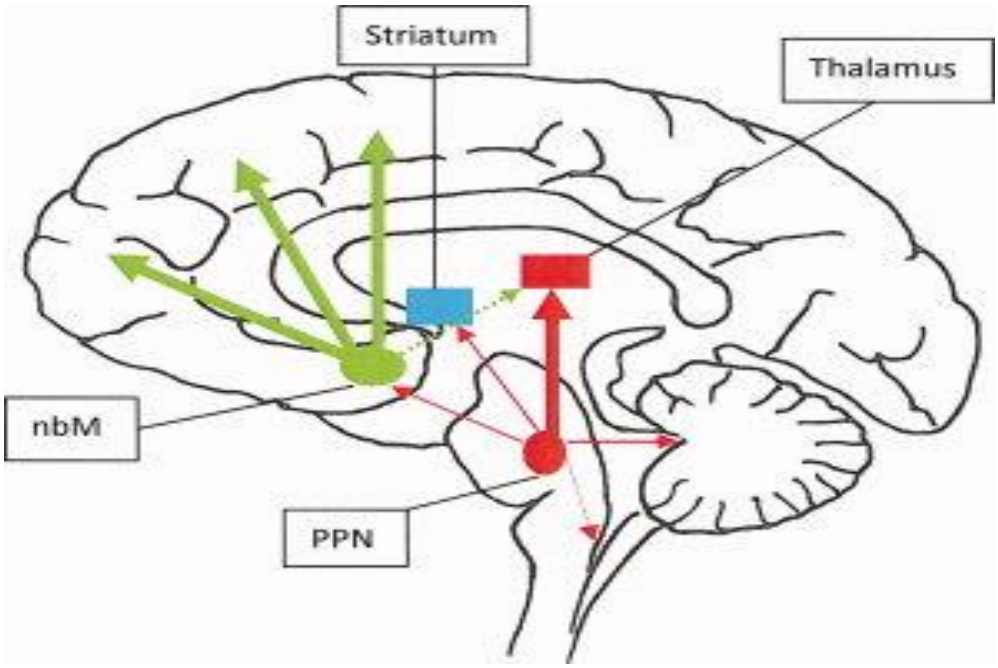
Furthermore, because dopamine transporters are relatively absent in the DLPFC, levels of COMT are the major factor in regulating dopamine levels (Kehagia et al., 2013). Four hundred and twenty-five COMT stratified PwPD merged from two separate but clinically similar cohorts in the CamPaIGN cohort had executive function tested using the CANTAB version of the TOL. It was shown that in 'early PD' (<1.6 years disease duration) the methionine homozygotes performed worse but in the 'later' PD group (>1.6 years since diagnosis) performance was improved (Williams-Gray et al., 2009). This suggests that, in the early stages of PD, methionine homozygosity, and therefore relative inefficiency of COMT, results in overdosing of the DLPFC leading to impaired executive function. As the disease progresses, and dopaminergic stimulation of the mesocortical pathway is reduced, the inefficiency of COMT metabolism results in higher, more optimum, levels of DLPFC dopamine. Further advancement of disease then reduces available dopamine in the DLPFC leading to impaired executive function due to dopamine deficiency. Each individual with PD will have a different starting point on this 'inverted U shape' pattern (poorer performance, better performance, poorer performance) depending on COMT polymorphism status (Vaillancourt et al., 2013, Williams-Gray et al., 2009).

2.6.2 The role of acetylcholine in the cognitive profile of Parkinson's disease

Acetylcholine (ACh) is a neurotransmitter found throughout the brain and there is growing evidence to suggest that it may play a fundamental role in the cognitive deficits seen in PD. The two major acetylcholine receptor types are muscarinic (mAChR) and nicotinic (nAChR). The predominant nAChR subtype is α4β2 and the distribution of nAChR is greatest in the SNpc, striatum and thalamus (Court and Clementi, 1995). The major site of mAChR is the striatum although high levels are also found throughout the neocortex as well as the amygdala and hippocampus (Muller and Bohnen, 2013). Cholinergic projections originate from three main sources in the

brain (Figure 13). The cortex is supplied by the basal forebrain nuclei, particularly the nucleus basalis of Meynert (nbM). The pedunculopontine nucleus (PPN) is the major source of cholinergic projections to the thalamus as well as projecting to the spinal cord, the cerebellum and numerous brainstem nuclei (Muller and Bohnen, 2013, Yarnall et al., 2011). The third source of acetylcholine are the cholinergic interneurons of the striatum, which account for less than 2% of the total cholinergic neuron population (Yarnall et al., 2011).

Figure 13: The three major sources of acetylcholine in the human brain



Legend: The PPN projects predominately to the thalamus (red); the nbM is the major source of cholinergic projections to the cortex (green). The interneurons of the striatum are shown in blue. Abbreviations: nbM, nucleus basalis of Meynert; PPN, pedunculopontine nucleus. Reproduced from Yarnall et al., 2011 with permission (Yarnall et al., 2011).

ACh is thought to be particularly important in regulating attention via projections from the basal forebrain nuclei to the DLPFC in humans (Bloem et al., 2014). Evidence to support this comes from animal models in which lesions to the prefrontal cortex produce attentional deficits and also neurophysiological studies that demonstrate poorer performance on visual

attention tasks after cholinergic deafferation of the prefrontal cortex (Totah et al., 2009). The exact mechanism by which ACh modulates attention is unknown although it is established that ACh levels within the prefrontal cortex are transiently increased during attentional tasks in rats and humans (Howe et al., 2013).

It has long been established that both the nbM and the PPN undergo degeneration in PD. For example, compared to HC and in the absence of cortical pathology to suggest AD, the nbM is significantly depleted in in post-mortem studies of PwPD (Nakano and Hirano, 1984). The PPN has been shown to lose about 50% of its laterally placed large neurons in PD, in contrast to AD where the PPN remains relatively intact (Zweig et al., 1989). The caudal-rostral progression of Lewy pathology proposed by Braak et al. (Braak et al., 2003) suggests that α-syn deposition within the nbM and PPN occurs at approximately the same time as deposition with the SNpc, i.e. the two major ACh projections in the brain are affected by the time that the first motor symptoms of PD emerge.

Radiological studies using PET and single-photon emission computed tomography (SPECT) to investigate the cholinergic system in PwPD are compatible with the pathological changes seen at post-mortem. Using ACh analogues as PET tracers is one common method employed. The analogue is metabolised and trapped by the enzyme acetylcholinesterase (AChE) and therefore the tracers act as a marker of AChE, which is considered a consistent marker of cholinergic pathways (Muller and Bohnen, 2013). An important study using this technique is that of Bohnen et al. who studied 12 subjects with 'mild' AD, 14 with PDD, 11 with PD and ten HC (Bohnen et al., 2003). The diagnostic criteria used to define the groups are not stated but the mean MMSE scores were 22.2, 22.8, 27.3 and 29.4, respectively. It was demonstrated that compared to the HC, the PDD group had the greatest average reduction (of 20%) in AChE activity across the frontal, temporal and parietal cortex. The second most affected group were PwPD

with average reduction of 12.9% compared to controls. The AD group had the smallest average cortical reduction compared to HC (9.1%) (Bohnen et al., 2003).

A larger study by the same research group compared 101 PwPD - with an average age 65.3, disease duration 5.9 years and H&Y stage of 2.3 – with 29 HC (Bohnen et al., 2012). All subjects underwent cognitive testing of memory, attention, executive and visuospatial function and an average score based on normative means was calculated for each subject. PDD subjects were excluded and the subjects were not separated into those with MCI and those with normal cognition. Analysis of AChE activity was divided into neocortical activity (a surrogate marker of the integrity of nbM) and thalamic activity (a surrogate marker of PPN activity). Abnormalities were defined if a subject with PD had AChE levels five percent or lower than cognitively normal elderly HC. The results showed that 65 of the PwPD had normal levels of AChE in both the thalamus and cortex. Thirty-one PwPD had reduced neocortical activity and the global cognitive score of this group was significantly different to the PwPD with normal AChE levels. Post-hoc inspection of results showed the low cortical AChE group had significantly worse cognitive scores in executive function, attention and verbal learning. Eighteen PwPD had low levels of AChE in the thalamus. The only significant difference between those subjects and the 83 other PwPD was a history of falls (Bohnen et al., 2012). This study supports the heterogeneous nature of neurotransmitter change in PD because the majority of subjects had normal levels of AChE. However, those with low levels of AChE within the cortex had worse global cognitive scores.

PET studies therefore support the histological findings of a global reduction in ACh in PwPD and some evidence exists to suggest that greater ACh deficiency might be associated with greater cognitive dysfunction. Deficits of attention in a cohort of PwPD at baseline have been associated with a

more rapid cognitive decline in a cohort study (Taylor et al., 2008). Thirty-nine PD subjects were followed for three years and multivariate analysis demonstrated that poor attention at baseline was an independent predictor of greater decline in MMSE and a Cambridge Cognitive Examination (CAMCOG) scores. Another independent predictor of greater cognitive decline in this study was the PIGD phenotype. The authors proposed that the independent association of PIGD and attentional deficit with greater cognitive decline implies that different pathophysiological processes must govern these functions, at least initially (Taylor et al., 2008). ACh deficit is proposed to be the unifying link between PIGD and attention (Yarnall et al., 2011) and it could be that PPN degeneration is associated with gait and falls whereas nbM degeneration causes deficits in attention, as supported to some extent by PET studies (Bohnen et al., 2012). However, this is likely to be too simplistic given the heterogeneous pathological process occurring in every individual with PD.

Further supportive evidence for the role of ACh in cognitive dysfunction in PwPD comes from studies that suggest an improvement in cognitive function in those with PDD who take cholinesterase inhibitors (ChEIs), i.e. drugs that indirectly increase the availability of ACh (Rolinski et al., 2012). In addition, there is evidence to suggest that anti-cholinergics, drugs reducing the availability of ACh in the brain, are associated with more rapid cognitive decline. For example, in a cohort of 235 PwPD it was shown that those taking anti-cholinergics at baseline had a higher median reduction in MMSE at eight years (6.5 points) than those not who were not (1 point). Regression analysis adjusting for age, depression and baseline cognition suggested that duration and load of anti-cholinergics were both significantly associated with decline on MMSE score (Ehrt et al., 2010).

2.6.3 A role for noradrenaline and other neurotransmitters?

Just as with ACh, loss of noradrenergic neurons (from the locus coeruleus) and serotonergic neurons (from the dorsal and median raphe nuclei)

occurs in PDD (Halliday et al., 2014). The exact role that depletion of these neurotransmitters plays in the development of cognitive dysfunction is yet to be fully elucidated. One small study comparing the selective noradrenaline reuptake inhibitor atomoxetine with placebo in 55 PwPD over eight weeks showed a small improvement in cognition in the atomoxetine group, but this was a secondary outcome measure and although significantly different, the difference in MMSE change between the groups over eight weeks was only 1.3 points (Weintraub et al., 2010). A single dose of atomoxetine has also been given to 25 PwPD in a double-blind, randomised, crossover trial in which participants undertook neuropsychological tests of executive function. Some significant changes in test scores, including a reduction in impulsivity, were seen after taking atomoxetine (Kehagia et al., 2014). In summary, there is a suggestion that facets of cognition, both global and those related to executive function, may be improved by increasing the cortical levels of noradrenaline in PwPD. Further research is required in this area.

2.6.4 The dual syndrome hypothesis

As has been outlined in section 2.6.1, executive dysfunction in PD appears to be mediated to a large extent by dopaminergic dependent frontostriatal changes. Dopamine improves or worsens aspects of executive function as governed by the dopamine overdose hypothesis and genetic factors, including COMT polymorphism, that indirectly regulate dopamine levels within the DLPFC. The CamPaGIN cohort demonstrated that executive dysfunction at baseline (as measured using the CANTAB version of the TOL) was not a predictor of dementia at 3.2 or 5 years of follow-up (Williams-Gray et al., 2007, Williams-Gray et al., 2009). Neither was phonetic fluency [9], a cognitive task mediated by the frontal lobes (Robinson et al., 2012). In contrast, semantic fluency and pentagon copying, mediated by the

[9] Phonetic fluency – a type of verbal fluency test based on sounds in languages. For example, asking participants to name as many words as possible beginning with a certain letter in a minute.

temporal lobe and parieto-occipital cortex, respectively, were strongly identified as risk factors for developing dementia (Williams-Gray et al., 2007, Williams-Gray et al., 2009). Broadly speaking, the dual syndrome hypothesis proposes that if PD-MCI is characterised by executive dysfunction this is likely to be primarily driven by underlying changes to catecholamine based neurotransmitter systems (dopaminergic – there is greater evidence for this – but also noradrenergic) and may not be a risk factor for developing PDD. Rather, those subjects who demonstrate early evidence of posterior cortical dysfunction (visuospatial, memory and language deficits) and those with the PIGD motor phenotype are at the greatest risk of rapid cognitive decline and dementia (Kehagia et al., 2010b, Kehagia et al., 2013). In these subjects it is proposed that ACh depletion is the primary cause of the deficits, driven by infiltration of the cholinergic basal forebrain nuclei and PPN by ascending α-syn pathology, as well a variable contribution by tau and amyloid. However, the proposition of a catecholamine-based executive dysfunction on one hand and a cholinergic-based visuospatial and memory dysfunction based on the other is not absolute, as acknowledged by the proposers of the theory (Kehagia et al., 2010b, Kehagia et al., 2013). For example, ACh depletion has been implicated in attentional deficits, mediated by the DLPFC as already discussed (Bloem et al., 2014). In addition, it is feasible that dopaminergic deficit is a driver in posterior cortical dysfunction as the mesocortical dopaminergic pathway innervates the parietal and temporal lobes as well as the DLPFC, although the lack of improvement in associated cognitive domains is against this (Lange et al., 1992).

The ICICLE-PD study is a two-centre UK based cohort study of 219 patients with incident PD (Yarnall et al., 2014). Its objective is to identify biomarkers – anatomical, biochemical and genetic – that predict dementia so that clinicians and researchers can target those at risk and ultimately provide tailored, individualised treatment (Kehagia et al., 2013). The dual-syndrome hypothesis is being investigated prospectively by this study. The

effect of three common polymorphisms involved in the genetic risk of cognitive decline in PD - COMT polymorphism, MAPT haplotype and APOE (section 2.3.3) - were recently investigated using fMRI in 169 patients from the ICICLE-PD cohort and 85 HC (Nombela et al., 2014). Participants performed three neuropsychological tests whilst in the scanner, each chosen to test different aspects of cognition; TOL for executive function, a spatial rotation task for visuospatial function and the Memory Encoding Task for memory function. Deficits in each task were demonstrated in the PD cohort compared to HC and it was also shown that polymorphisms influenced cortical activation of the relevant areas of the brain as predicted by previous studies (Williams-Gray et al., 2007, Williams-Gray et al., 2009). For example, prefrontal cortex activation when performing the TOL varied according to COMT polymorphism in keeping with the inverted U-shape already discussed (section 2.6.1) (Vaillancourt et al., 2013) and the posterior cortex and prefrontal region were less activated in the MAPT H1 homozygote PD subjects when performing the spatial rotation task (Nombela et al., 2014). This study therefore suggests that even in newly diagnosed PwPD there is evidence of fMRI changes that can be linked to cognitive deficit and that genetic factors influence performance on tests of specific cognitive domains. This is supportive of the dual syndrome hypothesis but longitudinal follow-up is required to determine the validity of these potential genetic and radiological biomarkers.

2.6.5 Summary

Over the last two decades researchers have tried to piece together data from pathological and longitudinal studies with the results of cognitive tests of individuals with PD. The culmination of this has been the dual syndrome hypothesis. This is now being tested using data from the ICICLE-PD study and may ultimately lead the individualised management of cognitive decline in PD, rather than the current 'one-size fits all' approach.

2.7 Treatment of cognitive impairment in Parkinson's disease

The general approach to treatment of those with PDD should begin with an exclusion of other causes of cognitive dysfunction such as delirium and depression. Medications need to be reviewed and rationalised because some that are commonly prescribed, for example anti-cholinergics and dopamine agonists, can have a detrimental effect on cognition in PwPD (Emre et al., 2014). It seems sensible to infer that the identification of PD-MCI should prompt a similar course of action.

In relation to pharmacological therapy, and as briefly discussed in section 2.6.2, ChEI have been shown to improve cognitive dysfunction in those with PDD. Although there are a number of smaller, open label studies, only two large randomised controlled trials (RCTs) have been performed. One compared the ChEI donepezil 5mg daily, 10mg daily and placebo over 24 weeks in 550 participants (Dubois et al., 2012) and the other compared rivastigmine at doses of between 3mg and 12mg per day (highest well-tolerated dose maintained) with placebo in a 2:1 ratio over 24 weeks in 541 participants (Emre et al., 2004). These trials suggest both drugs are of benefit for cognition in PDD, with marginally better evidence to support the use of rivastigmine. Two meta-analyses have concluded that ChEI have a beneficial effect on cognition, behaviour and ADLs in those with PDD (Rolinski et al., 2012, Wang et al., 2014).

Another drug that has been studied in PDD is the N-methyl-D-aspartate (NMDA) receptor antagonist memantine, a drug that blocks activity of the excitatory neurotransmitter glutamate. Three RCTs have been performed to date on a total of 299 subjects, each comparing memantine 20mg per day with placebo. A recent meta-analysis of these studies concluded that there was no evidence that memantine improves cognition in PDD or DLB (Wang et al., 2014).

In relation to PD-MCI, a recent 24-week, randomised, double-blind, placebo-controlled, crossover study of rivastigmine was performed in 28 PwPD, of whom 26 completed the trial and 23 tolerated medication for both phases (a placebo patch phase and a rivastigmine patch phase - increased to a maximum of 9.6mg daily over four weeks) (Mamikonyan et al., 2015). All subjects were classified as having PD-MCI using criteria pre-dating the MDS definition. The primary outcome measure of the study was the Alzheimer's Disease Cooperative Study—Clinical Global Impression of Change, which takes account of clinician and caregiver input. Only a trend towards significance was demonstrated (*p* 0.096) in this measure and all secondary outcome measures of cognition, including MoCA score, were not significantly different between placebo and rivastigmine. As stated by the authors, it is possible that the small size of the trial, particularly when compared to the large RCT of rivastigmine in PDD (Emre et al., 2004), could have influenced results, as could the fact that 9.6mg per day of a rivastigmine patch may be suboptimal (Mamikonyan et al., 2015).

2.7.1 Summary

There is a suggestion that atomoxetine, by increasing availability of noradrenaline, may have a positive effect on cognition in PwPD but definitive evidence is lacking and RCTs are required (see 2.6.3) (Weintraub et al., 2010, Kehagia et al., 2014). The one published RCT of ChEI use in PD-MCI did not show any significant benefit (Mamikonyan et al., 2015). In PDD there is evidence that ChEI have a beneficial effect on cognition, although this is modest (Emre et al., 2004, Dubois et al., 2012).

Some with PD-MCI, for example those with executive dysfunction, may be more likely to benefit from catecholamine based treatment than from treatment with ChEI, whereas the opposite may be true for those whose PD-MCI is characterised by deficits in memory or visuospatial function. Until medication trials of PD-MCI subdivide groups based on cognitive profile this cannot be proven. As has been demonstrated by pathological

studies, significant damage has already occurred to brain structures by the time that motor and cognitive symptoms develop (Braak et al., 2003); this is likely to be a factor in the limited benefit of ChEI in PDD.

2.8 Conclusion

Cognitive impairment in PD is common, even at the time of diagnosis (Broeders et al., 2013, Yarnall et al., 2014), and the majority of those who survive long enough will develop dementia (Hely et al., 2008). The pathological causes of cognitive decline are complex, driven by ascending α-syn deposition in the form of Lewy pathology with variable co-existing tau and Aβ involvement (Irwin et al., 2013, Halliday et al., 2014). Damage to brain structure cause changes to multiple neurotransmitter systems, influencing the cognitive domains affected in PD-MCI and the risk of progression to PDD (Kehagia et al., 2010b, Kehagia et al., 2013).

Accurate identification of those at risk of developing PDD would allow for better understanding of the causes of increased risk, targeted early recruitment to pharmacological studies and may also improve the efficacy of current pharmacological treatments via earlier prescription to those most likely to benefit. Identifying biomarkers, or panels of biomarkers, to stratify risk of cognitive impairment is underway (Yarnall et al., 2014, Nombela et al., 2014). In relation to reach and grasp, differences identified in the movement kinematics between PD-NC, PD-MCI and PDD may increase understanding of associations between motor function and cognition, which could ultimately lead to the more widespread use of motor tests as biomarkers for cognitive decline.

Chapter 3

Abbreviations used in this chapter

2D	Two dimensional
3D	Three dimensional
AIP	Anterior intraparietal area in macaques/monkeys
aIPS	Anterior intraparietal area in humans
BOLD	Blood oxygenation level dependent
CT	Computerised tomography
FEF	Frontal eye field
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
ITC	Inferior temporal cortex
LIP	Lateral intraparietal area
M1	Primary motor cortex
MIP	Medial intraparietal area
MRI	Magnetic resonance imaging
PD	Parkinson's disease
PET	Positron emission tomography
PMd	Dorsal premotor cortex
PMv	Ventral premotor cortex
PO	Parieto-occipital
PPC	Posterior parietal cortex
PPC	Posterior parietal cortex
PRR	Parietal reach region
TMS	Transmagnetic stimulation
V3A	Visual area V3A
V6	Visual area V6
V6A	Visual area V6A
V6Ad	Dorsal visual area V6A
V6Av	Ventral visual area V6A
VIP	Ventral intraparietal area
WHP	Whole-hand prehension

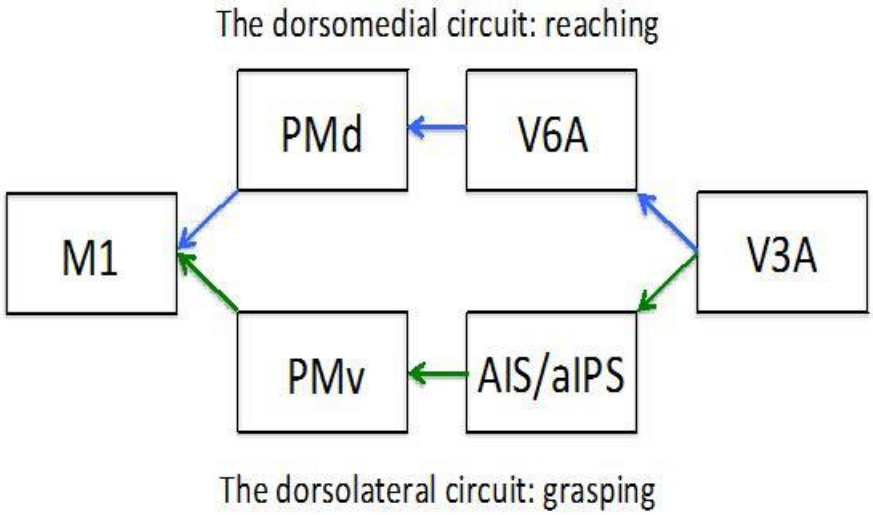
The Cortical Control of Reach and Grasp

The neural pathways – or circuits – controlling reach and grasp are both examples of highly specialised parieto-frontal networks. Studying the macaque monkey or other monkey species has principally driven current understanding of the dorsomedial reaching circuit and the dorsolateral grasping circuit. This chapter will review the circuits in more detail, and begins by providing an overview of each.

As discussed in Chapter 1.6, both circuits begin in the visual cortex, specifically V3A. The major posterior parietal node of the dorsomedial circuit is V6A, which along with MIP forms the PRR. The dorsomedial circuit then passes to PMd, specifically area F2 in the macaque, before terminating in M1, where an appropriate motor action is generated.

The major posterior parietal node of the dorsolateral grasping circuit is the anterior intraparietal area (AIP in macaques, aIPS in humans). The circuit then passes to the PMv, specifically area F5 in macaques, before terminating in M1. Both circuits are shown in detail in Figure 4 from Chapter 1.6. A simplified flow chart illustrating the major nodes of the pathways is shown in Figure 14.

Figure 14: The major nodes of the reach and grasp circuits



Legend: Both circuits begin in V3A and involve different regions in the posterior parietal cortex (V6A in the dorsomedial reaching circuit, AIS/aIPS in the dorsolateral grasping circuit) and different regions within the frontal premotor cortex (PMd in the dorsomedial reaching circuit, PMv in the dorsolateral grasping circuit). Abbreviations: V3A, visual area V3A of the visual cortex; V6A, visual area V6A of the posterior parietal cortex; AIS, anterior intraparietal area in the macaque; aIPS, anterior intraparietal area in humans; PMd; dorsal premotor cortex; PMv, ventral premotor cortex; M1, primary motor cortex.

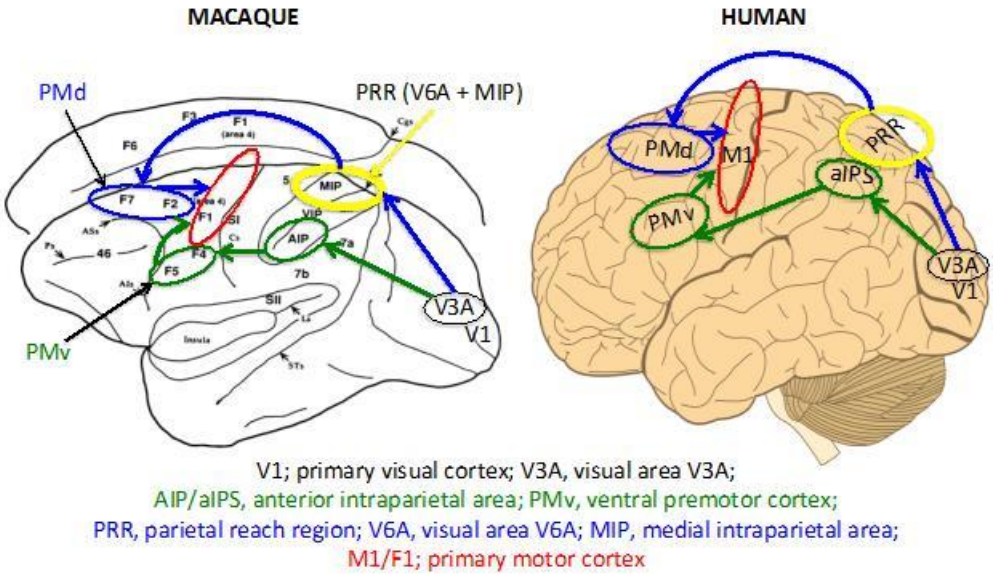
3.1 The dorsomedial reaching circuit

3.1.1 Visual area V6A

Throughout this chapter the component of the reach and grasp pathway under discussion will be highlighted in yellow on a standardised diagram (Figure 15).

V6A is the major posterior parietal node of the dorsomedial reaching circuit. It is connected to MIP and together these areas of the PPC are known as the PRR. V6A also has strong connections with visual area V6 (V6).

Figure 15: Visual area V6A is part of the parietal reach region and is highlighted in yellow



3.1.1.1 Visual area V6 in the macaque

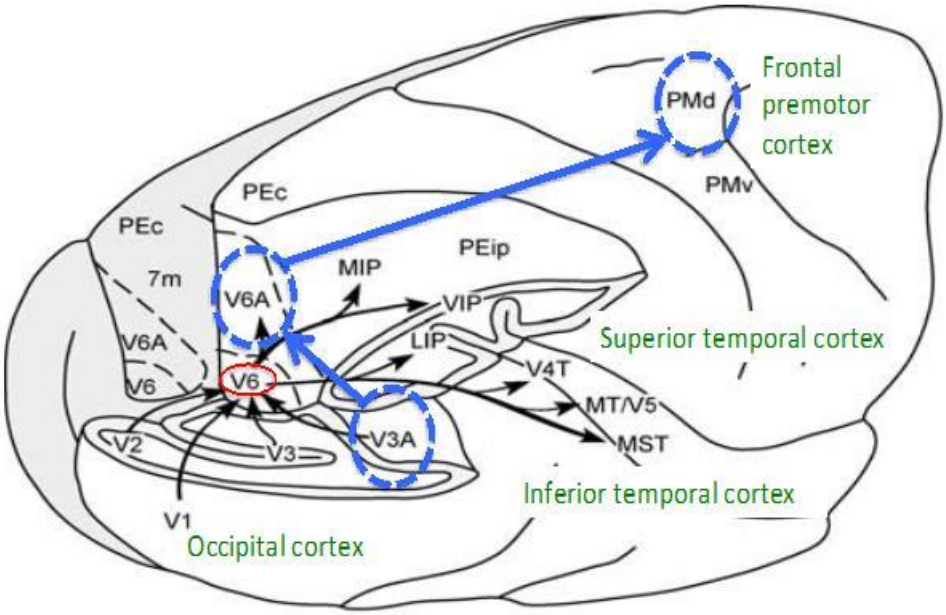
The discovery and understanding of V6A is tied to the discovery of a connected brain region now known as V6. In the late 1980's a section of the macaque brain located on the bank of the parieto-occipital sulcus, originally named 'area PO' (parieto-occipital), was found to have visually responsive neurons (Colby et al., 1988). Injection of neural tracers [10] into area PO revealed it had extensive retinotopic organisation [11] of input from visual areas V1-V4 and the medial temporal lobe. Output from area PO was predominantly to MIP, part of the PRR, with only a very limited output to the temporal cortex. Subsequent single cell microelectrode study of area PO has identified two distinct but strongly interconnected regions, referred to as V6 (located ventrally) and V6A (located dorsally) (Galletti et al., 1996).

[10] Neural tracer - a chemical injected into a specific part of the brain that is used to infer neural connectivity between different brain regions, by analysing the distribution of the chemical after a period of time.

[11] Retinotopic organisation - neurons form a two dimensional representation of an image formed on the retina such that neighbouring regions of the image are represented by neighbouring regions of the visual area. Much of the occipital cortex and certain parts of the posterior parietal cortex are retinotopically organised.

V6 neurons are all activated by visual stimuli, whereas V6A also contains a population of neurons activated by somatosensory function. It has been shown that V6 has point-to-point representation of the whole of the contralateral visual field (i.e. it is this section of area PO that is retinotopically organised). In addition, unlike most other areas of the visual cortex, there is very little over-representation of the central visual field in respect of the periphery (Galletti et al., 1999). The use of neural tracers has revealed a lack of connectivity between V6 and the ITC (Galletti et al., 2001). The ITC is the region of the temporal cortex thought to be responsible for object identification and therefore V6 is not thought to be part of the ventral stream of the perception-action model of the visual system (see Chapter 1.8) (Goodale and Milner, 1992). V6 has extensive connections to both the dorsomedial reaching and dorsolateral grasping circuits. In relation to reaching, V6 is connected to V6A, MIP (i.e. is connected to the PRR) and VIP (Figure 16).

Figure 16: Connectivity of visual area V6 in the macaque brain



Legend: Partially dissected macaque brain demonstrating proposed connectivity and flow of visual information to and from area V6 (circled in red). V6 receives visual information from primary visual cortex (V1) and other visual association areas, including V3A. It has widespread projections including V6A and MIP (which constitute the PRR) and VIP. There are no connections to the inferior temporal cortex (ITC). The dorsomedial reach pathway is shown in blue. Relevant abbreviations: V1; primary visual cortex; V6; visual area V6; V6A, visual area V6A; MIP, medial intraparietal area; VIP, ventral intraparietal area; PMd; dorsal premotor cortex; PMv, ventral premotor cortex. Adapted from Galletti et al., 2003 with permission (Galletti et al., 2003).

A number of cells within V6 are able to differentiate between movement of an object in the visual field and identical movement of the retina when the eyes are moved around a stationary target (Galletti et al., 2003). The combination of these so-called 'real motion detector cells', point-to-point representation of the contralateral visual field and relative emphasis of the peripheral visual field suggest that V6 is ideally suited for the detection of motion within the periphery (Fattori et al., 2009).

3.1.1.2 Visual area V6A in the macaque

Individual analysis of 1348 neurons from four macaque monkeys within V6A using single-cell microelectrode recording found that 61% of the

neuron population was visually responsive (Galletti et al., 1999). These neurons were particularly sensitive to the direction and orientation of a movement stimulus. V6A lacks retinotopic organisation and the visual and non-visual neurons are intermixed. The contralateral inferior visual field is represented more than the upper half of the visual field (Galletti et al., 1999). The presence of visual neurons sensitive to the location of an object in space (i.e. extrinsic properties such as object direction and orientation) and the overrepresentation of the inferior visual field (usually the arm passes through the inferior visual field when reaching towards a target) led the authors to speculate that V6A is involved in reaching (Galletti et al., 1999).

Analysis of non-visual neurons in V6A by the same research group showed that they are activated by upper limb somatosensory stimulation, the majority (68 of 78 recorded neurons) by stimulation proximally rather than distally. In contrast, somatosensory activation did not occur with lower limb stimulation (Breveglieri et al., 2002). It has been argued that the somatosensory neuron population within V6A provide proprioceptive information about the spatial location of the arm and hand, with respect to the body, that can be used in the planning and performance of reaching movements (Galletti et al., 2003).

Although MIP and VIP also receive input from V6 (Figure 16), a number of neuronal properties make V6A the most likely major parietal node of the dorsomedial reaching circuit in macaques:

- The visual population of neurons in V6A are exquisitely sensitive to movement parameters such as direction and orientation, which are ideal traits for encoding the spatial location of objects.

- The visual neurons in V6A over-represent the inferior visual field, through which the arm is likely to pass during a reaching movement.
- The non-visual neuron population in V6A has upper limb somatosensory properties that could provide proprioceptive information about the position of the arm and hand in space when reaching.
- V6A has extensive neuronal connectivity to the PMd (Galletti et al., 2001).

Alongside single cell microelectrode and neural tracer based studies has been the discovery that V6 and V6A have different cytoarchitectural structures. V6 has a cytoarchitectural structure similar to the occipital lobe and can be considered a classic extrastriate area [12], whereas area V6A has the same cytoarchitectural features as the PPC (Luppino et al., 2005). In fact, subtle differences in parietal cytoarchitecture and connectivity can be found within V6A itself, suggesting division into a ventral section (V6Av), which has some cytoarchitectural characteristics more reminiscent of the occipital cortex, and a dorsal section (V6Ad) that more closely resembles the somatosensory cortex (Luppino et al., 2005).

To grip an object is to take a firm hold of it and grasp it tightly; grip can therefore be considered the end point of a grasp. In addition to involvement in reaching, neurons in V6A have also been implicated in grip selection. In order to control for factors known to activate V6A neurons, macaques performed reach and grasp tasks in the dark whilst maintaining visual gaze and arm orientation (Fattori et al., 2010). Under these conditions it was established that neurons within V6A show selectivity for

[12] Extrastriate - a part of the occipital cortex located next to the primary occipital cortex.

specific grip types, for example whole-hand prehension (WHP) [13] or precision grip [14], to a similar degree as seen in area F5 of the PMv, part of the dorsolateral grasping circuit. This led the authors to speculate that the dorsomedial pathway might play a key role in both reach and grasp (Fattori et al., 2010), a view at odds with the theory of distinct but temporally integrated pathways as proposed by the visuomotor channel hypothesis (Jeannerod, 1999).

In support of V6A being important in the control of both reach and grasp, a single cell microelectrode analysis of V6Av and V6Ad concluded that both subsections contain neurons that discharge in response to reach direction, wrist orientation and grip formation (Gamberini et al., 2011). V6Av contained more visually sensitive neurons, in keeping with its cytoarchitectural makeup, whereas V6Ad contained more somatosensory neurons (Gamberini et al., 2011).

To summarise, it has been shown in the macaque that neurons from V6 over-represent the periphery of vision and provide a point-to-point representation of the contralateral visual field (Galletti et al., 1999). This area is strongly connected to V6A, which is cytoarchitecturally similar to the PPC rather than the occipital cortex (Luppino et al., 2005). V6A is proposed to play a crucial role in reach and to a lesser extent grasp, containing a mixture of visual and somatosensory responsive neurons that are sensitive to object location, direction, wrist orientation and specific grip types (Galletti et al., 1999, Galletti et al., 2003). This makes it ideal for the analysis of stationary and moving visual stimuli and the coordination of movement as the hand approaches and interacts with a target object.

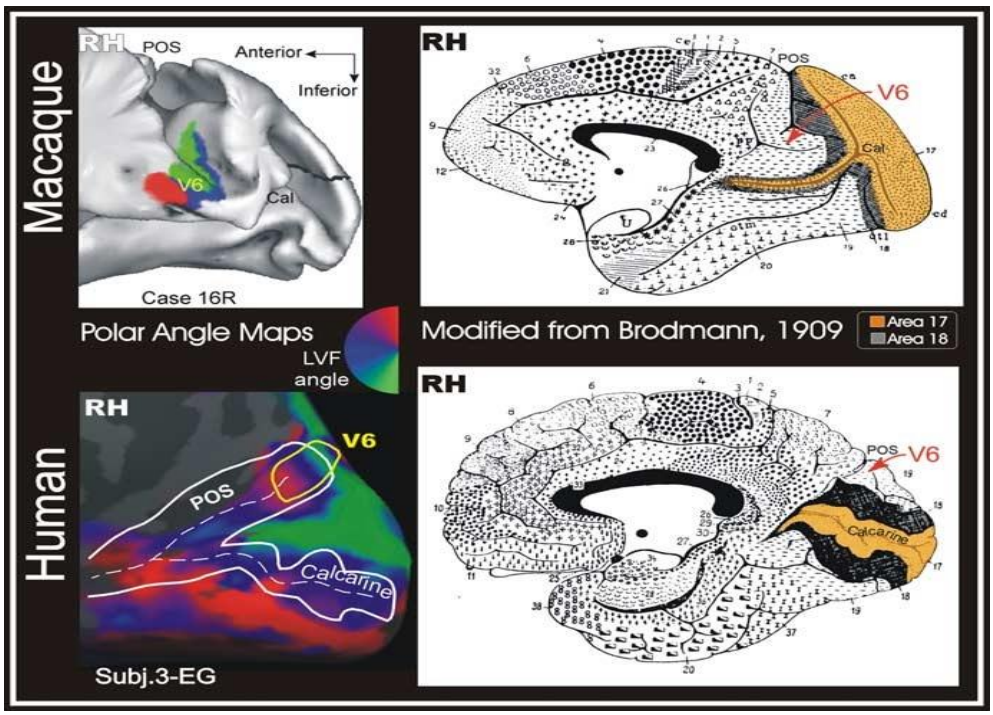
[13] Whole hand prehension – the flexion of all fingers around an object in such a way as to form a ring around it.

[14] Precision grip – a grip between the tips of the thumb and the index finger, for the manipulation of small and delicate objects.

3.1.1.3 Visual area V6 and visual area V6A in humans

Finding areas of the brain homologous to the macaque V6/V6A complex in humans has relied on the use of fMRI, although early studies were often technically flawed due to the difficulty of performing a reaching task within the constraints of the MRI scanner. In 2006 Pitzalis et al. used fMRI and a technique called wide-field retinotopic stimulation in 34 healthy subjects to identify an area of the brain they proposed to be human V6 (Pitzalis et al., 2006). In simple terms, participants were exposed to varying shapes and patterns of contrasting colours during visual fixation whilst undertaking fMRI of the brain. The blood oxygenation level dependent (BOLD) activation of the PPC and occipital cortex was used as a surrogate marker of neuronal activity to map the pattern of response to visual stimulation. Other areas of the brain including regions of the medial temporal cortex, the primary visual cortex and V3A have previously been mapped in humans using a similar technique. A region of the brain with characteristics analogous to the neuron population in macaque V6 was pinpointed. For example, this region does not over-represent the central visual field and provides a retinotopic map of the entire contralateral hemifield of vision. The location of the proposed human V6 is anatomically superior due to the medial movement of the primary visual cortex in humans, compared to a more posterior location in macaques (Figure 17) (Pitzalis et al., 2006).

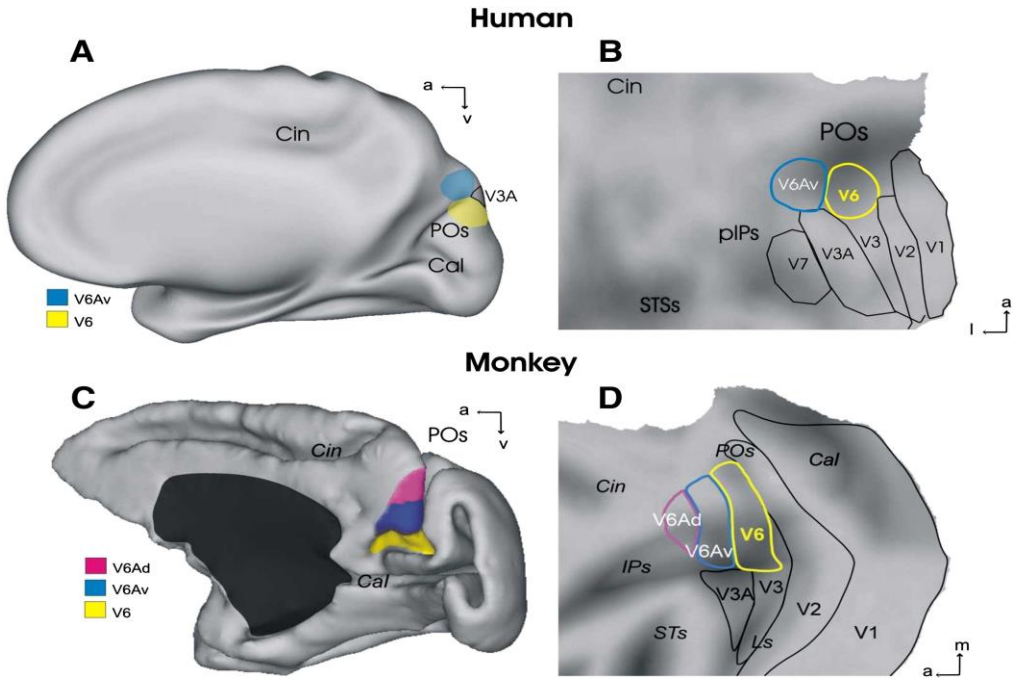
Figure 17: Comparing the location of visual area V6 in macaques and humans



Legend: The images on the left show the similarity of the retinotopic mapping of the contralateral visual field in macaques (upper) and humans (lower) in area V6. The images on the right show the anatomical location of V6, which is moved superiorly in humans (lower) compared to macaques (upper) as a result of the rearrangement of the primary visual cortex (which is labelled using the Brodmann classification as Brodmann Area 17 – shaded yellow) and secondary visual cortex (labelled as Brodmann Area 18 – shaded grey). Reproduced from Pitzalis et al., 2006 with permission (Pitzalis et al., 2006).

The same research group have used fMRI and retinotopic stimulation to identify an area of the brain thought to be the human equivalent of macaque V6A (Pitzalis et al., 2013). Unlike human V6, this area of the human brain only responds to peripheral visual stimulation and over represents the inferior visual field, as has been demonstrated in V6A of the macaque (Galletti et al., 1999). Another shared feature with macaque V6A is activation when performing finger-pointing movements requiring changes in wrist orientation, demonstrated by increased BOLD activation using fMRI (Pitzalis et al., 2013). The proposed location of the V6/V6A complex in macaques and humans is compared in Figure 18.

Figure 18: Proposed location of visual areas V6 and V6A in the macaque and human brain



Legend: This figure combines information from fMRI studies in humans and single neuron microelectrode studies in macaques to demonstrate the proposed location of the V6/V6A complex in humans (upper) and macaques (lower). More specifically, V6A in the macaque has been subdivided into V6Ad (which contains a greater number of neurons sensitive to somatosensory stimulation) and V6Av (which contains a number of neurons sensitive to visual stimulation). In humans, V6Av is shown (i.e. the area of the V6A sensitive to retinotopic stimulation). Relevant abbreviations: V1, primary visual cortex; V3A, visual area V3A; V6, visual area V6; V6Ad, dorsal visual area V6A; V6Av, ventral visual area V6A; POs, parieto-occipital sulcus; Cin, cingulate sulcus; Cal, calcarine sulcus; IPS, intraparietal sulcus; STS, superior temporal sulcus. Reproduced from Pitzalis et al., 2013 with permission (Pitzalis et al., 2013).

More recently, attempts have been made to establish whether human V6A has two distinct neuronal populations homologous to macaque V6Av and V6Ad (Tosoni et al., 2014). BOLD activation within human V6A was compared in 21 healthy adults during a visual stimulation paradigm and a delayed pointing and saccadic eye movement paradigm. A specific region of V6A was identified that had weak response to saccadic stimulation but strong response to pointing and wrist rotation. This area is located anteriorly and dorsally and is proposed to be human V6Ad, whereas an area of V6A with the opposite pattern of stimulation is proposed to be

human V6Av (Tosoni et al., 2014). It therefore appears that humans have a V6/V6A complex with the same topographical arrangement of specialisation as seen in macaques (Pitzalis et al., 2015).

Another way of analysing the role of this area of the brain in humans is to study patients with optic ataxia, a condition characterised by extreme difficulty in guiding reaching movements to targets in the periphery with preservation of reaching within the central visual field (Vingerhoets, 2014). In all human studies of optic ataxia the exact area and degree of damage to the brain varies from subject to subject, in contrast to the precise study of individual neurons that is possible in macaques. Despite this, analysis of 16 people with unilateral optic ataxia using high resolution computerised tomography (CT) and MRI found lesion overlap occurred in the PRR (i.e. included V6A) (Karnath and Perenin, 2005).

In a study of reach and grasp in a man who developed unilateral right-sided optic ataxia after a hypoxic brain injury predominately affecting the left cerebral hemisphere, it was demonstrated that deficits in grasping were only present when reaching for an object in the periphery of his right visual field with his right hand – i.e. no abnormality was found when grasping objects without the need to reach. MRI showed damage to the right dorsomedial parietal lobe, an area that contains the proposed human V6A. The proposed human aIPS was spared. This supports the role of human V6A in reaching as well as suggesting that isolated grasp deficits require damage to aIPS (Cavina-Pratesi et al., 2010a).

3.1.1.4 Summary of the role of visual area V6A

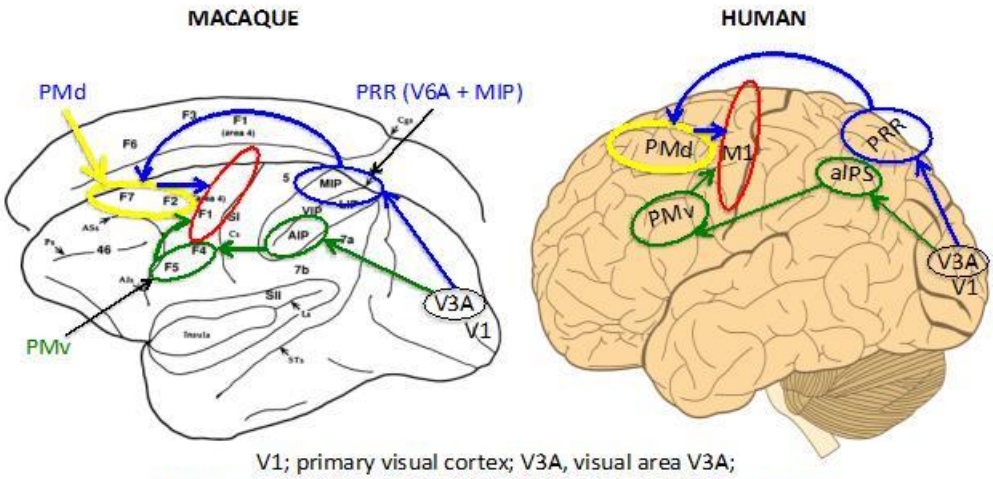
In conclusion, V6A of the PRR appears to be essential in both macaques and humans in the control of reaching. In both species V6A contains a mixture of neurons stimulated by visual and somatosensory stimuli (Galletti et al., 1999, Breveglieri et al., 2002, Tosoni et al., 2014). The visually responsive neurons over-represent the inferior visual field, through

which the arm passes whilst reaching, and are sensitive to peripheral stimuli relating to the direction and orientation of an object in space (i.e. its extrinsic properties) (Galletti et al., 1999). Somatosensory neurons in the macaque are activated by upper limb stimulation and neurons within human V6A are activated by wrist orientation. The area containing somatosensory neurons, known as V6Ad, is hypothesised to provide proprioceptive information about the position of the arm and hand in space as they approach a target object. Studies in macaques suggest that V6A could also be involved in grasp, as it contains a neuron population sensitive to specific handgrips (Fattori et al., 2010). This is not established in humans. The anatomical location of V6A is different in monkeys and humans, but in both species it is located next to, and has strong connections with, V6 (Galletti et al., 2001, Pitzalis et al., 2015). The neurons in V6 share a number of properties in humans and macaques that are thought to optimise the control of reach and grasp.

3.1.2 The dorsal premotor cortex

PMd is the major frontal node of the dorsomedial reaching circuit. As discussed in Chapter 1.5.2, cytoarchitectural analysis of the frontal premotor cortex in macaques, but not humans, has identified two specific areas within the PMd known as F2 and F7 (See Figures 2 and 19) (Matelli et al., 1991). F2 is thought to be the area of macaque PMd that forms the dorsomedial reaching circuit.

Figure 19: The dorsal premotor cortex is the major frontal node of the dorsomedial reaching circuit and is highlighted in yellow



3.1.2.1 The dorsal premotor cortex in macaques

F2, the posterior two thirds of PMd, has been shown to contain neurons sensitive to parameters of reach in relation to proximal (Castiello and Begliomini, 2008) and distal (Raos et al., 2004) forearm movements. A single cell microelectrode study of F2 in two macaques as they performed reaching tasks to a number of different three-dimensional (3D) objects in the light and dark has also identified neurons that discharge when grasping (Raos et al., 2004), suggesting that F2 may be integral to the control of both reach and grasp. The neurons in F2 that were activated by grasp did so in response to specific handgrips such as 'digging out with the index finger grip' or 'precision grip', rather than by individual finger movements. In addition, some F2 neurons are activated by object presentation – i.e. visual presentation of the object in question activated the neurons required to grasp the object (Raos et al., 2004). It has been hypothesised that the neurons activated by object presentation could either transfer information to M1 to enable the generation of a motor action or temporarily store information about the extrinsic properties of an object,

for example shape and size, as a 'motor representation' [15], which can then be combined with information from V6A as the hand approaches the object (Castiello and Begliomini, 2008). As discussed in Chapter 1.7, the visuomotor channel hypothesis proposes that the dorsomedial reaching pathway processes information about the extrinsic properties of an object, for example its position in space. Intrinsic object properties are theorised to be processed by the dorsolateral grasping pathway. There is therefore evidence in macaques from single cell microelectrode studies to suggest that the concept of distinct pathways controlling reach and grasp is incorrect and that some degree of overlap in these pathways is found in PMd (Raos et al., 2004) as well as V6A (Fattori et al., 2010, Gamberini et al., 2011).

3.1.2.2 The dorsal premotor cortex in humans

Activation of PMd in humans has been demonstrated in a number of imaging studies looking at reach and grasp but not in isolated studies of reaching (Jacobs et al., 2010, Cavina-Pratesi et al., 2010b). A TMS study inducing virtual lesions of bilateral PMd and PMv in ten healthy subjects who performed a grip and lift (not a reach and grasp) task with the right hand showed that TMS to the right (ipsilateral) PMd had no effect on grasp or lift, and TMS to the left (contralateral) PMd produced a delay in the recruitment of muscles for the lift part of the task (Davare et al., 2006). The authors of the study suggested that PMd inactivation using TMS leads to a decoupling of grasp and lift in humans (Davare et al., 2006) but the specific role of the human PMd in the control of reaching remains unknown.

3.1.2.3 Summary of the role of the dorsal premotor cortex

Macaque F2 of the PMd contains a mixture of neurons that are activated by the reaching arm and the grasping hand (Castiello and Begliomini, 2008,

[15] Motor representation – A process thorough which a motor action is intended, prepared and ultimately executed.

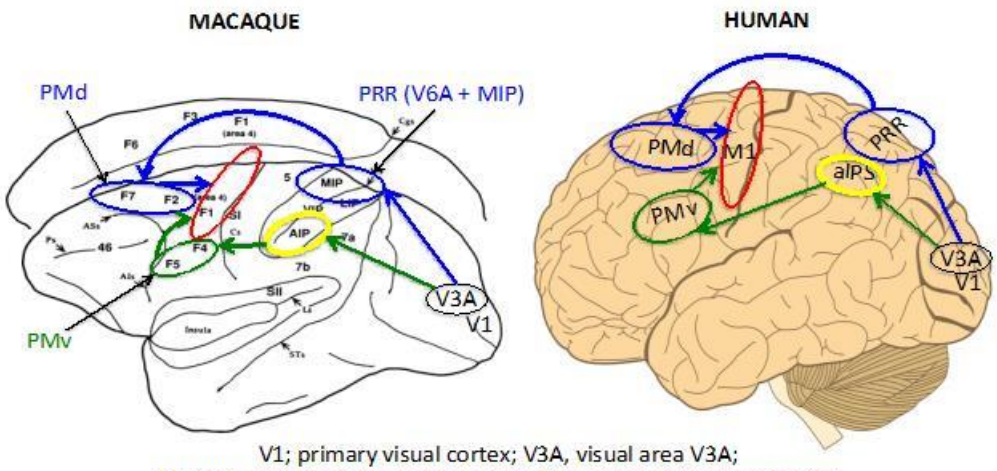
Raos et al., 2004). Visually responsive neurons in F2 are hypothesised to be able to store motor representations about the extrinsic properties of an object that can be combined with visual information from V6A of the dorsomedial reaching circuit as well as with information from the dorsolateral grasping circuit (Castiello and Begliomini, 2008). The visuomotor channel hypothesis of reach and grasp is challenged by the finding of neurons activated by extrinsic object properties in PMd of macaques (Raos et al., 2004). The lack of direct evidence of specific activation of PMd in humans in isolated tasks of reaching is also a challenge to the notion of distinct reach and grasp circuits, although this area of the brain is activated if humans perform reaching in the context of a reach and grasp task (Jacobs et al., 2010, Cavina-Pratesi et al., 2010b).

3.2 The dorsolateral grasping circuit

3.2.1 The anterior intraparietal area

The anterior intraparietal area (AIP in macaques, aIPS in humans) is the major parietal node of the dorsolateral grasping circuit (Figure 20).

Figure 20: The anterior intraparietal area is the major parietal node of the dorsolateral grasping circuit and highlighted in yellow

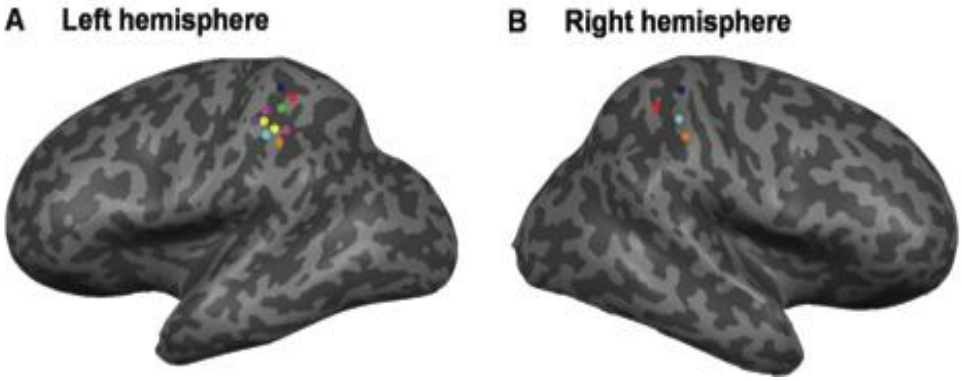


V1; primary visual cortex; V3A, visual area V3A;
AIP/aIPS, anterior intraparietal area; PMv, ventral premotor cortex;
PRR, parietal reach region; V6A, visual area V6A; MIP, medial intraparietal area;
M1/F1; primary motor cortex

A key discovery aiding understanding of the role of the PPC in grasping was the identification, via the use of single cell microelectrode recordings, of a subset of neurons in the inferior parietal lobe of the macaque that discharge during manipulation of objects (Mountcastle et al., 1975). This area of the brain is now known as AIP. AIP neurons did not respond to sensory stimuli and did not activate when the same muscle groups were used for motor tasks other than manipulation. Compelling evidence that AIP is essential for grasping comes from a study demonstrating abnormalities of grasp when this area was transiently damaged in a macaque by injecting a gamma-aminobutyric acid (GABA) receptor agonist called muscimol (Gallese et al., 1994). The hand contralateral to the inactivated AIP was affected and a mismatch between object shape and size and handgrip formation led to uncoordinated grasp, or grasp failure, when the macaque performed precision grip tasks. Parameters of reach were unaffected.

A number of MRI and PET neuroimaging studies looking at visually guided reach and grasp movements in humans have identified a grasp-specific area of activation at the junction of the anterior intraparietal sulcus and the post central sulcus (Figure 21) (Castiello and Begliomini, 2008). This area is thought to be the human homologue of macaque AIS and is referred to as aIPS in this thesis.

Figure 21: Summary of human anterior intraparietal activation from MRI and PET scan studies during visually guided reach and grasp movements using the right hand



Legend: Each of the coloured dots represents the specific region of the parietal cortex identified to be most active during a grasping task by a particular study. Adapted from Castiello and Begliomini, 2008 with permission (Castiello and Begliomini, 2008).

The extent of involvement of aIPS from the right and left cerebral hemispheres in the control of grasping has been studied in a number of different ways and overall the results intimate that aIPS function is contralateral, as in macaques (Gallese et al., 1994). For example, the first fMRI study to specifically study reach and grasp in both right and left handed people showed that aIPS activation was bilateral but that activation was greater in the aIPS contralateral to the reaching hand (Begliomini et al., 2008). A number of TMS studies in humans also suggest that grasp is mediated by the contralateral parietal lobe. In the study of Rice et al., for example, nine healthy subjects performed reach and grasp with both hands with and without TMS to aIPS. Parameters of grasp (for example the time taken to attain peak index finger to thumb aperture as a percentage of total movement time) were reduced in the reaching hand when contralateral TMS occurred (Rice et al., 2007). Similarly, clinical studies of humans with parietal lesions involving aIPS have demonstrated clear abnormalities of grasp in the contralateral hand (Jeannerod, 1986, Cavina-Pratesi et al., 2010a).

In contrast, one TMS study found that virtual inactivation of aIPS had to be bilateral in six healthy adults in order to cause abnormalities with the final finger position of the grasping hand on the manipulandum [16] (Davare et al., 2007). Unilateral repeated TMS to aIPS did not cause grasping abnormalities in either hand, leading the authors to suggest that aIPS function may be interchangeable in humans (Davare et al., 2007). The discrepancy of the study of Davare et al. may relate to the experimental design; TMS was given after reach initiation but 220 to 270ms before the completion of grasp and it has been argued that this may decrease the activation of aIPS because of a reduced need to provide online computation and feedback of the reaching hand (Rice et al., 2007).

To summarise, there is good evidence to suggest that AIP is essential for the control of grasping in macaques and the same appears to be true for aIPS in humans. Although there is limited evidence of compensation and interchangeability between aIPS, the majority of studies suggest grasp is predominantly mediated by the contralateral aIPS/AIP in humans and macaques.

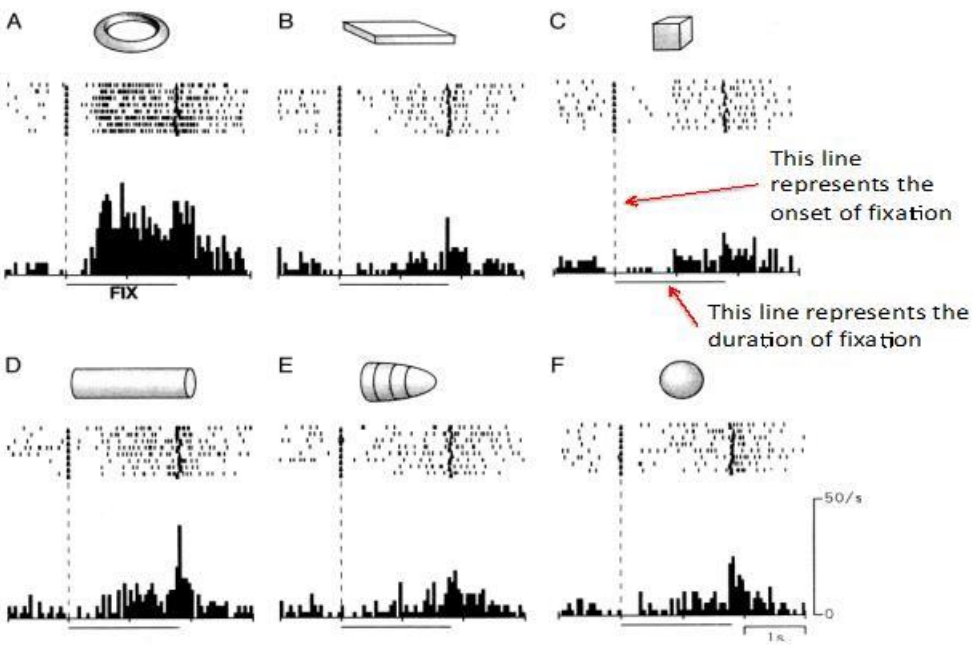
3.2.1.1 The specificity of neurons within anterior intraparietal area

Analysis of neurons within AIP using microelectrodes has identified subtypes that discharge when the hand is manipulating objects of different sizes, shapes and orientations. One hundred and eighty two AIP neurons were analysed, taken from four macaques that were trained to perform hand manipulation of different sized elementary 3D shapes – a cube, sphere, horizontal ring, cone, cylinder and plate. Manipulation was performed in the light and dark and the macaques were also trained to fixate on objects without grasping. Neurons were classified based on their activation: 'visual motor neurons' were more active during manipulation in the light than dark; 'visual dominant neurons' were inactive in the dark but

[16] Manipulandum – an object that is physically manipulated when testing a motor skill.

discharged during grasping in the light; 'motor dominant neurons' were equally active during manipulation in the light and dark but not active during object fixation. Neurons belonging to visual motor or visual dominant groups were both considered to be 'visually responsive neurons' (n = 135) and were subdivided into those activated by fixation ('object-type neurons', n = 81) and those that were not ('non-object-type neurons', n = 54). Selective activation in response to one of the six geometric shapes was analysed in a total of 132 neurons. Thirty-two of 66 object-type neurons were classified as highly selective (significantly greater levels of activation for one particular geometric shape) and 28 as moderately selective (non-significantly greater levels of activation). Figure 22 shows an example of a highly selective object-type visually dominant neuron.

Figure 22: A highly selective object-type visual-dominant neuron with preference for the horizontal ring



Legend: Grasping or fixating on an object in the light activates an object-type visual dominant neuron. In this case the activity of the neuron is recorded as the monkey fixates (i.e. is not grasping) on six different shapes. The histogram represents discharge from the neuron, which is greatest for the horizontal ring (shape A), i.e. this neuron selectively discharges when the macaque fixates on the horizontal ring. Adapted from Murata at al., 2000 with permission (Murata et al., 2000).

Some subclasses of neurons were found to be selective for object orientation and size in the same way that others were selective for specific objects. Of the non-object type neurons, 13 of 35 were highly selective and 16 moderately selective. Because non-object type neurons are not activated by object fixation, selectivity implies that these neurons are activated by either the sight of a handgrip and the grasped object or a specific handgrip corresponding to a specific shape – for example, a non-object type neuron might be activated by the sight of a handgrip employed to grasp the cone, but not the handgrips required to grasp the other shapes (Murata et al., 2000). Overall, this study strongly suggests that neurons within AIP have 3D shape selectivity.

Imaging studies have also been used to establish the 3D properties of AIP neurons. For example, Durand et al. recorded neuron activation in six rhesus monkeys using fMRI whilst they fixated on random-line segments representing 3D and two dimensional (2D) shapes, in order to compare the processing of structural and positional stereoscopic[17] information in different intraparietal regions (Durand et al., 2007). It was demonstrated that AIP has the ability to process depth as well as 2D shape, taken by the authors as support for the role of 3D shape selectivity in AIP demonstrated by Murata et al. (Murata et al., 2000). MIP and LIP were found to be activated by depth position as well as depth structure (Durand et al., 2007). The differences in processing visual 3D space in distinct intraparietal areas can be related to their involvement in different sensorimotor functions.

The concept of parieto-frontal networks controlling non-learnt behaviours was introduced in Chapter 1.5.4. Each network is highly specialised and the properties of the neurons reflect this (Luppino and Rizzolatti, 2000). LIP is the parietal component of the LIP-FEF network involved in voluntary eye movements and MIP is part of the PRR, forming reciprocal connections

[17] Stereoscopic – The processing of a 2D image to create a 3D illusion of depth by using visual information from both eyes.

with V6A in the control of reach. The ability of LIP and MIP to process depth position in addition to depth structure suggests that depth position is essential for interpretation of the visual world and for the processing of the moving arm towards a target during reach. The lack of this function in AIP neurons infers that the capacity to process depth position is not required in order to grasp.

In humans, aIPS demonstrated variable activation in an fMRI study depending on grip type employed to grasp an object. Whereas precision grip caused activation of aIPS, WHP did not cause activation at the adopted significance threshold (Begliomini et al., 2007). This could imply that a greater proportion of aIPS is dedicated to precision grip rather than WHP, as has been suggested in macaques, since selective abnormalities in precision grip but not other grip types are seen when AIP is transiently inactivated (Gallese et al., 1994).

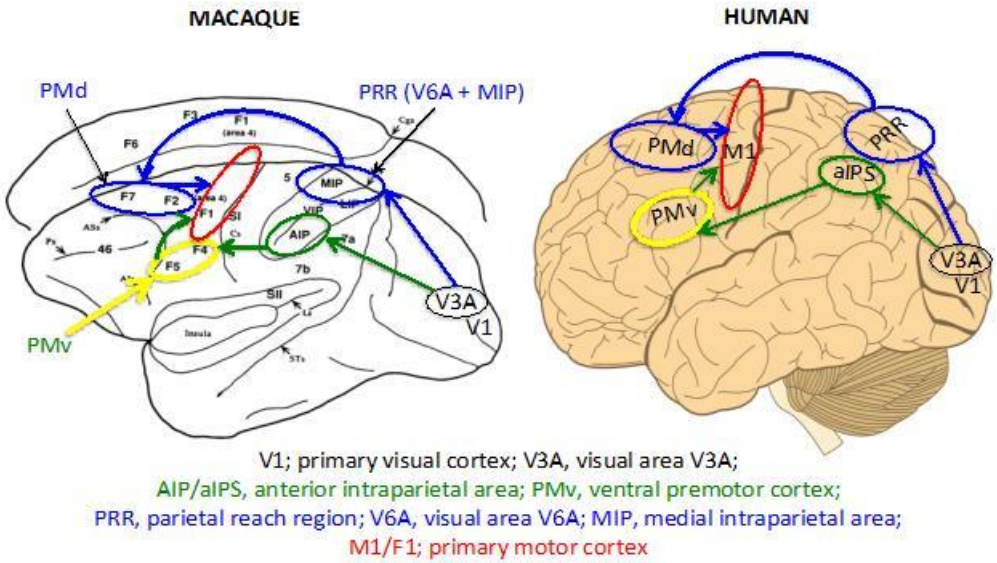
3.2.1.2 Summary of the role of the anterior intraparietal area

There is evidence from single cell recordings in macaques that neurons in AIP are sensitive to the manipulation and visual appearance of geometric shapes, and that selectivity for these shapes occurs. In addition, populations of neurons in AIP also appear to be sensitive to the visual appearance of specific handgrips. Functional MRI studies appear to support the sensitivity of AIP to 3D shapes. These findings have led to the suggestion that AIP utilises visual input to identify grasp-relevant features of an object, a theory that can be extrapolated to aIPS in humans.

3.2.2 The ventral premotor cortex

In the macaque, but not humans, it is possible to divide PMv into two distinct areas based on cytoarchitectural appearance. These areas are known as areas F4 and F5 (Matelli et al., 1991) (Figures 2 and 23).

Figure 23: The ventral premotor cortex is the major frontal node of the dorsolateral grasping circuit and is highlighted in yellow



Area F4 is thought to form a parieto-frontal network with VIP to mediate defensive movements when objects approach the peripersonal space, as discussed in Chapter 1.5.4 (Gentilucci et al., 1988, Cooke and Graziano, 2004, Luppino and Rizzolatti, 2000). F5 is the region of the PMv that forms the dorsolateral grasping circuit with AIP.

Single cell microelectrode studies on 216 F5 neurons from three macaques led to the discovery that neurons in this part of the macaque brain are activated by specific 'goal related' motor acts (Rizzolatti et al., 1988). Neurons were classified into four distal motor acts ('grasping with the hand', 'grasping with the hand and mouth', 'holding' or 'tearing') and two proximal motor acts ('reaching' and 'bringing to the mouth or to the body'). The specificity of these neurons for a motor act was evidenced by the discovery that they would not activate if the same muscle groups involved in the specific motor act were activated by a different task. No examples were provided, but one imagines that, for example, if a macaque pointed rather than reached, a process that like reaching requires

activation of proximal upper limb muscles, the 'reaching' neurons would remain inactive.

It was also demonstrated that within a particular motor act, only specific grip types activated subpopulations of neurons. For example, some 'grasping with the hand' neurons were activated only by precision grip, rather than WHP. In fact, 85% of the grasping neurons identified (a combination of 'grasping with the hand' and 'grasping with the hand and mouth' neurons) showed selectivity for a specific grip type. More neurons were selective for precision grip than other grip types, implying that a greater proportion of F5 is dedicated to the control of precision grip, as is suggested in macaque AIP (Gallese et al., 1994) and aIPS in humans (Begliomini et al., 2007).

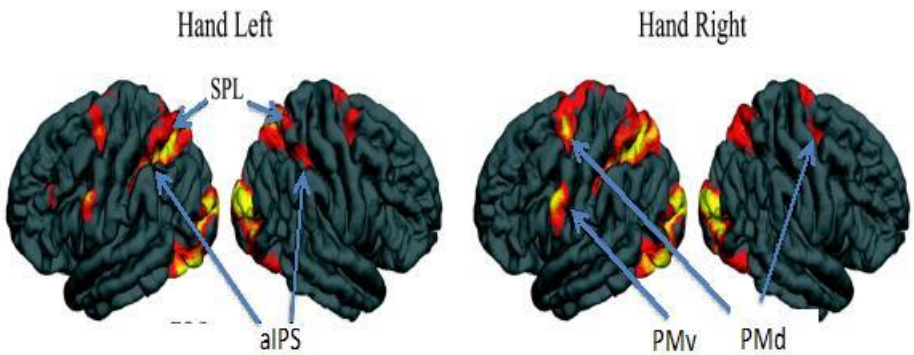
Area F5 has been found to contain neurons that can be classified as 'visual motor' and 'motor dominant' (Murata et al., 1997), according to the criteria outlined in the study of neurons within AIP (see 3.2.1.1) (Murata et al., 2000). However, F5 does not contain 'visual dominant' neurons. The object-type visual dominant neurons of AIP – that is those that are activated by grasping or fixating on an object in the light – are theorised to relay information to F5 regarding the 3D shape of objects (Murata et al., 1997), a concept that will be discussed later.

In humans, neuroimaging evidence of involvement of PMv in grasping is not as robust as evidence of aIPS activation. Some studies have identified PMv activation. For example, in an fMRI study involving five right-handed subjects performing precision grip and 'power grip' (using palmar opposition grasp to squeeze a cylindrical object) tasks with the right hand, it was demonstrated that the right (ipsilateral) PMv had increased activation during precision grip but not power grip (Ehrsson et al., 2000), as measured using BOLD activation. However, other fMRI studies that have identified activity in aIPS have failed to find evidence of activity in PMv

(Begliomini et al., 2007, Frey et al., 2005). The possibility of different organisation of the PMv in humans and monkeys has been proposed as a reason for this inconsistency (Castiello and Begliomini, 2008). Another suggestion is that aIPS activation may be specific to grasping whereas PMv activation may occur in both reach and grasp, and this dual activation may cancel out activity changes during fMRI analysis (Jacobs et al., 2010, Begliomini et al., 2007, Frey et al., 2005).

One fMRI study of 20 healthy right-handed adults has shown that PMv and aIPS are regions of the brain activated when *planning* to grasp objects with the hand (this study did not examine activation when physically grasping) (Jacobs et al., 2010) (Figure 24). Activation of the left-sided aIPS-PMv dorsolateral grasping circuit was greater than the right-sided circuit when planning to grasp with either hand.

Figure 24: Human brain activation using functional MRI when planning to grasp



Legend: There is consistent activation of the left dorsomedial grasping circuit – i.e. aIPS and PMv. The superior parietal lobule (SPL - containing V6A and MIP) and PMd are also activated, i.e. the dorsolateral reaching circuit. Other brain regions including the left middle frontal gyrus and cerebellum (not shown) were also activated. Abbreviations: SPL, superior parietal lobule; aIPS, anterior intraparietal area; PMv, ventral premotor cortex; PMd, dorsal premotor cortex. Adapted from Jacobs et al., 2010 with permission (Jacobs et al., 2010).

3.2.2.1 Summary of the role of the ventral premotor cortex

Area F5 of the PMv of the macaque contains neurons activated by specific motor tasks and specific grip types. As in AIP, the neuron population in the macaque can be classified into those most active during manipulation in the light ('visual motor neurons') and those equally active during manipulation in the light and dark but not active during object fixation ('motor dominant neurons'). However, 'visually dominant neurons' (those inactive in the dark but activated during grasping in the light) are not found in F5 (Murata et al., 1997). Evidence of specific involvement of human PMv in grasp using fMRI studies is inconsistent; some studies have identified activation during grasp (Ehrsson et al., 2000) and others have not (Begliomini et al., 2007, Frey et al., 2005). Planning to grasp an object with the hand is associated with activation of PMv along with aIPS and other regions of the brain including the dorsomedial reaching circuit (Jacobs et al., 2010).

In order to understand more precisely the role of PMd in grasping, the connections between F5 and AIP in the macaque will now be reviewed.

3.2.3 Connectivity between the anterior intraparietal area and the ventral premotor cortex

In a study of three macaque monkeys using neural tracers it was shown that injecting AIP led to highly selective labelling of F5 of the macaque PMv with an equally selective reciprocal connection between F5 and AIP (Luppino et al., 1999). This reciprocity has led to the proposition that a feedback loop exists allowing information from F5 to be relayed back to AIP and vice versa to ensure that handgrip selection is maximally suited to the 3D characteristics of the object to be grasped (Murata et al., 2000). Other work using neural tracers suggests that a smaller section within F5, referred to as anterior F5 ('F5a'), may in fact be more specifically involved in the integration of sensory information from AIP and other cortical areas

so that a suitable motor programme for grasping can be produced prior to transfer to M1 (Gerbella et al., 2011).

There are differences in the way that neurons from AIP and F5 process information about 3D objects in comparison to neurons in the ITC, the part of the temporal lobe involved in object recognition according to the perception-action model (Goodale and Milner, 1992). The process by which the brain obtains information about the depth of an object from the 2D images that are projected on to each retina is known as stereopsis, as briefly discussed in relation to the ability of AIP to process 2D shapes and depth structure (Durand et al., 2007). Stereopsis is achieved by utilising the subtle difference in position of images produced on the retina of each eye when a macaque (or human) looks at an object, caused by the horizontal separation of each eye, called 'parallax'. The difference in image location of an object as seen by the left and right eye is known as 'binocular disparity' (Theys et al., 2013).

By analysing the discharge of individual neurons from two rhesus monkey in response to a number of different 3D shapes it has been demonstrated that ITC neurons are highly sensitive to changes in depth. This is primarily as a result of curvedness, enabling a detailed representation of 3D shape for real world objects and suggesting that ITC neurons are capable of object identification (Janssen et al., 2000). Humans are able to discriminate 3D shape in the same detail as macaques, as shown by object identification studies using curved surfaces (Norman et al., 1991). Examining individual neurons has identified subtle differences in the representation of 3D shapes in AIP compared to ITC. It is suggested that AIP neurons extract more rudimentary information about 3D shape, evidenced by the ability of neurons in AIP to tolerate discontinuities in the disparity of shapes, i.e. shapes can be altered and still cause neuronal activation, whereas the same alteration of shapes would prevent activation

of relevant ITC neurons. Additionally, AIP neurons are faster to discharge than ITC neurons (Srivastava et al., 2009).

The same research group has expanded on these findings, discovering that the majority of neurons in AIP are selective for 3D boundaries, that is the contours and outlines of shapes and objects rather than surface depth information (Theys et al., 2013), as originally thought from fMRI studies (Durand et al., 2007). In contrast, ITC neurons are more selective for surface depth information, which is now thought to be essential for object recognition. The sensitivity of AIP neurons to contours suggests that AIP provides rapid information about object shape that could be used to guide pre-shaping of the hand during visually guided grasping, i.e. grasp selection can be made quickly using less sophisticated visual information than is required to identify an object (Theys et al., 2013). From an evolutionary perspective this has a survival advantage to tree dwelling primates such as monkeys because the ability to grasp branches quickly and accurately in order to find food and avoid capture is more important than *identifying* that what is bring grasped is a branch.

The reduced latency of AIP neuron activation (faster discharge) compared to ITC neurons when extracting information about 3D contours also supports the theory that although object representation occurs in AIP, object recognition does not. In contrast, ITC neurons, selective for surface information, appear to be essential for object recognition (Theys et al., 2013). These differences lend support to perception-action model of the visual system because object identification occurs in the ITC, part of the ventral stream, whereas motor action is driven through the dorsolateral grasping circuit, part of the ventral stream.

3.2.4 Summary of the role of the dorsolateral grasping circuit

The role of the dorsolateral circuit can be summarised as a pathway capable of rapidly interpreting and processing visual information about the

contour and outline (Srivastava et al., 2009, Theys et al., 2013) of an object to provide information on its intrinsic properties, such as size and shape, and utilise this information in order to select an appropriate grip. Neural tracer studies in macaques suggest that two key areas of the dorsolateral circuit, AIP and F5, are reciprocally linked (Luppino et al., 1999, Gerbella et al., 2011) and it is hypothesised that a feedback loop between these two areas allows maximum specificity of handgrip to be achieved based on neuron populations that are selective not only for object shape but also the shape of specific handgrips (Murata et al., 2000, Murata et al., 1997). Information about handgrip is transferred from F5 to M1 where motor actions are initiated.

In humans, radiological (Castiello and Begliomini, 2008) and TMS studies (Rice et al., 2007) support the presence of a grasp related area homologous to AIP, referred to as aIPS in this thesis. Less can be firmly concluded about the role of the PMv in the control of grasp in humans but some imaging studies suggest that this area of the brain is active during precision grip tasks (Ehrsson et al., 2000) and when humans think about grasping with the hand (Jacobs et al., 2010).

3.3 Interaction between the dorsomedial reaching circuit and the dorsolateral grasping circuit

Reviewing reach and grasp as two distinct but temporally integrated neural circuits provides a framework for understanding the key parts of the brain purported to be involved in reach and grasp in monkeys and humans. However, it is clear that the distinction between the circuits is far from absolute, which is especially true in the frontal premotor cortex. Neurons in F2 of the PMd of macaques have been identified that are sensitive to both reach and grasp (Raos et al., 2004), and neurons within F5 of the macaque PMv have been shown to discharge to extrinsic object properties such as object location and direction (Schwartz et al., 2004), considered the remit of the dorsomedial reaching pathway according to the visuomotor

channel hypothesis (Jeannerod et al., 1995, Karl and Whishaw, 2013). It is also noteworthy that there are neurons within macaque V6A that are involved in the process of grasp selection as well as parameters of reach (Gamberini et al., 2011), suggesting a degree of overlap is possible in parietal nodes of the reach and grasp circuits.

It is likely that PMd and PMv are closely related in the final stages of reach and grasp, supported by the discovery that single neurons encoding reach and grasp can be mixed together in both macaque PMd and PMv (Stark et al., 2007). One theory is that neurons from F5 encode information about an object's intrinsic properties to enable selection of an appropriate grip type. This information is relayed to neurons within F2 where the motor representation from F5 is combined with extrinsic object information from V6A and F2 as the hand is orientated towards the object to be grasped (Castiello and Begliomini, 2008). Understanding of the nuances of reach and grasp in humans is less refined in the frontal premotor cortex but support for a common final pathway of reach and grasp involving PMd and PMv can be found in some fMRI studies (Cavina-Pratesi et al., 2010b, Jacobs et al., 2010)

3.4 Conclusion

There is a wealth of evidence from the study of monkeys, most often macaques, and humans to support the existence of two pathways controlling reach and grasp. The dorsomedial reaching circuit and the dorsolateral grasping circuit are examples of highly specialised parieto-frontal networks and neuron populations within the major nodes of these pathways have specific characteristics optimised for the cortical control of these naturally acquired motor behaviours.

The visuomotor channel hypothesis proposes that the reach and grasp pathways are distinct but temporally integrated under visual guidance (Jeannerod, 1999, Jeannerod et al., 1995, Jeannerod, 1984) and this theory

retains support to this day (Karl and Whishaw, 2013). However, the ability to study individual neurons within the reach and grasp pathways has revealed some crossover of function, particularly in the dorsal premotor cortices, and it is too simplistic to conclude that the neural pathways are completely distinct. It appears that the separation is relative rather than absolute, as is the case for the perception-action model of the visual system (Schenk and McIntosh, 2010).

Future research utilising diffusion tensor imaging and advances in fMRI studies are likely to refine understanding of the integration between the dorsomedial and dorsolateral circuits in humans during reaching and grasping and, ultimately, may be able to determine the specific neural pathways that are activated during specific reach and grasp tasks. The importance of the parietal lobe in PD cognitive dysfunction and the importance of the parietal lobe in the control of reach and grasp provide a basis to explore associations between cognition and motor function.

Chapter 4

Abbreviations used in this chapter

%TAP	Time to peak aperture as a % of movement time
AD	Alzheimer's disease
AIP	Anterior intraparietal area in macaques/monkeys
aIPS	Anterior intraparietal area in humans
CBGD	Corticobasal ganglionic degeneration
FEF	Frontal eye field
GPi	Globus pallidus interna
H&Y	Hoehn & Yahr
HC	Healthy controls
HD	Huntington's disease
ITC	Inferior temporal cortex
LIP	Lateral intraparietal area
MCP	Metacarpal-phalangeal
MT	Movement time
PA	Peak acceleration
PD	Parkinson's disease
PD-MCI	Parkinson's disease - mild cognitive impairment
PD-NC	Parkinson's disease - normal cognition
PDD	Parkinson's disease dementia
PDe	Peak deceleration
PIP	Proximal interphalangeal
PMd	Dorsal premotor cortex
PMv	Ventral premotor cortex
PV	Peak velocity
PwPD	People with Parkinson's disease
RT	Reaction time
SNpr	Substantia nigra pars reticulate
TAP	Time to peak aperture
TPA	Time to peak acceleration
TPD	Time to peak deceleration
TPV	Time to peak velocity
UPDRS	Unified Parkinson's Disease Rating Scale
V6A	Visual area V6A
WHP	Whole-hand prehension

Kinematic studies of reach and grasp

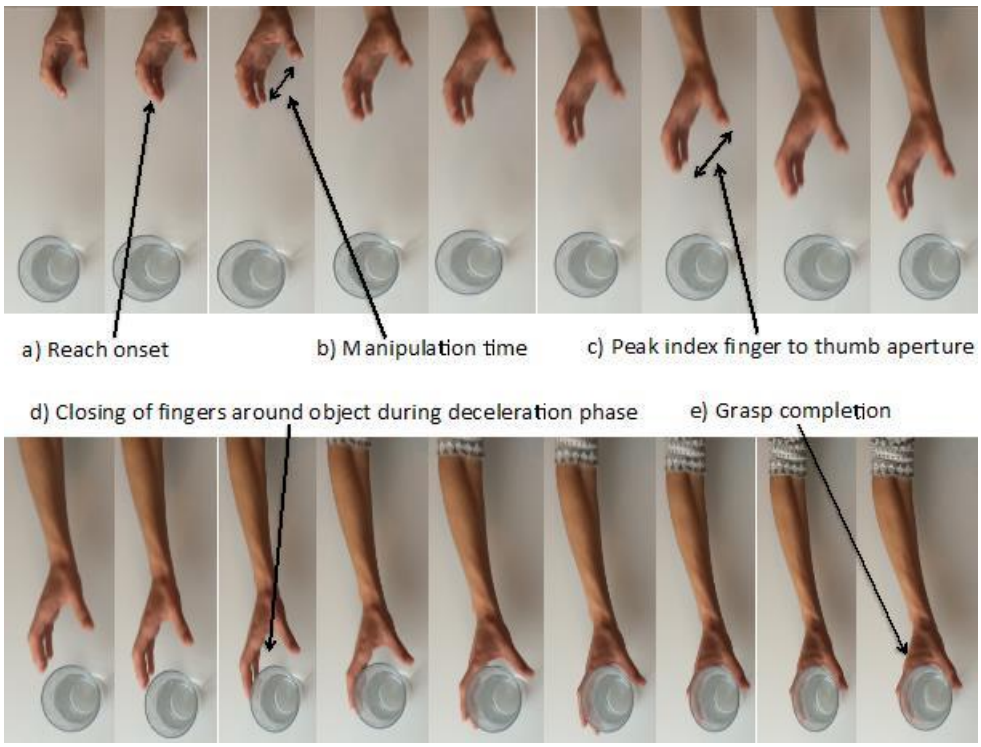
It became possible to accurately record and observe the human hand during a reach and grasp task in the early 1980's. As discussed in Chapter 1.4, Marc Jeannerod and others developed a mechanism for determining reach and grasp parameters such as velocity and acceleration by measuring the distance that key anatomical landmarks, for example the tip of the index finger, travelled during timed video recordings (Jeannerod, 2009, Jeannerod, 1984). The capacity to precisely measure the human hand and arm enabled investigation into the movement, or 'kinematics', of reach and grasp; a field of research popular throughout the 1990's, with key discoveries being made into the 2000's.

Pioneering results from early kinematic analysis of reach and grasp were combined with growing understanding of the dorsomedial reaching and dorsolateral grasping circuits, principally derived from single cell microelectrode studies in macaques and other monkey species, to propose the visuomotor channel hypothesis (Jeannerod, 1984, Jeannerod, 1999) The visuomotor channel hypothesis is discussed in Chapter 1.7 and theorises that distinct neural pathways that are temporally linked under visual guidance control reach and grasp. As with anatomical, imaging and electrophysiological studies reviewed in Chapter 3, kinematic studies of reach and grasp in humans can be interpreted as both supporting and refuting the visuomotor channel hypothesis.

This chapter is divided into two major sections; the first section will review kinematic studies in healthy human subjects, the second section will review kinematic studies of PwPD. Before proceeding further it is important to introduce some of the terminology used in the kinematic analysis of reach and grasp:

- **Movement time (MT):** The definition varies depending on the study in question but generally MT is considered the time in milliseconds or seconds from reach onset to grasp completion (Figure 25a and 25e). MT is considered a key kinematic parameter of reach.
- **Manipulation time:** The time in milliseconds or seconds between the onset of reach (i.e. the onset of MT) until the first detectable onset of grasp; often measured as the beginning of the separation of the index finger and thumb, or the beginning of an increase in the separation of the index finger and thumb if they are not touching at reach onset (Figure 25b).
- **Peak aperture:** The size, usually in millimetres or centimetres, of the maximal distance between the tip of the index finger and the tip of the thumb during reach and grasp (Figure 25c). The duration from the onset of MT until peak aperture is known as '**time to peak aperture'** (TAP) and is another important kinematic parameter. Both peak aperture and TAP are key parameters of grasp. After peak aperture the distance between index finger and thumb gradually reduces as the fingers close down around the object to be grasped (Figure 25d).
- **Grasp completion:** This is the time at which, when using WHP, the thumb and index finger are in opposition and all digits are flexed around the object in such a way as to form a ring around it (Figure 25e). It signifies the end of MT.

Figure 25: Key kinematic landmarks during a reach and grasp movement



Legend: Reach onset (a) signifies the beginning of MT. The time from reach onset until the first point at which the separation between the index finger and thumb increases is known as the manipulation time (b). Peak index finger to thumb aperture is an important kinematic parameter of grasp (c), and the time to attain this parameter from the onset of MT is TAP. After peak aperture the hand closes down around the object (d) until grasp completion (e), indicating the end of MT.

4.1 Reach and grasp in healthy humans

In a much-cited paper published in 1984, Jeanerrod et al. video-recorded and timed the movements of seven healthy adults as they reached and grasped for different sized objects, at different distances, under different visual conditions (Jeannerod, 1984). This experiment highlighted two key features of reach and grasp that have been replicated in subsequent studies: Firstly, a positive correlation was identified between the velocity and acceleration of arm movements and the distance the arm travels, i.e. when reaching a greater distance, the reaching limb accelerates more quickly and travels faster; secondly, peak aperture is linearly related to the size of the object to be grasped, i.e. when grasping a larger object, the grasping digits open wider.

This study also demonstrated that peak index finger to thumb aperture, followed thereafter by closing of the fingers around the object, occurred after peak deceleration of the hand (Jeannerod, 1984). Jeannerod used this invariant relationship to support his theory of temporal coupling between two independent reach and grasp circuits, a core principle of the visuomotor channel hypothesis (Jeannerod, 1986, Jeannerod, 1984), although this relationship has not been found in other studies (Marteniuk et al., 1990, Zackowski et al., 2002).

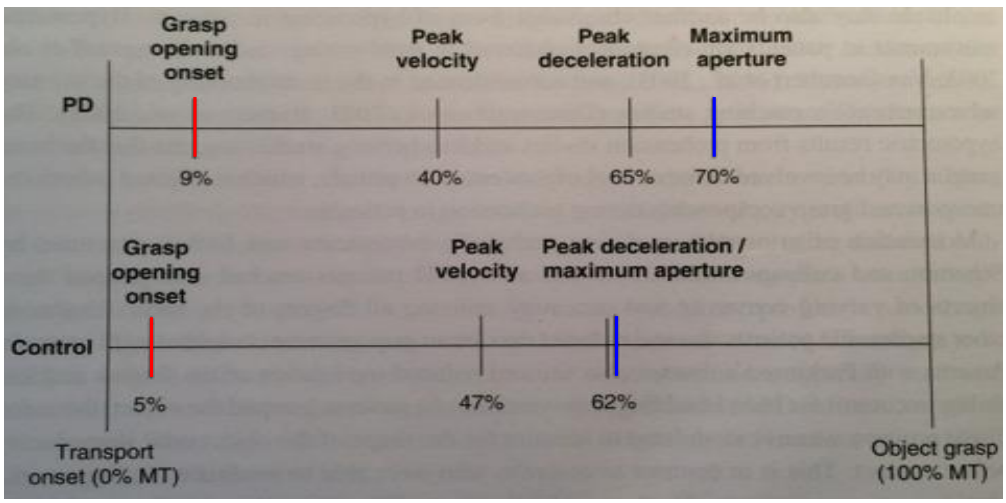
Paul Fitts proposed a trade-off between speed and accuracy in the 1950's (Fitts, 1954) that was extended to pointing movements a decade later (Fitts and Peterson, 1964). One basic proposition of 'Fitts' law' is that aiming movements toward a smaller target increases MT. This has been proven in reach and grasp tasks (Marteniuk et al., 1990, Bootsma et al., 1994). The additional MT required to reach for objects of smaller diameter occurs between peak deceleration (PDe) and object contact; peak acceleration (PA), time to peak acceleration (TPA) and the duration of acceleration are not significantly different. Therefore, the moving hand slows down for longer as it approaches a smaller object (Marteniuk et al., 1990, Bootsma et al., 1994).

It is well established, as common sense dictates, that MT is greater when reaching and grasping for objects that are further away (Marteniuk et al., 1990, Bootsma et al., 1994, Jeannerod, 1984). This is another proposition of Fitt's law (Fitts, 1954) and the relationship is true whether or not a precision grip or WHP is used to reach for an object, although when using precision grip peak aperture occurs earlier in MT than with WHP (Gentilucci et al., 1991).

4.1.1 Summary of kinematic principles in healthy people when reaching and grasping under visual guidance

- MT is prolonged when reaching for objects that are further away.
- When reaching for objects that are further away, the reaching limb generates greater acceleration and velocity than when reaching for objects that are closer.
- MT is prolonged when reaching towards smaller objects at the same distance as larger objects. Increased MT is as a result of a prolonged deceleration as the hand approaches the smaller object.
- Peak aperture is linearly related to object size.
- Peak aperture occurs earlier, as a percentage of MT, when reaching towards smaller objects and when using precision grip rather than WHP.
- Peak aperture occurs after approximately 60% of MT in healthy subjects (Figure 26).

Figure 26: A comparison of kinematic reach and grasp parameters in healthy people and people with Parkinson's disease



Legend: As a percentage of MT, grasp opening (red), i.e. the movement signifying manipulation time, is delayed in PD (upper timeline) compared to healthy subjects (lower timeline). Peak aperture, referred to as maximum aperture in this figure (blue), is also delayed in PD compared to healthy subjects. Adapted from Flink and Stelmach, 2009 with permission (Flink and Stelmach, 2009).

4.1.2 Modifying size and position of objects at movement onset

A number of experiments have been performed in which parameters of either reach or grasp are modified, or 'perturbed' at the time of movement onset. For example, six right-handed subjects were asked to reach and grasp an illuminated central dowel placed at 20 degrees to the right of midline. In 20% of procedures the trial was perturbed such that commencement of movement led to illumination of an alternate dowel at either ten or 30 degrees to the right of midline, requiring a change in the reaching trajectory (Paulignan et al., 1991b). MT was an average of 100ms longer when perturbation occurred and kinematic analysis revealed that parameters of both reach and grasp were altered. The change in direction of the wrist began 100ms after movement initiation, creating two sub-movements – an initial movement towards the central dowel followed by a second movement to the alternate dowel. It took between 250ms and 290ms for the wrist to complete the change in direction. PA and peak velocity (PV) of the first movement occurred earlier than in trials without perturbation which only had one movement. The second movement in perturbed trials had a smaller PA and PV than the first movement and a shorter deceleration period (Paulignan et al., 1991b).

Eighty percent of perturbed trials also resulted in two distinct peak apertures (remember, peak aperture is an important kinematic parameter of grasp). In these cases, the delay between PDe and peak apertures was significantly shorter for both compared to the time delay in non-perturbed trials. The discrepancy between the time required to change wrist direction and the additional time to complete the movement demonstrated that the second corrective movement was executed more quickly than a normal movement at the same target. The delay before initiating change in wrist direction was felt to be in keeping with previous studies that suggested 100ms is the minimum interval required for visual afferents to influence on-going movements (Paulignan et al., 1991b).

In summary, this study demonstrated that parameters of reach and grasp can be modified online (i.e. after onset of reach) and the latency required to achieve this is less than that required when the change in target location is made just prior to movement onset (Paulignan et al., 1991b). It was suggested that online reconfiguration of the reach and grasp programmes, mediated by the processing of visual information and proprioceptive signals from the arm, can occur more quickly than the generation of a new reach and grasp programme that would be required if object position changed prior to reach onset (Paulignan et al., 1991b). Current understanding of the dorsomedial reaching and dorsolateral grasping circuits supports the idea of online adjustment via reciprocal transfer of information between the major nodes of the circuits and the cross transfer of information regarding extrinsic and intrinsic object properties, which is thought to occur between the PMd and PMv (see Chapter 3) (Castiello and Begliomini, 2008).

Paulignan et al. also performed trials in which object size, rather than object position, was perturbed at movement onset (Paulignan et al., 1991a). MT increased by 175ms when object size was changed from a small to large dowel and 85ms when changed from large to small. The increase in MT was related to a prolonged low velocity phase following PDe – i.e. the point at which the hand is in close proximity to the dowel – and it was during this phase, after at least 330ms, when changes of index finger to thumb aperture were demonstrated. As with trials in which position was perturbed (Paulignan et al., 1991b, Paulignan et al., 1990), the variability of the spatial paths of the fingers decreased as MT progressed, suggesting that the fingers contacted the dowel at very similar positions on each repetition of the task (Paulignan et al., 1991a).

Taken together, the studies of Paulignan et al. demonstrate that perturbing object *size* – response to which is purportedly controlled by the dorsolateral grasping circuit comprising the anterior intraparietal area (aIPS

in humans, AIP in macaques) and the PMv – changes parameters of reach (MT) as well as grasp (change to peak aperture). Perturbing object *position* – response to which is purportedly mediated by the dorsomedial reaching circuit comprising V6A and PMd – changes parameters of grasp (two separate peak apertures) as well as reach (changes in wrist direction). Perturbation of object position leads to a change in reach parameters within 100ms but changes to index finger to thumb aperture following perturbation of object size take longer to develop, which could suggest that the online adjustment of grasp is more complex than the online adjustment of reach.

The kinematic coupling of reach and grasp was argued to be against the visuomotor channel hypothesis by some researchers, i.e. if the pathways are distinct then changing an intrinsic property should only alter parameters of grasp and changing an extrinsic property should only affect reaching parameters (Jakobson and Goodale, 1991). Paulignan et al. argued that the on-line adjustment of reach and grasp parameters to maintain temporal coupling (PDe was followed by peak aperture in both) supported integration of distinct pathways, i.e. supported the visuomotor channel hypothesis (Paulignan et al., 1991b, Paulignan et al., 1991a).

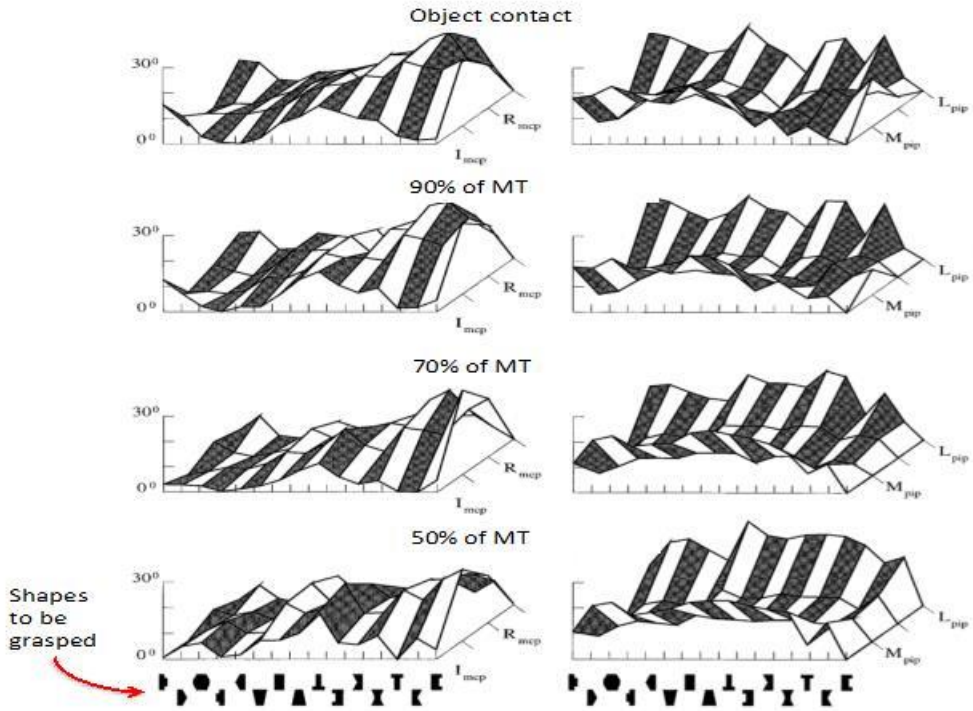
Studies of participant awareness of perturbation when performing reach and grasp revealed that vocalisation (any utterance of sound) in response to a change of object position (Castiello et al., 1991) or size (Castiello and Jeannerod, 1991) occurred 420ms after the change had occurred, therefore approximately 320ms after the wrist orientation begins to change in trials where position is perturbed, and approximately 100ms after grip parameters change in trials where size is perturbed. Presuming that vocalisation indicates identification of a perturbation, these studies suggest that alteration of the motor programmes controlling reach and grasp can occur before conscious awareness of such a change. This can be linked to visual illusion studies, as mentioned in Chapter 1.8, that have

shown parameters of reach and grasp remain correctly scaled to object size despite the fact that they are perceived as being incorrectly sized (Aglioti et al., 1995). It appears that automatic, subconscious change in online movement is possible in reach and grasp, as has been demonstrated in saccadic eye movement studies thought to involve the highly specialised LIP-FEF parieto-frontal network (Gaveau et al., 2014). Single cell microelectrode studies in macaques suggest that neurons within AIP provide a quick, coarse representation of object shape; they are not thought to be involved in object recognition, which is mediated by neurons within the ITC (see Chapter 3.2.3) (Srivastava et al., 2009, Theys et al., 2013). The apparent ability of individual neurons within AIP to process information to facilitate grasping before object identification occurs is further evidence of automatic, subconscious control of reach and grasp.

4.1.3 The effects of object shape and context of implementation on reach and grasp

Moulding of the grasping hand as it approaches objects of different shapes has been found to be a gradual process, evolving throughout reach. In one study, subjects were asked to grasp 15 differently shaped objects of a similar size using WHP whilst wearing gloves that record movement. It was shown that differences in hand configuration as the arm approached the objects, demonstrated by degrees of freedom at the metacarpal-phalangeal (MCP) and proximal interphalangeal (PIP) joints of the index, middle, ring and little fingers, were detectable at 50% of MT and evolved gradually thereafter (Santello and Soechting, 1998) (Figure 27).

Figure 27: Evolution of hand shape at different time periods during reach



Legend: Taken from one subject, this figure demonstrates that hand position, as measured by four degrees of freedom at MCP and PIP joints represented on the oblique axis, starts to become specific for the object to be grasped at 50% of MT with continued evolution of finger shape thereafter. The objects grasped are arranged progressively from convex (left) to concave (right) on the horizontal axis. Abbreviations: MT, movement time; L, little finger; M, middle finger; R, ring finger; I, index finger. Adapted from Santello and Soechting, 1998 with permission (Santello and Soechting, 1998).

In support of the theory that different hand contours are related to object shape rather than other object parameters such as size, it was shown that hand configurations could be grouped together for objects of similar shape (e.g. convex and concave) and that this grouping was apparent from 50% of MT onwards (Santello and Soechting, 1998). Peak aperture of the index finger and thumb, known to be linearly related to object size (Jeannerod, 1984, Paulignan et al., 1991a), was reached at between 30% and 70% of the MT and therefore it was demonstrated that hand shape continues to evolve after peak aperture (Santello and Soechting, 1998). This was a significant finding because it supports the concept of the online adjustment of the grasping motor programme during reach, i.e. the grasping hand is

capable of adjusting finger position up until object contact in order to maximise grasping efficiency.

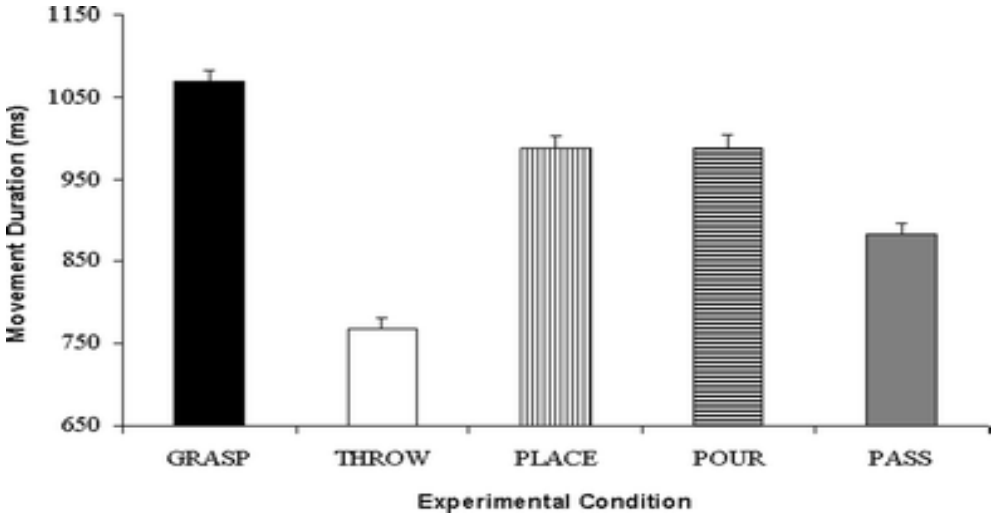
As well as size and shape, it has been demonstrated that parameters of reach and grasp are altered by the context of implementation, or, put simply, what happens to the object in question after it has been grasped. Ten healthy participants were asked to reach and grasp an object and then perform one of three tasks; lift the object, insert it into a niche of a similar shape and size, or insert into a rectangular niche much larger than the object (Ansuini et al., 2006). For the low-accuracy niche, that is the rectangular niche much larger than object, it was shown that MT (a major kinematic parameter of reach) was shorter than for the other two conditions and that configuration of the hand (i.e. grasping parameters) occurred at the beginning of the movement rather than gradually evolving as in the other conditions. This seems somewhat counter-intuitive in that one would expect that the lifting task requires less accuracy than either of the niche tasks. The authors speculate that precision constraints might have inadvertently occurred in the lifting task because subjects were instructed to lift the object and place it back in the same place and they may have tried to do this accurately (Ansuini et al., 2006).

The effect of action implementation on reach and grasp was further investigated when twenty healthy subjects were asked to reach and grasp a bottle of water and then either do nothing, or throw the bottle, place it accurately on a target, pour the water into a beaker or hand the bottle to another person (Ansuini et al., 2008). MT was greatest when reaching and grasping alone. This finding is a replication of previous studies (Gentilucci et al., 1997) that have consistently shown that the duration of reach and grasp is decreased when a subsequent action follows a reach and grasp task. Ansuini et al. proposed that MT might be longer in the reach and grasp alone task because:

"…the movement necessary to achieve the intended goal (i.e., grasping) is not specified by the dynamic constraints of the task, causing subject to rely more heavily on sensory feedback." (Ansuini et al., 2008)

Otherwise MT was longer for tasks in which the subsequent action after reach and grasp required more accuracy (Figure 28). This could be explained using Fitts' law (Fitts, 1954) (see 4.1) and suggests that reach and grasp motor programmes are influenced by the complexity of subsequent motor tasks.

Figure 28: The movement time of a reach and grasp task is dependent on context



Legend: MT, referred to as movement duration in this figure, is longest for grasp alone ('Grasp'). Significant differences (p <0.05) were found between all conditions except 'Place' and 'Pour'. Reproduced from Ansuini et al., 2008 with permission (Ansuini et al., 2008).

4.1.3.1 Summary

Parameters of reach and grasp are affected by the context in which an action is undertaken (Ansuini et al., 2006, Ansuini et al., 2008); MT is slower when the action subsequent to reach and grasp requires more accuracy and differences in hand shape can be seen depending on the context. When the hand reaches for different shaped objects, moulding of the fingers begins early, with differences visible from 50% of MT. As the hand approaches the object, further moulding of the fingers occurs, after

peak aperture has been obtained and the hand is closing down around the object (Santello and Soechting, 1998). Studies in macaques have shown that AIP contains neurons that are sensitive to specific object shapes (Murata et al., 2000) and has reciprocal connectivity with area F5 of PMv (Luppino et al., 1999). Information about the outline and contours of shapes are encoded by AIP (Theys et al., 2013) and the possibility of a feedback loop existing within the dorsolateral grasping circuit, whereby handgrip selection can be continually optimised to suit object shape as the hand approaches the object, has been hypothesised (Murata et al., 2000). Although there is only limited evidence to support involvement of the PMv in the human grasping circuit (Jacobs et al., 2010), the gradual moulding of the human hand during reaching could support such a theory. Changes, or perturbation, to object size or location after reach onset alters parameters of reach and grasp, which can been argued to both support (Paulignan et al., 1991a) and refute (Jakobson and Goodale, 1991) the visuomotor channel hypothesis.

4.1.4 The effects of visual feedback on reach and grasp

Temporal integration of the dorsomedial reaching and dorsolateral grasping circuits under visual guidance is the basis of the visuomotor channel hypothesis (Jeannerod, 1999, Jeannerod, 1984). It is therefore no surprise that the effect of visual feedback on reach and grasp has been extensively studied.

Jeannerod demonstrated that if subjects could see a target before they initiated movement but visual feedback was removed at movement onset, peak index finger to thumb aperture was still scaled for object size (i.e. was greater for the larger than smaller objects) but that the size of peak aperture was greater than when visual feedback was provided. MT was also found to be longer in the absence of visual feedback (Jeannerod, 1984). These findings were replicated in another study when visual feedback was absent in blocks of trials (i.e. consecutive tasks were performed during

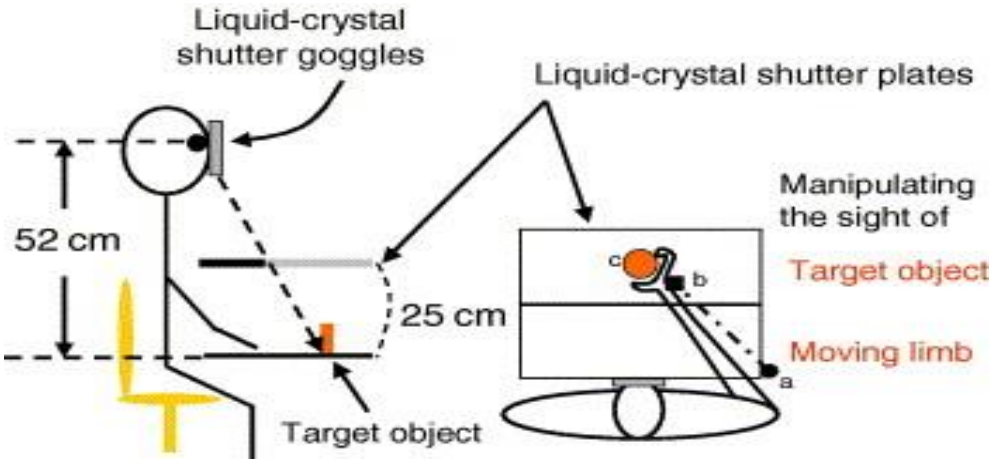
which visual feedback was removed at the onset of reach). In contrast, grasp parameters were different when visual feedback and no-visual feedback trials were randomly interspersed. In such trials no significant difference was found in peak aperture, which was of the same magnitude as seen when visual feedback was removed in the blocked trials, i.e. when visual feedback was non-predictably available, the grasping hand consistently opened wider, as it does when visual feedback is constantly unavailable (Jakobson and Goodale, 1991). The increase in peak index finger to thumb aperture in the absence of vision may be a means of preventing the fingers and the object colliding, or represent a means of compensating for errors in reach because a larger peak aperture is more likely to encompass the object to be grasped (Fukui and Inui, 2013).

The effect of visual feedback has also been studied when subjects reach and grasp for different shaped objects. In one study, participants were asked to reach and grasp three different shaped objects (a rectangular cube, a convex shaped block and a concave shaped block) of similar size under three different conditions: full vision, in darkness with the exception of a visually illuminated target and without any visual feedback (Schettino et al., 2003). Prior to each task subjects were allowed at least two seconds to look at the object to be grasped and were told to grasp the objects using WHP, as per previous studies of hand moulding (Santello and Soechting, 1998). In keeping with existing literature (Jeannerod, 1984, Jakobson and Goodale, 1991), it was demonstrated that MT was significantly prolonged when visual feedback was removed (either completely or when only the target was illuminated). Post-hoc analysis revealed that TAP occurred earlier in darkness and with object illumination only. This supports the theory that a margin of error is employed in the absence of visual feedback (the hand opens wider and sooner in these conditions). It was also demonstrated that differences in hand shaping were evident as early as 45% of MT as participants reached for the convex shape (requiring abduction) compared to the rectangular cube or the concave shape

(requiring adduction) in all visual conditions. However, in full vision hand shaping was not complete until 75% of MT, contrasting with earlier hand configuration (~45%) in visually altered conditions. The authors concluded that grip selection must be controlled by two mechanisms; target object shape must be included in the planning of reach and grasp and a feedback mechanism must exist to allow optimisation of grasp when performed under normal visual conditions (Schettino et al., 2003). This relates back to the online modification of grasping as the hand approached the object (see 4.1.3). However, in another study no difference in grasp kinematics were found during reaching for numerous differently shaped objects under full vision, memory guided vision (subjects reached and grasped in full vision towards a remembered target that had been removed) and to a virtual image (subjects could see a virtual image but could not see their hands) (Santello et al., 2002).

Two key questions regarding visual control in reach and grasp remain, namely; *if at all, at what point during reach and grasp does visual control exert an influence on grasp?* And *what type of visual information is most important during reach and grasp?* Using liquid-crystal shutter goggles in order to accurately manipulate vision at specific times during reach and grasp has enhanced understanding of this. It has been demonstrated that peak aperture is significantly larger if vision is occluded 150ms after reach initiation than if occluded 300ms after reach initiation. Conversely, if vision is initially occluded, peak aperture is significantly larger if vision is restored at 350ms rather than 150ms. This suggests that vision appears to be most important in regulating grasp between 150ms and 300ms after reach initiation (Fukui and Inui, 2006). Moreover, the same study used liquid-crystal shutters to regulate view of the hand and the target object at specific time points such that they were unable to see the hand and the object or could only see the hand as it approached the object (Figure 29).

Figure 29: Experimental design of Fukui and Inui, 2006



Legend: Liquid-crystal shutter plates were used to manipulate view of the limb and the target object. Reproduced from Fukui and Inui, 2006 with permission (Fukui and Inui, 2006).

MT and peak aperture were significantly increased when the hand and object were occluded at onset or at 150ms when compared to no occlusion. In contrast, when the target could be seen but the hand occluded, there was no significant difference in either parameter. This strongly suggests that early viewing of the target, rather than the hand, is important in regulating the parameters of grasp (Fukui and Inui, 2006). The finding that peak aperture differed in random trials of varied visual feedback contrasts with findings from the study of Jackobson and Goodale (Jakobson and Goodale, 1991).

Reach and grasp has also been analysed in four congenitally blind subjects who were asked to reach and grasp two dowels of different sizes at two distances (Castiello et al., 1993a). The results were compared with age and sexed match, blindfolded HC (who had not seen the experimental set-up) and HC using normal full visual guidance. When reaching a greater distance (30cm) the congenitally blind subjects showed a double peak of wrist velocity and for the shorter distance (20cm) they showed a plateau of wrist velocity towards the end of movement, previously termed the 'low velocity phase' (Jeannerod, 1984). Analysis of grasping kinematics showed

that congenitally blind subjects had a double pattern of finger opening and closing – the first at an average of 42% of MT, the second at 56% of MT. The congenitally blind subjects were able to scale index finger to thumb aperture to object size (prior to trial commencement all subjects were allowed to manipulate the objects) and showed a prolonged deceleration phase of reach as they approached the small cylinder compared to the larger cylinder, as is seen in healthy subjects under full visual guidance (Marteniuk et al., 1990, Bootsma et al., 1994). Temporal coupling of parameters of reach and grasp were preserved in HC with full vision (peak aperture occurred after PDe) and to an extent in blind subjects who showed, for example, a correlation between onset of the low velocity phase and the second peak aperture. Blindfolded subjects did not show any coupling between reach and grasp. It was concluded that vision is not a prerequisite for efficient reach and grasp although is likely required for single grip opening (Castiello et al., 1993a).

More recently, it has been demonstrated that participants blindfolded prior to, and throughout, a reaching and grasping task in which they are unaware of object identity are unable to modify reaching parameters but gradually modify parameters of grasp, including peak index finger to thumb aperture and index finger to thumb aperture at time of object contact (Karl et al., 2013). The authors suggest the decoupling of reach and grasp is supportive of distinct neural circuits controlling reach and grasp, in keeping with the visuomotor channel hypothesis, and theorise that grasping can be modified in the absence of vision because its evolutionary basis derives from food handling, in which haptic feedback (i.e. touch) is used to guide food to the mouth (Karl and Whishaw, 2013, Karl et al., 2013).

4.1.4.1 Summary

It is suggested that a lack of visual guidance disrupts the temporal coupling between reach and grasp (Castiello et al., 1993a). MT is longer when there is no visual feedback at all (Jeannerod, 1984, Jakobson and Goodale, 1991,

Schettino et al., 2003) or when visual feedback of the reaching limb is removed and only the object to be grasped is illuminated (Schettino et al., 2003). One study has demonstrated that hand shaping for specific objects still occurs in the absence of visual feedback although arrests sooner in the reaching process (Schettino et al., 2003), but an alternate study did not find this (Santello et al., 2002). A number of studies suggest that peak aperture occurs earlier, and is of greater size, when reaching and grasping without vision (Jeannerod, 1984, Jakobson and Goodale, 1991, Schettino et al., 2003). Vision appears to be most important during early reaching (150-300ms) and seeing the target object, rather than the hand, appears to be important in the regulation of grasp (as measured by peak aperture) (Fukui and Inui, 2006, Fukui and Inui, 2013). Blind subjects show some degree of coupling between reach and grasp, in contrast to blindfolded HC, although they adopt a double pattern of finger opening and closing (Castiello et al., 1993a).

4.2 Reach and grasp in Parkinson's disease

4.2.1 Core features of reach and grasp in Parkinson's disease

PwPD have been compared to HC when the reaching distance and size of the object are varied in a reach and grasp task. For example, eight PD subjects with mild disease (H&Y I or II) tested whilst *on* were compared with eight age matched HC as they reached and grasped either a small (0.7cm) or large (8cm) diameter dowel at three distances (15cm, 27.5cm and 40cm) (Castiello et al., 1993b). A similar pattern of change was observed in the PwPD as had already been demonstrated in healthy subjects (Jakobson and Goodale, 1991, Jeannerod, 1984) (see 4.1.1). For both groups:

- MT was prolonged when reaching for objects furthest away (40cm) compared to the shorter distances.
- PA, PV and PDe were greater as the reaching distance increased.

- TAP was prolonged as the reaching distance increased.
- When grasping using precision grip (for the small diameter dowel), TAP occurred earlier than when reaching the same distance using WHP (to grasp the larger dowel).
- PV occurred earlier using precision grip than WHP, allowing a prolonged deceleration phase as the hand approached the small dowel compared to the large dowel (Castiello et al., 1993b).

Despite the similarities, PwPD are slower than HC, even when tested whilst *on*:

- MT is longer when reaching the same distance towards the same sized object in PwPD.
- Values of PA, PV and PDe are reduced in PwPD.
- Time to attain peak reaching parameters, i.e. TPA, time to peak velocity (TPV) and time to peak deceleration (TPD) are prolonged in PwPD.
- TAP is prolonged and occurs later as a percentage of movement time (%TAP) in PwPD (Castiello et al., 1993b).

In summary, there is evidence to suggest that PwPD are able to adapt kinematic parameters of reach and grasp in the same way as HC but they are generally slower, even whilst *on.*

4.2.2 Modifying size and position of objects at reach onset in Parkinson's disease

Perturbation of object distance has been compared between PwPD and HC (Scarpa and Castiello, 1994). In 20 of 60 recorded reach and grasp tasks, the reaching distance was unexpectedly increased from 15cm to either 27cm or 40cm at movement onset. It was shown that PwPD demonstrate two sub-movements when distance is perturbed and that PA, PV and peak aperture occur earlier in this situation. The changes are identical to those

seen in HC (Paulignan et al., 1991b). One difference between the groups was that PwPD have a prolonged 'manipulation time' (the time from onset of reach to the commencement of grasp – see Figure 25) (Scarpa and Castiello, 1994). This will be discussed in 4.2.3.

Perturbing object size at movement onset has revealed that PwPD are able to modify movement parameters in the same way as HC (Castiello and Bennett, 1994). MT was not statistically longer in either group when object size changed, necessitating alteration of grasp from WHP to precision grip or vice versa. Perturbing object size also leads to an earlier peak aperture in both HC and PwPD, the difference being more obvious when changing grasp from WHP to precision grip. Additionally, peak aperture was smaller in trials where object size was changed from large to small than when grasping the large cylinder without perturbation in both groups, suggesting that WHP was aborted before reaching its peak in order to execute precision grip (Castiello and Bennett, 1994). As with previous studies in healthy people (Paulignan et al., 1991a), perturbation of object size led to changes in parameters of reach in addition to grasp in PwPD . For example, PDe was greater and occurred earlier in perturbed trials; the hand 'brakes' when approaching the cylinder to allow change of grip type (Castiello and Bennett, 1994).

4.2.3 Difficulty with sequential tasks and uncoupling of reach and grasp in Parkinson's disease

One difference that has been identified in some studies of reach and grasp in PwPD is a delay in the onset of manipulation during reach – the point at which the grasp begins, measured by an increase in separation of the index finger and the thumb (Castiello et al., 1993b, Castiello and Bennett, 1994, Scarpa and Castiello, 1994). This finding has been used to support the idea of an interruption between the usual temporal coupling of reach and grasp under full visual guidance in PD.

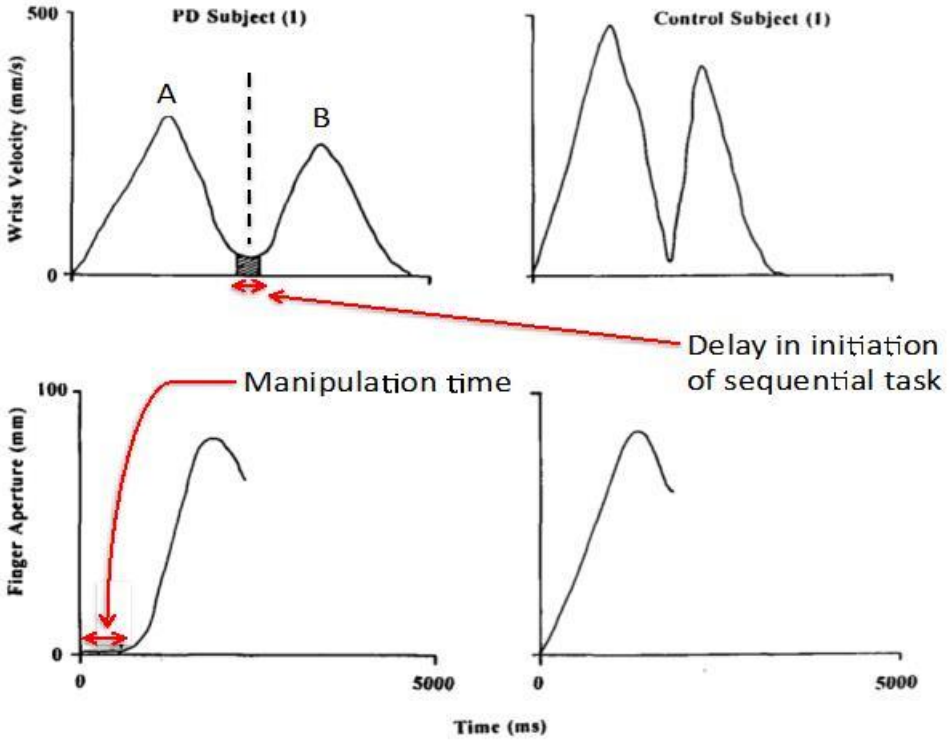
Increased manipulation time has also been used to support the theory that PwPD struggle to perform sequential tasks, as suggested by a number of studies of different motor acts. For example, Benecke et al. demonstrated that PwPD take longer to perform two simple tasks in sequence than the total time taken to perform each task independently; an additional delay between the completion of one task (isometric squeezing) and the commencement of the next task (elbow flexion) was found in PwPD compared to HC (Benecke et al., 1987). In another study, PwPD hesitated more often (42% of trials versus 24% of trials) and for longer than HC when transitioning between two movement segments in an experiment looking at the effect of context in PD (Weiss et al., 1997). Finally, during a reaching task involving synchronous movements of the arm and trunk, in contrast to HC, PwPD generate large timing intervals between the two tasks but maintain accuracy (Poizner et al., 2000).

A number of reach and grasp studies have demonstrated a delay in the onset of manipulation in those with PD. For example, manipulation began at 3% of MT in HC but 8% of MT in PwPD in Castiello et al.'s study considered in detail in 4.2.1 (Castiello et al., 1993b). In support of difficulty with movement sequencing, perturbing object size from a small to large cylinder necessitating a change from precision grip to WHP was slower to occur in PwPD (28% of MT versus 9% of MT) and in 73% of trials was associated with a plateau likely to be indicative of peak aperture for the small cylinder before opening the hand further for the larger cylinder. In contrast, HC demonstrated a smooth transition between grip types (Castiello and Bennett, 1994). For the converse perturbation, from large to small cylinder (and thus WHP to precision grip), PwPD took longer, delayed by ten percent of MT, to change to a precision grip, i.e. there was a delay in the transition between grip types (Castiello and Bennett, 1994). When object distance is varied, delayed manipulation is still present in PwPD compared to HC although is reduced in perturbed trials (Scarpa and Castiello, 1994). The latter finding suggests that in response to

perturbation, which appears to be a subconscious process (Castiello et al., 1991, Castiello and Jeannerod, 1991), parameters of reach and grasp can be partially recoupled in PD whereas otherwise they appear to be executed sequentially rather than concurrently (Scarpa and Castiello, 1994).

An experiment in which nine PwPD (H&Y I or II) were asked to reach and grasp a beaker of water and then bring the beaker to the mouth demonstrates a delay in manipulation during reach and grasp *and* a delay in the initiation of sequential tasks (Bennett et al., 1995). Firstly, onset of manipulation when reaching to grasp the glass was delayed in PwPD compared to HC, occurring at nine percent of MT compared to 3.3% of MT in HC; secondly, eight of the nine PwPD demonstrated a delay between grasping the beaker and the onset of bringing the beaker to the mouth (Figure 30). Overall, this delay was apparent in 38% of trials in the PD group, lasting for an average of 340ms, or seven percent of MT. In HC, a single trial from one participant showed a delay between the motor tasks. The authors were unable to find any association between the trials demonstrating a delay between the motor tasks in PwPD and subject age, sex, disease severity or movement parameters including PA, PDe and MT but this may have been due to the small numbers of subjects (Bennett et al., 1995). The delay in manipulation time was associated with a delay in attaining peak aperture between index finger and thumb in PwPD, occurring at 27% of reach to grasp MT compared to 21% in HC.

Figure 30: Parkinson's disease subjects have a prolonged manipulation time and show a delay between sequential tasks



Legend: The upper images plot wrist velocity on the *y*-axis and time on the *x*-axis. In the PD subject (upper left) there is a plateau in wrist velocity between completion of the reach and grasp task (A) and bringing the glass of water to the mouth (B). This is not present in HC ('control subject' - upper right). In the lower images, index finger to thumb aperture is shown for the reach and grasp component of the task. There is a delay in the separation of the index finger and thumb in the PD subject (lower left); the time from reach onset to index finger to thumb opening is the manipulation time. Abbreviations: A, Reach and grasp component of the task; B, 'bringing in the glass to the mouth' component of the task. Adapted from Bennett et al., 1995 with permission (Bennett et al., 1995).

4.2.3.1 Summary

A prolonged manipulation time when reaching and grasping has been found in a number of studies in PwPD (Castiello et al., 1993b, Bennett et al., 1995) and has been considered as evidence to support a difficulty in sequencing motor programmes in reach and grasp, as has been found in other motor acts (Benecke et al., 1987, Weiss et al., 1997, Poizner et al., 2000) and in perturbation trials in PwPD (Castiello and Bennett, 1994). In relation to reach and grasp, difficulty in sequencing the reach and grasp

motor programmes can be used as evidence to support breakdown between the temporal coordination of the dorsomedial and dorsolateral pathways in PD, i.e. an invalidation of the visuomotor channel hypothesis. However, delayed manipulation is not a universal finding. For example, it was not found when six PwPD were compared with six HC and six Huntington's disease (HD) subjects as they reached and grasped for a glass at normal speed and as quickly as possible (Bonfiglioli et al., 1998). Even when present, there is significant intra-subject variation in manipulation time; in the study of Bennett et al. 67% of PD values were within the HC range and in one PD subject, for example, manipulation time ranged between 50ms and 234ms between trials (Bennett et al., 1995).

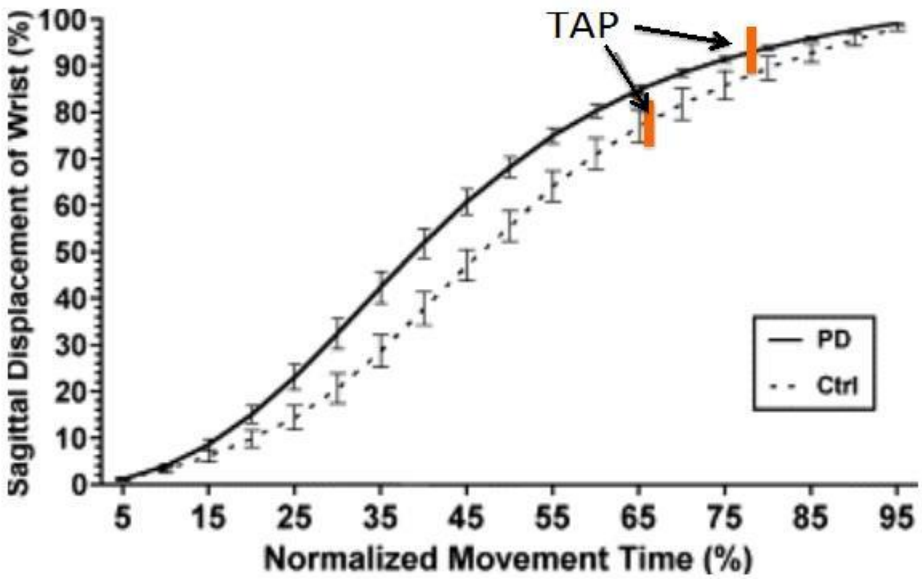
4.2.4 The effect of object shape and role of context on reach and grasp in Parkinson's disease

Hand preshaping during reach and grasp is a gradual process in healthy humans, with detectable differences identified from as little as 50% of MT when reaching to grasp differently shaped objects (see 4.1.3) (Santello and Soechting, 1998). Using three objects identified by Schettino et al. (Schettino et al., 2003) to produce highly discriminatory grasp configurations in healthy people, the same research group compared nine PD subjects with H&Y stage II or III disease, tested whilst *off*, with nine age matched HC. As expected, PwPD had prolonged MT and reduced PV. Modulation of hand shape was found to be highly variable between subjects of both groups, but those with PD tended to produce less movement of the joints of the hand than HC, particularly abduction and adduction at the base of the fingers and movement of the PIP joints. Using a mathematical process called discriminant analysis [18], post-hoc statistical tests revealed that the PD subjects had significantly more variation in hand shape than HC between 55-95% of MT, suggesting that PwPD are slower to

[18] Discriminant analysis – In this context: *"a measurement of the error of hand preshaping during the transport phase of the movement and an estimate of the predictive value of this measure of the final hand shape per object type".* (Schettino et al., 2004)

specify hand shape than HC (Schettino et al., 2004). In addition, as already demonstrated in previous trials (Castiello et al., 1993b), peak aperture (measured using a surrogate technique) was smaller and occurred later in PwPD (occurring at 95% of sagittal wrist displacement compared to 75% of displacement in HC - Figure 31).

Figure 31: Sagittal displacement of the wrist plotted against normalised movement time in healthy people and people with Parkinson's disease



Legend: TAP (orange line) occurs later as a percentage of normalised movement time (*x*-axis) and when the wrist has travelled further (*y*-axis) in PD subjects compared to HC. Abbreviations: TAP, time to peak aperture; PD, Parkinson's disease subjects; Ctrl; healthy controls. Adapted from Schettino et al., 2004 with permission (Schettino et al., 2004).

Schettino et al. argued that the delay in hand preshaping seen in PD could be related to difficulties with appropriate grip selection (Schettino et al., 2004), which is predominantly mediated by the dorsolateral grasping circuit (see Chapter 3) (Castiello and Begliomini, 2008, Karl and Whishaw, 2013). Neural tracer studies in monkeys have shown that both major nodes of the dorsolateral grasping circuit receive direct output from the basal ganglia; the globus pallidus interna (GPi) is connected to the PMv via the thalamus (Hoover and Strick, 1993) and the caudal two-thirds of the substantia nigra pars reticulata (SNpr) is connected to AIP, again via the

thalamus (Clower et al., 2005). If such connectivity existed in humans it is possible that damage to the basal ganglia in PD, caused by degeneration and death of dopaminergic neurons and Lewy pathology, could directly impair grip selection by altering output to the dorsolateral grasping circuit.

Reach and grasp kinematics are altered depending on a subsequent task in healthy subjects – this has been referred to as the 'context effect' (Marteniuk et al., 1987) (see 4.1.3). There are no published studies specifically investigating the context effect during reach and grasp in PwPD. In a two stage drawing task in which the accuracy requirements of the second task were altered, PwPD showed similar movement patterns to HC, suggesting that their ability to modify motor programmes depending on context is intact (Weiss et al., 1997). The process of moving the arm when drawing in that study was similar to the movement of the arm when reaching, allowing comparisons to be made.

Another study by the same authors compared nine PwPD and nine HC as they reached and grasped with and without an accurate 'precue' towards an illuminated large or small cylinder (Weiss et al., 1999). The precue was illumination of one of the cylinders before each trial with instructions to prepare to grasp that cylinder as quickly as possible; precision grip was required for the small cylinder, WHP for the large cylinder. In 75% of trials, the cylinder illuminated in the precue phase was once again illuminated to signal task initiation, but in 25% of randomly interspersed cases the alternate cylinder was illuminated, requiring subjects to alter their prepared reach (direction) and grasp (grip type). It was shown that both groups had shorter reaction times (RT) when provided with an accurate precue compared to an inaccurate precue (Weiss et al., 1999). No difference was identified in the kinematic reach and grasp parameters of either group when reaching for the larger cylinder irrespective of precue. However, when given a correct precue for the small cylinder, the PD group had reduced MT and prolongation of time spent in deceleration compared

to their values when given the incorrect precue; i.e. an improvement in reaching parameters. Grasp kinematics including peak aperture were not affected. The authors speculated that PD subjects may initiate reach and grasp before fully preparing the motor programmes during precision grip (Weiss et al., 1999).

4.2.4.1 Summary

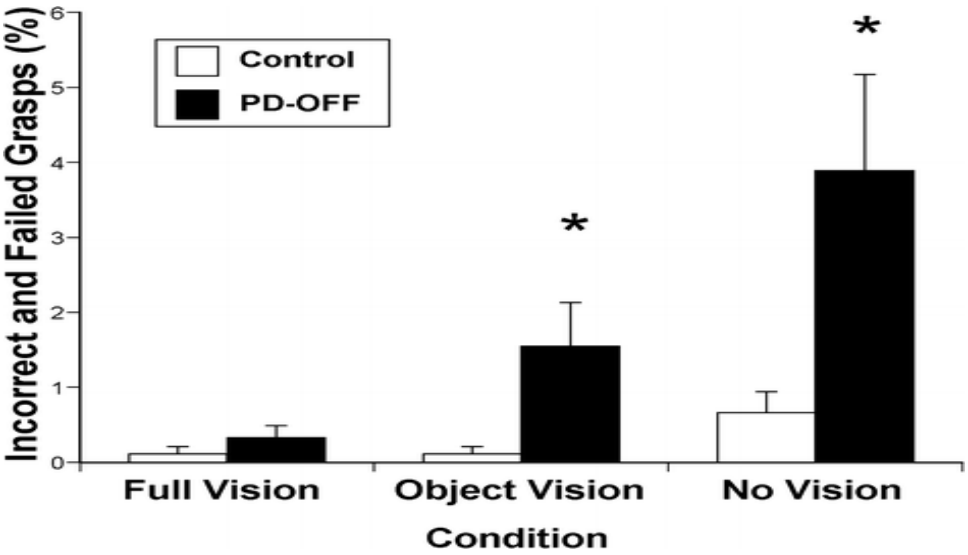
There is evidence that PwPD are slower than HC to specify hand shape when grasping objects (Schettino et al., 2004). This can be linked to studies that demonstrate a prolonged manipulation time (Bennett et al., 1995), and suggests that PwPD are slow to initiate and complete grasp compared to HC. This may be caused by impaired innervation as a result of basal ganglia damage and direct connectivity between the basal ganglia and the major nodes of the dorsomedial grasping circuit has been demonstrated in monkeys (Hoover and Strick, 1993, Clower et al., 2005). It has been proposed that the implementation and sequencing of reach and grasp motor programmes is impaired in PwPD, rather than the programmes themselves. There is some evidence to suggest that the sequencing of reach motor programmes might be delayed in PD compared to HC (Weiss et al., 1999).

4.2.5 The effect of visual feedback when reaching and grasping

Studies of finger pointing and reach and grasp suggest that PwPD have a greater dependence on visual feedback than healthy subjects. For example, nine PwPD and nine HC pointed at a target in three different visual conditions; complete darkness, illumination of the pointing finger only, and illumination of the target only. PwPD were significantly less accurate than HC when pointing to a target in the dark or when the target was illuminated but their pointing finger was not (Adamovich et al., 2001). Both of these conditions require integration of proprioceptive information from the arm with visual information or information stored as a visual memory (Adamovich et al., 2001).

Reach and grasp has been analysed in nine PD subjects by the same research group in full vision, complete darkness and when only the object to be grasped was illuminated. The PD subjects had a mean disease duration of 8.8 years, H&Y stage of between 1.5 and III and were tested whilst *off* (Schettino et al., 2006). It was shown that PwPD were less accurate than HC when grasping in the dark or when the only the object to be grasped was illuminated, as evidenced by a significantly increased number of grasping errors when post-hoc inspection of the effect of visual feedback was explored (Figure 32) (Schettino et al., 2006).

Figure 32: The effect of visual feedback on grasping errors in healthy people and people with Parkinson's disease



Legend: PwPD made more grasping errors than HC when only the object to be grasped was illuminated in otherwise total darkness ('Object Vision') or in total darkness ('No Vision'). The asterisks denote a statistically significant change after post-hoc inspection of the effect of visual feedback. Reproduced from Schettino et al., 2006 with permission (Schettino et al., 2006).

Using discriminant analysis to look at classification error revealed that PwPD have greater variability in hand shape than HC between 35% and 85% of normalised MT when reaching and grasping under full visual guidance. This finding is an extension of an earlier study (Schettino et al., 2004) (see 4.2.4) and is further evidence that PwPD are slower to specify

hand shape than HC (Schettino et al., 2006). It has been suggested that the delay may occur because impaired integration of proprioceptive signals from the reaching arm renders PwPD dependent on being able to see both the object and the grasping hand in the same field of view before specifying grip type (Schettino et al., 2004). When the object to be grasped was illuminated in otherwise total darkness the significant difference in classification error was increased to between 35% and 95% of normalised MT, implying that hand shape is even slower to develop in PwPD when the reaching arm cannot be visualised.

Hand shape variability was only significantly different between PwPD and HC at 25-35% of normalised MT when reaching and grasping in complete darkness, i.e. evolution of grasp is more similar between the groups in the absence of visual feedback (Schettino et al., 2006). As has already been discussed, one of the core kinematic findings of grasp in HC is that although still scaled for object size, peak index finger to thumb aperture is greater and occurs earlier in the dark (Jeannerod, 1984, Jakobson and Goodale, 1991, Schettino et al., 2003), perhaps acting as a 'safety net' to reduce the risk of failed grasp. Schettino et al. argued that this might explain their results (Schettino et al., 2006).

4.2.5.1 Summary

From the limited evidence it is suggested that PwPD tested whilst *off* are more reliant on visual feedback to guide reach and grasp; they make more errors than HC when grasping an object in the dark and take longer to specify appropriate hand shape (Schettino et al., 2006). In full vision, and in contrast to HC, PwPD do not finalise the shape of the grasping hand until they have visual feedback of both the hand and the object, perhaps because of impaired ability to integrate proprioceptive information from the reaching arm with visual information (Schettino et al., 2004). This proposed deficit in the integration of proprioceptive information is also suggested to explain abnormalities when PwPD point towards objects in

the dark or when only the target object is illuminated (Adamovich et al., 2001).

4.2.6 Abnormalities of grip force and internal regulation of motor output in Parkinson's disease

One theory about bradykinesia is that PwPD lose the ability to internally regulate motor output. Evidence to support this comes from studies that show a reduction in bradykinesia when PwPD perform a task in response to an external cue compared to performing at their self-determined maximal speed. For example, contingent auditory cues improve the RT and MT of PD subjects when pressing a series of buttons in sequence (Georgiou et al., 1993). Visual cueing is also beneficial and has been found to improve movement velocity when assessing gait and upper limb movements (Sidaway et al., 2006).

In studies of reach and grasp, six H&Y stage III PwPD tested whilst *on* and six HC had their movements analysed as they reach for a stationary ball as quickly as possible and as they reached for a moving ball whilst it passed through a 'contact zone' (Majsak et al., 1998). The visuotemporal stimulus provided by the rolling ball led to increased reach velocity in the PD group, such that they exceeded their self-regulated maximal speed and attained velocities comparable to HC. The increase in reaching velocity did not lead to a reduction in accuracy. Components of grasp were not analysed and the authors were unable to determine which aspect of their experimental cue – visual, temporal, or both – caused the increased reach velocity.

To answer this, eight H&Y Stage III PwPD tested whilst *off* and eight HC were asked to grasp a stationary ball as quickly as possible, a stationary ball that dropped from view after a period of time and a rolling ball (Majsak et al., 2008). The dropped and rolling ball conditions decreased MT of the PwPD by producing comparable reaching velocities as HC. Analysis of grasp parameters demonstrated that, across trial types, PwPD generated a

smaller peak aperture and took longer to attain this (i.e. increased TAP). Despite the differences, PwPD were able to modulate grasp parameters according to task demands – for example, peak aperture was greater when reaching to the moving ball than the dropped or stationary ball (Majsak et al., 2008).

The authors suggested that the results of their study supported a decoupling of the reach and grasp pathways in PD. This is because a time constraint alone (the dropped ball task) can increase movement velocity in PD and cause a normalisation of MT, i.e. reach, but key grasp parameters remain abnormal in PwPD compared to HC. Interestingly, the PD subjects were more likely to unsuccessfully grasp the ball during time constrained tasks and therefore a slower self-paced reach may be a compensatory mechanism to allow more time for grasp selection and implementation (Majsak et al., 2008).

4.2.6.1 Summary

An external time constraint, or cue, is able to speed up reaching movements in PwPD (Majsak et al., 2008).

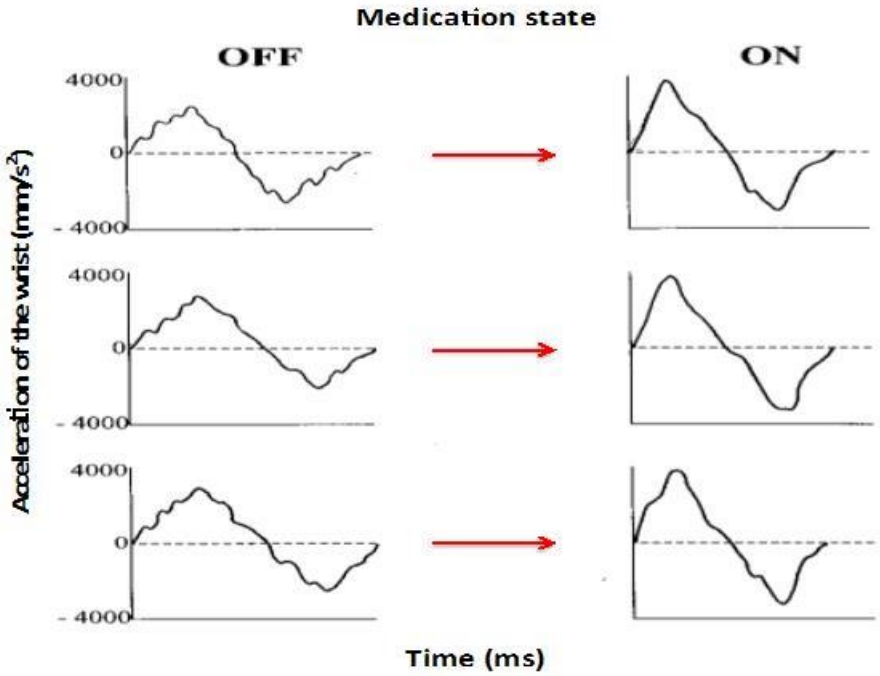
4.2.7 Effects of levodopa on reach and grasp

Levodopa has been shown to have a beneficial effect on components of bradykinesia – such as velocity and amplitude – as well as rigidity, tremor and postural instability in PD (Olanow et al., 2009). Studies looking at the effect of levodopa on the kinematic parameters of reach and grasp have generally demonstrated that reaching velocity is increased but parameters of grasp are not improved.

In one study a significant reduction in MT and a significant increase in PA, PV and PDe has been demonstrated in 14 PwPD when reaching and grasping an eight cm diameter cylinder at a distance of 30cm whilst *on* compared to *off* (Castiello et al., 2000). Eleven of the 14 PwPD showed

smoother acceleration and deceleration profiles whilst reaching when *on* (Figure 33) and levodopa led to a significantly more direct reaching trajectory, as measured by the maximum deviation along the horizontal and vertical axis (Castiello et al., 2000). These findings suggest that levodopa refines reaching movements in PD, leading to a reduction in MT.

Figure 33: Change in acceleration and deceleration profiles as a result of levodopa when people with Parkinson's disease reach and grasp



Legend: Acceleration (a positive deflection on the graphs) and deceleration (a negative deflection) are smoother and of greater magnitude in the *on* medication state compared to *off* in three PwPD. Adapted from Castiello et al., 2000 with permission (Castiello et al., 2000).

The same study found the levodopa had no effect on the prolongation of manipulation time in PwPD (Castiello et al., 2000). As discussed in 4.2.3, increased manipulation time is thought to be a manifestation of the known difficulty that PwPD have in executing sequential movement programmes, leading to a breakdown in the temporal coupling of the dorsomedial and dorsolateral grasping pathways when reaching and grasping. A link between the dorsolateral grasping circuit and basal ganglia has been

demonstrated in monkeys and intuitively it might be expected that if impaired output from the basal ganglia to the dorsolateral circuit is linked to a delay in grasp initiation, levodopa should improve this, i.e. decrease manipulation time.

Eight subjects with Parkinson's disease taking levodopa have been compared to eight treatment naïve PwPD (Negrotti et al., 2005). The 'treatment naïve group' had average disease duration of 3.1 years, Unified Parkinson's Disease Rating Scale (UPDRS) motor score of 26 and were H&Y stage II or III. The 'levodopa group' had disease duration of 9.6 years, a UPDRS motor score of 46 when *off* and were H&Y stages III or IV. Levodopa was found to improve kinematic parameters of reach, specifically PA and PV in the levodopa group, such that the two PD groups had similar measurements that remained slower than those seen in HC. However, in contrast to the study of Castiello et al. (Castiello et al., 2000), MT was not reduced by levodopa and did not significantly differ between PD groups when *on* or *off*. The only grasp parameter to improve in the levodopa group was peak velocity of finger opening – there was no improvement in peak aperture or TAP (Negrotti et al., 2005).

In another study that tested nine PwPD whilst *on* and *off*, levodopa increased PV but no comment was made about MT. However, no change was found in the grasp parameter measured including preshaping of the hand (as measured using discriminant analysis) or number of grasping errors (Schettino et al., 2006).

Kelly et al. tested whether a visual cue and levodopa had an additive effect on reaching movements towards a target performed as accurately as possible and then as quickly as possible, in nine PwPD tested whilst *on* and *off* (Kelly et al., 2002). PV was reduced and MT longer in the PD subjects compared to HC in all tasks and whether *on* or o*ff*. Visual cueing and levodopa both increased PV in the PD group but were not additive.

Specifically, levodopa increased PV more for self-initiated movements than when the visual cue was present and in accurate movements more than movements performed as fast as possible.

4.2.7.1 Summary

There is evidence to suggest that levodopa can 'speed up' a reaching movement but has much less effect on parameters of grasp. One theory to explain this discrepancy is that levodopa treatment helps to ameliorate generalised reduction in motor output from the basal ganglia, i.e. improves velocity and therefore enhances reach kinematic parameters such as PV (with subsequent reduction in MT). Analysis of the separable components of bradykinesia when PwPD perform finger tapping, hand grasping and pronation-supination movements of the arm supports this because velocity improves when PwPD are *on* compared to *off*. In contrast, other separable components of bradykinesia are less (amplitude) or non-responsive to levodopa (rhythm, decrement in velocity and amplitude) (Espay et al., 2011). It could be that grasping is more dependent on the amplitude and rhythm/timing of movement than reaching. Additionally, sequencing of motor programmes may be non-levodopa responsive, as suggested by a lack of change in manipulation time (Castiello et al., 2000), although there are some inconsistencies. For example, in a non reach and grasp task a reduction in inter-onset latency was found when subjects were tested whilst *on*, suggesting an improvement in sequential tasks with levodopa (Benecke et al., 1987). In addition, manipulation time appears to be a highly variable phenomenon and is not always prolonged when reaching and grasping in PwPD, i.e. sequencing of the reach and grasp programmes may not always abnormal in PD (Bennett et al., 1995, Bonfiglioli et al., 1998).

4.3 Reach and grasp in Parkinson's disease cognitive impairment

There are no published studies of reach and grasp in people with PD-MCI or PDD and there is only one study of reach and grasp that includes people

with dementia. Caselli et al. studied the effect of limb apraxia [19] on reach and grasp in eight HC and eight apraxic participants, consisting of three with dementia (one with autopsy confirmed AD at the time of publication) and five without dementia (one with autopsy confirmed corticobasal ganglionic degeneration (CBGD) at the time of publication) (Caselli et al., 1999). The experimental procedure was straightforward; participants were asked to reach and grasp an eight cm diameter cylinder placed 27cm in front of them with either hand for a total of ten successful trials. Marked differences were seen between the eight apraxic participants and HC. For example, reach kinematic parameters such as TPV, PV and MT were all abnormal in the apraxic group. Subgroup analysis showed that this finding was valid for demented and non-demented apraxic subjects when compared separately against HC. Likewise, grasp kinematics were abnormal in the apraxic subjects; manipulation time and TAP were prolonged and peak aperture was smaller. These findings were consistent in both the dementia and non-dementia sub-groups.

The difference between the apraxic group and HC is likely to have been severely underestimated because between three and five unsuccessful trials were observed in the apraxic group for each successful reach and grasp. Overall, the most substantial difference in the apraxic subjects versus controls was slowness of movement – both MT and the time to attain peak parameters of reach (i.e. TPA, TPV, TPD) (Caselli et al., 1999).

Limb apraxia is not thought to be a common feature of cognitive impairment in PD (Litvan et al., 2012, Emre et al., 2007) and it is uncertain how transferable the results from this study will be to the result of the PD-MCI and PDD groups in our study.

[19] Limb apraxia – *"a wide spectrum of higher-order motor disorders that result from acquired brain disease affecting the performance of skilled and/or learned movements with the forelimbs, with or without preservation of the ability to perform the same movement outside the clinical setting in the appropriate situation or environment"* (Leiguarda and Marsden, 2000).

4.4 Conclusion

The kinematic parameters of reach and grasp have been extensively investigated in healthy subjects and in PwPD. The major findings are summarised below:

- When reaching towards objects that are further away the arm accelerates faster and attains greater velocity in HC and PwPD, but PD subjects are slower than HC (Jeannerod, 1984, Castiello et al., 1993b).
- Peak aperture is correlated with object size in both HC and PwPD, but peak aperture is smaller and TAP is prolonged in those with PD (Jeannerod, 1984, Castiello et al., 1993b).
- If the size or location of an object to be grasped is modified at reach onset, the parameters of reach and grasp are altered in a similar way in HC and PwPD but there is a delay in the instigation of different grip types in those with PD, suggesting difficulty in sequencing motor programmes (Paulignan et al., 1991b, Paulignan et al., 1991a, Scarpa and Castiello, 1994, Castiello and Bennett, 1994).
- Manipulation time is prolonged in some studies of PwPD, suggesting a decoupling of reach and grasp and supporting a difficulty in the sequencing of motor programmes (Castiello et al., 1993b, Bennett et al., 1995).
- Reach and grasp kinematics are influenced by context in healthy subjects. Reaching and grasping takes longer when there is no subsequent motor task and MT increases as the complexity of the subsequent task increases. There are no direct studies of context in PwPD (Ansuini et al., 2008).
- Moulding of the grasping hand is a gradual process that begins early during reach and continues after peak aperture. In PwPD, specification of hand shape is prolonged and this may occur because PwPD have an increased reliance on visual feedback; they

might need to see both the hand and the object in the same field of view in order to finalise hand shape (Santello and Soechting, 1998, Schettino et al., 2004, Schettino et al., 2006).

- In the absence of visual feedback MT is longer, peak aperture is larger but remains scaled for object size and TAP occurs earlier in both HC and PwPD. However, PwPD appear to be more dependent on visual feedback to guide reach and grasp, evidenced by increasing grasping errors and a prolonged time to specify hand shape (Jeannerod, 1984, Schettino et al., 2004, Schettino et al., 2006).
- External cueing in PwPD appears to improve reaching speed, i.e. decrease MT, when *on* and *off (Majsak et al., 2008, Majsak et al., 1998).*
- Levodopa improves reach, as evidenced by reduced MT, reduced time to peak reach parameters such as TPV, and increased PV. In contrast, levodopa does not appear to influence grasp parameters (Castiello et al., 2000, Negrotti et al., 2005, Kelly et al., 2002).

The visuomotor channel hypothesis states that temporal integration of the dorsomedial and dorsolateral circuits is dependent on visual feedback (Jeannerod, 1999) and this is supported by kinematic analysis when visual guidance is modified (Schettino et al., 2006). Otherwise, the validity of this theory can be reinforced or questioned based on the results of different studies, as has been discussed at various points throughout this chapter.

One idea used to explain some of the differences in reach and grasp parameters between HC and those with PD, including an apparent increased dependence on visual feedback (Schettino et al., 2006), is abnormal integration of proprioceptive and other somatosensory modalities with visual information. This will be explored in more detail in Chapters 6 and 7.

The effect of cognition on reach and grasp is not well researched, and no published studies have analysed reach and grasp in PD-MCI and PDD. The results of our study will be analysed based on extrapolation of existing kinematic studies of PD-NC, the neural control of reach and grasp discussed in Chapter 3 and the pathological and neurochemical changes that drive cognitive impairment in PD, discussed in Chapter 2.

Chapter 5

Abbreviations used in this chapter

%RT	Reaction time as a % of total movement time
%TPA	Time to peak acceleration as a % of movement time
%TPD	Time to peak deceleration as a % of movement time
%TPV	Time to peak velocity as a % of movement time
2D	Two dimensional
3D	Three dimensional
AD	Alzheimer's disease
ANOVA	Analysis of variance
B-C	Benson Copy
B-R	Benson Recall
bv-FTD	Behavioural variant of fronto-temporal dementia
C-CI	Healthy control subjects with cognitive impairment
C-NC	Healthy control subjects with normal cognition
CDR	Clinical Dementia Rating scale
DT	Distance travelled
EM	Electromagnetic
GDS-15	Geriatric Depression Scale – Short Form
GP	General practitioner
H&Y	Hoehn & Yahr
HC	Healthy controls
JoLO	Benton Judgment of Line Orientation
LEDD	Levodopa equivalent daily dose
LGI	Leeds General Infirmary
LTHT	Leeds Teaching Hospitals NHS Trust
MA	Mean acceleration
MAX	Condition 3 - Maximum speed
MCP	Metacarpal-phalangeal
MDS	International Parkinson and Movement Disorder Society
MDS-UPDRS	Movement Disorders Society – Unified Parkinson's Disease Rating Scale
MEM	Condition 4 - Memory guided
MoCA	Montreal Cognitive Assessment
MT	Movement time
MV	Mean velocity
NAT	Condition 1 - Natural speed
NPI-Q	Neuropsychiatric Inventory - Questionnaire
PA	Peak acceleration
PD	Parkinson's disease
PD-CI	PD cognitive impairment
PD-MCI	Parkinson's disease - mild cognitive impairment
PD-NC	Parkinson's disease - normal cognition
PDD	Parkinson's disease dementia

PDe	Peak deceleration
PIP	Proximal interphalangeal
PV	Peak velocity
PwPD	People with Parkinson's disease
RT	Reaction time
SEU	Systems electronic unit
TAP	Time to peak aperture
TMT	Trail Making Test
TMT B-A	Trail Making Test Part B score - Trail Making Test Part A score
TMT-A	Trail Making Test Part A
TMT-B	Trail Making Test Part B
TMTi	Total movement time
TPA	Time to peak acceleration
TPD	Time to peak deceleration
TPV	Time to peak velocity
VIS	Condition 2 - Visually cued
WHP	Whole-hand prehension

Methodology

5.1 Participants

5.1.1 Ethical approval

This thesis is based around the study *'A novel diagnostic device for the objective diagnosis of Parkinson's disease with and without dementia'*, which received National Regional Ethics Service approval (reference code 10/H1308/5) and local Research and Development approval from Leeds Teaching Hospitals NHS Trust (LTHT) (reference code UI10/9232). It was conducted in Leeds, UK. Recruitment began in December 2013. Fifty-eight PwPD and 29 HC were assessed between February 2014 and October 2014.

5.1.2 Recruitment

Patients with a clinically confirmed diagnosis of PD attending the outpatient clinics of two movement disorder specialists (Dr. Jamieson and Dr. Alty, both Consultant Neurologists) were asked during their clinic appointment if they would be interested in taking part in the study. If agreeable they were either provided with an invitation letter and patient information sheet or sent copies through the post. In situations where eligible patients attended with a friend, partner, family member or spouse, that person was asked if they would like to consider being a HC and if agreeable an invitation letter and control information sheet was given to them or posted out. Three participants were recruited from Consultant Neurologists other than Dr. Jamieson or Dr. Alty. Such participants were provided with an 'invitation from other clinical teams' letter but otherwise the recruitment process was identical.

Potential recruits were asked to make contact with the clinical researcher (Dr. Cosgrove) by post, email or telephone if they wished to participate. Once the potential recruit made contact, the clinical researcher arranged a convenient time and location for an assessment to take place.

Assessments were undertaken in the Outpatient Departments of hospitals belonging to LTHT, either Leeds General Infirmary (LGI) or Wharfedale Hospital.

5.1.3 Consent

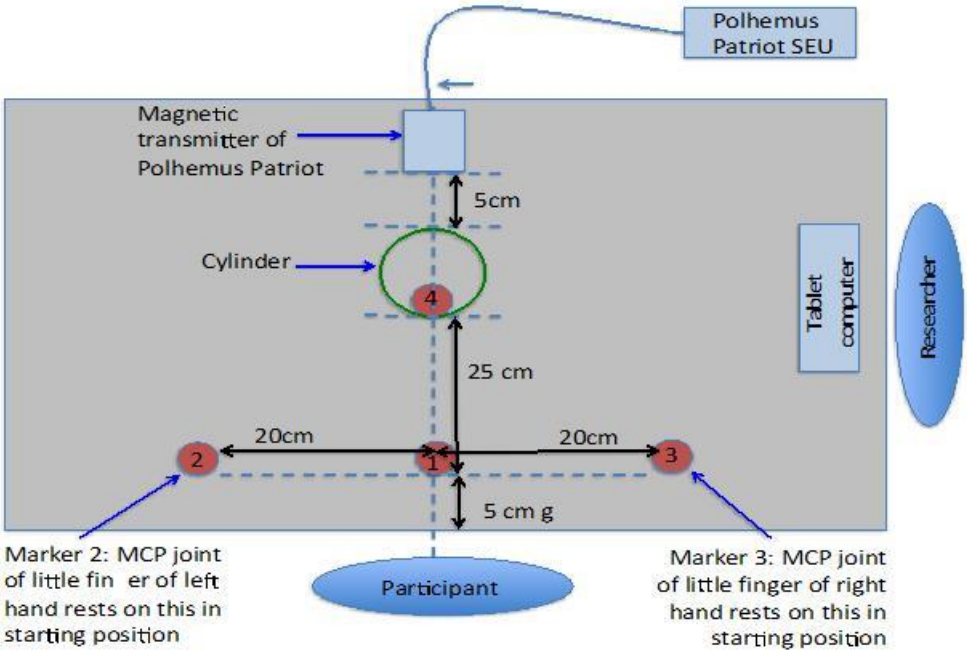
Consent was taken when participants attended for assessment. The clinical researcher ensured that each recruit had received and read the relevant information letter and then outlined the assessment protocol before answering any questions. All participants then signed a consent form and were given a copy of this.

5.2 Apparatus and equipment

5.2.1 Apparatus and set-up

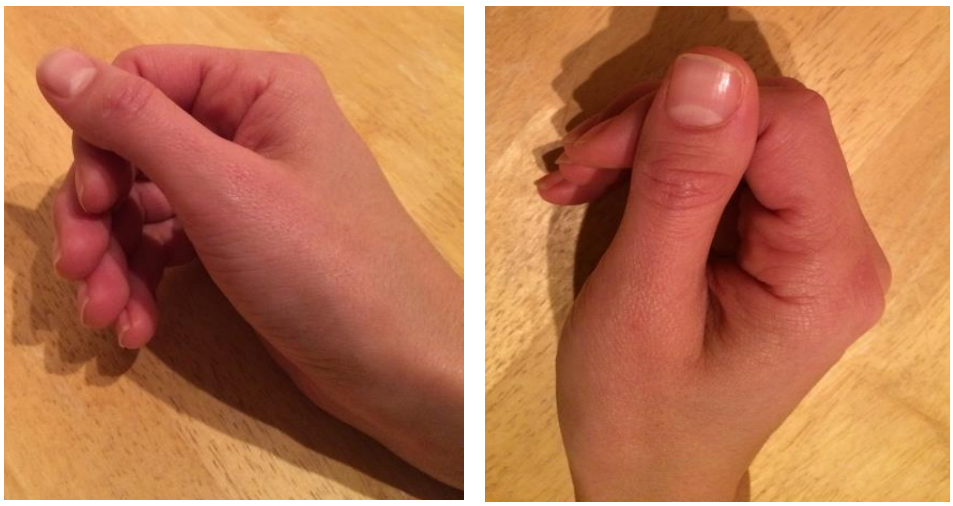
An aerial view of the apparatus set up is provided in Figure 34. Participants were asked to sit in a non-swivel high-backed chair with their midline in line with the middle of the cylinder. They were positioned at an adequate distance from the table edge so that they could place their hands in the correct starting position whilst maintaining 90 degrees of flexion at the elbow. The correct starting position for each hand was semi-pronate such that the ulnar border of each hand was resting on the table. The little finger MCP joint of each hand was placed on the relevant 'marker' (markers 2 and 3 from Figure 34), five cm from the table edge and 20cm from the midline. Recruits were asked to hold their hands in a lightly closed position with the wrist in a neutral position (i.e. in line with the forearm) (Figure 35). The reaching distance from markers 2 or 3 to marker 4 was 32cm.

Figure 34: An aerial view of the apparatus set-up



Legend: Not to scale. **Abbreviations**: MCP, metacarpal-phalangeal; SEU, systems electronic unit.

Figure 35: The starting position of the hand

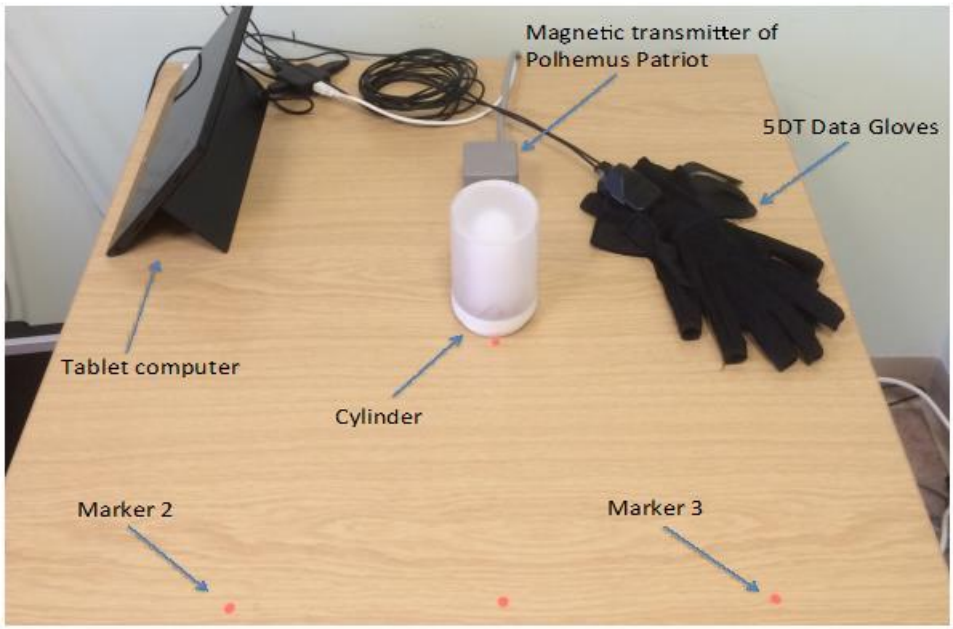


Legend: Hands were in a lightly closed position, semi-pronate with the ulnar border resting on the table. Participants wore data gloves, which are not shown in this photo.

The cylinder to be grasped was a Philips Imageo rechargeable candlelight, eight cm diameter and 11.5cm height (Koninklijke Philips N.V., Amsterdam, Netherlands), modified to incorporate Bluetooth connectivity. This was

placed on marker 4 so that its nearest point in relation to the patient was in the midline, 30cm from the table edge. The magnetic transmitter of the Polhemus Patriot (Polhemus Inc., Vermont, U.S.A) was placed in the midline, five cm behind the cylinder. The reach and grasp software was installed on Microsoft Windows 8 Pro on a Microsoft Surface Tablet (Microsoft Corporation, Washington, U.S.A). The tablet was placed at right angles to the participant, on the right or left of the table depending on the room in which the assessment took place. The participant was unable to see the screen of the tablet during the assessment. A photograph of the equipment set-up at LGI is shown in Figure 36.

Figure 36: A photograph of the apparatus set-up



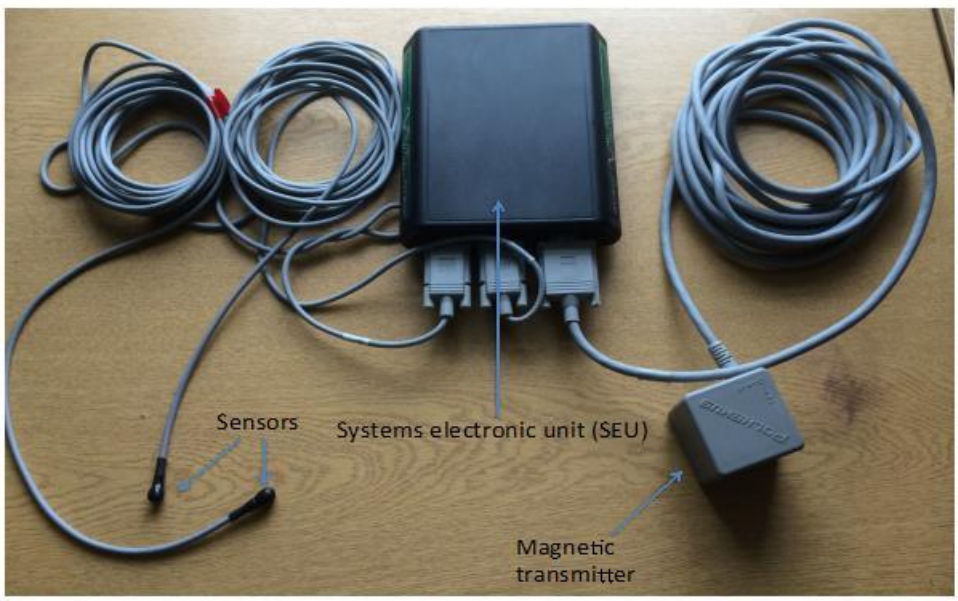
Legend: The equipment ready for use, taken in a clinic room of the Outpatient Department at LGI.

To measure the position of the hands in space a Polhemus Patriot electromagnetic (EM) tracking sensor system was used. Movements of the fingers and thumb were recorded using 5DT Data Gloves 5 Ultra (Fifth Dimension Technologies, California, U.S.A), referred to as 'data gloves' from now on.

5.2.2 Polhemus Patriot EM tracking sensor system

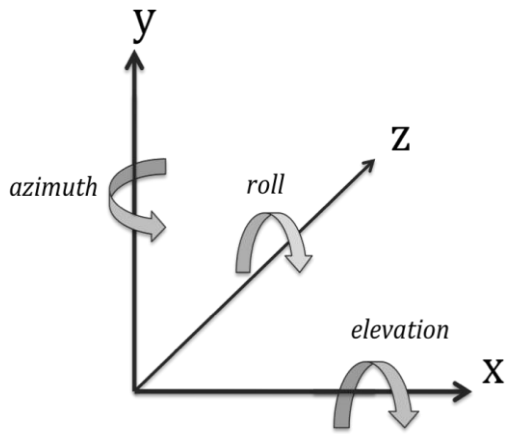
The Polhemus Patriot is an EM tracking device composed of a systems electronic unit (SEU), two sensors and a magnetic transmitter (Figure 37). Within the sensors and magnetic transmitter there are three EM coils arranged on orthogonal axes. An alternating current is passed through each EM coil within the magnetic transmitter leading to the emission of consecutive magnetic pulses at different orientations. The magnetic pulses are detected by the EM coils within each of the sensors allowing the position and orientation of the sensors, relative to the magnetic transmitter, to be stored by the SEU (Polhemus Incorporated, 2014, Alty, 2014). Information from the SEU can be used for off-line analysis as required. The Polhemus Patriot enables the location of each of the sensors to be calculated in six degrees of freedom; three positional coordinates (*x, y* and *z*) and three coordinates relating to orientation (azimuth, role and elevation) (Figure 38).

Figure 37: The Polhemus Patriot electromagnetic tracking system



Legend: The system consists of two sensors, a magnetic transmitter and a SEU.

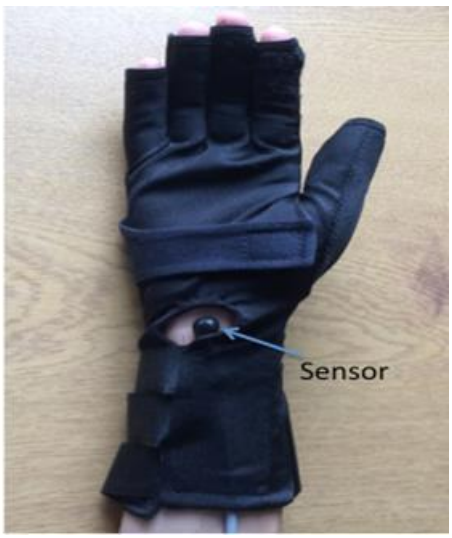
Figure 38: The six degrees of freedom detected by the sensors of the Polhemus Patriot



Legend: Each sensor can be accurately mapped in 3D space in relation to the magnetic transmitter using positional (*x, y, z*) and orientation coordinates (azimuth, roll, elevation). Reproduced from Alty, 2014 with permission (Alty, 2014).

The Polhemus Patriot was used to detect the orientation and position of the wrist in space during the reach and grasp assessment. A sensor was attached to the forearm of each hand, at the palmar aspect of the wrist, by passing the wire of the sensor under the Velcro straps of the data gloves (Figure 39).

Figure 39: Positioning of the sensor at the wrist



Legend: Each sensor was held in place at the wrist by passing the wire of the sensor under the Velcro straps of the data gloves.

The position and orientation of each sensor was sampled at a frequency of 60Hz by the SEU – i.e. 60 times per second – meaning that the position and orientation of the wrist could be effectively measured in real time. The accuracy of the Polhemus Patriot is quoted to be within 1.5mm of *x, y* and *z* coordinates and within 0.4 degrees for azimuth, role and elevation providing that the distance between the sensors and magnetic transmitter is less than 76cm (Polhemus Incorporated, 2008), which was the case in our study. At a distance greater than 76cm the strength of the magnetic field created by the magnetic transmitter diminishes and as a result the accuracy for recording sensor position and orientation is reduced. Polhemus recommend a maximum distance of 1.5m using the standard sized magnetic transmitter (Polhemus Incorporated, 2014).

A disadvantage of EM technology is that metallic objects and magnetic or electronic devices, including mobile phones, can disrupt the EM field. Steps were taken to reduce the risk of this during the assessment procedure (e.g. mobile phones were kept away from the Polhemus Patriot when in use).

5.2.3 5DT Data Gloves 5 Ultra

The data gloves are made of Lycra so that one size of glove can fit a range of hand sizes. Each glove contains five sensors that are used to measure the flexion of the fingers and thumb. This is done by providing an average value of flexion at the MCP and PIP joints of each digit (Fifth Dimension Technologies, 2014). Similar technology incorporated into a glove has been used to study hand shape in a number of studies looking at reach and grasp (Santello and Soechting, 1998, Schettino et al., 2004, Schettino et al., 2003).

The combination of using the Polhemus Patriot and data gloves provides the capacity to record and measure the orientation and position of the

wrist in space (the reach) and the movements of the digits of each hand (the grasp).

5.3 Assessment Protocol

5.3.1 Demographic Details

After consent had been taken, the first component of the assessment protocol was to collect demographic data. Each participant's age, sex and handedness were recorded. All participants provided information about their past medical history and a list of medications. PwPD provided a time to the nearest six months since PD diagnosis as well as a detailed medication regimen (drug, dose, times taken). In those with PD, if details regarding diagnosis or medication regimen were unknown, the clinical researcher gathered relevant information from the participant's clinical records. All participants were assessed without any change to medication and PwPD were assessed whilst *on*. The mean levodopa equivalent daily dose (LEDD) of dopaminergic drugs was calculated using standard conversion factors, where appropriate (Tomlinson et al., 2010).

5.3.2 Motor Examination

All participants were assessed using the Movement Disorders Society – Unified Parkinson's Disease Rating Scale (MDS-UPDRS) – Part 3. This is a validated scale that assesses the motor signs of PD (Goetz et al., 2008). Permission to use this scale was obtained in October 2013. All participants were also graded using H&Y stage, an extensively used five-point scale of motor symptoms in PD (Hoehn and Yahr, 1967).

5.3.3 Cognitive Tests

All participants undertook four tests of cognitive function:

- **Montreal Cognitive Assessment (MoCA)**

The MoCA is a global test of cognitive function (Nasreddine et al., 2005) and permission to use this test was obtained in October 2013. It takes approximately ten minutes to complete the MoCA and the maximum score

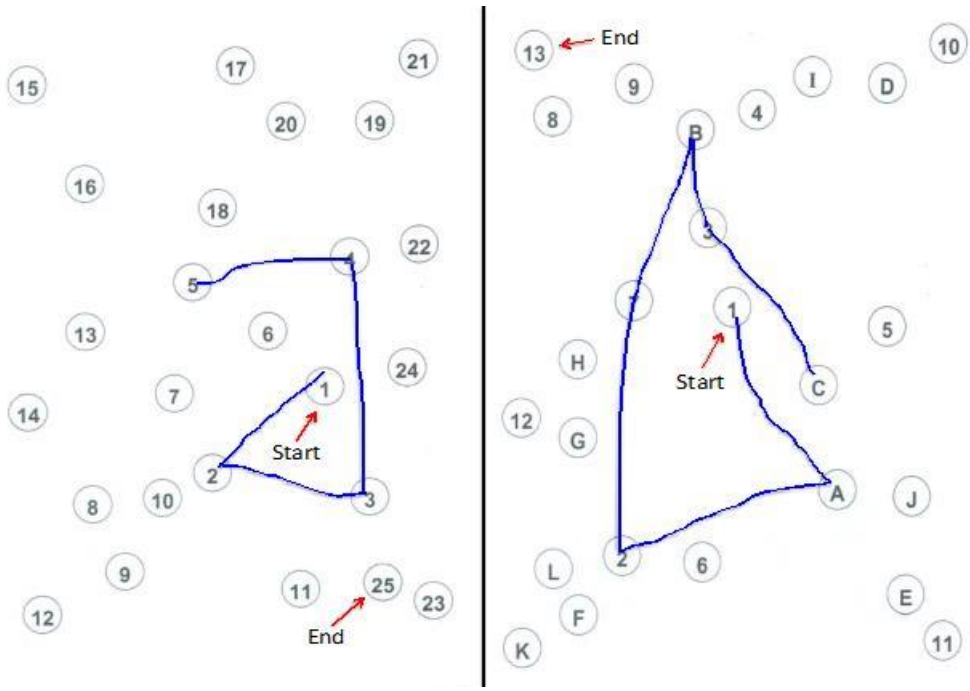
is 30. An additional point is allocated to a participant's total score if they have received ≤12 years of formal education. The MoCA tests a number of different cognitive domains: visuospatial and executive function, naming, memory, attention, language, abstraction and orientation. It has been validated in PwPD (Hoops et al., 2009, Kandiah et al., 2014, Dalrymple-Alford et al., 2010) and is a recommended global screening test for making a level one diagnosis of PD-MCI according to MDS criteria (Litvan et al., 2012). This is reviewed in more detail in Chapter 2.1.1.

As part of the consent procedure it was explained to participants that with permission their General Practitioners (GP) or other healthcare members would be informed if the study identified health concerns. In cases where the MoCA score revealed cognitive impairment that was previously undetected and concerns were raised by the participant and/or accompanying person, the participant's GP or consultant was informed by letter.

- **Trail Making Tests – Parts A and B**

The Trail Making Test (TMT) is a widely used neuropsychological test. Part A (TMT-A) requires participants to draw lines on a piece of paper to connect 25 encircled numbers in the correct sequence (1, 2, 3 … 25). Part B (TMT-B) requires participants to alternate between numbers and letters in the correct sequence (1, A, 2, B, 3, C…) (Figure 40). TMT can be scored in various different ways. For this study the score for each part of the TMT was the time taken to complete the task in seconds. There is considerable debate within the literature as to which cognitive domains are being tested by the TMT. A literature review in 2009 suggested that TMT-A is predominately a test of visual perception, whilst TMT-B is primarily a test of task-switching and working memory (Sanchez-Cubillo et al., 2009). It has been suggested that subtracting time to complete TMT-A from TMT-B (TMT B-A) produces a *"relatively pure"* measure of executive function (Sanchez-Cubillo et al., 2009).

Figure 40: Trail Making Tests - Parts A and B



Legend: TMT-A (left) requires connection of the 25 encircled numbers in the correct order as quickly as possible (e.g. 1, 2, 3, 4, 5…). TMT-B (right) requires connection of the alternate encircled numbers and letters in the correct order as quickly as possible (e.g. 1, A, 2, B, 3, C…). Both tests have been partially completed to provide an example. Adapted from Lundstrom, 2012, open access (Lundstrom, 2012b, Lundstrom, 2012a).

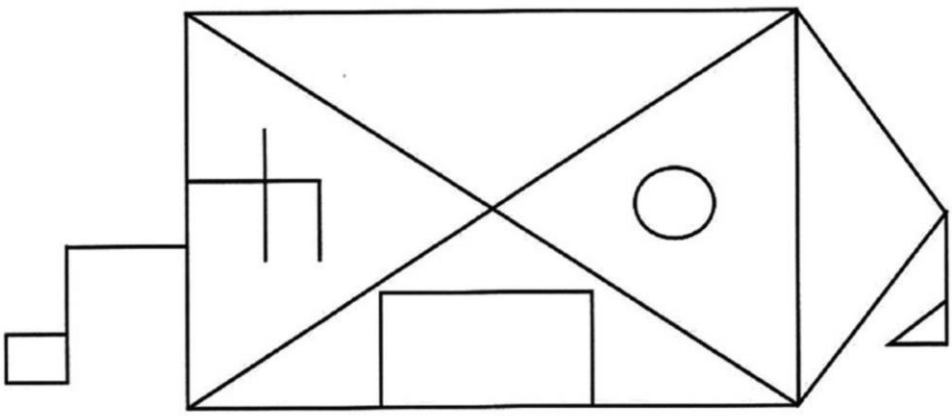
- **Benton Judgment of Line Orientation**

The Benton Judgment of Line Orientation (JoLO) is a test of visuospatial judgment (Benton et al., 1978). Permission to use this test is implicit in the purchase of the assessment book. Participants are required to identify the orientation of two partial line segments on the upper page of the assessment book by matching them with the correctly numbered lines from a selection on the lower page. The original JoLO consists of 30 different trials, but for this study alternate trials were used to reduce the length of the assessment protocol. A correct point was recorded if both partial line segments were correctly identified. No half points were awarded and therefore the maximum score was 15.

- **Benson Figure Copy and Recall**

The 'Benson Figure' (Figure 41) is a simplified version of the Rey-Osterrieth figure (Osterrieth, 1944) developed by Frank Benson (Possin et al., 2011). Participants were initially asked to accurately copy the figure without a time restriction – Benson Copy (B-C). They were informed that they would be asked to draw it again later from memory. This was done after 20 minutes in our study – Benson Recall (B-R). Each figure was retrospectively scored to a maximum of 17 points, accounting for accuracy and placement of different components. This test has been used before in the assessment of visuospatial function in subjects with AD and the behavioural variant of fronto-temporal dementia (bv-FTD) (Possin et al., 2011). B-C is considered a test of visual construction and B-R a test of visual memory.

Figure 41: The Benson Figure



5.3.4 Mood Screening Test

Each patient undertook a mood-screening test in the form of the Geriatric Depression Scale – Short Form (GDS-15). The original 30 question GDS has been well validated and the abbreviated GDS-15 is highly correlated with the full version (Lesher and Berryhill, 1994). Each of the 15 questions requires a yes or no answer and the simplicity of the test makes it appropriate to detect mood problems in those with cognitive impairment.

Five or more 'incorrect' answers from the GDS-15 is likely to indicate a low mood or possible depression (Lesher and Berryhill, 1994).

A number of participants scored greater than five on the GDS-15 and if potential low mood was newly identified, or concerns were raised from the participant and/or accompanying person, the participant's GP or consultant was informed by letter.

5.3.5 Reach and Grasp Assessment

Equipment was set up as already outlined and the participant was appropriately positioned. 'Calibration' of the data gloves was performed by asking each participant to alternately stretch their hands and then clench their fists twice, on the second occasion fully flexing the thumb before closing the fist. This provided values for maximal flexion and extension of the digits, required for processing of grasp data (see 5.6).

Instructions were provided to each participant, emphasising the following points:

- The importance of ensuring that their hands were in the appropriate position before each task (i.e. MCP joint of little finger resting on markers 2 and 3 – Figures 34 and 36).

- The need to grasp the cylinder *"as though it was a cup"* – i.e. using WHP. A demonstration was provided.

- Once grasped, the cylinder was to be lifted *"by anything over three inches"* before being placed back down on the table. Participants were informed that the reach and grasp components of the task were of interest and that there was no need to accurately place the cylinder back on its marker (marker 4 – see Figure 34). A demonstration was provided.

- That a delay of between three and seven seconds would occur between the 'preparation signal' to prepare for the task (a verbal command of *"right hand ready"* or *"left hand ready"*) and the 'go signal' to start the reach and grasp (an auditory tone generated by the tablet computer or the illumination of the cylinder – see below).

All participants alternated between their dominant and non-dominant hand for each reach and grasp until five reach and grasps per hand, a total of ten reach and grasps per condition, had been completed. Participants then repeated this process for the next condition. There were four different conditions:

- **Condition 1 – natural speed (NAT):** Participants were asked to reach and grasp at a natural speed after the auditory tone *"as you would do at home if you were reaching for a cup from the table".*

- **Condition 2 – visually cued (VIS):** Participants were asked to reach and grasp at a natural speed when the cylinder lit up (red light). The room was darkened as much as possible for this task. As well as illumination of the cylinder there was a simultaneous auditory tone, as used in the other conditions.

- **Condition 3 – maximum speed (MAX):** Back under normal lighting conditions, participants were asked to reach and grasp the cylinder *"as quickly as possible"* after the auditory tone.

- **Condition 4 – memory guided (MEM):** Subjects were asked to close their eyes before being given the verbal command to prepare for the task (e.g. *"right hand ready"*). Participants were asked to reach and grasp the cylinder at a natural speed whilst keeping their eyes closed. The go signal was the auditory tone. Once the cylinder had

been lifted and placed back on the table the subject was instructed to open their eyes. Eyes then remained open whilst preparing for the next trial with the alternate hand. If eyes were opened during the reach and grasp the trial was repeated.

Throughout the protocol the clinical researcher reminded subjects of the instructions and helped with appropriate repositioning of the hands where required. This was particularly important for patients with more severe cognitive impairment. The clinical researcher also ensured that the cylinder was repositioned correctly before each reach and grasp. A photograph of the protocol in progress is shown in Figure 42. The reach and grasp was repeated in the rare event that participants failed to adequately grasp the cylinder.

Figure 42: A participant in the study performs a reach and grasp

Legend: Note that the left hand is medial to marker 2; reminding participants about hand positioning was required regularly during the assessment protocol.

5.3.6 Informant interview

All participants with PD were asked to nominate a friend or relative so that an informant interview could be undertaken. In many cases the nominated person was also participating as a HC. In such cases the informant interview was performed on the same day, after the informant had signed the 'consent to participate in research study informant interview' form. In cases where the nominated informant did not attend as a HC, the participant was asked to sign a 'request for a research study 20 minute telephone interview' form. This was sent to the informant by post asking them to return a signed consent form with an appropriate contact telephone number so that the informant interview could be completed at a later date.

The informant interview involved two assessments – the Clinical Dementia Rating Scale (CDR) and the Neuropsychiatric Inventory - Questionnaire (NPI-Q):

- **Clinical Dementia Rating Scale**

The CDR is a semi-structured interview originally designed for the assessment of AD that scores impairment in six cognitive categories on a five-point scale (0 = normal, 0.5 = questionable cognitive impairment, 1 = mild dementia, 2 = moderate dementia, 3 = severe dementia) (Morris, 1993). The categories are memory, orientation, judgment and problem solving, community affairs, home and hobbies and personal care. The overall, or global, CDR score is calculated using an algorithm that weighs towards memory dysfunction and uses the same five-point scale as each of the six cognitive categories used to derive it. Alternative forms of calculating the overall CDR score, for example using a 'sum of boxes' approach have been investigated and validated in subjects with AD but not PD (O'Bryant et al., 2008). The CDR has been used in a number of studies in PwPD to provide information regarding activities of daily living and functional abilities (Goldman et al., 1998, Camicioli et al., 2003). One of the key differentiators between PD-MCI and PDD according to MDS criteria

is whether or not cognitive impairment interferes with functional independence (Litvan et al., 2012, Emre et al., 2007) and the CDR allows that to be assessed. In this study the conventional global CDR score was used rather than the sum of boxes score because the former method has been used in previous studies of PwPD (although both scores were calculated and there was no difference in the overall categorisation of PwPD in to cognitive groups in the cohort recruited for this study).

- **Neuropsychiatric Inventory - Questionnaire**

Permission to use the NPI-Q was granted in October 2013. It consists of 12 questions relating to different neuropsychiatric domains (Kaufer et al., 2000). The informant is asked a question which contains a key symptom of each domain. If the participant has had a particular symptom in the last month, the informant is asked to grade the severity (1 = mild, 2 = moderate, 3 = severe) and the caregiver distress (0 = not distressing, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe, 5 = extreme) caused by that symptom. A total score is calculated from summing the severity and caregiver distress scores. The NPI-Q is widely used in studies of AD and PD (Fitts et al., 2015). Neuropsychiatric symptoms are associated with PDD (Riedel et al., 2010) and have also been found to be more common in those with PD-MCI compared to PD-NC (Monastero et al., 2013).

5.4 Categorisation of participants into cognitive groups

5.4.1 Categorising people with Parkinson's disease

The PwPD recruited for this study were categorised into PD-NC, PD-MCI and PDD according to category 1 MDS criteria (Litvan et al., 2012, Emre et al., 2007) by using the MoCA and global CDR score. MoCA score separated those with PD-NC (MoCA ≥26) and those with PD-CI (MoCA <26). The global CDR score was used to separate the PD-CI group; a score of 0 or 0.5 was categorised as PD-MCI and a score of ≥1 was categorised as PDD. This is summarised in Table 5.

Table 5: Criteria for categorising the Parkinson's disease subjects into cognitive groups

Cognitive group	Diagnostic criteria
PD-NC	MoCA score ≥ 26
PD-MCI	MoCA score <26, global CDR 0 – 0.5
PDD	MoCA score <26, global CDR ≥ 1

5.4.2 Categorising healthy control subjects

An unexpected finding was that a significant proportion of HC scored <26 on the MoCA. There was no informant interview for HC so they were divided into healthy control subjects with normal cognition (C-NC, MoCA ≥26) and healthy control subjects with cognitive impairment (C-CI, MoCA <26). Only results from C-NC are included in this thesis.

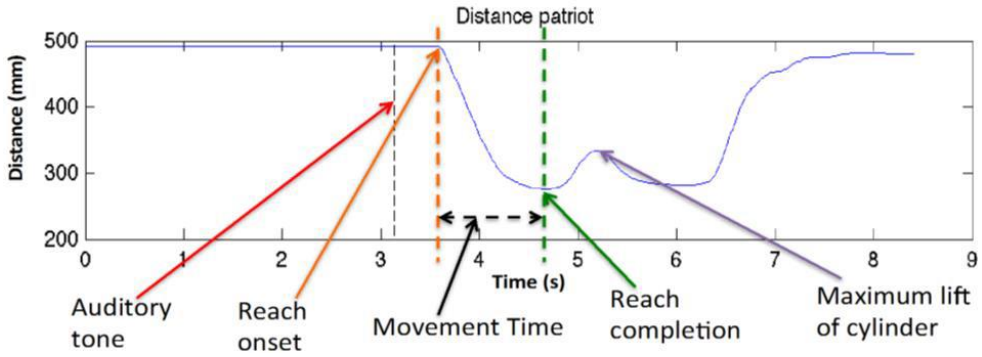
5.5 Data processing

5.5.1 Processing of reach data

Only positional data was used in this study. The *x, y* and *z* coordinates from the wrist sensors were used to calculate the Euclidean distance (positional separation), D, between the wrist sensor and the magnetic transmitter for every 1/60th second time point using the following formula: $D = \sqrt{(x^2 + y^2 + z^2)}$ where *x, y* and *z* are the coordinate distances of the wrist sensor relative to magnetic transmitter. The position of the wrist sensor relative to the magnetic transmitter for each reach was generated. From that data the reach onset and reach completion points were calculated. Reach onset was defined as the first point after the auditory tone that the wrist sensor began to move towards the magnetic transmitter (and therefore the cylinder). As the hand continues to approach the cylinder the distance from the wrist sensor to the magnetic transmitter progressively decreases and then plateaus as the grasp is completed. The nearest point between the wrist sensor and the magnetic transmitter was defined as reach completion. MT is the time from reach onset to reach completion. In cases where the distance between the wrist sensor and the

magnetic transmitter plateaus, reach completion was defined as the earliest point of the plateau phase. The movement of the wrist sensor away from the magnetic transmitter that immediately follows reach completion is the 2D representation of the cylinder being lifted in the air (and therefore away from the magnetic transmitter), and the movement back towards the magnetic transmitter is the 2D representation of the cylinder being placed back on the table surface (Figure 43).

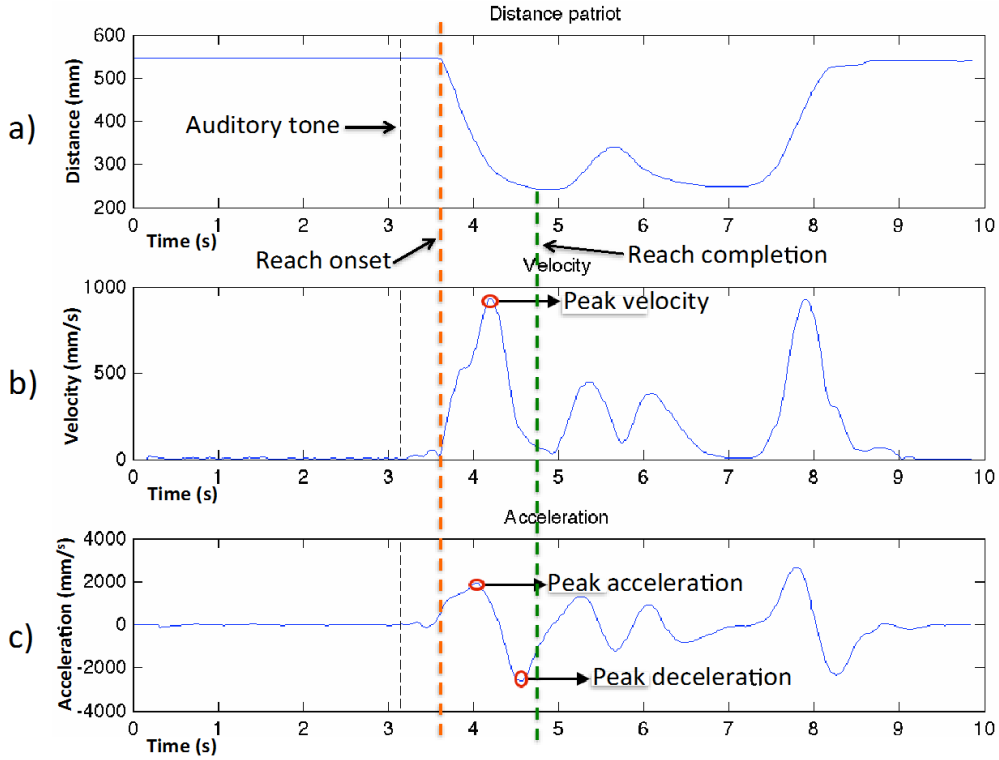
Figure 43: The Euclidean distance of the wrist sensor relative to the magnetic transmitter in a participant with Parkinson's disease



Legend: Auditory tone is highlighted, as are reach onset and reach completion. The time between reach onset and reach completion is MT. Following reach completion, the distance between the wrist sensor and the magnetic transmitter increases and then decreases – this is the 2D representation of the cylinder being lifted. Maximum lift of the cylinder is highlighted in this figure. *Original data series produced by Chiara Picardi.*

For each participant the Euclidean distance was then differentiated to produce the speed time data (dD/t) and differentiated again to produce acceleration time data (dD^2/t). An example of this is shown in Figure 44.

Figure 44: An example of differentiated reach data



Legend: The Euclidean distance from the wrist sensor to the magnetic transmitter in mm (a) was differentiated to produce velocity in mm/s (b) and acceleration in mm/s^2 (c) time data. The *x*-axis denotes time in seconds. Peaks of acceleration, velocity and deceleration are demonstrated. *Original data series produced by Chiara Picardi.*

5.5.2 Calculation of kinematic reach parameters

A number of reach parameters were calculated from the processed reach data. These are defined below and, where possible, shown on Figure 45:

- **Movement time (MT)** – Time in seconds from reach onset to reach completion.

- **Reaction time (RT)** – Time in seconds from auditory tone until onset of MT.

- **Total movement time (TMTi)** – RT + MT (seconds).

- **%Reaction time (%RT)** – RT/TMT x 100.

- **Distance travelled (DT)** – The direct distance between the position (i.e. the calculated Euclidean distance from the wrist sensor to the magnetic transmitter in mm) of the wrist sensor at movement onset and reach completion (mm). This direct distance does not take hand trajectory into consideration and is therefore a 2D measurement of a 3D movement.

Peak reach parameters

- **Peak acceleration (PA)** – maximum acceleration data point (mm/s^2).
- **Peak velocity (PV)** – maximum velocity data point (mm/s).
- **Peak deceleration (PDe)** – maximum deceleration data point (mm/s^2).

Mean reach parameters

- **Mean acceleration (MA)** – sum of all acceleration data points/number of data points (mm/s^2).
- **Mean velocity (MV)** – sum of all velocity data points/number of data points (mm/s).

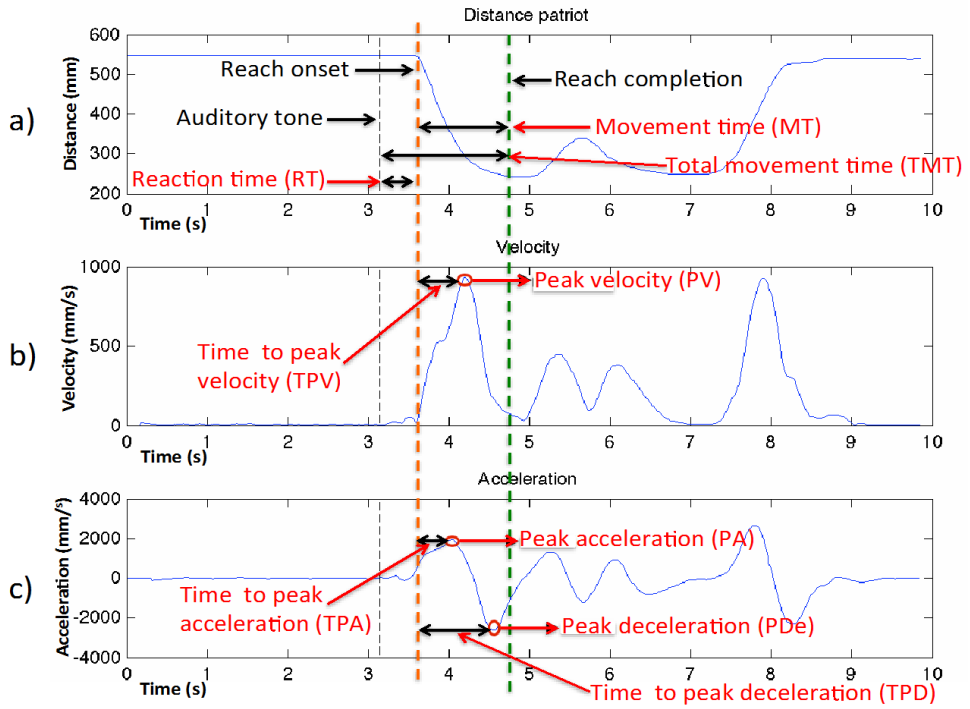
Time to peak wrist parameters

- **Time to peak acceleration (TPA)** – Time from MT onset until PA (seconds).
- **Time to peak velocity (TPV)** – Time from MT onset until PV (seconds).
- **Time to peak deceleration (TPD)** – Time from MT onset until PDe (seconds).

Time to peak reach parameters as a percentage of movement time

- **% Time to peak acceleration (%TPA)** – TPA/MT x 100.
- **% Time to peak velocity (%TPV)** – TPV/MT x 100.
- **% Time to peak deceleration (%TPD)** – TPD/MT x 100.

Figure 45: Examples of some of the calculated kinematic reach parameters



Legend: A number of the calculated kinematic reach parameters are shown in red on the distance (a), velocity (b) and acceleration (c) time data series. The *x*-axis denotes time in seconds. *Original data series produced by Chiara Picardi.*

5.6 Processing of grasp data

Extraction of meaningful information from the data gloves proved to be more difficult than expected because the data glove software provided flexion and extension data as a series of arbitrary integer values. At maximal flexion the integer value of each sensor was largest and became smaller as the fingers extended (often becoming a negative number) (Figure 46).

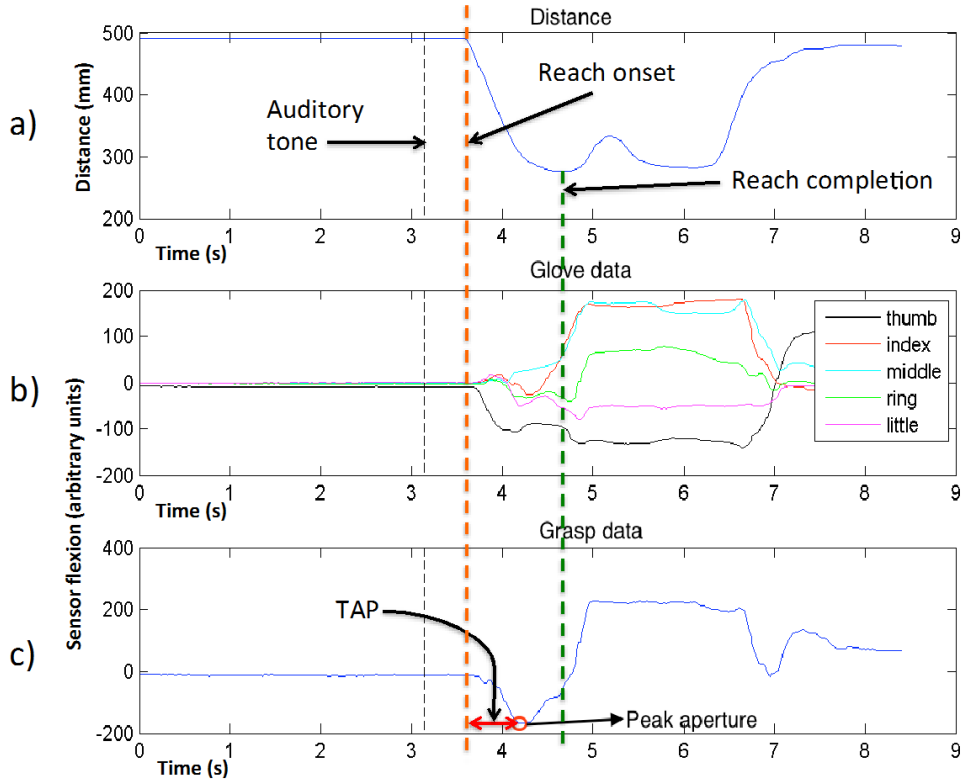
Calibration of the data gloves involved extending and then flexing the fingers and thumb (i.e. spreading the fingers as straight and wide as possible and then making a clenched fist). The plan was to identify peak index finger to thumb aperture by finding the point of maximal extension of the index finger and thumb during reach (i.e. during movement time). This can be identified as the point at which integer values from the index

finger and thumb sensors are closest to the values recorded during the extension phase of calibration.

However, unidentified damage to the data gloves (see Chapter 6.1.2.5) meant that the degree of movement recorded by the index finger sensor was variable from participant to participant and was minimal in some cases. It was decided that information from the middle, ring and little fingers would be added to thumb and index finger data. Peak aperture was therefore identified as the point at which the average integer value from the five sensors during the reaching phase was closest to the average value recorded when the hand was maximally extended during calibration. The time from movement onset to this point is time to peak aperture (TAP) (Figure 46). As a result, TAP is a measure of time to maximal hand opening in our study, rather than the more traditional measure of time to peak index finger to thumb aperture.

It was not possible to calculate the amplitude of peak index finger to thumb aperture because the distance between the index finger and thumb could not be assessed using the data glove. It was also not possible to establish the first point at which the index finger began to extend during the reach phase, which has been considered to represent the start of grasp and has been referred to as 'manipulation time' in previous studies (see Chapter 4.2.3) (Scarpa and Castiello, 1994, Castiello and Bennett, 1997, Castiello et al., 1993b).

Figure 46: An example of the calculation of time to peak aperture from a participant with Parkinson's disease



Legend: (a) The Euclidean distance of the wrist sensor to the magnetic transmitter (reach data). (b) The integer values of the sensors of each digit in one hand. The larger the values on the *y*-axis the greater the flexion of the digit in question; the smaller the values on the *y*-axis the greater the extension of the digit. (c) The average value of flexion from the five sensors (i.e. the five digits of the hand). Peak aperture is identified as the smallest integer value on the *y*-axis during the reach phase (i.e. during MT). TAP is defined as the time from reach onset to peak aperture. *Original data series produced by Chiara Picardi.*

5.7 Statistical analysis

Statistical analysis was performed using IBM Statistical Package for the Social Sciences version 22 (Chicago SPSS Inc., U.S.A). Statistical significance was denoted as a *p* value of <0.05. Categorical demographic and clinical data between groups were compared using Chi-squared test or Fisher's exact test. Normally distributed continuous demographic and clinical data between groups were compared using independent-t test or one-way analysis of variance (ANOVA) applying Levene's test for equality of variance(s). Post-hoc inspection of ANOVA was performed after Bonferroni

correction. Non-normally distributed continuous demographic and clinical data and results from the cognitive tests were compared using Mann-Whitney U-test or Kruskal Wallis test.

Kolmogorov-Smirnov test was used to ascertain if calculated reach and grasp parameters were normally distributed. In cases where normal distribution was violated, a logarithmic transformation of the data was performed and Kolmogorov-Smirnov test repeated. Normally distributed data between groups was compared using independent-t test or ANOVA applying Levene's test for equality of variance(s). If data remained non-normally distributed after logarithmic transformation, Mann-Whitney U-test or Kruskal Wallis test was used. Intra-group analysis of reach and grasp parameters between different conditions was compared using paired-t test.

When logarithmic transformation normalised the reach and grasp data, the mean value was back-transformed using the antilog. This value is presented in the results and is known as the geometric mean. It differs slightly from the traditional – or arithmetic – mean and is calculated by multiplying all the observations and taking the n'th root. In situations where the geometric mean is presented the values in parenthesis are not the traditional 95% confidence intervals. This is because the difference between the logarithms of two geometric means is the logarithm of their ratio. The 95% confidence limits were back-transformed and the values in parenthesis when the geometric mean is provided therefore represent the 95% confidence limits for the ratio between the mean values of the two groups for the parameter in question (Bland, 2015).

Spearman's rank correlation coefficient was used to explore the relationship between reach and grasp parameters, cognitive tests and clinical and demographic details. Data was inspected for distribution and residuals to ensure assumptions of normality were not violated and then

simple and multiple linear regression was performed to further explore associations between reach and grasp parameters and cognitive tests.

Chapter 6

Abbreviations used in this chapter

%TAP	Time to peak aperture as a % of movement time
%TPA	Time to peak acceleration as a % of movement time
%TPD	Time to peak deceleration as a % of movement time
%TPV	Time to peak velocity as a % of movement time
3D	Three dimensional
AIP	Anterior intraparietal area in macaques/monkeys
aIPS	Anterior intraparietal area in humans
B-C	Benson Copy
B-R	Benson Recall
C-CI	Healthy control subjects with cognitive impairment
C-NC	Healthy control subjects with normal cognition
CDR	Clinical Dementia Rating scale
DBS	Deep brain stimulation
DT	Distance travelled
EM	Electromagnetic
fMRI	Functional magnetic resonance imaging
GPi	Globus pallidus interna
H&Y	Hoehn & Yahr
HC	Healthy controls
JoLO	Benton Judgment of Line Orientation
LEDD	Levodopa equivalent daily dose
LP	Lateral posterior (nucleus of the thalamus)
M1	Primary motor cortex
MA	Mean acceleration
MAX	Condition 3 - Maximum speed
MCP	Metacarpal-phalangeal
MDS-UPDRS	Movement Disorders Society – Unified Parkinson's Disease Rating Scale
MEM	Condition 4 - Memory guided
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MT	Movement time
MV	Mean velocity
NAT	Condition 1 - Natural speed
PA	Peak acceleration
PD	Parkinson's disease
PD-CI	PD cognitive impairment
PD-MCI	Parkinson's disease - mild cognitive impairment
PD-NC	Parkinson's disease - normal cognition
PDD	Parkinson's disease dementia
PDe	Peak deceleration
PIGD	Postural instability gait disorder

PIP	Proximal interphalangeal
PMd	Dorsal premotor cortex
PMv	Ventral premotor cortex
PPN	Pedunculopontine nucleus
PRR	Parietal reach region
PV	Peak velocity
PwPD	People with Parkinson's disease
RT	Reaction time
SMA	Supplementary motor area
SNpr	Substantia nigra pars reticulate
STN	Subthalamic nucleus
TAP	Time to peak aperture
TMS	Transmagnetic stimulation
TMT B-A	Trail Making Test Part B score - Trail Making Test Part A score
TMT-A	Trail Making Test Part A
TMT-B	Trail Making Test Part B
TPA	Time to peak acceleration
TPD	Time to peak deceleration
TPV	Time to peak velocity
V6	Visual area V6
V6A	Visual area V6A
V6Ad	Dorsal visual area V6A
V6Av	Ventral visual area V6A
VIS	Condition 2 - Visually cued
VL	Ventral lateral (nucleus of the thalamus)
VLPFC	Ventrolateral prefrontal cortex
WHP	Whole-hand prehension

Analysis of reach and grasp in Parkinson's disease with normal cognition: Results and discussion

This chapter begins by presenting the demographic details of all recruits to the study followed by a review of unusable data. The reach and grasp results of PD-NC and C-NC will then be explored, followed by a discussion of the pertinent findings.

6.1 Details of all recruits and unusable data

6.1.1 Demographic and clinical details of all recruits

Fifty-eight PwPD and 29 HC were recruited and assessed in this study. The demographic and clinical details are presented in Table 6. The HC group are younger than those with PD but this difference is not statistically significant (p 0.099). The groups are not matched for gender; there are significantly more males in the PD group (p <0.001). PD is more common in men (Gillies et al., 2014) and the fact that HC were predominately the spouses or partners of the PD subjects has exaggerated the gender difference. The MoCA score is significantly lower in the PD group (p <0.001).

Table 6: The demographic and clinical details of all assessed recruits

	PD (n = 58)	HC (n = 29)	p
Age, years	69.2 (8.4, 44-85)	66.1 (7.6, 50-79)	0.099
Gender, M : F	38 : 20	5 : 24	**<0.001**
Handedness, R: L	51 : 7	22 : 7	0.215
Disease duration, years	6.2 (4.7, 0.5-20)	-	-
H&Y stage I (%)	8 (13.8)	-	-
H&Y stage II	47 (81)	-	-
H&Y stage III	3 (5.2)	-	-
MDS-UPDRS Part 3	28.8 (11.5, 3 - 56)	-	-
LEDD, mg/day	662.7 (560.9)	-	-
MoCA score	23.1 (4.1, 12 - 29)	26.3 (3.0, 18 - 30)	**<0.001**

Abbreviations: PD; Parkinson's disease; HC, Healthy controls; H&Y, Hoehn and Yahr; MDS-UPDRS, Movement Disorders Society – Unified Parkinson's Disease Rating Scale; LEDD, Levodopa equivalent daily dose; MoCA, Montreal Cognitive Assessment.

6.1.2 Unusable and compromised data

6.1.2.1 Parkinson's disease subjects without an informant interview

In total six PwPD did not have an informant interview and so no assessment of their functional abilities could be made. In all cases the participant declined to recommend an informant. Three subjects who declined had a MoCA score of ≥26 and would therefore be considered as PD-NC according to the diagnostic criteria used to classify PwPD in this study. These subjects were included in the results. Three PwPD who declined to recommend an informant scored <26 on the MoCA (scores of 25, 21 and 19). Since a global CDR score was unavailable it was not possible to categorise these PD-CI into PD-MCI or PDD according to the classifications used in this study. Although it is likely these subjects had PD-MCI (each was able to attend for an assessment independently, suggesting that functional dependence was intact) they were excluded from the results. The total number of PwPD included in the final results is therefore 55.

6.1.2.2 Data loss due to programming error

The 55 PD subjects and 29 HC performed a reach and grasp for each of the four conditions using the right and left hand. This should have resulted in 168 ((55+29) x2) datasets. Unfortunately, a programming error prevented the storage of data from the right hand and this was not identified until 18 participants (12 PD, six HC) had been recruited. Therefore the total datasets available for the results is reduced to 150 (168-18). Of the 150, 84 are from the left hand and 66 from the right hand. For PwPD this results in 98 datasets, 55 from the left hand and 43 from the right hand. For HC there are 52 datasets, 29 from the left hand and 23 from the right hand.

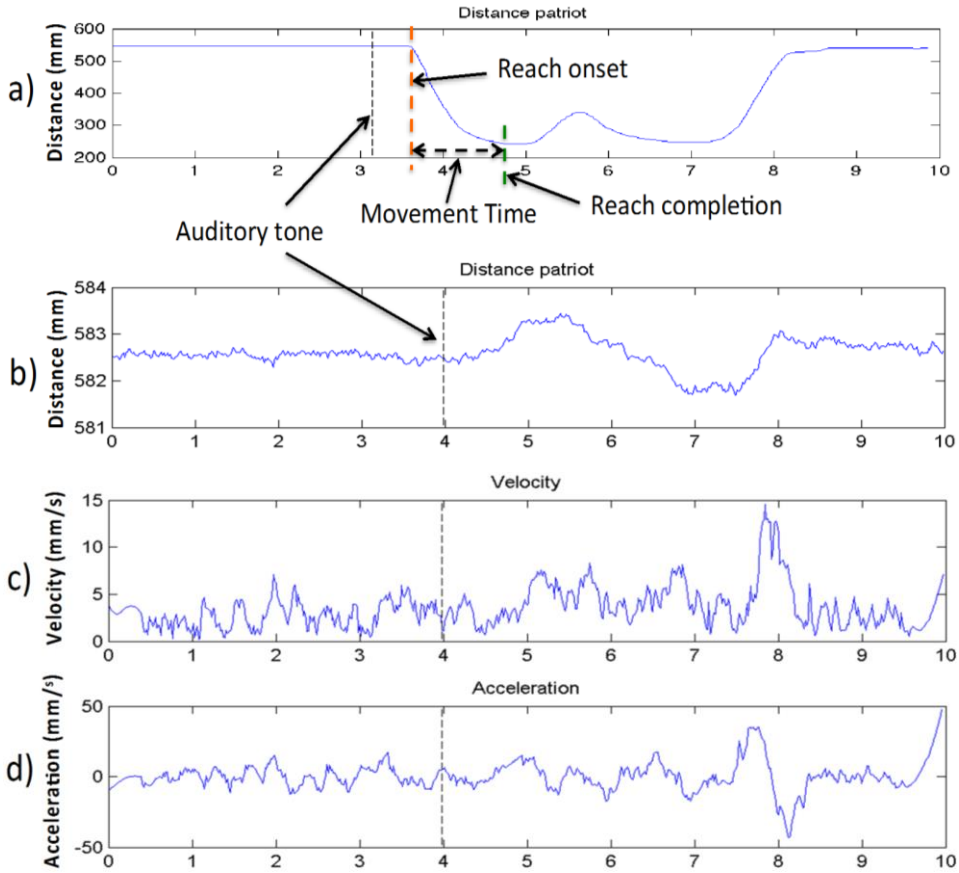
6.1.2.3 Unusable reach data

Every participant performed each of the four reach and grasp conditions five times with each hand, a total of 20 reach and grasps with each hand per participant. The value of each dataset should be the mean of the five repeats in each condition. Put another way, the total number of repeats used to derive the values for the 150 datasets for each condition should be 750 (5x150). However, a number of reach and grasp repeats were unusable and as a consequence the dataset value was derived from fewer than five repeats. For PD the maximum number of repeats per condition is 490 (98x5). In Condition 1 (NAT) a total of 454 (92.7%) repeats were usable. In Condition 2 (VIS) 462 (94.3%) repeats were usable, Condition 3 (MAX) 459 (93.7%) repeats were usable and in Condition 4 (MEM) 454 (92.7%) were usable. For HC the maximum number of repeats per condition is 260 (52x5). For NAT and VIS 247 (95%) repeats were usable, for MAX 245 (94.2%) were usable and 249 (95.8%) were usable for MEM. In total, 1829 from a possible 1960 (93.3%) repeats were usable for PD and 985 from a possible 1040 (92.1%) were usable for HC.

6.1.2.4 Reasons for unusable reach data

Reach data was considered to be invalid if the plot of the Euclidean distance between the EM sensor placed at the wrist and the magnetic transmitter did not correspond to the characteristic pattern observed in usable cases (see Chapter 5.5.1). An example is shown in Figure 47. In such cases the reach onset and offset could not be determined and therefore MT and the other reach parameters could not be calculated.

Figure 47: An example of unusable reach data



Legend: The expected pattern of the graph plotting Euclidean distance between the EM sensor in the wrist and the magnetic transmitter is shown in (a). This pattern is discussed in Chapter 5.5.1. In contrast, (b) shows an example of unusable distance data during a reach recording. The *y*-axis suggests that in this particular example the movement recorded by the Polhemus Patriot was incredibly small, only a few millimetres. There is no defined onset and offset of reach. The differentiated velocity (c) and acceleration (d) time data from the unusable reach distance data (b) has a very different pattern from that seen in usable data (see Figure 44).

The percentage of usable reach data was greater in the right hand of both PD and HC. This discrepancy was in part due to a low number of repeats being usable from the left hand in the early stages of recruitment. Data from the right hand during this period was lost completely (see 6.1.2.2) and is not included in the results, skewing the proportion of lost data towards the left hand. It is possible that in the early phase of the trial the clinical researcher did not adequately ensure the starting position of the hand was accurately maintained throughout each repeat. Another possibility is that some form of intermittent software abnormality occurred that was later fixed (a number of software updates were incorporated into the reach and grasp computer programme during the recruitment period).

6.1.2.5 Compromised grasp data

The Lycra material holding the index finger sensor in place to provide an average value for flexion in the MCP and PIP joints became worn. This occurred in both gloves and caused the index finger sensor to be pulled back towards the wrist. As a result, the sensor on each index finger did not accurately measure PIP flexion, causing an under-estimation of index finger flexion and therefore an incorrect assessment of TAP in the index finger. This problem was only identified at the end of recruitment so it is unknown how many data sets were affected and to what extent. It is very difficult to estimate the impact that this problem has on TAP values used in this study as they are derived by considering average flexion of all five digits (see Chapter 5.6). However, the overall effect is to make TAP data (and therefore %TAP) in our study unreliable, markedly reducing the capacity to make firm conclusions about grasp from the results. This is very disappointing.

6.1.2.6 Summary of unusable data

Three PwPD with PD-CI were excluded from the results because it was not possible to classify them into PD-MCI or PDD. The first 18 recruits to be assessed did not have right hand data recorded due to a programming

error. One hundred and fifty datasets from a total of 55 PwPD and 29 HC make up the 'approved' results and these are derived from approximately 92.5% of the data collected. TAP data is unreliable, making it difficult to compare our grasp results with existing studies.

6.2 Results

6.2.1 Demographic and clinical details for PD-NC and C-NC

From the original 55 PwPD who had usable results, 22 (40%) were categorised as PD-NC. Of the 29 HC with usable results, 19 (65.5%) were categorised as C-NC and ten (34.5%) were categorised as C-CI, i.e. they scored <26 on the MoCA.

The remainder of this chapter focuses on the results of PD-NC and C-NC and the demographic and clinical details of these participants are outlined in Table 7.

Table 7: The demographic and clinical details of PD-NC and C-NC

	PD-NC (n = 22)	C-NC (n = 19)	p
Age, years	66.5 (9.4, 44-84)	63.8 (7.9, 50-75)	0.328
Gender, M : F	16: 6	4: 15	**0.002**
Handedness, R: L	20 : 2	15 : 4	0.390
Disease duration, years	5.1 (3.7, 0.5-15)	-	-
H&Y stage I (%)	6 (27.3)	-	-
H&Y stage II	15 (68.2)	-	-
H&Y stage III	1 (4.5)	-	-
MDS-UPDRS Part 3	25.9 (11.0, 3 - 49)	-	-
LEDD, mg/day	656.0 (621.7, 0 – 2836.3)	-	-
MoCA score	26.9 (1.1, 26-29)	27.9 (1.5, 26 – 30)	**0.019**
GDS-15	3.0 (2.6, 0-11)	2.0 (2.3, 0 - 6)	0.171

The mean age of PD-NC and C-NC is not statistically significant (*p* 0.328). The distribution of males and females amongst the groups is unequal, with

significantly more males present in PD-NC (*p* 0.002). The likely reason for this has been discussed (see 6.1.1). PD-NC have a mean disease duration of 5.1 years and over two-thirds are H&Y stage II. The mean MDS-UPDRS Part 3 score of PD-NC, all tested when *on*, was 25.9 and the mean LEDD was 656mg. Although both groups scored within the normal range on the MoCA, it should be noted that the mean score for PD-NC was significantly lower than the score for C-NC (*p* 0.019).

6.2.2. Cognitive test results of PD-NC and C-NC

In addition to MoCA a number of other cognitive tests were performed on the recruits and the results are shown in Table 8. TMT-A score – a measure of the time taken to complete the test in seconds – was significantly prolonged in PD-NC but the other cognitive test scores were not significantly different between the groups. An interesting observation is that JoLO and B-R score are non-significantly greater in PD-NC, i.e. they performed better than C-NC.

Table 8: The scores from cognitive tests other than MoCA in PD-NC and C-NC

	PD-NC (n = 22)	C-NC (n = 19)	p
TMT-A	34.4 (9.7, 21-52)	29.5 (15.5, 14 – 80)	**0.041**
TMT-B	73.9 (27.5, 41-133)	57.9 * (17.1, 34 – 107)	0.147
TMT B-A	39.5 (22.6, 12-86)	28.8 * (11.1, 4-49)	0.286
JoLO	13.1 (1.3, 10-15)	11.7 (2.7, 5-14)	0.080
Benson Copy	16.2 ^ (0.8, 14-17)	16.3 ^^ (0.8, 15-17)	0.813
Benson Recall	10.2 ^ (3.0, 4-15)	9.7 ^^ (2.4, 7-15)	0.426

Legend: * n = 19; ^ n = 21; ^^ n = 18. **Abbreviations:** TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; TMT B-A, Trail Making Test A – Trail Making Test Part B; JoLO, Benton Judgment of Line Orientation.

The results of the cognitive tests suggest that although both groups have a normal range score on a validated test of global cognition (MoCA), PD-NC score significantly worse and therefore are 'less cognitively normal' than C-NC. TMT-A score is also significantly worse for PD-NC but motor

dysfunction as well as cognitive issues could explain this. The remainder of the cognitive tests, assessing task-switching and working memory (TMT-B), executive function (TMT B-A) and various aspects of visuospatial function (JoLO, B-C, B-R) are not significantly different between the groups.

6.2.3 Correlation of reach and grasp parameters

Spearman's correlation coefficient, r_s, is a non-parametric method of assessing the direction and strength of association between the reach and grasp kinematic parameters. This has been calculated for NAT in PD-NC and is shown in Table 9. The correlogram highlights a number of important points that need to be considered during the analysis of reach and grasp parameters for PwPD and C-NC in this chapter and Chapter 7:

- The peak reach parameters (PA, PV and PDe [20]) are all highly correlated. In other words, a reach with a large PA will also have a large PV and a large PDe.
- The times to attain peak reach parameters (TPA, TPV and TPD) are all highly correlated with each other and are highly negatively correlated with peak reach parameters. For example, a larger PA is associated with a shorter TPA and shorter TPV. In simple terms, the faster the wrist moves the shorter the time taken to attain peak reach parameters.
- The time to peak reach parameters as a percentage of movement time (%TPA, %TPV, %TPD) are highly correlated with each other but are not correlated with %TAP.

[20] Due to the number of abbreviations in this section, a reminder of the full terms for the calculated reach and grasp parameters is provided:

PA, peak acceleration; PV, peak velocity; PDe, peak deceleration; TPA, time to peak acceleration; TPV, time to peak velocity; TPD, time to peak deceleration; %TPA, time to peak acceleration as a % of movement time; %TPV, time to peak velocity as a % of movement time; %TPD, time to peak deceleration as a % of movement time; MT, movement time.

- MT is highly correlated with TPA, TPV and TPD and highly negatively correlated with PA, PV and PD. A shorter MT is associated with shorter time to attain peak reach parameters and higher values of peak reach parameters. Put simply, the faster the wrist travels, the shorter the MT.

Table 9: Correlogram of reach and grasp parameters for PD-NC from NAT

	PA	TPA	%TPA	MA	PV	TPV	%TPV	MV	PDe	TPD	%TPD	TAP	%TAP	RT	%RT	MT	TMTi	DT
PA		-.57 **	.23	.98 **	.75 **	-.61 **	.33 *	.84 **	-.75 **	-.68 **	.27	-.66 **	.19	-.49 **	.28	-.76 **	-.79 **	.04
TPA	-.57 **		.34 *	-.64 **	-.09	.91 **	.12	-.39 **	.11	.94 **	.02	.59 **	-.24	.37 *	-.43 **	.76 **	.74 **	-.29
%TPA	.23	.34 *		.16	.53 **	.29	.84 **	.45 **	-.55 **	.21	.80 **	-.14	.27	-.12	.17	-.27	-.26	-.35*
MA	.98 **	-.64 **	.16		.72 **	-.68 **	.28	.84 **	-.72 **	-.73 **	.24	-.70 **	.13	-.50 **	.31	-.79 **	-.81 **	.05
PV	.75 **	-.09	.53 **	.72 **		-.10	.61 **	.87 **	-.98 **	-.19	.32	-.34 *	.06	-.31	.11	-.44 **	-.45 **	-.40 **
TPV	-.61 **	.91 **	.29	-.68 **	-.10		.20	-.40 *	.11	.94 **	.01	.65 **	-.18	.33 *	-.45 **	.75 **	.72 **	-.37 *
%TPV	.33 *	.12	.84 **	.28	.61 **	.20		.61 **	-.64 **	.02	.76 **	-.22	.29	-.31	.11	-.44 **	-.44 **	-.40 **
MV	.84 **	-.39 **	.45 **	.84 **	.87 **	-.40 *	.61 **		-.87 **	-.49 **	.49 **	-.59 **	.16	-.47 **	.25	-.73 **	-.73 **	-.15
PDe	-.75 **	.11	-.55 **	-.72 **	-.98 **	.11	-.64 **	-.87 **		.21	-.36 *	.37 *	-.06	.33 *	-.10	48 **	.49 **	.44 **
TPD	-.68 **	.94 **	.21	-.73 **	-.19	.94 **	.02	-.49 **	.21		-.08	.68 **	-.28	.35 *	-.49 **	.84 **	.80 **	-.31
%TPD	.27	.02	.80 **	.24	.32	.01	.76 **	.49 **	-.36 *	-.08		-.27	.42 **	-.20	.35 *	-.53 **	-.49 **	-.07
TAP	-.66 **	.59 **	-.14	-.70 **	-.34 *	.65 **	-.22	-.59 **	.37 *	.68 **	-.27		.19	.57 **	-.25	.75 **	.78 **	-.15
%TAP	.19	-.24	.27	.13	.06	-.18	.29	.16	-.06	-.28	.42 **	.19		.07	.48 **	-.38 **	-.30	.15
RT	-.49 **	.37 *	-.12	-.50 **	-.31	.33 *	-.31	-.47 **	.33 *	.35 *	-.20	.57 **	.07		.43 **	.47 **	.69 **	-.20
%RT	.28	-.43 **	.17	.31	.11	-.45 **	.11	.25	-.10	-.49 **	.35 *	-.25	.48 **	.43 **		-.53 **	-.30	.01
MT	-.76 **	.76 **	-.27	-.79 **	-.44 **	.75 **	-.44 **	-.73 **	.48 **	.84 **	-.53 **	.75 **	-.38 **	.47 **	-.53 **		.96 **	-.09
TMTi	-.79 **	.74 **	-.26	-.81 **	-.45 **	.72 **	-.44 **	-.73 **	.49 **	.80 **	-.49 **	.78 **	-.30	.69 **	-.30	.96 **		-.14
DT	.04	-.29	-.35 *	.05	-.40 **	-.37 *	-.40 **	-.15	.44 **	-.31	-.07	-.15	.15	-.20	.01	-.09	-.14	

Legend: * denotes p <0.05 (2-tailed), ** denotes p <0.01 (2-tailed). **Abbreviations:** PA, peak acceleration; TPA, time peak acceleration; %TPA, TPA as a % of MT; MA, mean acceleration; PV, peak velocity; TPV, time peak velocity; %TPV, TPV as a % of MT; MV, mean velocity; PDe, peak deceleration; TPD, time peak deceleration; %TPD, TPD as a % of MT; TAP, time to peak aperture; %TAP, TAP as a % of MT; RT, reaction time; %RT, RT as a % of TMT; MT, movement time; TMTi, total movement time; DT, distance travelled.

Key: Grey shadings and correlation coefficient:

≥ 90 | 0.80 – 0.89 | 0.70-0.79 | 0.60-0.69 | 0.50- 0.59

6.3 Results from the four conditions

6.3.1 Condition 1 – Natural Speed (NAT)

In this condition the participants were asked to reach and grasp at a natural speed after an auditory tone *"as you would do at home if you were reaching for a cup from the table"*. The results are presented in Table 10. Right and left hand data is considered together for each group, producing 37 datasets from the 22 PD-NC and 34 datasets from the 19 C-NC.

RT is not statistically different between the groups (*p* 0.312). MT is non-significantly prolonged in PD-NC (*p* 0.07). All of the peak and mean reach parameters are reduced in PD-NC but the only statistically significant reduction is in PA (*p* 0.027). PD-NC take significantly longer to attain all peak reach parameters and TAP. There is no significant difference in the time to attain peak reach parameters as a percentage of MT but %TAP is significantly prolonged in PD-NC (*p* <0.001).

The results suggest that PD-NC take longer to complete NAT than C-NC but the prolongation is non-significant. The non-significant difference in reach parameters as a percentage of movement time suggests that the programming of reach is not different between groups for this condition. In contrast %TAP is very different between the groups.

Table 10: Condition 1 - NAT

	PD-NC (n = 37)	C-NC (n = 34)	p (95% CI)
PA, mm/s^2 (SD, range)	1800.3 * (1.30, 1043.1 – 3533.3)	2053.5 * (1.26, 1339.4 – 3261.7)	**0.027** (1.02 – 1.28)
TPA, s	0.41 * (1.27, 0.26 – 0.70)	0.35 * (1.17, 0.22 – 0.49)	**0.005** (0.79 – 0.96)
MA, mm/s^2	966.9 * (1.32, 544.6 – 1863.1)	1103.1 * (1.26, 720.5 – 1900.7)	**0.033** (1.0 – 1.3)
PV, mm/s	700.0 (162.7, 506.3 – 1126.6)	737.2 (164.9, 499.7 – 1044.0)	0.343 (-40.4 – 114.8)
TPV, s	0.56 (0.12, 0.39 – 0.90)	0.48 (0.06, 0.37 – 0.62)	**0.001** (-0.12 – -0.03)
MV, mm/s	333.5 (77.3, 204.2 – 530.3)	348.9 (74.5, 241.4 – 494.6)	0.397 (-20.6 – 51.4)
PDe, mm/s^2	-1839.5 (614.6, -3212.9 – -978.4)	-1951.7 (681.3, -3065.8 – -959.7)	0.486 (-419.0 – 194.6)
TPD, s	0.87 (0.15, 0.53 – 1.28)	0.77 (0.11, 0.51 – 0.94)	**0.003** (-0.16 – -0.03)
TAP, s	0.87 (0.24, 0.30 – 1.50)	0.61 (0.17, 0.34 – 1.05)	**<0.001** (-0.36 – -0.15)
RT, s	0.54 (0.11, 0.33 – 0.85)	0.52 (0.12, 0.33 – 0.77)	0.312 (-0.08 – 0.03)
MT, s	1.23 (0.30, 0.77 – 2.21)	1.11 (0.22, 0.74 – 1.57)	0.07 (-0.24 – 0.01)
TMTi, s	1.77 (0.37, 1.11 – 2.88)	1.63 (0.24, 1.09 – 2.06)	0.061 (-0.29 – 0.01)
DT, mm	272.8 (25.9, 225.9 – 311.8)	268.5 (33.9, 193.1 – 307.2)	0.774 (-15.8 – 11.8)
%TPA	34.8 (5.9, 23.2 – 48.4)	33.0 (4.8, 24.6 – 41.5)	0.166 (-4.3 – 0.8)
%TPV	46.5 (6.7, 31.9 – 58.1)	44.4 (6.9, 32.1 – 59.4)	0.202 (-5.3 – 1.1)
%TPD	72.2 (7.8, 52.5 – 81.9)	70.4 (6.6, 55.9 – 78.7)	0.112 **
%TAP	71.0 (13.1, 22.3 – 86.7)	57.7 (13.4, 33.9 – 79.4)	**<0.001 ****
%RT	31.1 (4.3, 23.5 – 40.3)	32.0 (6.5, 23.6 – 47.8)	0.982 **

Legend: * denotes geometric mean – See Chapter 5.7, ** denotes non-parametric *p* value. **Abbreviations**: PA, peak acceleration; TPA, time peak acceleration; MA, mean acceleration; PV, peak velocity; TPV, time peak velocity; MV, mean velocity; PDe, peak deceleration; TPD, time peak deceleration; TAP, time to peak aperture; RT, reaction time; MT, movement time; TMTi, total movement time; DT, distance travelled; %TPA, TPA as a % of MT; %TPV, TPV as a % of MT; %TPD, TPD as a % of MT; %TAP, TAP as a % of MT; %RT, RT as a % of TMT.

6.3.2 Condition 2 – Visually guided (VIS)

For this condition the participants were asked to reach and grasp at a natural speed when the cylinder lit up. There was also a simultaneous auditory tone (as used in the other conditions). The room was darkened as

much as possible. Results are presented in Table 11. RT and MT are non-significantly prolonged and all peak and mean reach parameters are non-significantly reduced in PD-NC. As with NAT, PD-NC take significantly longer to attain all peak reach parameters and TAP. The only significant difference in terms of time to peak parameters as a percentage of movement time is for %TAP, which is significantly prolonged in PD-NC (p <0.001).

In summary, the changes between the groups for VIS are very similar to those seen in NAT.

Table 11: Condition 2 - VIS

	PD-NC (n = 37)	C-NC (n = 34)	p (95% CI)
PA, mm/s^2 (SD, range)	1842.7 * (1.30, 1012.3 – 3229.2)	2005.0 * (1.28, 1053.6 – 3133.8)	0.166 (0.96 – 1.23)
TPA, s	0.41 (1.29, 0.20 – 0.92)	0.37 (1.14, 0.30 – 0.50)	**0.045** (0.82 – 0.98)
MA, mm/s^2	1031.8 (292.4, 528.1 – 1926.9)	1111.9 (260.5, 561.3 – 1797.3)	0.229 (-51.5 – 211.7)
PV, mm/s	708.7 (161.0, 414.5 – 1036.7)	729.2 (169.9, 412.8 – 1021.0)	0.604 (-57.9 – 98.8)
TPV, s	0.55 (0.12, 0.36 – 1.04)	0.49 (0.07, 0.38 -0.63)	**0.011** (-0.11 – -0.01)
MV, mm/s	332.7 (79.4, 175.3 – 545.0)	346.9 (75.8, 206.7 – 491.1)	0.445 (-22.6 – 51.0)
PDe, mm/s^2	-1881.2 (628.6, -3080.9 – -744.0)	-1944.2 (703.3, -3133.0 – -701.2)	0.691 (-378.3 – 252.3)
TPD, s	0.87 (0.16, 0.46 – 1.38)	0.80 (0.11, 0.66 – 1.13)	**0.039** (-0.13 – 0.004)
TAP, s	0.82 (0.21, 0.51 – 1.58)	0.64 (0.18, 0.34 – 1.15)	**<0.001** (-0.28 – -0.09)
RT, s	0.47 (0.11, 0.27 – 0.78)	0.44 (0.12, 0.29 – 0.80)	0.227 (-0.09 – 0.02)
MT, s	1.20 * (1.27, 0.73 – 2.14)	1.11 * (1.21, 0.84 – 1.77)	0.140 (0.84 – 1.03)
TMTi, s	1.71 (0.38, 1.00 – 2.71)	1.58 (0.26, 1.20 – 2.23)	0.082 (-0.29 – 0.02)
DT, mm	268.5 (25.6, 211.1 – 310.5)	269.4 (31.5, 201.0 – 302.1)	0.447 **
%TPA	34.1 (5.2, 23.0 – 44.4)	33.5 (5.4, 22.6 – 48.2)	0.599 (-3.3 – 1.8)
%TPV	45.3 (6.0, 32.4 – 55.2)	44.1 (6.4, 32.3 – 58.3)	0.431 (-4.1 – 1.8)
%TPD	71.6 (7.3, 53.5 – 79.8)	71.8 (6.3, 54.0 – 82.0)	0.809 **
%TAP	70.4 (10.2, 44.2 – 85.3)	57.9 (11.0, 39.3 – 79.0)	**<0.001 ** **
%RT	27.6 * (1.17, 19.9 – 37.3)	27.5 * (1.23, 20.3 – 46.1)	0.890 (0.91 – 1.08)

Legend: * denotes geometric mean, ** denotes non-parametric *p* value.

6.3.2.1 Comparing intra-group change between NAT and VIS

It is possible to compare the reach and grasp parameters between conditions by using NAT as a baseline. To begin with the difference between conditions is compared separately for PD-NC and C-NC, i.e. an *intra-group* analysis is performed. A comparison of intra-group reach and grasp parameters for VIS and NAT for PD-NC and C-NC is shown in Table 12.

Table 12: Intra-group comparisons of NAT and VIS

	PD-NC NAT	PD-NC VIS	p (95% CI)	C-NC NAT	C-NC VIS	p (95% CI)
PA, mm/s^2 (SD)	1800.3 * (1.30)	1842.7 * (1.30)	0.377 (0.93 – 1.03)	2108.1 (506.9)	2063.7 (500.3)	0.268 (-35.7 – 124.6)
TPA, s	0.42 (0.11)	0.42 (0.12)	0.988 (-0.03 – 0.03)	0.36 (0.05)	0.37 (0.05)	0.074 (-0.03 – 0.00)
MA, mm/s^2	966.9 * (1.32)	994.8 * (1.31)	0.257 (0.46 – 1.24)	1132.9 (276.7)	1111.9 (260.5)	0.411 (-30.3 – 72.3)
PV, mm/s	683. 3 * (1.24)	691.3 * (1.25)	0.446 (0.96 – 1.02)	737.2 (164.9)	729.2 (169.9)	0.377 (-10.2 – 26.2)
TPV, s	0.56 (0.12)	0.55 (0.12)	0.553 (-0.02 – 0.03)	0.48 (0.06)	0.49 (0.07)	0.128 (-0.03 – 0.003)
MV, mm/s	333.5 (77.3)	332.7 (79.4)	0.894 (-11.4 – 13.1)	348.9 (74.5)	346.9 (75.8)	0.731 (-9.8 – 13.9)
PDe, mm/s^2	-1839.5 (614.6)	-1881.2 (628.6)	0.400 (-57.7 – 141.1)	-1951.7 (681.3)	-1944.2 (703.3)	0.828 (-77.3 – 62.3)
TPD, s	0.87 (0.15)	0.87 (0.16)	0.768 (-0.35 – 0.26)	0.76 * (1.17)	0.80 * (1.14)	**0.029** (0.92 - 0.99)
TAP, s	0.87 (0.24)	0.82 (0.21)	0.447 (-0.03 – 0.07)	0.61 (0.17)	0.64 (0.18)	0.140 (-0.06 – 0.01)
RT, s	0.54 (0.11)	0.47 (0.11)	**<0.001** (0.04 – 0.10)	0.52 (0.12)	0.44 (0.12)	**<0.001** (0.05 – 0.10)
MT, s	1.23 (0.30)	1.24 (0.32)	0.549 (-0.06 – 0.03)	1.11 (0.22)	1.14 (0.23)	0.332 (-0.08 – 0.03)
TMTi, s	1.77 (0.37)	1.71 (0.38)	0.072 (-0.01 – 0.12)	1.63 (0.24)	1.58 (0.26)	0.136 (-0.02 – 0.12)
DT, mm	272.8 (25.9)	268.5 (25.6)	**0.004** (1.5 – 7.3)	266.2 * (1.15)	269.8 * (1.12)	**0.021** (0.98 – 1.00)
%TPA	34.8 (5.9)	34.1 (5.2)	0.270 (-0.53 – 1.84)	33.0 (4.8)	33.5 (5.4)	0.395 (-1.60 – 0.65)
%TPV	46.5 (6.7)	45.3 (6.0)	0.050 (0.0 – 2.3)	44.4 (6.9)	44.1 (6.4)	0.650 (-0.86 - 1.36)
%TPD	72.2 (7.8)	71.6 (7.3)	0.356 (-0.7 – 1.8)	70.4 (6.6)	71.8 (6.3)	0.090 (-3.0 – 0.2)
%TAP	71.0 (13.1)	70.4 (10.2)	**0.022 ****	57.7 (13.4)	57.9 (11.0)	0.856 (-3.1 – 2.6)
%RT	31.1 (4.3)	28.0 (4.5)	**<0.001** (1.9 – 4.3)	32.0 (6.5)	28.1 (6.4)	**<0.001** (2.9 – 4.9)

Legend: * denotes geometric mean, ** denotes non-parametric *p* value.

Both groups have a statistically significantly shorter RT for VIS compared to NAT (p <0.001). However, MT and peak and mean reach parameters are not statistically different between the conditions for either group. Time to attain peak reach parameters and TAP are not different between the conditions for either group with the exception TPD, which is significantly prolonged in VIS compared to NAT for C-NC (p 0.029). Both groups have a significant difference in distance travelled (DT) but the pattern of change is

reversed; for PD-NC DT is reduced in VIS (*p* 0.004) but DT is greater in VIS for C-NC (*p* 0.021). %RT occurs significantly sooner in VIS than NAT for both groups (*p* <0.001). This can be explained by the significant reduction in RT for VIS seen in both groups in the absence of a significant change in MT.

6.3.2.2 Comparing inter-group change between NAT and VIS

By using NAT as a baseline it is also possible to directly compare changes between PD-NC and C-NC during VIS, i.e. compare *inter-group* changes. This can be achieved by dividing the value of a parameter in NAT by the value of the same parameter in VIS to get a ratio value (NAT:VIS) for PD-NC and C-NC. This ratio value can then be compared between the two groups. A ratio value of 1.0 would imply that the parameter value for NAT and VIS was the same, a value of <1 would imply that the value for the parameter is greater in VIS than NAT and a value of >1 would imply that the value for the parameter is greater in NAT than VIS. This is summarised in Table 13 and the ratio values for NAT:VIS are shown in Table 14.

Table 13: The relationship between ratio values and parameter values

Ratio value	Parameter values
1.0	NAT = VIS
<1.0	NAT < VIS
>1.0	NAT > VIS

Table 14: Inter-group comparisons of NAT and VIS

	PD-NC (n = 37)	C-NC (n = 34)	p (95% CI)
PA (SD)	0.99 (0.15)	1.03 (0.12)	0.193 (-0.02 – 0.11)
TPA	1.02 (0.16)	0.97 (0.10)	0.264 **
MA	0.97 * (1.16)	1.02 * (1.14)	0.163 (1.02 – 1.12)
PV	0.99 * (1.10)	1.01 * (1.09)	0.221 (0.98 – 1.07)
TPV	1.02 (0.12)	0.98 (0.09)	0.119 (-0.09 – 0.10)
MV	1.01 (0.11)	1.01 (0.10)	0.944 (-0.05 – 0.05)
PDe	1.00 (0.16)	1.02 (0.14)	0.469 0.05 – 0.10)
TPD	1.00 (0.11)	0.96 (0.10)	0.259 **
TAP	1.04 (0.20)	0.97 (0.16)	0.140 (-0.16 – 0.02)
RT	1.17 (0.19)	1.19 (0.19)	0.610 (-0.07 – 0.11)
MT	1.00 (0.11)	0.99 (0.13)	0.683 (-0.07 – 0.05)
TMTi	1.04 (0.11)	1.04 (0.11)	0.980 (0.06 – 0.05)
DT	1.02 (0.03)	0.98 (0.04)	**<0.001 ** **
%TPA	1.02 (0.10)	0.99 (0.09)	0.091 **
%TPV	1.03 (0.08)	1.01 (0.07)	0.273 (-0.06 – 0.02)
%TPD	1.01 (0.05)	0.98 (0.07)	0.070 (-0.05 – 0.002)
%TAP	1.02 (0.12)	0.99 (0.14)	0.128 **
%RT	1.12 (0.15)	1.15 (0.11)	0.407 (-0.04 – 0.09)

Legend: * denotes geometric mean, ** denotes non-parametric *p* value. Value <1 = NAT < VIS, Value >1 = NAT > VIS.

The only statistically significant ratio change between PD-NC and C-NC when comparing NAT and VIS is DT (p <0.001). With that exception, the results suggest that the degree of change in the parameters of reach and grasp between VIS and NAT is similar for both groups.

6.3.2.3 Summary of results of NAT and VIS

In NAT and VIS there is a trend towards PD-NC having prolonged MT and lower peak reach parameters but there is not a significant difference between the groups. PD-NC have significantly prolonged times to attain peak reach parameters in both conditions. PD-NC and C-NC both have a significantly reduced RT in VIS compared to NAT and the proportional reduction in RT between the groups is not different when ratio differences are compared. Overall, with the exception of DT, both groups show a similar pattern of change between NAT and VIS, suggesting that VIS does not disproportionally affect PD-NC compared to C-NC.

6.3.3 Condition 3 – Maximal speed (MAX)

For this condition the participants were asked to reach and grasp the cylinder as quickly as possible after the auditory tone under full visual guidance. The results are presented in Table 15. In contrast to NAT and VIS, RT is significantly different between the groups in MAX, and is prolonged in PD-NC (p 0.002). MT is non-significantly prolonged in PD-NC (p 0.106), as is also seen in NAT and VIS. There is no significant difference between the groups in either the values of peak and mean reach parameters or the time taken to attain peak reach parameters, although the pattern of the results is that PD-NC have lower peak reach values and take longer to attain them. TAP, as in NAT and VIS, occurs significantly later in PD-NC (p <0.001). %TPD occurs significantly earlier in PD-NC (p 0.044), as does %TAP (p <0.001).

Table 15: Condition 3 - MAX

	PD-NC (n = 37)	C-NC (n = 34)	p (95% CI)
PA, mm/s^2 (SD, range)	2590.7 * (1.22, 1826.2 – 3866.1)	2691.8 * (1.16, 2186.4 – 3568.9)	0.371 (0.95 – 1.13)
TPA, s	0.25 * (1.43, 0.11 – 0.49)	0.22 * (1.26, 0.15 – 0.39)	0.062 (0.76 – 1.07)
MA, mm/s^2	1475.3 (348.7, 1024.8 – 2196.1)	1559.3 (249.5, 1156.1 2045.8)	0.080 **
PV, mm/s	884.4 * (1.15, 632.7 – 1261.4)	905.1 * (1.22, 727.8 – 1152.9)	0.577 (0.94 – 1.11)
TPV, s	0.38 * (1.30, 0.22 – 0.71)	0.34 * (1.22, 0.23 – 0.49)	0.051 (0.81 – 1.00)
MV, mm/s	486.7 * (1.27, 298.9 – 749.9)	509.7 *(1.16, 399.4 – 678.6)	0.332 (0.95 – 1.15)
PDe, mm/s^2	-2343.1 (706.5, -3638.2 – -1082.5)	-2210.7 (514.0, -3479.3 – -1514.0)	0.687 **
TPD, s	0.53 * (1.38, 0.24 – 1.82)	0.47 * (1.22, 0.34 – 0.74)	0.059 (0.78 – 1.01)
TAP, s	0.55 * (1.34, 0.30 – 1.26)	0.40 * (1.25, 0.23 – 0.66)	**<0.001** (0.64 – 0.83)
RT, s	0.41 (0.08, 0.28 – 0.64)	0.36 (0.07, 0.25 – 0.58)	**0.002** (-0.08 - -0.02)
MT, s	0.76 (0.24, 0.46 – 1.71)	0.67 (0.11, 0.49 – 0.96)	0.106 **
TMTi, s	1.18 (0.26, 0.80 – 2.17)	1.04 (0.14, 0.80 – 1.38)	**0.008 ** **
DT, mm	276.6 (26.8, 218.9 – 315.1)	277.9 (34.3, 196.8 – 325.2)	0.434 **
%TPA	34.6 (4.8, 23.3 – 42.0)	33.2 (4.1, 27.9 – 42.0)	0.170 (-3.6 – 0.6)
%TPV	52.0 (5.7, 36.9 – 65.0)	51.5 (5.5, 40.0 – 61.2)	0.665 (-3.2 – 2.1)
%TPD	73.3 (7.2, 52.7 – 82.3)	71.5 (5.6, 61.3 – 82.4)	**0.044 ** **
%TAP	76.8 (8.9, 44.2 – 90.7)	64.3 (12.9, 35.7 – 87.4)	**<0.001 ** **
%RT	36.0 (6.8, 21.1 – 47.1)	35.1 (4.5, 25.5 – 46.2)	0.499 (-3.6 – 1.8)

Legend: * denotes geometric mean, ** denotes non-parametric *p* value.

6.3.3.1 Comparing intra-group change between NAT and MAX

Intra-group changes can be compared between NAT and MAX in the same way as they were compared between NAT and VIS (Table 16). The changes seen are very similar in PD-NC and C-NC. RT is significantly shorter for both groups in MAX (p <0.001). As might be expected, MT is significantly reduced in both groups for MAX (p <0.001). In addition, both groups have significantly reduced values for peak reach parameters and significantly shorter time to attain peak reach parameters in MAX. TAP occurs

significantly sooner in MAX for both groups (p <0.001). %TPA and %TPD are not significantly different between the conditions for either group but both groups have a significant increase in %TPV and %TAP in MAX.

Table 16: Intra-group comparisons of NAT and MAX

	PD-NC NAT	PD-NC MAX	p (95% CI)	C-NC NAT	C-NC MAX	p (95% CI)
PA, mm/s^2 (SD)	1863.9 (540.2)	2643.5 (553.2)	**<0.001 ****	2108.1 (506.9)	2722.4 (420.8)	**<0.001** (-709.4 - -519.3)
TPA, s	0.42 (0.11)	0.27 (0.09)	**<0.001 ****	0.36 (0.05)	0.23 (0.05)	**<0.001** (0.11 - 0.16)
MA, mm/s^2	1005.7 (309.7)	1475.4 (348.7)	**<0.001 ****	1132.9 (276.7)	1559.3 (249.5)	**<0.001** (489.4 - -363.5)
PV, mm/s	700.0 (162.7)	902.3 (184.4)	**<0.001 ****	737.2 (164.9)	913.9 (130.8)	**<0.001** (-202.3 - -151.2)
TPV, s	0.56 (0.12)	0.39 (0.10)	**<0.001 ****	0.48 (0.06)	0.35 (0.07)	**<0.001** (0.10 – 0.16)
MV, mm/s	333.5 (77.3)	500.7 (121.4)	**<0.001**(-195.4 - -138.9)	348.9 (74.5)	515.3 (76.8)	**<0.001** (-186.6 - -146.1)
PDe, mm/s^2	-1839.5 (614.6,)	-2343.1 (706.5)	**<0.001** (304.2 -702.9)	-1951.7 (681.3)	-2210.7 (514.0)	**0.009** (70.0 – 448.0)
TPD, s	0.87 (0.15)	0.56 (0.18)	**<0.001** (0.24 – 0.37)	0.77 (0.11)	0.48 (0.10)	**<0.001** (0.24 – 0.33)
TAP, s	0.86 (0.24)	0.57 (0.18)	**<0.001** (0.21 – 0.37)	0.61 (0.17)	0.41 (0.09)	**<0.001** (0.15 – 0.26)
RT, s	0.54 (0.11)	0.41 (0.08)	**<0.001 ****	0.52 (0.12)	0.36 (0.07)	**<0.001** (0.12 – 0.18)
MT, s	1.19 * (1.26)	0.73 * (1.33)	**<0.001** (1.49 – 1.77)	1.09 * (1.22)	0.66 * (1.17)	**<0.001** (1.54 – 1.74)
TMTi, s	1.77 * (0.37)	1.18 * (0.26)	**<0.001** (0.49 – 0.70)	1.61 * (1.17)	1.03 * (1.14)	**<0.001** (1.49 – 1.65)
DT, mm	272.8 (25.9)	276.6 (26.8)	**0.025** (-7.1 - -0.5)	268.5 $ (33.9)	280.3 (31.6)	**<0.001** (-16.7 - -7.0)
%TPA	34.8 (5.9)	34.6 (4.8)	0.906 (-2.2 – 2.4)	33.0 (4.8)	33.2 (4.1)	0.878 (-2.5 – 2.1)
%TPV	46.5 (6.7)	52.0 (5.7)	**<0.001** (-7.6 - -3.6)	44.4 (6.9)	51.5 (5.5)	**<0.001** (-10.6 - -3.5)
%TPD	72.2 (7.8)	73.3 (7.2)	0.478 (-4.4 – 2.1)	70.4 (6.6)	71.5 (5.6)	0.460 (-4.0 – 1.8)
%TAP	70.0 * (1.28)	76.2 * (1.14)	**0.020** (1.17 – 0.99)	56.0 (1.28)	63.0 (1.24)	**0.004** (0.83 – 0.96)
%RT	31.1 (4.3)	36.0 (6.8)	**<0.001** (-6.9 - -3.0)	32.0 (6.5)	35.1 (4.5)	**<0.001** (-4.7 - -1.5)

Legend: * denotes geometric mean, ** denotes non-parametric p value.

6.3.3.2 Comparing inter-group change between NAT and MAX

The ratio changes between NAT and MAX are presented in Table 17. The only statistically significant difference between the groups is in DT (*p* 0.007).

Table 17: Inter-group comparisons of NAT and MAX

	PD-NC (n = 37)	C-NC (n = 34)	p (95% CI)
PA	0.71 (0.16)	0.77 (0.11)	0.085
(SD)			(-0.01 – 0.12)
TPA	1.73 (0.68)	1.67 (0.43)	0.721 **
MA	0.69 (0.16)	0.72 (0.11)	0.326
			(-0.03 – 0.10)
PV	0.78 (0.12)	0.80 (0.09)	0.435
			(-0.03 – 0.07)
TPV	1.50 (0.45)	1.43 (0.35)	0.827 **
MV	0.68 (0.12)	0.68 (0.10)	0.950
			(-0.05 – 0.05)
PD	0.78 * (1.36)	0.85 * (1.34)	0.214
			(0.95 – 1.35)
TPD	1.60 * (1.34)	1.60 * (1.22)	0.937
			(0.89 – 1.13)
TAP	1.51 * (1.45)	1.47 * (1.31)	0.755
			(0.84 – 1.14)
RT	1.31 * (1.19)	1.41 * (1.19)	0.073
			(0.99 – 1.17)
MT	1.68 (0.44)	1.67 (0.32)	0.696 **
TMTi	1.53 (0.29)	1.58 (0.24)	0.218 **
DT	0.99 (0.04)	0.95 (0.06)	**0.007 ** **
%TPA	1.02 (0.20)	1.01 (0.20)	0.841
			(-0.11 – 0.09)
%TPV	1.03 (0.08)	1.01 (0.07)	0.273
			(-0.06 – 0.02)
%TPD	0.98 * (1.15)	0.98 * (1.13)	0.997
			(0.94 – 1.06)
%TAP	0.93 (0.14)	0.91 (0.19)	0.180 **
%RT	0.87 (1.20)	0.90 (1.15)	0.352
			(0.96 – 1.12)

Legend: * denotes geometric mean, ** denotes non-parametric *p* value. Value <1 = NAT < MAX, Value >1 = NAT > MAX.

6.3.3.3 Summary of results for MAX

As in NAT and VIS, there is a trend towards PD-NC having prolonged MT (with the associated changes to peak reach parameters and time to attain

peak reach parameters) but there is no significant difference between the groups. RT is significantly prolonged in PD-NC for MAX. Both groups are significantly quicker in MAX than NAT and the lack of ratio changes suggests that the changes in parameters are proportionally similar between the groups for this condition. DT is the only ratio difference between the groups but the usefulness of this parameter is questionable (see 6.4.6).

6.3.4 Condition 4 – Memory guided (MEM)

In this condition the participants were asked to close their eyes. They were then given a verbal command to prepare for the task (e.g. *"right hand ready"*). After the auditory tone, participants reached for and grasped the cylinder at a natural speed whilst keeping their eyes closed. The results are displayed in Table 18. There are more significant differences between the groups for this condition than the previous conditions. RT is significantly prolonged in PD-NC (p 0.026). MT is also significantly prolonged in PD-NC (p <0.001). In keeping with the difference in MT between the groups, PD-NC have significantly reduced PA, MA, PDe and MV and significantly prolonged values for TPA, TPV and TPD. %TAP is significantly delayed in PD-NC (p 0.013), as it is in the other conditions. %TPD occurs significantly sooner in PD-NC in MEM (p 0.018), the opposite of what was found in MAX.

Table 18: Condition 4 - MEM

	PD-NC (n = 37)	C-NC (n = 34)	p (95% CI)
PA, mm/s^2 (SD, range)	1613.6 * (1.44, 713.4 – 3866.1)	1946.3 * (1.24, 1188.0 – 3133.8)	**0.010** (1.05 – 1.39)
TPA, s	0.41 (0.09, 0.30 – 0.63)	0.36 (0.06, 0.30 – 0.54)	**0.001 ****
MA, mm/s^2	876.4 * (1.45, 379.9 – 2121.8)	1068.5 * (1.25, 639.1 – 1790.1)	**0.007** (1.06 – 1.41)
PV, mm/s	604.4 * (1.37, 301.9 – 1286.9)	682.3 * (1.23, 419.9 – 1032.8)	0.063 (0.99 – 1.29)
TPV, s	0.61 (0.17, 0.39 – 1.18)	0.49 (0.09, 0.39 – 0.68)	**<0.001 ****
MV, mm/s	306.2 (100.8, 129.2 – 556.3)	346.8 (62.9, 176.7 – 448.2)	**0.044** (0.45 – 80.8)
PDe, mm/s^2	-1499.6 (769.8, -3550.5 - -354.7)	-1694.9 (565.4, -2894.7 - -751.5)	**0.045 ****
TPD, s	0.95 (0.20, 0.64 – 1.46)	0.80 (0.09, 0.69 – 1.05)	**0.001 ****
TAP, s	0.96 (1.80, 0.57 – 2.66)	0.66 (1.35, 0.30 – 1.04)	**<0.001** (0.58 – 0.80)
RT, s	0.51 (0.11, 0.34 – 0.72)	0.46 (0.10, 0.34 – 0.73)	**0.026 ****
MT, s	1.54 (0.45, 0.88 – 3.08)	1.19 (0.25, 0.90 – 1.92)	**<0.001 ****
TMTi, s	2.06 (0.53, 1.28 – 3.80)	1.65 (0.31, 1.29 – 2.63)	**0.001 ****
DT, mm	271.2 (25.1, 219.9 – 310.4)	278.9 (29.6, 218.0 – 315.0)	0.135 **
%TPA	28.3 (7.6, 15.5 – 52.5)	30.7 (5.2, 19.6 – 41.0)	0.131 (-0.7 – 5.5)
%TPV	41.0 (9.1, 25.0 – 64.1)	42.3 (6.9, 24.0 – 55.2)	0.509 (-2.6 – 5.1)
%TPD	63.9 (9.6, 40.5 – 84.0)	69.3 (9.1, 42.9 – 83.3)	**0.018** (1.0 – 9.8)
%TAP	67.9 (10.3, 44.9 – 86.5)	59.8 (13.5, 22.9 – 77.7)	**0.013 ****
%RT	25.7 (4.3, 19.3 – 36.7)	28.1 (4.3, 20.2 – 37.5)	**0.023** (0.3 – 4.4)

Legend: * denotes geometric mean, ** denotes non-parametric *p* value.

6.3.4.1 Comparing intra-group change between NAT and MEM

The intra-group changes are presented in Table 19. Both groups show a statistically significant reduction in RT for MEM compared to NAT (PD-NC *p* 0.042, C-NC *p* 0.008). In contrast, MT is significantly prolonged in MEM for PD-NC (*p* <0.001) but there is no significant difference between NAT and MEM for C-NC (*p* 0.137). Both groups have significantly reduced PDe in MEM but PA (*p* 0.015) and PV (*p* <0.001) are also significantly reduced in MEM for PD-NC but not for C-NC. PD-NC also have significantly prolonged

TPV (*p* 0.004) and TPD (*p* <0.001) in MEM but there is no difference in these parameters between NAT and MEM for C-NC. TAP is significantly prolonged in MEM for both groups. As a percentage of movement time, all peak reach parameters occur significantly sooner in MEM for PD-NC but only %TPA occurs significantly sooner in MEM for C-NC. There is no difference in %TAP between the conditions for either group.

Table 19: Intra-group comparisons of NAT and MEM

	PD-NC NAT	PD-NC MEM	p (95% CI)	C-NC NAT	C-NC MEM	p (95% CI)
PA, mm/s^2 (SD)	1800.3 * (1.30)	1613.6 * (1.44)	**0.015** (1.02 – 1.22)	2108.1 (506.9)	1992.7 (450.5)	0.142 (-40.8 – 271.5)
TPA, s	0.42 (0.11)	0.41 (0.09)	0.734 **	0.36 (0.05)	0.36 (0.06)	0.822 (-0.02 – 0.02)
MA, mm/s^2	1005.7 (309.7)	941.4 (401.4)	**0.002 ** **	1103.1 * (1.26)	1068.5 * (1.25)	0.440 (0.95 – 1.12)
PV, mm/s	700.0 (162.7)	635.9 (222.2)	**<0.001 ** **	737.2 (164.9)	697.0 (147.4)	0.058 (-1.5 – 81.8)
TPV, s	0.56 (0.12)	0.61 (0.17)	**0.004** (0.88 – 0.97)	0.48 (0.06)	0.49 (0.09)	0.356 (-0.04 – 0.02)
MV, mm/s	333.5 (77.3)	306.2 (100.8)	**0.004 ** **	348.9 (74.5)	346.8 (62.9)	0.845 (-19.9 – 24.1)
PDe, mm/s^2	-1839.5 (614.6)	-1499.6 (769.8)	**<0.001 ** **	-1951.7 (681.3)	-1694.9 (565.4)	**0.006** (-433.8 - -79.8)
TPD, s	0.87 (0.15)	0.95 (0.20)	**<0.001** (-0.13 - -0.04)	0.77 (0.11)	0.80 (0.09)	0.120 (-0.08 – 0.01)
TAP, s	0.81 * (1.35)	0.96 * (1.80)	**0.004** (0.75 – 0.94)	0.61 (0.17)	0.68 (0.18)	**0.021** (-0.13 - -0.01)
RT, s	0.54 (0.11)	0.51 (0.11)	**0.042** (0.001 – 0.06)	0.52 (0.12)	0.46 (0.10)	**0.008** (0.02 – 0.10)
MT, s	1.23 (0.30)	1.54 (0.45)	**<0.001 ** **	1.11 (0.22)	1.19 (0.25)	0.137 (-0.18 – 0.03)
TMTi, s	1.77 (0.40)	2.06 (0.53)	**<0.001 ** **	1.61 * (1.17)	1.63 * (1.19)	0.765 (0.92 – 1.06)
DT, mm	272.8 (25.9)	271.2 (25.1)	0.315(0.99 – 1.02)	266.2 * (1.15)	279.2 * (1.11)	**<0.001** (0.93 – 0.98)
%TPA	34.8 (5.9)	28.3 (7.6)	**<0.001** (1.15 – 1.36)	32.6 * (1.16)	30.3 * (1.19)	**0.036**(1.01 – 1.16)
%TPV	46.5 (6.7)	41.0 (9.1)	**<0.001** (3.1 – 7.7)	44.4 (6.9)	42.3 (6.9)	0.089 (-0.3 – 4.4)
%TPD	72.2 (7.8)	63.9 (9.6)	**<0.001** (5.15 – 11.45)	70.4 (6.6)	69.3 (9.1)	0.485 (-2.12 – 4.37)
%TAP	70.7 * (1.28)	67.1 * (1.17)	0.309 (0.95 – 1.17)	57.7 (13.4)	57.9 (11.0)	0.856 (-3.1 – 2.6)
%RT	31.1 (4.3)	25.7 (4.3)	**<0.001** (4.1 – 6.7)	32.0 (6.5)	28.1 (4.3)	**<0.001** (2.1 – 5.8)

Legend: * denotes geometric mean, ** denotes non-parametric *p* value

6.3.4.2 Comparing inter-group change between NAT and MEM

Table 20 displays the ratio changes for NAT and MEM. There are a number of statistically significant differences between PD-NC and C-NC. The ratio difference for MT is statistically significant (*p* 0.003), suggesting that the prolongation of MT seen in MEM compared to NAT is disproportionately greater for PD-NC. The reduction in MV in MEM compared to NAT is also disproportionately greater in PD-NC (*p* 0.022) and there is a similar trend in PA, PV and PDe (*p* value for ratio change all <0.1).

%TPA, %TPV and %TPD all have statistically significant ratio changes, and in each case the values suggest that the reduction in time to attain these parameters in MEM is disproportionately greater in PD-NC than in C-NC.

Table 20: Inter-group comparisons of NAT and MEM

	PD-NC (n = 37)	C-NC (n = 34)	p (95% CI)
PA (SD)	1.15 (0.27)	1.08 (0.26)	0.066 **
TPA	1.00 * (1.26)	1.01 * (1.19)	0.958 (0.91 – 1.10)
MA	1.14 (0.25)	1.06 (0.27)	0.237 (-0.20 – 0.05)
PV	1.13 * (1.19)	1.06 * (1.19)	0.102 (0.86 – 1.01)
TPV	0.93 (0.15)	0.99 (0.16)	0.128 (0.02 – 0.13)
MV	1.12 * (1.21)	1.00 * (1.22)	**0.022** (0.82 – 0.98)
PDe	1.30 * (1.33)	1.15 * (1.36)	0.074 (0.76 – 1.01)
TPD	0.92 (0.12)	0.96 (0.16)	0.202 (-0.02 – 0.11)
TAP	0.88 (0.27)	0.92 (0.21)	0.567 (-0.09 – 0.16)
RT	1.08 (0.19)	1.15 (0.25)	0.198 (-0.04 – 0.17)
MT	0.82 (0.15)	0.96 (0.22)	**0.003** (0.05 – 0.21)
TMTi	0.88 (0.14)	1.01 (0.20)	**0.002** (0.05 – 0.21)
DT	1.01 (0.04)	0.95 (0.07)	**<0.001 ****
%TPA	1.29 (0.36)	1.10 (0.25)	**0.007 ****
%TPV	1.15 * (1.17)	1.05 * (1.19)	**0.029** (0.85 – 0.99)
%TPD	1.15 (0.17)	1.03 (0.17)	**0.001 ****
%TAP	1.09 (0.25)	0.99 (0.23)	0.114 (-0.22 – 0.02)
%RT	1.06 (1.18)	1.12 (1.25)	0.281 (0.96 – 1.16)

Legend: * denotes geometric mean, ** denotes non-parametric *p* value. Value <1 = NAT < MEM, Value >1 = NAT > MEM.

6.3.4.3 Summary of results for MEM

MT is significantly prolonged for PD-NC in this condition and furthermore the prolongation of MT is disproportionate when ratio changes are compared between the groups. This suggests that PD-NC have particular

difficultly reaching in the absence of vision. Put another way, PD-NC are more dependent on visual feedback to guide reaching. The ratio differences in %TPA, %TPV and %TPD suggest that MEM also has a disproportionate effect on the programming of reach in PD-NC.

RT is also significantly prolonged for PD-NC compared to C-NC in this condition but the prolongation compared to NAT is proportional (i.e. the inter-group ratio change is non-significant).

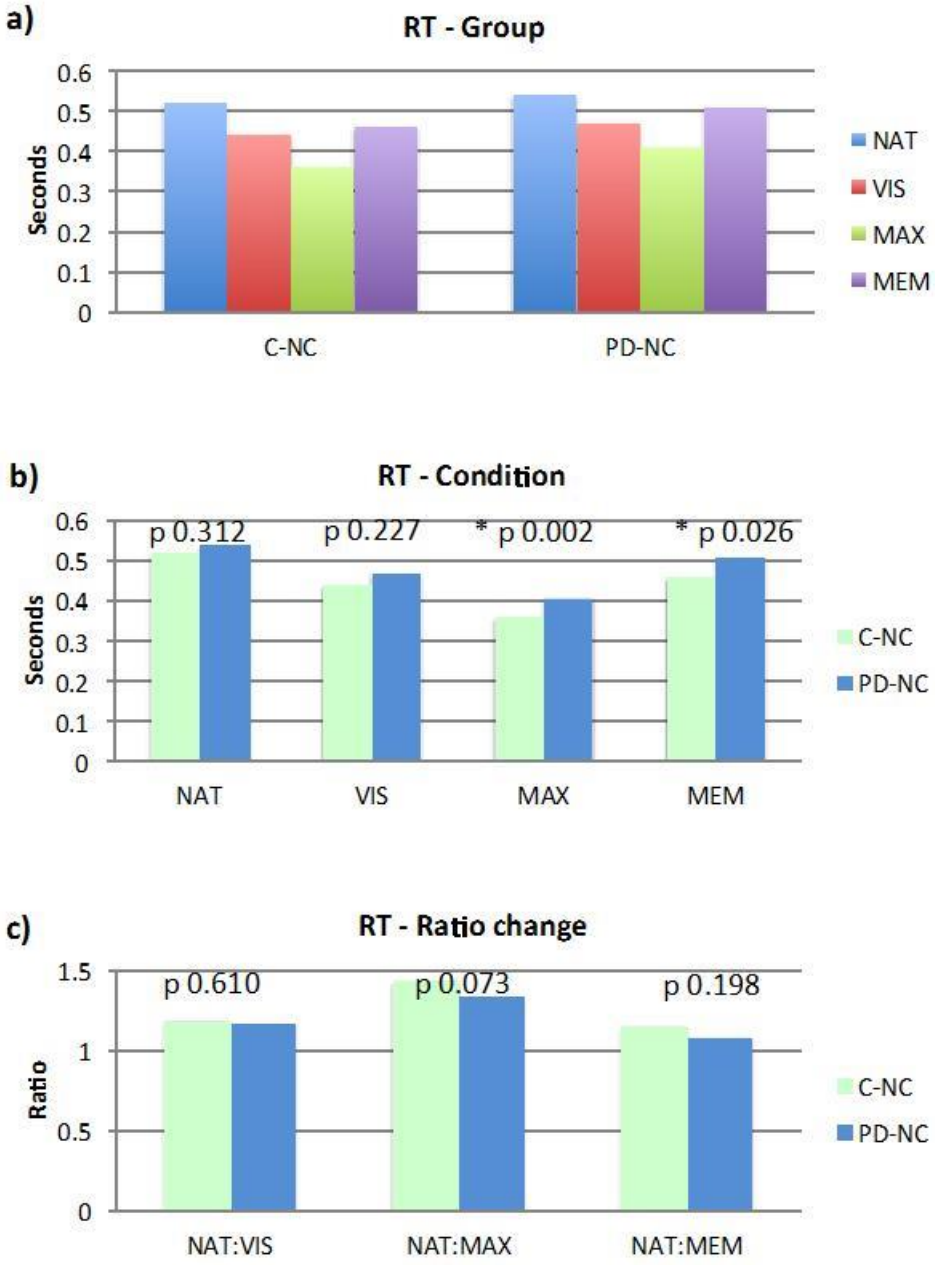
6.4 Comparing the parameters of reach and grasp across the different conditions

Comparing the pattern of change of the reach and grasp parameters across the different conditions is another way of analysing the results, providing further insight into the similarities and differences of reach and grasp in PD-NC and C-NC. This forms the next section of the chapter.

6.4.1 Reaction time

RT for PD-NC and C-NC follows the same pattern across the four conditions (Figure 48a). MAX has the shortest RT, VIS the second shortest, MEM the third and NAT the longest. Although RT is shorter for C-NC in all conditions, the difference is only significant for MAX (p 0.002) and MEM (p 0.026) (Figure 48b). For both groups the intra-group analysis demonstrates that RT for VIS, MAX and MEM is significantly quicker than for NAT. When ratio differences are compared the proportional reduction in RT compared to NAT is always greater in C-NC than PD-NC. This difference never reaches statistical significance, although there is a trend towards a greater reduction in RT for C-NC in MAX (p 0.073) (Figure 48c). Overall, the results suggest that both groups have a very similar RT response across the different reach and grasp conditions and, although C-NC react significantly quicker than PD-NC for MAX and MEM, this reduction is proportional.

Figure 48: Reaction times in PD-NC and C-NC



Legend: a) RT across each task by group – the pattern is the same, b) RT by condition – PD-NC have a significantly prolonged RT in MAX and MEM, c) RT ratio-change – there are no significant differences between the groups.

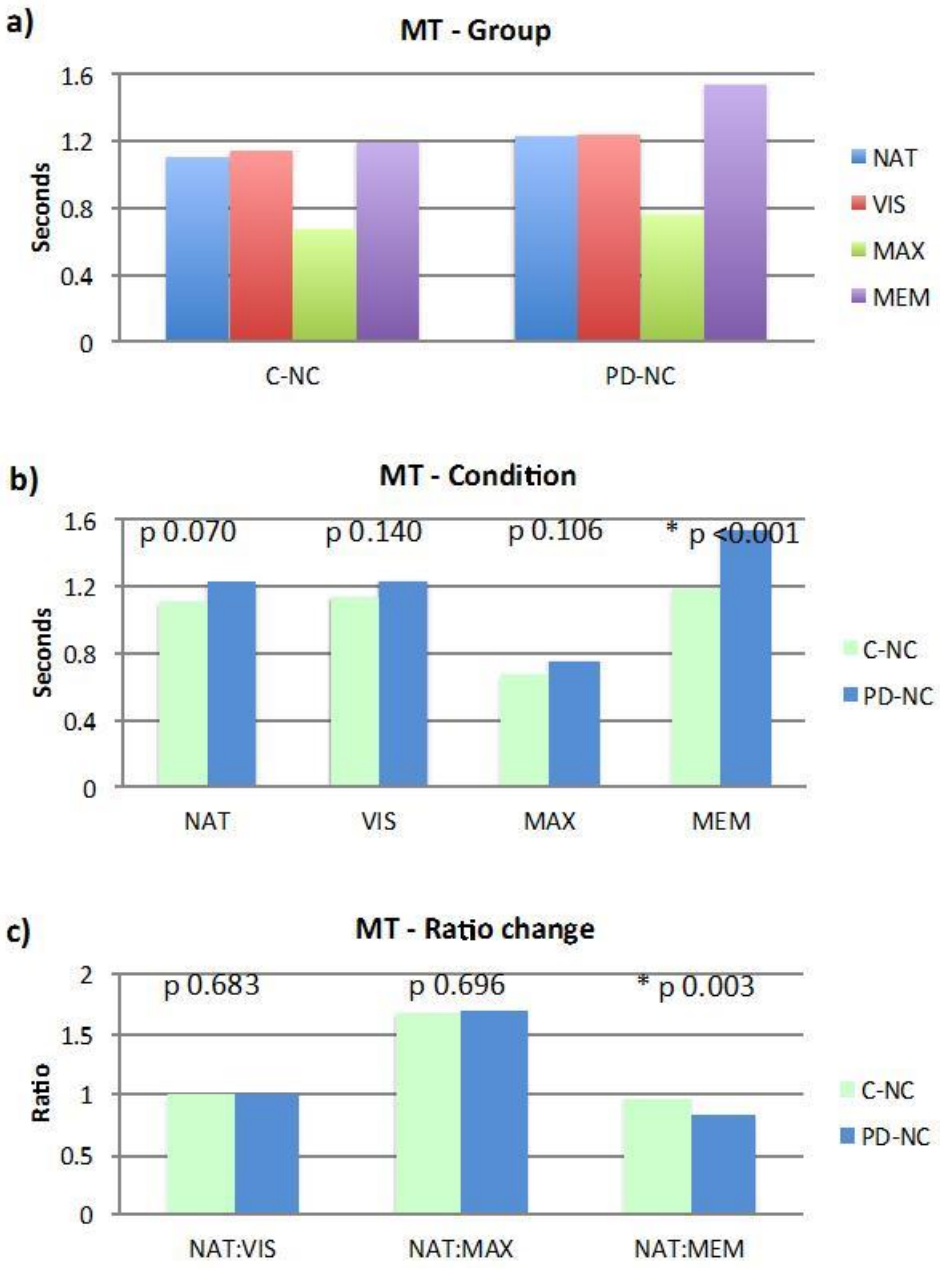
6.4.2 Movement time

The pattern of MT across the conditions is the same for both groups (Figure 49a). The shortest MT is seen in MAX, the second shortest in NAT, then VIS, then MEM. There is no significant difference in MT between the groups for NAT, VIS or MAX but PD-NC have a significantly prolonged MT in

MEM (p <0.001) (Figure 49b). The intra-group analysis reveals that for both groups there is no significant difference between MT for NAT and VIS (PD-NC p 0.549, C-NC p 0.332) and that MT is significantly quicker for MAX than NAT (both groups p <0.001). A difference in the intra-group changes is seen when MEM is compared with NAT; for C-NC MT is not significantly prolonged in MEM (p 0.137) but is significantly prolonged in PD-NC (p <0.001). The inter-group ratio differences are non-significant between the groups for NAT:VIS and NAT:MAX but are highly significant for NAT:MEM (p 0.003) (Figure 49c).

In summary, MT response to NAT, VIS and MAX is similar in both groups, whereas MT in MEM is disproportionately prolonged for PD-NC. This suggests that PD-NC are disproportionally affected when reaching in the absence of visual guidance.

Figure 49: Movement times in PD-NC and C-NC



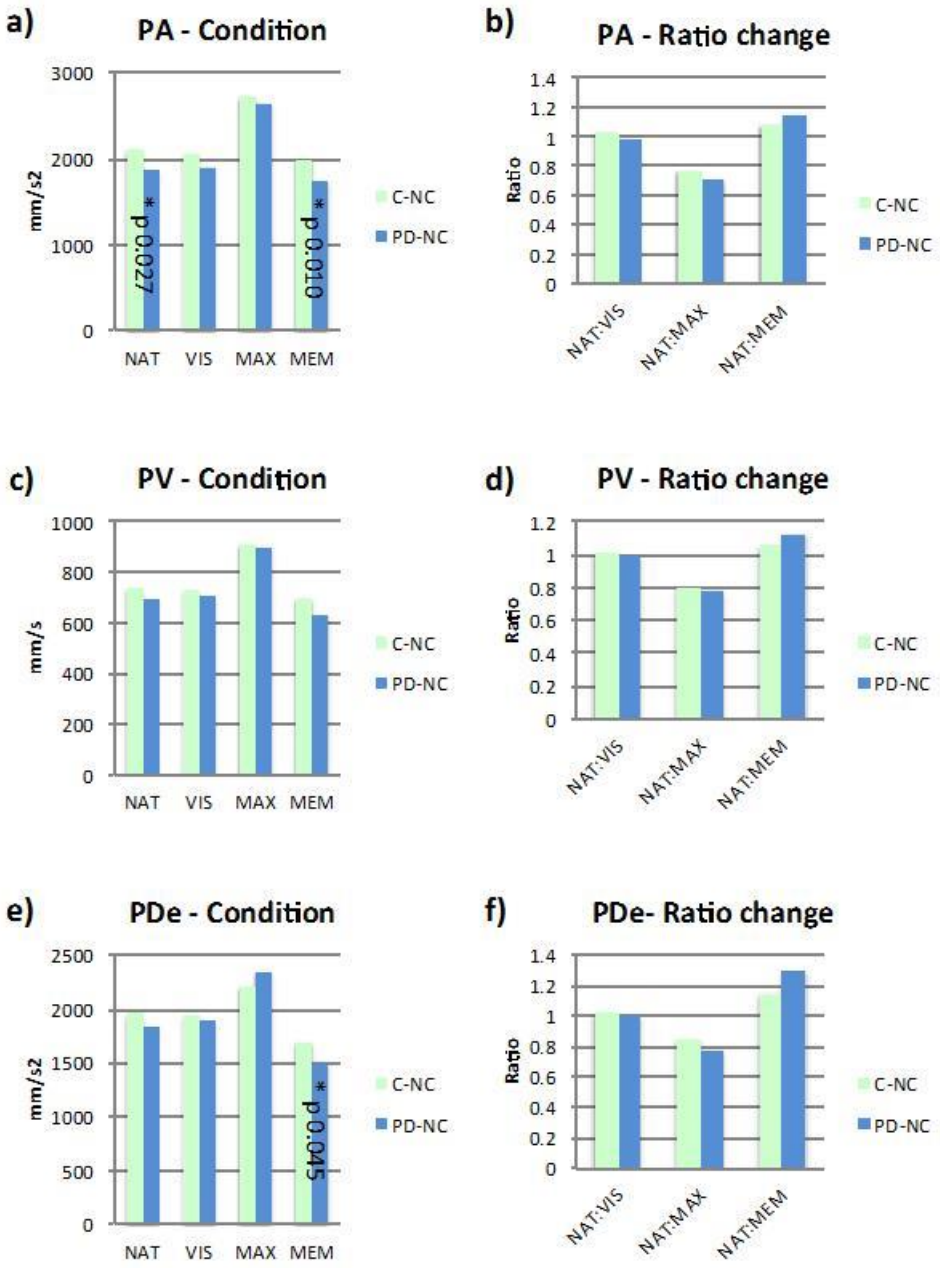
Legend: a) MT across each task by group – the pattern is the same, b) MT by condition – PD-NC have a significantly prolonged MT in MEM, c) MT ratio-change – the prolongation of MT in MEM is significantly greater for PD-NC.

6.4.3 Peak reach parameters

There are only a small number of significant differences between the groups when PA, PV and PDe are compared across the four conditions; PA is significantly reduced in NAT (*p* 0.027) and MEM (*p* 0.010) for PD-NC, and PDe is significantly reduced in MEM for PD-NC (*p* 0.045) (Figures 50a and

50e). The pattern across the conditions is that PD-NC attain lower peak reach parameters than C-NC with the exception of PDe in MAX. Intra-group analysis shows that PA and PV are significantly reduced for PD-NC in MEM compared to NAT but not for C-NC. Although the inter-group ratio differences are not significant in any condition (Figures 50 b, d, f) there is a trend towards a significant difference in NAT:MEM, with a greater proportional reduction in peak reach parameters in PD-NC (PA *p* 0.066, PV *p* 0.102, PDe *p* 0.074). This is in keeping with the results of MT, and is evidence of the correlation between peak reach parameters and MT (see 6.2.3).

Figure 50: Peak reach parameters in PD-NC and C-NC



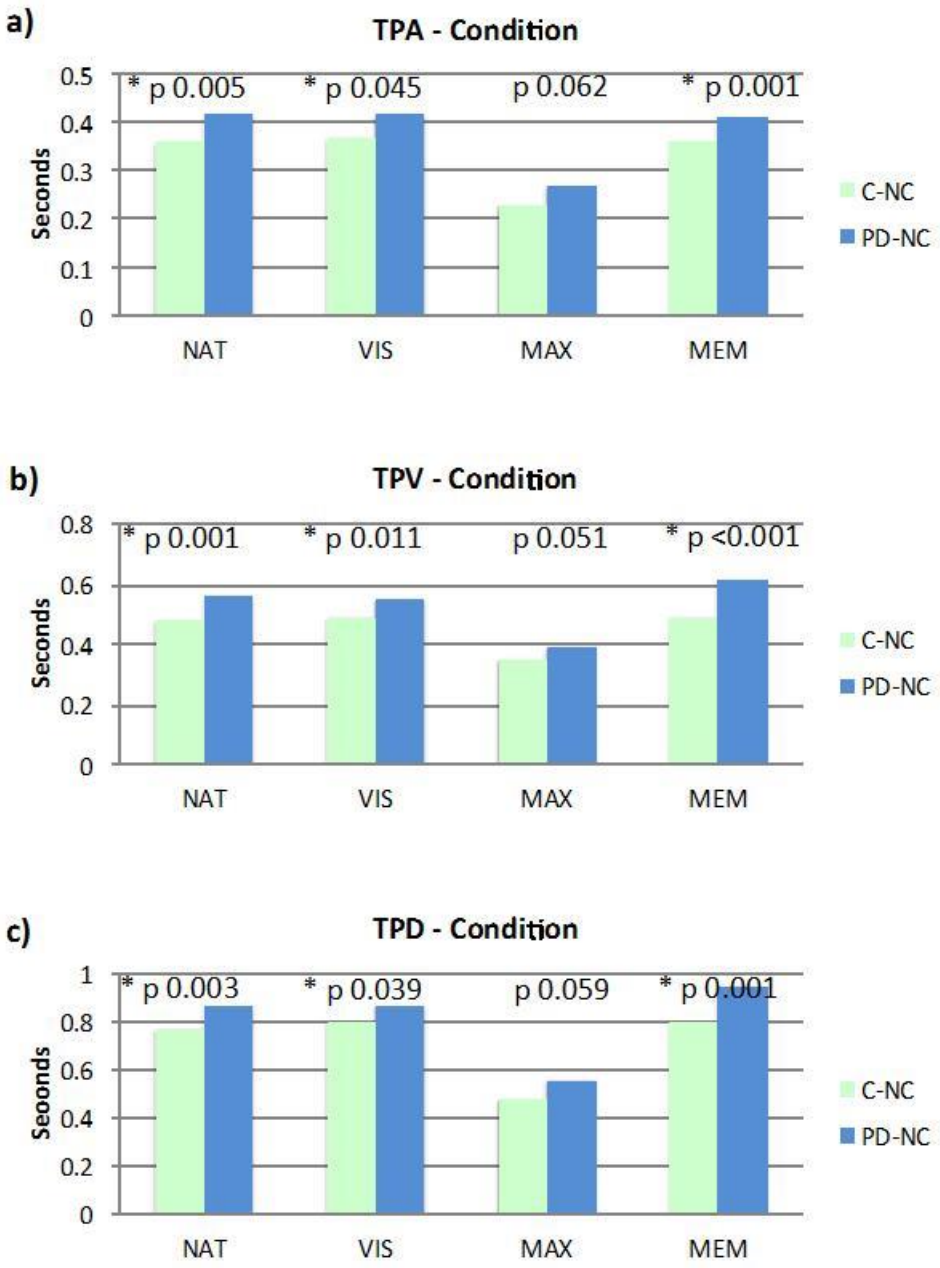
Legend: a, c, e) The values for the peak wrist parameters across the group. Significant differences are shown. b, d, f) The ratio changes. There was a trend towards a significant difference for NAT:MEM for all three peak reach parameters.

6.4.4 Time to peak reach parameters

The times to attain peak reach parameters have a high correlation with each other and a high negative correlation with the peak reach parameter values (see 6.2.3). The pattern of change in TPA, TPV and TPD is therefore similar, and similar to that seen in PA, PV and PDe. However, whereas the

values of the peak parameters are often not significantly different between the groups, this is not the case for time to peak reach parameters, which are significantly prolonged for PD-NC in NAT, VIS and MEM. The prolongation of TPA, TPV and TPD is not quite statistically significant for MAX (Figure 51). There are no significant differences in the inter-group ratio changes for any condition, suggesting that the variations in time to peak reach parameters are proportional between the groups.

Figure 51: Time to attain peak reach parameters in PD-NC and C-NC



Legend: TPA, TPV and TPD across the different conditions. PD-NC take longer to attain peak parameters, significantly so in NAT, VIS and MEM.

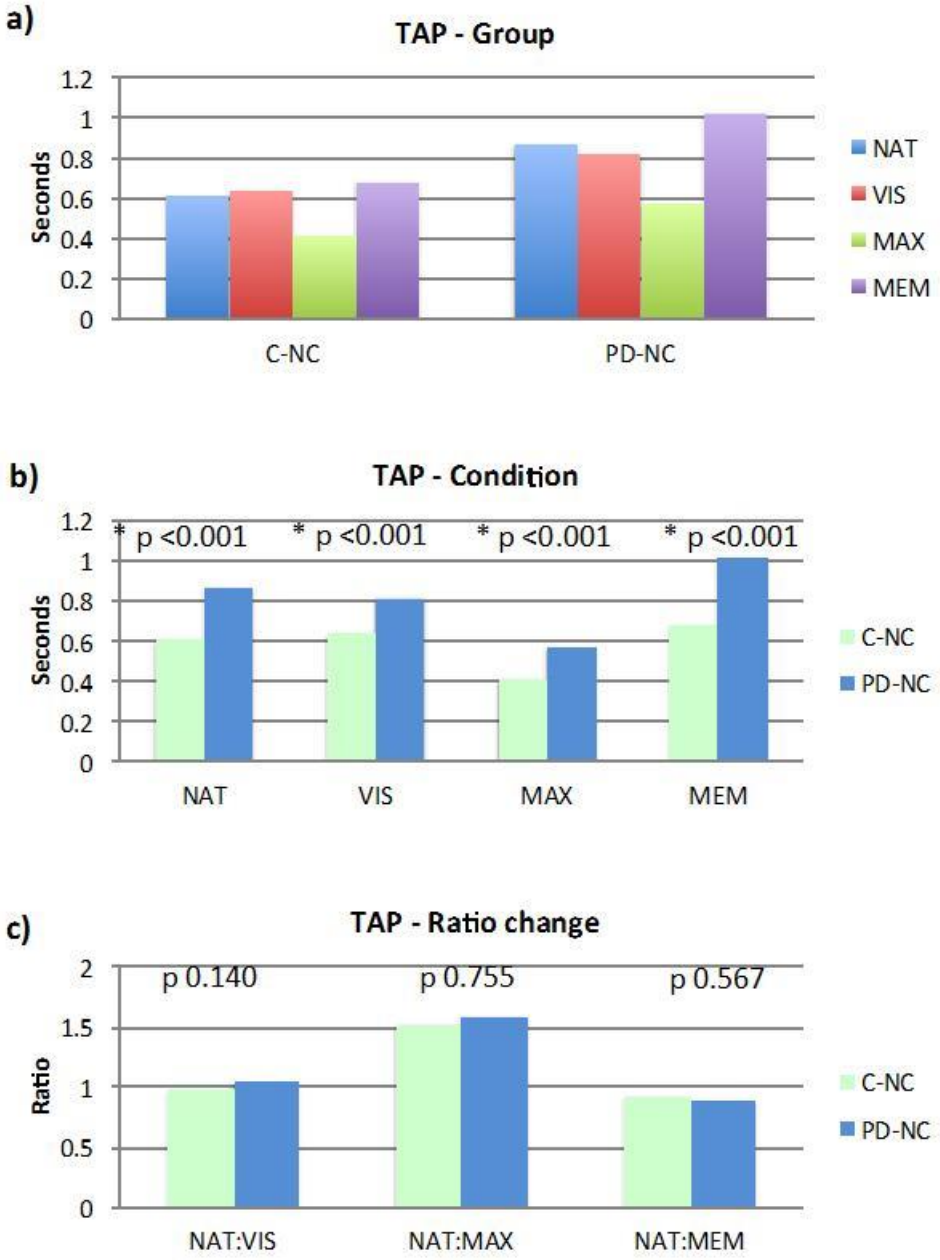
6.4.5 Time to peak aperture

The pattern of TAP is different between the groups; TAP occurs sooner in NAT than VIS for C-NC, but the reverse is true for PD-NC (Figure 52a). TAP is significantly prolonged in PD-NC in all four conditions (Figure 52b). Intra-group changes are similar for both groups; non-significant between VIS and NAT (PD-NC *p* 0.447, C-NC *p* 0.140), significantly reduced between MAX

and NAT (p <0.001) and significantly prolonged between MEM and NAT (PD-NC p 0.004, C-NC p 0.021). There are no significant differences in the inter-group ratio changes, suggesting that the similar pattern of change seen between the groups is proportional when they are compared.

However, the validity of the TAP data from this study is compromised by a problem with the data glove that was not identified during recruitment (see 6.1.2.5). This means that the degree of flexion seen in the index finger of both hands, particularly flexion at the PIP joint, is likely to have been underestimated in an unknown number of cases.

Figure 52: Time to peak aperture in PD-NC and C-NC



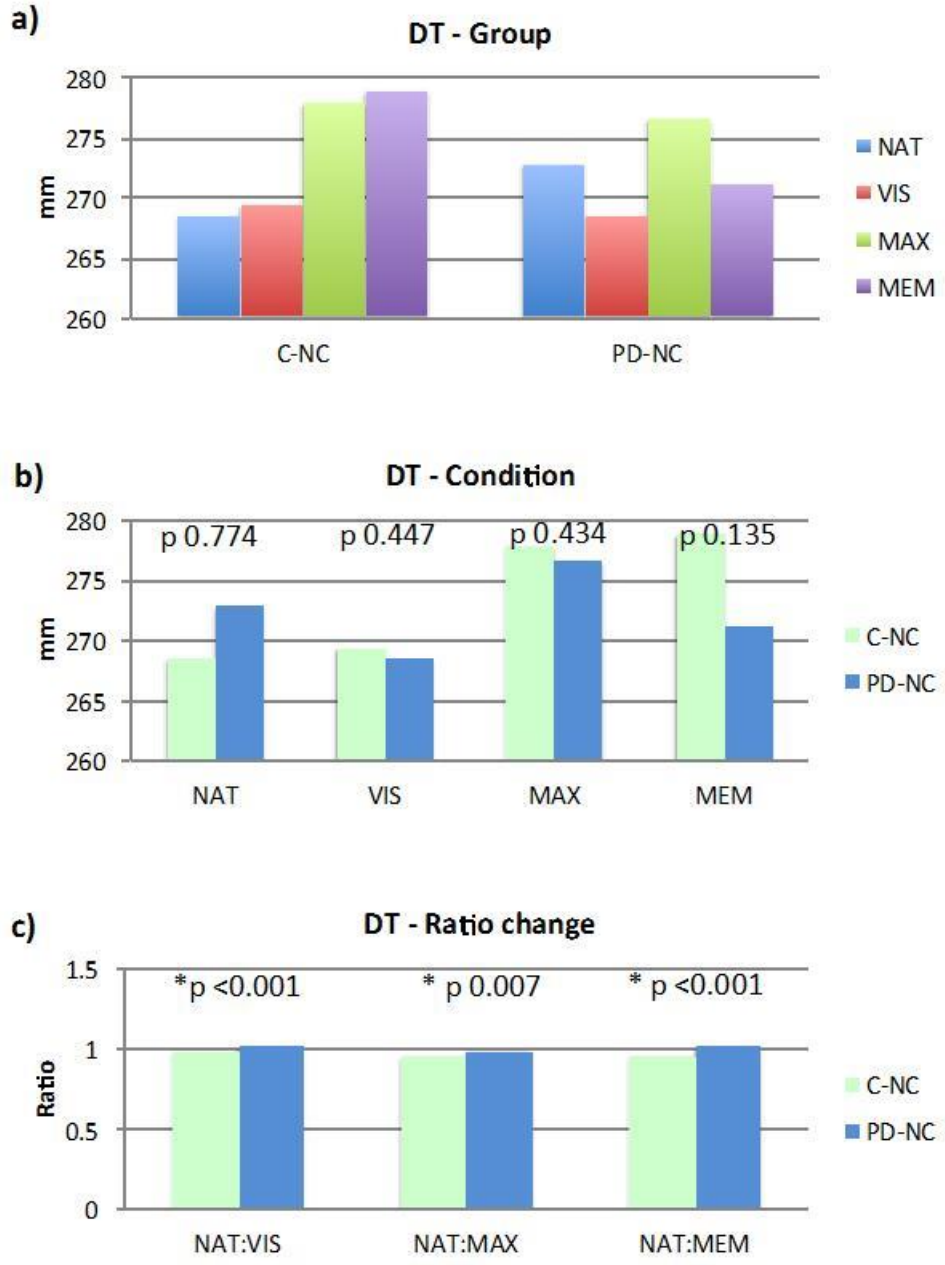
Legend: a) TAP across each task by group, b) TAP by condition – PD-NC have a significantly prolonged TAP in all conditions, c) TAP ratio-change – there are no significant differences between the groups.

6.4.6 Distance travelled

As explained in Chapter 5.5.2, DT is a measure of the Euclidean distance between the EM wrist sensor and the magnetic transmitter at reach onset and reach completion. It does not take into account the trajectory of the arm. There is no significant difference in DT across the four conditions

between the groups (Figure 53b). However, the pattern of DT is different (Figure 53a). The difference in the pattern of change leads to statistically significant ratio changes between the groups (Figure 53c). It is difficult to make conclusions about the importance of the differences in DT between the groups because of the way that it has been calculated.

Figure 53: Distance travelled in PD-NC and C-NC



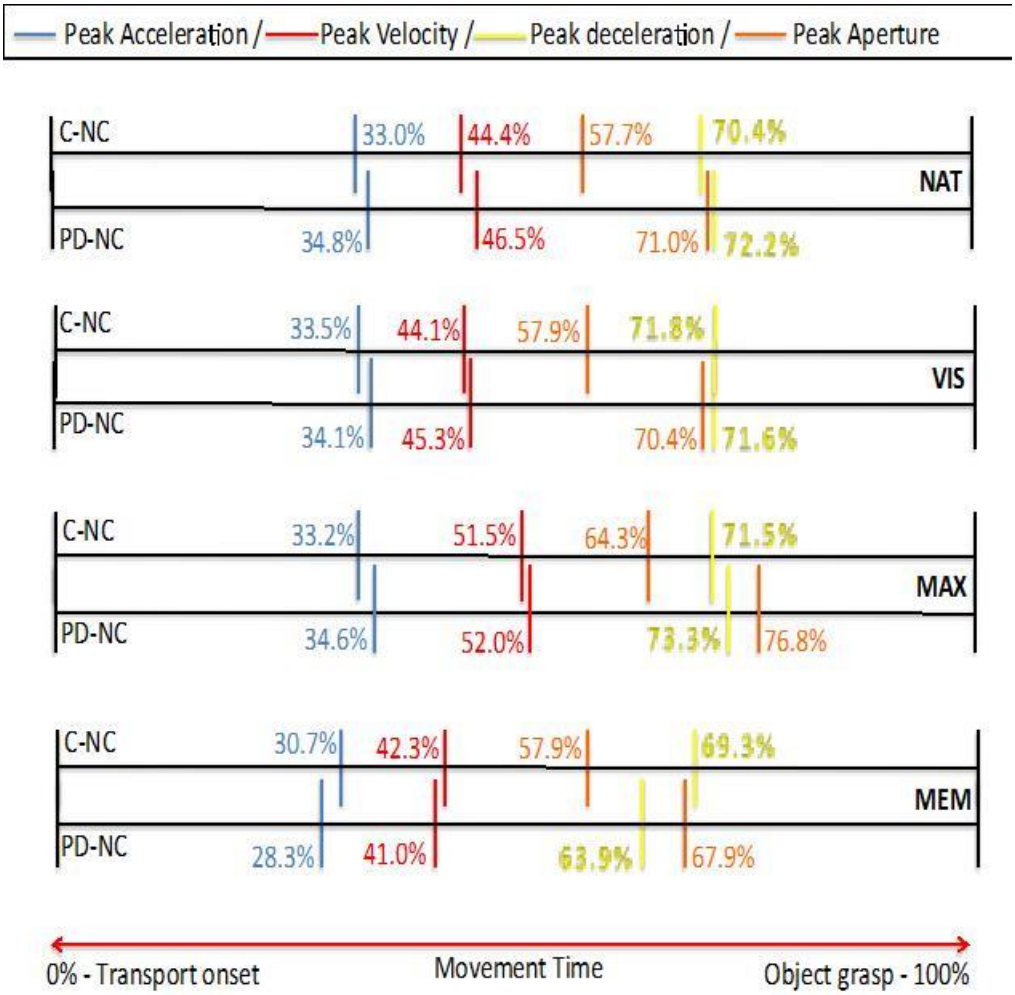
Legend: a) DT across each condition follows a different pattern in the two groups b) there is no statistical difference in DT when the conditions are compared c) the ratio changes are statistically significant.

6.4.7 Time to peak reach and grasp parameters as a percentage of movement time

There are no significant differences in %TPA, %TPV and %TPD between the groups in NAT and VIS. In MAX and MEM, %TPD is statistically different, occurring later for PD-NC in MAX (*p* 0.044) and earlier for PD-NC in MEM (*p*

0.018). In all conditions %TAP occurs significantly later for PD-NC than C-NC (Figure 54). The inter-group ratio changes are not significant for NAT:VIS or NAT:MAX, but for NAT:MEM %TPA (*p* 0.007), %TPV (*p* 0.029) and %TPD (*p* <0.001) are all significantly different. This suggests that the reduction in time to attain reach parameters as a percentage of movement time is disproportionally greater in MEM for PD-NC than C-NC.

Figure 54: Time to peak reach parameters and time to peak aperture as a percentage of movement time in PD-NC and C-NC



Legend: Peak aperture (orange) occurs significantly earlier as a percentage of MT in C-NC than PD-NC in all conditions. In MEM, the reduction in time to %TPA, %TPV, %TPD and %TAP is significantly greater in PD-NC than C-NC when inter-group ratios are compared.

In summary, as a percentage of MT the results suggest that; a) throughout all conditions PD-NC have a prolonged %TAP and the pattern of change

to %TAP is not different when ratio changes are considered, b) peak reach parameters are disproportionately affected in MEM, occurring earlier as a percentage of MT, indicating a difference to the programming of reach in the absence of visual guidance.

6.5 Summary of reach and grasp results for PD-NC and HC

The results obtained from analysing the parameters of reach and grasp PD-NC and C-NC are summarised below [21]:

- Reach and grasp at a natural speed in full vision (NAT) demonstrates that PD-NC have non-significantly prolonged MT and RT.
- Reach and grasp towards an illuminated target at natural speed in a darkened room (VIS) produces significantly shorter RT for both groups compared to NAT, but MT is not significantly different for either group compared to NAT.
- There is no significant difference in MT and RT between PD-NC and C-NC in VIS, and the lack of meaningful inter-group ratio suggests PD-NC and C-NC change parameters of reach and grasp similarly in VIS compared to NAT.
- When reaching and grasping at maximal speed in full vision (MAX) PD-NC have a significantly prolonged RT but a non-significantly prolonged MT compared to C-NC. Both groups were significantly quicker than in NAT and there was no meaningful ratio change difference between the groups, suggesting that PD-NC and C-NC were equally able to change parameters of reach and grasp compared to NAT.

[21] A reminder of the full terms for the calculated reach and grasp parameters is provided:

MT, movement time; RT, reaction time; DT, distance travelled; %TPA, time to peak acceleration as a % of movement time, %TPV, time to peak velocity as a % of movement time; %TPD, time to peak deceleration as a % of movement time; TAP, time to peak aperture; %TAP, time to peak aperture as a % of movement time.

- PD-NC have significantly prolonged RT and MT compared to C-NC when reaching and grasping with eyes closed (MEM).
- MT for C-NC was not significantly prolonged in MEM compared to NAT, but in contrast was significantly prolonged for PD-NC. This caused a significant ratio difference for MT between the groups and suggests that PD-NC are disproportionately affected when reaching in the absence of visual feedback.
- Despite the significant difference in RT between PD-NC and C-NC in all conditions and MT in MEM, the *pattern* of RT and MT is the same across the conditions in both groups.
- DT does not provide information on hand trajectory and is therefore of limited value.
- %TPA, %TPV and %TPD are all significantly different between the groups when ratio changes are compared between NAT and MEM. This implies that the adaptations to the programming of reach are different between the groups and supports the MT ratio difference seen in MEM. This is therefore further evidence that reaching in PD-NC is disproportionately affected in MEM.
- TAP and %TAP occur significantly later in PD-NC in all conditions. However, there were technical problems with the data glove that may have compromised results.

6.6 Discussion

This chapter has focused on the analysis of reach and grasp in PD-NC and C-NC under four different conditions. The changes in individual parameters of reach and grasp between the different conditions have been compared with condition 1, NAT, which has acted as a 'baseline' to allow intra- and inter-group analysis. Different aspects of the study will now be discussed in greater detail.

6.6.1 Comparing reaching and grasping at natural speed with previous results in the literature

Reaching and grasping at natural speed (NAT) is particularly important because of the way it has been used to allow intra- and inter-group comparisons of VIS, MAX and MEM to be made. Any abnormalities with the values of parameters calculated for NAT would affect subsequent analysis. A study by Casteillo et al. of eight PwPD and eight HC as they reached and grasped objects of differing sizes at three different distances serves as a useful comparator of our results for several reasons: the PwPD were tested whilst *on*; one of the distances tested (27cm) is similar to the distance of the hand from the cylinder in this study (32cm); the same type of grasp – WHP – was used; the participants were asked to reach at a natural speed (Castiello et al., 1993b).

The pattern of results and the values of key parameters are similar between that study and our study. For example, MT, TPA, TPV and TPD were prolonged and PA, PV and PDe were reduced in the PD group of both studies and MT values for the PD groups (1.21s versus 1.23s) and HC (1.02s versus 1.11s) are comparable (Castiello et al., 1993b).

Comparing the values for TAP is more complex because Castiello et al. (Castiello et al., 1993b, Castiello and Bennett, 1994) and others (Caselli et al., 1999) used infrared sensors on the index finger and thumb to provide a value of TAP between the index finger and thumb whereas our study calculated average flexion of the whole hand (with the limitations associated with the damage to the data gloves – see 6.1.2.5). However, TAP values for PD groups (0.91s compared to 0.87s) and HC are similar (0.63s compared to 0.61s) in our study and that of Castiello et al. (Castiello et al., 1993b), which could suggest that the novel approach used to calculate TAP in our study is valid. However, the damage to the data gloves means that the results cannot be considered to be reliable.

Various studies of grasp have utilised information from flexion sensors at the MCP and PIP joints using similar data gloves to our study to produce estimates of peak index finger to thumb aperture (and hence time to that value). These studies have also used data from individual finger sensors to allow comparison of hand preshaping between HC and PD to be performed (Santello and Soechting, 1998, Santello et al., 2002, Schettino et al., 2004, Schettino et al., 2003, Schettino et al., 2006). Unfortunately this has not been possible in our analysis.

Overall, the *pattern* of results and the values of reach parameters obtained in NAT in our study are comparable with existing literature. For example, PD-NC have prolonged MT, take longer to attain peak reach parameters and TAP and have reduced values of peak reach parameters compared to C-NC when reaching and grasping under full visual guidance, although these differences are often not statistically significant. The delay in manipulation time that has been seen in a number of studies of PwPD and has been considered as evidence to suggest a decoupling of reach and grasp (Scarpa and Castiello, 1994, Bennett et al., 1995, Castiello et al., 1993b) cannot be commented on in our study because of the limitations of data analysis from the data gloves and the damage to them.

6.6.2 Reaching and grasping at maximum speed

The results from our study suggest that PD-NC are as able as C-NC to make modifications to reach and grasp parameters in order to reach and grasp at a maximal speed (Condition 3, MAX). This is evidenced by the lack of a significant difference between the groups when inter-group ratio differences are compared. As with NAT, PD-NC had non-significantly prolonged MT (and associated changes to peak and time to peak reach parameters). Although PD-NC were able to modify their reaching speed, it still remained (non-significantly) slower than C-NC. However, in contrast to MT, RT was significantly prolonged for PD-NC in MAX. RT will be discussed in more detail in Chapter 7.

How do the results of MAX compare to previous studies of reach and grasp? In one study six PwPD in the *on* state and six HC were asked to reach and grasp a stationary ball and then a moving ball at maximal speed (Majsak et al., 1998). The results showed that when reaching and grasping the stationary ball PwPD had prolonged MT and TPV and a reduced PV. The paper does not state whether these differences were statistically significant but the pattern of results is the same as our study. Otherwise there is a paucity of studies in which PwPD have been tested in the *on* state only and asked to reach and grasp as quickly as possible. As our study did not compare PD-NC in the *on* and *off* state it is not possible to comment on the role that dopaminergic medication may have had on the parameters of reach and grasp in MAX or any of the other conditions. However, as summarised in Chapter 4.2.7, there is evidence to suggest that parameters of reach, particularly acceleration, velocity and deceleration, are increased by levodopa when reaching and grasping at natural speed (Castiello et al., 2000) and as quickly as possible (Negrotti et al., 2005), whereas parameters of grasp appear to be less affected.

The study of Majsak et al. found that when a moving visual stimulus (the moving ball) was used PwPD, but not HC, were able to reach faster than their self-determined maximal speed (Majsak et al., 1998). The authors suggested several different reasons for this observation: PwPD were able to reach more quickly during the moving-ball stimulus because the condition warranted more attentional resource; PwPD may have reduced self-initiated maximum speeds as part of a behavioural strategy to increase the chances of successful grasping; PwPD were able to increase reaching beyond self-initiated maximum speed because the visual stimulus acted as an external cue to overcome the proposed deficit in internal motor drive (see 6.6.5 and Chapter 7.7.8.2) (Majsak et al., 1998). Their results therefore suggest the possibility that PD-NC in our study may have the conscious or subconscious ability to further increase reaching speed in response to external cueing. VIS was performed in reduced ambient light

but not complete darkness. It is conceivable that if asked to reach and grasp as quickly as possible in VIS, the illumination of the cylinder may have acted as a visual cue and produced faster reaching speeds for PD-NC than in MAX. However, this remains speculation only.

6.6.3 The role of vision on reach and grasp

Our results demonstrate that in both PD-NC and C-NC, VIS did not significantly change the parameters of reach and grasp when compared to NAT. In other words, the illumination of the target in a darkened room did not alter reach and grasp when compared to full visual guidance. In MEM, MT was prolonged in both groups compared to NAT but this was disproportionate for PD-NC, as evidenced by the inter-ratio changes. A number of parameters correlated with MT were also significantly different between PD-NC and C-NC in MEM, including PA, PDe, TPA, TPV and TPD. The results from our study therefore suggest that reaching in the absence of visual feedback leads to a prolongation of MT that is disproportionately worse in PD-NC.

A number of other studies of pointing, reaching and grasping have been conducted under differing degrees of visual feedback and can be compared with our results. Santello et al. analysed reach and grasp of 20 everyday objects in four HC under three different conditions; memory guided, a virtual image – created by using a concave mirror to project a 3D image of the object – and the real object (Santello et al., 2002). The principal focus of their paper was on grasp, using flexion at the MCP and PIP joints as well as abduction and adduction to detect changes in hand shape in the different conditions. Limitations of the data glove in our study mean we cannot accurately compare grasp but it is interesting to equate reach parameters. It was shown that when reaching and grasping the remembered object or the virtual object HC had increased PV and reduced MT (Santello et al., 2002). This is the opposite of what was found in our study for both C-NC and PD-NC. However, memory guided reach and grasp

in their study was defined as reaching and grasping with eyes open towards where the object in question had been placed before it was removed. Therefore HC had full vision of their arm and hand during the reach and grasp procedure, whereas in our experiment MEM was tested by asking patients to reach and grasp with eyes closed, i.e. participants had no vision of the object or their upper limb.

In another study nine HC were asked to grasp three differently shaped objects under normal visual guidance, or when only the object to be grasped was illuminated, or in total darkness (Schettino et al., 2003). The first two visual conditions are therefore similar to those in our study and reaching and grasping in total darkness is comparable to reaching and grasping with eyes closed (i.e. MEM). It was demonstrated that MT increased as visual feedback decreased; i.e. MT was shortest for full vision and longest in total darkness (Schettino et al., 2003). The results of C-NC (and PD-NC) follow a similar pattern in our study. In the study of Schettino et al. (Schettino et al., 2003) and in other studies (Jackson et al., 1995), %TAP also followed the level of visual feedback, occurring soonest in darkness and latest in full vision. The magnitude of peak aperture, not measured in our study, is also greater in reduced visual conditions (Fukui and Inui, 2013). Therefore the hand opens earlier and wider so as to provide a margin of error to counter reduced levels of visual feedback (Fukui and Inui, 2013, Schettino et al., 2003). In our results %TAP for HC remains remarkably similar for NAT, VIS and MEM (~57% of MT) in contrast to the studies considered above. However, this discrepancy has to be considered in the context of the damage to the data gloves and the way TAP has been defined in our study.

Previous research has suggested that PwPD are more impaired than HC when *pointing* at a natural speed to a remembered target in the dark and when the target is illuminated in an otherwise darkened room (Adamovich et al., 2001). In both situations PwPD made more errors of distance and

direction than HC. Conversely, when the pointing finger was illuminated and the participants were asked to point at a remembered target in darkness, the number of distance and directional errors was not significantly different between the groups. Furthermore, whereas the reduction in the number of errors was greater for PwPD than HC when the pointing finger was illuminated compared to total darkness (the condition in which both groups made the most errors), PwPD did not reduce errors as much as HC when the target only was illuminated compared to total darkness (Adamovich et al., 2001), potentially suggesting a problem with proprioception or integration of proprioceptive information. It is of interest that the MT, acceleration and velocity of the finger during each of the *pointing* conditions was not different between PwPD and HC, in contrast to *reach and grasp* studies, ours included (Schettino et al., 2006, Schettino et al., 2003, Santello et al., 2002). However, reach and grasp requires integration of two distinct motor programmes according to the visuomotor channel hypothesis (Jeannerod et al., 1995, Jeannerod, 1999), whereas pointing does not.

The same research group who studied HC as they reached and grasped under normal visual guidance, or when only the object to be grasped was illuminated, or in total darkness also investigated PwPD (Schettino et al., 2006). Nine PD subjects in the *off* state and nine HC were compared and significantly more grasping errors were made by the PwPD with only the target illuminated in otherwise total darkness (Figure 32). MT and PV were significantly slower in the PD group than HC in all conditions and post-hoc analysis showed that MT increased as visual feedback decreased (Schettino et al., 2006).

How do the results from our study compare to existing research? Unlike previous studies of pointing or reach and grasp, target illumination (VIS) did not cause a marked change in kinematic parameters compared to full vision (NAT) in our study. The most likely reason for this is the failure to

make the environment completely dark for VIS. Although attempts were made to minimise ambient light levels in our study, the degree of background light in VIS was variable and total darkness was never achieved. The lack of a dedicated research room with facilities to prevent external light, for example a black-out blind, meant that the reduction in ambient light was dependent on the quality of curtains/blinds in the hospital room in which the assessment took place, as well as the time of year and time of day. Even when VIS was carried out in as dark a room as possible the arm was still visible and therefore reliance on proprioception was reduced compared to other studies of reaching and grasping at a natural speed in which total darkness was achieved (Schettino et al., 2004, Schettino et al., 2006, Santello et al., 2002).

For MEM eyes were kept closed so although the research room was not completely dark a direct comparison with existing literature is valid. As with previous reach and grasp studies, MT was prolonged in the absence of visual feedback for both C-NC and PD-NC in our study, but compared to NAT the prolongation of MT was only significant in PD-NC. In addition, our study tested PD-NC whilst *on* whereas the PD group were tested *off* in the comparable study of Schettino et al. (Schettino et al., 2006). Our study therefore adds to the existing literature by demonstrating that the prolongation of MT in the absence of visual guidance remains present in PwPD in the *on* state and, importantly, the prolongation of MT in PwPD is disproportionate compared to HC. Schettino et al. did not specifically comment on this but MT was significantly longer for PwPD in all three conditions and the relative difference in MT looks uniform from inspection of graphs in their paper (Schettino et al., 2006).

Why then is reach, as measured via MT, disproportionately affected by MEM for PD-NC in our study? There are three potential explanations. The first is that PwPD are more dependent on visual feedback to guide reach and grasp than HC because they are less able to integrate visual

information (or information from visual memory when eyes are closed/in complete darkness) with proprioceptive signals from the arm (Schettino et al., 2006). This hypothesis has been proposed previously and is supported by the apparent difficulties of PwPD compared to HC when pointing (Adamovich et al., 2001) or reaching and grasping (Schettino et al., 2006) towards an illuminated target in *total darkness,* in contrast to reaching towards a remembered target with visual illumination of the finger or hand.

A second possibly is that in our study visual memory plays a larger role than in the study by Schettino et al. (Schettino et al., 2006), in which the PD subjects were screened for cognitive impairment using the MMSE and required a score of >25 for inclusion. They are therefore likely to have comparable cognition to PD-NC in our study. However, the interval between eye closure and reach commencement was less than one second in the study of Schettino et al. whereas it was between three and seven seconds in our study. A prolonged interval between eye closure and reach initiation could place increased demand on visual memory and this may explain the disproportionate prolongation of MT in PD-NC in our study. B-R scores – a test of visual memory – were not significantly different between PD-NC and C-NC in our study although PD-NC performed worse and there was a trend towards significance (p 0.098). Intuitively one may expect that if visual memory is impaired the reaching arm would travel further overall in MEM as it 'searches' for the cylinder. This may well have been the case but because of the way DT is calculated in our study it is impossible to know.

The third possibility is that the abnormalities of reach detected in MEM for PD-NC in our study are caused by a combination of factors, including both increased dependence on visual feedback and impaired visual memory. Visual memory and the role of cognition in reach and grasp will be discussed in Chapter 7. The potential role of impaired proprioception and

sensorimotor integration in causing an increased reliance on visual feedback in PwPD will now be reviewed.

6.6.4 Do people with Parkinson's disease have impaired proprioception and sensorimotor integration?

A number of studies have detected impaired proprioception in PwPD. For example, elbow position sense in nine PwPD was found to be abnormal when compared to age matched HC and participants with a degenerative cerebellar disorder (Maschke et al., 2003). Specifically, it was demonstrated that only 55% of PwPD could detect a one-degree displacement of the forearm whereas more than three quarters of HC and those with cerebellar degeneration could do so. To attain a 75% detection rate of forearm movement the required displacement in PwPD was 2.10 degrees, compared with 1.03 degrees for HC and 1.15 degrees for the cerebellar disorder group (Maschke et al., 2003). As well as joint position sense, passive motion detection has also been demonstrated to be abnormal in PD. Across a range of motion velocities eight PD subjects took on average 92-166% longer to detect movement of the forearm compared to eight age-matched HC (Konczak et al., 2007). Five of the PwPD were tested whilst *on* but no significant correlation with LEDD was detected. In summary, there is evidence to suggest that joint position sense and detection of movement velocity in the limbs is impaired in PwPD.

Sensorimotor integration is the assimilation of afferent sensory information with motor commands, in order to guide or select appropriate movements (Conte et al., 2013). It is a key role of the basal ganglia as evidenced by animal studies confirming that neurons within the caudate nucleus and substantia nigra are able to integrate auditory, visual and somatosensory stimuli (Nagy et al., 2006). Haptics – the capacity to extract object information by touch – requires the integration of proprioception and pressure cues with efferent motor commands to produce exploratory motor movements (Conte et al., 2013). In other words, haptic function

requires sensorimotor integration. In one study 12 blindfolded PwPD and HC were required to detect if the manipulandum they grasped with their hand travelled in a fixed curve or variable curve (Konczak et al., 2012). It was demonstrated that the PD group were less able to perceive curvature and less able to discriminate between fixed and variable curves, i.e. they had reduced sensitivity of detection and reduced ability to discriminate between detectable haptic stimuli. Furthermore, this abnormality was present during both active (when the manipulandum was moved by the participant) and passive (when the manipulandum was moved automatically) limb movement. Impairment of haptic function suggests that PwPD have impaired sensorimotor integration.

6.6.5 Does impaired sensorimotor integration cause people with Parkinson's disease to rely on visual feedback?

Impaired sensorimotor processing, caused by compromised basal ganglia function due to dopaminergic denervation and Lewy pathology, may be the reason that PwPD were disproportionately affected by MEM in our study, and could also explain the deficits seen in PwPD in other studies when the target, but not the arm, is illuminated (Schettino et al., 2003, Schettino et al., 2006).

As well as impaired processing of somatosensory afferents, basal ganglia dysfunction in PwPD may result in abnormal handling of motor commands, i.e. the motor component of sensorimotor integration may be compromised as well as the sensory component. A motor action, for example a tennis serve, consists of a number of motor subroutines; the appropriate grip of the tennis racquet, the stance, the throw of the tennis ball and the swing of the racquet etc. Goldberg proposed that the SMA plays a key role in the initiation and integration of the multiple motor subroutines that make up a motor action (Goldberg, 1985), and that motor subroutines are context dependent and 'anticipatory' (Goldberg, 1985, Schettino et al., 2006). As part of a so-called 'medial-circuit', the SMA and

basal ganglia use an internal 'forward model' [22] system based on past-experience to predict the required motor action for a situation. Conversely, a 'lateral circuit', connecting the pre-motor and parietal cortices, was proposed to be responsive rather than anticipatory, driven by external stimuli rather than an internal forward model (Goldberg, 1985, Conte et al., 2013). Damage to the basal ganglia in PwPD would, put simply, cause the medial circuit to malfunction, and there is now good evidence that the SMA is underactive in PD (see Chapter 7.7.8.2). Abnormalities in the integration of motor subroutines would result in abnormal motor actions, causing abnormal movements. Furthermore, it has been argued than in response to impairment of the medial circuit, movements may become more dependent on the lateral circuit, i.e. result in a greater dependence on external stimuli to generate and modify movements, which could translate into a greater reliance on visual feedback (Goldberg, 1985, Schettino et al., 2006).

Forward models of movement selection have modern-day support and are similar to that proposed by Goldberg; an appropriate motor action is selected by comparing sensory input, for example proprioception, with internal estimates of body position based on prior experience (Conte et al., 2013, Kording and Wolpert, 2006). The process is continuous and on-line adjustments are made as sensory input and experience change. A role for the basal ganglia in this process is supported by the fact that proprioception and sensorimotor function have been shown to improve in 11 PwPD who underwent deep brain stimulation (DBS) of the subthalamic nuclei (STN) (Wagle Shukla et al., 2013). Interestingly, improvement was

[22] Forward model – A model that assumes the central nervous system has an internal representation of how a body part, for example the hand, will react in the environment. Specifically, a copy of a motor action (the 'efference copy') is fed into the model, which then predicts the effect of the motor action on the sensorimotor system. In other words the forward model aims to predict the behaviour of the sensorimotor system of the organism in response to a motor action.

only evident after six months, suggesting that protracted stimulation was required to appropriately recalibrate the forward model.

6.6.6 Is medial circuit dysfunction compatible with the visuomotor channel hypothesis?

The visuomotor channel hypothesis proposes that the separate pathways controlling reach and grasp are temporally integrated during full visual guidance (Jeannerod et al., 1995, Jeannerod, 1999, Jeannerod, 1986, Jeannerod, 1984). The neural pathways proposed to control reach and grasp both have major 'nodes', or loci, in the parietal and premotor cortices. The dorsomedial circuit, controlling reach, processes visual information in V6A of the PRR and then transfers this to the PMd (Prodoehl et al., 2009, Karl and Whishaw, 2013). The dorsolateral circuit, controlling grasp, processes visual information in the anterior intraparietal sulcus (aIPS in humans) and the PMv (Karl and Whishaw, 2013, Prodoehl et al., 2009) (see Figure 4). Both pathways would therefore be considered components of the lateral circuit according to Goldberg (Goldberg, 1985). The basal ganglia dysfunction in PD, causing impairment of anticipatory motor actions, would place increased reliance on the lateral circuit. Therefore the theory that incorrect motor actions, or movement, in PwPD might be in part caused by impaired production of anticipatory motor-subroutines is compatible with the visuomotor channel hypothesis because the channels are part of the lateral circuit.

6.6.7 How might impaired proprioception affect the reach and grasp circuits?

As discussed, there is evidence that PwPD have impaired proprioception (Maschke et al., 2003) and/or impaired processing of proprioceptive information (sensorimotor processing) (Konczak et al., 2012). An attempt will now be made to hypothesise how this might *directly* affect the reach and grasp circuits.

The integration of reach and grasp is dependent on visual guidance (Jeannerod et al., 1995, Jeannerod, 1999, Jeannerod, 1986, Jeannerod, 1984). In macaques it has been possible to study individual neurons using single cell microelectrode studies. As discussed in detail in Chapter 3, it has been established that the major parietal nodes of the dorsomedial and dorsolateral circuits contain neurons that are exquisitely sensitive to visual information. In V6A there are subpopulations of neurons sensitive to an object's position and orientation in space (extrinsic properties), one of a number of characteristics that make neurons from this part of the brain able to maximise the accuracy of the reaching arm (Galletti et al., 1999). The results of neuronal stimulation and cytoarchitectural analysis suggest that these visually stimulated neurons make up a distinct region of V6A in the macaque, known as V6Av (Breveglieri et al., 2002, Galletti et al., 2003). Neuron sub-populations within the anterior intraparietal sulcus (AIP in macaques), so-called 'visually responsive neurons', discharge in response to specific shapes, orientations and sizes (intrinsic properties) (Murata et al., 2000). These neurons are not thought to be involved in the process of object recognition, but rather provide a rapid and coarse interpretation of 3D boundaries so that an appropriate handgrip can be selected (Srivastava et al., 2009, Theys et al., 2013).

However, V6A, AIP and the areas of the frontal premotor cortex comprising the dorsomedial and dorsolateral circuits are also dependent on somatosensory information. From an evolutionary perspective it is theorised that this dependence predates development of an advanced visual system and the resultant integration of visual information into the control of reach and grasp (Karl and Whishaw, 2013). It has been shown that a neuronal sub-population within V6A is stimulated by different somatosensory modalities (Breveglieri et al., 2002). In one study a total of 240 single neurons from four macaque monkeys were analysed. To prevent activation of the visually responsive neurons in V6A the experimental procedure was performed in compete darkness. A distinct

discharge in response to somatosensory stimulation was found in 72 (32%) of the 240 neurons studied. Of these, 59% discharged in response to passive rotation of the limb – a component of proprioception – and the majority of these specifically to passive shoulder rotation (31/46). Nineteen percent of the 72 somatosensory responsive neurons were sensitive to light tactile stimulation of the skin and 13 of the 72 discharged after deep palpation of the subcutaneous tissue (Breveglieri et al., 2002). As with passive limb rotation, the majority of discharging neurons to tactile stimuli or deep palpation did so to proximal rather than distal limb stimulation, in keeping with the accepted understanding that the process of reaching utilises proximal arm muscles (Castiello and Begliomini, 2008, Prodoehl et al., 2009, Karl and Whishaw, 2013). This neuron population has a distinct cytoarchitectural structure compared to V6Av and is known as V6Ad (Luppino et al., 2005). The presence of a somatosensory neuron population within V6A – the major node of the dorsomedial reaching circuit – provides a theoretical reason as to why abnormal proprioception or processing of proprioception in PwPD might *cause* reaching to be abnormal in the absence of visual feedback (as evidenced by disproportionate prolongation of MT in our study). It should also be noted that in macaque V6A (Fattori et al., 2010) and area F2 of the PMd (Raos et al., 2004) there are neurons that discharge in response to grasping of different objects, and so it could be hypothesised that impaired somatosensory processing may also directly influence grasp by the same mechanism. Similarly, populations of neurons within the major nodes of the dorsolateral grasping circuit in the macaque – AIP (Murata et al., 2000) and F5 (Rizzolatti et al., 1988) – discharge to somatosensory stimuli, providing another theoretical mechanism by which proprioceptive deficits might cause grasping abnormalities in PwPD (as identified in other reach and grasp studies (Schettino et al., 2004, Schettino et al., 2006)).

This theory has two major problems to overcome. The first is extrapolating findings from single neuron microelectrode studies in the macaque brain to

the human brain. In relation to the dorsomedial circuit, fMRI and retinotopic mapping has led to the discovery of proposed human homologues of macaque areas V6 (Pitzalis et al., 2006) and V6A (Pitzalis et al., 2013), as discussed in Chapter 3.1.1.3. The human V6/V6A complex appears to have the same topographical arrangement of neurons as seen in macaques and shares some of the highly specialised characteristics that enable efficient reaching (Pitzalis et al., 2015). For example, the visual neurons in human V6A – the proposed human V6Av – over-represent the inferior visual field that the reaching arm must pass through (Pitzalis et al., 2013), whilst the somatosensory population – the proposed human V6Ad – appear to provide proprioceptive information about the arm as it travels towards an object when reaching (Tosoni et al., 2014).

The second problem to overcome is that any abnormality with the sensorimotor processing of proprioceptive information in the basal ganglia of PwPD must directly affect V6A, specifically V6Ad. As discussed in Chapter 2.6.1, a seminal although simplistic (Parent et al., 2000) model of basal ganglia function proposes that output to other brain structures from the basal ganglia is mediated by a series of parallel neural networks – motor, cognitive and limbic (Alexander et al., 1986). The major outputs of the basal ganglia for each of the neural networks are the SNpr and GPi, which both have strong projections to the thalamus and PPN (Alexander et al., 1986, Lewis and Barker, 2009). The ultimate destination of output depends on the neural network in question. A number of different thalamic nuclei are thought to be involved in the motor loop including the centromedian, parafasicular, ventral anterior and ventral lateral (VL) (Galvan et al., 2015). The thalamic output of the motor loop includes the SMA, M1 and the frontal premotor cortex (see Figure 12) (Galvan et al., 2015). Recently, thalamic connectivity to V6 and V6A has been studied in nine macaques using retrograde tracer injections (Gamberini et al., 2015). It was revealed that both V6Av and V6Ad have strong connections with the lateral posterior (LP) nucleus (approximately 60% of labelled LP afferents

were connected). Afferents from the medial subdivision of the pulvinar nucleus and VL nucleus also had connectivity with V6A (Gamberini et al., 2015). Although this is a single study and the percentage of labelled afferents with connectivity to V6A was low (~2% to V6Av and ~15% to V6Ad), it appears that in the macaque the VL nucleus of the thalamus has a direct output to V6A. If the same were true in humans then one of the major thalamic nuclei of the motor loop would have a direct connection to the major parietal reaching node of the dorsomedial circuit, and the thus the capacity for V6Ad to be *directly* affected by impaired proprioceptive processing is theoretically possible.

Connectivity between the basal ganglia and AIP via the thalamus has also been identified by retrograde tracer injections in cebus monkeys (Clower et al., 2005), and so the same theoretical capacity exists for impaired proprioception or proprioceptive processing to directly affect grasp. As discussed in Chapter 3.2.1, there is convincing radiological (Castiello and Begliomini, 2008) and TMS (Davare et al., 2007) support for a human AIP equivalent, the aIPS.

In summary, there is evidence that PwPD have impaired proprioception and impaired sensorimotor integration and this, in addition to the reduced activity of the basal ganglia-SMA medial circuit, could lead to impaired anticipatory motor output. As a result, PwPD may be more dependent on the parieto-frontal circuits during motor actions such as reaching and grasping. The dorsomedial reaching and dorsolateral grasping circuits require visual feedback in order to function optimally, and so removing visual feedback may disproportionately affect PwPD. In addition, it can be hypothesised that impaired proprioception may have a directly negative consequence on reaching, and perhaps grasping, because neurons in the proposed human V6Ad may be connected to the basal ganglia output of the motor neural network via the thalamic VL nucleus. Both of these theories may explain why PD-NC had a disproportionate prolongation of

MT, a surrogate marker of reach, in the absence of visual feedback (MEM) in our study.

6.7 Strengths and limitations

A major strength of this study is that in terms of the number of participants it is the largest study of reach and grasp in PwPD. As a result it is larger than the major previous study to look at the effect of visual feedback on reach and grasp in PwPD, which involved nine PD subjects and nine HC (Schettino et al., 2006). It is the only study of reach and grasp to perform a range of cognitive tests on all recruits (utilisation of this will be made in Chapter 7). The reach parameters calculated for our study are comparable in magnitude to other studies, suggesting that the data capture and processing are robust.

Unlike all previous reach and grasp studies, people with tremor have not been excluded from our study. As a strength, it can be argued that our study is more representative of PwPD because previous studies may have contained many PD subjects with the PIGD motor phenotype. As a negative, the presence of tremor may have affected the calculated parameters or explained some of the corrupt reach data. Likewise, the analysis of data from both hands of participants could be considered as a strength because the findings are more representative of PwPD in the community. Conversely, including the less affected, sometimes asymptomatic, limb of PD-NC participants may have diluted our results.

There are a number of major limitations to our study, which mean that the conclusions need to be interpreted with some caution. They can be divided into equipment and assessment limitations:

6.7.1 Equipment limitations

- Damage to the data gloves, not identified until result analysis, rendered results for TAP and %TAP of limited use in our study.

Because of this the primary focus has been on parameters of reach with limited focus on grasp or the integration of reach and grasp.

- Beyond the damage to the data gloves, the abstraction of information from them has been suboptimal compared to previous studies. For example, it has not been possible to look at the amplitude of peak aperture (or a surrogate marker), nor has it been possible to look at variation in individual joint flexion as the hand closes down around the cylinder. This degree of accuracy has been possible in previous studies using data gloves (Santello and Soechting, 1998, Santello et al., 2002, Schettino et al., 2004, Schettino et al., 2003, Schettino et al., 2006).

- Another equipment limitation of our study has been the inability to measure the trajectory of the reaching arm. Various studies of reaching have looked at this, providing novel information on directional change and variation (Castiello et al., 2000). Studies in which trajectory has been closely analysed have tended to video-record the assessment, often using infrared cameras to detect motion analysis sensors.

- The loss of right hand data from the first 20 recruits is regrettable and is a limitation, but nonetheless the number of datasets in our study remains greater than any previous study of reach and grasp.

- In hindsight, two relatively simple and cost-neutral changes to the equipment selection would have provided more robust results: EM sensors could have been attached to the index finger and thumb in addition to the wrist of each hand, instead of using the data gloves. This would have provided reliable data on index finger to thumb aperture, allowing comparison with other reach and grasp studies;

video-recording the assessments would have been of immense help when trying to establish the reasons for corrupt reach data.

6.7.2 Assessment limitations

- Failure to completely darken the room has likely affected the results from VIS (which are very similar to NAT) compared to other studies in which target illumination occurred in otherwise total darkness (Schettino et al., 2003, Schettino et al., 2006, Adamovich et al., 2001). In addition, if subjects had been asked to reach and grasp the illuminated cylinder as quickly as possible as well as at a natural speed, it would have been possible to investigate the value of the illuminated lamp as a cue in PwPD.

- The PD-NC and C-NC groups were not gender matched, with significantly more males in the PD-NC group. This may have influenced the results but there is no literature to suggest a gender difference when reaching and grasping.

- Previous studies have generally suggested that dopaminergic medications improve reach parameters but do not influence parameters of grasp. Ideally the assessment of reach and grasp in PD-NC should have been performed in both the *on* and *off* medication state. This would have increased the novelty of our study and allowed further insight into the role of dopaminergic medication on reach and grasp under different degrees of visual feedback.

6.8 Conclusions

PD-NC in the *on* medication state do not have significantly different reaching parameters compared to age-matched C-NC when reaching and grasping at a natural speed in full vision (NAT) and when reaching and grasping at maximal speed in full vision (MAX). In contrast, when reaching

and grasping with eyes closed (MEM), parameters of reaching are markedly different between the groups; PD-NC have significantly prolonged MT and time to peak wrist parameters (TPA, TPV and TPD) and significantly lower values of peak wrist parameters (PA, PV and PDe). The major new finding of our study is that the prolongation of MT in PwPD when reaching in the absence of visual feedback (MEM) occurs when *on* and is *disproportionate* compared to C-NC. This finding builds on established literature suggesting that PwPD have an increased dependence on visual feedback to guide reach whilst *off* (Schettino et al., 2006). One potential explanation of this finding is that PwPD have impaired proprioception and/or sensorimotor integration. This has been discussed in detail and a theoretical direct link between this and V6A, the major parietal node of the dorsomedial reaching circuit, has been proposed.

Chapter 7

Abbreviations used in this chapter

%RT	Reaction time as a % of total movement time
%TAP	Time to peak aperture as a % of movement time
%TPA	Time to peak acceleration as a % of movement time
%TPD	Time to peak deceleration as a % of movement time
%TPV	Time to peak velocity as a % of movement time
α-syn	Alpha synuclein
2D	Two dimensional
ACh	Acetylcholine
AD	Alzheimer's disease
aIPS	Anterior intraparietal area in humans
Aβ	Amyloid beta plaques
B-C	Benson Copy
B-R	Benson Recall
BP	Bereitschaftspotential
C-NC	Healthy control subjects with normal cognition
CDR	Clinical Dementia Rating scale
CRT	Choice reaction time
CSF	Cerebrospinal fluid
DLPFC	Dorsolateral prefrontal cortex
DT	Distance travelled
EEG	Electroencephalogram
EM	Electromagnetic
EMG	Electromyography
FEF	Frontal eye field
fMRI	Functional magnetic resonance imaging
GDS-15	Geriatric Depression Scale – Short Form
H&Y	Hoehn & Yahr
ICICLE-PD	Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation – Parkinson's Disease
IIV	Intra-individual variability
ITC	Inferior temporal cortex
JoLO	Benton Judgment of Line Orientation
LEDD	Levodopa equivalent daily dose
LIP	Lateral intraparietal area
LTM	Long term memory
MA	Mean acceleration
MAX	Condition 3 - Maximum speed
MDS	International Parkinson and Movement Disorder Society
MDS-UPDRS	Movement Disorders Society – Unified Parkinson's Disease Rating Scale
MEM	Condition 4 - Memory guided
MMSE	Mini-Mental State Examination

MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MT	Movement time
MV	Mean velocity
NAT	Condition 1 - Natural speed
NFT	Tau neurofibrillary tangles
NPI-Q	Neuropsychiatric Inventory - Questionnaire
PA	Peak acceleration
PD	Parkinson's disease
PD-ID	Parkinson’s disease with incipient dementia
PD-MCI	Parkinson's disease - mild cognitive impairment
PD-NC	Parkinson's disease - normal cognition
PDD	Parkinson's disease dementia
PDe	Peak deceleration
PET	Positron emission tomography
PPC	Posterior parietal cortex
PV	Peak velocity
PwPD	People with Parkinson's disease
RT	Reaction time
SMA	Supplementary motor area
SPECT	Single-photon emission computed tomography
SRT	Simple reaction time
STM	Short term memory
SWM	Spatial working memory
TAP	Time to peak aperture
TMT B-A	Trail Making Test Part B score - Trail Making Test Part A score
TMT-A	Trail Making Test Part A
TMT-B	Trail Making Test Part B
TMTi	Total movement time
TPA	Time to peak acceleration
TPD	Time to peak deceleration
TPV	Time to peak velocity
V6A	Visual area V6A
VIS	Condition 2 - Visually cued
WCST	Wisconsin Card-Sorting Test
WM	Working memory

Analysis of reach and grasp in people with Parkinson's disease and impaired cognition: Results and discussion

This chapter presents the results of reach and grasp in three PD cognitive groups: PD-NC, PD-MCI and PDD. PD-NC is the same group as presented in Chapter 6. Results will follow the same format as the previous chapter but will also include correlations and associations between reach and grasp parameters and cognitive tests. A discussion of the major findings follows the results.

7.1 Demographic and clinical details of results for PD-NC, PD-MCI and PDD

From the 55 PwPD who had usable results, 22 (40%) were categorised as PD-NC, 23 (42%) were categorised as PD-MCI and ten (18%) were categorised as PDD. The demographic and clinical details are presented in Table 21.

Table 21: The demographic and clinical details of the three Parkinson's disease cognitive groups

	PD-NC (n = 22)	PD-MCI (n = 23)	PDD (n = 10)	p
Age, years	66.5 (9.4, 44-84)	70.0 (8.0, 47-85)	72.6 (5.30, 64-83)	0.129
Gender, M:F	16:6	14:9	6:4	0.700
Handedness, R:L	20:2	20:3	8:2	0.677
Disease duration, years	5.1 (3.7, 0.5-15)	5.7 (4.0, 0.5-15)	10.5 (6.4, 1.0-20)	**0.007**
H&Y stage I (%)	6 (27.3)	2 (8.7)	0	
H&Y stage II	15 (68.2)	20 (87.0)	10 (100%)	0.192
H&Y stage III	1 (4.5)	1 (4.3)	0	
MDS-UPDRS Part 3	25.9 (11.0, 3 – 49)	28.3 (11.5, 7 – 52)	34.4 (12.8, 12 – 57)	0.155
LEDD, mg/day	656.0 (621.7, 0 – 2836.3)	632.5 (492.8, 100.0 – 2046.5)	835.8 (636.3, 0 – 2210.0)	0.630
MoCA score	26.9 (1.1, 26-29)	22.1 (2.3, 17 – 25)	17.6 (4.0, 12 – 23)	**<0.001**
GDS-15	3.0 (2.6, 0-11)	3.6 (3.1, 0-11)	5.6 (3.3, 2-13)	0.063

Abbreviations: PD-NC; Parkinson's disease normal cognition; PD-MCI, Parkinson's disease mild cognitive impairment; PDD, Parkinson's disease dementia; H&Y, Hoehn and Yahr; MDS-UPDRS, Movement Disorders Society – Unified Parkinson's Disease Rating Scale; LEDD, levodopa equivalent daily dose; MoCA, Montreal Cognitive Assessment; GDS, Geriatric Depression Scale.

The three cognitive groups are well matched for gender and handedness. There is no statistical difference between the groups for age (*p* 0.129), MDS-UPDRS Part 3 motor score (*p* 0.155), H&Y stage (*p* 0.192) or LEDD (*p* 0.630). However, disease duration is significantly different (*p* 0.007) and post-hoc inspection suggests that PDD have significantly longer duration of disease than both PD-NC (*p* 0.008) and PD-MCI (*p* 0.018). MoCA scores were used in the definition of the cognitive groups for this study. This is explained in Chapter 5.4.1 but to recap: PD-NC were defined by a MoCA score of ≥ 26; PD-MCI by a MoCA score of <26 and a global CDR score of 0 – 0.5; PDD by a MoCA score of <26 and a global score CDR ≥ 1. It is noteworthy that MoCA score is significantly lower in PDD than PD-MCI (Table 21). The mean GDS-15 score for the PDD subjects is greater than

five, which suggests that these patients may be at risk of low mood/depression.

7.1.1 Cognitive test results

Participants undertook a number of other cognitive tests in addition to the MoCA, as outlined in Chapter 5.3.3. The results are shown in Table 22. Non-parametric statistics have been used because the results do not follow a normal distribution despite logarithmic transformation. PD-NC score highest and PDD lowest in the cognitive tests, all of which are significantly different between the three groups. Directly comparing the cognitive test results between PD-NC and PD-MCI reveals that PD-NC score significantly higher in all tests. In contrast, directly comparing scores between PD-MCI and PDD indicates no statistical difference in TMT-B, TMT B-A, B-C or B-R. However, nine of the PDD group abandoned TMT-B leaving only one valid result for this and TMT B-A. This clearly suggests that PDD perform worse than PD-MCI on TMT-B despite the lack of statistical difference when the results are compared.

Table 22: The cognitive scores of PD-NC, PD-MCI and PDD

	PD-NC (n = 22)	PD-MCI (n =23)	PDD (n = 10)	p all groups	p PD-NC v MCI	p PD-MCI v PDD
MoCA	26.9 (1.1, 26-29)	22.1 (2.3, 17 – 25)	17.6 (4.0, 12 – 23)	**<0.001**	**<0.001**	**<0.001**
TMT-A	34.4 (9.7, 21-52)	42.9 (15.3, 26 – 83)	65.8 (27.4, 37 – 130)	**<0.001**	**0.044**	**0.010**
TMT-B	73.9 (27.5, 41-133)	106.1 (29.2, 63 – 179) ^	171 ^^	**0.003**	**0.002**	0.211
TMT B-A	39.5 (22.6, 12-86)	66.8 (25.7, 34-113) ^	111 ^^	**0.004**	**0.002**	0.211
JoLO	13.1 (1.3, 10-15)	10.7 (2.6, 4-15)	8.2 (2.9, 5 – 14)	**<0.001**	**0.001**	**0.022**
Benson Copy	16.2 § (0.8, 14-17)	15.2 (1.8, 9-17)	14.1 (3.3, 6-16) §§	**0.019**	**0.032**	0.409
Benson Recall	10.2 § (3.0, 4-15)	7.3 (3.4, 0-16)	5.3 (3.5, 0-10) §§	**0.001**	**0.004**	0.246

Legend: ^n = 18; ^^ n = 1; § n = 21; §§ n = 9. **Abbreviations:** TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; TMT B-A, Trail Making Test A – Trail Making Test Part B; JoLO, Benton Judgment of Line Orientation.

7.1.2 Summary of demographic and cognitive test results

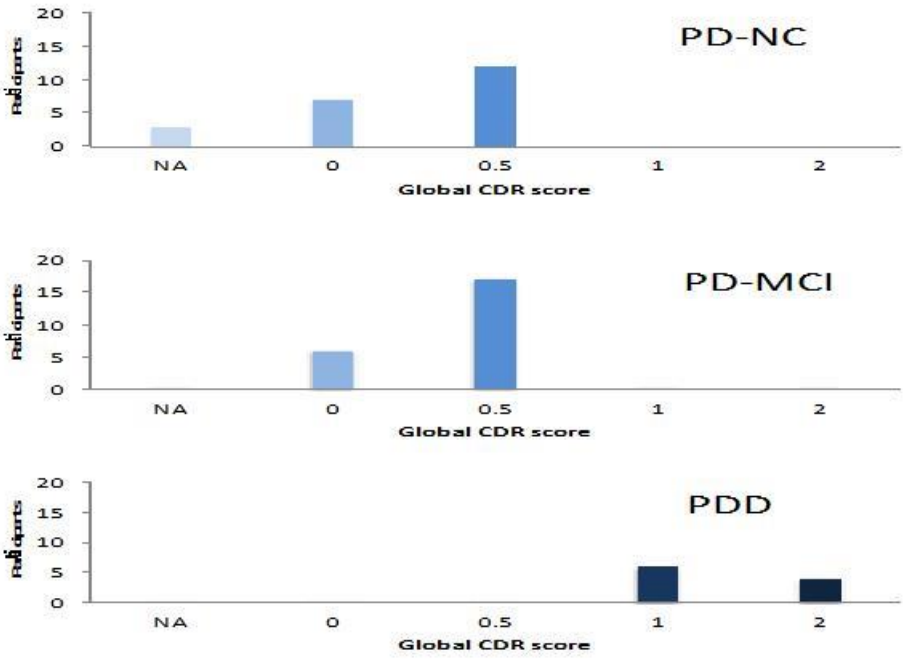
PDD are the oldest group, have a significantly longer disease duration and more severe motor signs when *on*. MoCA score and all of the other cognitive test results are significantly different between the three groups. PD-NC score significantly better than PD-MCI on all cognitive tests. Nine of ten PDD were unable to complete TMT-B. PD-MCI and PDD do not have significantly different scores for B-C and B-R.

7.1.3 Clinical Dementia Rating and Neuropsychiatric Inventory Questionnaire scores

In our study any PD participant with a MoCA score of ≥ 26 was classified as PD-NC independent of the CDR score. The validity of the classification method would be thrown into question if members of PD-NC had global CDR scores of >0.5. As demonstrated in Figure 55, this is not the case. In both PD-NC and PD-MCI the global CDR score was divided between 0

(normal) and 0.5 (questionable cognitive impairment). This distribution was non-significant between the groups (*p* 0.453), suggesting that it is the MoCA score only that differentiates between PD-NC and PD-MCI in our study. This finding can be used to justify the classification of three PwPD into PD-NC despite the fact they did not have an informant interview (i.e. CDR and NPI-Q data is not available – see Chapter 6.1.2.1).

Figure 55: Global CDR scores in PD-NC, PD-MCI and PDD



Legend: Three PD-NC subjects did not nominate an informant and so CDR (and NPI-Q) data is unavailable. The remainder of PD-NC and all PD-MCI have CDR scores of 0 to 0.5. PDD had global CDR scores of 1 (mild dementia) or 2 (moderate dementia). Abbreviations: CDR, Clinical Dementia Rating; NA, not available.

Neuropsychiatric symptoms including visual hallucinations and delusions are often associated with cognitive decline in PwPD (Riedel et al., 2008) and can be used to support a diagnosis of PDD according to MDS criteria (Emre et al., 2007). NPI-Q scores are shown in Table 23. There is a statistically significant difference between the three groups in total severity and total caregiver distress scores. PD-NC and PD-MCI have a non-significant difference between results and in fact it is the PD-NC groups who score higher in both domains. One NPI-Q inquiry relates to sleep and

"excessive naps in the day" is a component of this question. PwPD may sleep in the day for reasons unrelated to cognition, for example due to the use of dopamine agonist medication, and this question in particular was one that many of the informants rated as present in PD-NC. This partially explains the NPI-Q score in PD-NC. PDD have the highest NPI-Q score by some way.

Table 23: Neuropsychiatric Inventory Questionnaire scores in PD-NC, PD-MCI and PDD

	PD-NC (n = 19) *	PD-MCI (n =23)	PDD (n = 10)	p all groups	p PD-NC v PD-MCI	p PD-MCI v PDD
Symptom severity total	3.2 (3.1, 0 – 9)	2.4 (2.6, 0 – 9)	8.9 (6.2, 0 – 20)	**0.005**	0.396	**0.001**
Caregiver distress total	3.6 (4.4, 0 – 16)	2.2 (3.3, 0 – 12)	11.9 (8.8, 0 – 29)	**0.001**	0.285	**0.001**
Total NPI score	6.8 (7.3, 0 – 25)	4.7 (5.7, 0 – 19)	20.8 (14.5, 0 – 49)	**0.003**	0.318	**0.001**

In summary, global CDR and NPI-Q scores between PD-NC and PD-MCI are similar, indicating that the MoCA score is the only difference between these groups in our study. By definition, PDD have higher CDR scores but also higher NPI-Q scores, in keeping with the known association between PDD and neuropsychiatric disturbance (Riedel et al., 2008).

7.2 Results from the four conditions

The results of reach and grasp across the four conditions are presented in the same format as Chapter 6. Right and left hand data is again considered together. PD-NC consists of the same 37 datasets as Chapter 6. There are 42 datasets from PD-MCI and 19 datasets from PDD.

7.2.1 Condition 1 – Natural Speed (NAT)

Results for NAT are presented in Table 24. The only statistically significant differences between the groups are RT (p <0.001) and %RT (p <0.001). Post-hoc inspection suggests that PDD have a significantly prolonged RT compared to both PD-NC (p 0.003) and PD-MCI (p <0.001) and the post hoc inspection of %RT is similar. It is interesting to note that PDD have the highest absolute values for the peak reach parameters (PA, PV, PDe) as given their (non-significantly) higher MDS-UPDRS Part 3 score one might expect them to be slowest. The instruction for this task was to grasp *"as you would do at home if you were reaching for a cup from the table"*. It is possible that the higher values in PDD reflect their inability to fully understand the instructions.

Table 24: Condition 1 - NAT

	PD-NC (n = 37)	PD-MCI (n = 42)	PDD (n = 19)	p
PA, mm/s^2 (SD, range)	1800.3 * (1.30, 1043.1 – 3533.3)	1820.4 * (1.27, 953.4 – 3261.7)	1863.7 * (1.33, 972.6 – 2981.0)	0.891
TPA, s	0.42 (0.11, 0.26 – 0.70)	0.38 (0.07, 0.22– 0.64)	0.42 (0.09, 0.28 – 0.62)	0.095 **
MA, mm/s^2	966.9 * (1.32, 544.6 – 1863.1)	992.4 * (1.28, 502.7 – 1863.1)	980.1 * (1.32, 512.9 – 1571.8)	0.639
PV, mm/s	683. 3 * (1.24, 507.8 – 1130.0)	672.4 * (1.28, 372.4 – 1107.7)	713.1 * (1.28, 419.9 – 1002.2)	0.669
TPV, s	0.55 * (1.23, 0.39 – 0.90)	0.52 * (1.16, 0.37 – 0.72)	0.56 * (1.23, 0.37 – 0.86)	0.332
MV, mm/s	333.5 (77.3, 204.2 – 530.3)	329.6 (78.0, 144.5 – 507.0)	333.4 (83.3, 201.4 – 559.2)	0.971
PDe, mm/s^2	-1839.5 (614.6, -3212.9 – -978.4)	-1811.4 (684.1, -3404.4 - -629.7)	-1944.9 (654.2, -3089.7 – -810.7)	0.757
TPD, s	0.87 (0.15, 0.53 – 1.28)	0.85 (0.12, 0.62 – 1.11)	0.85 (0.16, 0.51 – 1.19)	0.780
TAP, s	0.83 * (1.36, 0.30 – 1.51)	0.84 * (1.26, 0.49 – 1.51)	0.76 * (1.32, 0.46 – 1.26)	0.389
RT, s	0.53 * (1.23, 0.33 – 0.85)	0.51 * (1.25, 0.33 – 1.65)	0.67 * (1.36, 0.36 – 1.11)	**<0.001**
MT, s	1.19 * (1.26, 0.76 – 2.20)	1.20 * (1.27, 0.78 – 2.59)	1.19 * (1.32, 0.69 – 2.59)	0.993
TMTi, s	1.73 * (1.23, 1.11 – 2.89)	1.72 * (1.23, 1.21 – 3.19)	1.89 * (1.27, 1.38 – 3.03)	0.232
DT, mm	272.8 (25.9, 225.9 – 311.8)	280.5 (30.2, 215.0 – 325.9)	265.3 (30.0, 212.9 – 311.0)	0.095 **
%TPA	34.3 * (1.19, 23.1 – 48.4)	31.1 * (1.25, 15.8 – 41.3)	34.3 * (1.17, 24.3 – 43.8)	0.054
%TPV	46.5 (6.7, 31.9 – 58.1)	44.4 (7.9, 24.6 – 56.3)	47.4 (6.0, 35.0 – 56.7)	0.250
%TPD	72.2 (7.8, 52.5 – 81.9)	70.6 (9.3, 42.9 – 82.5)	70.2 (7.3, 55.2 – 79.0)	0.480 **
%TAP	71.0 (13.1, 22.3 – 86.7)	71.4 (12.2, 37.9 – 87.3)	65.8 (10.8, 49.3 – 84.9)	0.081 **
%RT	31.1 (4.3, 23.5 – 40.3)	30.0 (5.2, 18.9 – 38.5)	36.2 (7.6, 22.4 – 49.8)	**<0.001**

Legend: * denotes geometric mean – See Chapter 5.7, ** denotes non-parametric *p* value.

7.2.2 Condition 2 – Visually guided (VIS)

The results for VIS are presented in Table 25. RT and %RT are again significantly different between the groups and, as with NAT, post-hoc inspection suggests that PDD have a significantly longer RT than both PD-NC and PD-MCI (both p <0.001). TPA is significantly different between the groups (p 0.007). PDD have the greatest value and PD-MCI the smallest. TPA was calculated using non-parametric methods and no-post hoc test

has been performed. Overall, as with NAT, the results for VIS are similar between the three cognitive groups.

Table 25: Condition 2 - VIS

	PD-NC (n = 37)	PD-MCI (n = 42)	PDD (n = 19)	p
PA, mm/s^2 (SD, range)	1904.9 (508.7, 1011.3 – 3223.1)	1830.4 (444.9, 961.3 – 2980.0)	1681.1 (405.2, 1156.3 – 2449.3)	0.236
TPA, s	0.42 (0.12, 0.20 – 0.93)	0.39 (0.08, 0.24 – 0.69)	0.46 (0.11, 0.35 – 0.71)	**0.007 ****
MA, mm/s^2	994.8 (1.31, 528.5 – 1919.8)	958.4 (1.28, 550.0 – 1719.9)	850.6 (1.29, 607.9 – 1274.1)	0.102
PV, mm/s	691.3 * (1.25, 415.7 – 1032.8)	654.8 * (1.26, 441.4 – 1085.7)	642.9 * (1.29, 441.4 – 906.9)	0.452
TPV, s	0.54 * (1.22, 0.36 – 1.04)	0.54 * (1.23, 0.36 – 1.01)	0.59 * (1.20, 0.44 – 0.90)	0.847
MV, mm/s	332.7 (79.4, 175.3 – 545.0)	324.2 (85.6, 164.4 – 556.8)	299.7 (64.0, 210.0 – 445.6)	0.339
PDe, mm/s^2	-1881.2 (628.6, -3080.9 – -744.0)	-1756.4 (688.7, -3369.3 - -817.4)	-1675.9 (626.1, -2534.4 - -714.0)	0.498
TPD, s	0.87 (0.16, 0.46 – 1.38)	0.87 (0.14, 0.63 – 1.35)	0.92 (0.12, 0.74 - 1.18)	0.223 **
TAP, s	0.82 * (1.21, 0.51 – 1.58)	0.81 * (1.35, 0.38 – 1.48)	0.83 * (1.27, 0.59 – 1.32)	0.914
RT, s	0.47 (0.11, 0.27 – 0.78)	0.45 (0.10, 0.27 – 0.66)	0.63 (0.18, 0.23 – 0.99)	**<0.001**
MT, s	1.20 * (1.27, 0.73 – 2.14)	1.24 * (1.28, 0.84 – 2.20)	1.31 * (1.19, 0.96 – 1.72)	0.405
TMTi, s	1.71 (0.38, 1.00 – 2.71)	1.73 (0.38, 1.12 – 2.86)	1.96 (0.36, 1.34 – 2.61)	0.050
DT, mm	268.5 (25.6, 211.1 – 310.5)	284.1 (25.8, 220.2 – 327.7)	262.1 (25.9, 207.0 – 291.7)	**0.003 ****
%TPA	34.1 (5.2, 23.0 – 44.4)	31.4 (6.4, 18.8 – 43.2)	34.7 (6.0, 23.9 – 43.9)	0.057
%TPV	45.3 (6.0, 32.4 – 55.2)	44.6 (6.0, 32.4 – 55.2)	45.2 (5.7, 33.9 – 52.3)	0.913
%TPD	71.6 (7.3, 53.5 – 79.8)	70.1 (9.9, 43.7 – 83.3)	69.9 (7.6, 56.7 – 80.9)	0.765 **
%TAP	70.4 (10.2, 44.2 – 85.3)	67.8 (14.5, 33.0 – 88.2)	64.2 (9.5, 42.9 – 80.8)	0.050 **
%RT	28.0 (4.5, 19.9 – 37.4)	26.4 (4.6, 18.3 – 37.2)	31.0 (5.5, 15.9 – 38.7)	**0.003**

Legend: * denotes geometric mean, ** denotes non-parametric *p* value.

Table 26: Intra-group comparisons for NAT and VIS

	PD-NC NAT	PD-NC VIS	p (95% CI)	PD-MCI NAT	PD-MCI VIS	p (95% CI)	PDD NAT	PDD VIS	p (95% CI)
PA, mm/s^2 (SD)	1800.3 * (1.30)	1842.7 * (1.30)	0.377 (0.93 – 1.03)	1820.4 * (1.27)	1778.3 * (1.27)	0.366 (0.97 – 1.08)	1933.4 (526.3)	1681.1 (405.2)	**0.001** (123.2- 381.4)
TPA, s	0.42 (0.11)	0.42 (0.12)	0.988 (-0.03 – 0.03)	0.38 (0.07)	0.39 (0.08)	0.179 **	0.42 (0.09)	0.46 (0.11)	**0.026** (-0.08 – 0.01)
MA, mm/s^2	966.9 * (1.32)	994.8 * (1.31)	0.257 (0.46 – 1.24)	992.4 * (1.28)	958.4 * (1.28)	0.222 (0.98 – 1.10)	1016.0 (275.3)	877.2 (228.2)	**0.002** (56.8 – 220.7)
PV, mm/s	683. 3 * (1.24)	691.3 * (1.25)	0.446 (0.96 – 1.02)	672.4 * (1.28)	654.8 * (1.26)	0.253 (0.98 – 1.08)	733.4 (170.8)	662.2 (161.4)	**0.001** (35.8 – 106.7)
TPV, s	0.56 (0.12)	0.55 (0.12)	0.553 (-0.02 – 0.03)	0.52 * (1.16)	0.54 * (1.23)	0.077 (0.93 – 1.00)	0.56 * (1.23)	0.59 * (1.20)	0.158 (0.88 – 1.02)
MV, mm/s	333.5 (77.3)	332.7 (79.4)	0.894 (-11.4 – 13.1)	329.6 (78.0)	324.2 (85.6)	0.434 (-8.5 – 19.5)	333.4 (83.3)	299.7 (64.0)	**0.007** (10.4 – 57.0)
PDe, mm/s^2	-1839.5 (614.6)	-1881.2 (628.6)	0.400 (-57.7 – 141.1)	-1811.4 (684.1)	-1756.4 (688.7)	0.268 (-153.7 – 43.8)	-1944.9 (654.2)	-1675.9 (626.1)	**0.001** (-418.5 – - 119.6)
TPD, s	0.87 (0.15)	0.87 (0.16)	0.768 (-0.35 – 0.26)	0.85 (0.12)	0.87 (0.14)	0.197 (-0.06 – 0.01)	0.85 (0.16)	0.92 (0.12)	**0.013** (-0.13 – 0.02)
TAP, s	0.87 (0.24)	0.82 (0.21)	0.447 (-0.03 – 0.07)	0.86 (0.21)	0.84 (0.24)	0.369 (-0.03 – 0.07)	0.79 (0.22)	0.85 (0.21)	**0.026** (-0.12 – - 0.01)
RT, s	0.54 (0.11)	0.47 (0.11)	**<0.001** (0.04 – 0.10)	0.51* (1.25)	0.44 * (1.24)	**<0.001** (1.08 – 1.23)	0.71 (0.22)	0.63 (0.18)	0.088 (-0.01 – 0.17)
MT, s	1.23 (0.30)	1.24 (0.32)	0.549 (-0.06 – 0.03)	1.24 (0.33)	1.28 (0.33)	0.202 (-0.10 – 0.02)	1.24 (0.35)	1.33 (0.23)	**0.036** (0.18 – -0.01)
%TPA	34.8 (5.9)	34.1 (5.2)	0.270 (-0.53 – 1.84)	31.8 (6.1)	31.4 (6.4)	0.846 **	34.6 (5.1)	34.7 (6.0)	0.951 (-1.9 – 1.8)
%TPV	46.5 (6.7)	45.3 (6.0)	0.050 (0.0 – 2.3)	43.7 * (1.22)	43.7 * (1.23)	0.932 (0.96 – 1.03)	47.4 (6.0)	45.2 (5.7)	0.069 (-0.2 – 4.5)
%TPD	72.2 (7.8)	71.6 (7.3)	0.356 (-0.7 – 1.8)	70.6 (9.3)	70.1 (9.9)	0.526 (-1.1 – 2.1)	70.2 (7.3)	69.9 (7.6)	0.813 (-2.2 – 2.7)
%TAP	71.0 (13.1)	70.4 (10.2)	**0.022 ****	71.4 (12.2)	67.8 (14.5)	**0.006** (1.1 – 6.1)	65.8 (10.8)	64.2 (9.5)	0.391 (-2.4 – 5.7)

Legend: * denotes geometric mean, ** denotes non-parametric *p* value.

7.2.2.1 Comparing intra-group change between NAT and VIS

Intra-group comparisons between NAT and VIS are shown in Table 26. Results for DT, TMTi and %RT have been omitted from the intra-group analysis tables in this chapter to save space, allowing the tables to be presented on a single page. However, they are included in the inter-group comparisons.

RT is shorter in VIS compared to NAT in all groups but only significantly so for PD-NC and PD-MCI (both p <0.001). MT for PD-NC and PD-MCI is non-significantly increased in VIS whereas the increase is significant for PDD (p 0.036). Associated with this, peak and mean wrist parameters are significantly reduced and TPA, TPD and TAP are significantly prolonged in PDD but not in the other groups.

There are no significant differences in %TPA, %TPV or %TPD for the groups but %TAP occurs significantly earlier in VIS than NAT for PD-NC and PD-MCI.

7.2.2.2 Comparing inter-group change between NAT and VIS

The ratio values for NAT:VIS are shown in Table 27. As in Chapter 6, the ratio values allow the groups to be compared with each other (i.e. inter-group analysis). RT is not significantly different (p 0.901), implying that the reduction in RT in VIS compared to NAT is proportional between the groups. The ratio difference for MT is also non-significant (p 0.090), but the increase in MT for VIS compared to NAT is greatest for PDD. For peak and mean wrist parameters there is a significant difference between the groups and where post-hoc inspection is possible the results show that PDD is significantly different from PD-NC but not PD-MCI. Finally, TPD is also significantly different between the groups and again the greatest change between NAT and VIS is seen in PDD.

Table 27: Inter-group comparisons for NAT and VIS

	PD-NC (n = 37)	PD-MCI (n = 42)	PDD (n = 19)	p
PA (SD)	0.98 * (1.17)	1.02 * (1.18)	1.14 * (1.16)	**0.004**
TPA	1.02 (0.16)	0.99 (0.17)	0.92 (0.16)	0.087 **
MA	0.97 * (1.16)	1.04 * (1.20)	1.15 * (1.20)	**0.003**
PV	0.99 (0.09)	1.04 (0.17)	1.12 (0.12)	**0.002 ****
TPV	1.01 * (1.12)	0.97 * (1.13)	0.95 * (1.17)	0.126
MV	1.01 * (1.11)	1.02 * (1.15)	1.10 * (1.15)	**0.035**
PDe	0.98 * (1.18)	1.03 * (1.24)	1.18 * (1.19)	**0.005**
TPD	1.00 (0.11)	0.98 (0.11)	0.92 (0.13)	**0.039**
TAP	1.01 * (1.23)	1.04 * (1.20)	0.92 * (1.16)	0.069
RT	1.17 (0.19)	1.18 (0.24)	1.17 (0.31)	0.901 **
MT	1.00 (0.11)	0.98 (0.14)	0.92 (0.14)	0.090
TMTi	1.03 * (1.11)	1.02 * (1.16)	0.98 * (1.15)	0.351
DT	1.02 (0.03)	0.99 (0.06)	1.01 (0.04)	0.058 **
%TPA	1.02 (0.10)	1.03 (0.19)	1.01 (0.11)	0.529 **
%TPV	1.03 (0.08)	1.00 (0.11)	1.05 (0.11)	0.195
%TPD	1.01 * (1.05)	1.01 * (1.08)	1.00 * (1.08)	0.980
%TAP	1.02 (0.12)	1.07 (0.16)	1.03 (0.12)	0.745 **
%RT	1.12 (0.15)	1.14 (0.13)	1.18 (0.19)	0.390

Legend: * denotes geometric mean, ** denotes non-parametric *p* value. Value <1 = NAT < VIS, Value >1 = NAT > VIS.

7.2.2.3 Summary of results for NAT and VIS

Directly comparing the parameters of reach and grasp for NAT and VIS between the groups suggests that RT is significantly prolonged for PDD in both conditions. Otherwise the results are generally non-significant. The inter and intra-group analyses suggest that PDD were most affected by VIS when compared to their reach and grasp parameters in NAT, demonstrating the greatest proportional prolongation of MT – although

this was non-significant – with associated changes to peak reach and time to peak reach parameters.

7.2.3 Condition 3 – Maximal speed (MAX)

The results for MAX are shown in Table 28. RT is again significantly different between the groups (p <0.001) and – in keeping with NAT and VIS – post-hoc inspection suggests PDD have a significantly longer RT than PD-NC and PD-MCI (both p <0.001). In contrast to NAT and VIS, MT is significantly different between the groups (p 0.014). Post-hoc inspection suggests that MT is significantly longer in PDD than PD-MCI (p 0.020) and PD-NC (p <0.001). As expected from the strong correlation between peak reach parameters and MT (see Chapter 6.2.3), the trend of peak parameters shows PDD have the lowest values and PD-NC the highest although there are no significant group differences. However, MA (p 0.023) and MV (p 0.020) are significantly different between the groups. There are significant group differences for TPA (p 0.016), TPV (p 0.012) and TPD (p 0.016) and as expected from MT and peak reach parameter results, PDD have the largest values and PD-NC the smallest. The only statistical group difference when values are considered as a percentage of MT is %TAP, occurring soonest in PDD (68%) and latest in PD-NC (76.8%) (p 0.006). It was shown in Chapter 6 that %TAP occurred at 64.3% of MT for C-NC.

Table 28: Condition 3 - MAX

	PD-NC (n = 37)	PD-MCI (n = 42)	PDD (n = 19)	p
PA, mm/s^2 (SD, range)	2643.5 (553.2, 1827.2 – 3872.3)	2471.6 (347.6, 1779.0 – 3250.3)	2345.9 (513.6, 1275.8 – 3203.7)	0.064
TPA, s	0.27 (0.09, 0.11 – 0.49)	0.29 (0.06, 0.15 – 0.41)	0.32 (0.05, 0.21 – 0.42)	**0.016**
MA, mm/s^2	1439.0 * (1.25, 1022.5 – 2186.4)	1362.5 * (1.16, 962.9 – 1808.0)	1222.1 * (1.27, 685.4 – 1808.0)	**0.023**
PV, mm/s	902.3 (184.3, 630.2 – 1264.4)	858.2 (137.5, 605.6 – 1147.2)	821.4 (174.5, 457.8 – 1037.0)	0.196
TPV, s	0.39 (0.10, 0.22 – 0.71)	0.43 (0.07, 0.30 – 0.66)	0.46 (0.05, 0.35 – 0.57)	**0.012**
MV, mm/s	500.7 (121.4, 298.3 – 751.7)	471.3 (88.0, 287.7 – 640.2)	418.5 (86.4, 226.0 – 547.2)	**0.020**
PDe, mm/s^2	-2343.1 (706.5, -3638.2 - -1082.5)	-2140.2 (562.1, -3201.7 - - 1195.4)	-2233.4 (662.7, -3115.7 - -842.5)	0.375
TPD, s	0.56 (0.18, 0.24 – 1.07)	0.61 (0.12, 0.41 – 0.84)	0.67 (0.09, 0.46 – 0.83)	**0.016 ****
TAP, s	0.55 * (1.34, 0.30 – 1.26)	0.57 * (1.30, 0.27 – 0.93)	0.57 * (1.25, 0.34 – 0.73)	0.786
RT, s	0.41 * (1.19, 0.28 – 0.64)	0.41 * (1.20, 0.27 – 0.61)	0.53 * (1.31, 0.30 – 0.84)	**<0.001**
MT, s	0.73 * (1.33, 0.46 – 1.72)	0.80 * (1.24, 0.53 – 1.23)	0.89 * (1.21, 0.58 – 1.34)	**0.014**
TMTi, s	1.15 * (1.23, 0.79 – 2.16)	1.21 * (1.17, 0.89 – 1.79)	1.44 * (1.16, 1.11 – 1.97)	**<0.001**
DT, mm	276.6 (26.8, 218.9 – 315.1)	293.2 (23.1, 239.3 – 333.7)	266.4 (24.8, 220.5 – 303.5)	**<0.001**
%TPA	34.6 (4.8, 23.3 – 42.0)	35.8 (4.9, 27.7 – 47.2)	36.2 (3.5, 26.3 – 41.6)	0.395
%TPV	52.0 (5.7, 36.9 – 65.0)	53.9 (7.0, 38.0 – 66.4)	51.5 (6.2, 35.9 – 59.5)	0.290
%TPD	73.3 (7.2, 52.7 – 82.3)	74.7 (6.0, 61.3 – 84.3)	74.4 (5.3, 57.6 – 79.7)	0.872 **
%TAP	76.8 (8.9, 44.2 – 90.7)	73.0 (10.9, 40.7 – 92.1)	68.0 (9.5, 50.1 – 83.2)	**0.006 ****
%RT	36.0 (6.8, 21.1 – 47.1)	34.1 (5.8, 24.4 – 46.4)	37.2 (7.5, 22.7 – 50.2)	0.184

Legend: * denotes geometric mean, ** denotes non-parametric *p* value.

Table 29: Intra-group comparisons of NAT and MAX

	PD-NC NAT	PD-NC MAX	p (95% CI)	PD-MCI NAT	PD-MCI MAX	p (95% CI)	PDD NAT	PDD MAX	p (95% CI)
PA, mm/s^2 (SD)	1863.9 (540.2)	2643.5 (553.2)	**<0.001** **	1872.0 (456.8)	2471.6 (347.6)	**<0.001** (-721.9 – -477.2)	1933.4 (526.3)	2345.9 (513.6)	**<0.001** (-591.2 – -233.7)
TPA, s	0.42 (0.11)	0.27 (0.09)	**<0.001** **	0.38 (0.07)	0.29 (0.06)	**<0.001** (0.06 - 0.11)	0.42 (0.09)	0.32 (0.05)	**<0.001** (0.06 - 0.13)
MA, mm/s^2	1005.7 (309.7)	1475.4 (348.7)	**<0.001** **	1022.6 (258.9)	1377.5 (206.0)	**<0.001** (-425.3 – -284.5)	1016.0 (275.3)	1254.2 (280.9)	**<0.001** (-342.9 – -133.6)
PV, mm/s	700.0 (162.7)	902.3 (184.4)	**<0.001** **	692.5 (172.0)	858.2 (137.5)	**<0.001** (-199.8 – -131.6)	733.4 (170.8)	821.4 (174.5)	**<0.001** (-129.9 – -46.1)
TPV, s	0.56 (0.12)	0.39 (0.10)	**<0.001** **	0.53 (0.08)	0.43 (0.07)	**<0.001** (0.07 – 0.12)	0.57 (0.12)	0.46 (0.05)	**0.001** (0.06 – 0.17)
MV, mm/s	333.5 (77.3)	500.7 (121.4)	**<0.001** (-195.4 – -138.9)	329.6 (78.0)	471.3 (88.0)	**<0.001** (-164.7 – -118.7)	333.4 (83.3)	418.5 (86.4)	**<0.001** (-119.3 – -50.9)
PDe, mm/s^2	-1839.5 (614.6,)	-2343.1 (706.5)	**<0.001** (304.2 – 702.9)	-1811.4 (684.1)	-2140.2 (562.1)	**<0.001** (187.5 – 470.3)	-1944.9 (654.2)	-2233.4 (662.7)	**0.008** (85.1 – 491.7)
TPD, s	0.87 (0.15)	0.56 (0.18)	**<0.001** (0.24 – 0.37)	0.85 (0.12)	0.61 (0.12)	**<0.001** (0.20 – 0.28)	0.85 (0.16)	0.67 (0.09)	**<0.001** (0.10 – 0.25)
TAP, s	0.86 (0.24)	0.57 (0.18)	**<0.001** (0.21 – 0.37)	0.84 * (1.26)	0.57 * (1.30)	**<0.001** (1.38 – 1.58)	0.79 (0.22)	0.58 (0.12)	**<0.001** (0.10 – 0.30)
RT, s	0.54 (0.11)	0.41 (0.08)	**<0.001** **	0.52 (0.13)	0.42 (0.08)	**<0.001** (0.07 – 0.14)	0.71 (0.22)	0.55 (0.14)	**0.003** (0.06 – 0.26)
MT, s	1.19 * (1.26)	0.73 * (1.33)	**<0.001** (1.49 – 1.77)	1.20 * (1.27)	0.80 * (1.24)	**<0.001** (1.40 – 1.61)	1.24 (0.35)	0.91 (0.18)	**<0.001** (0.07 – 0.17)
%TPA	34.8 (5.9)	34.6 (4.8)	0.906 (-2.2 – 2.4)	31.8 (6.1)	35.8 (4.9)	**0.001** (-6.2 – -1.7)	34.6 (5.1)	36.2 (3.5)	0.110 (-3.6 – 0.4)
%TPV	46.5 (6.7)	52.0 (5.7)	**<0.001** (-7.6 – -3.6)	44.4 (7.9)	53.9 (7.0)	**<0.001** (-11.6 – -7.3)	47.4 (6.0)	51.5 (6.2)	**0.001** (-6.3 – -2.0)
%TPD	72.2 (7.8)	73.3 (7.2)	0.478 (-4.4 – 2.1)	70.6 (9.3)	74.7 (6.0)	**0.011** (-7.2 – -1.0)	70.2 (7.3)	74.4 (5.3)	**0.014** (-7.4 – -1.0)
%TAP	70.0 * (1.28)	76.2 * (1.14)	**0.020** (1.17 – 0.99)	71.4 (12.2)	73.0 (10.9)	0.178 (-4.0 – 0.8)	65.8 (10.8)	68.0 (9.5)	0.507 (-8.7 – 4.5)

Legend: * denotes geometric mean, ** denotes non-parametric *p* value.

7.2.3.1 Comparing intra-group change between NAT and MAX

Intra-group changes between NAT and MAX are shown in Table 29. For all three groups RT, MT, time to peak and mean reach parameters and TAP are significantly quicker in MAX. Likewise, the values of peak reach parameters are significantly greater in MAX for all three groups. For all groups %TPA, %TPV, %TPD and %TAP occur later in MAX than NAT but whether or not the changes are significant varies.

7.2.3.2 Comparing inter-group change between NAT and MAX

Table 30 presents the comparison of ratio differences for NAT:MAX. There is no significant difference between the groups for RT (*p* 0.672), suggesting the reduction in RT seen in MAX compared to NAT is proportional between groups. In contrast, MT is significantly different (*p* 0.017) and post-hoc inspection suggests that the significant difference is between PDD and PD-NC (*p* 0.013). With the exception of PDe, all peak reach and time to peak reach parameters show significant group change. All the results demonstrate that compared to NAT, PDD are least able to 'speed up' in MAX.

Only %TPA (*p* 0.026) shows a significant group difference when time to reach and grasp parameters are normalised for MT.

7.2.3.3 Summary of results for MAX

All groups are significantly quicker in MAX than NAT. Post-hoc inspection of results suggests that PDD have significantly prolonged MT and RT compared to PD-NC and PD-MCI in this condition. Furthermore, the ratio difference analysis intimates than PDD are less able than PD-NC to increase MT in MAX compared to NAT.

Table 30: Inter-group comparisons of NAT and MAX

	PD-NC (n = 37)	PD-MCI (n = 42)	PDD (n = 19)	p
PA (SD)	0.71 (0.16)	0.76 (0.15)	0.83 (0.16)	**0.034**
TPA	1.62 * (1.44)	1.32 * (1.30)	1.27 * (1.21)	**0.002**
MA	0.69 (0.16)	0.74 (0.16)	0.82 (0.17)	**0.021**
PV	0.78 (0.12)	0.80 (0.13)	0.90 (0.11)	**0.004**
TPV	1.50 (0.45)	1.24 (0.20)	1.25 (0.27)	**0.022 ****
MV	0.68 (0.12)	0.70 (0.14)	0.81 (0.15)	**0.004**
Pde	0.82 (0.26)	0.85 (0.22)	0.88 (0.21)	0.589
TPD	1.67 (0.51)	1.44 (0.29)	1.28 (0.26)	**0.007 ****
TAP	1.59 (0.53)	1.51 (0.35)	1.37 (0.37)	0.207 **
RT	1.33 (0.25)	1.26 (0.20)	1.33 (0.38)	0.672 **
MT	1.63 * (1.29)	1.51 * (1.25)	1.33 * (1.30)	**0.017**
TMTi	1.51 * (1.21)	1.41 * (1.20)	1.31 * (1.26)	**0.047**
DT	0.99 (0.04)	0.96 (0.05)	1.00 (0.05)	**0.005 ****
%TPA	1.02 (0.20)	0.90 (0.21)	0.96 (0.11)	**0.026**
%TPV	1.03 (0.08)	1.00 (0.11)	1.05 (0.11)	0.195
%TPD	0.98 * (1.15)	0.94 * (1.16)	0.94 * (1.12)	0.297
%TAP	0.93 (0.14)	0.98 (0.11)	0.98 (0.19)	0.323 **
%RT	0.87 * (1.20)	0.88 * (1.14)	0.97 * (1.18)	**0.027**

Legend: * denotes geometric mean, ** denotes non-parametric *p* value. Value <1 = NAT < MAX, Value >1 = NAT > MAX.

7.2.4 Condition 4 – Memory guided (MEM)

As with the previous four conditions, RT is significantly different between the groups (p <0.001) and PDD have the longest RT (Table 31). Post-hoc tests are not possible because a non-parametric statistical test has been used. PDD have the longest MT by some way with a trend towards significance (p 0.081). PDD have lower peak and mean reach parameters than PD-NC and PD-MCI, with significant group differences for PA (p 0.007)

and MA (*p* 0.003). Likewise TPA, TPV and TPD are all significantly different between the groups and in each case PD-MCI and PD-NC have similar values whereas the values for PDD are greater. However, no-post hoc inspection has been performed because non-parametric tests have been used. TAP is non-significantly different between the groups and there are no significant group differences for %TPA, %TPV, %TPD and %RT.

Table 31: Condition 4 - MEM

	PD-NC (n = 37)	PD-MCI (n = 42)	PDD (n = 19)	p
PA, mm/s^2 (SD, range)	1613.6 * (1.44, 713.4 – 3866.1)	1630.4 * (1.24, 953.4 – 2556.7)	1246.0 * (1.50, 572.5 – 2591.5)	**0.007**
TPA, s	0.41 (0.09, 0.30 – 0.63)	0.45 (0.19, 0.26 – 1.02)	0.57 (0.21, 0.34 – 1.10)	**0.001 ****
MA, mm/s^2	876.4 * (1.45, 379.9 – 2121.8)	911.0 * (1.26, 528.5 – 1408.1)	671.0 * (1.47, 290.0 – 1261.4)	**0.003**
PV, mm/s	604.4 * (1.37, 301.9 – 1286.9)	592.9 * (1.29, 333.6 – 972.6)	511.8 * (1.48, 237.5 – 953.4)	0.140
TPV, s	0.61 (0.17, 0.39 – 1.18)	0.62 (0.28, 0.37 – 1.42)	0.81 (0.29, 0.47 – 1.48)	**0.002 ****
MV, mm/s	291.0 * (1.38, 129.0 – 555.6)	297.2 * (1.35, 125.2 – 487.8)	259.5 * (1.42, 1.30 – 464.1)	0.295
PDe, mm/s^2	-1499.6 (769.8, -3550.5 - -354.7)	-1372.9 (563.3, -2727.9 - -558.4)	-1245.4 (670.7, -2516.7 – 267.2)	0.280 **
TPD, s	0.95 (0.20, 0.64 – 1.46)	0.99 (0.40, 0.67 – 2.28)	1.31 (0.55, 0.76 – 2.36)	**0.009 ****
TAP, s	0.96 * (1.80, 0.57 – 2.66)	0.93 * (1.58, 0.33 – 2.66)	1.00 * (1.59, 0.45 – 2.32)	0.803
RT, s	0.51 (0.11, 0.34 – 0.72)	0.48 (0.10, 0.30 – 0.83)	0.68 (0.21, 0.35 – 1.15)	**<0.001 ****
MT, s	1.54 (0.45, 0.88 – 3.08)	1.55 (0.70, 0.86 – 4.15)	1.85 (0.69, 1.00 – 3.15)	0.081 **
TMTi, s	2.06 (0.53, 1.28 – 3.80)	2.03 (0.75, 1.30 – 4.75)	2.53 (0.76, 1.62 – 4.16)	**0.007 ****
DT, mm	271.2 (25.1, 219.9 – 310.4)	292.5 (26.5, 239.1 – 364.0)	269.1 (33.8, 196.7 – 312.5)	0.323
%TPA	27.4 * (1.29, 15.5 – 52.5)	29.3 * (1.24, 16.9 – 44.3)	31.5 * (1.24, 20.7 – 45.6)	0.101
%TPV	41.0 (9.1, 25.0 – 64.1)	41.5 (9.5, 24.0 – 59.7)	44.9 (8.6, 26.4 – 59.1)	0.306
%TPD	63.9 (9.6, 40.5 – 84.0)	66.5 (11.4, 38.1 – 82.2)	70.1 (6.9, 55.3 – 81.0)	0.094
%TAP	67.9 (10.3, 44.9 – 86.5)	66.3 (13.7, 33.4 – 86.6)	63.0 (12.2, 40.3 – 82.4)	0.484
%RT	25.3 * (1.18, 19.3 – 36.6)	24.8 * (1.28, 12.9 – 38.9)	27.0 * (1.37, 15.5 – 41.3)	0.431

Legend: * denotes geometric mean, ** denotes non-parametric *p* value.

7.2.4.1 Comparing intra-group change between NAT and MEM

Intra-group analysis (Table 32) demonstrates that RT in MEM is significantly quicker than NAT for PD-NC (*p* 0.042) and PD-MCI (*p* 0.028) but not PDD (*p* 0.566). In contrast, all groups have significantly longer MT in MEM than NAT (*p* <0.001). Associated with the prolonged MT in MEM, all groups have significantly reduced values for peak reach parameters. The general pattern of change is that all groups take longer to attain peak reach parameters and TAP, although whether or not the prolongation is significant varies between the groups.

%TPA, %TPV and %TPD occur earlier in MEM compared to NAT for all groups but the difference is only significant for PD-NC and PD-MCI. %TAP also occurs earlier in MEM across the groups but non-significantly.

7.2.4.2 Comparing inter-group change between NAT and MEM

Results are presented in Table 33. The ratio difference for RT is non-significant between the groups (*p* 0.946). MT shows a significant group difference (*p* 0.025) and post-hoc inspection suggests that the prolongation of MT in PDD is significantly greater than that seen in PD-MCI (*p* 0.022) but not PD-NC (*p* 0.098). Significant group differences are also seen in PA, MA, PV and PDe. In each case the results demonstrate that PDD have the largest reduction in these parameters. Where possible (PV, PDe), post-hoc inspection suggests the ratio difference for PDD is significantly different to both PD-NC and PD-MCI. There are also significant group differences for TPA, TPV and TPD and again the greatest ratio change is seen in PDD, implying prolongation of the parameters is greatest in that group.

%TPA and %TPD also show significant group differences. In both cases the ratio difference implies that the reduction in %TPA and %TPD seen in MEM compared to NAT is greatest in PD-NC.

Table 32: Intra-group comparisons for NAT and MEM

	PD-NC NAT	PD-NC MEM	p (95% CI)	PD-MCI NAT	PD-MCI MEM	p (95% CI)	PDD NAT	PDD MEM	p (95% CI)
PA, mm/s^2 (SD)	1800.3 * (1.30)	1613.6 * (1.44)	**0.015** (1.02 – 1.22)	1872.0 (456.8)	1667.4 (353.2)	**0.004** (68.4 – 340.9)	1933.4 (526.3)	1347.5 (570.3)	**<0.001** (361.2 – 810.7)
TPA, s	0.42 (0.11)	0.41 (0.09)	0.734 **	0.37 * (1.19)	0.42 * (1.40)	**0.043** (0.80 – 1.00)	0.42 (0.09)	0.57 (0.21)	**0.001** (-0.24 – -0.07)
MA, mm/s^2	1005.7 (309.7)	941.4 (401.4)	**0.002 ****	992.4 (1.28)	911.0 (1.26)	**0.017** (1.02 – 1.17)	980.1 * (1.32)	671.0 * (1.47)	**<0.001** (1.27 – 1.68)
PV, mm/s	700.0 (162.7)	635.9 (222.2)	**<0.001 ****	672.4 * (1.29)	592.9 * (1.29)	**<0.001** (1.06 – 1.21)	733.4 (170.8)	549.5 (212.5)	**<0.001** (119.4 – 248.5)
TPV, s	0.56 (0.12)	0.61 (0.17)	**0.004** (-0.09 – -0.02)	0.53 (0.08)	0.62 (0.28)	0.152 **	0.57 (0.12)	0.81 (0.29)	**0.002** (-0.37 – 0.10)
MV, mm/s	333.5 (77.3)	306.2 (100.8)	**0.004 ****	329.6 (78.0)	309.6 (85.6)	0.102 (-4.1 – 44.2)	323.9 * (1.28)	259.5 * (1.42)	**0.001** (1.12 – 1.39)
PDe, mm/s^2	-1839.5 (614.6)	-1499.6 (769.8)	**<0.001**	-1811.4 (684.1)	-1372.9 (563.3)	**<0.001** (-611.9 – -265.1)	-1944.9 (654.2)	-1245.4 (670.7)	**<0.001 ****
TPD, s	0.87 (0.15)	0.95 (0.20)	**<0.001** (-0.13 – -0.04)	0.85 (0.12)	0.99 (0.40)	0.052 **	0.85 (0.16)	1.31 (0.55)	**0.002 ****
TAP, s	0.81 * (1.35)	0.96 * (1.80)	**0.004** (0.75 – 0.94)	0.84 * (1.26)	0.93 (1.58)	0.091 (0.81 – 1.02)	0.79 (0.22)	1.11 (0.55)	**0.019** (-0.59 – -0.06)
RT, s	0.54 (0.11)	0.51 (0.11)	**0.042** (0.00 – 0.06)	0.52 (0.13)	0.48 (0.10)	**0.028** (0.00 – 0.07)	0.71 (0.22)	0.68 (0.21)	0.566 (-0.07 – 0.12)
MT, s	1.23 (0.30)	1.54 (0.45)	**<0.001 ****	1.24 (0.33)	1.55 (0.70)	**<0.001 ****	1.24 (0.35)	1.85 (0.69)	**<0.001** (-0.90 – -0.32)
%TPA	34.8 (5.9)	28.3 (7.6)	**<0.001** (3.8 – 9.0)	31.8 (6.1)	30.0 (6.3)	**0.024 ****	34.6 (5.1)	32.2 (7.0)	0.080 (-0.3 – 5.1)
%TPV	46.5 (6.7)	41.0 (9.1)	**<0.001** (3.1 – 7.7)	44.4 (7.9)	41.5 (9.5)	**0.028 ****	47.4 (6.0)	44.9 (8.6)	0.214 (-1.6 – 6.5)
%TPD	72.2 (7.8)	63.9 (9.6)	**<0.001** (5.1 – 11.5)	70.6 (9.3)	66.5 (11.4)	**0.012** (0.9 – 7.3)	70.2 (7.3)	70.1 (6.9)	0.954 (-5.0 – 5.2)
%TAP	70.7 * (1.28)	67.1 * (1.17)	0.309 (0.95 – 1.17)	71.4 (12.2)	66.3 (13.7)	0.013 (1.1 – 9.1)	65.8 (10.8)	63.0 (12.2)	0.489 (-5.7 – 11.3)

Legend: * denotes geometric mean, ** denotes non-parametric *p* value.

Table 33: Inter-group comparisons for NAT and MEM

	PD-NC (n = 37)	PD-MCI (n = 42)	PDD (n = 19)	p
PA (SD)	1.15 (0.27)	1.14 (0.26)	1.56 (0.44)	**0.001 ****
TPA	1.03 (0.25)	0.94 (0.30)	0.79 (0.26)	**0.004 ****
MA	1.14 (0.25)	1.12 (0.26)	1.52 (0.42)	**<0.001 ****
PV	1.13 * (1.19)	1.13 * (1.24)	1.39 * (1.26)	**0.001**
TPV	0.93 (0.15)	0.93 (0.22)	0.78 (0.33)	**0.007 ****
MV	1.14 (0.22)	1.11 (0.29)	1.28 (0.27)	0.066
PDe	1.30 * (1.33)	1.32 * (1.36)	1.71 * (1.43)	**0.005**
TPD	0.92 (0.12)	0.93 (0.23)	0.74 (0.30)	**0.003**
TAP	0.84 * (1.39)	0.91 * (1.43)	0.76 * (1.60)	0.229
RT	1.08 (0.19)	1.08 (0.19)	1.07 (0.26)	0.946
MT	0.81 * (1.21)	0.84 * (1.32)	0.69 * (1.40)	**0.025**
TMTi	0.87 * (1.17)	0.89 * (1.27)	0.78 * (1.35)	0.090
DT	1.01 (0.04)	0.96 (0.06)	1.00 (0.14)	**<0.001 ****
%TPA	1.29 (0.36)	1.09 (0.21)	1.10 (0.20)	**0.022 ****
%TPV	1.16 (0.18)	1.10 (0.21)	1.08 (0.20)	0.285
%TPD	1.14 * (1.15)	1.07 * (1.18)	1.00 * (1.17)	**0.017**
%TAP	1.09 (0.25)	1.11 (0.24)	1.09 (0.29)	0.907
%RT	1.23 (0.17)	1.20 (0.20)	1.34 (0.25)	0.053

Legend: * denotes geometric mean, ** denotes non-parametric *p* value. Value <1 = NAT < MEM, Value >1 = NAT > MEM.

7.2.4.3 Summary of results for MEM

As with NAT, VIS and MAX, RT is significantly different between the groups and is longest in PDD. The ratio difference for RT is non-significant, implying that the reduction seen in RT for each group in MEM compared to NAT is proportional. PDD have the longest MT but this is not significantly different between the groups. However, the ratio difference between NAT and MEM is significant between the groups and PDD have the biggest ratio

change, suggesting that reaching is more affected in MEM for PDD than PD-NC or PD-MCI. When peak reach and grasp parameters are considered as a percentage of movement time there are no significant differences between the groups but the inter-group comparison suggests that the reduction seen in %TPA and %TPD in all groups is disproportionally greater in PD-NC than the other groups.

7.3 Comparing the parameters of reach and grasp across the different conditions

As in Chapter 6, an alternative way of presenting the data is to compare reach and grasp parameters in the cognitive groups across the different conditions.

7.3.1 Reaction time

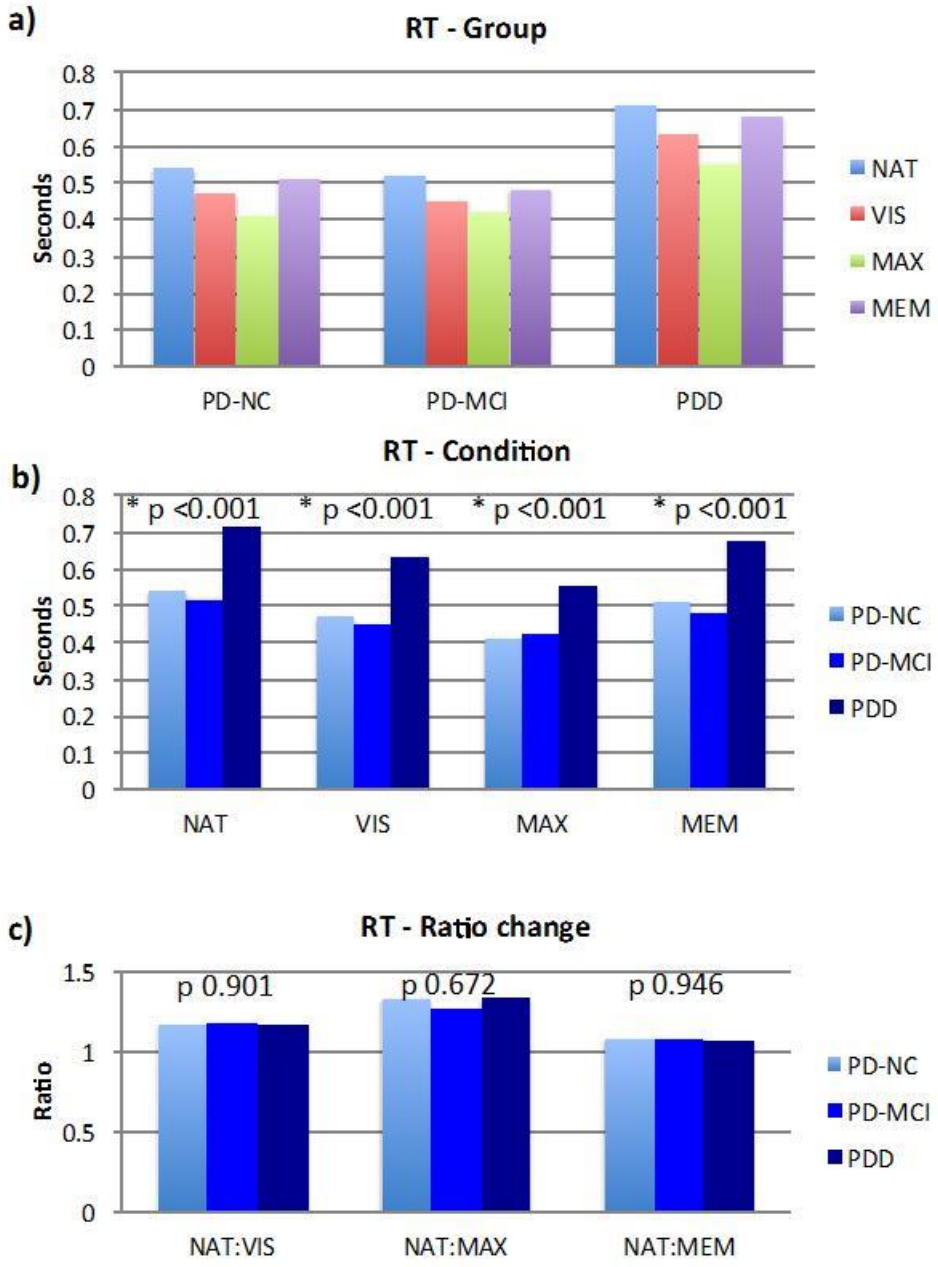
All of the PD cognitive groups follow the same pattern of RT across the conditions (Figure 56a); MAX < VIS < MEM < NAT. This is also the pattern seen in C-NC (Chapter 6). RT is significantly different (p <0.001) in all four conditions (Figure 56b). Where post-hoc inspection is possible (NAT, VIS, MAX) the results suggest that RT is significantly longer in PDD than the other two groups, but there is no significant difference in RT between PD-NC and PD-MCI. The pattern of results is similar in MEM.

The reduction in RT seen in VIS and MEM compared to NAT is significant for PD-NC and PD-MCI but not PDD, whereas all groups have a significantly shorter RT when MAX is compared to NAT. Despite this, the ratio change between NAT:VIS (p 0.901), NAT:MAX (p 0.672) and NAT:MEM (p 0.946) are non-significant between the groups, suggesting that the reduction in RT seen in VIS, MAX and MEM is proportional for each of the cognitive groups (Figure 56c).

Overall, PDD appear to have a significantly prolonged RT compared to PD-NC and PD-MCI in all conditions, but the prolongation does not

disproportionally change in any condition. The PD cognitive groups and C-NC follow the same pattern of RT across the conditions.

Figure 56: Reaction time for PD-NC, PD-MCI and PDD



Legend: RT follows the same pattern across the conditions (a). There is a highly significant difference in RT in all conditions and in each case PDD have the longest RT (b). Ratio differences are non-significant, suggesting proportional RT changes in the cognitive groups (c).

7.3.2 Movement time

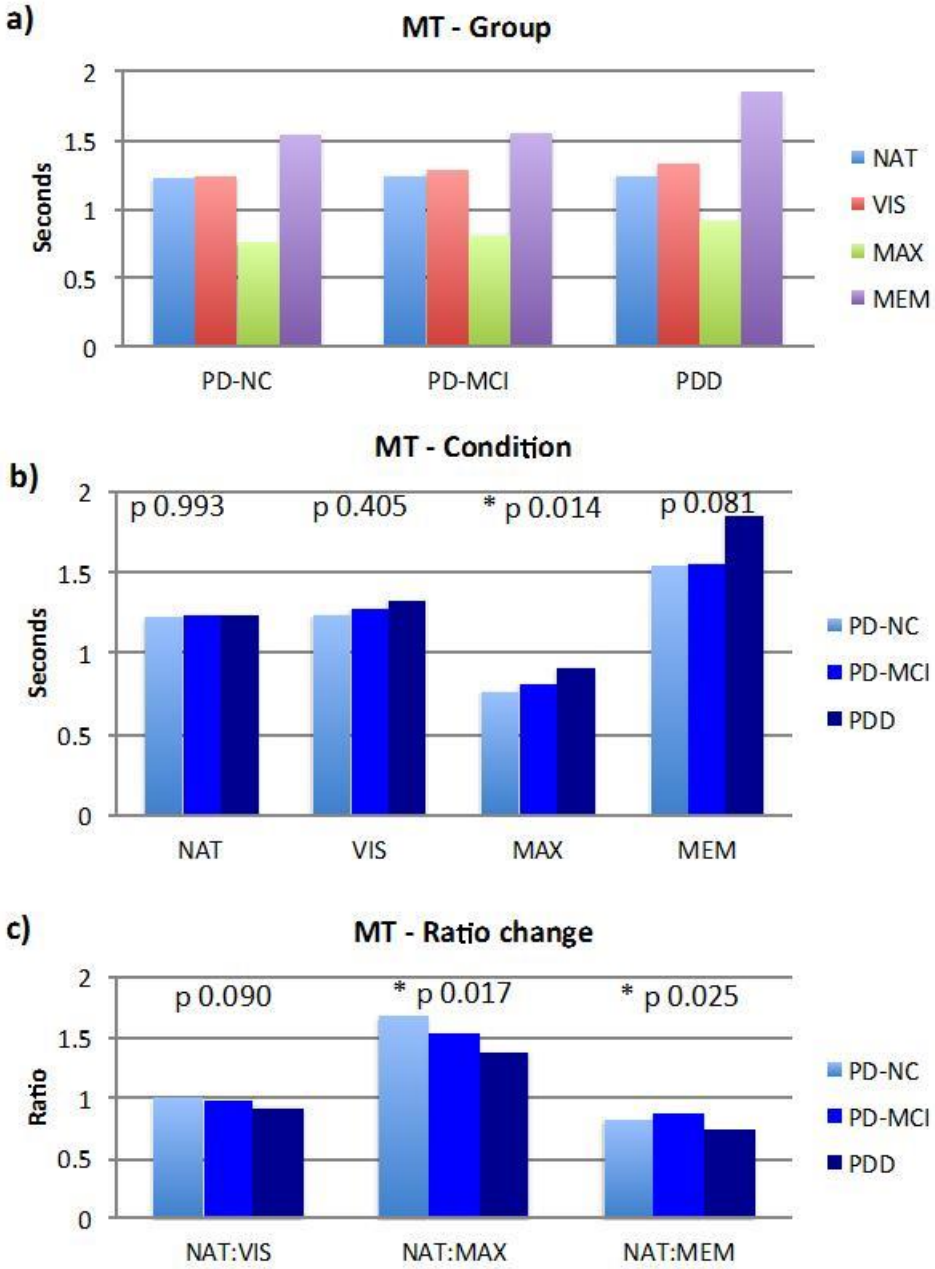
MT follows a similar pattern in the three cognitive groups; MAX < NAT < VIS < MEM (Figure 57a). There is no significant difference in MT between the groups for NAT (*p* 0.993), VIS (*p* 0.405) or MEM (*p* 0.081) (Figure 57b). The intra-group prolongation of MT in VIS compared to NAT is non-significant for PD-NC (*p* 0.549) and PD-MCI (*p* 0.202) but is significant for PDD (*p* 0.036). The inter-group analysis confirms that PDD have the greatest prolongation of MT in VIS compared to NAT but overall there is no significant difference between the groups (*p* 0.090) (Figure 57c).

For MEM, all groups have significantly prolonged MT in comparison to NAT (*p* <0.001). Unlike VIS, the ratio difference is statistically significant between the groups (*p* 0.025) and post-hoc inspection suggests that the difference lies between PDD and PD-MCI (*p* 0.022).

There is a statistically significant difference in MT between the groups for MAX (*p* 0.014). Post-hoc inspection indicates MT in PDD is significantly longer than both PD-MCI (*p* 0.020) and PD-NC (*p* <0.001). All groups have significantly reduced MT in MAX compared to NAT but the ratio difference is significant (*p* 0.017) and post-hoc inspection suggests PDD are significantly less able to reduce MT than PD-NC in MAX.

Overall, the results suggest that MT is most prolonged for PDD in VIS and MEM, with little difference between PD-NC and PD-MCI. For MAX, PDD are disproportionally less able to reduce MT compared to PD-NC.

Figure 57: Movement times in PD-NC, PD-MCI and PDD



Legend: MT follows the same pattern across the groups (a). MT for MAX is significantly different between the groups (b) and ratio change is significantly different between the groups for NAT:MAX and NAT:MEM (c).

7.3.3 Peak reach parameters

The only statistically significant difference in peak reach parameters across the cognitive groups is PA in MEM (*p* 0.007). However, there are a number of significant differences in the ratio changes (Figure 58b, d, f). In NAT:VIS there is a significant ratio change for PA (*p* 0.004), PV (*p* 0.002) and PDe (*p*

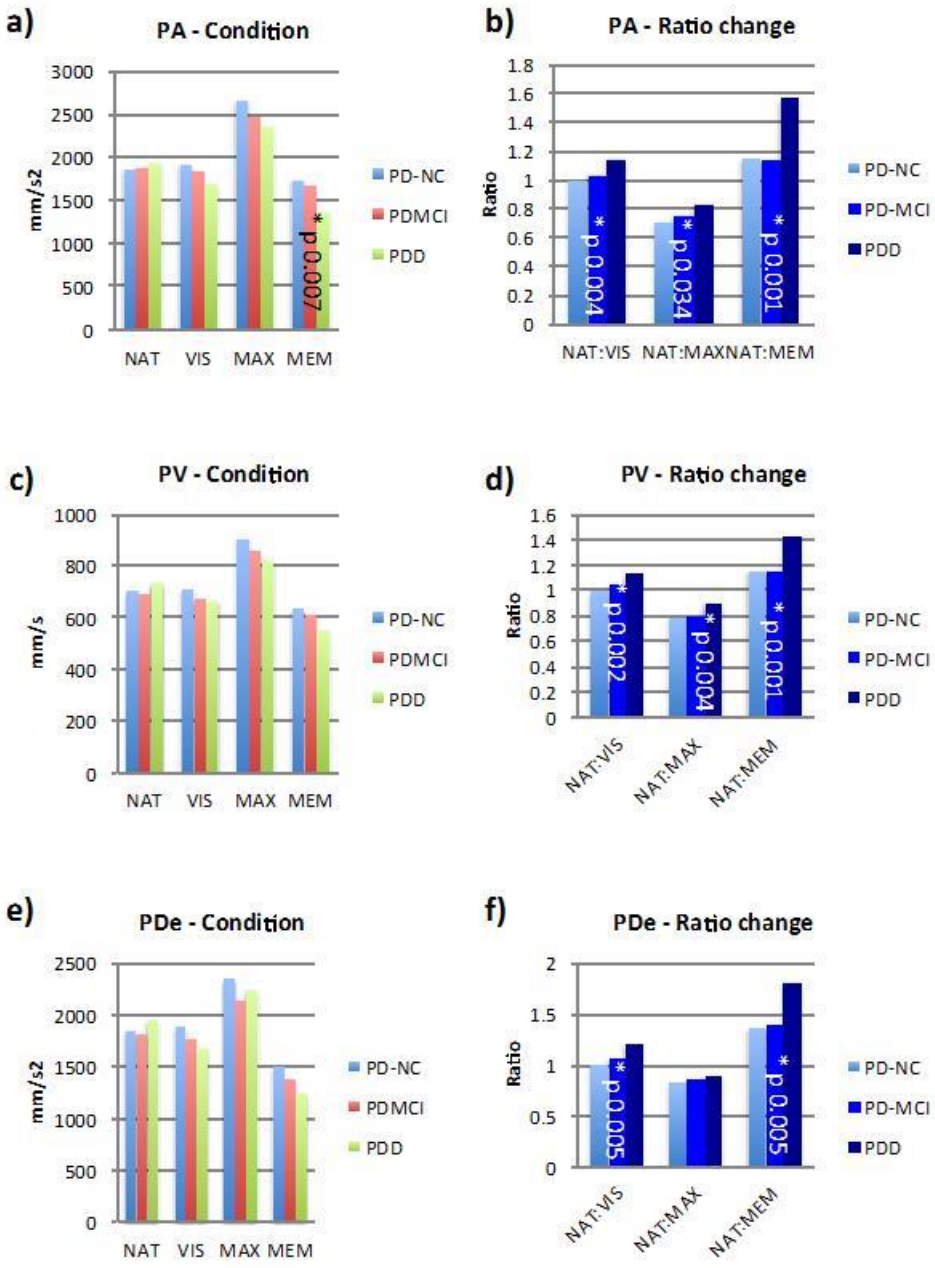
0.005). Where possible, post-hoc inspection suggests PDD have a significantly greater reduction in PA than PD-NC (*p* 0.003) and in PDe than both PD-NC (*p* 0.003) and PD-MCI (*p* 0.040) for VIS compared to NAT.

For NAT:MAX there are significant ratio changes for PA (*p* 0.034) and PV (*p* 0.004). Post-hoc inspection intimates that PDD are disproportionately less able to increase PA compared to PD-NC, and PV compared to both PD-NC (*p* 0.003) and PD-MCI (*p* 0.020).

The ratio change for NAT:MEM is significant between the groups for all peak reach parameters (PA *p* 0.001, PV *p* 0.001, PDe *p* 0.005). Post-hoc inspection follows the trend seen in VIS; for PA PDD have a disproportionate reduction compared to PD-NC (*p* 0.001) and PD-MCI (*p* 0.001). For PDe the pattern is the same and shows a disproportionate reduction in PDD compared to both other groups (PD-NC *p* 0.007, PD-MCI *p* 0.010).

Overall, the inter-group ratio changes follow the pattern of change seen in MT (peak reach parameters and movement time are highly negatively correlated – see Chapter 6.2.3).

Figure 58: Peak reach parameters in PD-NC, PD-MCI and PDD



Legend: There is only one significant difference in peak reach parameters across the groups (a) but a number of significant differences in ratio changes are seen (b, d, f).

7.3.4 Time to peak reach parameters

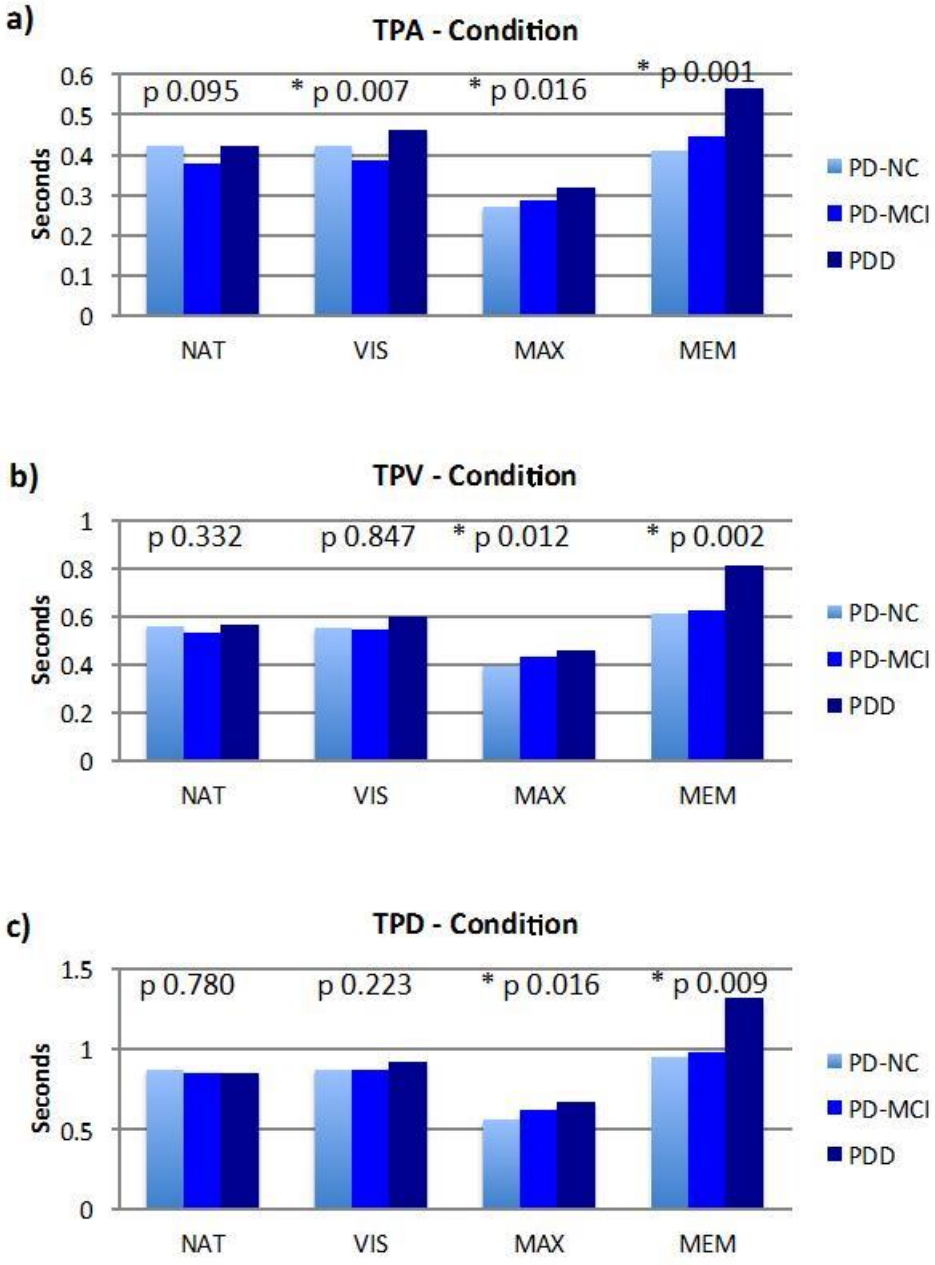
For NAT and VIS the only significantly different time to peak reach parameter is TPA in VIS (Figure 59a). The inter-group ratio difference for NAT:VIS is only significantly different between the groups for PDe (*p* 0.039).

For MAX, there are significant differences in TPA, TPV and TPD between the cognitive groups. Furthermore, the ratio difference for NAT:MAX is also statistically significant for the reach parameters and the pattern is a replication of MT; PDD are least able to decrease MT in MAX compared to NAT whereas PD-NC are most able. Post-hoc inspection is possible for TPD and shows that the reduction in TPD in PD-NC is significantly greater than both PD-MCI (*p* 0.007) and PDD (*p* 0.012).

For MEM, as with MAX, there are significant differences in all peak reach parameters between the groups. PDD have the greatest increase in peak reach parameters in MEM compared to NAT, and for TPD post-hoc inspection indicates that PDD are significantly different from PD-NC (*p* 0.007) and PD-MCI (*p* 0.022).

In summary, the changes in time to peak reach parameters in MAX support the results of MT and peak reach parameter in suggesting that PD-NC are most able, and PDD least able, to reduce time to peak parameters. Additionally, the results show that time to peak reach parameters are most prolonged in MEM compared to NAT in PDD, in keeping with the findings of MT and peak reach parameters for this condition.

Figure 59: Time to peak reach parameters in PD-NC, PD-MCI and PDD



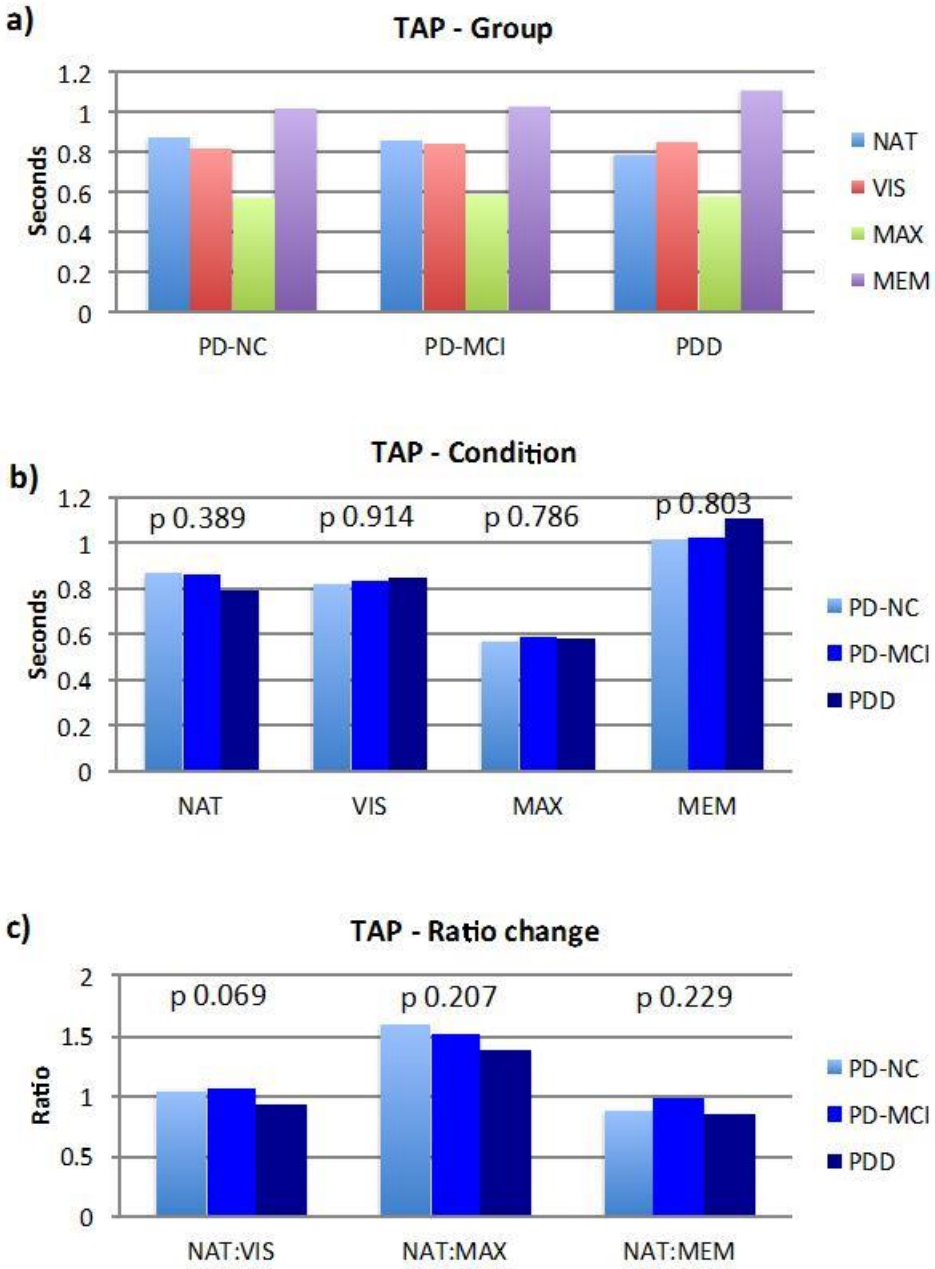
Legend: TPA, TPV and TPD across the conditions. The peak reach parameters are highly correlated with each other and therefore show a similar pattern of change.

7.3.5 Time to peak aperture

The measurement of TAP has limitations, as discussed in Chapter 6.1.2.5. The pattern of TAP is different across the groups but in all cases TAP occurs soonest in MAX and latest in MEM. There are no significant differences in TAP between the groups and the ratio differences are also non-significant. The results suggest that, in contrast to reach parameters, TAP remained

similar for the groups and the changes seen across the conditions remained proportional.

Figure 60: Time to peak aperture in PD-NC, PD-MCI and PDD



Legend: TAP is not significantly different between the groups in any condition and the changes are proportional.

7.3.6 Distance travelled

As discussed previously, DT provides a 2D measurement between Euclidean distance of the EM sensor from the magnetic source at the time

of movement onset and the end of the reach (see Chapters 5.5.2 and 6.4.6). It is not useful and will not be discussed further.

7.3.7 Time to peak reach and grasp parameters as a percentage of movement time

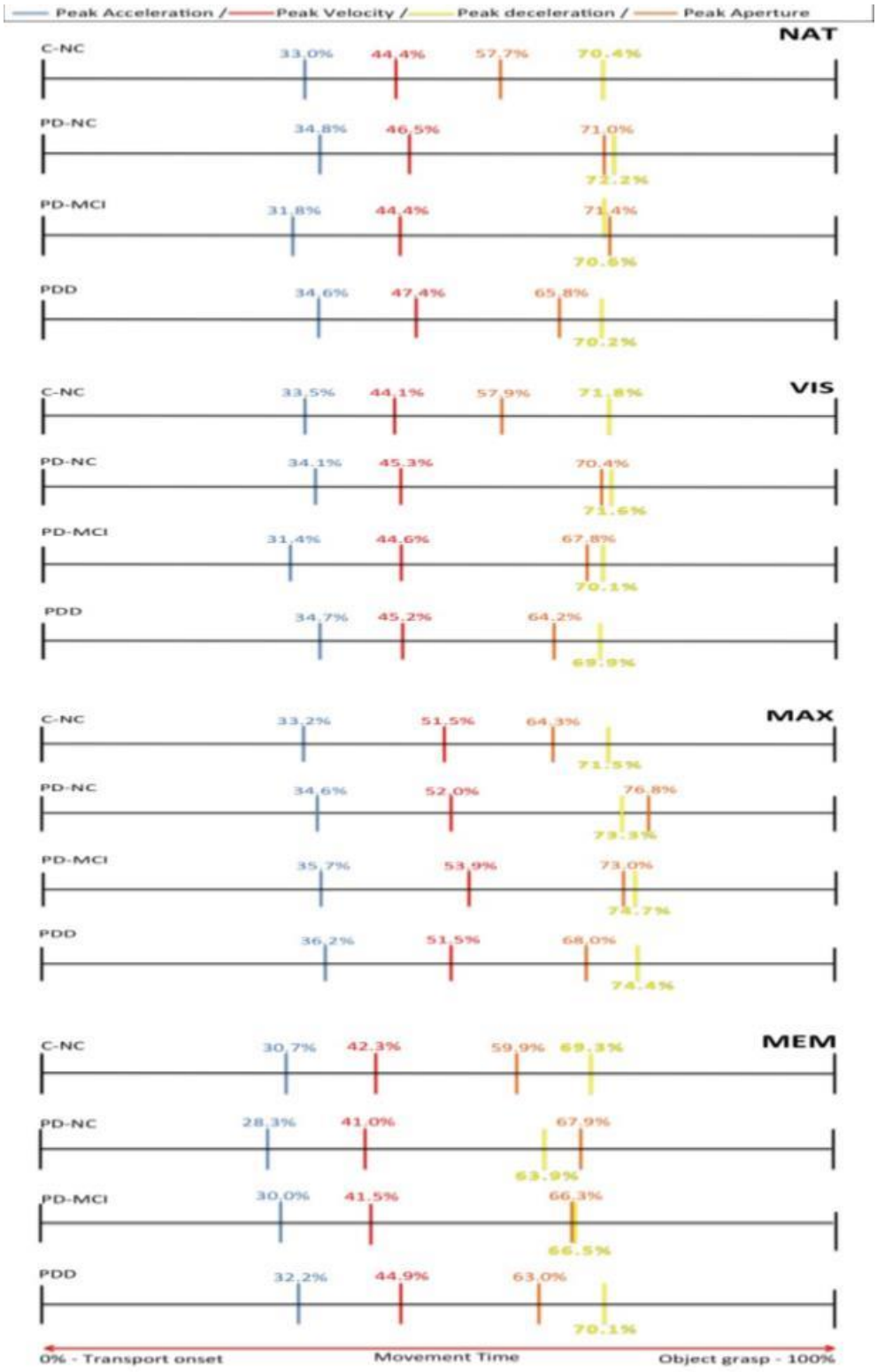
For NAT, VIS and MEM there are no significant differences in %TPA, %TPV, %TPD and %TAP between the groups. As shown in Figure 61, the pattern of %TAP occurring earliest in PDD compared to PD-NC and PD-MCI is seen in all conditions and for MAX there is a significant difference between the groups (*p* 0.006).

There are no significant ratio differences for reach parameters or %TAP between the cognitive groups for NAT:VIS, implying that the adjustment between the conditions is proportional. For MAX, the ratio difference for %TPA is significantly different (*p* 0.026) and post-hoc testing suggests that the difference lies between PD-NC and PD-MCI (*p* 0.021). For MEM, the only significant ratio difference is in %TPD (*p* 0.017) and post-hoc inspection suggests that the difference lies between PDD and PD-NC (*p* 0.015). Overall, the results generally suggest that reach and grasp parameters are similar between the groups when considered as a percentage of MT.

One noticeable feature of our results is that %TAP only rarely occurs after %TPD, and never so for PDD and C-NC. One of the core physiological findings on which Jeannerod based the visuomotor channel hypothesis was that TAP invariably occurred after TPD under visual guidance in healthy subjects (Jeannerod, 1984), although this was not always replicated in other studies (Marteniuk et al., 1987, Bootsma et al., 1994). In PwPD the suggested breakdown in the temporal coordination of reach and grasp often results in TAP being delayed compared to HC, occurring later than TPD (Castiello et al., 1993a) (see Figure 26 from 4.1.1 for a comparison of these landmarks normalised for MT – i.e. %TPD and %TAP – in HC and

PwPD). The discrepancy in our results may be a reflection of the way that TAP was calculated in this study, being a measure of time to maximal hand opening rather than maximal index finger to thumb aperture (see Chapter 5.6). Another difficulty in the interpretation of grasp data (TAP and %TAP) is that the size, or amplitude, of peak index finger to thumb aperture is unknown. Perhaps PDD attain %TAP earlier than PD-NC and PD-MCI because they have smaller amplitude of peak aperture. The grasp results from this chapter are intriguing but will be not be discussed further in this thesis because of the lack of validity of our method of calculating TAP compared to the conventional assessment and, most crucially, the potential unreliability of the grasp data caused by damage to the data gloves (see Chapter 6.1.2.5).

Figure 61: Time to peak reach parameters and time to peak aperture as a percentage of movement time in PD-NC, PD-MCI and PDD



Legend: Generally speaking, values for %TPA, %TPV and %TPD are similar between the PD cognitive groups across the four conditions. %TAP always occurs soonest in PDD, making this value closest to the %TAP values seen in C-NC.

7.4 Summary of reach and grasp results for PD-NC, PD-MCI and PDD

The results obtained from analysis of reach and grasp parameters in the three PD cognitive groups are outlined below:

- The order of increase in RT is the same for all three cognitive groups and is the same as observed in C-NC: MAX < VIS < MEM < NAT.
- Throughout all four conditions RT is significantly different between the groups and in all cases PDD have the longest RT.
- Despite the significant difference in RT between the groups for each condition, the ratio changes are non-significant. This suggests that each cognitive group modifies RT to a similar degree in each condition.
- Parameters of reach and grasp are not significantly different between the cognitive groups when reaching and grasping at a natural speed under full visual guidance (NAT).
- Reach and grasp towards an illuminated target at natural speed in a darkened room (VIS) produces no significant difference in MT between the cognitive groups but the intra- and inter-group analyses suggest that PDD have the greatest prolongation of MT in VIS compared to NAT. This finding is supported by significant differences in the inter-group ratio differences for peak reach parameters. There is therefore a suggestion that reaching is more affected for PDD in VIS than the other two cognitive groups.
- Reach and grasp with eyes closed (MEM) shows that PDD have the longest MT (non-significant, p 0.081) and inter-ratio changes imply that the prolongation of MT in MEM compared to NAT is disproportionate in PDD (p 0.025). This finding is supported by associated changes to peak reach and time to peak reach parameters. There is therefore some evidence to suggest reach is more affected for PDD than PD-NC or PD-MCI in MEM.

- Placed in context with the findings from Chapter 6, MEM appears to have a greater affect on reach in PDD compared to PD-NC, and on PD-NC compared to C-NC.
- Reaching and grasping at maximal speed under full visual guidance (MAX) takes significantly longer for PDD and there is evidence from the inter-group ratio changes that PDD are significantly less able to reduce MT in MAX compared to NAT than PD-NC. This finding is supported by associated changes to peak reach and time to peak reach parameters.
- Across the four conditions the parameters of reach and grasp in PD-NC and PD-MCI are very similar. It is PDD who appear to be most affected when reaching in VIS, MAX and MEM and they account for the significant differences seen across the cognitive groups.
- When normalised for MT, the peak reach and grasp parameters are generally non-significant between the groups. %TAP always occurs soonest in PDD and that value is closet to the value attained in C-NC. However, technical problems with the data glove may have influenced the results.

7.5 Associations between reach and grasp parameters and cognitive test scores

It has already been demonstrated that all cognitive test scores are significantly different across the PD groups (Table 22). This next section will present results of associations between parameters of reach and grasp and cognitive test scores, i.e. associations between motor and cognitive function. MT will continue to be used as a surrogate marker of reach in this section of the results. TAP results are potentially compromised because of the defective data glove and so will be excluded from this section. Therefore associations between reach and cognition, but not grasp and cognition, will be explored. RT will also be explored in this

section because it has been demonstrated that the cognitive groups follow the same pattern of RT across the four conditions.

Our results so far suggest that reach in PDD is more impaired than in the other cognitive groups in MEM and there is also some suggestion that PDD are most affected by VIS. Visuospatial function is one of the major domains affected in PD-CI (Emre et al., 2007, Litvan et al., 2012, Litvan et al., 2011) and our cognitive test scores support this. In keeping with the objectives of our study, correlation and regression will be used to test the hypothesis that prolonged MT (i.e. reach) is associated with poorer performance on tests of visuospatial function (JoLO, B-C and B-R) and that this association is greatest in MEM.

Attention is a component of RT according to some researchers (Wong et al., 2015), whilst others consider attention to be a constituent of executive function (Yarnall et al., 2011). For that reason the hypothesis that prolonged RT is associated with poorer performance on tests of executive function (TMT-B, TMT B-A) will also be tested.

7.5.1 Correlation between reaction time, movement time and cognitive test scores

Spearman's correlation coefficient, r_s, is a non-parametric assessment of the direction and strength of association. The results for MT, RT and the cognitive test scores are presented in a correlogram (Table 34). MT in one condition is strongly correlated with MT in the other conditions and the same is true for RT. MoCA score (i.e. global cognition) is significantly correlated with all the other cognitive tests results (the negative correlation with TMT-A, TMT-B and B-A occurs because a higher score in these tests indicates poorer performance).

There are a number of significant correlations between cognitive tests and MT or RT and these are also shown in Table 35 for clarity. Global cognition

is negatively correlated with MT in MAX and RT in VIS, MAX and MEM, i.e. a prolonged MT or RT correlates with lower MoCA score (i.e. worse global cognition). There is some limited support for the hypothesis linking visuospatial function with MT because JoLO is negatively correlated with MT in VIS and MAX. The other significant correlations are between visuospatial scores and RT. There are no significant correlations between executive function scores and RT.

Table 34: Correlogram of movement time, reaction time and cognitive tests scores for PD-NC for NAT

	MT-N	MT-V	MT-Ma	MT-Me	RT-N	RT-V	RT-Ma	RT-Me	MoCA	TMT-A	TMT-B	B-A	JoLO	B-C	B-R
MT-N		.83 **	.48 **	.59 **	.32 **	.28 **	.19	.25 *	.08	.09	.03	-.01	-.14	-.06	-.07
MT-V	.83 **		.61 **	.58 **	.30 **	.43 **	.27 **	.33 **	-.10	.12	.13	.02	-.26 **	.00	-.13
MT-Ma	.48 **	.61 **		.56 **	.06	.16	.16	.22 *	-.29 **	.13	.20	.06	-.21 *	-.19	.17
MT-Me	.59 **	.58 **	.56 **		.26 **	.18	.18	.43 **	-.09	.10	.14	.01	-.12	-.11	-.02
RT-N	.32 **	.30 **	.06	.26 **		.71 **	.64 **	.73 **	-.16	-.01	-.01	-.12	-.20	-.35 **	-.23 *
RT-V	.28 **	.43 **	.16	.18	.71 **		.58 **	.60 **	-.26 **	.06	-.07	-.17	-.23 *	-.16	-.30**
RT-Ma	.19	.27 **	.16	.18	.64 **	.58 **		.64 **	-.30 **	.09	.04	-.21	-.29 **	-.39 **	-.28 **
RT-Me	.25 *	.33 **	.22 *	.43 **	.73 **	.60 **	.64 **		-.22 *	-.03	0.1	-.03	-.14	-.28 **	-.16
MoCA	.08	-.10	-.29 **	-.09	-.16	-.26 **	-.30 **	-.22 *		-.31**	-.57 **	-.40**	.52 **	49 **	.56 **
Trail A	.09	.12	.13	.10	-.01	.06	.09	-.03	-.31 **		.53 **	-.32**	-.29 **	-.18	-.36 **
Trail B	.03	.13	.20	.14	-.01	-.07	.04	0.1	-.57 **	.53 **		.96 **	-.30 **	-.18	-.36 **
B-A	-.01	.02	.06	.01	-.12	-.17	-.11	-.03	-.40**	-.32**	.96 **		-.18	.10	-.03
JoLO	-.14	-.26 **	-.21 *	-.12	-.20	-.23 *	-.29 **	-.14	.52 **	-.29 **	-.30 **	-.18		.35 **	.48 **
B-C	-.06	.00	-.19	-.11	-.35 **	-.16	-.39 **	-.28 **	.49 **	-.18	-.18	.10	.35 **		.54 **
B-R	-.07	-.13	-.17	-.02	-.23 *	-.30 **	-.28 **	-.16	.56 **	-.36 **	-.36 **	-.03	.48 **	.54 **	

Legend: * denotes p <0.05 (2-tailed), ** denotes p <0.01 (2-tailed). **Abbreviations:** MT-N, Movement time in NAT; MT-V, MT-VIS; MT-Ma, MT-MAX; MT-Me, MT-MEM; RT-N, Reaction time in NAT; RT-V, RT-VIS; RT-Ma, RT-MAX; RT-Me, RT-MEM; MoCA, Montreal Cognitive Assessment; TMT-A, Trail Making Test Part A; TMT-B, Trail Making Test Part B; B-A; TMT-B score – TMT-A score; JoLO, Benton Judgment of Line Orientation; B-C, Benson Figure Copy; B-R, Benson Figure Recall.

Key: Grey shadings and correlation coefficient:

≥ 80 | 0.70 – 0.79 | 0.60-0.69 | 0.50-0.59 | 0.40- 0.49

Table 35: Significant correlations between movement time, reaction time and cognitive test scores (2-tailed)

Parameter	Condition	Cognitive test (r_s, p)
MT	VIS	JoLO (-.26, 0.009)
	MAX	MoCA (-.29, 0.004), JoLO (-.21, 0.039)
RT	NAT	B-C (-.35, <0.001), B-R (-.23, 0.021)
	VIS	MoCA (-.26, 0.009), JoLO (-.23, 0.023), B-R (-.30, 0.003)
	MAX	MoCA (-.30, 0.002), JoLO (-.29, 0.004), B-C (-.39, <0.001), B-R (-.28, 0.005)
	MEM	MoCA (-.22, 0.027), B-C (-.28, 0.005)

Abbreviations: MT, movement time; RT, reaction time; JoLO, Benton Judgment of Line Orientation; MoCA, Montreal Cognitive Assessment; B-C, Benson Figure Copy; B-R, Benson Figure Recall.

7.5.2 Simple linear regression models

Simple linear regression can be used to further identify associations between MT, RT and cognitive domains in the PwPD. It is a means of predicting the value of one variable (the dependent variable, e.g. MT or RT) from the value of another (the independent variable, e.g. score on a cognitive test). Two regression models have been used. In the first model MT for NAT was entered as the dependent variable and MoCA score was entered as the independent variable. This process was repeated for MT in conditions VIS, MAX and MEM and then the whole process repeated for RT in each of the four conditions. MoCA score has been explored in a separate model because it provides a marker of global cognition and it has been used to categorise PwPD into cognitive groups in this study. In addition, a similar technique has been employed in a recent study looking for associations between gait and cognition in PwPD (Lord et al., 2014). Statistically significant results are shown in Table 36.

In the second model the process was the same except all cognitive tests of executive function and visuospatial function were entered as independent variables instead of MoCA. An enter procedure was used for both models. Statistically significant associations are shown in Table 37.

Table 36: Simple linear regression for movement time and reaction time – Model 1

Parameter	Condition	Cognitive test	Beta	p (95% CI)	Adjusted R^2	ANOVA	p
MT	MAX	MoCA	-.256	0.011 (-.0022 – -0.003)	0.056	F (1,96) = 6.7	0.011
	MEM		-.199	0.049 (-.0059 – 0.000)	0.030	F (1,96) = 4.0	0.049
RT	NAT		-.246	0.015 (-0.017 – 0.002)	0.051	F (1,96) = 6.2	0.015
	VIS		-.317	0.001 (-0.016 – 0.004)	0.091	F (1,96) = 10.8	0.001
	MAX		-.483	<0.001 (-0.017 - -0.008)	0.225	F (1,96) = 29.2	<0.001
	MEM		-.419	<0.001 (-0.022 - -0.008)	0.167	F (1,96) = 20.4	<0.001

Abbreviations: MT, movement time; RT, reaction time; MoCA, Montreal Cognitive Assessment.

Table 37: Simple linear regression for movement time and reaction time – Model 2

Parameter	Condition	Cognitive test	Beta	p (95% CI)	Adjusted R^2	ANOVA	p
MT	MEM	TMT-B	.331	0.005 (0.002 – 0.010)	0.097	F (1,70) = 8.6	0.005
MT	VIS	JoLO	-.245	0.015 (-0.037 – -0.004)	0.050	F (1,96) = 6.1	0.015
RT	MAX	TMT-A	.238	0.018 (0.000 – 0.002)	0.047	F (1,96) = 5.8	0.018
RT	NAT	JoLO	-.201	0.047 (-0.018 – 0.000)	0.031	F (1,96) = 4.1	0.047
	VIS		-.239	0.018 (-0.016 – -0.002)	0.047	F (1,96) = 5.8	0.018
	MAX		-.272	0.007 (-0.013 – -0.002)	0.064	F (1,96) = 7.7	0.007
RT	NAT	B-C	-.451	<0.001 (-0.028 – -0.012)	0.195	F (1,96) = 24.4	<0.001
	VIS		-.296	0.003 (-0.018 – -0.004)	0.078	F (1,96) = 9.2	0.003
	MAX		-.369	<0.001 (-0.016 - -0.005)	0.127	F (1,96) = 15.2	<0.001
	MEM		-.297	0.003 (-0.020 – -0.004)	0.079	F (1,96) = 9.3	0.003
RT	NAT	B-R	-.306	0.002 (-0.020 – -0.004)	0.084	F (1,96) = 9.9	0.002
	VIS		-.337	0.001 (-0.018 – -0.005)	0.104	F (1,96) = 12.3	0.001
	MAX		-.366	<0.001 (-0.015 – -0.005)	0.125	F (1,96) = 14.9	<0.001
	MEM		-.272	0.007 (-0.017 – -0.003)	0.064	F (1,96) = 7.7	0.007

Abbreviations: MT, movement time; RT, reaction time; TMT-B, Trail Making Test Part B; JoLO, Benton Judgment of Line Orientation; TMT-A, Trail Making Test Part A; B-C, Benson Figure Copy; B-R, Benson Figure Recall.

In Model 1 the adjusted R^2 suggests that MoCA score, a measure of global cognition, accounts for a small amount of the variance of MT in MAX (5.6%)

and MEM (3%). For RT the variance explained by global cognition is greatest for MAX (22.5%), and the unstandardised coefficient (B) suggests that each single point reduction in total MoCA score is associated with an increase in RT of 0.012s. RT in MEM accounts for 16.7% of the variance of RT and every point reduction in MoCA score accounts for a 0.015s prolongation of RT.

Model 2 demonstrates that prolonged MT in VIS is associated with a lower JoLO score, explaining 5.0% of the variance. However, there were no other associations between visuospatial cognitive test results and MT. A higher TMT-B score (worse performance) is associated with a prolonged MT in MEM but it must be considered that a TMT-B result was only available for one of the ten PDD subjects.

There are a number of associations in Model 2 between tests of visuospatial function (some authors consider TMT-A to be predominantly a test of visual perception – see Chapter 5.3.3 (Sanchez-Cubillo et al., 2009)) and RT. As demonstrated in Table 34**,** JoLO, B-C and B-R scores are all significantly correlated with each other so an association with one of these tests is likely to mean an association with another. There is no clear pattern to the level of variance explained by the visuospatial test scores across RT in the four conditions but it is B-C score that overall explains the greatest variance. B-C score in NAT explains 19.5% of the variance of RT and 12.7% of the variance of RT in MAX. The unstandardised coefficients indicate that RT in NAT is prolonged by 0.020s, and RT in MAX is prolonged by 0.011s, for every single point decrease in B-C score.

7.5.3 Multiple linear regression models

Multiple linear regression represents linear relationships between a dependent variable and one or more independent variables. It is a useful tool because so far other factors that might influence MT or RT in PwPD have not been considered. For example, MT may be affected by the

severity of motor symptoms in PD and studies have confirmed that motor performance in humans slows with increasing age (Jimenez-Jimenez et al., 2011). Duration of disease is significantly different across the cognitive groups and this may also indirectly increase RT or MT, as those with longer disease duration may have more severe motor symptoms and are more likely to have cognitive dysfunction (Aarsland et al., 2007). For these reasons the same two models used for simple linear regression have been repeated but age, disease duration and MDS-UPDRS Part 3 score have been added to the independent variables to create two multiple regression models. The results are shown in Tables 38 and 39.

Table 38: Multiple linear regression for movement time and reaction time - Model 1

Parameter	Condition	Cognitive test	Beta	p (95% CI)	Adjusted R^2	ANOVA	p
RT	NAT	MoCA	-.248	0.016 (-0.017 – -0.002)	0.171	F (4,93) = 6.0	<0.001
		Disease duration	.361	<0.001 (0.006 – 0.019)			
	VIS	MoCA	-.301	0.004 (-0.017 – -0.003)	0.117	F (4,93) = 4.2	0.003
		Disease duration	.226	0.022 (0.001 – 0.012)			
	MAX	MoCA	-.484	<0.001 (-0.017 – -0.007)	0.251	F (4,93) = 9.1	<0.001
		Disease duration	.210	0.021 (0.001 – 0.009)			
	MEM	MoCA	-.436	<0.001 (-0.022 – -0.009)	0.225	F (4,93) = 8.0	<0.001
		Disease duration	.256	0.006 (0.002 – 0.014)			

Abbreviations: RT, reaction time; MoCA, Montreal Cognitive Assessment.

In Model 1 the inclusion of age, disease duration and MDS-UPDRS motor score has removed any significant association between MT and global cognition. In contrast, RT remains associated with global cognition in all

conditions and disease duration is also associated. The greatest variance is seen in MAX (25.1%) and MEM (22.5%). The unstandardised coefficients indicate that in PD subjects of identical age and disease duration with identical MDS-UPDRS Part 3 scores each single point reduction in MoCA would cause a 0.012s prolongation of RT in MAX and a 0.016s prolongation of RT in MEM.

Table 39: Multiple linear regression for movement time and reaction time - Model 2

Parameter	Condition	Cognitive test	Beta	p (95% CI)	Adjusted R^2	ANOVA	p
MT	MEM	TMT-B	.342	0.006 (0.002 – 0.010)	0.098	F (4,67) = 2.9	0.027
RT	MAX	TMT-A	.446	<0.001 (0.001 – 0.003)	0.198	F (4,90) = 6.8	<0.001
		Disease duration	.244	0.011 (0.001 – 0.009)			
	NAT	JoLO	-.195	0.049 (-0.017 – 0.000)	0.153	F (4,93) = 5.4	0.001
		Disease duration	.374	<0.001 (0.006 – 0.019)			
	VIS	JoLO	-.218	0.035 (-0.016 – 0.001)	0.078	F (4,93) = 3.1	0.021
		Disease duration	.245	0.015 (0.001 - 0.013)			
	MAX	JoLO	-.240	0.019 (-0.013 – -0.001)	0.099	F (4,93) = 3.7	0.008
		Disease duration	.249	0.013 (0.001 – 0.010)			
	NAT	B-C	-.381	<0.001 (-0.025 – -0.009)	0.256	F (4,93) = 9.3	<0.001
		Disease duration	.289	0.002 (0.004 – 0.016)			
	VIS	B-C	-.240	0.020 (-0.016 – -0.001)	0.088	F (4,93) = 3.3	0.013
	MAX	B-C	-.313	0.002 (-0.015 – -0.003)	0.173	F (4,93) = 4.9	0.001
	MEM	B-C	-.231	0.023 (-0.018 – -0.001)	0.108	F (4,93) = 3.9	0.005
		Disease duration	.248	0.016 (0.002 – 0.014)			
	NAT	B-R	-.337	0.001 (-0.021 – -0.005)	0.210	F (4,93) = 7.5	<0.001
		Disease duration	.342	<0.001 (0.005 – 0.018)			
	VIS	B-R	-.346	0.002 (-0.019 – -0.005)	0.131	F (4,93) = 4.7	0.002
		Disease duration	.213	0.030 (0.001 – 0.012)			
	MAX	B-R	-.358	0.001 (-0.015 – -0.004)	0.149	F (4,93) = 5.3	0.001
		Disease duration	.218	0.025 (0.001 – 0.009)			
	MEM	B-R	-.274	0.012 (-0.018 – -0.002)	0.119	F (4,93) = 4.3	0.003
		Disease duration	.269	0.007 (0.002 – 0.015)			

Abbreviations: MT, movement time; RT, reaction time; TMT-B, Trail Making Test Part B; TMT-A, Trail Making Test Part A; JoLO, Benton Judgment of Line Orientation; B-C, Benson Figure Copy; B-R, Benson Figure Recall.

In Model 2 the majority of significant associations are between RT and tests of visuospatial function, as seen in the simple linear regression model. In many cases disease duration is also significantly associated with RT. For RT in NAT, B-C score and disease duration account for 25.6% of the variance and the unstandardised coefficient implies that for each single point reduction in B-C score the RT of a PD subject of the same age, disease duration and motor score will increase by 0.017s.

7.6 Summary of results for associations between reach and grasp parameters and cognitive test score

- Prolonged MT in VIS and MAX has a significant correlation with worsening JoLO score but there are no other significant correlations between tests of visuospatial function and MT.
- A number of statistically significant although relatively weak correlations exist between prolonged RT and worsening global cognition (MoCA score) and prolonged RT and worsening visuospatial function (JoLO, B-C and B-R score). The strongest correlations involve RT in MAX.
- There are no correlations between tests of executive function (TMT-B, TMT B-A) and RT.
- Simple linear regression suggests a significant association between worsening global cognition and prolonged MT in MAX and MEM and with prolonged RT in all four conditions.
- A worse performance on any of the tests of visuospatial function is associated with prolonged RT, and B-C score explains the most variance of RT.
- When controlling for age, disease duration and motor score, global cognition remains significantly associated with RT in all conditions. The greatest association is with RT in MAX, where each single point reduction in MoCA score causes an increase in RT of 0.012s

- Multiple linear regression confirms that tests of visuospatial function remain associated with RT.

Overall, there is no convincing evidence to support the hypotheses that MT is significantly associated with visuospatial function or that RT is associated with executive function. The main finding is that worse global cognition and worse visuospatial function test scores are associated with a prolongation of RT in the PwPD in our study.

7.7. Discussion

This chapter has presented the results of reach and grasp across four different conditions in subjects with PD-NC, PD-MCI and PDD. In addition, correlations and associations between RT and MT and the results of cognitive tests have been explored. The same issues relating to the reliability of the data glove outlined in Chapter 6 mean that the primary focus of the discussion will again be on reach, rather than grasp.

7.7.1 Comparison with previous studies

There have been no previous published studies of reach and grasp in PDD or PD-MCI and so our results represent novel work. In the commonest form of dementia, AD, there is a single published study of reach and grasp (Caselli et al., 1999). Three subjects with AD who had limb apraxia (one of whom had confirmed pathological diagnosis at the time of publication) were included in a group of eight apraxic subjects who were compared with eight age-matched HC. Reach and grasp was performed at a natural speed under full visual guidance (comparable to NAT). The AD subjects had markedly impaired reach and grasp compared to HC, characterised by reduced time to attain peak reach and grasp parameters, deviation of trajectory of the reaching arm and a lack of temporal coupling between reach and grasp (Caselli et al., 1999).

In another study, 12 AD subjects were compared with 12 non-demented PwPD (disease duration 2.1 years) and 12 HC as they performed a reaching task using a pen on a digitising tablet whilst unable to see the reaching arm (Ghilardi et al., 2000). For the first task subjects were provided with visual feedback via a cursor on a computer screen, which was removed for the second task. AD subjects had significantly reduced mean velocity compared to PwPD and HC in both conditions. There were no significant differences in reaching accuracy between the three groups when visual feedback was provided but in its absence the AD subjects were significantly less accurate than the other groups. The authors speculated that the changes identified in the AD group represented early manifestations of limb apraxia (Ghilardi et al., 2000).

Limb apraxia is one form of apraxia and is a complex phenomenon caused primarily by damage to the parietal lobes, both inferior and superior (Leiguarda and Marsden, 2000). Apraxia is thought to be uncommon in PDD (Emre et al., 2007) although its detection may be hindered by the presence of motor abnormalities caused by dopaminergic deficiency. AD and PDD are both characterised pathologically by neocortical infiltration of abnormal forms of protein with associated degeneration and atrophy (Svenningsson et al., 2012). Direct damage to the major parietal nodes of reach and grasp is possible in both types of dementia and may explain, in part, the findings of the PDD group in our study and the previous studies of reach in AD (Caselli et al., 1999, Ghilardi et al., 2000). To ascertain the exact degree of damage to the parietal lobes at the time participants undertake reach and grasp experiments would require radiological correlation, ideally with structural imaging and imaging techniques capable of characterising the volume and distribution of α-syn, tau and amyloid.

7.7.2 The role of impaired proprioception and sensorimotor integration on reach and grasp under reduced visual guidance in Parkinson's disease dementia

The main finding in Chapter 6 was that reach (measured via MT) in PD-NC appears to be disproportionally affected in MEM compared to C-NC. It was argued that impaired proprioception and/or sensorimotor integration of proprioception could explain these results. How does that theory tie in with results from this chapter, which demonstrate that PDD appear to be more affected than PD-NC and PD-MCI by MEM, with some additional evidence to suggest that PDD are more affected by VIS?

Braak et al. proposed a pathological staging system for PD based on the caudo-rostral propagation of α-syn from the lower brainstem to the neocortex (Braak et al., 2003). According to that system the spread of Lewy pathology is associated with worsening damage to brain structures already involved (Braak et al., 2003). The correlation of pathological change with cognitive impairment in PD is complex but there are studies that suggest an association between Braak stage and cognition (Braak et al., 2005, Kempster et al., 2010, Braak et al., 2006). Furthermore, it is accepted that Lewy pathology in the neocortex is the major pathological driver of cognitive dysfunction in PDD (Halliday et al., 2014, Irwin et al., 2013). Although rather simplistic, it follows that those with Lewy pathology in the neocortex are in general more likely to have greater damage to the basal ganglia than those without Lewy pathology in the neocortex. In support of this, PDD have the highest MDS-UPDRS Part 3 score, the highest LEDD and the longest duration of disease in our study, although only the latter is statistically significant. Worsening of basal ganglia function may result in greater impairment of proprioceptive sensorimotor integration and therefore increased reliance on visual feedback to guide reach. In other words, if PDD have more severe basal ganglia dysfunction than PD-NC, impaired sensorimotor integration can be used as a theory to explain the findings of PDD in VIS and MEM, in addition

to the findings of PD-NC compared to C-NC. Deficits in proprioception and/or somatosensory integration are not directly related to cognitive function, but rather to the degree of damage to the basal ganglia, which progressively increases as α-syn propagates caudo-rostrally over time.

7.7.3 Visuospatial dysfunction in reach and grasp

An alternate cause to explain the apparent increased reliance on visual feedback to guide reach in PD-NC, which is then magnified in PDD, is an impairment of visuospatial function, which is well known to occur in PwPD (Litvan et al., 2011).

Before proceeding further it is important to discuss the concept of visuospatial function in more detail. It is a term that describes the ability of a person (or animal) to see, allowing perception of, and interaction with, the environment. This enables navigation and a recollection of where one has been (Possin, 2010). A number of schemas of this complex facet of cognition exist. One example is the perception-action model of the visual system (Goodale and Milner, 1992), discussed in Chapter 1.8. This proposes that motion and location information involved in the real-time transformation into motor actions pass from the primary visual cortex to the parietal lobes in the dorsal stream. The dorsomedial and dorsolateral reach and grasp circuits are both considered part of the dorsal stream according to this model. Parietal control of the dorsal stream is contralateral but there is a right hemisphere dominance (Possin, 2010). The ventral stream is involved in object recognition and identification. Progressively complex processing occurs as information passes from the primary visual cortex to visual association areas V2 – V5, the ITC and ultimately the ventrolateral prefrontal cortex (VLPFC) (Linden, 2007). The ventral stream has both ipsilateral and contralateral function (Possin, 2010). For clarity purposes, dorsal stream function will from now be considered as ‘visual spatial’ and ventral stream function will be considered as ‘visual perceptual’.

Another schema of visuospatial function is one which considers both egocentric and allocentric reference frames. The difference between the two can been demonstrated by using the study of rats placed in a water-maze containing an invisible platform (Morris, 1984). A rat attempts to find dry land by swimming around the water-maze within which are placed a number of visual cues. It eventually locates the invisible platform and is able to rest. If placed back in the water-maze at a different starting location, the rat may swim directly back to the platform or erroneously swim in the same direction it did previously in an attempt to find the platform. The former approach demonstrates an egocentric reference frame because object position is processed in reference to the rat itself (i.e. self-to-object). The latter approach is allocentric because the rat is presumed to use environmental cues in reference to each other to guide movement, rather than itself (i.e. object-to-object) (Possin, 2010). Extrapolating from this, an egocentric approach is important when interacting directly with the environment, such as when reaching and grasping, which requires continuous processing and interpretation of the spatial environment relative to the arm and hand (Castiello and Begliomini, 2008).

Different facets of visuospatial function are examined by the cognitive tests used in our study. JoLO is considered as a test of visual spatial function (dorsal stream) (Benton et al., 1978). Testing the ventral stream often involves recognition, for example shapes or faces, and is not examined in isolation by the cognitive tests in our study. However, B-C is a test of visuospatial construction, which requires both visual spatial and perceptual function, i.e. it examines both the dorsal and ventral streams. B-R is a test of visual memory, more specifically 'episodic visual memory', because recall occurs after 20 minutes (Possin et al., 2011). Deficits in visual memory may explain the reliance on visual feedback in PD-NC and PDD seen in our study.

7.7.4 Explaining the discrepancy between the results of visuospatial cognitive tests and reach and grasp parameters in MEM

In Chapter 6 it was shown that PD-NC and C-NC had non-significantly different scores for JoLO, B-R and B-C. This chapter demonstrates that all three visuospatial tests were significantly different across the cognitive groups, with PDD scoring lowest and PD-NC highest. JoLO was significantly different between all three groups whereas B-C and B-R scores were not significantly different between PD-MCI and PDD. The results imply that PD-NC have normal (as compared to C-NC) visual spatial and perceptual function as well intact episodic visual memory, with progressive abnormalities seen in PD-MCI and PDD. How is it possible to explain the difficulties that PD-NC encounter in MEM compared to C-NC in terms of visuospatial dysfunction if the groups have similar scores on the visuospatial cognitive tests performed? Likewise, how can the lack of significant associations between MT and JoLO, B-R and B-C using multiple regression analysis be explained if visuospatial impairment is a cause of reach dysfunction in MEM? Firstly, the visuospatial tests performed in our study are in no way exhaustive and deficits may have been identified if additional tests had been performed, as has occurred in large studies of PwPD who have normal cognition defined using global cognitive screening tests (Burdick et al., 2014). Secondly, it is feasible that PD-NC do show evidence of visuospatial dysfunction on the cognitive tests used in our study but the numbers are too small to detect a significant difference. Thirdly, the discrepancy could be explained because MEM is testing a different facet of visuospatial function than the cognitive tests in our study. More specifically, although B-R is a test of visual spatial memory, the delay between B-C and B-R is 20 minutes, mandating engagement of the hippocampal episodic memory system. In contrast, MEM requires subjects to remember where the cylinder is in space relative to the body (oneself) for a short period of time (eye closure to auditory tone was between three and seven seconds) and can therefore be considered a test of egocentric SWM.

7.7.5 Spatial working memory

Memory can be classified as long or short term. Long-term memory (LTM) can be divided in to procedural, a process of motor learning that is predominantly subconscious (for example, learning to ride a bike), or declarative. Declarative memory can be further divided into semantic memory and episodic memory. Semantic memory is the memory of facts independent of personal experience, for example the knowledge of capital cities. Episodic memories are personal memories attached to an event, for example the memory of a birthday or receiving exam results (Ullman, 2004). Short-term memory (STM) and working memory (WM) are terms that are often interchanged within medical literature. WM can be considered *"the interface between perception and action"* (Linden, 2007) and allows the retention and manipulation of information whilst attending to a task. It is temporary and cannot be improved by learning, in contrast to LTM. STM is the maintenance of information in the absence of manipulation. In theory WM and STM have an equal capacity but the process of information manipulation in WM often reduces capacity; for example, the recall of a digit span in the backwards order is reduced compared to recall in the correct order (Linden, 2007). MEM is a test of SWM rather than STM because spatial information is manipulated, rather than just stored, in the process of instigating the reach and grasp motor programmes.

An influential model of WM, initially proposed in 1974 and most recently updated in 2000 (Baddeley, 2000), suggests that auditory and verbal information (within the 'phonological loop') and visuospatial information (within the 'visuospatial sketchpad') are separate subsystems of WM which function as 'slave systems' to a 'central executive' that coordinates between the two and allocates attentional resource (Siegert et al., 2008). Each subsystem is linked to episodic LTM by the 'episodic buffer' (Baddeley, 2000). Within the visuospatial sketchpad there is now evidence to suggest that spatial and perceptual WM are functionally specialised, in the same

way that the dorsal and ventral streams can be considered functionally separate for the processing of visual spatial and perceptual information (Goodale and Milner, 1992).

In terms of SWM, single-cell microelectrode studies in macaques have identified neurons in the DLPFC (Niki and Watanabe, 1976) and PPC, specifically area 7A of the superior parietal lobe (Gnadt and Andersen, 1988), that remain active during a delay period before saccadic eye movements are made towards remembered targets in the dark. These so-called 'memory cells' (Olson and Berryhill, 2009) are thought to represent the loci of SWM, supported by studies that demonstrate an impairment in SWM if these neurons are transiently impaired by cooling (Quintana and Fuster, 1993). In the macaque, area 7A is in close proximity to V6A, the major parietal node of the dorsomedial reach pathway, and cooling of PPC neurons also leads to impairments of reach (Quintana and Fuster, 1993). Human studies using fMRI have also generally supported the concept of a spatial and perceptual visual WM (Olson and Berryhill, 2009).

7.7.6 Impairment of spatial working memory in Parkinson's disease

A number of studies have identified deficits in SWM in PwPD. As mentioned in Chapter 2.6.1, Owen et al. (Owen et al., 1992) and Lange et al. (Lange et al., 1992) demonstrated such deficits and showed that they were more severe in moderate versus mild disease and *off* versus *on* state, respectively. The caudate nucleus has strong connections with the DLPFC as part of the dopaminergic cognitive neural network (Alexander et al., 1986, Lewis and Barker, 2009), and dopaminergic depletion of the caudate is therefore likely to impair SWM (Possin et al., 2008). There is in fact pathological evidence that dopamine depletion in the caudate follows a dorsal-ventral gradient in PwPD (Piggott et al., 1999), just as in the putamen (Fearnley and Lees, 1991), and segregation of connectivity to the caudate from the PPC (dorsal stream, visual spatial function) and ITC (ventral stream, visual perception) may account for the comparative

worsening of SWM compared to perceptual WM that has been found in PwPD by some studies (Possin et al., 2008).

It was speculated in Chapter 6 that visual memory may be more relevant in explaining the results for PD-NC (and also PDD) in MEM than in previous comparable studies (Schettino et al., 2006, Adamovich et al., 2001) because of the longer delay between eye closure and reach initiation in our study. Interestingly, in a study of 18 PwPD and 18 HC it was demonstrated that deficits in SWM in PwPD, in contrast to deficits in perceptual WM, did not change as the duration of information storage was tested at one, five and ten seconds, implying that impaired maintenance of SWM is not affected in PwPD (Possin et al., 2008). Whether this would be the case in a reach and grasp experiment is unknown.

An important consideration is that all PwPD in this study were tested whilst *on*. This may have influenced SWM but as pointed on by Possin et al. (Possin et al., 2008), previous research suggests that dopamine improves (Lange et al., 1992) or has no influence on SWM performance, suggesting that our findings are related to underlying pathology.

To summarise, dopaminergic depletion of the caudate nucleus, which forms a SWM network with the PPC and DLPFC (Possin, 2010, Linden, 2007, Olson and Berryhill, 2009), may account for the difficultly experienced by PD-NC in MEM compared to C-NC. Other studies have suggested that SWM worsens with dopaminergic deficiency (Owen et al., 1992, Lange et al., 1992) and therefore, as with deficits in somatosensory sensorimotor integration, the worsening performance of PDD in MEM could be explained from a SWM perspective because PDD are likely to have more severe basal ganglia dysfunction than PD-NC.

7.7.7 Summary of the role of visual feedback on reach and grasp in the Parkinson's disease cognitive groups

Two alternate theories have been explored and discussed in this chapter and Chapter 6 in an attempt to explain the effect of visual feedback on reach in our study. The first is an impairment of proprioception and/or impairment of proprioceptive (somatosensory) sensorimotor integration. The second is impairment of egocentric SWM. Compared to C-NC it was demonstrated that PD-NC have a disproportionate prolongation of MT in MEM. No significant difference between C-NC and PD-NC was identified in VIS. It was suggested in Chapter 6 that in relation to impairment of proprioception and/or sensorimotor integration, the inability to fully darken the room in VIS made the task less difficult for PD-NC, allowing them to reach and grasp in a manner comparable to C-NC. VIS does not require SWM because participants are able to visualise the cylinder and the hand. Relative impairment of PDD in VIS must therefore be explained by an alternate mechanism. The visuospatial cognitive tests in our study showed that PDD were more impaired than PD-NC and PD-MCI and it is possible that visual spatial dysfunction – a greater impairment of the dorsal pathway, tested in our study by JoLO and B-C – caused reach to be more abnormal in VIS for PDD than the other cognitive groups.

In relation to MEM, it has been argued that greater impairment of basal ganglia function, mediated by dopaminergic denervation and Lewy pathology infiltration, may explain why PDD are more affected that PD-NC. This explanation is relevant for both somatosensory integration and SWM, as both depend on neural circuits involving the basal ganglia.

Furthermore, the neocortical infiltration of Lewy and AD related pathology (NFT and Aβ) in PDD (Irwin et al., 2012, Compta et al., 2011) might directly affect the PPC. In support of this, structural MRI scans have found parietal atrophy in PDD (Melzer et al., 2012) whilst other MRI studies have found a correlation between parietal grey matter atrophy in PDD and performance

on tests of visuospatial function (Pereira et al., 2009). Major nodes of reach (V6A), grasp (AIP in macaques, aIPS in humans) and SWM (7A in macaques) all reside in the parietal cortex and may be directly damaged by the structural and neurochemical changes that occur to this part of the brain in PDD.

7.7.8 Reaction time

It has been demonstrated that global cognition, as determined by MoCA score, is significantly associated with RT in all four conditions of our study, including after controlling for age, duration of disease and MDS-UPDRS Part 3 score. This can be linked to the similar pattern of RT in the four conditions for PD-NC, PD-MCI and PDD, because although MoCA score was not the only criteria used to categorise PwPD in our study it did differ significantly between groups. Our results also demonstrate that tests of visuospatial function are variably associated with RT across the conditions. RT is usually studied when volitional movements are made at the highest possible speed and therefore only the results from MAX will be discussed further.

7.7.8.1 What is reaction time?

RT is the time taken to respond to a stimulus. Simple RT (SRT) is when a stimulus elicits a known, or predetermined, response. SRT is measured in our study because participants were aware that they needed to reach for and grasp the cylinder and then lift it from the table surface. Choice RT (CRT) is when a variable stimulus requires a variable response.

7.7.8.2 Simple reaction time in Parkinson's disease

SRT is prolonged in PwPD, as evidenced by a number of studies reviewed in detail by Gauntlett-Gilbert and Brown (Gauntlett-Gilbert and Brown, 1998). This was confirmed in our study, which showed that PD-NC had significantly longer RT than C-NC in MAX (p 0.002). Our results also

demonstrated that RT in MAX was significantly different between the three PD cognitive groups (p <0.001).

RT involves movement preparation and movement execution. Both components can be considered as features of bradykinesia and have been shown to abnormal in PwPD (Berardelli et al., 2001). A number of different investigation techniques including electroencephalogram (EEG), PET and fMRI have explored brain activity in PwPD in the period of time just before movement onset, i.e. during movement preparation. The overall findings suggest that the SMA of PwPD is underactive compared to HC, whereas the lateral premotor areas are overactive (Berardelli et al., 2001). For example, recording of the Bereitschaftspotential [23] (BP) using EEG has shown that the initial component – which reflects SMA activity – is reduced in PwPD, whereas the second component – reflecting activity in the lateral motor cortices – is larger in PwPD than HC. Furthermore, changes in BP in PwPD are dopamine dependent (Dick et al., 1989).

As discussed in Chapter 6.6.5, SMA inactivity is thought to reduce the generation of internal motor-sub routines which are used to create a motor action (Goldberg, 1985). EEG activity in PwPD has been shown to normalise when movements are performed to an external stimulus rather than being self-paced (Jahanshahi et al., 1995), and it is argued that the attention required to respond to external stimuli activates the parietal and pre-motor cortices (lateral circuits), which compensate for the lack of internally generated motor actions in the basal-ganglia and SMA (medial circuits) (Goldberg, 1985, Berardelli et al., 2001). An increased reliance on external stimulation has been hypothesised to explain why PwPD appear to be more dependent on visual feedback to guide reach and grasp from a somatosensory sensorimotor integration perspective and is also thought to explain improvements in hand movements (Georgiou et al., 1993) and gait

[23] Bereitschaftspotential – EEG activity in the motor cortex and SMA preceding voluntary muscle movement.

(Thaut et al., 1996) when PwPD use auditory or visual cues. A deficiency of internal generation of movement caused by SMA under-activity has also been argued to explain why PwPD have prolonged SRT compared to HC. Furthermore, progressive dopaminergic deficiency has been linked to RT by some studies. For example, in 32 untreated PwPD a significant correlation was found between RT and nigrostriatal dopaminergic degeneration as determined by dopamine transporter SPECT scans (Muller et al., 1999). In our study PDD are likely to have more severe basal ganglia dysfunction, potentially explaining post-hoc inspection of our results that suggest PDD have a significantly longer RT than PD-NC and PD-MCI.

PwPD have difficulty with rapid muscle activation; it has been shown that the normal electromyography (EMG) tri-phasic pattern of muscle activation is lost in PwPD. In contrast to HC, the first agonist burst is smaller and subsequent bursts larger; a pattern that is improved but not normalised by levodopa (Hallett and Khoshbin, 1980). RT in our study was determined as the time from stimulus to movement onset and so delayed muscle activation – and therefore movement – could explain the prolongation of RT in PD-NC compared to C-NC. As with movement preparation, PDD could be more impaired than PD-NC from a movement execution perspective because they have more severe basal ganglia dysfunction.

7.7.8.3 Reaction time and cognition

Our results suggest that bradykinesia is not the only contributor to prolongation of RT in PwPD. Although bradykinesia specifically was not controlled for in our multiple linear regression models, an attempt was made to account for motor dysfunction more generally (including bradykinesia) by using MDS-UPDRS Part 3 score as one of the independent variables. Despite this (and as well as controlling for age and disease duration) a significant association between MoCA and RT in MAX was found in Model 1 and RT in MAX was significantly associated with TMT-A, JoLO, B-C and B-R in Model 2. Before proceeding further it should be

highlighted that MoCA score is significantly correlated with each of the cognitive tests used in Model B (see Table 34). It follows that if MoCA is associated with RT then it is likely that the other cognitive tests will also have a significant association. The lack of association between RT and TMT-B and B-A in MAX could be because data was only included from one of the PDD group.

A number of studies have found an association between RT, cognition and mortality in elderly people without PD. However, rather than individual SRT or CRT measurements, RT 'intra-individual variability (IIV)' [24] appears to be the most robust predictor. For example, in a 17-year prospective cohort study of nearly 900 elderly adults, increased RT IIV was associated with increased mortality even after adjustment for a range of baseline risk factors including age, gender and education (Batterham et al., 2014). In another cohort study of 212 elderly adults it was demonstrated that RT IIV at baseline significantly predicted those likely to develop or remain cognitively impaired at five years (Bielak et al., 2010). But why is RT IIV associated with increased risk of dementia or mortality? The answer is unknown but support for RT IIV as a marker of neurological dysfunction comes from a number of studies highlighting an association with structural brain changes, for example MRI white matter intensity burden within the frontal lobes (Bunce et al., 2007). In the study of Batterham et al. (Batterham et al., 2014), it was theorised that RT IIV might be driven by increased 'neural noise', causing reduced ability to process information. This is thought to be the result of a general decline in catecholamine-based neurotransmitter function seen with advancing age (Li et al., 2001).

There are some studies of RT IIV in PD. For example, de Frias et al. reported 18-month follow-up on 31 PwPD with normal cognition at

[24] Intra-individual variability – a measure of transient and rapid fluctuations of an individual's performance over brief periods of time, i.e. trial-to-trial (de Frias et al. 2012).

baseline (defined as MMSE >26) and 43 HC (de Frias et al., 2012). Ten of the 31 PwPD were retrospectively categorised as 'Parkinson's disease with incipient dementia (PD-ID)' because at 36 months of follow-up (i.e. another 18 months later) they had developed PDD or PD-MCI. One of the study findings was that RT IIV increased over 18 months in PD-ID but not in PD or HC, and that the degree of change in RT IIV for the PD-ID group increased according to complexity of the CRT stimulus. The authors concluded that RT IIV is a better predictor of incipient cognitive impairment in PwPD than SRT or CRT values (de Frias et al., 2012).

Other researchers have found links between SRT values and cognition in PwPD, as has been demonstrated in our study. For example, in a study of 66 PwPD Jordan et al. found a significant correlation between RT (both SRT and CRT) and global cognition (as determined memory and cognition component of the Blessed Dementia Scale), as well as SRT and performance on the Wisconsin Card-Sorting Test (WCST) [25] (Jordan et al., 1992). Berry et al. also found that PwPD classified as having frontal lobe dysfunction by performance on the WCST had slower SRT that those with normal frontal lobe function (Berry et al., 1999), whilst a more recent study of 31 non-medicated PwPD reported that those with abnormal performance on the three-step Luria test [26] had longer SRT than those who performed normally (Kwon et al., 2014). There is therefore some evidence that executive dysfunction, thought to be driven by dopamine levels in frontostriatal cortical loops and the DLPFC (Kehagia et al., 2010b, Kehagia et al., 2013), is linked with prolongation of SRT in PwPD. Unfortunately, the tests of executive function in our study (TMT-B and TMT B-A) were only completed by one of the ten subjects with PDD. This may account for the lack of association and means that conclusions about the relationship

[25] WCST – A neuropsychological test of 'set shifting' that incorporates goal directed behaviour and impulsivity modulation. It is considered as a test of executive function.

[26] Three-step Luria test – A test of motor sequencing in which participants are required to perform three motor tasks (fist, edge, palm) in order. It is considered a non-verbal test of executive function.

between SRT and executive function cannot be made from our results. However, we can conclude that global cognition (as measured by MoCA score) and tests of visuospatial function are associated with SRT in our study.

Some models of movement preparation – a component of RT – propose that visual attention is required in order to select the correct motor plan, i.e. in the process of observing the environment and selecting the object of interest (Wong et al., 2015). Visual attention has been studied in macaques and is known to involve parieto-frontal circuits, specifically LIP – FEF (Katsuki and Constantinidis, 2014). It is not possible to determine how visual attention affected RT in our study because no specific tests of visual attention were employed. From a neurochemical perspective, and as discussed in Chapter 2.6.2, it is thought that ACh levels within the DLPFC are important in the regulation of attention (Bloem et al., 2014, Yarnall et al., 2011), and in support of this experiments in macaques have shown that visual attention is impaired when the DLPFC is inactivated (Suzuki and Gottlieb, 2013). The major ACh producing nuclei within the brain degenerate in PwPD (Nakano and Hirano, 1984) and ACh levels in PDD are lower than in PD-NC, which in turn are lower than in HC (Bohnen et al., 2003). In addition, an association has been found between brain ACh levels and global cognition in PwPD (Bohnen et al., 2012). It is possible that the association between prolongation of RT and worsening cognition in PwPD in our study is related to progressive reduction of ACh within the DLPFC.

In summary, our results have shown a robust association between RT and worsening global cognition and visuospatial function. This association is present even after motor function and age have been considered, which is a novel finding and strengthens the existing body of literature suggesting that SRT is linked to cognition in PwPD. From our study it is impossible to determine which specific cognitive functions, and therefore which

particular regions of the brain, are most associated with prolongation of RT. Previous studies have found an association between RT and tests of executive function (Jordan et al., 1992, Berry et al., 1999, Kwon et al., 2014) but the lack of an association in our study could be because nine of the ten PDD subjects did not have data from tests of executive function included in the correlation or regression analysis. Attention is also thought to be important in the processes that constitute RT (Wong et al., 2015) and can be impaired in PwPD (Litvan et al., 2011). Every individual with PD has varying levels of dysfunction to dopaminergic and ACh neurotransmitter systems within the brain and it is possible that both executive function and visual attention deficits – both of which involve neuronal populations within the DLPFC – are responsible for RT prolongation in PwPD as seen in our study (and has been proposed in healthy people as they age (Li et al., 2001)). To better understand the anatomical, pathological and neurochemical causes of the association between RT and cognition in PwPD requires longitudinal cohort studies such as ICICLE-PD, which has incorporated RT with other potential biomarkers of PD-CI including serial MRI imaging and CSF constituent analysis (Yarnall et al., 2014).

7.7.9 The similarities between reach and grasp parameters in PD-NC and PD-MCI

In situations where statistical differences in the parameters of reach and grasp arise between the cognitive groups in our study, post-hoc inspection almost always suggests that PDD have values that are significantly different from PD-NC and/or PD-MCI. In contrast, PD-NC and PD-MCI have similar, non-significantly different, parameters of reach and grasp in all four conditions. What does this mean? The major focus of discussion in this chapter and Chapter 6 has related to the role of reduced visual feedback on reach and grasp, and a number of potential contributing factors to the finding that PDD seem to be more affected than PD-NC who are more affected than C-NC have been proposed. The lack of significant difference in reach and grasp parameters in PD-NC and PD-MCI could imply that the

factors proposed to cause increased reliance on visual feedback are impaired to a similar degree in these groups. It is interesting to note that markers of motor severity (such as MDS-UPDRS Part 3 score and H&Y stage) are similar between PD-NC and PD-MCI (and are more similar than between PD-NC and PDD). Worsening motor function (i.e. basal ganglia function) has been hypothesised to explain why PDD appear to be most affected by reduced visual feedback from an impaired sensorimotor integration and impaired visual SWM perspective; PD-NC and PD-MCI may have similar values for the calculated reach and grasp parameters because they have similar amounts of basal ganglia damage.

In contrast to markers of motor severity, results of cognitive tests (MoCA and all of the tests of executive and visuospatial function) are significantly different between PD-NC and PD-MCI. The significant difference in cognitive results compared to a lack of significant difference in the results of parameters of reach and grasp could suggest that cognition is not a factor in reach and grasp. However, the lack of statistical differences between PD-NC and PD-MCI may be related to the number of participants in our study. Alternately, the way that PD-MCI has been defined in our study may have reduced the likelihood of finding a statistical difference. Although our study has been able to make a level 1 diagnosis of PD-MCI according to MDS criteria (Litvan et al., 2012), there is evidence to suggest that using global screening tests of cognition to diagnose PD-MCI lacks sensitivity and specificity compared to the testing of specific cognitive domains required to make a level 2 diagnosis (Marras et al., 2013).

The dual syndrome hypothesis proposes that PD-MCI is heterogeneous, consisting of subtypes with differing risks of dementia development (Kehagia et al., 2010b, Kehagia et al., 2013). Our study has not allowed the grouping of PD-MCI by number or type of cognitive domains affected. This may have prevented the identification of PD-MCI subgroups that may have had significantly different parameters of reach and grasp compared to PD-

NC. It could be, for example, that those with PD-MCI characterised by memory or visuospatial dysfunction – who have been found to be most at risk of PDD development and whose deficits are thought to be primarily driven by reduced levels of ACh in the brain (Williams-Gray et al., 2007, Williams-Gray et al., 2009, Kehagia et al., 2010b, Kehagia et al., 2013) – may have similar patterns of change to reach and grasp parameters in reduced visual feedback (i.e. VIS and MEM) as PDD.

As previously stated, there are no published studies of reach and grasp in PD-MCI or PDD. The majority of literature regarding motor function and cognition in PwPD is related to gait analysis and there are very few studies that specifically look at associations between motor function and PD-MCI. However, one study found that those with PD-MCI, diagnosed on the basis of detailed neuropsychological tests that would meet the criteria for MDS level 2 diagnosis, had a number of differences in specific gait characteristics compared to PD-NC and HC (Amboni et al., 2012). This could be used to justify a follow-on study of reach and grasp in which PD-MCI is defined according to level 2 MDS criteria.

Another potential reason why PDD, but not PD-MCI, have significant changes in the parameters of reach and grasp compared to PD-NC is the degree of damage to the parietal lobe, and therefore V6A and aIPS. Large autopsy studies are required to better define the pathological changes that characterise PD-MCI but they are likely to be similar though less severe than those seen in PDD (Halliday et al., 2014); i.e. PD-MCI may have less damage to the major parietal reaching nodes than PDD. However, it must be considered that autopsy represents the end point of pathological damage in an individual and does not provide information regarding neurotransmitter change or pathological damage at the time when participants perform reach and grasp.

7.8 Strengths and limitations

The same strengths and limitations documented in Chapter 6.7 are relevant to the results presented in this chapter and will not be discussed again.

The major strength of this section of the study is its novelty. There are no published studies of reach and grasp in PD-MCI and PDD and so this chapter has presented new findings. However, there are limitations of the study that have reduced the ability to make firm conclusions. It is regrettable that the majority of PDD subjects were unable to complete TMT-B (and therefore TMT B-A) because this has prevented associations between executive function and MT and RT from being fully explored. It is likely that an association does exist between RT and executive function (as has been demonstrated between RT and global cognition and visuospatial function) but this has been masked by the exclusion of 90% of the PDD group from the analysis.

Another limitation, already discussed, is the way in which PD-MCI (and PDD) were defined. Ideally, detailed neuropsychological evaluation of all participants would have been performed to enable level 2 diagnoses of PD-MCI to be made and therefore MCI subgroup analysis to be investigated. However, such tests would require neuropsychological expertise, greatly increasing the cost of our study. In addition to financial implications, the need for neuropsychological testing would increase the time demands on participants, who would likely need to attend for one or more neuropsychology appointments in addition to the reach and grasp assessment. My experience from talking to those who took part in our study is that the single assessment session was one reason why they were prepared to partake and it is possible that multiple assessment sessions might deter some PwPD and HC from agreeing to participate.

7.9 Conclusions

When reaching and grasping at natural speed (NAT) and when reaching and grasping towards an illuminated object in a darkened room (VIS), only RT is significantly different between PD-NC, PD-MCI and PDD subjects defined using level 1 MDS diagnostic criteria and tested whilst *on*. However, intra- and inter-group analysis of our results suggest than when compared to NAT, PDD are more affected by VIS than PD-NC and PD-MCI. When reaching and grasping in the absence of visual feedback (MEM) our results show that PDD take significantly longer to attain peak parameters of reach (TPA, TPV and TPD) and have significantly lower peak and mean parameters of acceleration (PA, MA). PDD have a longer MT – the major kinematic parameter of reach in our study – in MEM but the difference is not statistically different between the cognitive groups. As with VIS, intra and inter-group analysis of our data suggests that PDD are most affected by the absence of vision to guide reach.

In summary, the calculated parameters of reach and grasp can be taken as evidence to suggest that PDD are more reliant on visual feedback to guide reaching. This is a novel finding as there are no previous published studies of reach and grasp in those with PD-MCI or PDD. In this chapter and in Chapter 6 it has been argued that both impaired visual SWM and impairment of proprioception and/or somatosensory sensorimotor integration could explain the results of VIS and MEM in C-NC and the PD cognitive groups, as could direct infiltration of the major parietal nodes of reach and grasp by Lewy and AD related pathology.

A significant association between RT and both global cognition and tests of visuospatial function has been described in this chapter. The fact that this association persists after controlling for age, disease duration and MDS-UPDRS Part 3 (motor score) is a novel finding and supports the idea that SRT and other RT measurements could be potential biomarkers of cognitive decline in PwPD. It is been speculated that dysfunction of

dopaminergic and acetylcholinergic neural circuits involving the DLPFC may be responsible for the RT changes in our study.

No significant differences in the parameters of reach and grasp have been identified between PD-NC and PD-MCI in our study despite significant differences in tests of global cognition, executive and visuospatial function. Reasons why this may be the case, including the way in which cognitive groups have been categorised in our study, have been discussed.

Chapter 8

Abbreviations used in this chapter

2D	Two dimensional
3D	Three dimensional
α-syn	Alpha synuclein
AUC	Area under the curve
Aβ	Amyloid beta plaques
B-C	Benson Copy
B-R	Benson Recall
C-CI	Healthy control subjects with cognitive impairment
C-NC	Healthy control subjects with normal cognition
CDR	Clinical Dementia Rating scale
CGP	Cartesian genetic programming
CRT	Choice reaction time
DT	Distance travelled
EAs	Evolutionary algorithms
EM	Electromagnetic
H&Y	Hoehn & Yahr
HC	Healthy controls
ICICLE-PD	Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation – Parkinson's Disease
JoLO	Benton Judgment of Line Orientation
M1	Primary motor cortex
MA	Mean acceleration
MAX	Condition 3 - Maximum speed
MCP	Metacarpal-phalangeal
MDS	International Parkinson and Movement Disorder Society
MDS-UPDRS	Movement Disorders Society – Unified Parkinson's Disease Rating Scale
MEM	Condition 4 - Memory guided
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MT	Movement time
NAT	Condition 1 - Natural speed
NFT	Tau neurofibrillary tangles
PA	Peak acceleration
PD	Parkinson's disease
PD-MCI	Parkinson's disease - mild cognitive impairment
PD-NC	Parkinson's disease - normal cognition
PDD	Parkinson's disease dementia
PDe	Peak deceleration
PIP	Proximal interphalangeal
PV	Peak velocity
PwPD	People with Parkinson's disease
ROC	Receiver operating characteristic

RT	Reaction time
SRT	Simple reaction time
SWM	Spatial working memory
TMT-A	Trail Making Test Part A
TPA	Time to peak acceleration
TPD	Time to peak deceleration
TPV	Time to peak velocity
VIS	Condition 2 - Visually cued
VOSP	Visual Object and Space Perception

Conclusions

8.1 Summary of the research and original contributions

This thesis has explored kinematic parameters of reach and grasp in healthy controls with normal cognition (C-NC, n = 19) and PD subjects categorised into those with normal cognition (PD-NC, n = 22), those with mild cognitive impairment (PD-MCI, n = 23) and those with dementia (PDD, n = 10). Reach and grasp was performed in four different conditions:

- Condition 1 – NAT – natural speed with full visual guidance after an auditory tone.
- Condition 2 – VIS – natural speed after simultaneous cylinder illumination and auditory tone in a darkened room.
- Condition 3 – MAX – as quickly as possible with full visual guidance after an auditory tone.
- Condition 4 – MEM – natural speed with eyes closed after an auditory tone.

Parameters of reach were calculated from measurements at the palmar aspect of the wrist using EM tracking sensors. Parameters of grasp were calculated using data gloves with imbedded movement sensors to detect flexion in the five digits of the hand. All reach and grasp parameters have been analysed using standard statistical methods. As discussed in Chapters 5, 6 and 7, unrecognised damage to the data gloves during recruitment meant that the main focus of this thesis has been on reach.

There are four main contributions to the existing literature of reach and grasp in PD. Each will now be summarised:

- Results from MEM have demonstrated that when reaching and grasping in the absence of visual guidance, PD-NC tested whilst *on*

have a significantly prolonged MT compared to C-NC (1.54s versus 1.19s, p <0.001), whereas there is no significant difference in MT between PD-NC and C-NC in NAT, VIS or MAX. In addition, values of PA, MA and PDe are significantly reduced and values of TPA, TPV and TPD are significantly prolonged in PD-NC compared to C-NC in MEM. In other words, in the absence of vision to guide reach, PD-NC take longer to reach, longer to attain peak acceleration and deceleration and obtain lower peak values of acceleration and deceleration.

Our study has also shown that when compared to reaching and grasping at a natural speed in full vision (NAT:MEM), MT in MEM is disproportionately prolonged in PD-NC compared to C-NC (intergroup ratio value 0.82 versus 0.96, p 0.003), whereas there is no significant difference between PD-NC and C-NC when comparing NAT:VIS or NAT:MAX.

As has been discussed in Chapter 6.6.3, a number of studies have investigated the effect of visual feedback on reach and grasp in HC and PD (Santello et al., 2002, Schettino et al., 2003, Schettino et al., 2006). The study most similar to ours is that of Schettino et al. published in 2006, but the PwPD were tested whilst *off* and there is no direct comparison of MT with and without visual guidance (Schettino et al., 2006). Studies of the effect of levodopa have generally revealed that parameters of reach are improved in PwPD whilst *on* (see Chapter 4.2.7) *(Castiello et al., 2000, Kelly et al., 2002, Negrotti et al., 2005, Schettino et al., 2006)*. Our results add to current understanding of how PD-NC movements differ to HC (C-NC in our study) by demonstrating that MT becomes disproportionately prolonged in PD-NC, tested *on,* when visual input is removed.

- Our study revealed that PDD have a prolonged MT compared to PD-NC when reaching and grasping in the absence of visual feedback (MEM), and that this approaches statistical significance when the three PD cognitive groups are compared (PD-NC 1.54s, PD-MCI 1.55s and PDD 1.85s, *p* 0.081). Furthermore, there are statistically significant differences between the three cognitive groups in PA and MA (PDD have the smallest values) and TPA, TPV and TPD (PDD have the largest values). When ratio differences of MT between NAT and MEM are compared between the cognitive groups there is evidence that PDD are most affected by MEM (PD-NC 0.81, PD-MCI 0.84 and PDD 0.69, *p* 0.025). Taken together, these results demonstrate that when reaching and grasping in the absence of visual feedback, MT is more impaired in PDD than in PD-NC and PD-MCI, despite the fact that there is no significant difference between the three cognitive groups in MDS-UPDRS Part 3 score or H&Y stage.

Combining these findings provides evidence of a spectrum of change to MT – the principal surrogate marker of reach in our study – when reaching and grasping in the absence of visual feedback: PD-NC are disproportionately affected compared to C-NC and PDD are disproportionately affected compared to PD-NC. Three theories have been proposed and discussed to explain this:

  - The first is that PwPD may have impaired proprioception and impaired sensorimotor integration of somatosensory afferents (see Chapter 6.6.5 - 6.6.7 and Chapter 7.7.2). It was argued that increased MT in PDD compared to PD-NC could be because PDD have more damage to basal ganglia function, as suggested by their significantly longer duration of disease and non-significantly greater MDS-UPDRS Part 3 score and H&Y stage.

- The second theory is that dopaminergic depletion of the caudate nucleus in PwPD causes disruption to the neural network controlling SWM (see Chapter 7.7.6). There is existing evidence that SWM deteriorates with increasing dopaminergic deficiency (Owen et al., 1992, Lange et al., 1992) and so, as with impairment of sensorimotor integration, the PDD group may be more affected by this than PD-NC not because of cognitive function per se, but because they have greater disruption of basal ganglia function.
- Thirdly, PDD may be more impaired than PD-NC when reaching because of direct damage to the major nodes of the dorsomedial reaching pathway by neocortical infiltration of Lewy pathology, in keeping with the caudo-rostral propagation of α-syn proposed by Braak et al. (Braak et al., 2003), as well as variable infiltration of NFT and Aβ (see Chapter 7.7.7).

- Our study has demonstrated that RT is significantly different between the PD cognitive groups in all four reach and grasp conditions and that PDD have the longest RT. Furthermore, RT has been shown to be significantly associated with MoCA score – a measure of global cognition – in all four conditions after controlling for age, disease duration and MDS-UPDRS Part 3 score using a multiple regression model. RT is usually considered when performing subsequent movements as quickly as possible and therefore discussion in Chapter 7.7.8 primarily focussed around RT in MAX, where each single point reduction in MoCA score results in a 0.012s prolongation of RT in the PD subjects.

  Using a second multiple regression model has revealed that RT in MAX is significantly associated with tests of visuospatial function,

specifically TMT-A (visual perception), JoLO (visual spatial function), B-C (visuospatial construction) and B-R (episodic visual memory) in the PD subjects. However, MoCA score is significantly correlated with all of the tests of visuospatial function (Table 34) and so the importance of the association between visuospatial function and RT over and above the association with global cognition is difficult to determine.

- The final contribution to the existing literature is a negative rather than positive finding: our study has revealed that the kinematic parameters of reach and grasp across the four different conditions are not significantly different between PD-NC and PD-MCI, defined using MDS PD-MCI level 1 criteria (Litvan et al., 2012). This may be because subtyping of PD-MCI by the number and type of cognitive domains affected has not been possible (see 8.2.3 and Chapter 7.8).

8.2 Study limitations

Limitations of the study from which this thesis is derived have been discussed in Chapters 6.7 and 7.8. The major problems are summarised below:

8.2.1 Inability to reliably interpret grasp data

This occurred because of unrecognised damage to both data gloves, caused by dislodging of the movement sensor detecting flexion of the MCP and PIP joints of the index finger. The index finger sensor in both data gloves slid back towards the wrist, meaning that flexion of the PIP joint in particular was underestimated. Unfortunately, this problem was not identified until after all participants had been assessed and so it was not possible to convincingly determine at what point the problem began. Our research group now ensures that data is analysed in batches throughout the recruitment process, rather than at the end. By doing this we hope to minimise the chance of unidentified data corruption in future experiments.

One of the most important concepts in the study of reach and grasp is the visuomotor channel hypothesis, which proposes that a temporal integration of distinct reach and grasp pathways occurs under visual guidance. The lack of reliable grasp data has made it impossible to explore the visuomotor channel hypothesis; specifically, how this is affected by the different conditions under which reach and grasp was performed and how, if at all, it is differentially affected in the PD cognitive groups in our study. However, the grasp data may still be of use in future research (see 8.3.1).

8.2.2 Lack of reaching trajectory data

Although the Euclidean distance between the wrist sensor and the magnetic transmitter was recorded 60 times per second, DT in our study was calculated as a direct, straight-line, measurement from the position of the wrist sensor relative to the magnetic transmitter at movement onset and reach completion. In other words, DT in our study can be considered as a 2D measurement of a 3D movement.

As discussed in 8.1, two of the most important findings from this thesis relate to differences in MT amongst participants when reaching and grasping without visual guidance. Accurate calculation of reach trajectory would have provided further information about *why* MT was prolonged in PDD compared to PD-NC and in PD-NC compared to C-NC. It has been hypothesised that SWM deficits may explain the differences in PwPD by rendering them less able to locate the cylinder in the absence of visual guidance. This theory would be supported if trajectory data was available and suggested that the reaching arm of PD subjects 'searches' for the cylinder when the hand is in close proximity to it.

Although trajectory information was not included in our results, it could be calculated from the data collected. In addition, only the *x*, *y*, and *z* coordinates of the EM sensor have been analysed in this thesis but data

from the orientation coordinates (azimuth, roll, elevation) was also collected and could be used in the future.

8.2.3. Categorisation of the Parkinson's disease cognitive groups

This was based on total MoCA score and global CDR score. As discussed in Chapter 2.1.1, the MoCA is an approved global screening tool for the definition of PD-MCI according to level 1 MDS criteria (Litvan et al., 2012). The 'diagnostic rating sheet' (Dubois et al., 2007) (Figure 8) for a level 1 diagnosis of PDD according to MDS criteria was followed in our study, although the MoCA, rather than MMSE, was the global cognitive screen. The MoCA is generally considered better than MMSE in the assessment of cognitive impairment in PD (Dalrymple-Alford et al., 2010, Hoops et al., 2009).

One of the key differences between a diagnosis of PD-MCI and PDD according to MDS diagnostic criteria is that cognitive function does not significantly interfere with functional independence in PD-MCI, but does in PDD (Emre et al., 2007, Litvan et al., 2012). The global CDR score was used in our study to make a decision about functional independence to classify PwPD who scored <26 on the MoCA into either PD-MCI or PDD. In summary, our study can justify the method used to classify PwPD into PD-NC, PD-MCI and PDD according to level 1 MDS criteria.

However, there is evidence that using the MoCA to diagnose PD-MCI may lack diagnostic accuracy in some studies (Marras et al., 2013), although performance has been better in others (Kandiah et al., 2014). Level 1 criteria for PDD (Dujardin et al., 2010) (Figure 7) and the MDS diagnostic rating sheet (Barton et al., 2012) have been shown to lack sensitivity when compared to level 2 diagnostic criteria. It can therefore be argued that a limitation of our study is the failure to use MDS level 2 criteria to classify PwPD into PD-MCI and PDD because our cognitive groups may not be completely accurate.

Another limitation of using level 1 MDS diagnostic criteria is that the PD-MCI group could not be subtyped by cognitive domain affected. If this had been possible then the reach and grasp parameters between those with PD-MCI thought to be more at risk of dementia (impairment of visuospatial, language and memory function) could have been compared to those with a reduced risk (executive dysfunction) (Kehagia et al., 2010b, Kehagia et al., 2013). The hypothesis proposed in the aims and objectives of this thesis (see Chapter 1.10) was that both PD-MCI and PDD would be more impaired when reaching and grasping with reduced levels of visual feedback. Our results for PD-MCI do not support this but perhaps only those PD-MCI subjects with predominant visuospatial deficits have reach and grasp parameters distinct from PD-NC and more similar to PDD.

Any study using level 1 MDS diagnostic criteria could be criticised for not using level 2 criteria and so perhaps this limitation is tempered by the fact that our study is the first to analyse reach and grasp using any form of approved diagnostic criteria for PD-MCI and PDD. It must also be borne in mind that level 2 classification of PD-MCI and PDD would have mandated extra time and neuropsychological expertise.

8.3 Future research

8.3.1 Evolutionary algorithm analysis of reach and grasp data

This thesis has applied standard statistical tests to kinematic reach and grasp data. However, the major focus of our research group is the utilisation of self-learning algorithms, specifically 'evolutionary algorithms' (EAs), to movement data. EAs are a type of artificial intelligence inspired by Darwinian evolution, and can be considered as:

"…a number (or population) of candidate solutions (individuals) to a classification problem that are repeatedly refined (or evolved) over a number of iterations (generations) until a suitably accurate classifier algorithm is obtained or the computational resources have been

exhausted." *(Smith et al., 2015)*

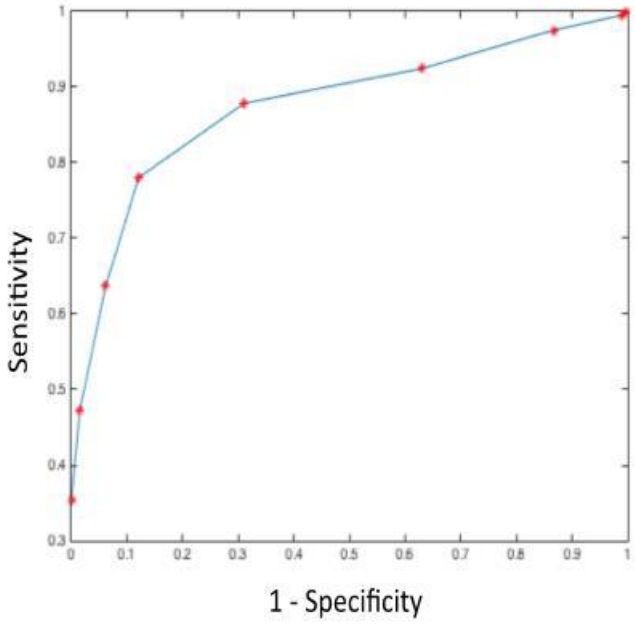
The representation of the individuals and the specifics of the evolutionary process can be modified by the programmer and so a number of different types of EA exist. Our research group use 'Cartesian genetic programming' (CGP) to process data (Smith et al., 2005, Smith et al., 2007). A detailed discussion of CGP is beyond the scope of this thesis but one of the major advantages of CGP compared to other EA types is that when a classifier algorithm – a map from one set of data to another – has been evolved, it is possible to decode the CGP network to derive a mathematical expression (Smith et al., 2015). In other words, CGP EAs are not simply a 'black box' from which data emerges but instead allow the classification process to be interrogated, potentially providing valuable insight into the most discriminating movement features between groups.

Preliminary application of CGP EAs to the reach and grasp data has been performed by Chiara Picardi. So far, ten of the calculated kinematic parameters for this thesis – including MT, RT, the peak parameters of reach (PA, PV, PDe) and time to attain peak parameters (TPA, TPV, TPD) – have been used as 'inputs' to the CGP EAs in order to classify PwPD (i.e. PD-NC, PD-MCI and PDD) from HC (i.e. C-NC and C-CI [27]). ROC curves [28] have produced an area under the curve (AUC) of 0.82 when distinguishing between PwPD tested *on* and HC (Figure 62).

[27] C-CI – Control subjects with abnormal cognition (MoCA <26). This group has not been included in the results of this thesis – see Chapters 5.4.2 and 6.2.1.

[28] Area under the ROC curve (AUC) – the quantification of how well a test distinguishes between two groups, in this case PwPD and HC. An AUC of 1.0 is a perfect test, and AUC of 0.5 is no better than chance. See Figure 6 for further details.

Figure 62: Provisional classification of Parkinson's disease and healthy control reach and grasp data using evolutionary algorithms



Legend: ROC AUC of 0.82 has been attained using CGP EAs to classify reach and grasp data from PwPD (PD-NC + PD-MCI + PDD) and HC (C-NC + C-CI). *Original data series produced by Chiara Picardi.*

Over the coming 12 to 18 months our research groups aims to refine the application of CGP EAs to the reach and grasp data and establish the classification accuracy when comparing the three PD-cognitive groups. One of the most interesting questions is whether the CGP EAs are able to more accurately classify PD-NC and PD-MCI than the standard statistical analysis of kinematic parameters.

EAs use features of movement data within each group (for example PwPD and HC) that are most distinguishing in order to produce a classifier algorithm. The grasp data from this thesis can be utilised by CGP EAs when all movement data is analysed together because the problem with the data gloves affected both groups in the study, i.e. HC and PwPD. In addition, flexion data from the index finger is just one component of the grasp data (flexion data is available from all five digits of both hands), and could potentially be excluded from EA analysis if found to be a key discriminatory

feature of the classifier equation.

EAs are stochastic and make no prior assumption about which aspects of the data are most likely to be discriminatory, enabling them to potentially discover new clinical information. It will be exciting to see what insights can be made about the PD cognitive groups using this novel technology.

8.3.2 Analysis of reach and grasp in PD-MCI subtypes

As discussed in 8.2.3, classification of PD-MCI according to cognitive domain(s) affected was not possible in this thesis. However, ten of the PD-MCI group agreed to undertake more detailed cognitive testing by a neuropsychologist at a subsequent date to their reach and grasp assessment. Tests of visuospatial function (object decision and number location of the Visual Object and Space Perception (VOSP) battery) and executive function (Stroop Test, the Brixton Spatial Anticipation Test and Zoo Map from the Behavioural Assessment of the Dysexecutive Syndrome) were performed. Preliminary analysis has identified variability amongst the ten subjects on tests of executive function but that all subjects performed similarly well in the visuospatial tests. One potential explanation for this is that the chosen tests of visuospatial function were not difficult enough.

Over the coming months this data will be added to the cognitive tests performed as part of this thesis. The reach and grasp kinematic parameters of the PD-MCI subjects with the best and worst performance on tests of executive function will be compared with the PD-MCI subject with the best and worst performance on tests of visuospatial function. Although this will be a comparison of only a small number of subjects, it will provide clues as to whether those with worse visuospatial function have parameters of reach and grasp that are more similar to those with PDD. This would lend support to a further study in which reach and grasp is compared in those with PD-MCI defined by level 2 MDS criteria (Litvan et

al., 2012).

8.3.3 A prospective longitudinal study of reach and grasp

This thesis has shown that kinematic analysis of reach and grasp, particularly of MT when reaching and grasping without visual feedback and RT when reaching and grasping as quickly as possible, are able to distinguish between PD cognitive groups. Unlike future research plans discussed so far, which are directly related to this thesis and already underway, a prospective longitudinal study of reach and grasp is a theoretical next step in the assessment of reach and grasp as biomarker of cognitive decline in PD. SRT and CRT are both being used in ICICLE PD as part of a measure of attention (Yarnall et al., 2014), but only by specifically measuring reach and grasp could it be determined whether subtle differences in reach and grasp kinematic parameters shortly after PD diagnosis could help to identify those most at risk of developing PDD.

8.4 Final summary

Reach and grasp is a non-learnt motor behaviour that is integral to everyday life. Neural control of reach and grasp is via distinct neural circuits that begin in the visual association area, pass through the posterior parietal lobe to the frontal premotor cortex and terminate via the production of a motor action in M1. The dorsomedial reaching and dorsolateral grasping circuits are highly specialised, as demonstrated via the analysis of individual neurons using single cell microelectrode studies in the macaque and other monkey species. Functional MRI and other techniques suggest that humans have similar reach and grasp pathways to macaques. The analysis of kinematic parameters of reach and grasp in PwPD have generally shown that they are slower than HC, that they find it more difficult to temporally integrate reach and grasp and that they are more reliant on vision to guide reach and grasp.

Cognitive impairment in PD is common and has complex pathological and

neurochemical correlates. The dual syndrome hypothesis has arisen from studies suggesting that transition from PD-MCI to PDD is not linear (Williams-Gray et al., 2013, Williams-Gray et al., 2007, Williams-Gray et al., 2009). Exploration of the dual syndrome hypothesis and of potential biomarkers to predict those most at risk of PD-CI is underway (Yarnall et al., 2014, Nombela et al., 2014).

This thesis has analysed kinematic parameters of reach and grasp in PD-NC, PD-MCI and PDD and tried to identify associations between motor function and cognition. Our results have lent further support to the importance of visual feedback when PD-NC are reaching and grasping and have also demonstrated that dependence on vision to guide reach persists in the *on* state and appears to be particularly important in those with PDD. We have also demonstrated that prolonged RT is associated with impaired cognition in a reach and grasp task after controlling for age, disease duration and motor function. Problems with data capture have hindered the ability to explore parameters of grasp in this thesis, preventing result analysis in the context of the visuomotor channel hypothesis. However, grasp data will be analysed by EAs in future studies.

The simplicity of performing a reach and grasp task and the detailed understanding of the neural control of reach and grasp make it an attractive candidate through which to explore correlations and associations between motor and cognitive function in PwPD. Current understanding would be enhanced by neuroimaging correlation and integration of kinematic analysis of reach and grasp in to larger, longitudinal studies of PD.

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Abbreviations

α-syn	Alpha synuclein
%RT	Reaction time as a % of total movement time
%TAP	Time to peak aperture as a % of movement time
%TPA	Time to peak acceleration as a % of movement time
%TPD	Time to peak deceleration as a % of movement time
%TPV	Time to peak velocity as a % of movement time
2D	Two dimensional
3D	Three dimensional
ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
ADL	Activities of daily living
AIP	Anterior intraparietal area in macaques/monkeys
aIPS	Anterior intraparietal area in humans
ANOVA	Analysis of variance
APOE	Apolipoprotein E
AUC	Area under the curve
Aβ	Amyloid beta plaques
B-C	Benson Copy
B-R	Benson Recall
BA4	Brodmann area 4
BA6	Brodmann area 6
BOLD	Blood oxygenation level dependent
bv-FTD	Behavioural variant of fronto-temporal dementia
C-CI	Healthy control subjects with cognitive impairment
C-NC	Healthy control subjects with normal cognition
CAMCOG	Cambridge Cognitive Examination
CamPaIGN	Cambridgeshire Parkinson's Incidence from GP to Neurologist study
CANTAB	Cambridge Neuropsychological Test Automated Battery
CBGD	Corticobasal ganglionic degeneration
CDR	Clinical Dementia Rating scale
CGP	Cartesian genetic programming'
ChEI	Cholinesterase inhibitors
COMT	Catechol-O-methyltransferase
CRT	Choice reaction time
CSF	Cerebrospinal fluid
CT	Computerised tomography
DBS	Deep brain stimulation
DLB	Dementia with Lewy bodies
DLPFC	Dorsolateral prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
DT	Distance travelled

EAs	Evolutionary algorithms
EM	Electromagnetic
FEF	Frontal eye field
fMRI	Functional magnetic resonance imaging
GABA	Gamma-aminobutyric acid
GDS-15	Geriatric Depression Scale – Short Form
GP	General practitioner
GPi	Globus pallidus interna
H&Y	Hoehn & Yahr
HC	Healthy controls
HD	Huntington's disease
ICICLE-PD	Incidence of Cognitive Impairment in Cohorts with Longitudinal Evaluation – Parkinson's Disease
IIV	Intra-individual variability
ILBD	Incidental Lewy body disease
IPL	Inferior parietal lobe
IPS	Intraparietal sulcus
ITC	Inferior temporal cortex
JoLO	Benton Judgment of Line Orientation
LEDD	Levodopa equivalent daily dose
LGI	Leeds General Infirmary
LIP	Lateral intraparietal area
LP	Lateral posterior (nucleus of the thalamus)
LTHT	Leeds Teaching Hospitals NHS Trust
LTM	Long term memory
M1	Primary motor cortex
MA	Mean acceleration
mAChR	Muscarinic acetylcholine receptor
MAPT	Microtubule associated protein tau
MAX	Condition 3 - Maximum speed
MCI	Mild cognitive impairment
MCP	Metacarpal-phalangeal
MDS	International Parkinson and Movement Disorder Society
MDS-UPDRS	Movement Disorders Society – Unified Parkinson's Disease Rating Scale
MEM	Condition 4 - Memory guided
MIP	Medial intraparietal area
MMSE	Mini-Mental State Examination
MoCA	Montreal Cognitive Assessment
MRI	Magnetic resonance imaging
MSA	Multiple-system atrophy
MT	Movement time
MV	Mean velocity
nAChR	Nicotinic acetylcholine receptor
NAT	Condition 1 - Natural speed
nbM	Nucleus basalis of Meynert

NFT	Tau neurofibrillary tangles
NMDA	N-methyl-D-aspartate
NPI-Q	Neuropsychiatric Inventory - Questionnaire
PA	Peak acceleration
PD	Parkinson's disease
PD-CI	PD cognitive impairment
PD-ID	Parkinson’s disease with incipient dementia
PD-MCI	Parkinson's disease - mild cognitive impairment
PD-NC	Parkinson's disease - normal cognition
PDD	Parkinson's disease dementia
PDe	Peak deceleration
PET	Positron emission tomography
PIGD	Postural instability gait disorder
PIP	Proximal interphalangeal
PMd	Dorsal premotor cortex
PMv	Ventral premotor cortex
PO	Parieto-occipital
PPC	Posterior parietal cortex
PPN	Pedunculopontine nucleus
PRR	Parietal reach region
PV	Peak velocity
PwPD	People with Parkinson's disease
RCT	Randomised controlled trial
REM	Rapid eye movement
ROC	Receiver operating characteristic
RT	Reaction time
SCOPA-COG	Scales for Outcomes of Parkinson’s disease–Cognition
SDs	Standard deviations
SEU	Systems electronic unit
SMA	Supplementary motor area
SNpc	Substantia nigra pars compacta
SNpr	Substantia nigra pars reticulate
SPECT	Single-photon emission computed tomography
SPL	Superior parietal lobe
SRT	Simple reaction time
STM	Short term memory
STN	Subthalamic nucleus
SWM	Spatial working memory
TAP	Time to peak aperture
TD	Tremor dominant
TMS	Transmagnetic stimulation
TMT	Trail Making Test
TMT B-A	Trail Making Test Part B score - Trail Making Test Part A score
TMT-A	Trail Making Test Part A
TMT-B	Trail Making Test Part B
TMTi	Total movement time

TOL	Tower of London test
TPA	Time to peak acceleration
TPD	Time to peak deceleration
TPV	Time to peak velocity
UKPDBBC	United Kingdom Parkinson's Disease Brain Bank Criteria
UPDRS	Unified Parkinson's Disease Rating Scale
V3A	Visual area V3A
V6	Visual area V6
V6A	Visual area V6A
V6Ad	Dorsal visual area V6A
V6Av	Ventral visual area V6A
VIP	Ventral intraparietal area
VIS	Condition 2 - Visually cued
VL	Ventral lateral (nucleus of the thalamus)
VLPFC	Ventrolateral prefrontal cortex
VOSP	Visual Object and Space Perception
WCST	Wisconsin Card-Sorting Test
WHP	Whole-hand prehension
WM	Working memory