

**MUSIC NORMALIZES VISUAL AND PROPRIOCEPTIVE CONTROL OF
MOVEMENT IN PARKINSON'S DISEASE**

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Dedication

For my family

You were always there when I needed encouragement.

Thesis Abstract

The sensory control of movements has been shown to be impaired with Parkinson's disease. I investigated the task, reach-to-eat, in which advancing of the limb towards a target is guided by vision and withdrawal of the grasped target to the mouth is guided by somatosensation (i.e., haptics and proprioception). Parkinson's diseased subjects display an alteration in the balance of visual and proprioceptive guidance, such that they display increased visual fixation on the target prior to movement onset that persists following the grasp. Music therapy can normalize the balance between visual and proprioceptive guidance on the reach-to-eat task, as visual fixation with the target prior to movement onset is consistent with controls, and disengagement following grasp no longer differs from mild Parkinson's disease subjects. These results are the first to demonstrate that music can have an ameliorating effect on the sensory impairments seen in the control of forelimb movements in Parkinson's disease.

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List of Abbreviations

ANOVA	Analysis of Variance
BG	Basal ganglia
GP	Globus pallidus
GPe	Globus pallidus external segment
GPi	Globus pallidus internal segment
ms	Millisecond
OAC	Old adult control
PD	Parkinson's disease
RAS	Rhythmic Auditory Stimulation
SN	Substantia nigra
SNC	Substantia nigra pars compacta
SNr	Substantia nigra pars reticulata
STN	Subthalamic nucleus
YAC	Young adult control

Chapter 1: General Introduction

Chapter 1: General Introduction

There are a variety of disorders that affect movement, the most common of which is Parkinson's disease (PD). The following introduction will first give a historical overview of PD from the time of its first clinical description to more recent documentation of its cause. This will be followed by an overview of the anatomical basis of the disease, its causes, and treatments. Findings related to the disease have given PD the distinction of being one of the major sources of insight into understanding the motor system. The introduction will conclude with the rationale for the present thesis, as well as the methodology employed. This section will provide the background for understanding why music could serve to help overcome motor problems associated with the disease.

Historical Overview

The following section will cover a brief historical overview of PD. It will first describe the contributions of Parkinson, who gave the first detailed account of PD, then called *paralysis agitans*. Next, Charcot's contribution will be described. He was the first person to document rigidity and freezing, and also renamed the disease "Parkinson's disease." This will be followed by Blocq, Marinesco, and Tretiakoffs' discovery that the degeneration of the substantia nigra pars compacta (SNc) causes PD. The section will conclude with the clinical features of PD.

The First Clinical Definition of PD

James Parkinson was the first person to describe the clinical features of PD, then known as *paralysis agitans*. In "An essay on the shaking palsy" (1817), he described six

cases of PD, three from his own medical practice, and three he watched progress in the streets of London (Parkinson, 2002). He observed that the disease traversed a set of symptoms from onset of the disorder until death. The onset of symptoms was slight, almost unnoticeable to the subject and others. Initial unilateral weakness and trembling in the hand and arm progressed bilaterally and often to the legs. As the disease progressed, posture stooped and festination (progressively faster gait that often ends in falls) often occurred. Writing and use of utensils faltered, and muscular power diminished. At the offset, tremors became violent. Patients could not feed themselves, were incontinent, and fell into a constant sleepiness (Parkinson, 2002). Parkinson believed the disorder was located in the medulla because the disease progressed without impairment in senses and intellect. He was unsure of the cause of PD, however (Parkinson, 2002). Parkinson recommended bleeding from the upper neck and drainage of applied blisters as treatments (Parkinson, 2002). Parkinson's contribution to the understanding of PD was two fold. He gave the first detailed description of the progressive nature of PD and described two of the four cardinal features of the disorder, tremor and postural instability. The remaining two cardinal features, bradykinesia and rigidity, were described by Charcot and colleagues (Goldman & Goetz, 2005).

PD Symptoms and Neurological Cause

Following Parkinson's description of *paralysis agitans* as a medical disease, many physicians, among them Elliotson and Gibson, attempted to treat PD patients. Although they claim to have cured these patients, it is likely that they suffered from a different disorder (Elmer, 2005). More than a half-century after Parkinson's description

of PD, bradykinesia, rigidity, and freezing of gait were described and documented by Charcot and colleagues (Elmer, 2005). Charcot acknowledged the contribution Parkinson made to the understanding of *paralysis agitans* by renaming the disorder “Parkinson’s disease”, confirming Parkinson’s place in medical history (Elmer, 2005). Although Charcot advanced the understanding of PD symptoms, he believed PD was not a neurological condition based on post mortem analysis of parkinsonian brains that revealed no obvious lesion (Elmer, 2005). The first mention of a neurological cause for PD came in 1893 by Blocq and Marinesco. The case study described the onset of unilateral PD in a 38 year old man suffering from a tuberculoma. Because the tuberculoma was located in the substantia nigra (SN) of the midbrain, Blocq and Marinesco concluded that damage to the SN was the neurological basis of the disorder (Blocq & Marinesco, 1893, as c.f. Elmer, 2005). Nevertheless, SN degeneration was largely ignored as the cause of PD until Tretiakoff’s experimental evidence of SN involvement in the development of PD (Tretiakoff, 1919).

Current Clinical Features of PD

PD is the second most common neurodegenerative disorder, after Alzheimer’s disease. Less than one percent of the total population and 1% of those over age 60 are affected by PD in industrialized countries (de Lau & Breteler, 2006). PD is characterized by four cardinal features (Checkoway & Nelson, 1999):

1. *Resting tremor*. A shaking of the limb at a frequency between 4 and 6 Hz. It appears unilaterally in the distal portions of the limb, and the most recognized form is “pill-rolling” (supination and pronation) of the hand (Jankovic, 2008).

2. *Bradykinesia*. A general slowing of movement that can interfere with movement initiation, execution, and sequencing (Berardelli, Rothwell, Thompson, & Hallett, 2001).

3. *Muscular rigidity*. An increased muscular resistance to passive movement. It may present in a “cogwheel” fashion when associated with tremor (Jankovic, 2008).

4. *Postural instability*. This usually presents in later stages of the disease and is the most common cause of falls for this population (Williams, Watt, & Lees, 2006).

Summary

The history of PD spans over a century. Beginning with Parkinson’s 1817 detailed account of *paralysis agitans*, to Charcot’s redefinition and renaming of *paralysis agitans* as “Parkinson’s disease.” The cause of PD remained a mystery until Blocq and Marinesco’s report in 1893 of a gentleman who presented with parkinsonian symptoms following a tumor in the SN. This report was largely ignored until Tretiakoff’s 1919 thesis which provided experimental evidence that degeneration of the SN pars compacta (SNc) was indeed the cause of PD. The current definition of PD has changed little since 1919.

Recent Developments in Parkinson’s Disease

The following section will describe three of the recent developments in PD research. The section will begin with an anatomical overview of the disease. Both the direct and indirect pathways of the basal ganglia (BG) will be discussed. This will be followed by risk factors and proposed causes of the disease. This section will conclude with drug and surgical treatments for PD.

The Anatomy of PD

Progressive neurodegeneration of the SNc, input nuclei to the basal ganglia (BG), is the cause of PD. The BG are a group of subcortical nuclei comprised of the caudate, putamen, and globus pallidus (GP) (Rouse, Marino, Bradley, Awad, Wittmann, & Conn, 2000). The caudate and putamen (striatum) processes information from the cerebral cortex and projects to the GP to control motor activity via feedback loops with the cerebral cortex and brainstem (Graybiel, Aosaki, Flaherty, & Kimura, 1994). The SNc projects to the striatum and modulates functioning of the BG and its feedback loops (Rouse et al., 2000). Information from the cerebral cortex enters the BG via corticostriatal fibers that project to medium spiny neurons of the striatum. Information is sent from the striatum to output nuclei of the BG via the direct and indirect pathways (Rouse et al., 2000). The direct pathway provides inhibition for the BG. Inhibitory information from the striatum is sent to the globus pallidus internal segment (GPi) and substantia nigra pars reticulata (SNr), the major output nuclei of the BG. The GPi and SNr normally send inhibitory information to the thalamus. Activation of the striatopallidal pathway, however, causes the GPi and SNr to become inhibited and the net result is thalamocortical cell disinhibition. Conversely, the indirect pathway provides excitation for the BG. Inhibitory information from the striatum is sent to the globus pallidus external segment (GPe), an output nuclei of the BG. The GPe normally inhibits the subthalamic nucleus from sending excitatory information to the GPi and SNr. Activation of the striatopallidal pathway causes the GPe to become inhibited, resulting in thalamocortical cell excitation (Bergman, Wichmann, & DeLong, 1990).

In healthy individuals, the direct and indirect pathways work together to fine-tune movement control. In the normal condition, the SNc modulates striatal projections to the globus pallidus via D1 and D2 dopamine receptors. D1 receptors are primarily involved in the direct pathway. They work by exciting the striatum, resulting in a net effect of excitation. D2 receptors are primarily involved in the indirect pathway. They work by inhibiting the striatum, resulting in a net effect of inhibition (Gerfen et al., 1990; Albin, Young, & Penney, 1989). With PD, the SNc degenerates, and its modulation of the striatum diminishes (Rouse et al., 2000). With a loss of dopamine from the SNc, activity in the direct pathway decreases and activity of the indirect pathway increases. The overall effect is thalamocortical cell inhibition (Rouse et al., 2000). This is believed to be the cause of rigidity, bradykinesia, akinesia, and tremor associated with PD (Rouse et al., 2000). For a schematic representation of BG circuitry in healthy and PD individuals, see Figure 1.1.

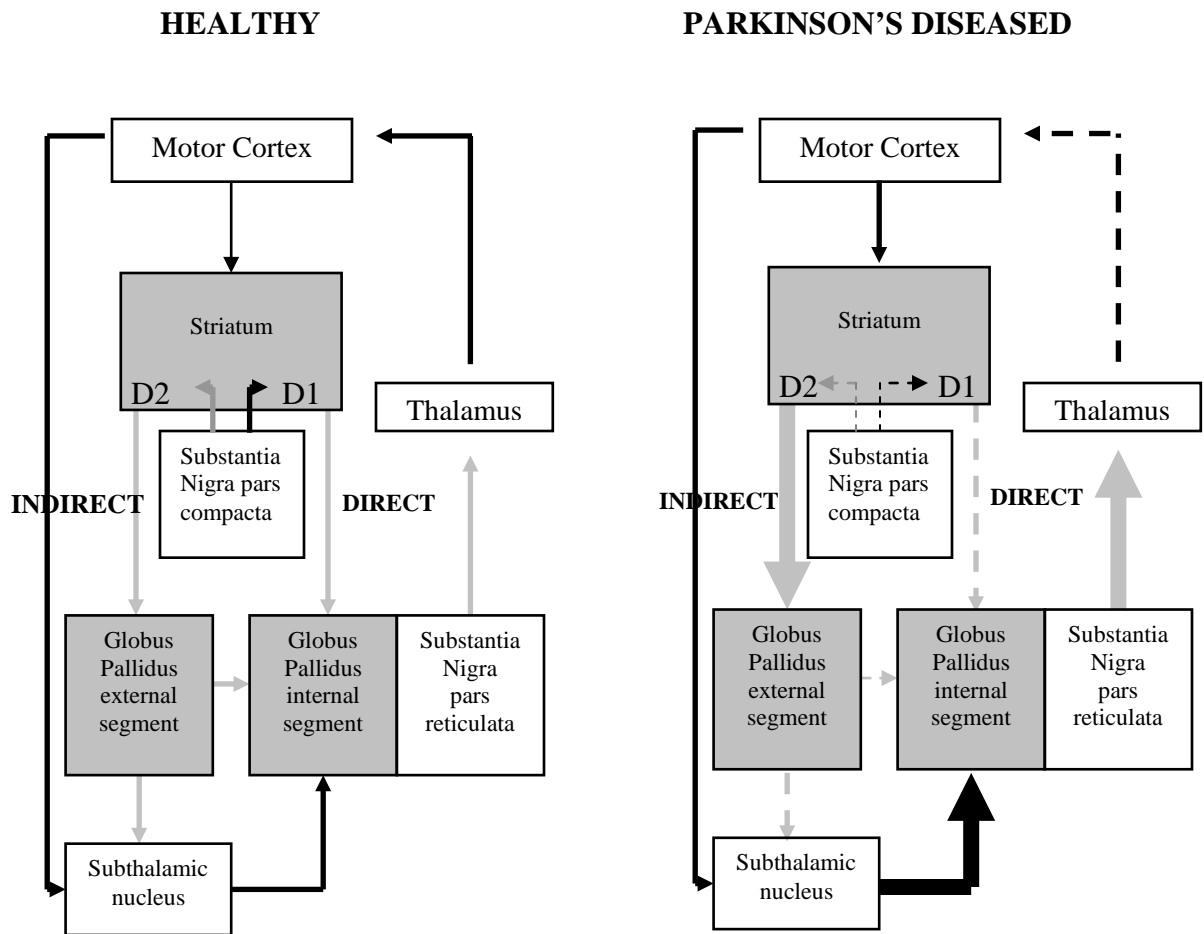


Figure 1.1. Schematic representation of basal ganglia circuitry indicating the direct and indirect pathways in healthy and PD individuals. Areas in grey boxes are nuclei of the basal ganglia, areas in white boxes are external to the basal ganglia. Grey arrows indicate inhibitory signals, Black arrows indicate excitatory signals. Fat arrows indicate increased activity, dotted arrows indicate decreased activity.

Risk Factors for the Development of PD and Proposed Causes of SNc Cell Death

Epidemiological studies have indicated several risk factors for the development of PD: 1) rural living; 2) drinking well water; 3) exposure to pesticides, such as rotenone and paraquat; 4) exposure to heavy metals, such as iron, mercury, and manganese; 5) encephalitis; 6) carbon monoxide poisoning; 7) head trauma; 8) personality traits, such as shyness and low risk taking; 9) genetic predisposition (Korell and Tanner, 2005); and 10) advancing in age (Calne & Langston, 1983).

Apart from genetics, a causative agent(s) has yet to be discovered. The focus of research into causative agent(s) for idiopathic (of unknown cause) PD is the mechanism of SNc cell death. Several theories have been postulated, including increased production of *reactive oxygen species*, which cause impairment of complex I of the mitochondria electron transport chain (Fahn, 1997; Schapira et al., 1990). Another proposed cause is *excitotoxicity*, which disinhibits the subthalamic nucleus (Rodriguez et al., 1998).

Inactivated phagocytotic microglia due to a prolonged *inflammatory* response has also been suggested to cause SNc cell death (Jenner et al., 2006). Exposure to chemical *toxins*, such as 1-methyl-4-phenyl-1, 2, 3, 6-tetrahydropyridine (MPTP) and rotenone are also believed to result in SNc cell death via inhibition of the mitochondrial electron transport chain (Przedborski, Tieu, Perier, & Vila, 2004; Sherer, Kim, Betarbet, & Greenamyre, 2003). *Abnormal protein metabolism* theories suggest mutations to genes for alpha synuclein (Spillantini, Schmidt, Lee, Trojanowski, Jakes, & Goedert, 1997) and ubiquitin ligase E3 (Hilker et al., 2001) as the cause of SNc cell death. A major hindrance to discovering the root cause of the disease lies in determining the primary, secondary,

tertiary, etc mechanisms involved in the cascade of pathological events leading to SNc cell death (Jenner, 2003).

Treatment of PD

Because a causative agent of PD has yet to be discovered, treatment remains largely symptomatic (Jenner & Olanow, 2006). The earliest treatments for PD were anticholinergics and monoamine oxidase (MAO) inhibitors. The mechanism of action of anticholinergics in PD is largely unknown (Jabbari et al., 2005). Selegiline, a MAO-B inhibitor, is thought to block the metabolism and reuptake of dopamine. It also increases synthesis of dopamine, and blocks its' autoreceptors (Glover, Sandler, Owen, & Riley, 1977; Heinonen & Rinne, 1989). Despite the advantages of MAO-B inhibitors, many negative side-effects warranted the discovery of an alternative drug treatment (Heinonen & Rinne, 1989).

The discovery of Levodopa revolutionized PD treatment. Since the 1960's, it remains the cornerstone antiparkinsonian treatment (Fahn, 1989; Marsden, 1994). Patients respond well at levodopa onset, but the drug becomes less effective as the disease progresses (Nutt & Holford, 1996; Koller, 1982). It can lead to a dramatic ON-OFF syndrome - symptoms are improved for a shorter period of time before "OFF"-like (no treatment) symptoms appear (Marek, et al., 2002; Whone, Rakshi, Watts, & Brooks, 2002). For some patients, dyskinesia, or involuntary twisting/turning movements, may also develop as a result of levodopa treatment (Marek et al., 2002; Whone et al., 2002). Lesion or deep brain stimulation of the thalamus, globus pallidus, or subthalamic nucleus is considered as a last resort when drug treatment is no longer a viable option (Baba et al.,

2005; Laitinen, Bergenheim, & Hariz, 1992; Baron et al., 1996; Pahwa et al., 1997; Gross et al., 1997; Limousin et al., 1998).

Although not currently a viable treatment, transplantation of stem cells may become a future treatment for PD. A problem with transplantation of dopamine-producing cells is that many people believe it will serve as a cure for PD. Transplantation is not likely to result in a cure for PD as replacement of lost dopamine cells is not likely to impact the changes seen in other neurotransmitter systems and protein synthesis (Pfeiffer, 2005).

Due to the negative side-effects of antiparkinsonian drug treatments, and feasibility of surgical treatments, alternative therapies have become popular. One potential non-medical treatment is music. In PD, music therapy has been used to facilitate movement initiation and execution of gait (Holten, 2005). Improvements in velocity, cadence, and stride length were documented in patients who received music therapy when compared to patients who were not receiving music therapy (Thaut, McIntosh, Rice, Miller, & Rathbun, 1996). Beneficial effects of music therapy have not been shown for other movement impairments in PD, however (Thaut et al., 1996).

Summary

PD is caused by the progressive neurodegeneration of the SNc. With the loss of dopamine projections from the SNc to the striatum, modulation of motor feedback loops is interrupted. Specifically, the direct pathway decreases in activity and the indirect pathway increases in activity. The net effect is rigidity and bradykinesia resulting from inhibition of motor cortex. Currently, the cause of SNc cell death is unknown, although

several theories have been proposed. The most likely candidate is impairment of complex I of the mitochondria electron transport chain. With the root cause of the disorder unknown, treatment remains symptomatic. Replacement of lost dopamine remains central to treating the disorder.

The Problems with Parkinson's Disease

PD by definition implies motoric deficit associated with impairments in only the motor system. This definition is debatable as the contribution of sensory system in motor actions has also been reported. The following section will describe the problem with identifying PD as a pure movement disorder. It will conclude by illustrating that PD is a complex disorder, with impairment in both motor and sensory systems.

PD as a Pure Movement Disorder

Originally, PD was suggested as a syndrome of pure motor origin, without impairment in intellect or the senses (Parkinson, 2002). This concept is still popular among many researchers and clinicians. In fact, current neurological examination and diagnostic criteria mainly focuses on the four cardinal features of the disorder (i.e., bradykinesia, rigidity, tremor, and postural instability) (Snider, Fahn, Isgreen, & Cote, 1976; Benecke, Rothwell, Dick, Day, & Marsden, 1986). Impairment in the production of voluntary movement is associated with the execution of multiple motor tasks simultaneously e.g. tasks with bimanual movements (Benecke et al., 1986). Given a simple task to perform, such as grasping an object at normal speed, PD subjects are no different from controls (Bonfiglioli, de Berti, Nichello, Nicoletti, & Castiello, 1998). There is a problem with the definition of symptomology appearing during complex tasks,

however. Completion of simple tasks, such as walking through a doorway (Giladi et al., 1992) can result in freezing of gait, a severe motor impairment. In addition, there is at least one report showing enhanced movement accuracy during bimanual activity in PD patients (Brown & Jahanshahi, 1998). The majority of PD subjects showed more accurate unimanual peg placement at placing pegs in a board if they were required to repetitively tap fingers on their opposite hand simultaneously (Brown & Jahanshahi, 1998). The authors suggested that sensory feedback from finger tapping likely facilitated movement performance of the PD subjects. It therefore seems likely that both sensory and motor systems interact in PD to produce motor impairment. This is in line with recent literature (Alexander & Crutcher, 1990; Flaherty & Graybiel, 1994; Parent & Hazarati, 1995).

Is the Sensory Control of Movement Impaired in PD?

The contribution of the sensory system in PD motor symptoms was first described by Flowers in 1976. He showed that without visual feedback, PD patients suffered from systematic hypometria (undershooting of a target). Flowers suggested that PD patients are unable to sense the location of their hand in space, i.e., have impairment in proprioception. As a result, PD patients must continually monitor their movements with visual feedback (Flowers, 1976; Prochazka, 1996), a now recognized symptom of Parkinson's disease (Hore, Meyer-Lohmann, & Brooks, 1977).

Recently, the sensory control of voluntary movement in PD has been confirmed by other clinicians in tasks involving step-tracking (Baroni, Benvenuti, Fantini, Pantaleo, & Urbani, 1984), and pointing to remembered targets (Adamovich et al., 2001). These tasks have shown that PD patient performance is less accurate in the absence of visual

feedback. When provided with an external visual or auditory cue, PD patients improve appreciably (Morris, Jansek, Matyas, & Summers, 1996; McIntosh, Brown, Rice, & Thaut, 1997). Thus, this line of research suggests that PD subjects experience a proprioception impairment that negatively affects voluntary movements when performed in the absence of visual feedback.

Most of the results on impaired proprioception in PD came from studies that used laboratory-based tasks (Baroni et al., 1984; Adamovich et al., 2001). Although these tasks revealed impaired proprioception, generalizability of the results beyond the laboratory is questionable. Therefore, an ethologically valid task, such as reaching for a piece of food that is placed in the mouth for eating (reach-to-eat), can be used to examine the influence of PD on the sensory control of a real-world reaching task.

Summary

Researchers and clinicians still refer to PD as a movement disorder. With this view, impairments present themselves during completion of complex tasks (Benecke et al., 1986). Gait literature contradicts this definition of PD, however. Walking through a doorway can result in freezing of gait, a severe motor impairment (Giladi et al., 1992). Bimanual tasks have also shown improvement of performance for PD subjects (Brown et al., 1998). Results such as these are not easily explained by motor impairment alone. Recently, research has begun to look at sensory systems in PD. It has been shown that proprioception is impaired and may account for a portion of the motor impairment (Flowers, 1976; Adamovich et al., 2001).

Organization and Rationale of the Thesis

The following section will describe the rationale for the present thesis, including the theory of how normal movement is produced, the hypotheses that were examined, and a brief description of the three experiments used to test the hypothesis.

Theory

Normally, movement is sequentially controlled by the visual and proprioceptive systems, in which the visual system selects a course of action and the proprioceptive system ensures its execution.

Hypotheses

Hypothesis 1. In Parkinson's disease, the proprioceptive system is impaired, thus requiring excessive visual guidance.

Hypothesis 2. Music activates proprioception, thus reducing visual dependence.

Experiments

The thesis proceeded in the following three experiments:

Experiment 1: To develop a task that reveals the roles of visual and proprioceptive guidance of motor control. The task that was chosen was reaching-to-eat. While seated, subjects reached for a Cheerio™ that was placed in the mouth for eating. Subjects wore eye-tracking glasses to monitor eye movements, visual occlusion glasses to block visual feedback, and light-reflective markers to track forelimb movement. It was observed that

vision was tightly locked with reaching towards and grasping the target. Withdrawal of the target to the mouth for eating was monitored by somatosensation (i.e., proprioception and tactile).

Experiment 2: To determine whether Parkinsonian subjects displayed alterations in the balance of visual and proprioceptive control. To examine this, young and old healthy adults (control groups) and mild and advanced PD subjects performed the reaching-to-eat movement under two experimental conditions: with and without visual guidance.

Experimental set-up was the same as in Experiment 1. It was observed that advanced PD subjects relied on visual feedback to reach for and grasp the target as well as withdrawal of the target to the mouth, and both these movements were slowed under visual occlusion. Control and mild PD subjects relied on visual feedback to reach for and grasp the target, and only this movement was slowed with visual occlusion.

Experiment 3: To determine whether the balance of visual and proprioceptive control in Parkinsonian subjects is normalized by music. Music was chosen because previous research has shown that the use of auditory cueing could improve PD performance (Morris et al., 1996; McIntosh et al., 1997). Young and old adults (control group), and mild and advanced PD subjects performed the reach-to-eat movement. Experimental set-up was similar to Experiment 1 and 2, but the effect of music on visual occlusion was not explored. On half of the reaching trials, subjects listened to preferred music while performing the reaching action. It was observed that music during the reach-to-eat movement improved measures of sensory control in PD subjects.

Taken together, these three experiments describe the contribution of sensory control in an ethologically valid reach-to-eat movement and the effect that age, disease, and music therapy has on motor and sensory impairment induced by PD.

Behavioural Assessment

The following section will briefly describe the methodology employed in the present thesis. The section will begin with a description of the reach-to-eat task used. This will be followed by description of the methods used to measure the contribution of vision to the reaching movement. Eye-tracking glasses can monitor and track subtle eye movements and visual occlusion glasses block visual feedback. Together, they allow for precise measurement of visual guidance during a behavioural task.

Behavioural Tasks

Reach-to-eat task. The reach-to-eat task is the human adaptation of the rodent Whishaw single pellet reaching task (Whishaw, Pellis, Gorny, & Pellis, 1991). Subjects perform a seated reach-to-eat task in which they reach to a pedestal for a food item that is grasped and transported to the mouth for eating (Whishaw, Suchowersky, Davis, Sarna, Metz, & Pellis, 2002; Melvin, Doan, Pellis, Brown, Whishaw, & Suchowersky, 2005). See Figure 1.2. This task provides two measures of movement performance. First, a gross measure of movement is determined from the length of time to complete the reach to grasp (*advance*) phase and withdrawal to the mouth (*withdrawal*) phase. Second, quality of the reach-to-eat movement is evaluated by scoring movement components (Whishaw et al., 2002) using conceptual framework derived from Eshkol-Wachmann Movement

Notation (Eshkol & Wachman, 1958). The following movements are scored: orientation to the target, lift and aim of the limb, pronation of the wrist, grasp of the target, supination I and II of the wrist, and return of the forelimb to the lap.

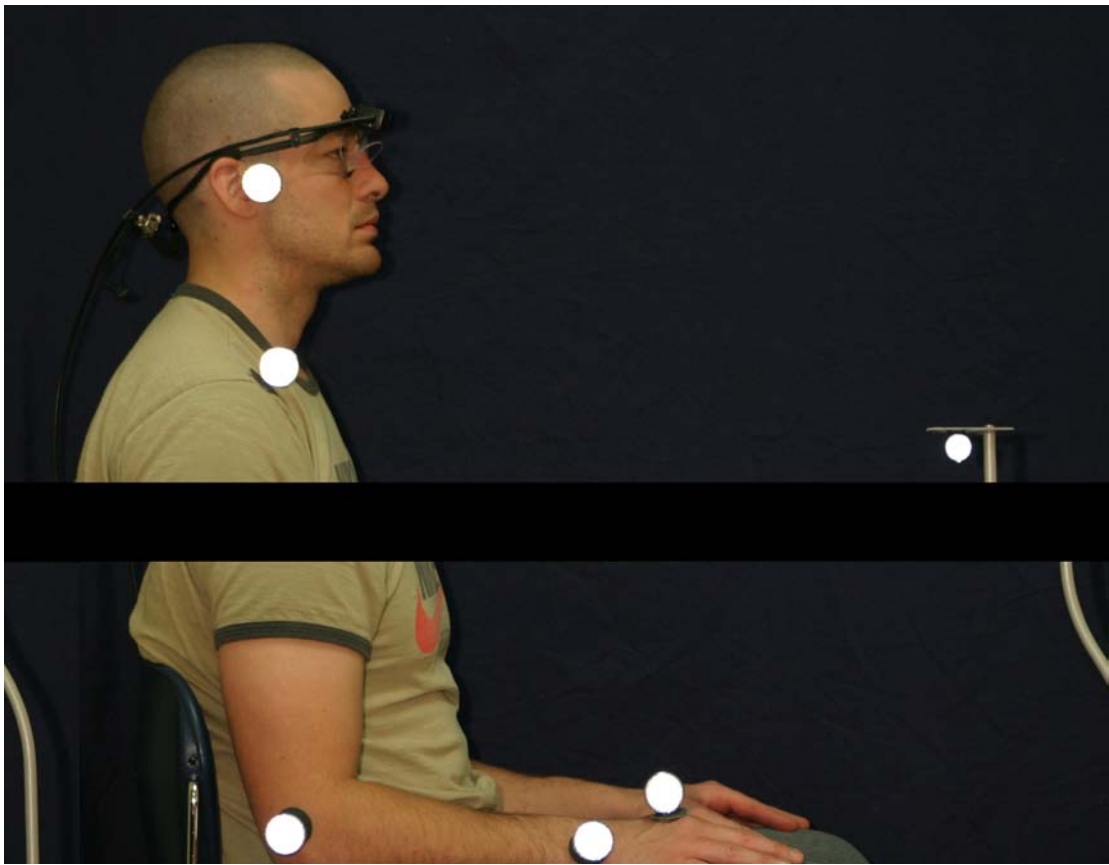


Figure 1.2. Experimental set-up of reach-to-eat task.

Visual Monitoring Systems

Eye-tracking system. Eye movements during performing the reach-to-eat task are tracked by a head-mounted, infrared eye tracking system (MobileEye v. 1.2, Applied Science Laboratories, Bedford, MA). See Figure 1.3. The system captures and measures rapid eye movements with high accuracy. The video record of the eye-tracking data is analyzed off-line. Visual guidance of the reach-to-eat movement is assessed using the following measures: *Engage to move* is the length of time (milliseconds (ms)) from the point the eyes first descend to fixate the target until the first movement of the forelimb; *Grasp to disengage* is the length of time (ms) from the first contact of the target with the digits to the point that the eyes first ascend from the target; *Total engagement duration* is the length of time (ms) from the point that the eyes first descend to fixate the target (*engage*) to the point that the eyes first ascend (*disengage*) from the target.

Visual occlusion system. PLATO vision-occluding glasses (Translucent Technologies, Toronto, ON) are used to assess the reach-to-eat movement in the presence or absence of visual feedback. See Figure 1.4. These conditions can be achieved via manipulating the transparency of the glasses during behavioral testing. The glasses can be made transparent to allow visual feedback or opaque to block visual feedback (Doan et al., 2006). In addition, the glasses were modified to occlude both central and peripheral vision by attaching a peripheral vision blocker. The glasses can therefore allow further description of the portion of the reaching movement under visual guidance

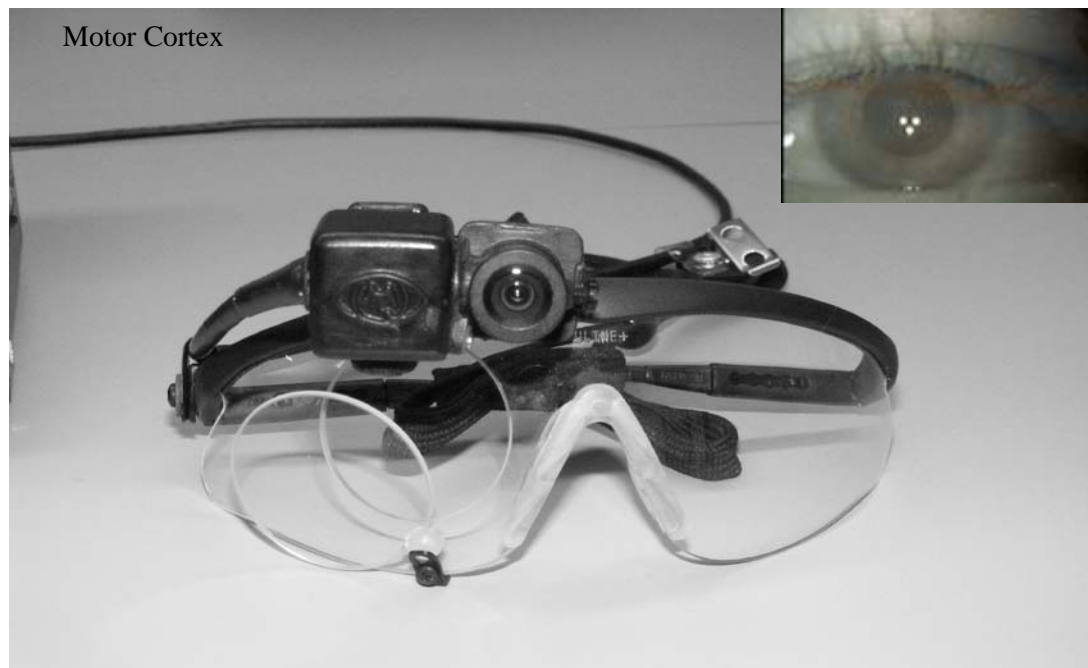


Figure 1.3. Eye-tracking system; inset is an image from video-record



Figure 1.4. Visual occlusion glasses.

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Chapter 2: Experiment 1

Visual Guidance for Hand Advance but Not Hand Withdrawal in a Reach-to-Eat Task in
Adult Humans: Reaching is a Composite Movement

Abstract

Reaching for food to place in the mouth (reach-to-eat) with a hand is used by many animal species and may be a movement primitive. Although visual guidance of reaching has been described in both normal and brain injured human and nonhuman primates, the contribution of vision during advance of the limb to grasp and withdrawal of the limb with food to the mouth has not been described. To evaluate visual contributions, eye movements were monitored in young adults as they reached for food with and without vision. Subjects visually engaged the target prior to the first hand movement, and disengaged as the food was grasped. Visual occlusion slowed limb advance and altered digit shaping but did not affect withdrawal. The dependence on visual control of advance but not withdrawal suggests that the reach-to-eat movement is a composite of two basic movements under visual and tactile/proprioceptive guidance respectively.

Introduction

Movements of the arm, hand, and digits provide the basis for many activities of daily living, including drinking, eating, and grooming. One class of forelimb movement, reach-to-grasp, in which a limb is transported towards a target and the digits are preshaped to grasp the target, has been the subject of many investigations in human and nonhuman primates (Bonfiglioli, De Berti, Nichelli, Nicoletti, & Castiello, 1998; Mackenzie & Iberall, 1994; Marteniuk, MacKenzie, Jeannerod, Athenes, & Dugas, 1987). The movement is characterized as being controlled by a “central generator” that initiates the action via parallel outputs that coordinate head, eye, arm and hand movements respectively (Arbib, 1981, 1990; Jeannerod, 1984, 1988). Vision plays an essential role in guiding the hand and preshaping the digits, as both extrinsic properties (e.g., distance) and intrinsic properties (e.g. size and orientation) of the target must be processed to achieve movement accuracy (Gentilucci et al. 1994, 1997; Goodale, Meenan, Bulthoff, Nicolle, Murphy, & Racicot, 1994; Goodale & Milner, 1992; Jeannerod, 1981, 1984 1999; Mackenzie & Iberall, 1994; Marteniuk et al., 1987; Marotta, Medendorp, & Crawford, 2003; Paulignan, MacKenzie, Marteniuk, & Jeannerod, 1990; Rizzolatti et al. 1988; Wallace & Weeks, 1988). Following contact with the target, haptic information is key in finalizing the grasp and exploring or manipulating the object (Mackenzie & Iberall, 1994; Xerri, Merzenich, Jenkins & Santucci, 1999). One of the most frequent manipulations of a target following grasp is placing the object in the mouth for eating. The movement of reaching for food to place it in the mouth (reach-to-eat) has also been examined in preclinical studies of animals to develop models of human neurological conditions (Whishaw, 2005), as well as being used to evaluate human

clinical disorders (Melvin, Doan, Pellis, Brown, Whishaw, & Suchowersky, 2005; Foroud & Whishaw, 2006; Doan, Whishaw, Pellis, Suchowersky, & Brown, 2006; Whishaw, Suchowersky, Davis, Sarna, Metz, & Pellis, 2002).

Because the reach-to-eat movement has been documented in a wide range of vertebrate species (Iwainuk & Whishaw, 2000) and is amongst the first limb movement displayed by developing infants (Twitchell, 1965), it is possible that the act is a movement primitive. On the other hand, electrophysiological mapping in primates, using long trains of electrical stimulation, shows that amongst the organized limb movements elicited, advance of a limb to a putative distal target and withdrawal of the limb to the mouth are elicited from different cortical locations (Graziano, Aflalo, & Cooke, 2005; Graziano, 2006; Stepniewska, Fang, & Kaas, 2005). This work would suggest that the reach-to-eat movement is a composite of two separate movements. The purpose of the present study was to further characterize the reach-to-eat movement by examining its temporal relationship to visual control. Given that the reach-to-grasp movement, or advance, is the first phase of the reach-to-eat movement, we hypothesized that visual guidance during the advance phase of the reach-to-eat movement would be similar to that of reach-to-grasp, i.e. vision will be used for sensory guidance. Because vision plays a role in the subsequent disposal of a grasped object, as occurs when an object is moved from one external location to another (Land, Mennie, & Rusted, 1999), suggests that vision may also be used for at least part of the withdrawal movement. Alternatively, given that when reaching toward ones' face, tactile/proprioceptive information concerning location of facial features, such as the nose, provides sufficient sensory information to accurately shape the digits for grasping (Edwards, Wing, Stevens, &

Humphrey, 2005), suggests that at least part of the withdrawal movement may not use vision. In addition to clarifying the relationship between vision and the reach-to-eat movement in normal subjects, understanding sensory control of the reach-to-eat movement is relevant to understanding alterations of the movement in pathological conditions (Whishaw et al., 2002), especially for those conditions in which the task is used for assessment.

In the present study, young adults were asked to reach for, grasp, and eat a small food item using their right forelimb. In the first experiment, kinematic and eye movement data were collected and time-coded for synchronicity to determine the point of engage and disengage in relation to hand and limb movements. In a second experiment, kinematic data was collected during test trials in which vision was and was not occluded for both the advance and withdrawal phases in order to test the contribution of visual guidance of the two aspects of the reach-to-eat movement.

Subjects and Reaching Task

Subjects

Subjects were 26 young adults (12 females and 14 males; ages 24.2 ± 4.5 years) recruited from the University of Lethbridge campus. All subjects were self-reported to be of good health with no history of neurological or motor disorders. All subjects had normal or corrected to normal (contact lenses) vision. The University of Lethbridge Human Subject Research Committee approved the study. Informed consent was obtained from subjects.

Reaching task. Subjects performed a seated reach-to-eat task in which they reached for, grasped, and transported a food item to the mouth for eating (Whishaw et al., 2002). Subjects were seated in a comfortable upright position, with their feet flat on the floor (Figure 2.1). A self-standing height adjustable pedestal was placed directly in front of the subject at a horizontal reach amplitude normalized to the subjects' arm length (100% of length from shoulder to tip of index finger with elbow at 180° flexion) and a vertical amplitude normalized to the subjects' trunk height (100% of height from floor to outstretched arm while seated and with shoulder at 90° flexion).

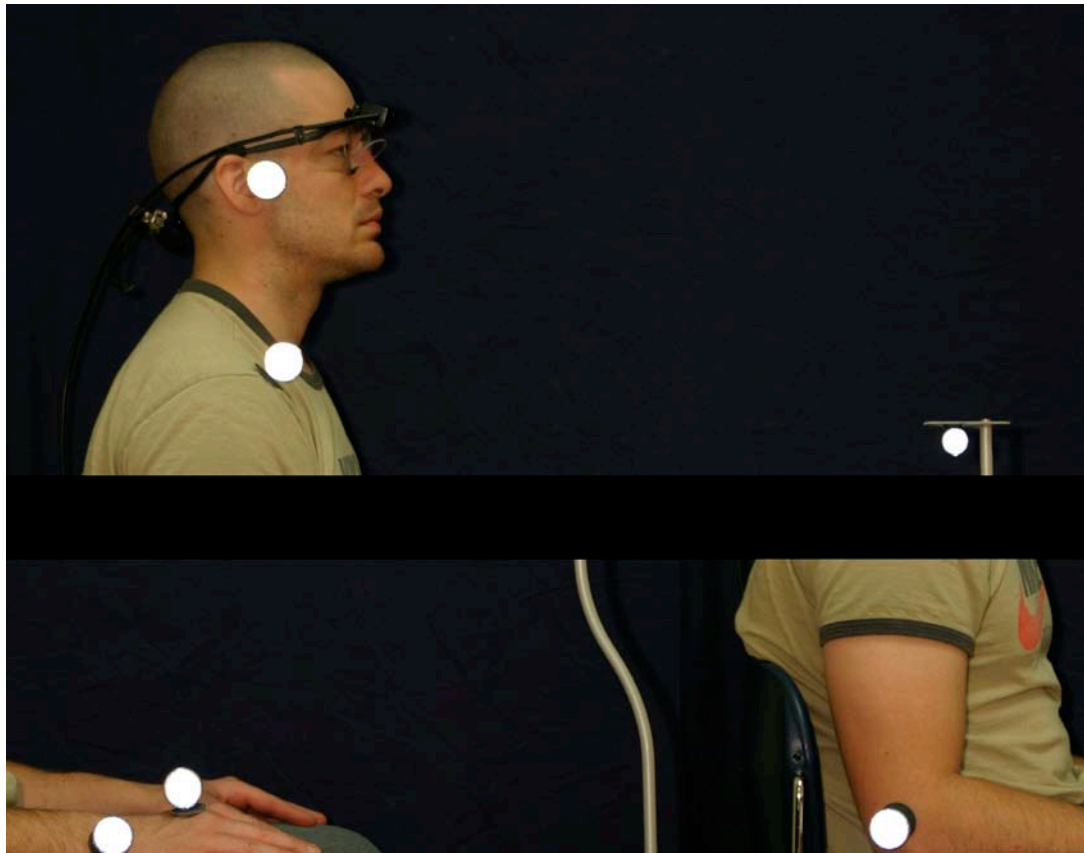


Figure 2.1. Diagram of the reach-to-eat design. Subjects are seated with both hands placed palm down on the ipsilateral thigh. Subjects were required to reach for a food item positioned on a pedestal placed at arm's length and height from the subject.

Reaching instructions. Once subjects were seated, they were asked to place their hands palm down on their thighs, and this instruction was not repeated. The experimenter stood to the left of the subject (i.e. in peripheral visual space) and placed a food item (choice of M&M™ or Skittle™) on the pedestal for each trial. The subjects were instructed to reach for food with their right hand. Each testing trial was initiated with a verbal “ready” signal, immediately followed by a verbal “go” signal as a permissive cue to start the trial at their leisure. Each trial concluded following successful placement of the food item in the mouth and return of the reaching hand to its start position on the lap. The experimenter maintained a casual relationship with the subjects, i.e., engaging in conversation, in order to maintain a quasi-natural testing condition. Because subjects were not informed their eye movements were under investigation, they were not asked to fixate on an object in the environment prior to trial initiation.

Behavioural Measures

Movement Tracking

Subjects were fitted unilaterally (right side) with reflective markers at (a) zygomatic bone, (b) acromion process, (c) lateral epicondyle of the humerus, (d) ulnar styloid process, and (e) head of the third metacarpal, or (a) head of the first metacarpal, and (b) head of the second metacarpal (Figure 2.1). A reflective marker was also placed on the pedestal under the target platform.

A digital video camera was positioned sagittal to the subject to record a reach-side view of the subject from lower leg to head at a sampling frequency of 30 Hz. Trial

reaches were digitized using the Peak Motus v. 8.3.0 2-D digitizing system (Peak Performance Technologies, Inc., Centennial, CO) to digitize the reflective markers on the image with an output of 30 Hz.

Marker data were filtered using a Butterworth low-pass filter with a cut-off frequency of 10Hz. Displacement and velocity data of the ulnar styloid process (reach wrist) were subsequently calculated (Peak Motus). The events of movement onset and offset were determined from the resultant reach wrist velocity using a custom-written algorithm (Microsoft Excel 2002), with minimal resultant velocity used to indicate the onset and offset events for the movement phases inherent to the reach-to-eat movement. Specifically, the reach-to-grasp phase (hereafter referred to as *advance*) was defined as the time between initial velocity onset (i.e. first movement of the hand) and the subsequent point of minimal velocity (i.e. as the hand contacts the food item). The grasp-to-eat phase (hereafter referred to as *withdrawal*) was defined as the time between the second velocity onset (i.e. first movement of hand away from pedestal) and the subsequent point of minimal velocity (i.e. as the food item contacts the mouth).

Eye-Tracking

A head-mounted infrared eye tracking system (MobileEye v. 1.2, Applied Science Laboratories, Bedford, MA) served to track and monitor eye movements with a sampling frequency of 30Hz. The MobileEye system uses Dark Pupil Tracking to compute the x and y coordinates of the pupil within the scene. In this technique, a set of three harmless near infrared lights are projected onto the eye, and reflected by the cornea (corneal reflection). By comparing the relative vectors from the sensor to the pupil and the cornea, the eye tracking system computes the position of the eye (point of gaze) relative to the

scene.

The video record of the data collected by the eye tracking system were subjected to off-line analysis to determine the following events of visual guidance: engage to move, grasp to disengage, and total engagement period. *Engage to move* was defined as the time between the first point that the eyes descend to fixate the target and first movement of the forelimb, and *grasp to disengage* was defined as the time between contact of the target with the digits and the first point that the eyes ascend from the target. The total visual engagement period was defined as the time between the first point that the eyes descend to fixate the target (*engage*) and the first point that the eyes ascend (*disengage*) from the target. A visual marker presented at the onset of the testing session was used to time-synchronize the video record of the biomechanical markers from the digital camera and the video record from the eye-tracking system offline using Final Cut Pro HD v.4.5 for Mac OS X v.10.2.8.

Visual Occlusion

Visual occlusion was achieved with PLATO vision-occluding goggles (Translucent Technologies, Toronto, ON), which was manipulated to allow vision (i.e., transparent) or occlude vision (i.e., opaque). The goggles were modified to occlude both central and peripheral vision by attachment of a peripheral vision blocker (i.e. black felt around the perimeter and fastened to the face with porous tape). Prior to the initiation of each trial, the occlusion goggles were either opened by the experimenter for a vision trial or remained closed for an occluded trial.

Grip aperture. Movement was digitized using the Peak Motus v. 8.3.0 2-D digitizing system (Peak Performance Technologies, Inc., Centennial, CO), which tracked the reflective markers on the image with an output of 30 Hz. Marker data were filtered using a Butterworth low-pass filter with a cut-off frequency of 10Hz. Peak grip aperture was determined from the segmental distance between the light reflective markers of the first and second metacarpals (thumb and index finger, respectively), and time to peak aperture was determined from the resultant reach index finger velocity using a custom-written algorithm (Microsoft Excel 2002). Minimal resultant velocity was used to indicate the onset and offset events for the advance phase of the reach-to-eat movement.

Procedure

Experiment 1: Reaching-to-Eat With Eye-Tracking

Eleven subjects (two females, nine males) were given the opportunity to reach for a maximum of five practice trials. Following the practice trials, subjects completed ten trials of the reaching task.

Experiment 2: Reaching-to-Eat With Visual Occlusion

Ten subjects (seven females, three males) were given the opportunity to reach for a maximum of four practice trials of the reaching task with vision, and a maximum of four practice trials without vision. Following the practice trials, subjects completed: (1) ten trials with vision and (2) ten trials without vision. The 20 test trials were presented in a random order for each subject.

Grip aperture. In a subsidiary experiment, grip aperture was assessed in five naive subjects (three females, two males) under conditions of vision and visual occlusion. Subjects completed a maximum of four practice trials of the reaching task with vision and a maximum of four practice trials without vision. Following the practice trials, subjects completed: (1) five trials with vision and, (2) five trials without vision. The ten trials were presented in a random order for each subject.

Statistical Analysis

Descriptive statistics were obtained using Microsoft Excel 2002. Data were analyzed using the Statistical Package for the Social Sciences (SPSS v. 13) paired *t*-test for comparison of vision and no-vision conditions across subjects. A *p* value of 0.05 was used to determine statistical significance.

Behavioural Results

Experiment 1: Reach-to-Eat With Eye-Tracking

Analysis of eye movements prior to the initiation of a reaching trial showed that eye movements were either directed at the experimenter who was engaged in conversation with the subject, or straight ahead, and were never fixated on the target (Figure 2.2-Start). The reach-to-eat sequence commenced with a downward deviation of the eye from the experimenter or straight ahead to orient towards the target. The arm begins to move towards the pedestal top, and the hand supinates and the digits shape in preparation to grasp the food item which is fixated by the eyes (Figure 2.2-Engage for

Advance). As the reach-to-eat sequence progresses, the trunk contralateral to the reaching hand moves forward and the hand pronates over the food item for grasping. At tactile contact with the food item, the eyes disengage from the food item, frequently with an accompanying blink (Figure 2.2-Blink at Grasp). The hand lifts, supinates, and is transported to the mouth by the lower arm. During this withdrawal phase, the trunk moves back towards its starting position, positioning the mouth to meet the hand. Further supination of the hand places the food item in the mouth. The eyes remain disengaged for the entire withdrawal phase (Figure 2.2-Disengage with Withdrawal). The food item is then released and the hand pronates and returns to the thigh through the movement of the upper and lower arm.

Analysis of the temporal sequencing of point of gaze indicated that the target was engaged immediately prior to initiation of hand movement ($M \& SE = 40 \pm 64$ ms) (Figure 2.3 A, B, C Engage and Move) and the target was disengaged ($M \& SE = 73 \pm 78$ ms) (Figure 2.3 B, C Disengage and Grasp) prior to grasp. Point of engagement was defined as a downward deviation of the eye to directly fixate the target, and the total engagement period was characterized by the absence of both eye movement and blinking. Disengagement was defined with either a blink or an upward deviation of the eyes from the target to look straight ahead, as was the case in 89 % of the total number of trials, or at the experimenter, for 11 % of the trials. All subjects used both strategies; however, disengagement occurred synchronously with a blink in 75% of the total number of trials. The eyes remained disengaged from the food item and the hand for all subjects during the entire withdrawal phase of the reach-to-eat movement (Figure 2.3B, C Disengage and Grasp – Eat). The subjects' point of gaze was idiosyncratic throughout the withdrawal

phase of the reach, for example, subjects either remained fixated on the experimenter or another object in the room, or performed a visual search of the objects in the room.

The mean duration of the reach-to-eat movement under visual engagement and disengagement for all eleven subjects is shown in Figure 2.4. Six of the eleven subjects engaged the target prior to the onset of initial hand movement ($M \& SE = 174 \pm 67$ ms), whereas the remaining five subjects engaged following the onset of initial hand movement ($M \& SE = 123 \pm 61$ ms). Nine of the eleven subjects disengaged prior to grasping the target ($M \& SE = 164 \pm 39$ ms), whereas the remaining two subjects disengaged following grasp ($M \& SE = 313 \pm 220$ ms). On average, subjects engaged the target for 51% of the reach-to-eat movement, and were disengaged from the target for 49% of the movement.

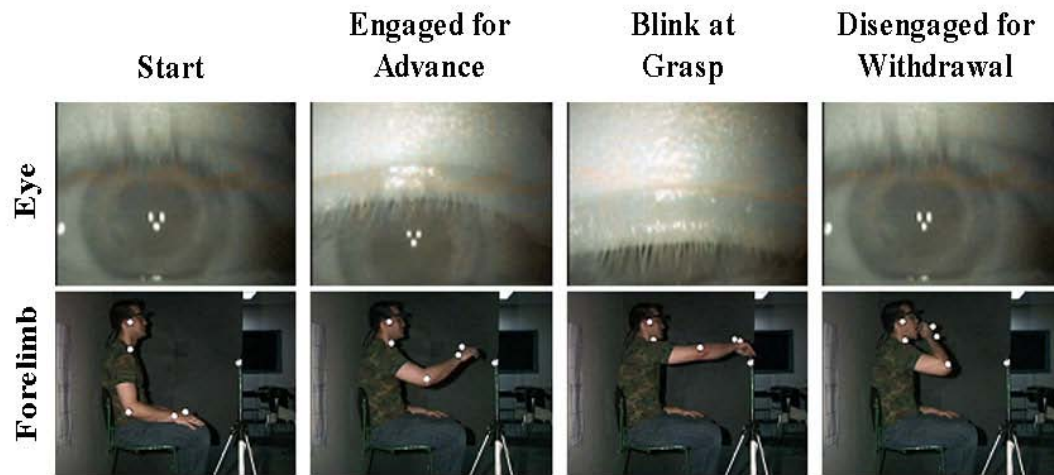


Figure 2.2. Left to right. Kinematic events and their corresponding eye movements during the two phases of the reach-to-eat movement. Note how the eye disengages with a blink following tactile contact with the food item.

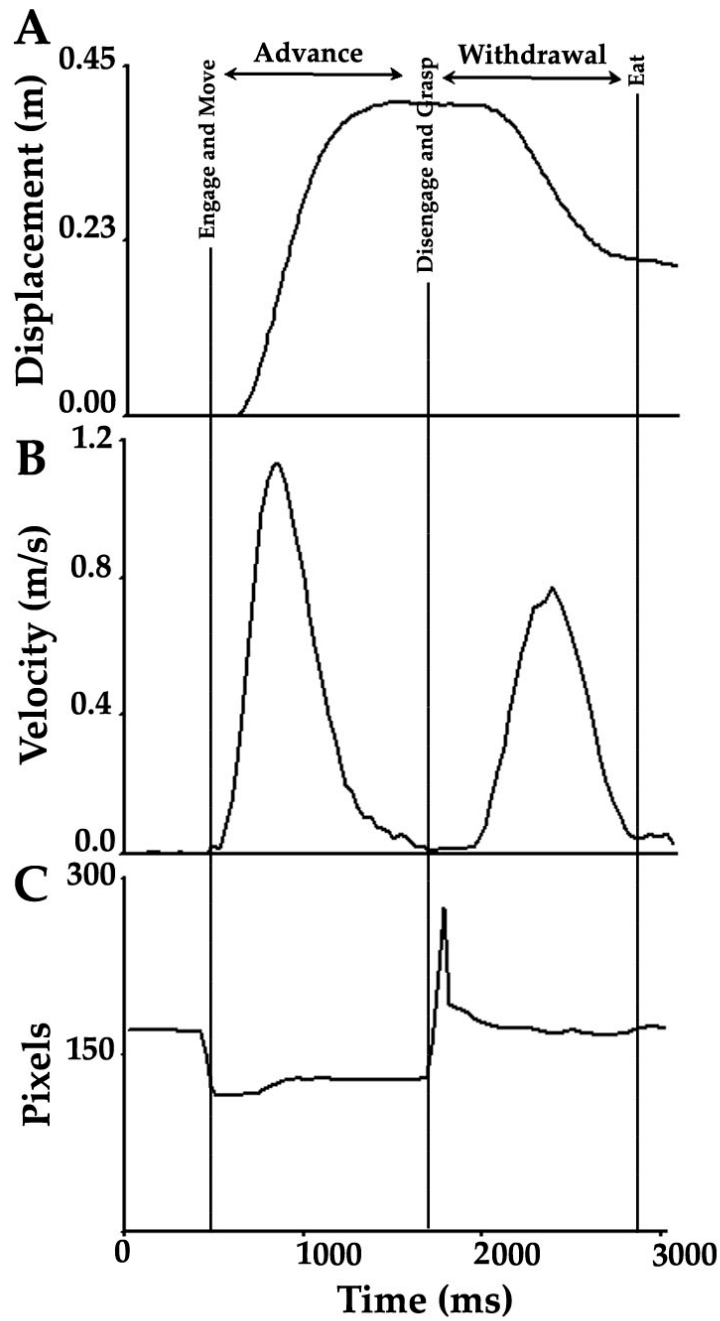


Figure 2.3. Top to bottom. Reach wrist resultant A) displacement, B) velocity, and C) pupil (right) movement in the vertical dimension for a representative subject during a single reach.

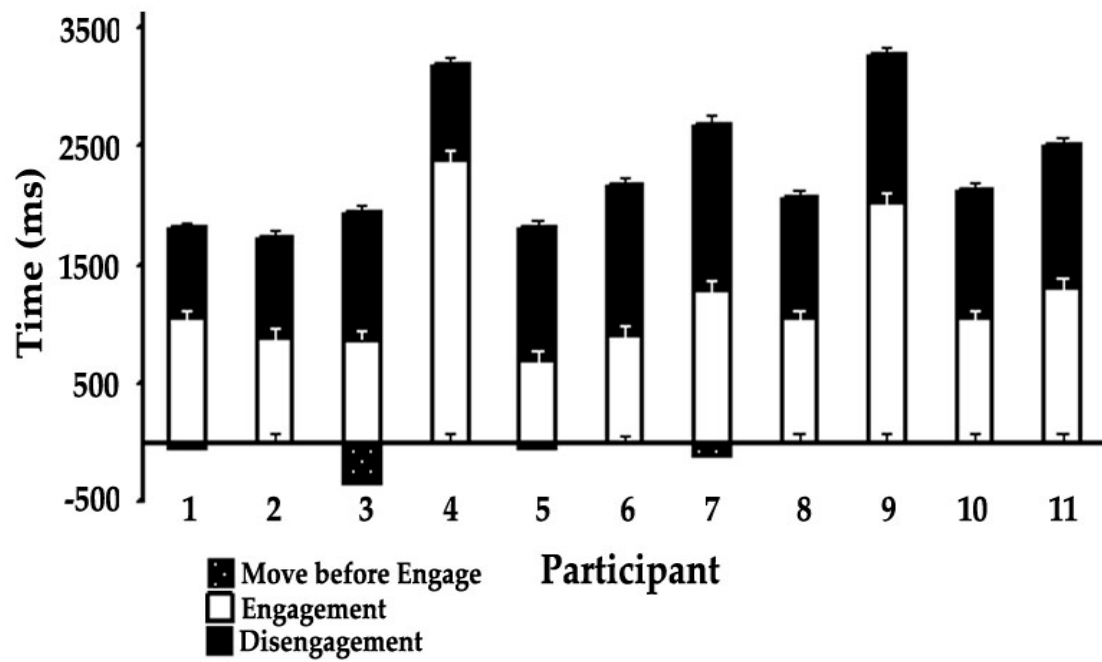


Figure 2.4. Visual engagement and disengagement in relation to the event "Engage". Values shown are means for each of the eleven subjects. As represented by a negative value, five subjects (one, three, five, six and seven) began "Move" prior to "Engage".

Experiment 2: Reach-to-Eat With Visual Occlusion

As presented in Figure 2.5, analysis of the kinematic data determined that the mean duration for the advance phase was longer without vision than with vision ($M \& SE = 1542 \pm 46$ ms vs. 2276 ± 104 ms; $t(99) = 7.76, p < 0.001$ respectively), and the mean duration for the withdrawal phase with and without vision was not different ($M \& SE = 1269 \pm 39$ ms vs. 1296 ± 40 ms; $t(99) = 0.60, p = 0.55$ respectively).

Visual occlusion also changed the characteristics of the grasp as subjects reached with the digits extended and did not shape the digits to grasp the food until they contacted the food with the ventral surface of the hand or digits. Analysis of the hand and digits during the grasp revealed a significant effect of vision, as subjects made an error of acquisition on 41 % of the occluded trials and were without error on the vision trials, $t(99) = 8.29, p < .001$. As presented in Figure 2.6, of the erred grasps, thirty-one percent were an undershooting of the target, and the remaining 10 % were an overshooting of the target. Following tactile contact with the food item, finger aperture was corrected and the grasp completed. There were no errors on either the occluded and vision trials for the act of placing food in the mouth.

As displayed in Figure 2.7A, analysis of peak grip aperture revealed a reliable effect of vision, with an over-shooting of the target size in the occluded condition relative to the vision condition, $t(25) = -5.29, p < 0.01$. A significant difference was also found for time to peak aperture, as demonstrated in Figure 2.7B, with the occluded trials taking significantly longer to reach peak aperture relative to the vision trials, $t(25) = -2.43, p < 0.05$. A representative aperture versus time plot for a vision trial and an occluded trial is presented in Figure 2.7 C and D respectively.

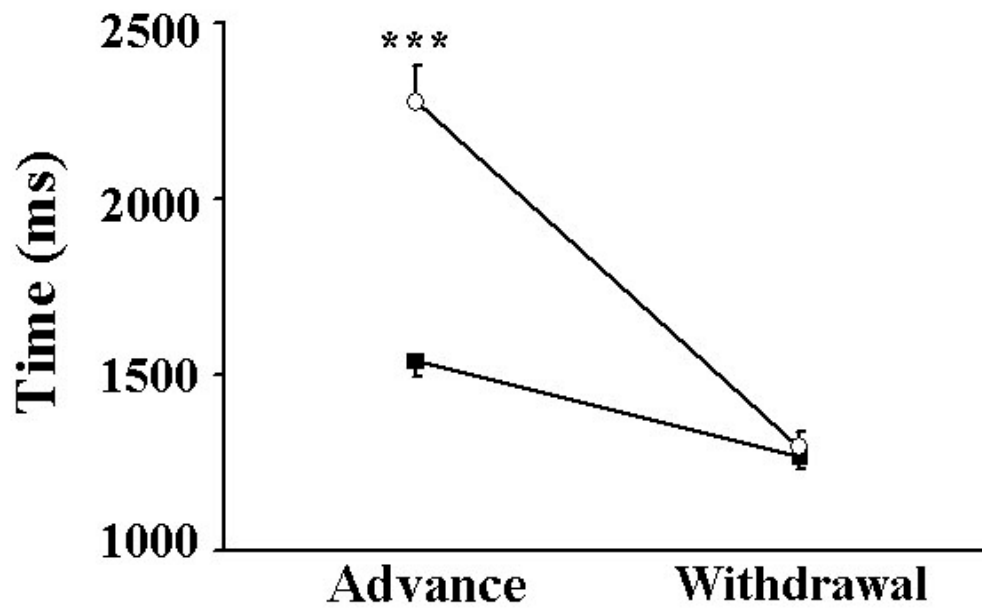


Figure 2.5. Values shown are means and standard errors for all eleven subjects for the advance and withdrawal phase durations during vision and visual occlusion reaches. Open circles represent occlusion scores, closed squares represent vision scores. *** = $p < 0.001$

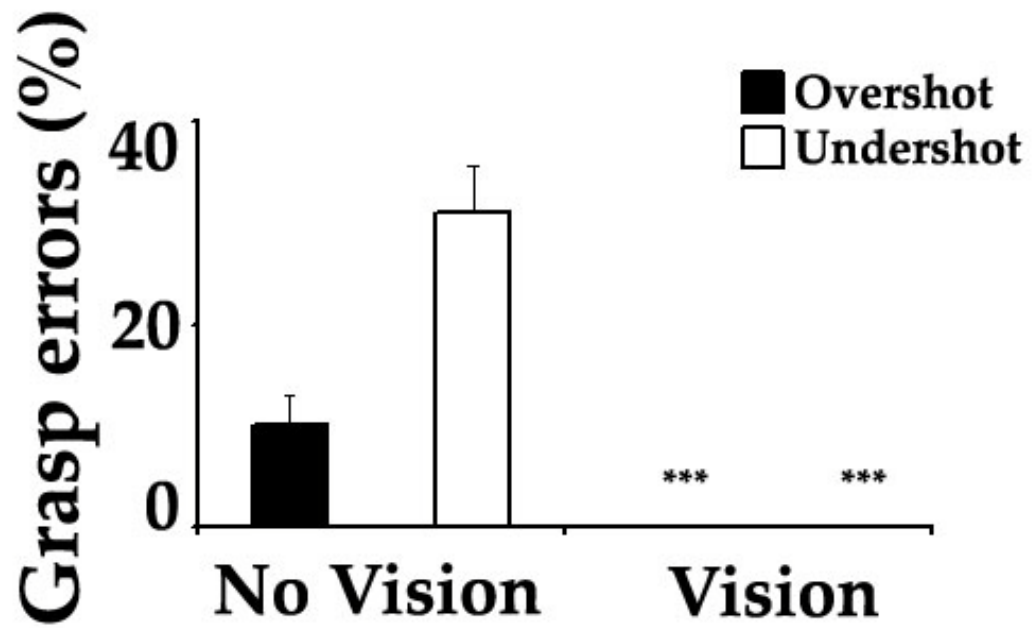


Figure 2.6. Values shown are means and standard errors for grasp errors made by all subjects during vision and occluded trials. *** = $p < 0.001$

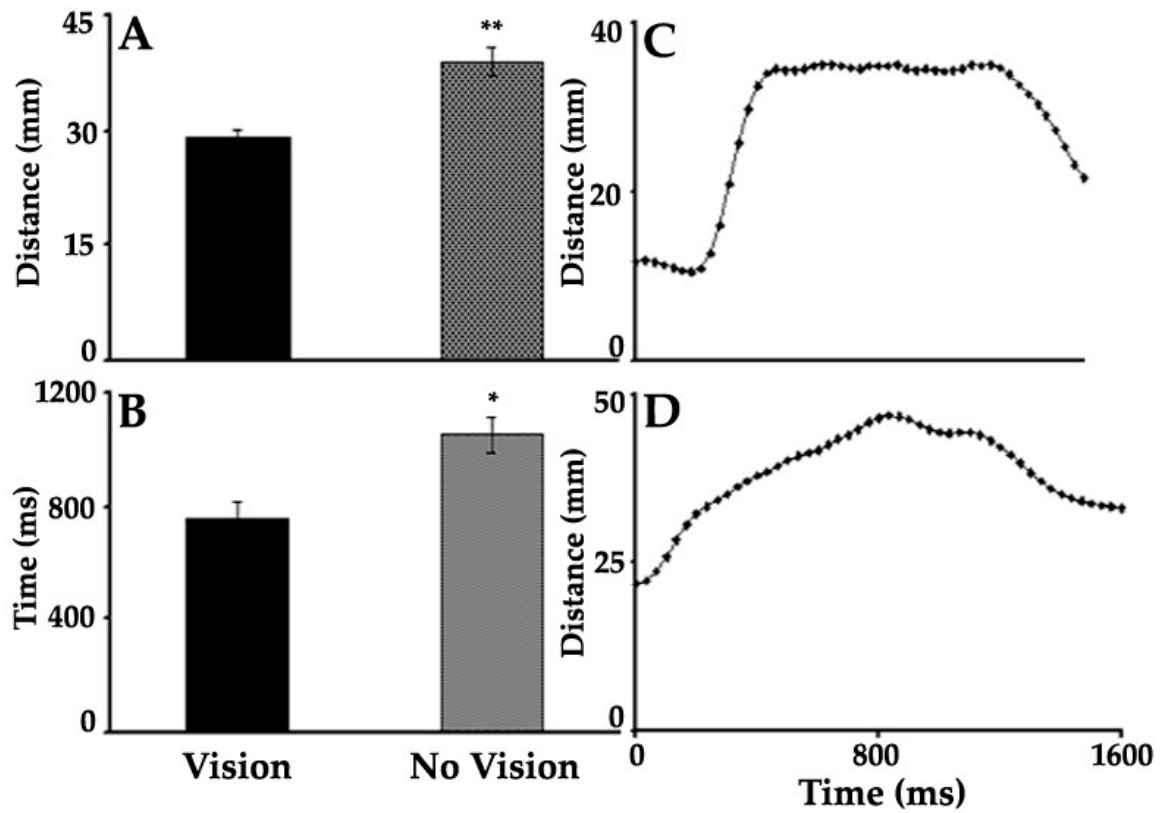


Figure 2.7. Top to bottom, left to right. Values presented are means and standard error for A) peak aperture, and B) time to peak aperture. A representative C) distance versus time plot for a vision trial, and D) distance versus time plot for an occluded trial, in the vertical dimension for a representative subject during a single reach. * = $p < 0.05$, ** = $p < 0.01$.

Discussion

The reach-to-eat movement using a hand is an ethologically natural movement that is used daily by many nonhuman animal species and humans. The purpose of the present study was to investigate the question of whether the movement is a movement primitive or a composite of more elementary movements. An examination of the relationship between eye movements and reaching movements showed that the eyes were directed to, and remained on, the target prior to initiation of hand advance to the time that the food is grasped, at which time they disengaged. Visual occlusion during hand advance was associated with slower advance and altered hand aperture. Withdrawal was unaffected by visual occlusion. The fractionation of the reach-to-eat movement into visual monitoring during advance but not withdrawal, suggests that the movement is a composite of at least two partially separate acts. The division of the reach-to-eat movement into a visually guided component and a component guided by haptics/proprioception is discussed in relation to the sensory guidance of the movement and the central organization of the movement.

For the experiments, subjects were given no special instructions about how to reach and they were given no indication that they should observe the target location or the food when it was placed on the target. In fact, examination of the eye movement record gave no indication that any of the subjects attended to the target or food prior to reaching. Indeed, they appeared to look at the experimenter, who stood to one side, or attended to other objects in the room. Nevertheless, measures of the temporal relationship between eye and hand movements, as well as the duration of visual engagement, revealed that the eyes engaged the target immediately prior to the initiation of first hand

movement, fixated the target during limb advance, and disengaged from the target, usually with a blink and an upward glance, as tactile contact with the food item was made. Vision remained disengaged from the target and hand during the withdrawal phase. Although some subjects engaged the target just after the first hand movement, eye data, in combination with kinematic data collected from the reach wrist, indicated a close coupling between the eye and limb movements, particularly the events of grasp and disengage, suggesting that limb advance is under visual guidance (Biguer, Jeannerod, & Prablanc, 1982). That the eyes then remained disengaged during the withdrawal phase of the reach-to-eat movement and replacement of the hand to its starting position on the lap, and did not reengage until the next reach was initiated, indicates the withdrawal phase is under other sensory guidance, presumably somatosensation.

The finding that eye movements engaged a target prior to reach initiation on average is consistent with a number of previous studies (Prablanc, Echallier, Komilis, & Jeannerod, 1979; Carlton, 1981; Foroud et al., 2006; Whishaw et al., 2002; Snyder, Calton, Dickinson, & Lawrence, 2002; van Donkelaar, Siu, & Waltarschied, 2004). Visual engagement is understandable because vision not only identifies the location of the target, but also identifies the intrinsic properties (e.g., size and shape) of the target, and contributes to preshaping of the hand for grasping (Snyder, 2002; Mackenzie et al., 1994; Berthier, et al., 1996). The finding that the eyes disengage from the target, and seemingly the reaching task, at tactile contact contrasts with a previous report that vision plays a role in transporting a grasped object from one external location to another (Land et al., 1999). Nevertheless, in that study the object was moved from one distal location to

another, a difference that suggests movement of the hand to a body target is distinct and special.

It is interesting that on 75 % of the trials, subjects blinked as they disengaged the target, and on the remaining trials just disengaged with an upward deviation of the eyes. Previous work shows that blinking accompanies gaze shifts (Evinger, Manning, & Sibony, 1991), with eye movements being completed within 60 to 70 % of the blink duration (Rottach, Das, Wohlgemuth, Zivotofsky, & Leigh, 1998), and the probability of a blink occurring is proportional to the size of the gaze shift (Evinger et al., 1991; Watanabe, Fujita, & Goyoba, 1980). When subjects visually disengaged the target at grasp, gaze was consistently directed upward from the pedestal, sometimes toward one side where the experimenter was positioned (11 % of trials) but more frequently straight ahead (89% of trials). Visual disengagement away from the target may serve a variety of functions, such as providing a visual anchor against which to stabilize posture when bringing the food to the mouth (Paillard, & Amblard, 1985; Clement, Pozzo, & Berthoz, 1988), preparing for a search for the next food item, as well as to engage the experimenter who was providing the food to indicate to the experimenter their readiness for subsequent trials. Thus, blinking and visual reorienting at tactile contact marked the end of visual engagement and likely the onset of reorientation of vision to a different spatial location.

Although Binsted et al. (2001) suggest that the eye has only to be in the general vicinity of the target to provide sufficient attention for grasping, for the present task, it was found that the target was directly fixated by all subjects on every reach. Direct visual fixation may be necessary because the target food item was small (M&M™ or Skittle™),

requiring a pincer grasp for purchase (Wong & Whishaw, 2004). In addition, direct visual engagement is proposed to be essential for unconscious reaching dependent upon guidance by the dorsal stream (Goodale et al, 1992; 1994).

In order to determine whether withdrawal of the hand to the mouth is under visual guidance and perhaps under guidance of peripheral vision of the lower visual fields (Danckert & Goodale, 2001; Previc, 1990; Whishaw, 1994), the kinematics of advance and withdrawal were compared under visual and visual occlusion conditions. Visual occlusion substantially changed the advance movement, as subjects took longer to reach peak aperture on occluded trials. Additionally, with visual occlusion, an error occurred on 41 % of the occluded trials, as subjects either overshoot or undershot the target location during grasp, but were without error on the vision trials, illustrating the importance of vision for the advance phase and the grasp. Occlusion did not prevent successful completion of the reach, however, as digit preshaping and grasp followed tactile contact of the food item by the ventral surface of the hand or digits, consistent with previous work (Chieffi & Gentilucci, 1993; Jackson, Jones, Newport, & Pritchard, 1997; Churchill, Hopkins, Ronnqvist, & Vogt, 2000; Fourkas, Marteniuk, & Khan, 2003). Comparatively, there were no changes in the kinematics of withdrawal, and subjects did not err on placement of the food item into the mouth for both occluded and vision trials, suggesting somatosensation is sufficient for successful completion of the withdrawal phase.

Thus, the findings under both visual and occluded conditions suggest that the reach-to-eat movement consists of two phases, advance under visual guidance and withdrawal under somatosensory guidance. Because tactile information is a relevant

sensory focus during the grasp and subsequent withdrawal phase (Gentilucci, Toni, Daprati, & Gangitano, 1997; Roland, O'Sullivan, & Kawashima, 1998; Johansson & Westling, 1987; Xerri et al., 1999), visual disengagement at the point of grasping may serve to re-prioritize the perception of somatosensory feedback. It may do so by enhancing kinesthetic awareness of the item that is grasped (Harada et al., 2004; Rothwell, Traub, Day, Obeso, Thomas, & Marsden, 1982), allowing the acquisition of intrinsic characteristics of the target for completion of digit closure and grasp (Mackenzie et al., 1994). With respect to the absence of visual guidance during withdrawal, it is relevant that Edwards et al. (2005) report that when reaching for one's nose, grasp aperture is adequately controlled by proprioceptive information. Thus, it might be more generally the case that movements directed toward a body target do not necessarily require visual guidance. Previous work using fMRI has suggested that advance of the limb to grasp an object is associated with activity in neural pathways involving visual and parietal cortex identified as the dorsal stream (Culham et al., 2003). It would be interesting to determine whether withdrawal with food to eat is associated with similar activity, or rather, is associated with pathways not involving visual cortex. A further dissociation of the reach-to-eat movement into phases based on central brain activity would suggest that changes in arm movement could be mediated by rapid central attentional shifts based in part on activity in brain regions representing different sensory modalities.

In conclusion, the results of the present study show that the reach-to-eat movement can be divided into two distinct phases based on sensory guidance; advancing the limb towards the food item under visual guidance, and withdrawal of the limb

towards the mouth under somatosensory guidance. This natural division of sensory control between movements directed to a visual target, such as a food item, and to a personal target, such as the mouth, may prove useful in understanding the neural basis of different portions of the reach-to-eat movement, as well as the effects of brain injury and disease on the reach-to-eat movement phases. The main findings of the study are thus consistent with electrophysiological studies suggesting that advance to grasp and withdrawal of the hand to the mouth are at least partially neurally separate (Graziano et al., 2005; Graziano, 2006; Stepniewska, et al., Fang, & Kaas, 2005). Together, the electrophysiological and behavioral results converge to suggest that the reach-to-eat movement is a composite of two movement primitives.

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Chapter 3: Experiment 2

Visual Guidance in a Reach-to-Eat Task in Advanced but not Mild Parkinson's Disease May Attenuate Proprioceptive Impairment

Abstract

Parkinson's disease (PD) is characterized by sensory and motor abnormalities including using the arm and hand to reach for food to eat (reach-to-eat movement). The reach-to-eat movement is associated two sequential sensory control strategies: (1) visual guidance involving fixation of the target at reach initiation to disengagement as the digits contact the target, (2) haptic/proprioceptive guidance of the hand from target contact to food release in the mouth. The present study examined whether this sensory guidance is conserved in PD. Eye movements and reach and kinematic measures of the reaching limb were collected from young and aged-matched control groups, and mild (Hoehn and Yahr <2.5) and advanced (Hoehn and Yahr >2.5) PD groups. Both PD groups displayed impairments in reaching as measured by a movement rating scale and by kinematic measures of reach duration. Nevertheless, mild PD subjects were similar to the control groups in that they only visually engaged the food target from first hand movement to the grasp. Advanced PD subjects visually engaged the food target prior to the first hand movement and continued to fixate the target after the grasp. Visual occlusion slowed the advance of all groups and also slowed the withdrawal movement for the advanced PD group. The results are discussed in relation to the idea that in the advanced stage of PD, vision is used to compensate for impaired haptic/proprioceptive control of movement.

Introduction

Parkinson's disease (PD) is characterized by bradykinesia, rigidity, tremor, and postural instability (Sacks, 1973; Martinez & Utterback, 1973), and is related to a progressive degeneration of dopamine producing neurons in the substantia nigra pars compacta (Dauer & Przedborski, 2003). Disease symptoms are manifest in many laboratory based motor tasks (Dunnewold, Jacobi, & van Hilten, 1997; Ponsen, Daffertshofer, Wolters, Beek, & Berendse, 2008) and real-world tasks (Tresilian, Stelmach, & Adler, 1997; Castiello, Bennett, Bonfigliolo, & Peppard, 2000; Doan, Whishaw, Pellis, Suchowersky, & Brown, 2006). Impairments in movement are often accompanied by impairments in sensory attention (i.e. the sensory system that is attending the target) (Flowers, 1976; Baroni, Benvenuti, Fantini, Pantaleo, & Urbani, 1984; Klockgether & Dichgans, 1994; Keijsers, Admiraal, Cools, Bloem, & Gielen, 2005). For example, studies on walking suggest that PD subjects rely more on visual guidance to survey potential obstacles in the room than are control subjects (Flowers, 1976; Baroni et al., 1984) and studies on memory-guided pointing demonstrate that PD subjects are more impaired than control subjects in the absence of vision (Klockgether et al., 1994; Keijsers et al., 2005). Additionally, PD subjects also suffer from abnormal eye movements, as demonstrated in saccade (Chan, Armstrong, Pari, Riopelle, & Munoz, 2005) and visual attention tasks (Lieb, Bucker, Bach, Els, Lucking, & Greenlee, 1999).

One of the earliest appearing motor symptoms of PD is in the reach-to-eat movement, in which subjects reach for a food item that is placed in the mouth for eating (Whishaw, Suchowersky, Davis, Sarna, Metz, & Pellis, 2002; Doan, Melvin, Pellis, Brown, Whishaw, & Suchowersky, 2005). Impairments occur in the postural adjustments

associated with movement of the arm, in the rotational movements of the arm and hand, and in digit shaping for grasping. At present it is not known whether impairments in sensory attention contribute to the impairments of the reach-to-eat movement. Doan et al. (2006), however, report that occluding vision in PD subjects reaching for a glass of water slows movement and increases movement errors, suggesting a role for visual attention in the reach-to-grasp movement. The temporal relationship between visual attention and reaching was not examined, however. Studies on healthy young adults show that the reach-to-eat movement is guided by two sequential modes of sensory attention. Vision is used to guide the hand from the point of first hand movement to the point that the digits contact the target. Haptics/proprioception is used to guide the withdrawal movement that brings the hand to the mouth and calibrate mouth opening to receive the food (de Bruin, Sacrey, Brown, Doan, & Whishaw, 2008). The sequential monitoring by visual and somatosensory attention is additionally supported by the finding that the advance phase of the reach, but not the withdrawal phase of the reach, is slowed in the absence of vision. That the reach-to-eat movement is dependent upon two modes of sensory attention raises the question of whether this temporally-based guidance is conserved in PD, and whether changes in sensory monitoring contributes to reach-to-eat movement impairments in PD. The present study examined whether PD is associated with changes in sensory guidance that becomes more severe in more advanced subjects.

For the study, young adult controls (YAC), age-matched controls (OAC), and adults with mild (mild PD) and advanced (advanced PD) PD reached for and eat a small food item that they placed in the mouth for eating. Subjects were fitted with light reflective markers to measure arm and hand movement, wore an eye-tracking system to

monitor eye movements, and on some trials, were fitted with goggles that could be manipulated to occluded vision during the reach. A rating of limb use during reaching and synchronized data from the biomechanical measures was compiled to determine the contribution of visual guidance to the reach-to-eat movement.

Subjects and Reaching Task

Subjects

On the basis of Hoehn and Yahr (HY) scores (Hoehn & Yahr, 1967), PD subjects were divided into two groups, mild PD (HY < 2.5; 6 females and 2 males; ages 63.88 ± 8.32 years; HY = 2.06 ± 0.42) and advanced PD (HY > 2.5; 2 females and 4 males; ages 72.50 ± 7.01 years; HY = 3.17 ± 0.93). Subjects were “ON” medications at the time of testing. For a complete profile of PD subjects, see Table 3.1. Two groups of age-matched old adult control (OAC) subjects (i.e. one for mild PD and one for advanced PD) were recruited from the City of Lethbridge (9 females and 7 males; ages 62.5 ± 6.52 to 75.91 ± 9.71 years). Eleven young adult control (YAC) subjects (4 females and 7 males; ages 22.27 ± 3.85 years) were recruited from the University of Lethbridge campus. All control subjects were self-reported to be of good health with no history of neurological disorder, and had normal or corrected to normal (contact lens) vision. The University of Lethbridge Human Subject Research Committee approved the study. Informed consent was obtained from subjects prior to initiation of the testing session. The study was conducted in accordance with the Declaration of Helsinki..

Table 3.1.

Parkinson's diseased subjects' characteristics

<u>Subject ID</u>	<u>Group</u>	<u>Age</u>	<u>Sex</u>	<u>H & Y</u>	<u>Medications</u>
1	Advanced	64	M	2.5	Carbidopa; Amantadine
2	Advanced	71	M	2.5	Levodopa/carbidopa
3	Mild	61	F	2	Pramipexole
4	Mild	75	M	2	Levodopa/carbidopa
5	Mild	70	F	1.5	Levodopa; Ropinirole
6	Mild	72	F	2	Levodopa/carbidopa
7	Mild	57	F	2	Levodopa/carbidopa; Ropinirole
8	Mild	61	F	2	Levodopa/carbidopa; Amantadine
9	Mild	50	F	1	Carbidopa; Pramipexole; Amantadine
10	Advanced	74	M	2.5	Levodopa/carbidopa
11	Mild	65	M	2	Levodopa/carbidopa
12	Advanced	75	F	4	Levodopa/carbidopa
13	Advanced	84	F	4	Levodopa/carbidopa
14	Advanced	67	M	3	Levodopa/carbidopa

Abbreviations: H & Y = Hoehn and Yahr score; M = male; F = female

Reaching Task

Subjects performed a seated reach-to-eat task in which they reached to a pedestal for a food item that was grasped and transported to the mouth for eating (Whishaw et al., 2002; Melvin et al., 2005; de Bruin et al., 2008). Once subjects were seated, they were asked to place their hands palm down on their thighs. The experimenter stood to the left of the subject and placed a food item (Cheerio™) on the pedestal for each trial. Subjects were instructed to reach for food with their dominant hand. The self-standing height adjustable pedestal was placed directly in front of the subject at a horizontal reach amplitude normalized to the subjects' arm length (100% of length from shoulder to tip of index finger with elbow at 180° flexion) and a vertical amplitude normalized to the subjects' trunk height (100% of height from floor to outstretched arm while seated and with shoulder at 90° flexion). Each testing trial was initiated with a verbal “ready” signal, immediately followed by a verbal “go” signal as a permissive cue to start the trial at their leisure, and concluded following successful placement of the food item in the mouth and return of the reaching hand to its start position on the lap.

Behavioural Measures

Reach Measure

The reach-to-eat movement was measured using biomechanical markers (de Bruin et al. 2008) and with a movement scoring scale (Whishaw et al., 2002; Melvin et al., 2005).

Biomechanical measures. Subjects were fitted unilaterally (right side) with reflective markers at (a) zygomatic bone, (b) acromion process, (c) lateral epicondyle of the humerus, and (d) ulnar styloid process (Figure 3.1). A reflective marker was also placed on the pedestal under the target platform. A digital video camera was positioned sagittal to the subject to record a reach-side view of the subject from lower leg to head at a sampling frequency of 30 Hz. Trial reaches were digitized using the Peak Motus v. 8.3.0 2-D digitizing system (Peak Performance Technologies, Inc., Centennial, CO) to digitize the reflective markers on the image with an output of 30 Hz. Marker data were filtered using a Butterworth low-pass filter with a cut-off frequency of 10Hz. Velocity data of the ulnar styloid process (reach wrist) were subsequently calculated by Peak Motus. The events of movement onset and offset were determined from the resultant (x, y, and z coordinates) reach wrist velocity using a custom-written algorithm (Microsoft Excel 2002), with minimal resultant velocity used to indicate the onset and offset events for the movement phases inherent to the reach-to-eat movement. Specifically, the reach-to-grasp phase (hereafter referred to as *advance*) was defined as the time between initial velocity onset (i.e. first movement of the hand) and the subsequent point of minimal velocity (i.e. as the hand contacts the food item). The grasp-to-eat phase (hereafter referred to as *withdrawal*) was defined as the time between the second velocity onset (i.e. first movement of hand away from pedestal) and the subsequent point of minimal velocity (i.e. as the food item contacts the mouth). *The total reach duration* was defined as the time between initial velocity onset (i.e. first movement of the hand) and the second subsequent point of minimal velocity (i.e. as the food item contacts the mouth).

Movement scoring. The first reach trial performed with vision for each subject was scored according to the reach-to-eat movement scale (Whishaw et al., 2002) to confirm that the sample population in the present study is representative of healthy and PD populations. The first reach trial performed with occlusion (see below) was also scored for each subject to compare the effect of occlusion on the reach-to-eat movement scale. “The scored reaches were the first test reach of the vision and occlusion conditions, respectively, as per methodology used in previous papers (Whishaw et al., 2002; Melvin et al., 2005). The scale is an extension of a traditional method of movement analysis (Eshkol & Wachman, 1958), consisting of 21 items combined into eight temporally sequenced elements. For each of the eight elements, a score of 0 was given if the movement was present and normal, 0.5 if the item was present but abnormal, and a score of 1 was given if the movement was absent (for a full description, see Whishaw et al., 2002; Melvin et al., 2005).

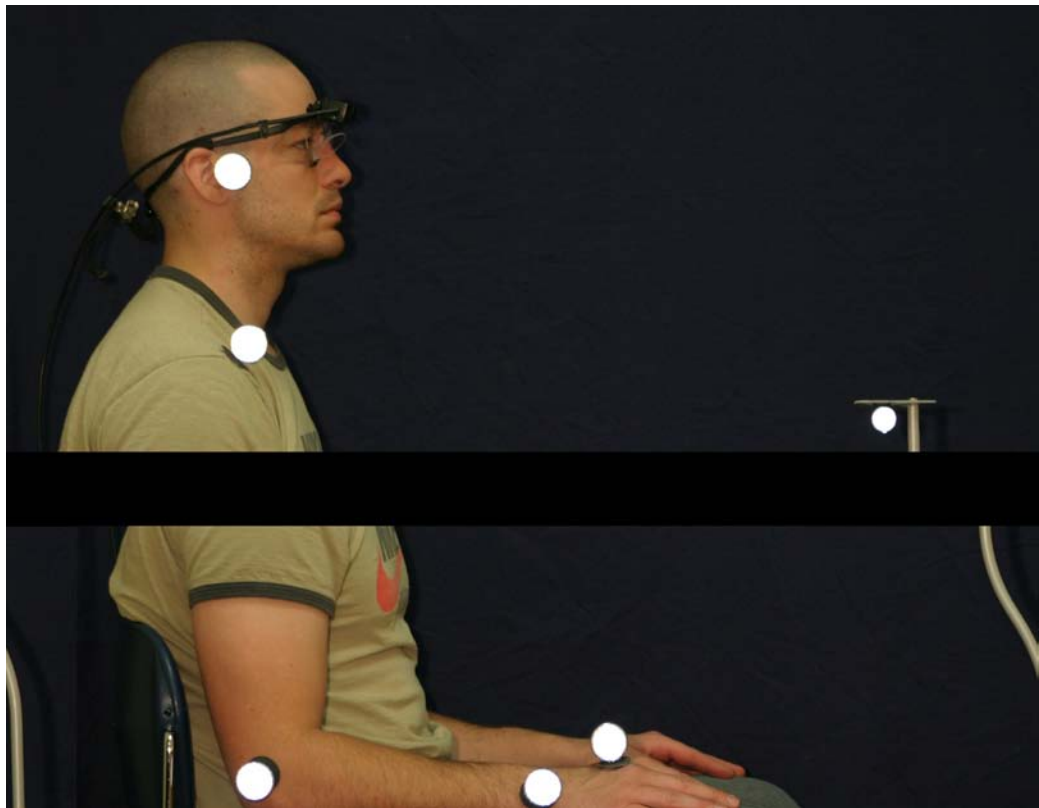


Figure 3.1. Experimental set-up. The white dots represent light reflective markers on the subject (left) and the food target (right).

Eye-Tracking

Subjects wore a head-mounted infrared eye tracking system (MobileEye v. 1.2, Applied Science Laboratories, Bedford, MA) to track eye movements with a sampling frequency of 30 Hz (de Bruin et al. 2008). The MobileEye system uses Dark Pupil Tracking to compute the x and y coordinates of the pupil within the scene. In this technique, a set of three harmless near infrared lights are projected onto the eye, and reflected by the cornea (corneal reflection). By comparing the relative vectors from the sensor to the pupil and the cornea, the eye tracking system computes the position of the eye (point of gaze) relative to the scene. The video record of the data collected by the eye tracking system were subjected to off-line analysis to determine the following events of visual guidance: engage to move, grasp to disengage, and total engagement period.

Engage to move was defined as the time between the first point that the eyes descend to fixate the target and first movement of the forelimb, and *grasp to disengage* was defined as the time between contact of the target with the digits and the first point that the eyes ascend from the target. The total visual engagement period was defined as the time between the first point that the eyes descend to fixate the target (*engage*) and the first point that the eyes ascend (*disengage*) from the target. A visual marker presented at the onset of the testing session was used to time-synchronize the video record of the biomechanical markers from the digital camera and the video record from the eye-tracking system offline using Final Cut Pro HD v.4.5 for Mac OS X v.10.2.8.

Visual Occlusion

Subjects were fitted with PLATO vision-occluding goggles (Translucent Technologies, Toronto, ON) which were manipulated to allow vision (i.e., transparent) or

occlude vision (i.e., opaque) (Doan et al., 2006; de Bruin et al., 2008). The goggles were modified to occlude both central and peripheral vision by attachment of a peripheral vision blocker (i.e. black felt around the perimeter and fastened to the face with porous tape). Prior to the initiation of each trial, the occlusion goggles were either opened by the experimenter for a vision trial or remained closed for an occluded trial.

Sex Differences

Sex differences were examined by comparing male versus female scores in eye-tracking and visual occlusion for the control group and PD group.

Procedure

For eye-tracking, subjects were given the opportunity to reach for a maximum of five practice trials, followed by ten test trials. For visual occlusion, subjects were given the opportunity to reach for a maximum of five practice trials with vision, and a maximum of five practice trials with occlusion, and ten test trials with vision and ten test trials with occlusion. The vision and occlusion trials were intermixed and presented randomly for each subject.

Statistical Analysis

Data were analyzed using repeated measures ANOVA (Statistical Package for the Social Sciences, SPSS v. 13). There were no statistical differences between the age-matched controls for the mild PD and advanced PD subjects, thus they were collapsed into a single group (OAC). For each subject, mean values were calculated for each dependent variable in each condition. Bonferroni correction for post-hoc tests was used for all pairwise comparisons. Paired samples *t*-tests were performed on each group (YAC,

OAC, mild PD, advanced PD) to compare the kinematics of reaches with vision to those with occlusion. We restricted comparisons between vision and occlusion to PD subjects who completed trials in both conditions (5 of 6 advanced PD).

Behavioural Results

Reach Measurement

The biomechanical marker measurements of reaching indicated that the reaching movement slowed with age and also as a function of PD, thus advanced PD subjects reached more slowly than the YAC, OAC, and mild PD subjects. The reach scoring indicated that both the mild PD group and the advanced PD group displayed movement element impairments relative to controls. All subjects performed reach trials successfully (i.e. grasped targets and placed them in the mouth for all trials). These results are described fully below:

Biomechanical measurement. I performed a 4 x 2 ANOVA on the movement time using GROUP (YAC, OAC, Mild PD, Advanced PD) and PHASE (advance, withdrawal) as independent variables. There was a significant effect of GROUP ($F(3,37) = 16.382, p < 0.001$) and PHASE ($F(1,37) = 40.449, p < 0.001$) but no GROUP X PHASE interaction ($F(3,37) = 0.371, p > 0.05$). As is illustrated in Figure 3.2, post hoc indicated advanced PD took significantly longer than YAC, OAC, and mild PD to complete advance ($ps < 0.001$) and withdrawal ($ps < 0.001$). I note that these post hoc analyses are of the interaction which did not reach significance; however, these analyses conform to the *a priori* planned comparisons.

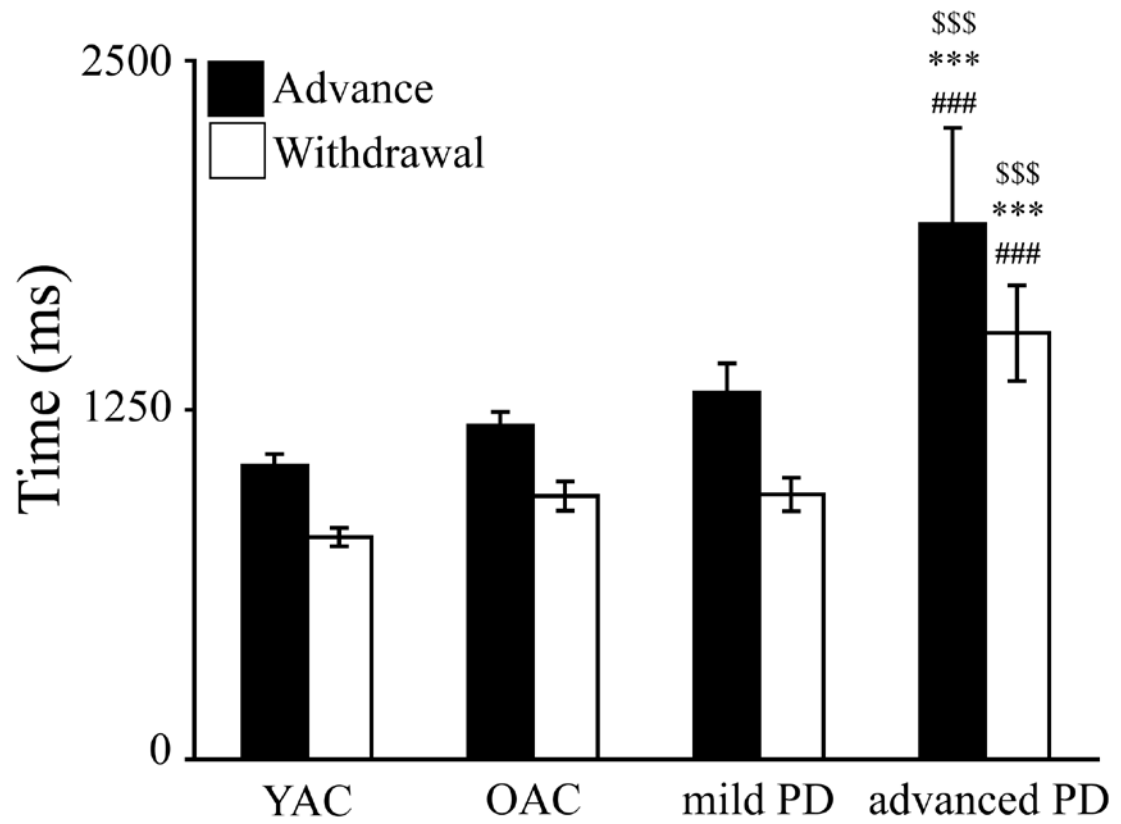


Figure 3.2. Mean and standard error for the duration of time to complete advance and withdrawal in milliseconds (ms) for the four experimental groups.

Significance: YAC at \$\$\$ = $p < 0.001$, OAC at *** = $p < 0.001$,

mild PD at ### = $p < 0.001$.

Movement scoring. I performed a 4 x 8x 2 ANOVA on the movement score using GROUP (YAC, OAC, Mild PD, Advanced PD), MOVEMENT ELEMENT (orient, lift, aim, pronate, grasp, supination I, supination II, return), and CONDITION (vision, occlusion) as independent variables. There was a significant effect for GROUP ($F(3,70) = 37.098, p < 0.001$), CONDITION ($F(1,70) = 55.490, p < 0.001$), CONDITION X MOVEMENT ELEMENT ($F(7,504) = 24.876, p < 0.001$), and GROUP X MOVEMENT ELEMENT ($F(21,504) = 1.996, p < 0.01$) effects. The GROUP X CONDITION interaction ($F(3,70) = 1.902, p > 0.05$) was not significant.

As shown in Figure 3, post hoc for the vision reaches indicated that advanced PD group had higher scores than did all of the other groups on most movement elements, except orient and supination I. The mild PD group had higher element scores than did the OAC and YAC on two measures, lift and supination II. For the occlusion condition, PD subjects performed worse than the controls, especially for movement involving aiming, pronating, and supinating the forelimb. I note that these post hoc analyses are of the interaction which did not reach significance; however, these analyses conform to the *a priori* planned comparisons.

Paired t-tests comparing movement elements with vision to those with occlusion resulted in a significant error with occlusion for orient and grasp for YAC ($t(11) = 9.75, p < 0.001$; $t(11) = 2.16, p < 0.05$, respectively), orient, aim, and grasp for OAC ($t(16) = 8.64, p < 0.001$; $t(16) = 5.42, p < 0.001$; $t(16) = 5.00, p < 0.001$, respectively), orient and lift for mild PD ($t(7) = 9.80, p < 0.001$; $t(7) = 2.65, p < 0.05$, respectively) and no difference for advanced PD.

Spearman's rho correlation of the total reach duration and total movement score for all subjects was significant ($\rho = 0.468, p < 0.01$). Correlations for all control subjects was not significant ($\rho = -0.003, p > 0.05$), whereas the correlation for the PD subjects ($\rho = 0.643, p < 0.01$) was significant. The regression line for PD subjects is shown in Figure 4.

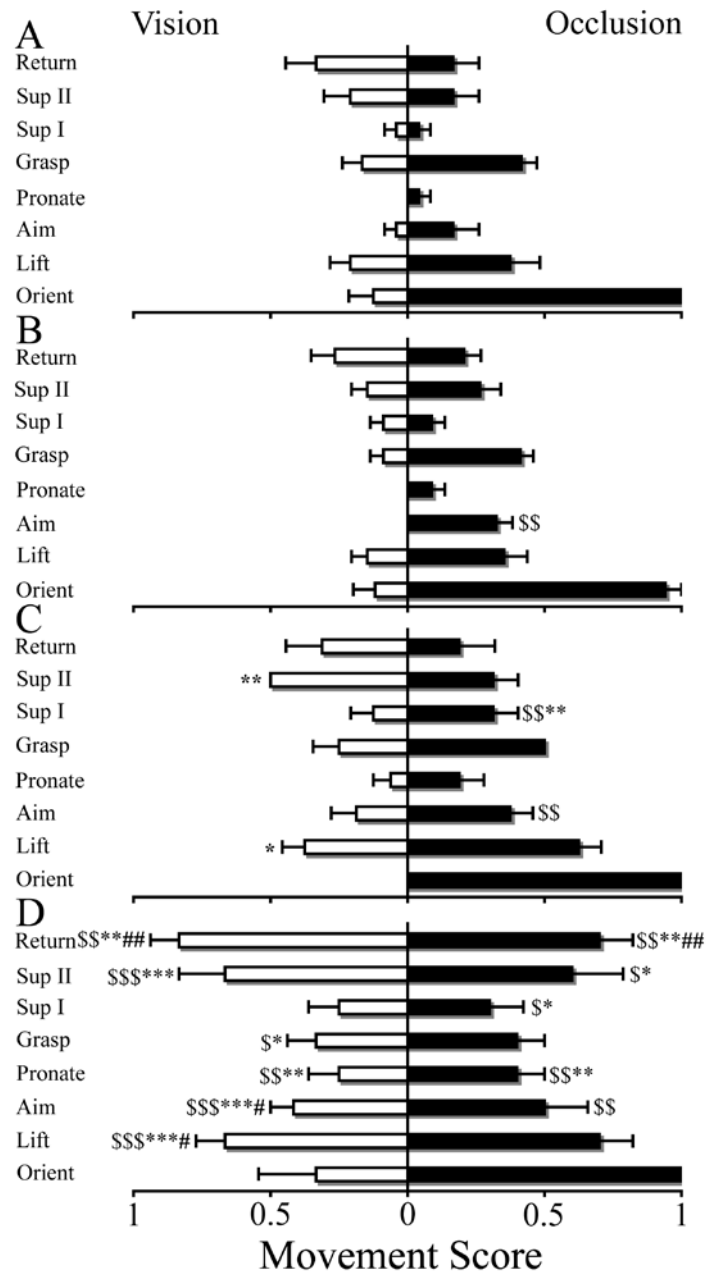


Figure 3.3. Mean and standard error of movement score for reaches completed with vision (white) and occlusion (black) for A) young adult controls, B) old adult controls, C) mild PD, D) advanced PD. Note the floor effect of advanced PD subjects. Significance: YAC at \$ = $p < 0.05$, \$\$ = $p < 0.01$, \$\$\$ = $p < 0.001$, OAC at * = $p < 0.05$, ** = $p < 0.01$, *** = $p < 0.001$, mild PD at # = $p < 0.05$, ## = $p < 0.01$.

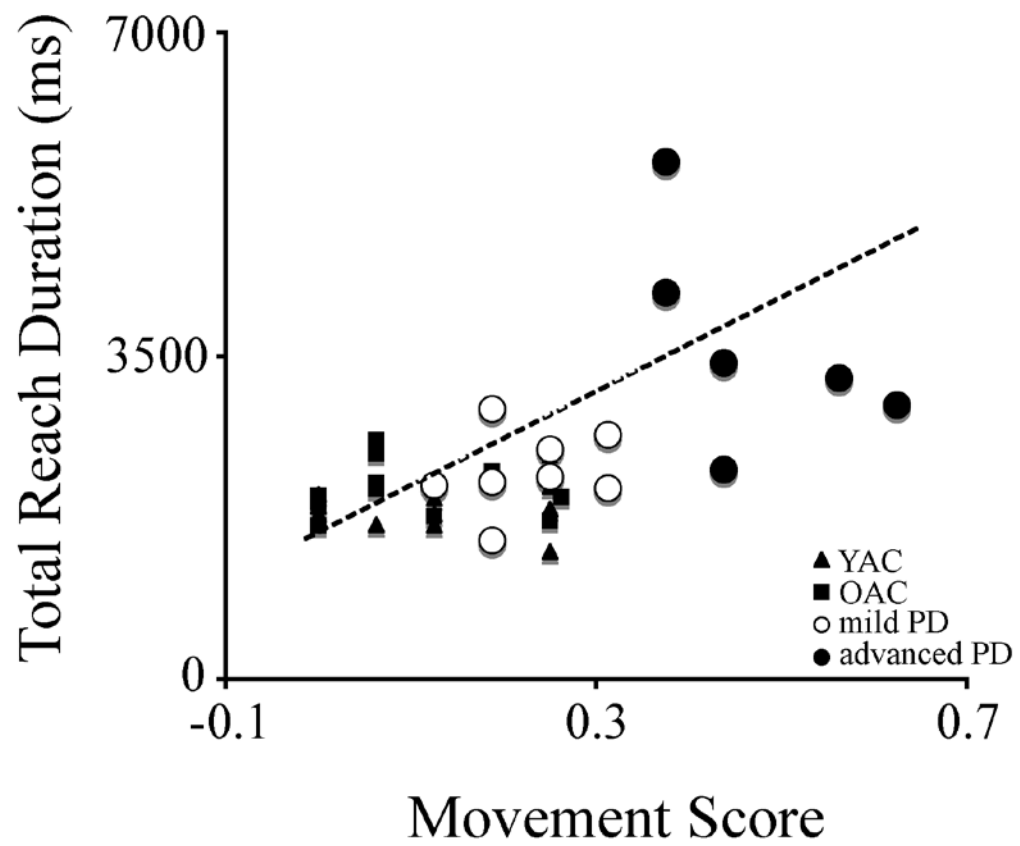


Figure 3.4. Correlation between movement score and total reach duration. The line represents the regression of the Parkinson's diseased groups.

Eye-Tracking

Measures of eye tracking showed that with the exception of the advanced PD group, the subjects visually engaged the food target just before initiating the reach movement and disengaged the target just as they grasped it with their digits. I performed a 4 x 2 ANOVA on the movement time using GROUP (YAC, OAC, Mild PD, Advanced PD) and EYE MEASURE (engage to move, grasp to disengage) as independent variables. There was a significant effect of GROUP ($F(3,37) = 4.616, p < 0.01$). The EYE MEASURE ($F(1,37) = 0.269, p > 0.05$) and the GROUP X EYE MEASURE ($F(3,37) = 0.365, p > 0.05$) effects were not significant. As presented in Figure 5, post hoc comparisons indicated advanced PD took longer than YAC, OAC, and mild PD to complete engage to move ($ps < 0.001$) and took longer than mild PD to complete grasp to disengage ($p < 0.05$). I note that these post hoc analyses are of the interaction which did not reach significance; however, these analyses conform to the *a priori* planned comparisons.

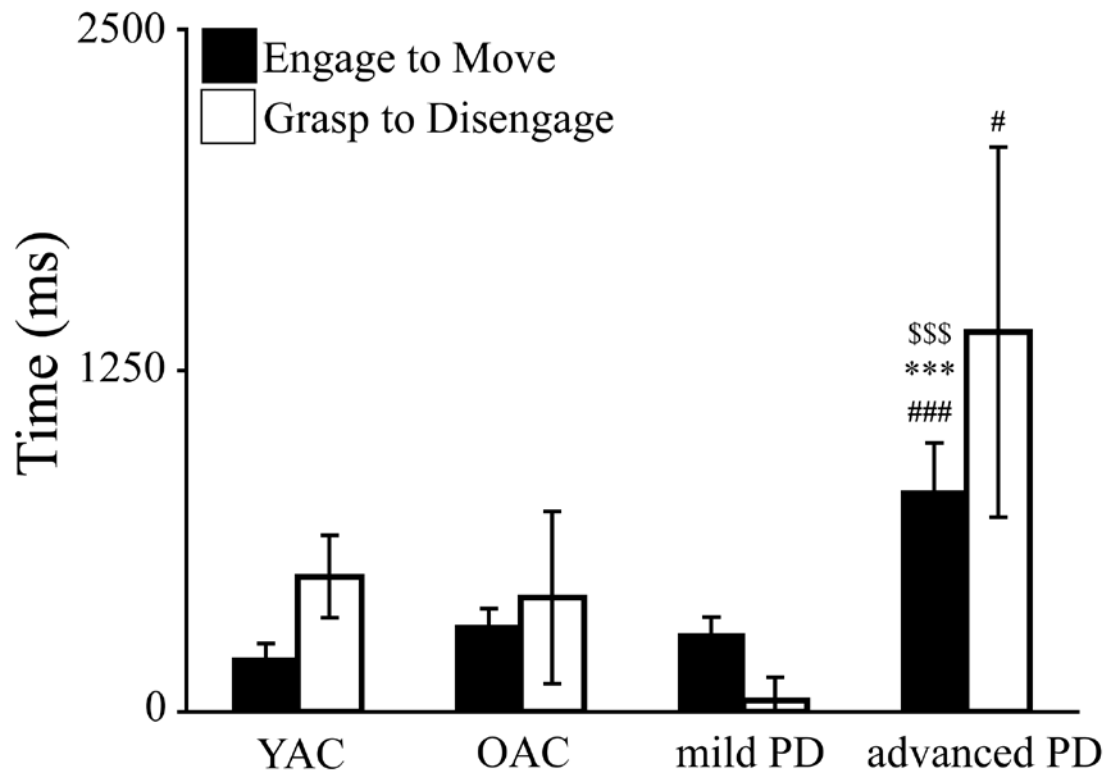


Figure 3.5. Mean and standard error for the duration of time to complete engage to move and grasp to disengage in milliseconds (ms) for the four experimental groups. Significance: YAC at \$\$\$ = $p < 0.001$, OAC at *** = $p < 0.001$, mild PD at # = $p < 0.05$, ### = $p < 0.001$.

Visual Occlusion

A 4 x 2 x 2 repeated measures ANOVA was performed on movement time using GROUP (YAC, OAC, Mild PD, Advanced PD) as the between subjects measure and PHASE (advance, withdrawal) and CONDITION (vision, occlusion) as the within subject measure. There was a significant effect of GROUP ($F(3,70) = 24.525, p < 0.001$), CONDITION ($F(1,70) = 28.552, p < 0.001$), and CONDITION X PHASE ($F(1,70) = 28.856, p < 0.001$) effect. The GROUP X PHASE ($F(3,70) = 2.134, p > 0.05$) interaction was not significant. As presented in Figure 6, post hoc indicated YAC, OAC, mild PD, and advanced PD took longer to complete the advance phase under visual occlusion ($p < 0.001, p < 0.001, p < 0.05, p < 0.05$, respectively), while the advanced PD group additionally took longer to complete the withdrawal phase under visual occlusion ($p < 0.01$).

Spearman's rho correlation of the total reach duration for vision vs. occlusion for all subjects was significant ($\rho = 0.863, p < 0.001$). Additionally, correlations for all control subjects was significant ($\rho = 0.775, p < 0.001$) as was the correlation for the PD subjects ($\rho = 0.797, p < 0.001$). The regression line for all control subjects is shown in Figure 7, suggesting that the reach impairment in the PD subjects was disproportionately increased in the occluded condition.

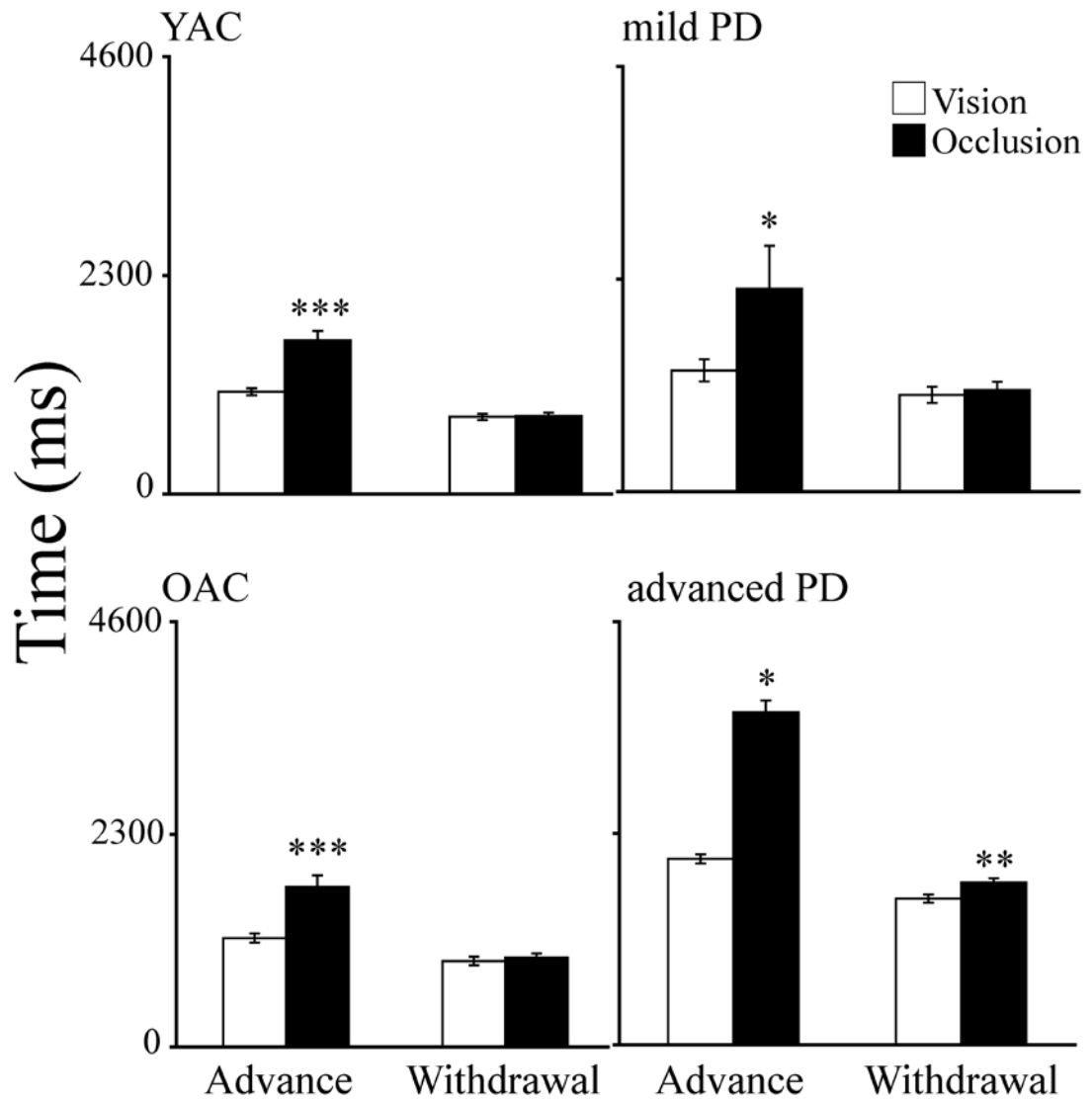


Figure 3.6. Paired comparisons of mean and standard error for the duration of time to complete advance and withdrawal in milliseconds (ms) for the four experimental groups. Significance: different from vision condition at $* = p < 0.05$, $** = p < 0.01$, $*** = p < 0.001$.

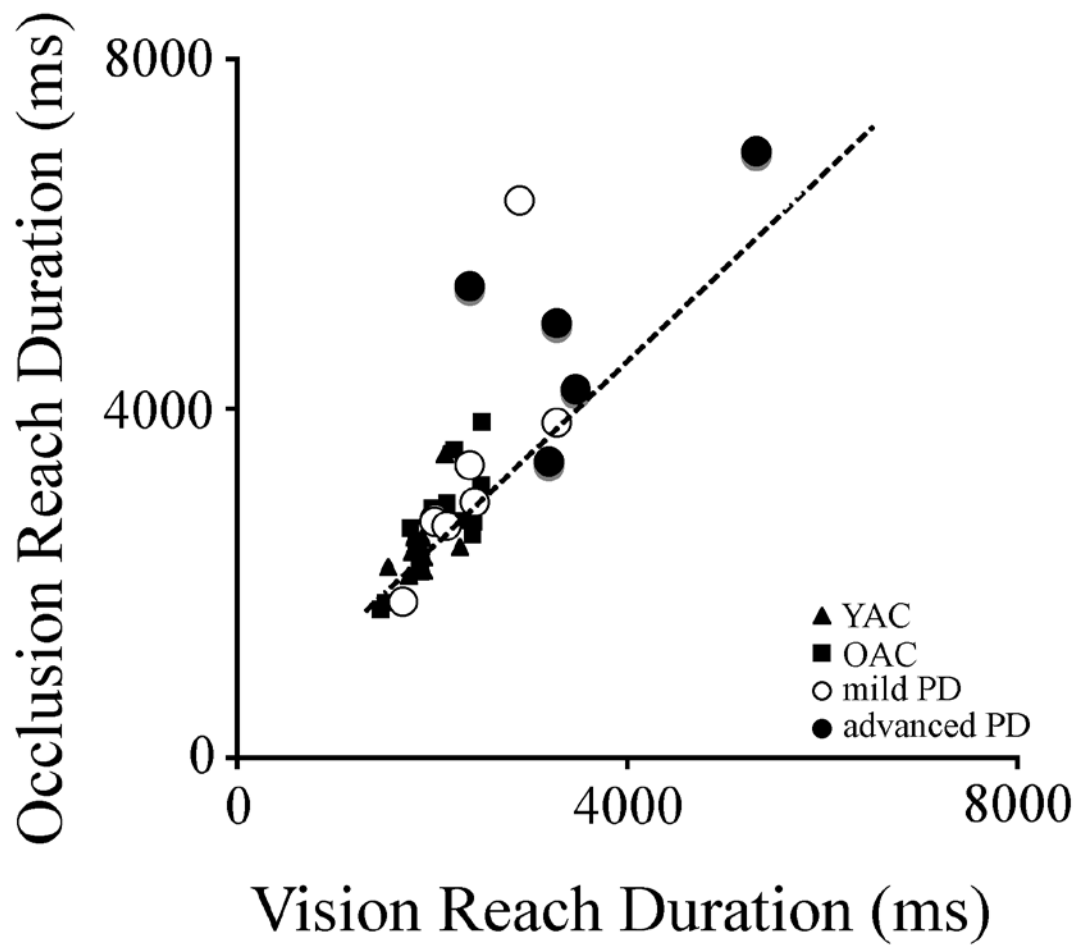


Figure 3.7. Correlation between total reach duration with vision and total reach duration with occlusion. The line represents the regression of the control groups.

Sex Differences

I performed a 4 x 2 x 2 x 2 ANOVA on the movement time using GROUP (YAC, OAC, Mild PD, Advanced PD), PHASE (advance, withdrawal), EYE MEASURE (engage to move, grasp to disengage) and SEX (male, female) as independent variables. There was not a significant effect of SEX for controls ($F(1, 24) = 1.181, p > 0.05$) or PD subjects ($F(1, 12) = 4.225, p > 0.05$). The 4 x 2 x 2 ANOVA on movement time GROUP (YAC, OAC, Mild PD, Advanced PD), PHASE (advance, withdrawal), and CONDITION (vision, occlusion) did not result in a significant SEX effect for controls ($F(1, 24) = 0.011, p > 0.05$), but did result in a SEX difference for PD subjects ($F(1, 10) = 22.479, p < 0.001$). Females with PD took less time than males with PD to complete the advance with vision (females vs. males $M \pm SD = 1143 \pm 145$ ms vs. 1955 ± 408 ms; $p < 0.001$), and the advance with occlusion (females vs. males $M \pm SD = 1663 \pm 377$ ms vs. 3672 ± 1219 ms; $p < 0.01$).

Discussion

This study provides the first description of the collaboration between visual and somatosensory attention in performing the reach-to-eat movement in PD. In order to characterize the temporal relationship between forelimb movement and eye movement when reaching for food, subjects were video recorded while performing a seated reach-to-eat task while wearing eye tracking glasses, visual occlusion glasses, and markers for kinematic measurement. Both mild and advanced PD groups displayed impairments in reaching movements, especially in arm rotation and these impairments were correlated with increased reaching time. Only the advanced PD group displayed a visual attentional impairment, however. They engaged the target for an extended period prior to first hand

movement and delayed disengagement from the target following the grasp. Under visual occlusion, all subjects displayed the expected slowing of the advance phase of the reach, but only the advanced PD group displayed a slower withdrawal phase. The results confirm that PD is associated with skilled movement impairments in its early stages which additionally become associated with impairments in sensory control the condition progresses.

The present study confirmed that PD subjects displayed impairments in hand and arm use when reaching for food in that they used less rotation of the hand for pronation and supination and their grasping tended to involve concurrent closing of all digits rather than more discrete use of the thumb and index finger (Whishaw et al., 2002; Melvin et al., 2005; Desmurget, Gaveau, Vindras, Turner, Broussolle, & Thobois, 2004; Doan, Melvin, Suchowersky, & Whishaw, 2008). In addition, movement speed in reaching was slowed (Berardelli, Rothwell, Thompson, & Hallett, 2001) and this slowing was proportional to the impairments displayed on the movement rating scale. The novel finding of the present study was that sensory attention also changes as PD symptoms worsen. Whereas in control subjects and in mild PD subjects, visual monitoring of the food was coupled to the advance phase of the reaching movement (de Bruin et al., 2008), the more severely affected PD subjects displayed exaggerated visual engagement with the target. They visually engaged the target for an extended period of time prior to initiating hand movement and they continued to visually fixate the target/hand as it was withdrawn to the mouth following the grasp.

An additional deficit in sensory attention was also observed in the advanced PD subjects. Unlike the control and mild PD groups, the withdrawal movement of the

advanced PD subjects was slowed in the absence of vision. When visual monitoring of the food item was prevented by activating the occlusion glasses, control subjects displayed slowed advancing of the limb and slowed grasping. In addition, the slowed advance was associated with less rotation of the hand and an open hand grasp, in which contact with the food target was made with the ventral surface of the hand rather than with the digits (de Bruin et al., 2008). The subjects in the mild PD group were similar to the control groups in that they also displayed a slowed advance and used an open hand strategy for contacting and grasping the food item. The subjects in the advanced PD group, however, not only displayed a slowing in limb advance that increased in proportion to the extent of the impairment they displayed in the sighted condition, their withdrawal time was significantly slowed.

The excessive visual attention and the exaggerated movement impairment in the absence of vision displayed by the advanced PD patients may be related. It has been proposed that normal reaching is associated with an attentional shift, with visual attention monitoring the advance phase of the reach and grasp and somatosensory attention guiding the withdrawal phase of the reach (de Bruin et al., 2008). The present results show that sensory guidance in reaching was not simply affected by aging or mild PD because the performance of the aged matched control subjects and the mild PD subjects was similar to that of the young control subjects. Because advanced PD subjects visually fixated the target for a longer period of time before reach initiation and continued to visually fixate the hand after grasping, and displayed slowed movements in both the advance and withdrawal phase of the reach under visual occlusion, suggests that they are excessively dependent upon visual guidance. In other words, it is possible that the advanced PD

subjects use vision not only for limb guidance but also as a crutch for somatosensory deficits in limb guidance.

This interpretation is consistent with findings of other lines of investigation showing that PD subjects frequently use vision to compensate for motor symptoms (Prochazka, 1996). Parkinsonian subjects make errors when performing pointing to remembered targets in the absence of vision, but when provided with an external sensory cue, such as a target to point at, they are able to overcome their proprioceptive deficit (Keijsers et al., 2005; Adamovich, Berkinblit, Hening, Sage, & Piozner, 2001). Similarly, continual fixation on the hand may serve as a dynamic visual cue. In an analogous example, PD subjects display a more normal gait when given visual cues (e.g. lines on the floor) to aid with their stepping response (Azulay, Mesure, Amblard, Blin, Sangla, & Pouget, 1999).

It is well known that PD symptoms worsen with disease progression (Samii, Nutt, & Ransom, 2004). The differential results of the mild and advanced PD groups in the present study are unlikely to be due to age, as aged-matched control subjects did not differ in movement performance from the young control subjects. Therefore the over reliance on vision reported here in the advanced PD group is likely related to disease progression. When pointing to a remembered target, advanced PD subjects perform worse than do mild PD subjects, and both groups perform worse than age-matched controls (Keijsers et al., 2005). Additionally, when reaches are performed with an illuminated target, only the advanced PD subjects improve their performance (Keijsers et al., 2005). Together these findings suggest that somatosensation impairments progresses

with disease progression, and that reliance on visual attention increases to accommodate this somatosensory impairment.

There are alternative interpretations of the present findings. PD subjects do have visual impairments, but such impairments have not been reported to cause attentional deficits (Hirayama & Ishioka, 2007). PD subjects also show a deficit in producing saccadic eye movements (Chan et al., 2005; Armstrong, Chan, Riopelle, & Munoz, 2002; Crawford, Medendorp, & Marotta, 2004) but an impairment in producing saccades would not easily explain why the subject would make an early saccade to the food item prior to initiating reaching. Although vertical saccade impairment has been shown in patients with Progressive Supranuclear Palsy (PSP) (Rafal, Posner, Friedman, Inhoff, & Bernstein, 1988), PD subjects in the present study used mostly horizontal saccades during the reaching task and were all diagnosed with idiopathic PD. Akinesia could also result in prolonged visual fixation with the target prior to moving (Lee, 1989), but does not explain continued fixation with the target following grasp. The PD impairment may also be related to a deficit in covert attention. Control subjects display covert attention to targets in a known location and can quickly orient when necessary (Slavutsкая & Shulgovskii, 2007). A deficit in covert attention may have caused the PD subjects to spend more time engaged with the target as a compensatory strategy. Parkinson disease subjects may also have impairment in disengaging visual attention from an object of interest (Posner & Raichle, 1994). Although a disengage deficit may explain the delay in averting gaze from the target once the food is grasped, it does not easily explain early visual fixation of the target. Finally, responses of PD subjects are reported to be slowed by distracting stimuli and are also more affected by distracting stimuli (Deijen,

Berendse, Wolters, Theeuwes, 2006), however, for the present study, distraction was minimized both by the simplicity of the task and by administering pre-training trials prior to the measured trials.

The subjects used in the present study were medicated. Performance on prehension tasks have been reported to be unaffected by medication condition (ON versus OFF) or with deep brain stimulator (Schettino, Adamovich, Hening, Tunik, Sage, & Poizner, 2006; Melvin et al 2005). Nevertheless, dopamine replacement medication has also been shown to lessen dependence on ongoing visual guidance (Baroni et al., 1984). In future studies, it would be thus worthwhile to examine visual guidance in unmedicated subjects. The numbers of subjects in the present study prevented a definitive assessment of sex differences and so future work could also evaluate comparative differences in male and female PD subjects (Haaxma et al. 2007). Finally, PD subjects do display cognitive deficits (Gotham, Brown, & Marsden, 1988) and it is possible that such deficits could contribute to reaching impairments. Despite these caveats, however, the present findings do shows that impairments in skilled reaching are associated with changes in sensory attention that made serve a compensatory role.

In conclusion, the results of the present study show that advanced PD subjects rely on ongoing visual feedback to assist the reach-to-eat movement; showing extended visual engagement prior to first hand movement and after grasping of the target with greater movement disruption occurring in the absence of vision. The over-reliance on visual attention by the advanced PD subjects suggests that they are using vision to compensate for proprioceptive/haptic impairments in directing their voluntary movements. The main findings of this study are thus consistent with studies suggesting

that increased reliance on visual feedback is a compensatory strategy for proprioceptive impairment (Flowers, 1976; Keijsers et al., 2005; Prochazka, 1996).

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Chapter 4: Experiment 3

Music Therapy Improves Movement Initiation in a Reach-to-Eat Task in Parkinson's Disease

Abstract

Parkinson's disease (PD) subjects display movement and sensory impairments on a skilled reaching-to-eat task. Advanced PD subjects (Hoehn & Yahr ≥ 2.5) take longer to complete the reaching movement (bradykinesia) and have increased scores on the movement component rating scale. They also showed exaggerated visual engagement with the target, in that they visually engaged the target for an extended period prior to movement initiation that persists following the grasp. Mild PD subjects (Hoehn & Yahr < 2.49) are similar to control subjects in that they do not display bradykinesia and visually engage the target just prior to movement initiation and disengage at the grasp. The present study examined the effect of music therapy on impairments seen in the reach-to-eat movement in PD. Eye movements and reach and kinematic measures of the reaching limb were collected from young and aged-matched control groups, and mild and advanced PD groups. Music therapy did not have an effect on time to complete the reaching movement or measures of the movement component rating scale for all subjects. Measures of visual engagement for the advanced PD group improved with music therapy, in that the length of time from engagement to movement initiation and disengagement following the grasp decreased. The results suggest that music therapy can normalize the balance between visual and proprioceptive guidance in the reach-to-eat task for PD subjects.

Introduction

Parkinson's disease (PD) is caused by the progressive neurodegeneration of dopamine producing neurons in the substantia nigra pars compacta (Dauer & Przedborski, 2003). The disorder is characterized by both movement and sensory impairments (Flowers, 1976; Sacle, Clark, & Whishaw, 2008). Changes in sensory systems have been shown to interact with changes in the motor system and may contribute to a portion of the motor impairment seen during a skilled reaching task (Sacle et al., 2008). It should therefore not be surprising that movement impairment has been shown to improve under sensory cueing (Chuma, 2007; Lehman, Toole, Lofald, & Hirsch, 2005; Thaut, McIntosh, Rice, Miller, Rathbun, & Brault, 1996; Caird, 1991). For example, when pointing to remembered targets, PD subjects make several errors, but when given an external visual cue to point at, they are able to overcome their deficit (Adamovich, Berkinblit, Henning, Sage, & Pionzer, 2001). Similarly, providing PD subjects with verbal instructions (i.e., take long steps) versus self-selected gait patterns (Lehman et al., 2005), or placing lines on the floor (Bagley, Kelly, Tunnicliffe, Turnbull, & Walker, 1991) can improve cadence, stride length, and velocity of gait.

Recent literature has begun to examine music as a sensory cue to overcome PD deficits (Pacchetti, Mancini, Aglieri, Fundaro, Martignoni, & Nappi, 2000; Thaut et al., 1996; Swallow, 1990; Sacks, 1982; Stern, Lander, & Lees, 1980). Rhythmic auditory stimulation (RAS)-embedded music has been shown to improve cadence, velocity and stride length of gait (Thaut et al., 1996), and active music therapy (i.e. instrument playing and singing) can improve Unified Parkinson's Disease Rating Scale (UPDRS) measures of bradykinesia, emotional state, and activities of daily living (ADL) (Pacchetti

et al., 2000). This finding that active music therapy improved measures of ADL, particularly utensil usage during eating, is one of the first reports suggesting that music could have an ameliorating effect on non-gait movement performance in PD. At present, the effect of music on a skilled forelimb task has not been examined in PD. One such task is reaching-to-eat, in which a subject reaches for a small food item, grasps it, and transports it to the mouth for eating (de Bruin, Sacrey, Brown, Doan, & Whishaw, 2008). On this task, PD subjects show increased movement time, impairments in aiming and rotating the forelimb, as well as prolonged visual fixation with the target prior to movement onset and following the grasp (Sacrey et al., 2008). Our finding that reaching-to-eat in PD subjects results in deficits to both movement and sensation raises the question of whether music can have an ameliorating effect on both the motor and sensory impairment. This question was examined in the present study. The expectation was that if deficits in movement and non-movement measures can be improved by music therapy, then the motor and sensory impairments seen in the reaching-to-eat task may also be improved by music therapy.

In the present study, young adult controls (YAC), age-matched controls (OAC), and adults with mild (mild PD) and advanced (advanced PD) PD were instructed to reach for and eat a small food item. Subjects were fitted with light reflective markers to measure arm and hand movement, wore an eye-tracking system to monitor eye movements, and on some trials, listened to preferred music while reaching. A rating of limb use during reaching and synchronized data from the biomechanical measures was compiled to determine the effects of preferred music on movements and visual guidance of the reach-to-eat task.

Subjects and Reaching Task

Subjects

On the basis of Hoehn and Yahr (HY) scores (Hoehn & Yahr, 1967), PD subjects were divided into two groups, mild PD (HY < 2.5; 6 females and 2 males; ages 63.88 ± 8.32 years; HY = 1.93 ± 0.56) and advanced PD (HY > 2.5; 3 females and 4 males; ages 75.00 ± 6.68 years; HY = 3.07 ± 0.67). Subjects were “ON” medications at the time of testing. For PD subject characteristics, see Table 4.1. Age-matched old adult control (OAC) subjects were recruited from the city of Lethbridge (8 females and 7 males; ages 62.80 ± 7.52 to 81.71 ± 5.02 years). Ten young adult control (YAC) subjects (3 females and 7 males; ages 21.30 ± 2.21 years) were recruited from the University of Lethbridge campus. All control subjects were self-reported to be of good health with no history of neurological disorder, and had normal or corrected to normal (contact lens) vision. The University of Lethbridge Human Subject Research Committee approved the study. Informed consent was obtained from subjects prior to initiation of the testing session. The study was conducted in accordance with the Declaration of Helsinki.

Table 4.1.

Parkinson's diseased subjects' characteristics

<u>Subject ID</u>	<u>Group</u>	<u>Age</u>	<u>Sex</u>	<u>H & Y</u>	<u>Medications</u>
1	Advanced	71	M	2.5	Levodopa/Carbidopa
2	Mild	61	F	2	Pramipexole
3	Mild	75	M	2	Levodopa/Carbidopa
4	Mild	70	F	1.5	Levodopa; Ropinirole
5	Mild	72	F	2	Levodopa/Carbidopa
6	Mild	57	F	2	Levodopa/Carbidopa; Ropinirole
7	Mild	61	F	2	Levodopa/Carbidopa; Amantidine
8	Mild	50	F	1	Carbidopa; Pramipexole; Amantidine
9	Advanced	74	M	2.5	Levodopa/carbidopa
10	Mild	65	M	2	Levodopa/carbidopa
11	Advanced	75	F	4	Levodopa/carbidopa
12	Advanced	84	F	4	Levodopa/carbidopa
13	Advanced	67	M	3	Levodopa/carbidopa
14	Advanced	70	M	2.5	Levodopa/carbidopa
15	Advanced	84	F	3	Levodopa/carbidopa

Abbreviations: H & Y = Hoehn and Yahr score; M = male; F = female

Reaching Task

Subjects performed a seated reach-to-eat task in which they reached to a pedestal for a food item that was grasped and transported to the mouth for eating (Whishaw, Suchowersky, Davis, Sarna, Metz, & Pellis, 2002; Melvin, Doan, Pellis, Brown, Whishaw, & Suchowersky, 2005; de Bruin et al., 2008). Once subjects were seated, they were asked to place their hands palm down on their thighs. The experimenter stood to the left of the subject and placed a food item (Cheerio™) on the pedestal for each trial. Subjects were instructed to reach for food with their dominant hand. The self-standing height adjustable pedestal was placed directly in front of the subject at a horizontal reach amplitude normalized to the subjects' arm length (100% of length from shoulder to tip of index finger with elbow at 180° flexion) and a vertical amplitude normalized to the subjects' trunk height (100% of height from floor to outstretched arm while seated and with shoulder at 90° flexion). Each testing trial was initiated with a verbal "ready" signal, immediately followed by a verbal "go" signal as a permissive cue to start the trial at their leisure, and concluded following successful placement of the food item in the mouth and return of the reaching hand to its start position on the lap.

Behavioural Measures

Reach Measure

The reach-to-eat movement was measured using biomechanical markers (de Bruin et al. 2008) and with a movement scoring scale (Whishaw et al., 2002; Melvin et al., 2005).

Biomechanical measures. Subjects were fitted unilaterally (right side) with reflective markers at (a) zygomatic bone, (b) acromion process, (c) lateral epicondyle of

the humerus, and (d) ulnar styloid process (Figure 4.1.). A reflective marker was also placed on the pedestal under the target platform. A digital video camera was positioned sagittal to the subject to record a reach-side view of the subject from lower leg to head at a sampling frequency of 30 Hz. Trial reaches were digitized using the Peak Motus v. 8.3.0 2-D digitizing system (Peak Performance Technologies, Inc., Centennial, CO) to digitize the reflective markers on the image with an output of 30 Hz. Marker data were filtered using a Butterworth low-pass filter with a cut-off frequency of 10Hz. Velocity data of the ulnar styloid process (reach wrist) were subsequently calculated (Peak Motus). The events of movement onset and offset were determined from the resultant reach wrist velocity using a custom-written algorithm (Microsoft Excel 2002), with minimal resultant velocity used to indicate the onset and offset events for the movement phases inherent to the reach-to-eat movement. Specifically, the reach-to-grasp phase (hereafter referred to as *advance*) was defined as the time between initial velocity onset (i.e. first movement of the hand) and the subsequent point of minimal velocity (i.e. as the hand contacts the food item). The grasp-to-eat phase (hereafter referred to as *withdrawal*) was defined as the time between the second velocity onset (i.e. first movement of hand away from pedestal) and the subsequent point of minimal velocity (i.e. as the food item contacts the mouth). *The total reach duration* was defined as the time between initial velocity onset (i.e. first movement of the hand) and the second subsequent point of minimal velocity (i.e. as the food item contacts the mouth).

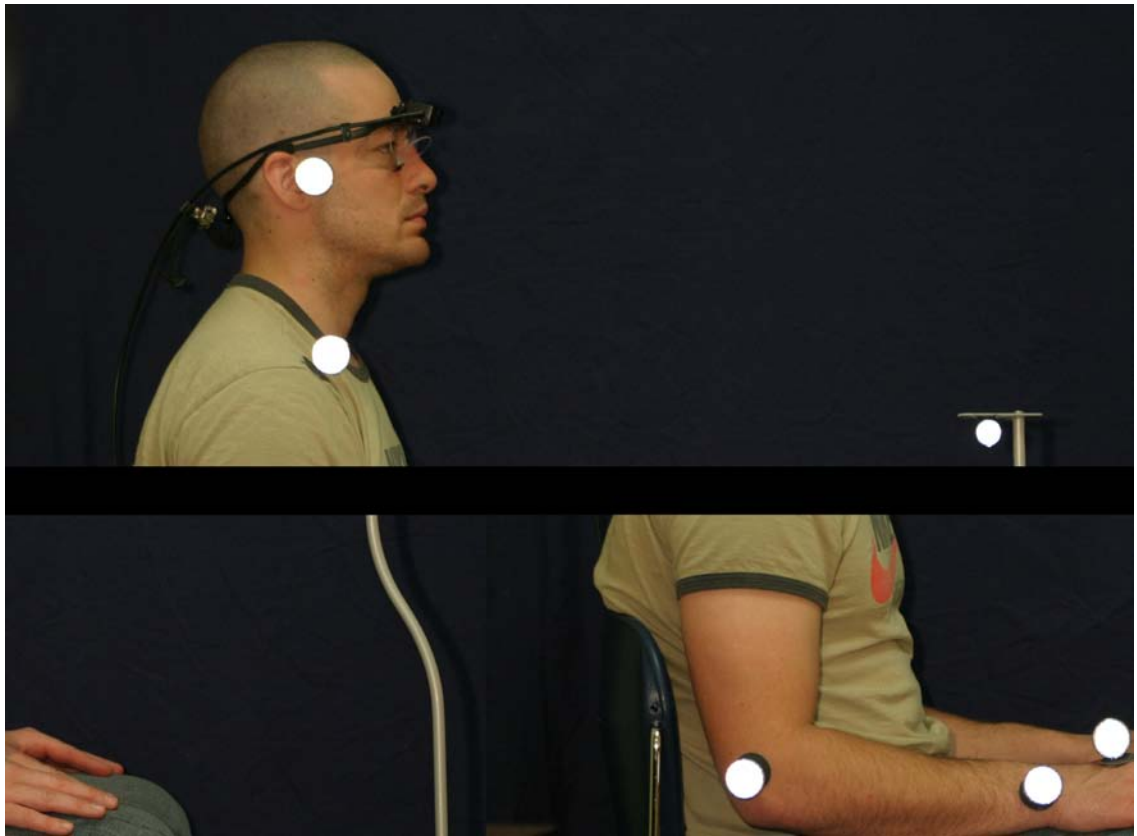


Figure 4.1. Experimental set-up for the reach-to-eat movement task.

Movement scoring. One reach trial performed without music for each subject was scored according to the reach-to-eat movement scale (Whishaw et al., 2002) to confirm that the sample population in the present study is representative of healthy and PD populations. One reach trial performed with music (see below) was also scored for each subject to compare the effect of music on the reach-to-eat movement scale. The scale is an extension of a traditional method of movement analysis (Eshkol & Wachman, 1958), consisting of 21 items combined into eight temporally sequenced elements. For each of the seven elements, a score of 0 was given if the movement was present and normal, 0.5 if the item was present but abnormal, and a score of 1 was given if the movement was absent (for a full description, see Whishaw et al., 2002; Melvin et al., 2005).

Eye Tracking

Subjects wore a head-mounted infrared eye tracking system (MobileEye v. 1.2, Applied Science Laboratories, Bedford, MA) to track eye movements with a sampling frequency of 30 Hz (Sacrey et al., 2008; de Bruin et al., 2008). The MobileEye system uses Dark Pupil Tracking to compute the x and y coordinates of the pupil within the scene. In this technique, a set of three harmless near infrared lights are projected onto the eye, and reflected by the cornea (corneal reflection). By comparing the relative vectors from the sensor to the pupil and the cornea, the eye tracking system computes the position of the eye (point of gaze) relative to the scene. The video record of the data collected by the eye tracking system were subjected to off-line analysis to determine the following events of visual guidance: engage to move, grasp to disengage, and total engagement period. *Engage to move* was defined as the time between the first point that

the eyes descend to fixate the target and first movement of the forelimb, and *grasp to disengage* was defined as the time between contact of the target with the digits and the first point that the eyes ascend from the target. The total visual engagement period was defined as the time between the first point that the eyes descend to fixate the target (*engage*) and the first point that the eyes ascend (*disengage*) from the target. A visual marker presented at the onset of the testing session was used to time-synchronize the video record of the biomechanical markers from the digital camera and the video record from the eye-tracking system offline using Final Cut Pro HD v.4.5 for Mac OS X v.10.2.8.

Music Therapy

Prior to initiation of the testing session, subjects were asked to select two songs from their favorite artist. The self-selected music was played on a personal listening device (iPod, Apple, Cupertino, CA) during reaching in the music condition. The music was not embedded with rhythmic auditory stimulation (RAS).

Procedure

Subjects were given the opportunity to reach for a maximum of five practice trials, followed by ten test trials for baseline performance (i.e., without music). Subject were given a five minute break immediately followed by ten test trials while listening to self-selected preferred music. This procedure was chosen to avoid any potential carry-over effects of music therapy.

Statistical Analysis

Data were analyzed using repeated measures ANOVA (Super ANOVA) to compare groups at baseline with music therapy. There were no statistical differences between the age-matched controls for the mild PD and advanced PD subjects, thus they were collapsed into a single group (OAC). For each subject, mean values were calculated for each dependent variable in each condition. Bonferroni post-hoc tests were used for all pairwise comparisons.

Behavioural Results

Reach Measurement

The biomechanical measurements of reaching indicated that music therapy had no effect on time to complete the reaching movement or scores on the movement component rating scale. These results are described fully below:

Biomechanical measurement. A 4 x 2 x 2 repeated measures ANOVA was performed on movement time using GROUP (YAC, OAC, Mild PD, Advanced PD) as the between subjects measure and PHASE (advance, withdrawal) and MUSIC (no music, music) as the within subject measure. Analyses revealed a significant effect of GROUP ($F(3,34) = 15.746, p < 0.0001$), and PHASE ($F(1,34) = 465.725, p < 0.0001$) effects, but no MUSIC ($F(1,34) = 0.350, p > 0.05$), GROUP X MUSIC ($F(3,34) = 0.189, p > 0.05$), or PHASE X MUSIC ($F(1,34) = 1.683, p > 0.05$) effects. As presented in Figure 4.2., post hoc comparisons indicated that at baseline, advanced PD took longer than YAC, OAC, and mild PD to complete advance ($ps < 0.001$), withdrawal ($ps < 0.001$), and total reach duration ($ps < 0.0001$). Music therapy had no effect on these measures as advanced PD continued to take longer than YAC, OAC, and mild PD to complete advance ($ps <$

0.001), withdrawal ($ps < 0.001$), and total reach duration ($ps < 0.001$). I note that these post hoc analyses are of the interaction which did not reach significance; however, these analyses conform to the *a priori* planned comparisons.

Spearman's *rho* correlation of the total reach duration with and without music for all subjects was significant ($\rho = 0.909, p < 0.0001$). Correlations for all control subjects ($\rho = 0.845, p < 0.0001$) and all PD subjects ($\rho = 0.945, p < 0.0001$) was significant.. The regression line for control subjects is shown in Figure 4.3.

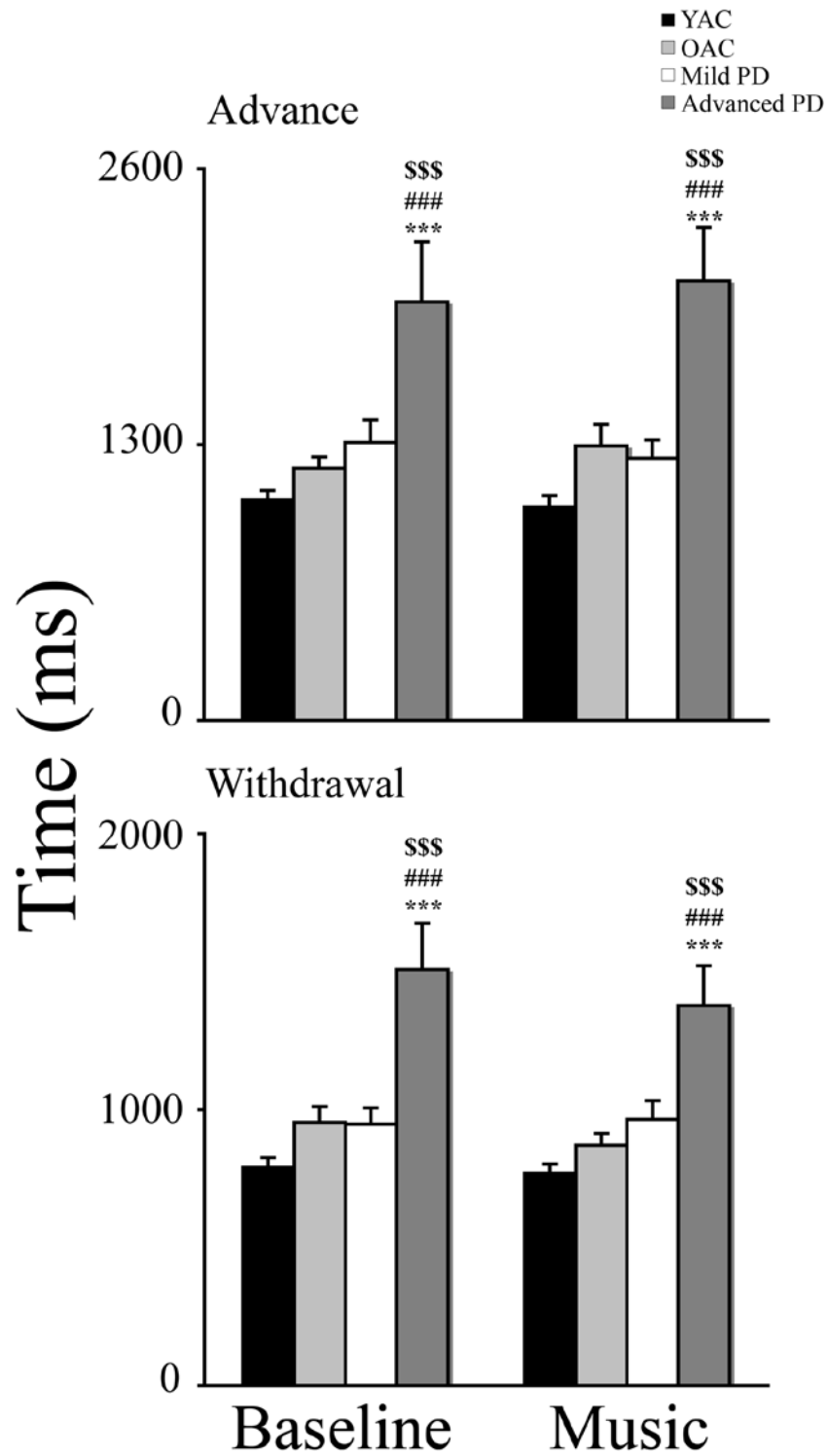


Figure 4.2. Mean and standard error for time to complete Advance and Withdrawal for each group. Significance: \$\$\$: YAC at $p < 0.0001$; ###: OAC at $p < 0.0001$; ***: Mild PD at $p < 0.0001$

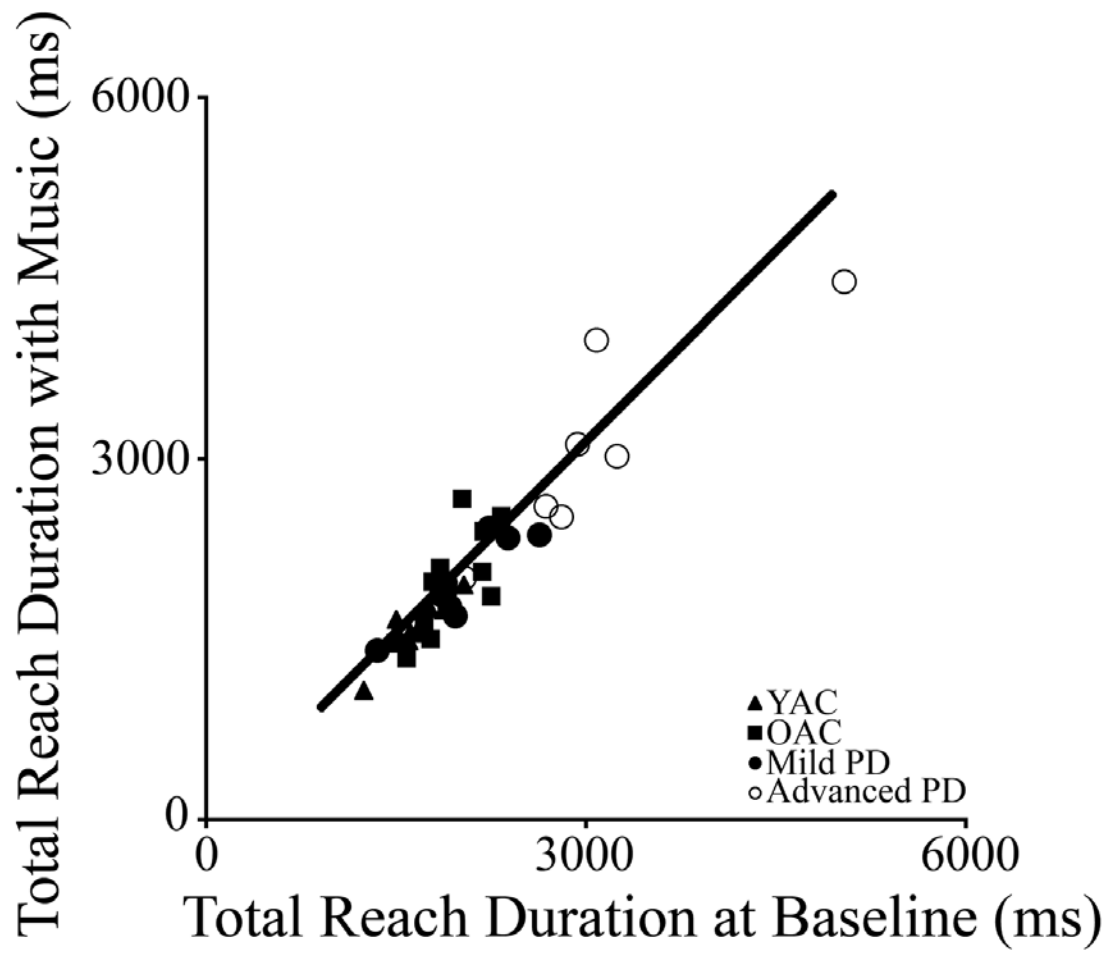


Figure 4.3. Correlation between total reach duration at baseline and with music therapy.

The line represents the regression of all subjects.

Movement scoring. I performed a 4 x 8 x 2 repeated ANOVA on the movement score using GROUP (YAC, OAC, Mild PD, Advanced PD) as the between subjects variable and COMPONENT (orient, lift, aim, pronate, grasp, supination I, supination II, return) and MUSIC (no music, music) as the within subjects variable. There was a significant effect of GROUP ($F(3,34) = 45.365, p < 0.0001$), COMPONENT ($F(7, 238) = 27.620, p < 0.0001$), GROUP X COMPONENT ($F(21, 238) = 3.718, p < 0.0001$), and GROUP X MUSIC ($F(3,34) = 2.945, p < 0.05$) effects, but no MUSIC ($F(1,34) = 0.707, p > 0.05$), or MUSIC X COMPONENT ($F(7,238) = 0.479, p > 0.05$) effects. As presented in Figure 4.4., post hoc for the no music reaches indicated that the PD subjects had higher scores than the controls for lift, aim, supination I, and supination II. Post hoc for the music therapy reaches indicated that the PD subjects had higher scores than the controls for aim, pronate, grasp, and supination II.

Spearman's *rho* correlation of the total movement score with and without music for all subjects was significant ($rho = 0.758, p < 0.0001$). Correlations for all control subjects was not significant ($rho = 0.360, p > 0.05$), whereas correlation for all PD subjects ($rho = 0.537, p < 0.05$) was significant. The regression line for control subjects is shown in Figure 4.5.

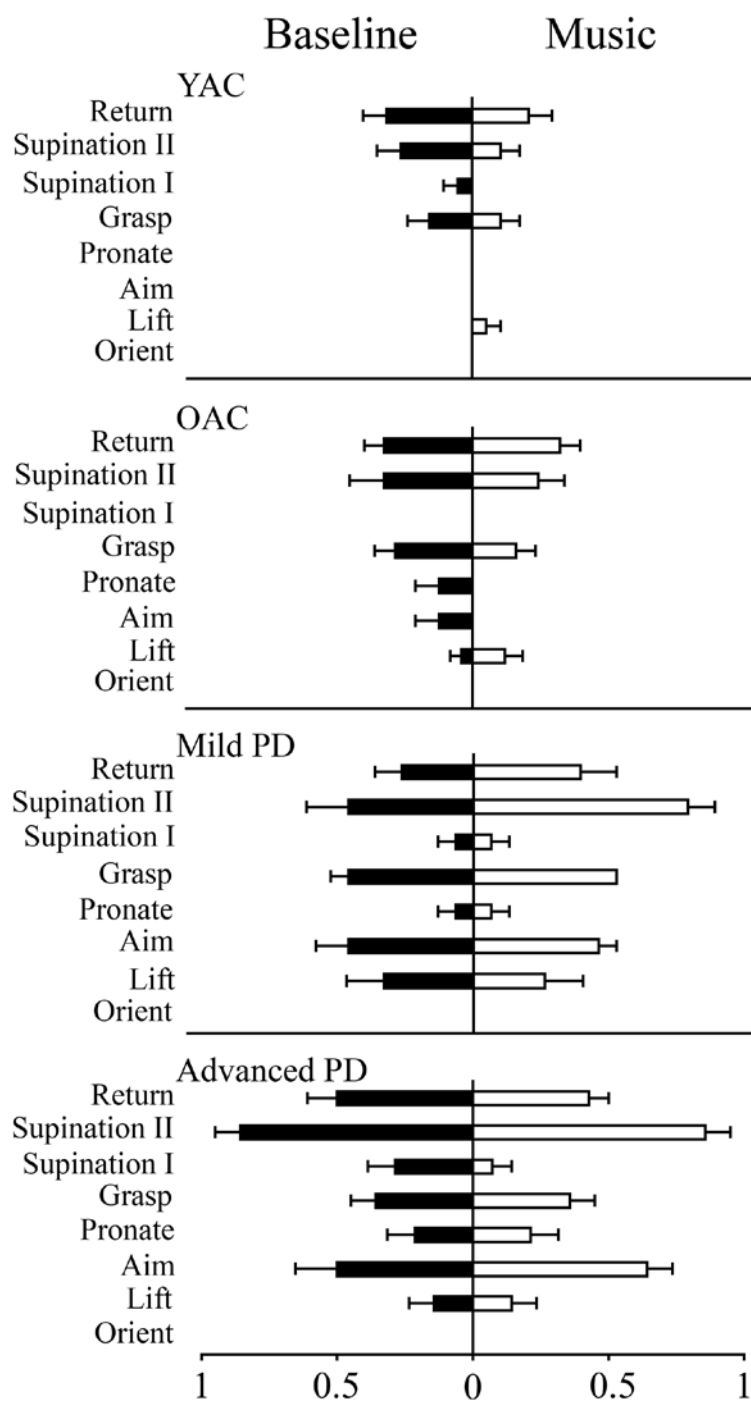


Figure 4.4. Mean and standard error of movement score for reaches completed at baseline and with music therapy.

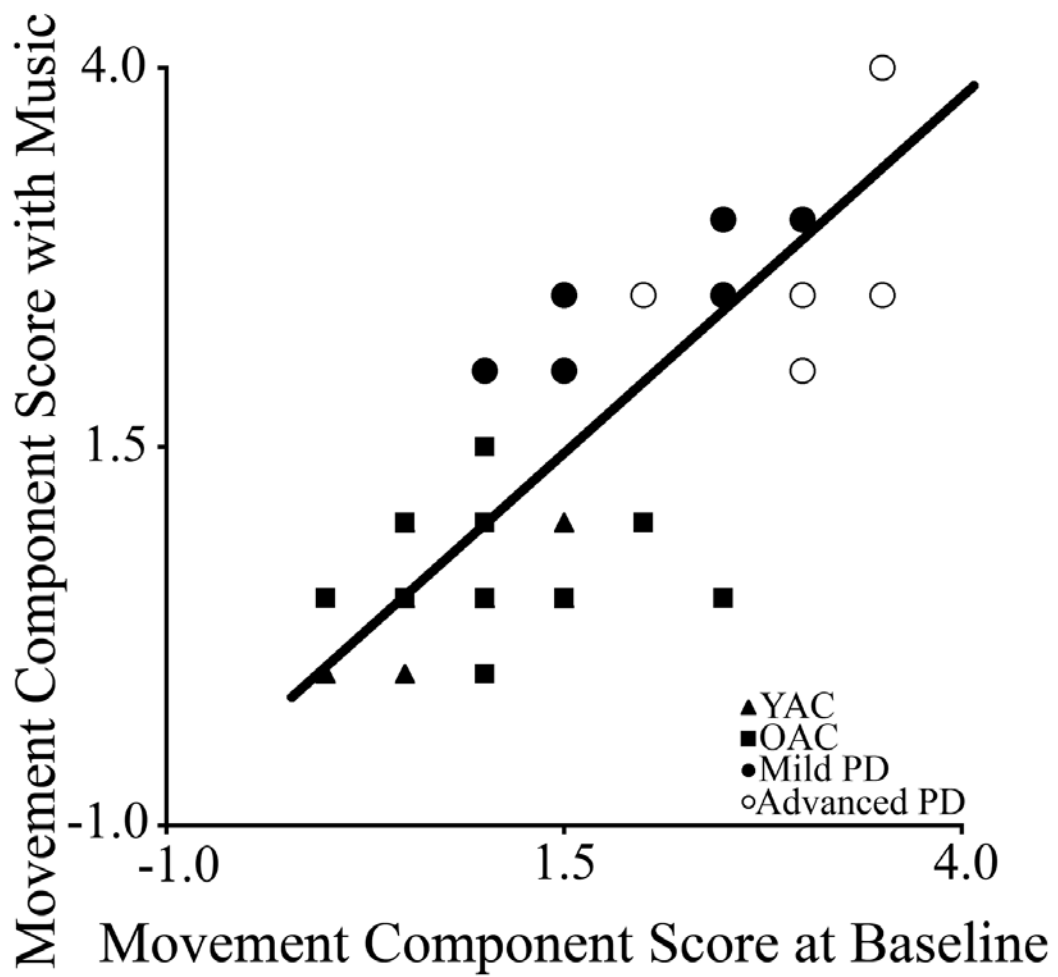


Figure 4.5. Correlation between movement component score at baseline and with music therapy. The line represents the regression of all subjects.

Eye-Tracking

Measures of eye tracking improved with music therapy. Advanced PD subjects spent less time fixated on the target prior to movement initiation. I performed a 4 x 2 x 2 repeated ANOVA on the movement time using GROUP (YAC, OAC, Mild PD, Advanced PD) as the between subjects factor and EYE MEASURE (engage to move, grasp to disengage) and MUSIC (no music, music) as the within subjects factor. There was a significant effect of GROUP ($F(3,34) = 13.259, p < 0.0001$), EYE MEASURE ($F(2,68) = 279.854, p < 0.0001$), MUSIC ($F(1,34) = 5.295, p < 0.05$), and GROUP X EYE MEASURE ($F(6,68) = 9.624, p < 0.0001$) effects, but no GROUP X MUSIC ($F(3,34) = 1.268, p > 0.05$) effect. As presented in Figure 4.6., post hoc comparisons at baseline indicated that advanced PD took longer than YAC, OAC, and mild PD to complete engage-to-move ($ps < 0.01$), and total engagement duration ($ps < 0.0001$). Advanced PD subjects took longer than OAC and mild PD to complete grasp-to-disengage ($ps < 0.05$). With music therapy, post hoc comparisons indicated that advanced PD subjects took longer than OAC to complete grasp-to-disengage ($p < 0.01$), and took longer than YAC, OAC, and mild PD to complete total engagement duration ($ps < 0.0001$). There were no significant differences between the groups for engage-to-move ($p > 0.05$). I note that these post hoc analyses are of the interaction which did not reach significance; however, these analyses conform to the *a priori* planned comparisons.

Spearman's *rho* correlation of total engagement duration with and without music for all subjects was significant ($rho = 0.792, p < 0.0001$). Correlations for all control subjects ($rho = 0.498, p < 0.05$) and all Parkinsonian subjects ($rho = 0.954, p < 0.0001$) was significant. The regression line for control subjects is shown in Figure 4.7.

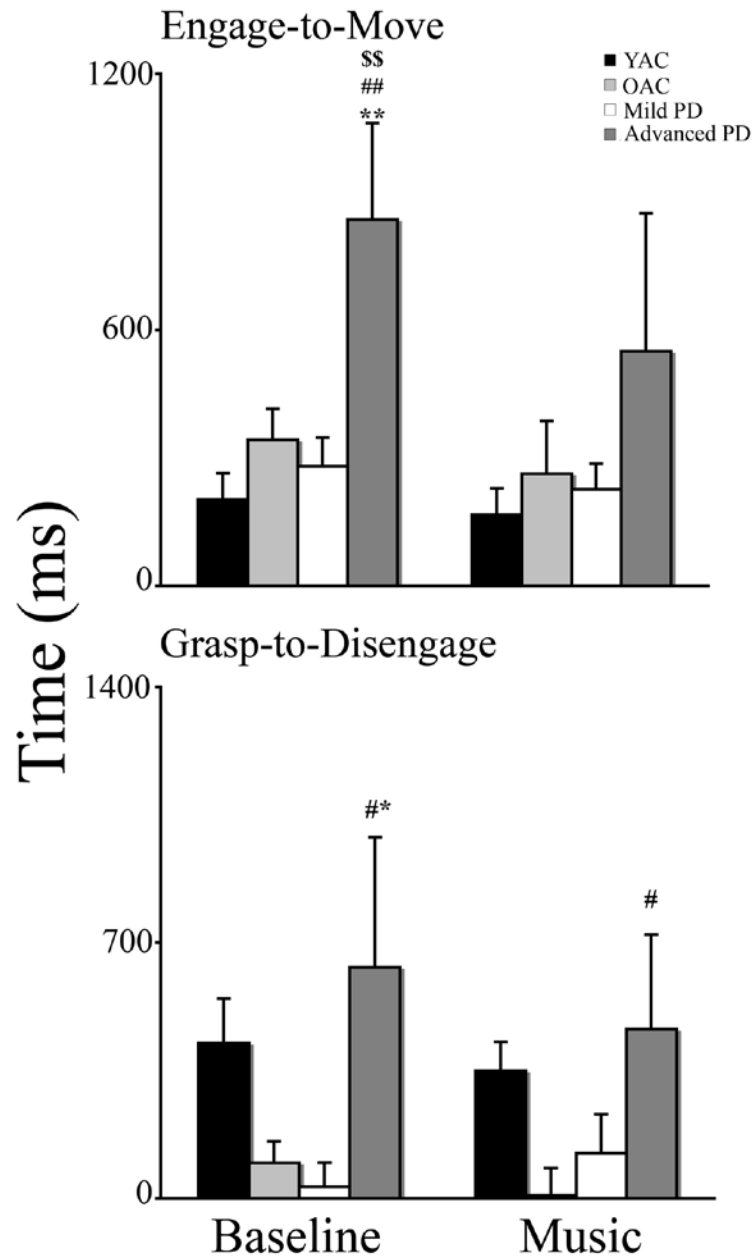


Figure 4.6. Mean and standard error of time to complete engage-to-move and grasp-to-disengage for the four groups at baseline and with music. Different from YAC at $$$ p < 0.01$; different from OAC at $##: p < 0.01$, $#: p < 0.05$; different from Mild PD at $**:$ $p < 0.01$, $*: p < 0.05$.

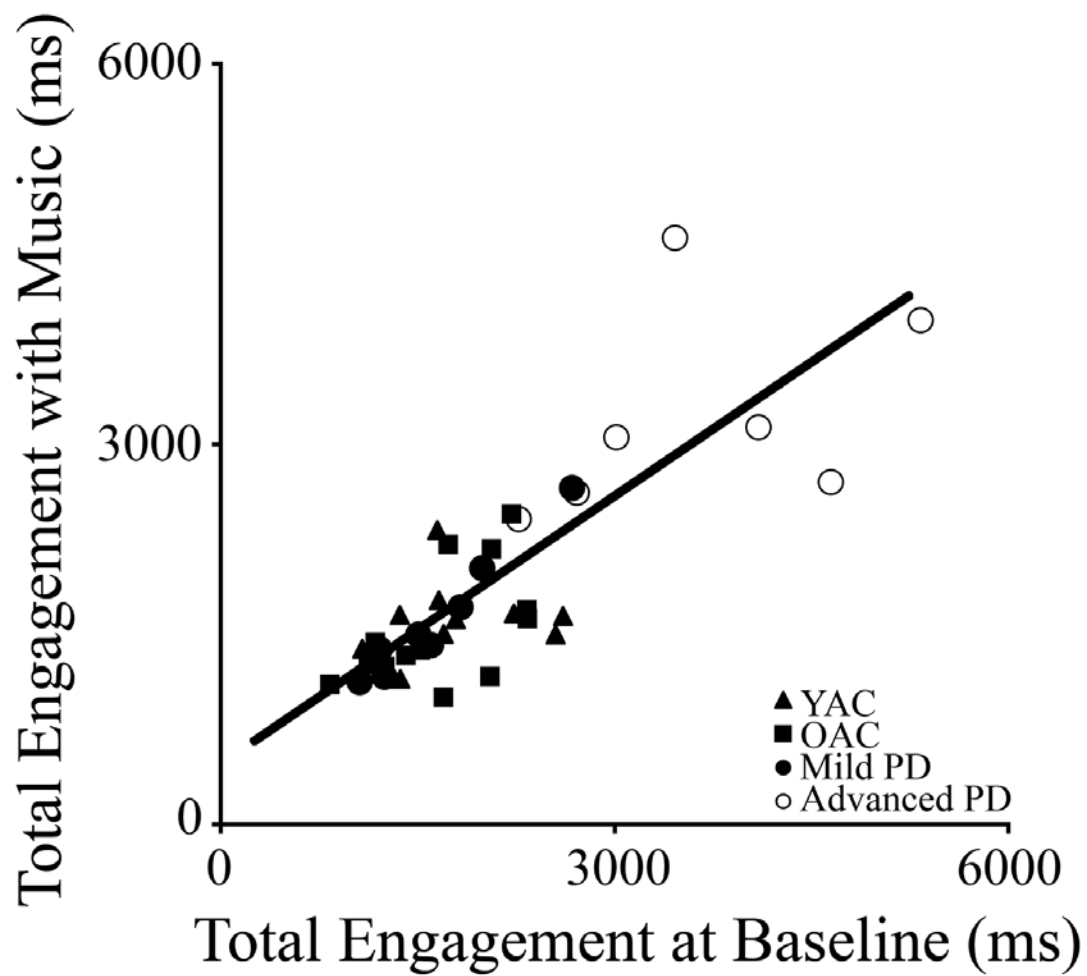


Figure 4.7. Correlation between total engagement duration at baseline and with music therapy. The line represents the regression of all subjects.

Discussion

This study provides the first description of the effect of non-RAS music therapy on the skilled reach-to-eat forelimb movement in PD. In order to characterize the effect of music on movement and sensory impairments seen in the reach-to-eat task, subjects were video-recorded while wearing eye-tracking glasses and biomechanical markers. Both mild and advanced PD groups displayed impairments in reaching components, especially in grasping of the target, aiming, and rotation of the forelimb, but these impairments were not affected by music therapy. Only the advanced PD group showed improvement in movement initiation following visual engagement with the target and following the grasp. The decrease in time for movement initiation to occur and for disengagement following grasp suggests that music therapy may act to normalize the balance between visual and proprioceptive guidance for advanced PD subjects.

The motor performance of mild and advance PD subjects and control subjects without music therapy is consistent with previous literature (Sacrey et al., 2008; Doan, Melvin, Suchowersky, & Whishaw, 2008; Whishaw et al., 2002; Melvin et al., 2005). PD subjects of the present study display impairment in forelimb use in that they use less rotation of the arm and undershoot the target when aiming, and this impairment is greater in the more advanced PD subjects. Advanced PD subjects also display increased movement time for both the advance and withdrawal phases of the reach-to-eat movement. The performance of young and age-matched controls was consistent with previous literature, in that they displayed little to no movement impairments on the movement component rating scale and were not different from one another on time to

complete the reaching movement (Sacrey et al., 2008; Berardelli, Rothwell, Thompson, & Hallett, 2001).

Visual guidance of the reach-to-eat movements for mild and advanced PD subjects, and young and age-matched controls without music was also consistent with previous results (Sacrey et al., 2008; de Bruin et al., 2008). Advanced PD subjects displayed exaggerated visual engagement with the target, in that the length of time from visual fixation with the target to movement onset, and the length of time from visual disengagement from the target following the grasp were prolonged. In contrast, mild PD subjects' visual engagement duration was similar to young and age-matched controls. They visually fixated the target just prior to movement initiation and visually disengaged from the target at the grasp.

Music therapy did not affect time to complete the movement or scores on the movement component rating scale of the control, mild, and advanced PD subjects. This finding is consistent with literature showing that non-RAS music alone does not improve movement execution (Howe, 2003; Thaut et al., 1996). For example, performance of gait was compared between PD subjects who received RAS-embedded music therapy, music therapy alone, or no music therapy. Significant improvements in cadence, stride length, and velocity of gait emerged only in the RAS treated group. The music only and no music groups did not show any improvement (Thaut et al., 1996). Similarly, parkinsonian performance on a skilled forelimb task of reaching for a pen and bringing it to paper also did not show improvements in movement execution with music therapy alone (Ma, Trombly, Wagenaar, & Tickle-Degnen, 2004).

Music therapy affected movement initiation following visual fixation with the target and disengagement following the grasp for PD subjects. With music therapy, advanced PD subjects were similar to the mild PD and control groups in that they spent less time visually fixated on the target prior to movement initiation. Advanced PD subjects continue to take longer than age-matched controls to visually disengage from the target following the grasp, but no longer differ from mild PD subjects. Music therapy did not affect measures of visual guidance for mild PD subjects or the young and age-matched control groups, suggesting that non-RAS music therapy is not an effective treatment for the sensory impairments seen in mild PD. Music therapy may act to normalize the balance between visual and proprioceptive guidance for advanced PD subjects, however..

The results of the present study suggest that music therapy does not have an effect on the motor impairments seen in skilled reaching in PD. Music therapy did not have an effect on time to complete the reaching movement or scores on the movement component rating scale for all subjects. Advanced PD subjects displayed a decrease in the length of time to initiate movement towards a visually fixated target and visual disengagement away from the target following the grasp was no longer different from mild PD subjects. The present results suggest that music therapy may act to normalize the balance between visual and proprioceptive guidance for the advanced PD subjects.

This interpretation is consistent with literature suggesting that external cueing has been shown to improve motor initiation in PD (Dibble, Nicholson, Shultz, MacWilliams, Marcus, & Moncur, 2004; Praamtra, Stegeman, Cools, & Horstink, 1998). For example, PD subjects show an increased force and velocity of initial steps when presented with a

cutaneous “go” signal during a step initiation gait task (Burleigh-Jacobs, Horak, Nutt, & Obeso, 1997). Visual cueing has also been shown to improve motor initiation of parkinsonian subjects on a choice reaction time task in which subjects have to save a cartoon character from getting run over. Parkinsonian subjects’ performance improved on externally cued trials in which they pushed a button that caused the traffic light to change from red to green. Conversely, control subjects performed better on trials in which the light changed on its’ own (Siegert, Harper, Cameron, & Abernethy, 2002). Although not examining parkinsonian subjects, Thaut and colleagues (2002) found similar results when looking at the effect of music therapy on the arm movements of hemi-paretic stroke patients. Patients were asked to reach out, touch a sensor, and return their arm to the start position. Like the results from the present thesis, music did not have an effect on the time to complete the reaching movement. Music did, however, improve the initiation of reaching movements (Thaut, Kenyon, Hurt, McIntosh, & Hoemberg, 2002). Furthermore, if external cueing is reduced following trials with external cueing, PD performance becomes impaired compared to controls on a button-to-button push task (Georgiou, Bradshaw, Iansek, Phillips, Mattingley, & Bradshaw, 1993). These results suggest that the performance of parkinsonian subjects is reliant on external cueing.

There are alternative interpretations of the present findings. The improvement in movement initiation following visual engagement may be related to attention shifts (Slavutskaya & Shulgovskii, 2007). Music may help facilitate shifts, allowing PD subjects to spend less time engaged with the target prior to movement initiation. Similarly, music may aid the disengagement of visual attention from an object of interest, accounting for the decreased length of time from grasp to visual disengagement (Posner

& Raichle, 1994). Music can also act as a distracting stimuli (Deijen, Stoffers, Berendse, Wolters, Theeuwes, 2006). This is a possible explanation for the increasing scores seen in the movement components rating scale. It may be beneficial to examine the effects of RAS-embedded music therapy on skilled reaching impairments seen in PD. Previous studies have shown that RAS-embedded music therapy but not music therapy alone improves motor performance on a gait task (Howe, 2003; Thaut et al., 1996). This begs the question of whether RAS-embedded music therapy could have an ameliorating effect on the motor impairments of skilled reaching displayed by advanced PD subjects.

In conclusion, the results of the present study show that music therapy may act to normalize the balance between visual and proprioceptive guidance in the reach-to-eat task for Parkinsonian subjects. Advanced PD subjects displayed decreased movement initiation times following visual engagement with the target and disengagement following the grasp. Other measures of the reach-to-eat movement were unaffected by music therapy, however. The main finding in the present study is thus consistent with studies suggesting that music can act as an external cue to initiate movements (Praagstra et al., 1998).

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Chapter 5: General Discussion

Chapter 5: General Discussion

The primary goal of the present work was to determine if Parkinsonian subjects displayed alterations in the balance of visual and proprioceptive guidance of the skilled forelimb movement, reaching-to-eat. A secondary goal was to determine whether the balance of visual and proprioceptive control in Parkinsonian subjects is normalized by music therapy. The present thesis used the ethologically valid movement, reaching-to-eat. This movement is amongst the first coordinated limb movements displayed by infants (Foroud, 2008; Twitchell, 1965), and has been examined in a wide range of vertebrate species (Iwainuk & Whishaw, 2000). The following discussion will detail the literature on reaching in control and parkinsonian populations, the key research questions that have not been answered, and how the present thesis aimed to ameliorate the missing gaps.

Novel Findings

Reach-to-Eat Sequentially Guided by Vision and Proprioception

Reaching in humans was first described by Jeannerod (1981) and Arbib (1981), who characterized the reach-to-grasp movement. The movement is comprised of at least two independent components: transport of the limb towards a target and orientation of the digits to grasp (Arbib, 1981; 1990; Jeannerod, 1981; 1984; 1988). The movement is believed to involve different muscle groups, with transportation of the limb involving proximal muscles and joints and digit orientation involving distal muscles and joints (Arbib, 1990; Jeannerod, 1984). Reaching towards a target to grasp is dependent on visual feedback, as egocentric properties provide the spatial location and distance of target with respect to the reaching limb, and intrinsic properties provide the size and

shape of the target for grasp (Jackson, Jackson, Kririkos, 1999; Jeannerod, 1984). Reaching to grasp a target involves several sensory systems in addition to vision. Proprioceptive information and vestibular feedback contribute to the control of reaching. They provide information about the position of the moving forelimb and location of the trunk with reference to the target (Whitney & Goodale, 2005). Tactile contact with the target often attenuates the role of visual feedback, and when paired with proprioception, allows haptic exploration and manipulation of the target (Mackenzie & Iberall, 1994).

Much of the knowledge gained about the sensory control of reaching comes from tasks involving the reach-to-grasp movement (Binsted, Chua, Helsen, & Elliott, 2001; Abrams, Meyer, & Kornblum, 1990; Biguer, Jeannerod, & Prablanc, 1982). Targets are rarely grasped without being manipulated, however. A literature search revealed few reports of tasks involving manipulation following grasp. Those that did were likely to come from the Whishaw laboratory and report results from the skilled reaching movement, reach-to-eat, in rodent lesion studies (Whishaw, Alaverdashvili, & Kolb, 2008; Whishaw, Pellis, & Gorny, 1992) or human lesion studies (Foroud & Whishaw, 2006; Melvin, Doan, Pellis, Brown, Whishaw, & Suchowersky, 2005). Unfortunately, there was not a report characterizing the movements of reach-to-eat and/or the sensory control of reach-to-eat in healthy young adults. The first goal of the present thesis therefore, was to characterize the role of vision and proprioception in a reach-to-eat task in healthy young adults.

The reach-to-eat movement is a natural extension of the reach-to-grasp movement described by Jeannerod (1981) and Arbib (1981). The reach-to-eat movement of the present thesis was described using biomechanical markers fitted to the reaching forelimb

and eye-tracking glasses to monitor eye movements during the reach. On some trials, visual occlusion goggles were used to block both central and peripheral vision. Analysis of data from the biomechanical markers showed that the movement is comprised of two phases: the advance phase consists of the reach-to-grasp movement as described by Jeannerod (1981) and Arbib (1981), in which the forelimb is transported towards a target for grasp; and the withdrawal phase consists of the grasp-to-eat movement, in which the grasped target is transported and placed into the mouth for eating. The eye-tracking glasses revealed that the advance phase of the reach relied on visual guidance, in that subjects engaged the target just prior to movement initiation and disengaged from the target at grasp. Subjects remained disengaged from the target for the withdrawal phase of the reach, indicating that a different sensory modality, likely somatosensation (i.e., proprioception and tactile), guides placement of the target into the mouth. Visual occlusion goggles corroborated these findings, as only the advance phase of the reach was affected (i.e., increased in duration), when vision was occluded. The first novel contribution of the present thesis therefore is the characterization of the sensory control of the reach-to-eat movement in healthy young adults. The movement consists of two phases, the advance phase governed by visual guidance, and the withdrawal phase governed by somatosensory guidance. Characterization of the sensory control of the reach-to-eat movement in healthy young adults lead us to our next experimental question: “Is the sensory control of the reaching movement conserved/affected with Parkinson’s disease?”

Parkinson's Disease Alters the Balance of Visual and Proprioceptive Guidance

Reaching literature on parkinsonian subjects also began with the reach-to-grasp movement described by Jeannerod (1981) and Arbib (1981). On this task, parkinsonian subjects display two non-specific motor impairments. First, the movements produced are less smooth, with jerk scores doubling controls. Second, PD subjects take approximately 30% longer to complete the movement and have peak velocities 25-30% lower than age-matched controls (Tresilian, Stelmach, & Adler, 1997; Bonfiglioli, De Berti, Nichello, Nicoletti, & Castiello, 1998; Poizner, Feldman, Levin, Berkinblit, Hening, Patel, & Adamovich, 2000). Parkinsonian subjects also display two specific movement impairments on this task. They are unable to assemble complex motor actions, such as combining the transport and grasp component of the reach (Castiello, Bennett, & Mucignat, 1993). They also have difficulty producing accurate movements in the absence of visual feedback (Poizner, Feldman, Levin, Berkinblit, Hening, Patel, & Adamovich, 2000).

Expanding findings from the reach-to-grasp literature, Whishaw and colleagues included a manipulation component i.e., transport of grasped target to the mouth for eating. His work has investigated both eating and drinking in parkinsonian subjects. For the eating task, parkinsonian subjects reach towards a pedestal for a small food target, grasp the target, and transport it to the mouth for eating. Whishaw, Suchowersky, Davis, Sarna, Metz, & Pellis (2002) found that although parkinsonian subjects could complete the movement successfully (i.e., grasp and place food in the mouth), there were impairments in production of the movement. Parkinsonian subjects displayed a reduction in rotary movements of the forearm, in that there was a reduction in pronation and

supination. They also relied more on proximal body parts to complete the movement. The impairment in producing specific movement components was surprising given that previous studies showed that the reaching movement was unchanged by Parkinson's disease (Gentilucci & Negrotti, 1999; Alberts, Tresilian, & Stelmach, 1998; Tresilian, Stelmach, & Adler, 1997; Muller & Stelmach, 1992). The drinking task used by Whishaw and colleagues is similar to the eating task in that subjects reach towards a glass of water which they then bring to the mouth for drinking (Doan, Whishaw, Pellis, Suchowersky, & Brown, 2006). For this task, parkinsonian subjects displayed slower movement times, consistent with previous literature (Tresilian et al., 1997; Bonfiglioli et al., 1998; Poizner et al., 2000) and showed reduced velocity and acceleration for higher task constraint (i.e., higher fill level of glass) (Doan et al., 2006). Although movement impairments of the reach-to-eat movement have been characterized for parkinsonian subjects, the sensory control of the movement has not been examined. The second goal of the present thesis therefore, was to determine if the balance of visual and proprioceptive guidance was altered for the reach-to-eat task.

It is only recently that neurological examination of parkinsonian patients' includes a description of impairment in the sensory system (Snider, Fahn, Isgreen, & Cote, 1976). A literature search reveals that impairments can be found in almost all sensory systems including cutaneous (Schenider, Diamond, & Markham, 1987), proprioception (Jobst, Melnick, Byl, Dowling, & Aminoff, 1997; Zia, Cody, & O'Boyle, 2000), vision (Hikosaka & Wurtz, 1989; Kimmig, Haubmann, Mergner, & Lucking, 2002), smell (Doty, Deems, & Stellar, 1988), and taste (Sienkiewicz-Jarosz et al., 2005). Because

impairments exist in almost all sensory systems, this begs the questions of whether sensory guidance of the reach-to-eat movement is conserved in Parkinson's disease.

The sensory modality of proprioception is critical for producing voluntary movements (Hore, Meyer-Lohmann, & Brooks, 1977). It is sufficient to execute reaching movements in the absence of visual guidance, even in the absence of prior visual experience (i.e., in the congenitally blind) (Dizio & Lackner, 2000). Yet, if denied proprioceptive guidance, as is the case with limb deafferentation, marked impairment in motor performance can be seen (Rothwell, Traub, Day, Obeso, Thomas, & Marsden, 1982; Seiss, Praamstra, Hesse, & Rickards, 2003). Proprioceptive dysfunction can also lead to an over-reliance on visual feedback (Hore et al., 1977). The first documentation of a proprioceptive impairment in PD was the 1976 report by Flowers. In his report, parkinsonian subjects and age-matched controls produced elbow extension and flexion movements in the horizontal direction to a target with and without visual feedback. Flowers found that parkinsonian subjects displayed systematic undershooting of target location in the absence of visual feedback. He concluded that parkinsonian subjects cannot 'sense' the location of their forelimb in space and must continually rely on vision to monitor both their movements and the external environment to maintain motor control.

Vision can substitute for an abnormal proprioceptive system (Scheidt, Conditt, Secco, & Mussa-Ivaldi, 2005). Examination of individuals with large-fiber sensory neuropathy (proprioception deprivation) has shown that vision is sufficient to guide forelimb movements (Ghez, Gordon, & Ghilardi, 1995). For example, when asked to use a digitizing tablet to trace targets shown on a computer screen, neuropathic subjects improved their performance when looking at their arm, in that they reduced directional

errors and improved path curvature (Ghez et al., 1995). Similar results have been found in the parkinsonian reaching literature (Flowers, 1976; Baroni, Benvenuti, Fantini, Pantaleo, & Urbani, 1984; Adamovich, Berkinblit, Hening, Sage, & Piozner, 2001; Keijsers, Admiraal, Cools, Bloem, & Gielen, 2005). PD subjects were impaired in directional and radial distance accuracy on pointing to remembered targets when performed in the absence of vision, providing support for a proprioceptive deficit. When allowed visual feedback of arm position, PD subjects were able to achieve accuracy consistent with controls (Adamovich et al., 2001). Findings from step-tracking studies (Baroni et al., 1984) and pointing to remembered targets (Keijsers et al., 2005) also demonstrate a proprioceptive impairment that is ameliorated when subjects are allowed visual feedback of the moving limb. It therefore appears that parkinsonian subjects compensate for their proprioceptive deficit by increasing their reliance on visual cues from their moving arm (Vaugoyeau, Viel, Assaiante, Amblard, & Azulay, 2007; Flowers, 1976; Adamovich, Berkinblit, Hening, Sage, & Piozner, 2001).

To determine whether the balance of visual and proprioceptive guidance is altered in Parkinsonian subjects on the reach-to-eat task, young and age-matched controls and mild (Hoehn and Yahr score: 0 – 2.49) and advanced (Hoehn and Yahr score: 2.5 - 5) parkinsonian subjects reached for a piece of food and then transported it to their mouth for eating. Subjects were fitted with biomechanical markers to measure their reaching limb and wore eye-tracking glasses to monitor eye movements during the reach. On some trials, subjects wore visual occlusion goggles that blocked both central and peripheral vision. It was found that mild parkinsonian subjects were similar to young adults and age-matched controls in that they visually fixated the target immediately prior to first hand

movement and visually disengaged away from the target at the grasp. Visual occlusion confirmed the reliance on vision for the advance phase in that the length of time to complete this phase was increased, leaving the withdrawal phase unaffected. Advanced parkinsonian subjects displayed exaggerated visual guidance. They visually fixated on the target for a longer period of time prior to first movement and remained visually fixated on the target for an extended period of time following the grasp. Visual occlusion goggles confirmed the reliance on vision for both the advance and withdrawal phases of the reach-to-eat movement, as the length of time to complete both phases of the reach were increased. Together, these results suggest that advanced PD subjects display exaggerated visual guidance to compensate for their proprioceptive impairment, consistent with previous literature (Flowers, 1976; Hore et al., 1977; Baroni et al., 1984; Adamovich et al., 2001; Keijsers et al., 2005; Vaugoyeau et al., 2007).

The second novel contribution of the present thesis is the characterization of the sensory control of the reach-to-eat movement in PD. Mild PD subjects are similar to young adults and age-matched controls in that they rely on vision to complete the advance phase of the reach-to-eat movement. In contrast, advanced PD subjects display exaggerated visual guidance, in that they rely on vision to complete both phases of the reach-to-eat movement. The over-reliance on vision by the advanced PD subjects suggests that they are using vision to compensate for proprioceptive/haptic impairments in directing voluntary movements.

Basal ganglia and the senses. The current definition of basal ganglia functioning centers on the control of movement. This definition, however disregards the role of basal ganglia in sensory processing (Kaji & Murase, 2001). Physiological and behavioural

studies have provided evidence of a sensory processing role for the basal ganglia (Kaji et al., 2001; Boecker et al., 1999; Passingham, Toni, Schluter, & Rushworth, 1998).

Recordings from the globus pallidus of monkeys who were either reaching towards visual targets or remembered targets display activity changes in 65% of task specific cells in response to task constraints (i.e., visual vs. remembered targets) (Mushiake & Strick, 1995). Similarly, stimulation of the basal ganglia has been shown to inhibit cortical evoked activity in response to visual stimuli (Kaji et al., 2001), and nigrostriatal lesions have been shown to disrupt somatosensory feedback (i.e., both cutaneous and kinesthetic information), resulting in abnormal movement control (Brown, Schneider, & Lidsky, 1997).

The role of basal ganglia in the sensory control of movement is debated in the literature. Results from PET studies suggest that the cerebellum, not the basal ganglia, is implicated in the sensory control of movements (Jueptner, Jenkins, Brooks, Frackowiak, & Passingham, 1996; Jueptner & Weiller, 1998). A recent behavioural task however, suggests the opposite. Humans with cerebellar dysfunction (spinocerebellar ataxia), basal ganglia dysfunction (Parkinson's disease), and age-matched controls performed a passive elbow movement task. Subjects with Parkinson's disease were less accurate at perceiving elbow displacement than both age-matched controls and cerebellar subjects. The cerebellar patients were not different from controls at perceiving displacement (Maschke, Gomez, Tuite, & Konczak, 2003), suggesting that the basal ganglia plays a role in sensory processing. Our finding that advanced PD subjects display impaired proprioceptive guidance also implicates the basal ganglia in kinesthetic and

proprioceptive feedback for online movement control. The apparent discrepancy between findings from behavioural studies and imaging studies still remains a mystery.

Music Therapy Normalizes the Balance between Vision and Proprioception Guidance

Treatment for PD following the long-term side-effects of dopamine replacement therapy (i.e. ON-OFF syndrome and dyskinesia) is limited. Relief of PD symptoms, including the side-effects of dopamine replacement therapy, follows lesioning or deep brain stimulation of the globus pallidus, thalamus, or subthalamic nucleus (Rubinstein, Giladi, & Hausdorff, 2002). Currently, however, surgery is a last-resort treatment and is recommended for only a small percentage of the patient population (Rubinstein et al., 2002). Because of its limited viability, associated cost and risk, there is a need for alternate treatment options. One such therapy on the forefront of parkinsonian research is music therapy (Pacchetti, Mancini, Aglieri, Fundaro, Martignoni, & Nappi, 2000).

Reports of music as a therapy for neurological impairment span back to World War II, in which music was used to calm soldiers suffering from shell shock (Roth & Wisser, 2004). Music has been increasingly used as a treatment in Palliative care since 1978 (Munroe & Mount, 1978) to treat social (e.g. isolation), emotional (e.g., depression), cognitive (e.g., neurological impairment), and physical (e.g., pain) impairment (Clements-Cortes, 2004; Hilliard, 2003; Cunliffe, 2003; Magill, 2001; O'Callaghan, 1996; Salmon, 1995; O'Callaghan, 1993). Music has also been used in hospitals to reduce preoperative and postoperative anxiety of patients undergoing cardiac surgery (Guzzetta, 1989; Barnason, Zimmerman, & Nieveen, 1995). Unfortunately, there

are few reports in the literature that suggest improvements in parkinsonian patients following music therapy.

Reports of effective music therapy in parkinsonian patients' are centered on gait literature, with the majority of reports coming from the laboratory of Michael Thaut. The form of music therapy used by the Thaut laboratory is Rhythmic Auditory Stimulation (RAS) embedded into a music piece. Thaut reports on improvements following one session with RAS embedded music therapy (McIntosh, Brown, Rice, & Thaut, 1997), three weeks of gait training with RAS embedded music therapy (Thaut, McIntosh, Rice, Miller, Rathbun, & Brault, 1996), and long-term effects of up to five weeks following RAS embedded music therapy (McIntosh, Rice, Hurt, & Thaut, 1998). Improvements seen in gait following one session of RAS embedded music therapy included increases in cadence, stride length, and velocity. These benefits transferred over into trials without rhythmic cueing that immediately followed cued trials (McIntosh et al., 1997). Similar improvements were seen in gait following three weeks of training with RAS embedded music therapy, in that cadence, stride length, and velocity improved by 10%, 12%, and 25%, respectively (Thaut et al., 1996). Following three weeks of training, gait was measured once a week for five weeks, during which no further training was carried out.. Thaut showed that improvements in velocity were preserved for three weeks following treatment, but declined to pretreatment values by five weeks following end of treatment. Similarly, cadence and stride length also declined over the five weeks of follow-up examination (McIntosh et al., 1998). These results suggest that RAS embedded music therapy can significantly improve several measures of gait, but such improvements are transient if therapy is not continually maintained.

There is at least one report in the literature that examines the effect of music therapy over a three month treatment period. Pacchetti and colleagues (2000) compared the effects of physical therapy (i.e. passive muscle stretch, weight shifting, and balance training) to music therapy (i.e. 13 weekly sessions of singing and instrument playing) on measures of movement performance (motor subset of UPDRS). For the three month training period, motor UPDRS scores, specifically bradykinesia, improved with music therapy, without an effect of physical therapy. A two month follow-up examination of motor scores showed that the benefit of music therapy was lost, whereas a long-term benefit of physical therapy was seen (Pacchetti et al., 2000). These results are consistent with those of the Thaut laboratory suggesting the benefit of music therapy is transient unless maintained over the long-term.

Another important finding from the study by Pacchetti and colleagues (2000) was the overall positive effect of music therapy on activities of daily living, including cutting food and dressing. The finding that music therapy improved arm usage in parkinsonian subjects was one of the first reports suggesting that music could have ameliorating effects on movements beyond gait. The third objective of the present thesis therefore was to determine if music therapy can normalize the balance between visual and proprioceptive guidance for the reach-to-eat task.

To examine the effects of music therapy on parkinsonian subjects, young and age-matched controls, and mild and advanced parkinsonian subjects reached for a small food target and then placed it in their mouth. On one half of the trials, subjects listened to self-selected preferred music without an embedded RAS. Prior to music therapy, advanced parkinsonian subjects displayed exaggerated visual engagement with the target in that

they visually fixated the target before initiation of the reaching movement and remained visually fixated on the target following the grasp. Mild parkinsonian subjects were similar to young adults and age-matched controls in that they fixated the target just prior to movement initiation and disengaged at the grasp. With music therapy, however, advanced PD subjects improved to control levels for movement initiation following visual engagement with the target. Unfortunately, music did not have an effect on disengagement following grasp, time to complete forelimb movements, or scores on the movement component rating scale. These results suggest that non-RAS embedded music therapy does not have a task-specific effect on skilled reaching for PD.

The third novel contribution of the present thesis is the characterization of the effect of music therapy on the balance of visual and proprioceptive guidance for the reach-to-eat movement in PD. Mild PD subjects are similar to young adults and age-matched controls in that music did not affect sensory or forelimb measures of the reach-to-eat movement. In contrast, the measure of movement initiation following visual fixation with the target was improved by music therapy for the advanced PD subjects. The ameliorating effect of music therapy for the advanced PD subjects was likely a result of music as an external cue.

External cueing and Parkinson's disease. External cueing is utilized by PD subjects to facilitate movement initiation (Dibble, Nicholson, Shultz, MacWilliams, Marcus, & Moncur, 2004; Praamtra, Stegeman, Cools, & Horstink, 1998). Cutaneous, visual, and auditory cues have been used to improve initiation of gait (Burleigh-Jacobs, Horak, Nutt, & Obeso, 1997; Howe, 2003; Thaut et al., 1996) and choice reaction time tasks (Siegert, Harper, Cameron, & Abernethy, 2002). Velocity and stride length of initial

steps have improved following external cutaneous cueing (Burleigh-Jacobs et al., 1997) and visual priming on a choice reaction time task has been shown to improve performance of PD subjects (Siegert et al., 2002). If external cueing is removed following training with cueing on a button-to-button push task, performance of parkinsonian subjects declines dramatically (Georgiou, Bradshaw, Iansek, Phillips, Mattingley, & Bradshaw, 1994). It is therefore likely that PD subjects display their greatest impairment when asked to internally generate movements without the assistance of an external cue (Cunnington, Iansek, Bradshaw, & Phillips, 1995).

This interpretation is corroborated by physiological evidence comparing self-generated movements and externally cued movements (Jahanshahi & Firth, 1998). PET shows that PD subjects display reduced activation in the “motor” loop of the basal ganglia (from the supplementary motor area (SMA) to the putamen) (Jahanshahi et al., 1998). PD subjects compensate for their dysfunctional “motor” loop by relying on alternative cortical loops, such as the cerebellar-parietal-lateral premotor loop. This pathway has been implicated in externally cued actions (Passingham, 1985). Recordings from the SMA during self-generated movements from PD subjects indicated that the SMA is underactive and the early BP component (reflecting motor preparation associated with SMA activation) is reduced in amplitude. During performance of externally cued movements however, recordings indicate that PD subjects and age-matched controls do not differ on these physiological measures (Jahanshahi, Jenkins, Brown, Marsden, Passingham, & Brooks, 1995). It appears that music can act as an external cue to bypass the dysfunctional “motor” loop and activate alternative functional pathways to allow more normalized movement initiation.

Conclusion

The results of the present thesis show that the skilled forelimb movement is sequentially guided by vision and proprioception, with ‘advance’ of the forelimb to grasp a food target guided by visual feedback, and ‘withdrawal’ of the grasped target for placement into the mouth guided by somatosensory (i.e., haptics and proprioception) feedback. The balance of visual and proprioceptive guidance of the reach-to-eat task is conserved with increasing age and in early stages of Parkinson’s disease (Hoehn and Yahr score < 2.49). With advancing Parkinson’s disease (Hoehn & Yahr > 2.49), the balance is altered. Advanced PD subjects display prolonged visual engagement with the target in that they visually fixate the target for an extended period prior to movement initiation and remain fixated on the target following the grasp. They additionally display increased movement time and higher scores on the movement component rating scale. The altered balance of visual and proprioceptive guidance for advanced PD subjects is normalized by music therapy, as time to move following engagement is normalized to control levels, and advanced PD subjects are no longer different from mild PD to disengage following the grasp. Movement times, scores on the movement component rating scale, and disengagement following grasp were not affected, however. These results converge to suggest that music can normalize the altered balance between visual and proprioceptive guidance on the reach-to-eat task.

Future Directions

The following section will describe three experiments that can expand on the findings of the present thesis. First, an examination of the temporal relationship between grasp and mouth opening could be achieved with the addition of an ‘eat’ movement component. Second, examine the effect of rhythmic auditory stimulation (RAS)-embedded music therapy on the motor impairments seen on the reach-to-eat task. Third, explore music as a therapy for dyskinesia and cognitive impairment, parkinsonian medication side-effects.

The effect of Parkinsonism on the movement component rating scale has been clearly established for both ON and OFF medications (Doan et al., 2006), deep brain stimulation (Melvin et al., 2005), music therapy (present thesis), and for different stages of the disorder (present thesis). There is however, one movement component that is evaluated in the rat literature but has been seemingly overlooked in the human literature. ‘Release’ is the evaluation of how the food item is placed in the mouth (Alaverdashvili, Lim, & Whishaw, 2007; Alaverdashvili, Foroud, Lim, Whishaw, 2008). Although not evaluated in the present thesis, I noticed that at least two of the parkinsonian subjects in the advanced group did not preshape their mouth for placement of the food item. Instead, these patients waited until the food item contacted their lips and then they opened their mouth for food placement. It would therefore be beneficial to examine the kinematics of mouth opening, particularly with respect to the temporal relationship between digit aperture, grasp, and mouth aperture in controls and parkinsonian subjects.

The improvement seen in the reach-to-eat movement for advanced Parkinson’s subjects following music therapy was suggested to result from normalization of the

balance between visual and proprioceptive control. It would be appropriate to investigate the effect of Rhythmic Auditory Stimulation (RAS) music therapy on the motor impairments seen in the reach-to-eat movement. Given that Thaut and colleagues (1996) have shown that RAS music therapy, and not non-RAS music therapy, is an effective treatment for gait impairment in PD, it seems reasonable that RAS music therapy may also be effective in improving the motor aspect of skilled reaching where non-RAS music was not.

The effectiveness of music therapy as a treatment for advanced Parkinsonism could further be expanded by examining the effect of music on side-effects of dopamine replacement therapy. Analysis of the movement components as well as the movement profiles for the advanced parkinsonian subject presenting with dyskinesia revealed that music had a positive effect. Without music therapy, the advanced PD subject showed severe dyskinesia and scored poorly on the movement component rating scale. With music therapy, the dyskinesia appreciably decreased and scores on the movement component rating scale improved. In addition, this patient was followed up to see if the positive effect of music therapy crossed over into other impairments. We chose to look at the effect of music on the cognitive tasks of verbal fluency and Mooney's faces. Results from this subject suggested that music had a negative effect on cognitive performance. Further examination of the effectiveness of music therapy on motor and cognitive measures is therefore warranted.

In sum, I propose to continue to examine the effects of music therapy as a viable treatment option for advancing Parkinsonism. This investigation should be expanded to include medication state ("ON" versus "OFF"), measures of movements (i.e., addition of

‘release’ and other motor abnormalities), sensory (i.e., effect of non-preferred music) and cognitive measures (i.e., verbal fluency, Mooney’s faces). Any insights gained from how music therapy affects these measures could be used to support or refute the effectiveness of music as a viable therapy for Parkinson’s disease.

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