ABSTRACT

Title of Thesis:	RETENTION OF A NOVEL VISUOMOTOR GAIN IN PATIENTS WITH PARKINSON'S DISEASE IS CONTEXT-SPECIFIC

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Hypometria or reduced movement amplitude is a major concern in Parkinson's disease (PD) since it impairs multiple functional activities of daily living, including fine motor control tasks, such as handwriting. Recent research using virtual or computer-based environments, wherein visual information about hand movement is altered and dissociated from perception (e.g., position sense or kinesthesia) of hand movement itself, has shown increases in handwriting size in patients with PD. In fact, preliminary findings in our laboratory have shown that gradual alterations in visual feedback of movement facilitate adaptation of handwriting size in patients with PD, plausibly by recruiting neural networks other than the basal ganglia, such as those in cerebellum. The purpose of this study was to determine whether these adaptive effects persist after a week following visuomotor training in patients with PD and can favorably transfer to other functional writing and drawing tasks. Thirteen patients with Parkinson's disease and twelve healthy, age-matched subjects practiced handwriting either under gradually manipulated (intervention) or intact (placebo) visual display of handwriting size. The results from this study show for the first time, that these adaptive effects may persist for at least up to a week in PD; however, a single training session seemed inadequate to transfer these acquired changes to paper-pen writing and drawing. Additionally, experimental manipulation of task demands during training also helped maintain movement quality in patients with PD as against the placebo

group. These findings have important implications in designing rehabilitative interventions to enhance functional sensorimotor performance in patients with PD.

RETENTION OF A NOVEL VISUOMOTOR GAIN IN PATIENTS WITH
PARKINSON'S DISEASE IS CONTEXT-SPECIFIC

By

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Chapter I

Introduction

Movement adaptation to changing environmental contexts is an important aspect of human sensorimotor control. This process of adaptation involves modifying existent mappings or even creating newer ones between the motor and sensory signals required for movement. Research has shown that humans can adapt point-to-point reaching movements to novel virtual environments wherein a visuomotor distortion is applied by manipulating the screen-cursor relationships as rotational or movement direction distortions (Buch et al, 2003; Kagerer, Contreras-Vidal, & Stelmach, 1997) and movement amplitude/size distortions (Prager & Contreras-Vidal, 2003; Krakauer et al., 2004). Interestingly, these altered sensorimotor mappings for rotational visuomotor distortions are retained in humans for as long as a year for pointing movements (Yamamoto et al, 2006). Further, this form of visuomotor adaptation has been shown to transfer from arm to head pointing movements (Seidler et al, 2001), from arm to wrist movements (Krakauer & Shadmehr, 2006), from aiming to acoustic targets (Kagerer & Contreras-Vidal, 2009) and across movement categories (Abeele & Bock, 2003). The generalization and retention properties of newly acquired sensorimotor mappings in humans present a unique opportunity for developing adaptation protocols as intervention methods for improving or enhancing movement control in populations with neurological movement disorders such as Parkinson's disease (PD).

PD is a progressive, degenerative disorder affecting the dopaminergic neurons in the substantia nigra of the midbrain. It affects about 1.5 million people, older than 65 years of age, in the United States of America. The clinical signs include resting tremor, rigidity and bradykinesia associated with hypometria. Hypometria, i.e., reduced movement

amplitude, affects several movements in PD as it is associated with reduced scaling of movement amplitude and a decrease in sustenance of force production throughout the range of motion (Desmurget et al, 2003). Predictably, hypometria has a significant impact on sequential motor behaviors such as handwriting that involve sequences of repetitive and simultaneous movement subcomponents where generation and maintenance of force and movement amplitude are extremely critical. The typical signs of handwriting disturbances in PD are progressive reduction in size of handwriting, fluctuations in the baseline, and slowness that collectively is called micrographia (Contreras-Vidal and Stelmach, 1995).

Interestingly, recent experiments show that patients with PD are able to adapt their handwriting size to visuomotor distortions of movement size (Contreras-Vidal et al, 2002; Teulings et al, 2002; Van Gemmert et al, 1999). This suggests that latent adaptation mechanisms in PD can be recruited under virtual reality conditions when indirect visual feedback of handwriting movement is provided through the screen display alone as vision of the moving hand is occluded (Contreras-Vidal et al, 2002). The beneficial effects of indirect visual feedback in PD could be associated with the resultant obviation of contextual cues that is probably more favorable for an impaired basal ganglial system. This is related to the fact that the underlying neural substrates mediating gain adaptation include bilateral lateral cerebellum and the putamen of the basal ganglia (BG) (Krakauer et al, 2004).

In the initial stages of gain adaptation, the BG seem to play a very important role in context recognition and recalibration of a sensory-motor association, in this case the mapping between visual feedback of handwriting and proprioceptive feedback of hand movement. However, in the later stages of this adaptive learning, the cerebellum seems to play a more critical role in the fine tuning of this internal model or sensory-motor association, by error-correction learning (Krakauer et al, 2004; Doya, 2000; LaForce &

Doyon, 2002; Kagerer et al, 1997; Ingram et al, 2000; Smith & Shadmehr, 2005, Grosse-Wentrup & Contreras-Vidal, 2007). Thus, it is likely that an implicit or gradually introduced change in this visuomotor mapping (in this context) may obviate the need for context recognition and engage the cerebellar error-corrective mechanisms to modify the existent sensorimotor map in PD. In fact, empirical studies in non-human primates have shown the role of cerebellum in mediating adaptation to gradual changes in visuomotor cursor rotational transformations (Robertson & Miall, 1999). Importantly, healthy elderly subjects (Buch et al, 2003) and patients with PD (Contreras-Vidal, 2003; unpublished observations) seem to adapt better to gradually introduced visuomotor distortions in point-to-point reaching movements than to sudden ones.

Thus, in this experiment, we wished to study the adaptive increase in handwriting size in patients with PD using gradual changes in visual display of handwriting size in a virtual environment. In order to minimize confound by practice effects in this experimental setup, we included placebo groups, both for PD and healthy subjects wherein the visual display gain was not experimentally manipulated during the training session. To our knowledge, it unknown whether such learning can be retained and/or transferred to functional activities of daily living (ADL) like paper pen writing and drawing in patients with PD, specifically after a time elapse following the visuomotor training. The significance of this study is in investigating if the visuomotor adaptation paradigm can be used effectively to produce functional increases in movement size, specifically handwriting movements in PD. Hence, the findings from this study will have implications in understanding behavioral neural plasticity promoted by movement in PD and designing effective early rehabilitative interventions for micrographia in PD.

The first specific aim of this study was to investigate sensorimotor adaptation to altered movement gain in a handwriting task in patients with PD and healthy controls. In this study, the vertical gain of the subject's handwriting was reduced to a proportion of actual gain (online during movement) and displayed on the computer screen; this gain reduction was performed in gradual steps. Such gradual changes in visuomotor mappings appear to engage the cerebellar error-correction mechanisms (Robertson & Miall, 1999; Ingram et al, 2000), making the adaptation of handwriting size more implicit and effective. Further, PD affects the BG, which is crucial for explicitly recognizing newer contexts, i.e., visuomotor mappings in this case and recalibrating the system. Thus, a gradual regime can facilitate adaptation in PD through fine-tuning (cerebellar mechanisms) to modify an existing sensory-motor association, bypassing the basal ganglial mechanisms. Consistent with these findings, it is expected that the gradual regime will promote adaptation of vertical size of handwriting in both patients with PD and healthy subjects. However, the effective handwriting size in the PD intervention group is expected to be smaller than the healthy intervention subjects, due to the effect of the disease process.

The second specific aim was to investigate the retention capabilities of handwriting gain adaptation in these two groups. Retention has been demonstrated for learning of visuomotor rotation distortions for point-to-point movements in humans for up to a year. Further, some evidence of retention, in terms of savings in a repeat performance of a novel task has been shown in elderly subjects (Seidler, 2007). It was thus expected that patients with PD and the age-matched healthy subjects in the intervention groups are expected to demonstrate an increased rate of adaptation, i.e., savings in performance or retention on retesting after a week.

The third and final aim of this study was to investigate the transfer of movement gain to other movement categories and handwriting contexts including paper writing and drawing. The use of a gradual alteration is likely to promote an adaptive increase in handwriting movement gain in the intervention groups of patients and healthy subjects by recruiting cerebellar error correction mechanisms. It is expected that the intervention groups of patients with PD (PD-I) and healthy subjects (C-I) are likely to transfer their acquired increase in handwriting movement gain to a different task such as drawing and to the functional paper-pen writing context. The placebo groups of patients (PD-P) and healthy subjects (C-P), who did not train under the adaptation protocol, should not have any increase and movement gain and hence, no transfer effects thus ensuring that the proposed experimental manipulation was responsible for the adaptation, carry-over benefits, and transfer to other tasks.

This thesis contains four additional chapters in addition to this first introductory chapter (Chapter I). The second chapter presents a review of the relevant literature about the pathophysiology of hypometria in PD, specifically associated with micrographia and visuomotor adaptation in PD and aging. It also presents the theoretical framework behind the experimental protocol to be used in this study and the potential for clinical translation of these experimental findings in patients with PD. The third chapter details the methods used in this study. The fourth and fifth chapters present the results and discuss the findings and future directions of this research respectively.

Chapter II

Review of Literature

Neurophysiological basis of hypometria in Parkinson's disease

Parkinson's disease (PD) is a degenerative disorder affecting the dopaminergic neurons in the substantia nigra of the midbrain. Though PD is one of the most frequently studied movement disorders, its pathophysiology is incompletely understood mainly due to the complexity of the basal ganglio-thalamocortical circuits. Hypometria, i.e., reduced movement amplitude, is a major concern in PD and affects several movements as it is associated with reduced scaling of movement amplitude and a decrease in sustenance of force production throughout the range of motion (Desmurget et al, 2003). Predictably, hypometria has a significant impact on the sequential motor tasks such as handwriting where generation and maintenance of force and movement amplitude are extremely critical. The underlying pathophysiological mechanisms in PD will be briefly discussed in the context of normal physiological connections of the basal ganglia (BG).

The normal skeletomotor control of the BG is based on the activity in two major pathways that link its different parts- indirect and direct pathways. The major input structures of the BG are the caudate and the putamen (comprising the striatum) while the output from these subcortical nuclei is mediated through the globus pallidum, especially the internal component (GPi) and the closely associated substantia nigra pars reticulata (SNr). The input to the striatum is mainly from the various motor cortical areas, namely, primary (M1), premotor and supplementary (SMA) and the other sensory cortical association areas; the output of the basal ganglia is mediated through the ventrolateral thalamic nuclei connecting to the cortical areas, completing the loop.
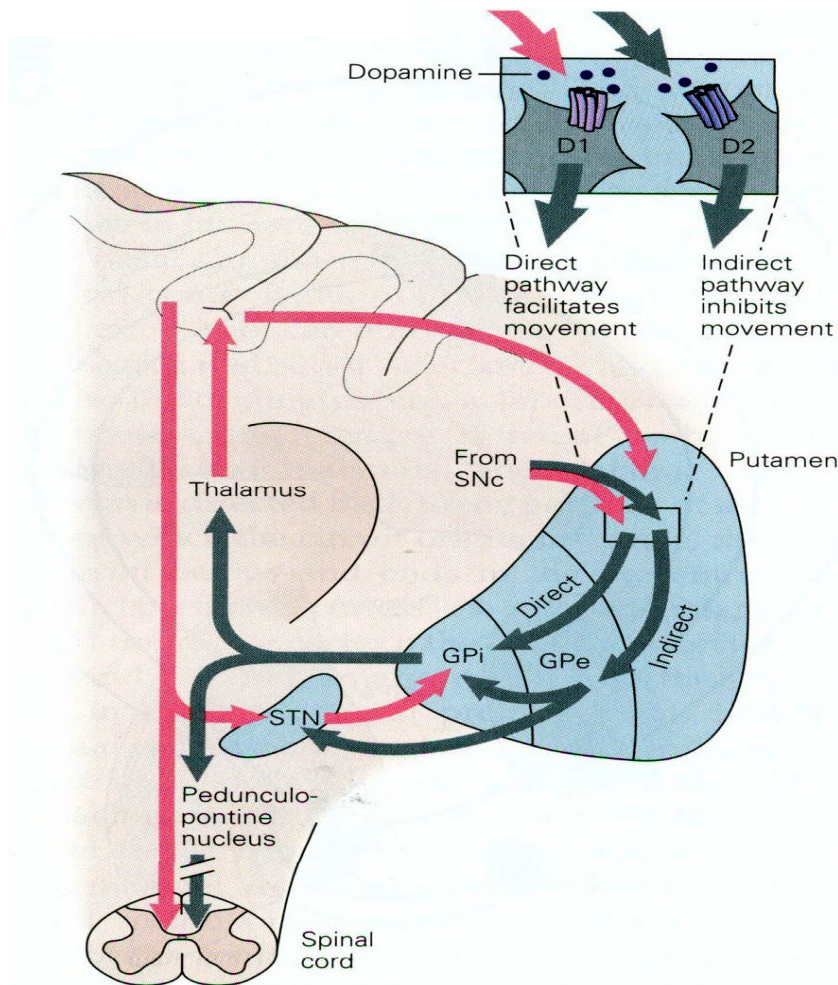
Figure 2.1: This diagram shows the connections in the corticostriatal and pallidothalamic circuits in the direct (pink arrows) and indirect (gray arrows) pathways; the corticospinal projections are also shown. The function of these pathways under normal conditions and in PD is described in detail in the following text. [SNc - Substantia Nigra pars compacta; STN - Subthalamic nucleus; GPe - Globus pallidum externa; GPi - Globus pallidum interna] (From Principles of Neural Science, 4th edition., E.R. Kandel, J.H. Schwarthz, T.M. Jessel; Chapter 43, p. 860)

The disinhibition of the subthalamic nucleus in the indirect pathway leads to excessive stimulation of the GPi causing inhibition of the excitatory ventral thalamo-cortical pathways; *hence activity in the indirect pathway leads to suppression of movement*. In contrast, the direct pathway circuit bypasses the subthalamic nucleus, and inhibition of the GPi disinhibits the excitatory thalamo-cortical pathways thereby facilitating movement. A very important aspect is the dopamine (DA) secreted by the substantia nigra compacta

(SNc); the striatal neurons participating in the indirect pathway express D2 receptors and are inhibited by DA while the neurons in the direct pathway express D1 receptors and are stimulated by DA. Thus, DA plays an important role in regulating motor cortical activity by modulating the function in both these pathways.

In PD, the degeneration of these crucial dopaminergic neurons of the SNc leads to excessive activity in the indirect pathway and relatively lesser activity in the direct pathway (shown in figure 2.1) The net result of this is reduced motor cortical activity (due to reduced thalamocortical facilitation.) It is thought that the regulated activity in the 2 pathways might have an influence in pallidal movement related signals in the following ways:

- When the signals from both pathways are directed to the same pallidal neurons, the inputs from the indirect pathway might help in braking and/or smoothing the movement as the inputs through the direct pathway simultaneously facilitate the movement. This reciprocal regulation would help in scaling the movement amplitude and velocity.

- On the other hand, signals from both pathways directed to different neurons will lead to facilitation of the desired movements and suppress the undesired movements and this would be very consistent with the context-related movement selection function of the BG.

As discussed above, the fine balance between the neurotransmitters in the nigrostriatopallidal circuits seems to be the most crucial factor in maintaining normal movement patterns. Thus, the depleted levels of DA seems to be responsible for producing smaller gating signals at the pallidothalamic synapses and prevents them from getting appropriately rescaled at the cortical level; thus, the ability to control variable movement speeds is compromised and this leads to a reduction in the amplitude of the movements that

are produced i.e. *hypometria* (Contreras-Vidal & Stelmach, 1995.) These abnormal thalamic gating signals might be a result of both aberrant patterns (connections between the GPi and GPe) and rates of pallidal firing.

An important neural network model that explains the kinematics of arm reaching movements from point-to-point is the Vector-Integration-To-Endpoint (VITE) model proposed by Bullock and Grossberg (1988.) According to this model, the motor plan to reach from a given point to another in space is computed by calculating the difference vector (DV) between the current/present position vector (PPV) and the target position vector (TPV) under the influence of the GO signal; the DV is used to update the PPV towards the TPV by gradual integration such that the DV slowly tends to zero. When this happens, the TPV becomes the PPV and the arm has reached the new endpoint.

Functionally, the corticocortical and the thalamocortical connections seem to operate within the VITE model based upon the GO signals generated from the BG through the pallidothalamic connections (shown in figure 2.2). The significance of this GO signal is that it is the neural correlate of a volitional command to start a movement that sets the global speed of the movement (Contreras-Vidal & Stelmach, 1995.) The dynamics of this GO signal could be controlled by the BG through the multiple parallel pallidothalamocortical loops; these are due to the diffuse corticostriatal projections. This could help in the simultaneous processing and linking of different subcomponents of a movement and thereby, produce a smooth motor act with appropriately controlled velocity and amplitude depending upon the requirements of the task.
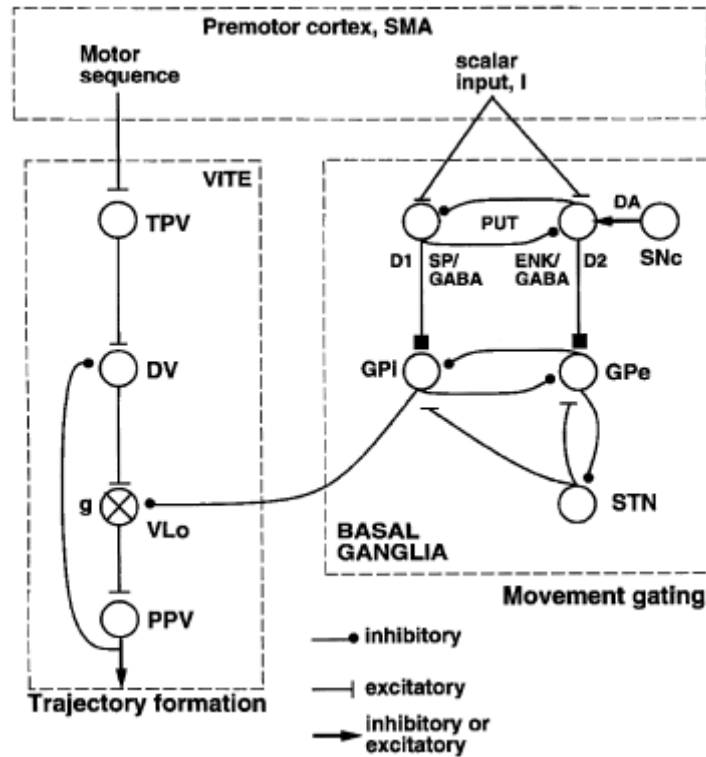
Figure 2.2: This figure shows the connections in the corticostriatal and pallidothalamic circuits in relation to the VITE model. For a movement trajectory to be planned, the striatum and pallidum play a critical role in the generation of the GO signal through the pallidothalamic projections in updating the DV which is crucial for scaling the movement, in addition to modifying the quality of movement. However, for the normal generation of this GO signal, a fine balance between DA, substance P, enkephalins and GABA (neurotransmitters) is required in the striatopallidal circuits. This balance is disrupted in PD (decrease in DA with concomitant increase in substance P) consequently affecting the GO signal. (A.W.A. Van Gemmert et al., p. 687; Neuropsychologia, 37 (1999): 685-694)

There seems to be a functional segregation at the level of the striatum in terms of movement initiation i.e. planning, and execution; these are executed through the striatal input to the parallel pallidothalamic signals to the different cortical areas, namely, SMA, premotor and motor cortex. Thus, depending on the DA loss in the different parts of the striatum, the motor deficits seen in PD either manifest as an increase in reaction time (RT) which suggests planning problems and/or prolongation of movement times (MT) and reduction in movement amplitudes (hypometria) suggesting execution problems. This also

seems to correlate with differences in the cortical projections to the striatum: the sensorimotor cortex tends to project to the putamen while the association cortex projects more to the caudate. As a corollary, it can be stated that with lesions affecting a larger portion of the striatum in PD, both forms of deficits might be more pronounced; it is likely that with progression of the disorder, the DA depletion might extend and affect larger portions of the striatum. The striatum is the key to modulation of the output through the GPi and effectively, the GPi output determines movement velocity. There is an inverse relationship between the activities of the GPi and the thalamus; higher modulation of the GPi results in greater thalamic activity and hence faster movement velocities.

Desmurget et al (2003) investigated the actual nature of the impaired motor performance in PD and attempted to correlate it with a problem in the planning of movement amplitude, which is considered a unique characteristic of PD. They controlled for initial localization errors of arm position at start position in reaching tasks, i.e. kinesthesia, which is known to be affected in PD (Contreras-Vidal & Gold, 2004), and observed that reduction in movement gain as observed through correlates such as peak velocity profiles was the only difference in the reaching exhibited by patients with PD and controls. Also, the amount of reduction in movement gain in the patients seemed to correlate significantly with the severity of the disease i.e., higher the severity, greater the reduction in movement gain. These results re-establish the movement amplitude planning function of the BG and this is even consistent with the single-cell recording of the pallidal neurons where amplitude/velocity effects have been identified.

Thus, based on the theoretical framework of the VITE model and the neurophysiological mechanisms of the BG, the striatal modulation of the pallidum in the BG, seems critical in the control of movement amplitude and the affection of the former in

PD due to DA depletion might be the underlying cause of the hypometric movements seen in PD.

Handwriting deficits associated with hypometria in PD

The functional consequence of disturbances of regulation of movement amplitude and speed and especially simultaneous control of different subcomponents of movement would be that sequential motor acts involving control of all these aforementioned factors would be affected in PD. Handwriting is a complex motor act that involves sequences of repetitive and simultaneous movement subcomponents; predictably handwriting is significantly affected in PD. The typical signs of handwriting disturbances in PD are progressive reduction in size of handwriting, fluctuations in the baseline and slowness (which is seen in other movements as well) and the cluster of these signs is called *micrographia* (McLennan et al, 1972; Contreras-Vidal and Stelmach, 1995)

Bullock et al (1993) developed a model for normal production of handwriting based on the VITE model described previously. This model, called the VITE-WRITE model, is hierarchical in nature that explains handwriting to be produced by a redundant hand with three degrees of freedom (DOF). According to this, the system models the three DOFs, namely, transverse movements of the pen by finger retraction/extension, and longitudinal strokes controlled by small vertical wrist rotations and left-to-right hand movements while writing controlled by horizontal wrist rotations. The VITE model plans the trajectories for each of these three movements by calculating TPVs to generate the required movement amplitude and velocity. The system is thus able to independently specify the size and speed of the handwriting movements by controlling the underlying muscle activity and temporal variations in the force produced.

In PD, the smaller GO signal produced by the pallidothalamic circuits seems to be the major issue; this consequently leads to reduction in the activity in the thalamocortical projections. The SMA is extremely important in planning complex movements; hence a reduction in the thalamocortical projections would impair the selection of the next subcomponent by the SMA in the motor sequence of handwriting. Also, reduction in the projections to the premotor and motor cortex leads to impaired production of the individual motor components itself (as shown by the VITE model simulations) (Contreras-Vidal et al, 1995.) This plausible nature of dysfunction in PD was correlated with the simulation of the VITE-WRITE model which showed Parkinsonian micrographia too.

Production and regulation of force amplitude is related to stroke size while development and release of force is related to stroke duration or speed; and according to Teulings and Stelmach (1991), patients with PD have a greater difficulty in the former. Van Gemmert et al (1999) investigated the actual problems faced by patients with PD in producing stroke size and/or duration in handwriting by requiring patients to write a given set of handwriting strokes in three conditions in addition to the baseline: as fast as possible, two times larger than the baseline and a combination of both i.e. as fast as possible and two times larger. The handwriting of the patients with PD were compared to age-matched controls and the experimental strokes consisted of relatively simple patterns because these would unmask the speed-size tradeoff in patients with PD who use bradykinesia a compensatory strategy to avoid speed-size tradeoff. The results of the patients with PD and the controls were compared to those generated by the simulation model (using VITE) for the same set of strokes.

An interesting finding of this study was that the patients with PD might possibly follow the *isochrony* principle like normal subjects do in handwriting: this principle refers

to the fact that movement time (MT) is maintained constant within a range of stroke lengths from 0.5-2 cm. This is reflected in the results of the patients with PD wherein they attempt to maintain and/or increase speed, but are unable to increase stroke size to two times larger than baseline. This is probably due to the fact that reducing stroke duration demands a more rapid force development (which may be possible in PD), but increasing the size requires maintenance and regulation of the force amplitude over a greater period of time, which might be the problem in PD. This correlated with the results seen wherein patients with PD showed maximum impairment in the condition where they had to write as fast as possible and also two times larger; this situation demands a great deal of regulation of force amplitude. Comparable results were found in the simulations too. Van Gemmert et al explain this to be a result of deficiency in recruiting motor units due to a lot of noise in the motor system (and force amplitude varies directly in proportion to the recruitment of motor units.) An alternative explanation that has been considered is the role of perception-action mismatch which causes patients to perceive their movements of larger amplitude than they actually are, leading them to undershoot. Though in this study, this phenomenon may not explain why patients with PD demonstrated constancy in their stroke duration even though they were unable to double the size.

These impairments in dynamic control of fine motor skills such as handwriting has been corroborated by Longstaff et al (2003) in their study of the movement scaling and accuracy in patients with PD while performing discrete circular drawing and continuous spiral drawing movements. They found that patients try to scale their movements depending upon the accuracy demands of the task and this typically caused a trade-off between movement size and accuracy; thus, reducing movement amplitude when more accuracy is

required in order to compensate for the variability in the performance was associated with a reduced quality of movement.

In summary, micrographia in PD seems to be due to the hypometria caused by DA depletion rather than just an aspect of the general manifestation of the motor deficits. The theoretical framework of the VITE-WRITE model explains this to be a consequence of the reduction in the amplitude of the GO signal.

Visuomotor gain adaptation in PD: a potential behavioral intervention for micrographia

Motor adaptation seems to be certainly impaired in PD, especially visuomotor adaptation; when a visuomotor distortion (novel environment) is provided, patients with PD seem to use sensory information on a trial-to-trial basis rather than updating their sensorimotor mapping (Contreras-Vidal et al, 2002; Contreras-Vidal & Buch, 2003.) This is demonstrated by the fact that aftereffects in patients with PD after such a distortion are comparatively diminished as against age-matched controls. This is probably associated with an impaired ability to update extant sensorimotor representations in novel environments since the striatum plays an important role in building a repertoire of motor actions with practice that can be executed in response to appropriate environmental stimuli i.e., contextual recognition and motor system recalibration (Laforce & Doyon, 2001).

However, gain distortion in visual feedback appears to be an interesting potential strategy to influence handwriting in PD. This is because patients with PD seem to rely on visual feedback of previous handwriting strokes to plan the subsequent ones (Teulings et al, 2002). In fact, this has been postulated as a mechanism that negatively reinforces the smaller size of handwriting in patients with PD which was validated by experimental findings wherein when a gain distortion is imposed, instead of adapting, patients tend to

produce successive stroke amplitudes that amplify the distortion effect (Teulings et al, 2002). However, Contreras-Vidal et al (2002) provided indirect visual feedback by displaying the manipulated handwriting on a computer screen wherein subjects wrote on a digitizer tablet with the vision of their hand and pen occluded (this was not occluded in the previous study) and compared the adaptation effects in patients with PD, age-matched elderly controls, and young controls. Interestingly, the patients showed comparable effects of gain adaptation with the controls in this study as against the previous study.
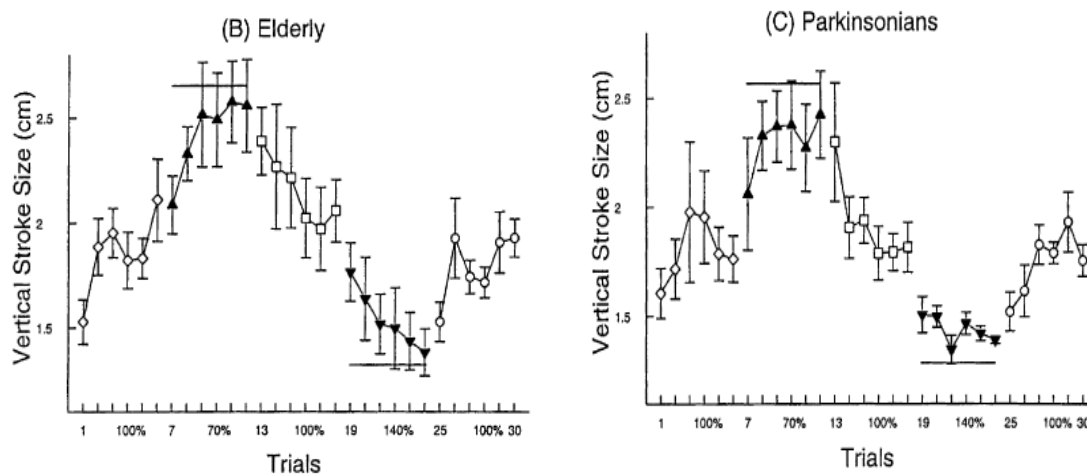
Figure 2.3: Adaptation to gain reduction (70%) and gain increase (140%) of original handwriting size. The diamonds represent baseline trials, triangles represent exposure trials and the circles represent aftereffects. Patients with PD show comparable aftereffects like the elderly, though slightly lower in amplitude, indicating adaptation (Contreras-Vidal, JL et al., p. 80; Parkinsonism & Related Disorders 9 (2002): 77-84)

It is seen that the patients with PD and the healthy elderly controls show comparable increases in stroke size when display gain of handwriting is reduced to 70%. This is evident in the post-exposure phase, i.e., the 100% gain condition following the trials during exposure to 70% gain. Similarly, when the display gain size is distorted and increased to 140% of original, both patients and controls show an adaptive decrease in handwriting

stroke size (as compared to baseline) as seen clearly in the post-exposure trials. Although the magnitude of aftereffects i.e., the relative, adaptive increase and decrease in handwriting stroke size in patients is smaller than that seen in controls, these findings suggest that visuomotor gain adaptation may be a very useful means to access and modify the gain control system in PD, especially pertinent to handwriting deficits. Is it possible that an impaired context recognition and motor recalibration (due to affection of the BG) benefits better from a lack of contextual cues like indirect visual feedback? If so, which neural mechanisms operate in such a case to cause the adaptation that was seen in this experiment?

In light of these experimental findings, it is important to understand the neural substrates mediating visuomotor gain adaptation in health and in PD; this will help determine experimental conditions that are more conducive to favoring an adaptive increase in handwriting size in PD.

Putative neural mechanisms mediating visuomotor gain adaptation in PD

Multiple neural networks are postulated to play a very critical role in modifying extant sensorimotor associations, i.e., updating extant internal models; the basal ganglia and cerebellum and their connections with multiple cortical areas seem to play a very important role in this regard. Krakauer et al (2004) studied and compared the brain regions activated during gain learning and rotation learning in healthy, young subjects using PET imaging and found significant differences in brain activation during adaptation under gain and rotation distortions. The most novel aspect of the methods used in this experiment is that the constant alternation between two opposing gain and rotation distortions allowed studying the difference between the rapid (first) phase and slow (secondary) phase of adaptation.

There was a clear distinction between the areas activated during the learning under distortions: rotation distortion activated the supplementary motor area (SMA) and posterior parietal cortex and with progression of learning, the activation of SMA decreased with concurrent increase in posterior parietal activation. On the contrary, initial learning of a gain distortion showed bilateral subcortical activation of the putamen and the cerebellum and as learning progressed, the activation patterns did not show a significant change from the baseline. These results correlate very well with fact that rotation adaptation involves learning a new reference frame and hence new cortical areas are activated, like the SMA and posterior parietal cortex; whereas, gain learning involves recognition and switching to a new context that has already been recalibrated, this is demonstrated by the transient activation of the BG and cerebellum. This also explains why gain learning is easier than rotation learning; and the bilateral activation is consistent with the ready interlimb transfer of gain adaptations.

Thus, in the initial stages of handwriting gain adaptation, the BG seems to play a very important role in context recognition and recalibration of a sensory-motor association; in this case, the mapping between visual feedback of handwriting and proprioceptive feedback of hand movement. However, in the later stages of this adaptive learning, the cerebellum may play a more critical role in the fine tuning of this internal model or sensory-motor association, by error-correction learning (Krakauer et al, 2004; Doya, 2000; LaForce & Doyon, 2002; Kagerer et al, 1997; Ingram et al, 2000; Smith & Shadmehr, 2005, Grosse-Wentrup & Contreras-Vidal, 2007).

Interestingly, differences in the time course of provision/presentation of the visuomotor distortion seem to engage different neural mechanisms for adaptation, consequently resulting in differential adaptive effects. It has been found that dentate

inactivation in monkeys, impaired adaptation to gradually varying distortions while preserving adaptation to sudden distortions (Robertson & Miall, 1999). This suggests a critical function of the cerebellar structures in adaptation to gradual kinematic distortions, wherein the process of adaptation appears to be more implicit. In this regard, studies have shown that in healthy elderly subjects, gradually changing visuomotor rotational distortions as against sudden ones seem to promote better adaptation, in terms of errors during exposure to the distortion (Buch et al, 2003).
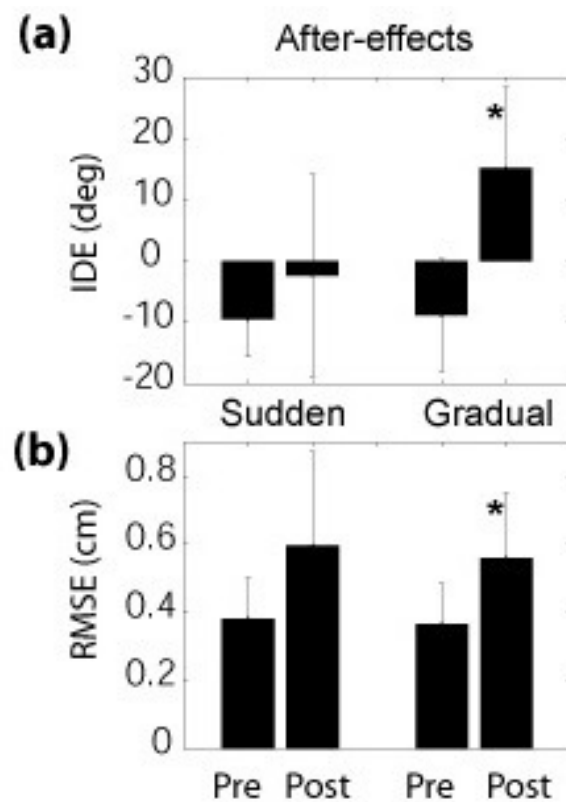
Figure 2.4: (a) Gradually increasing rotational distortions produce significant aftereffects as measured by the initial directional error (IDE) in patients with PD. This is seen as IDE significantly different and in the opposite direction in the aftereffects (post) as against the baseline (pre) condition. (b) Root mean square error (RMSE) is also significantly increased following adaptation in the gradual condition in the post as against the pre condition.

Further, similar effects have been shown for patients with PD wherein adaptation is facilitated by gradually increasing visuomotor rotational distortions, resulting in significant

aftereffects (reflected in initial directional errors) in the post exposure phase. On the contrary, patients with PD receiving sudden visuomotor distortions did not show adaptation and hence no significant aftereffects as compared to baseline (Contreras-Vidal et al, 2003; Unpublished observations) (Fig 2.4). Further, preliminary findings also suggest that gradual, and not sudden, visuomotor gain distortions seem to promote adaptive increases in handwriting stroke size in patients with PD (Fig 2.5).

Standardized mean stroke length of cursive '*l*'s
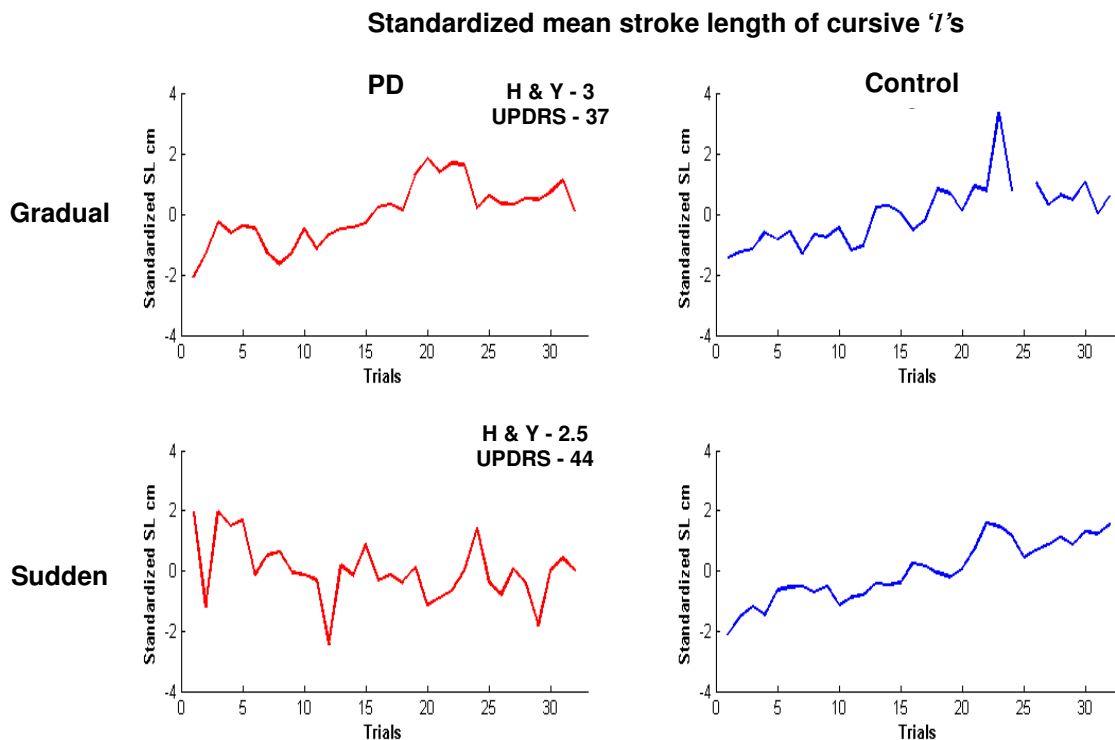
Figure 2.5: This figure shows data from a case study with one subject in each group. There is an increase in the standardized stroke length for the patient with PD receiving a gradual gain reduction; this is seen as an increase in stroke length as compared to baseline whereas the patient receiving the sudden distortion shows no/poor adaptation with increased variability in performance. Control subjects show similar performances in sudden and gradual conditions. [H & Y: Hoehn & Yahr stage of PD; UPDRS: Unified Parkinson's disease Rating Scale]

It is likely that an implicit or gradually introduced change in this visuomotor mapping (in this context) may obviate the need for context recognition and engages the

cerebellar error-corrective mechanisms more strongly. Another possibility is that gradual adaptation can be performed based on the actual error and the current internal model, rather than searching for appropriate mappings. This suggests that gradual distortions have a means to bypass the basal ganglial mechanisms that are required for contextual recalibration and this may explain the beneficial effects of this regime in patients with PD. In addition, the recent discovery of neural connections between the cerebellum and basal ganglia in non-human primates (Hoshi et al, 2005) also suggests that there may be other underlying neural mechanisms mediated by the cerebellum that may plausibly be recruited by a gradual regime.

Further, in the context of prism adaptation, the "true" adaptation is postulated to occur in the later stage of the process of adaptation which is slower and comprises of realignment i.e., reduction of smaller terminal errors; this is also mediated by the cerebellar hemisphere ipsilateral to the deviation introduced by the prisms (Pisella et al, 2006). In fact, recruitment of the cerebellar mechanisms has been associated with stronger aftereffects and more generalization of learning in stroke patients with visuospatial cognitive deficits (Rosetti et al, 1998; Pisella et al; 2006). Thus, the use of a gradual regime in providing visuomotor gain distortions seems to be optimal to promote adaptive increases in handwriting size in PD.

Additionally, visuomotor training may have other benefits such as amelioration of certain visuomotor impairments in PD (Stoffers et al, 2002) by plausibly serving as external cues to performing a simple day-to-day task like handwriting. Besides, external cues have been shown to be extremely beneficial in training and improving motor performance of patients with PD (Nieuwbower et al, 2007) because they allow for engaging alternate, plastic learning mechanisms (i.e., possibly cerebellar and cortical circuits); by improving

attention (Almeida et al, 2002); by facilitating movement planning and execution (Leis et al, 2005); and most importantly, by eliciting a motor response through a perceptual cue that makes the movement less automatic, thus freeing the BG circuits (Praamstra et al, 1998; Nieuwbower et al, 2007).

Retention and Transfer of visuomotor gain adaptation in Parkinson's disease

The effectiveness of any intervention is dependent on retention of learning and the potential to transfer any beneficial learning effects, in this case adaptive increases in handwriting size, to functional contexts outside the laboratory. It has been shown that adaptation to visuomotor rotational transformations during center-out reaching movements has retention for up to one year in humans (Yamamoto et al, 2006). However, such retention has not been investigated in patients with PD following visuomotor adaptation. Similarly, Bock & Girgenrath (2006) have shown transfer from adaptation during center-out movements to target tracking movements in healthy, young and elderly subjects.

Gain adaptation has been shown to transfer from arm to wrist movements (Krakauer et al, 2006) and from arm to head movements (Seidler et al, 2001) in healthy young subjects. Further, gain adaptation has also been shown to readily transfer across limbs (Seidler et al, 2001) and this is probably associated with the bilateral activation of the putamen in the BG and the cerebellum during gain adaptation in health, young subjects. Interestingly, adaptation appears to transfer more easily when the movements which are practiced under distortions involve a large ballistic component. This was seen as better transfer from adaptation during pointing movements to a tracking task following that (Abeele & Bock, 2003). This is important in the context of this experiment since the subjects perform cursive *l* writing during adaptation which can be considered closer to

ballistic movements in the context of handwriting, especially the up stroke written for each *l*. Since elderly subjects demonstrate some potential for retention of adaptation in terms of savings in performance based on prior adaptive experience, it seems worthwhile to investigate if such an effect is seen in patients with PD. Thus, to address the extant knowledge gap in the literature, this study is proposed to investigate if patients can demonstrate savings in performance in gain adaptation and also transfer adaptive increases in handwriting size to a different drawing task and a functional paper pen writing context.

Chapter III

Methods

Subjects

Thirteen patients with diagnosed with idiopathic PD and twelve healthy adults (18 males, 7 females total) participated in this study with voluntary consent. These were further sub-divided in to four groups (n=7 in PD intervention, n=6 each in PD placebo, Healthy Control intervention & placebo groups). Subjects with dementia, other co-morbid neurological disorders and those receiving deep brain stimulation or other surgical therapies were excluded. All subjects were screened for dementia using the Mini Mental State Examination (MMSE scores > 25). The patients belonged to local patient support groups, movement disorder clinics and from the local neighborhoods. All participants had normal or corrected-to-normal vision and were provided with financial compensation, as approved by the Institutional Review Board of the University of Maryland, College Park. All patients with PD had mild stages of the disease, stages 1-3 on the Hoehn-Yahr stages of PD and their motor deficits were also scored on the Unified Parkinson's disease rating scale (UPDRS) (Table 1). All but 1 (healthy subject) out of 24 subjects were right-handed; however, since micrographia is a central phenomenon (McLennan et al, 1972), handedness does not matter in the patients with PD and the healthy subjects. Patients were tested in their "on" state for medications since the purpose was to study the effectiveness of this regime as an adjunctive therapy to treat micrographia. One patient in the intervention group (PD-I (3)) was much more impaired than the others and had significant dyskinesia during the experimental sessions; since there was no patient in the placebo group matching his clinical

status, his data were excluded from further analyses. There was no significant difference in

ages across the 4 groups (p = 0.1372).

Table 2.1 – Parkinson's disease and healthy participants

Subject	Sex	Age (Yrs)	Handed	MMSE	UPDRS day1	UPDRS day8	H&Y	Yrs (PD)	Medication
PD-I(1)	M	60	Rt	27	26	24	3	4	Sinemet
PD-I(2)	M	63	Rt	30	23	18	2.5	4	Stalevo; Miraprex
PD-I(3)	M	52	Rt	30	38	47	3	10	Stalevo; Miraprex; Amantidine
PD-I(4)	M	74	Rt	29	24	24	3	5	Sinemet
PD-I(5)	M	75	Rt	28	20	20	2.5	8	Stalevo; Requip
PD-I(6)	F	74	Rt	29	32	33	2.5	2	Sinemet; Temazepam
PD-I(7)	F	63	Rt	28	10	10	2.5	2	Stalevo
			Mean	28.71	24.71	25.14	2.71		
			s.d.	1.11	8.88	11.89	0.27		
PD-P(1)	M	73	Rt	29	16	17	2.5	3	Stalevo; Cymbalta
PD-P(2)	M	65	Rt	29	22	22	2.5	3.5	Sinemet
PD-P(3)	F	59	Rt	29	29	23	2	10	Sinemet; Amantidine; Clonazepam
PD-P(4)	M	78	Rt	30	36	35	2.5	13	Sinemet; Stalevo
PD-P(5)	F	65	Rt	27	28	28	2.5	6	Sinemet; Miraprex
PD-P(6)	M	65	Rt	28	33	28	3	10	Sinemet; Miraprex; Amantidine
			Mean	28.67	27.33	25.5	2.5		
			s.d.	1.03	7.31	6.22	0.32		
	PD		*Mean*	**28.69**	**25.92**	**25.31**	**2.62**		
			s.d.	**1.03**	**7.97**	**9.32**	**0.3**		
C-I(1)	F	82	Rt	30	-	-	-	-	-
C-I(2)	M	67	Rt	28	-	-	-	-	-
C-I(3)	M	62	Lt	30	-	-	-	-	-
C-I(4)	M	72	Rt	29	-	-	-	-	-
C-I(5)	M	79	Rt	27	-	-	-	-	-
C-I(6)	M	77	Rt	30	-	-	-	-	-
			Mean	29					
			s.d.	1.26					
C-P(1)	M	63	Rt	27	-	-	-	-	-
C-P(2)	F	63	Rt	30	-	-	-	-	-
C-P(3)	M	62	Rt	28	-	-	-	-	-
C-P(4)	M	67	Rt	28	-	-	-	-	-
C-P(5)	F	65	Rt	29	-	-	-	-	-
C-P(6)	M	66	Rt	30	-	-	-	-	-
			Mean	28.67					
			s.d.	1.21					
	C		*Mean*	**28.83**					
			s.d.	**1.19**					

Note: UPDRS scores are only from the Motor section out of a total of 108.

<u>Experimental setup</u>

Participants were seated in front of a table facing a computer monitor (as shown in the figure 3.1), and allowed to write with a digitizer pen on a horizontally positioned digitizing tablet. Vision of the dominant hand/arm was prevented by a wooden pedestal over the

<u>Fig 3.1</u>: Experimental Setup

digitizing tablet; the monitor (with screen resolution 800 x 600 pixels) was positioned on top of this pedestal. A digitizing tablet (12" x 12" WACOM InTuos™ 9100 Series) was used to collect data on the pen position in x/y coordinates at 200 Hz sampling rate using custom software written in OASIS™ (KIKOsoft, Nijmegen). The room was dimly lit to allow for better visualization of the screen display for the subjects. The active area for writing on the tablet measured 19.5 cm x 14.5 cm (6 cm from the front of the tablet) which was mapped on the screen as a corresponding viewable area of 26.5 cm x 19.5 cm (Teulings et al, 2002; Contreras-Vidal et al, 2002). Thus, the distance between the eye and the screen display was about 1.35 times larger than the normal writing distance and hence the corresponding larger writing display area on the screen matched this, thereby making the handwriting appear proportionately larger. As the subjects wrote on the tablet, visual feedback of the pen movements on the digitizing tablet was provided in real-time on the computer monitor. For assessment of transfer to a functional context, subjects were allowed to write/draw on a sheet of paper taped on to the digitizer tablet with an inking pen ("inking tablet") analogous to paper-pen writing; this was done pre-training and one week post-training.

Task and Instructions

The experimental procedure involved handwriting (cursive 'l' or loops) and spiral drawing on a digitizer tablet. One group each of patients (PD-I) (mean age 65.9+8.7 yrs) and healthy subjects (C-I) (mean age 73.2+7.6 yrs) received the experimental intervention of reduction in visual display of handwriting size (intervention groups), while the other group of patients (PD-P) (mean age 67.5+6.8 yrs) and healthy subjects (C-P) (mean age 64.33+2 yrs) received a 'placebo' or dummy treatment with no change in visual display of handwriting size (placebo groups). This arrangement was used to control for the task/testing effects; thus, giving a factorial treatment structure (2 x 2 – disease by treatment).

Baseline: Ink tablet		Baseline: Pre-exp		Exposure	Retention	Transfer: Ink tablet	
I Spirals (10)	Loops (10)	Spirals (10)	Loops (20)	Gradual reduction in visual display size of loops to 50% (80)	Reduction in visual display size of loops to 50% (20)	Spirals (10)	Loops (10)
P Spirals (10)	Loops (10)	Spirals (10)	Loops (20)	Visual display size of loops – 100% (80)	Visual display size of loops – 100% (20)	Spirals (10)	Loops (10)
Day 1					Day 8		

Fig. 3.2: Summary of experimental protocol for the intervention (I) groups and the placebo (P) groups. The numbers in parentheses indicate number of trials performed.

Subjects performed the experimental sessions either in the Cognitive Motor Neuroscience laboratory at the University of Maryland, College Park or in the community centers/support group meeting areas and were made familiar with the digitizer apparatus by practice with writing and drawing on the tablet. As shown in fig 2, for intervention groups, on day 1, baseline assessments of spirals and loops were made, followed by adaptation/exposure trials involving writing cursive 'l's with a gradual reduction in visual display size of handwriting to 50% (10 steps; 5% per step; 8 trials per step). On day 8, retention was assessed as savings in performance of loop writing with visual display size of

handwriting at 50%. The "inking tablet" was used to simulate a functional context for paper-pen writing wherein transfer of adaptive effects could be assessed. For the placebo groups, all conditions remained the same except that during exposure and retention, visual display size of handwriting was displayed at 100 %, i.e., without any reduction. The rationale behind comparing patients and healthy subjects is to investigate if Parkinson's disease affects visuomotor adaptation, retention and/or transfer compared to healthy subjects. Moreover, the placebo groups helped differentiate practice effects from those due to the experimental intervention accounting for any changes in handwriting and spiral drawing at the time of transfer testing. Importantly, no assessments of aftereffects were made on day 1 to avoid partial washout of learning due to visual feedback of movement.

For the exposure phase (visuomotor training) and for retention assessment on day 8, subjects performed handwriting/drawing with indirect visual feedback of movement displayed as trajectories on the monitor. Subjects were instructed to trace their pen and move in to a home circle and hold their pen in that position till the circle turned green signaling movement onset. For the loop writing tasks, subjects were presented with a small circle in the margin about 7 cm above the home circle prior to movement onset as a representative target size for writing cursive *l* s. This disappeared once the home circle turns green since the task was intended to simulate normal handwriting and presentation of a continuous target will alter the neural planning signals for movement, particularly for the patients. Trajectories were displayed on the screen as soon as subjects touched the pen to the tablet, however, the kinematics of the movement were sampled after the home stimulus turned green. Recording ceased when the pen was lifted off the tablet (for more than 0.5 seconds).

Data processing

Kinematic data of loop and spiral trajectories were low-pass filtered with a fourth order, Butterworth filter at 4Hz cutoff (since tremor frequency in PD is 4-7Hz) (Contreras-Vidal et al, 2002). For each loop writing trial, the data were segmented in to up and down strokes based on zero crossings of vertical velocity profile (Teulings & Maarse, 1984). The average stroke length, normalized jerk (NJ) (as a measure of movement smoothness) and movement time (MT) were calculated for each trial. Exposure phase loop trials were divided into 10 blocks of 8 trials each, each block having the same visual display size of handwriting. The first 8 trials from the retention phase were used for further statistical analysis in order to minimize potential confound by re-learning or increased learning on day 8 with more trials. For the spiral data, Cartesian coordinates (x/y) were converted to polar coordinates (theta/rho). Correlation coefficient between theta and rho was calculated as a measure of idealness of spiral and slope of this linear regression line was used as a measure of global size of the spiral. As the spiral approximates an ideal spiral, the correlation coefficient is expected to increase. The global size of the spiral as reflected in the slope of the linear regression line is indicative of the relative distance between 2 successive revolutions of a spiral and hence was expected to be a standardized measure of the size of the spiral across both trials and subjects (Longstaff et al, 2003). All analyses were performed using custom written programs in MATLAB 7.2.

Statistical Analysis

The primary dependent variables included measures of movement size i.e., handwriting stroke size and spiral size; movement time (MT) and normalized jerk scores (NJ) as measures of movement speed and movement smoothness were also computed and

the statistical analyses were performed separately for studying retention and transfer. Outliers were rejected in the data preprocessing. For the spiral data, outliers included trials drawn too slowly or skipped trials; for loops, trials having less than 6 loops or skipped trials were excluded. Due to non-Gaussian nature of the data and small sample size, we used more conservative, non-parametric statistical methods (Kruskal-Wallis and Friedman methods of analysis of variance) to compare treatment effects on dependent measures across and within groups. Owing to the gradually decreasing visuomotor gain distortion, significant differences were not expected between successive adaptation blocks, hence preplanned contrasts were set up to compare 1st (early adaptation) and 10th (late adaptation) blocks of exposure phase to study adaptation of handwriting size within both intervention group. Retention was studied as differences among the last block of exposure phase and first 8 trials of retention phase of loop writing in the PD and healthy intervention groups (PD-I & C-I respectively). Friedman's test was used to compare these 3 blocks in a repeated measures design within each of the 4 groups. Further, for each of these 3 blocks, across group comparisons were performed using Kruskal-Wallis method in order to study the disease by intervention main and interaction effects. Transfer was studied by comparing all baseline corrected dependent measures to a zero median using the Wilcoxon Sign Rank test. Further, across group differences were studied using the Kruskal-Wallis method. All post-hoc pair-wise comparisons of block and group means were preplanned and performed using the least-square differences (LSD) method. Alpha was set at 0.05 for experiment wise error.

Chapter IV

Results

There were no differences in up and down stroke dependent measures per trial, hence these were collapsed to obtain average measures per trial. However, differences were found in baseline trial means of movement time (χ^2=8.72 (df 3); p=0.0333) across groups, thus, all dependent measures in adaptation, retention and transfer were corrected for these baseline differences. Fig. 4.1a and b shows a characteristic trial of writing (loops) for one subject each from the PD and healthy intervention groups across early, late adaptation and retention assessment and also pre (baseline) and post-training (transfer) paper-pen writing and drawing.
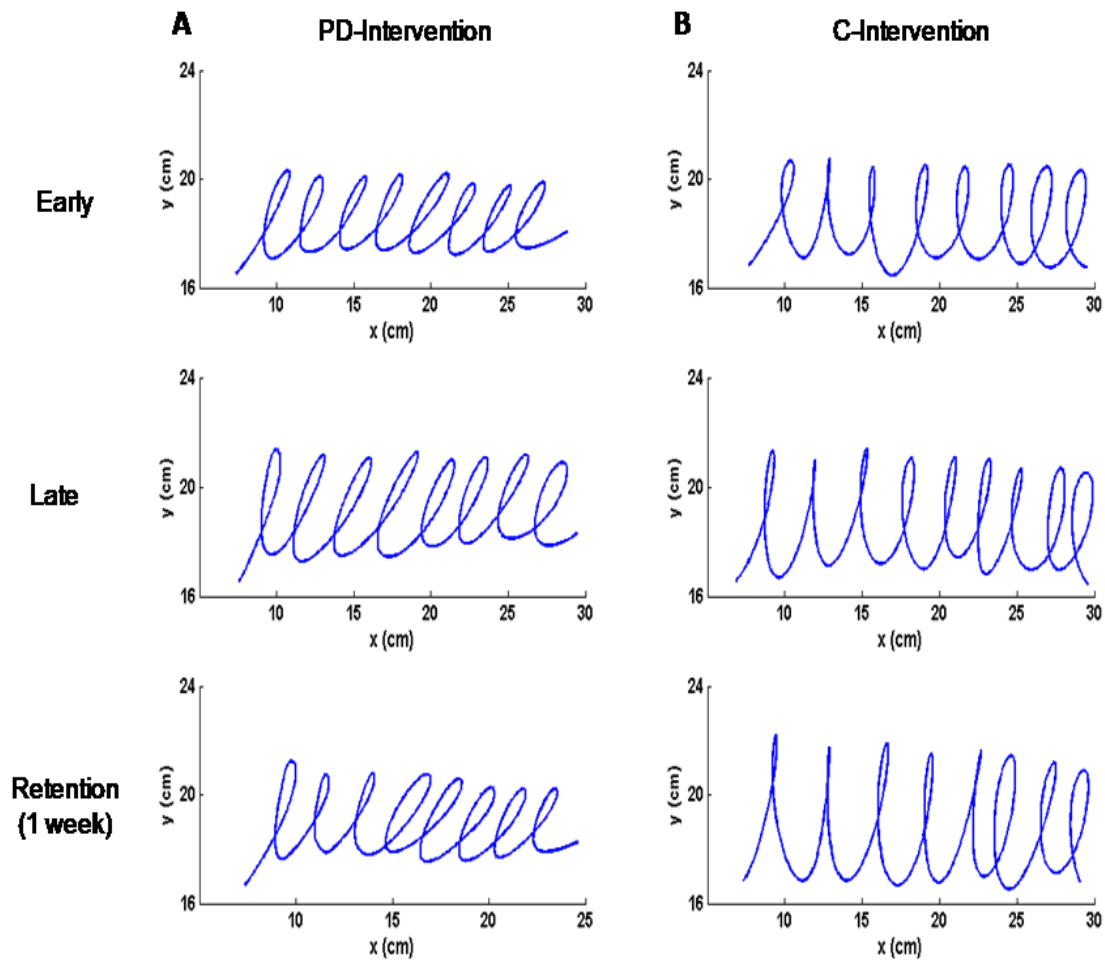
<u>Fig 4.1.a</u>: Single trial of representative subjects, PD-I (2) (A) and C-I (2) (B), (top to bottom) early and late adaptation and retention tested at 1 week after training, slowing a slight increase in stroke lengths in late adaptation and retention. Trials are from the middle (trial no. 5) of each of the blocks (8 trials per block).
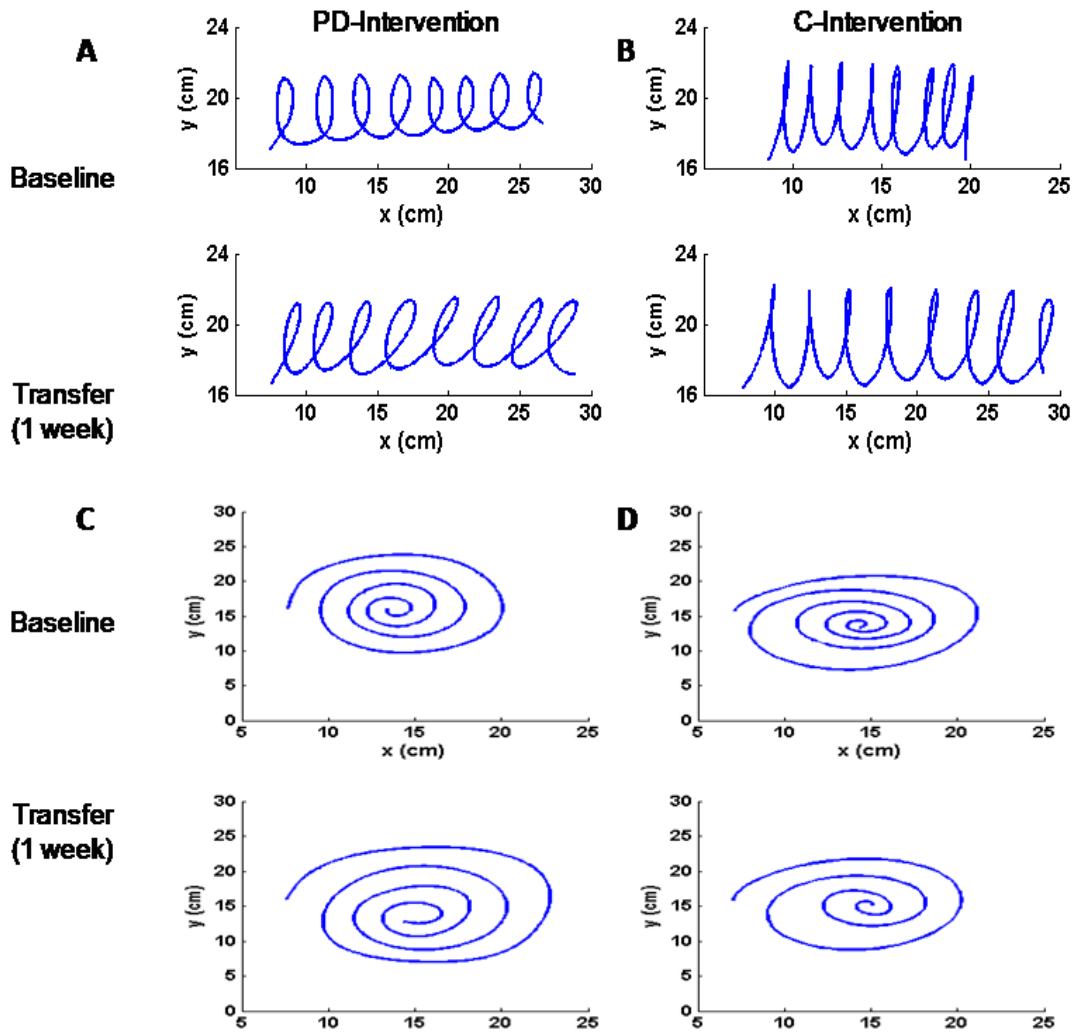
Fig 4.1.b.: Single trial of representative subjects, PD-I (2) (A) and C-I (2) (B), baseline (pre) and transfer (post-testing) for loop writing on paper; single trial for PD-1 (2) (C) and C-I (2) (D) baseline (pre) and transfer (post-testing) spiral drawing on paper. Trials are from the middle (trial no. 6) of each of the testing conditions (10 trials per condition).

Adaptation and Savings in performance (retention) in block means
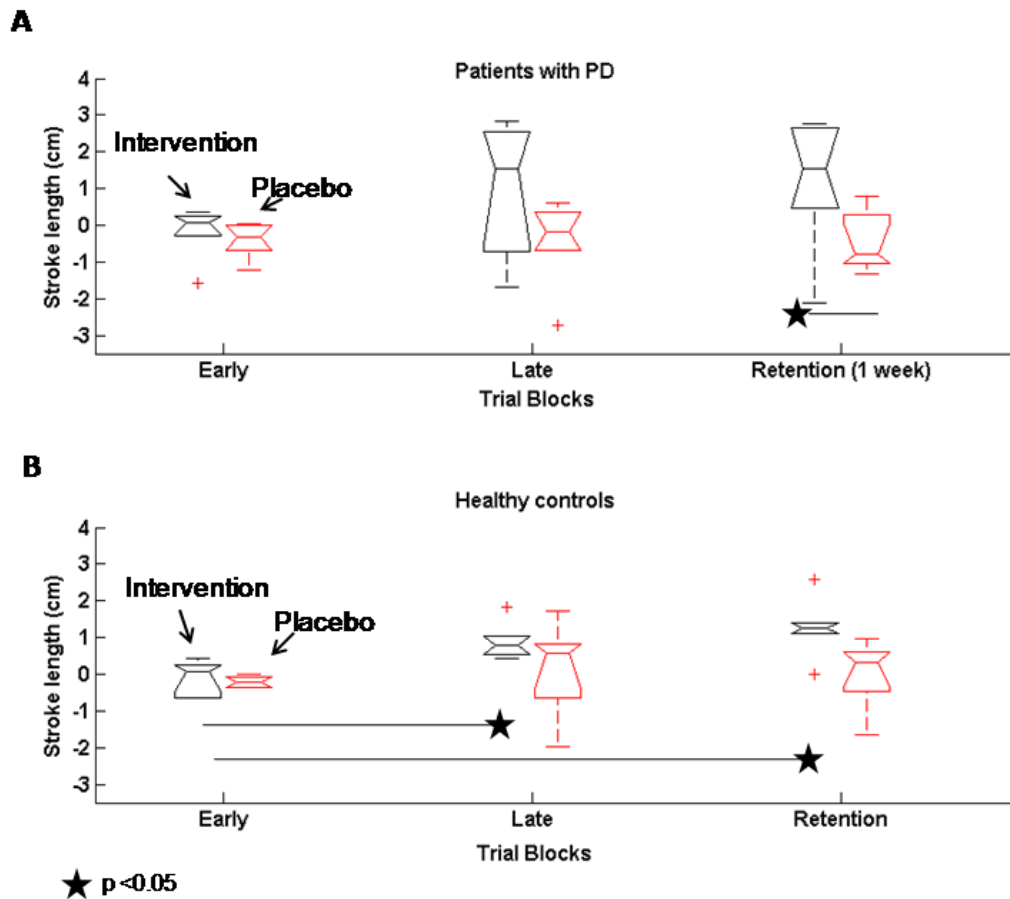
Fig 4.2: Box plots showing differences in early, late adaptation and retention blocks for stroke lengths (baseline corrected) within and across the 4 groups, (A) PD-I (black) and PD-P (red) and (B) C-I (black) and C-P (red). Significant differences are indicated by a connecting line and asterisk.

Adaptation effects are reflected in changes in dependent measures specifically between early and late adaptation blocks while retention or savings in performance was studied by comparing late adaptation and retention performances. As seen in fig. 4.2, within group comparison across blocks revealed a significant increase in stroke length for C-I group (χ^2=6.33 (df 2); p=0.0421) across blocks. Post-hoc pair-wise comparisons revealed a significant increase in late as compared to early adaptation (p<0.05). However, there were

no significant differences across blocks for PD-I, C-P and PD-P groups (p>0.3). Similarly, no significant differences were found for stroke length across groups at early and late adaptation blocks (p>0.12). However, post-hoc pair-wise comparisons revealed significantly higher stroke length in C-I as compared to PD-P (p<0.05) in late adaptation block.

Retention in C-I was significantly different from early adaptation (p<0.05) while not being different from late adaptation. Interestingly, across group comparison at retention revealed significant differences across groups (χ^2=9.056 (df 3); p=0.0287). Post-hoc pair-wise comparisons revealed significant increases in stroke length in C-I & PD-I groups as compared to PD-P (p<0.05) (fig 4.2). C-I and PD-I were not significantly different from each other.

There were no significant differences in stroke duration across blocks during adaptation and retention for any of the groups: C-I, PD-I, C-P and PD-P (p>0.11) (fig 4.3). Post-hoc comparisons revealed no significant differences between early and late adaptation (p>0.05). There appeared to an increase in variability in stroke duration in late adaptation in both placebo groups as compared to early adaptation and also intervention groups, but no significant differences were found across groups for adaptation and retention at each block (p>0.22).
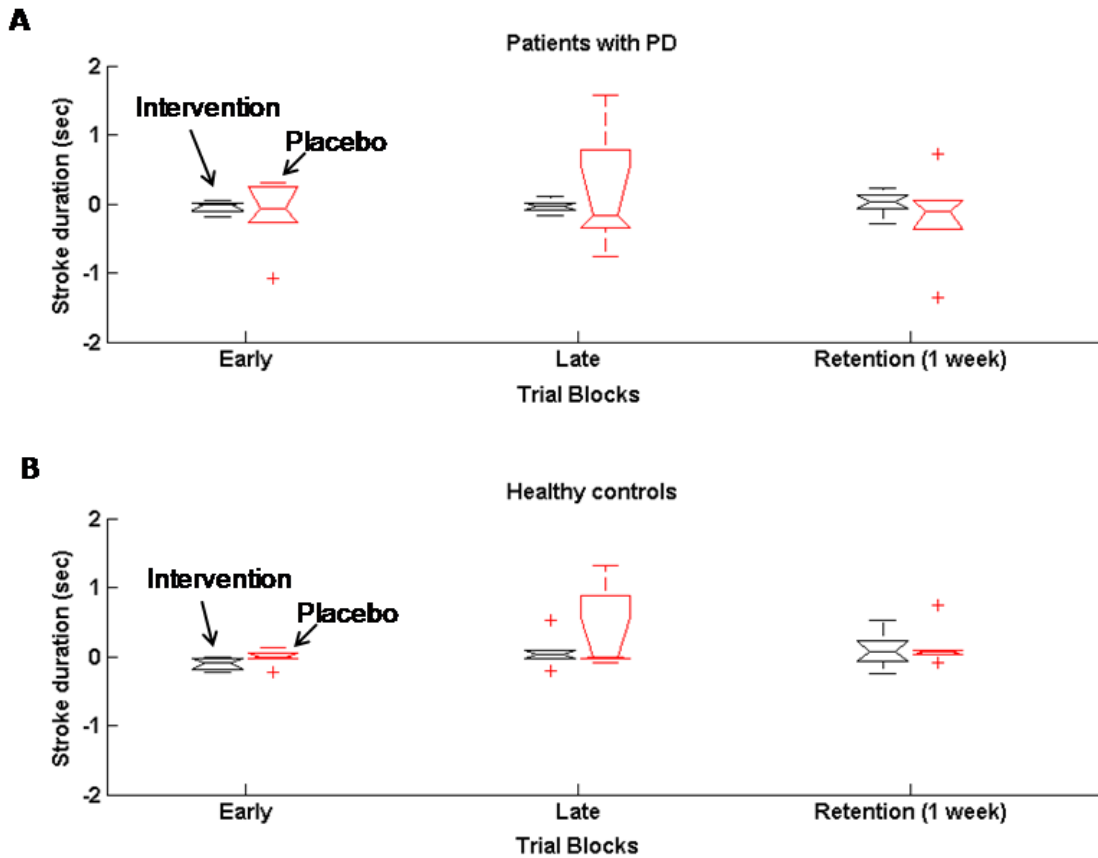
Fig 4.3: Box plots showing differences in early, late adaptation and retention blocks for stroke durations (baseline corrected) within and across the 4 groups, (A) PD-I (black) and PD-P (red) and (B) C-I (black) and C-P (red). There were no significant within and across groups.

Comparison of normalized jerk scores (fig 4.4) across blocks revealed no significant differences within groups during adaptation and retention (p>0.13). Post-hoc pair-wise comparisons revealed no significant differences (p>0.05). Normalized jerk scores across groups were not different in the early adaptation block (p>0.5). However, in the late adaptation group, a significant difference in jerk scores was seen across groups (χ^2=8.39 (df 3); p=0.0385). Pair-wise comparisons revealed a significant increase in normalized jerk scores in PD-P as compared to PD-I group (p<0.05). No other groups were different from

each other statistically, though, there appeared to be trend for increase in jerk scores in C-P as compared to C-I group. Interestingly, there were no significant differences in jerk scores across groups in retention (p>0.6).
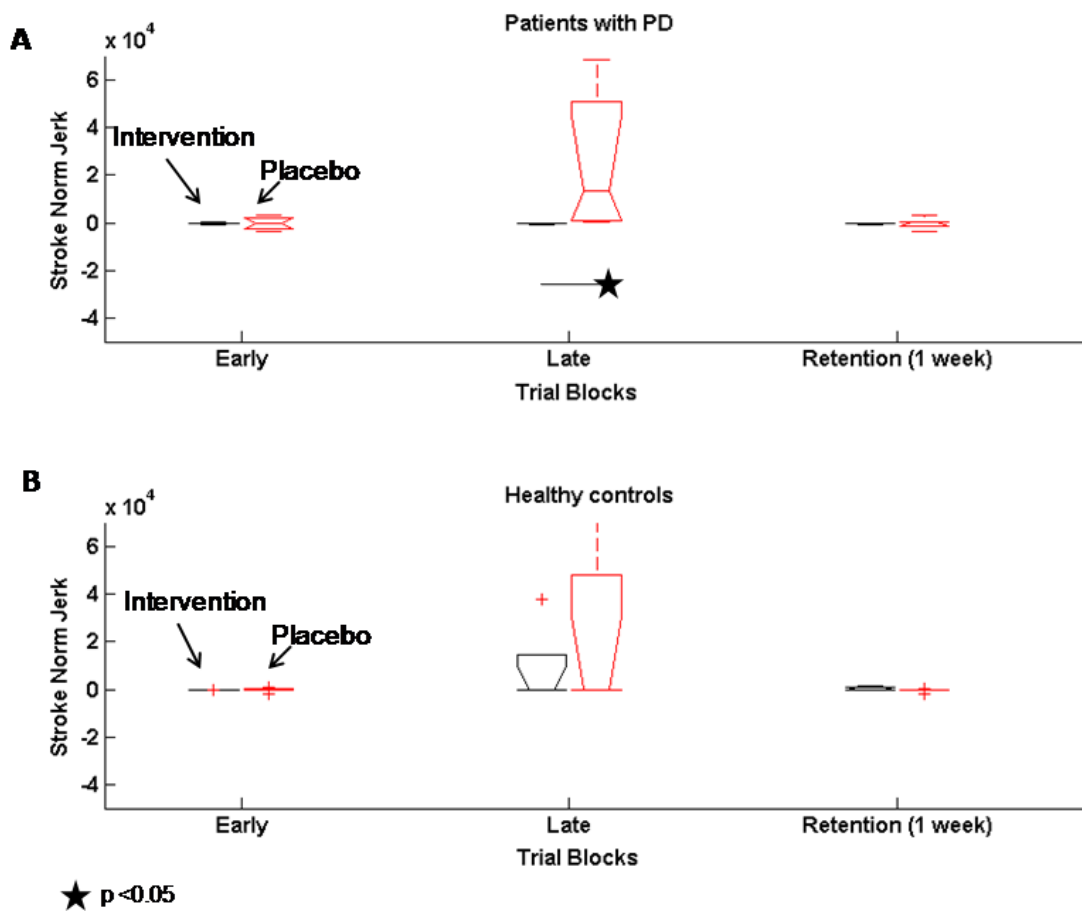
Fig 4.4: Box plots showing differences in early, late adaptation and retention blocks for stroke normalized jerk scores (baseline corrected) within and across the 4 groups, (A) PD-I (black) and PD-P (red) and (B) C-I (black) and C-P (red). Significant differences are indicated by a connecting line and asterisk.

In summary, the gradually reducing visual gain distortion mediated adaptive changes in handwriting in the healthy and PD intervention groups, particularly during retention. There were significant increases in stroke length, the primary dependent variable for the C-I group during adaptation. Predictably, the C-I group also maintained these significant

increases in stroke length during retention (savings in performance) while the PD-I group demonstrated a comparable increase in stroke length. On the contrary, the PD-P group deteriorated in quality of movement with significantly higher normalized jerk scores toward the end of adaptation, i.e., in the late adaptation block, as compared to PD-I group.

Transfer of adaptive changes to paper-pen writing
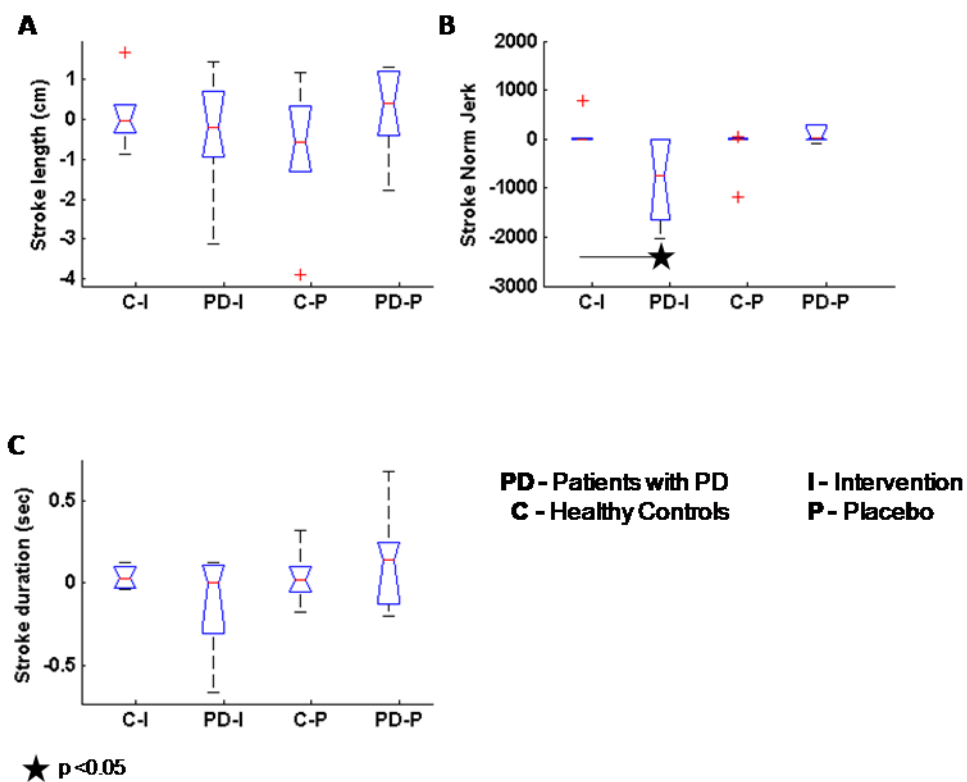
Fig 4.5: Box plots showing differences in (A) stroke length, (B) normalized jerk and (C) stroke duration across the 4 groups, C-I, PD-I, C-P and PD-P for baseline corrected measures at post-testing (transfer) after 1 week. Significant differences are indicated by a connecting line and asterisk in the normalized jerk scores between C-I and PD-I.

There were no significant differences across groups for baseline corrected stroke lengths and stroke durations ($p > 0.61$) (fig 4.5). There were no differences between any 2

groups in pair-wise comparisons (p>0.05). Similarly, there were no group differences in normalized jerk scores (p>0.11), however, post-hoc pair-wise comparisons revealed significantly lower jerk scores in PD-I as compared to C-I (post-training assessment) (p<0.05). There were no group medians significantly different from zero for any dependent measures (p>0.05, Wilcoxon Sign Rank test).

Transfer of adaptive changes to paper-pen drawing
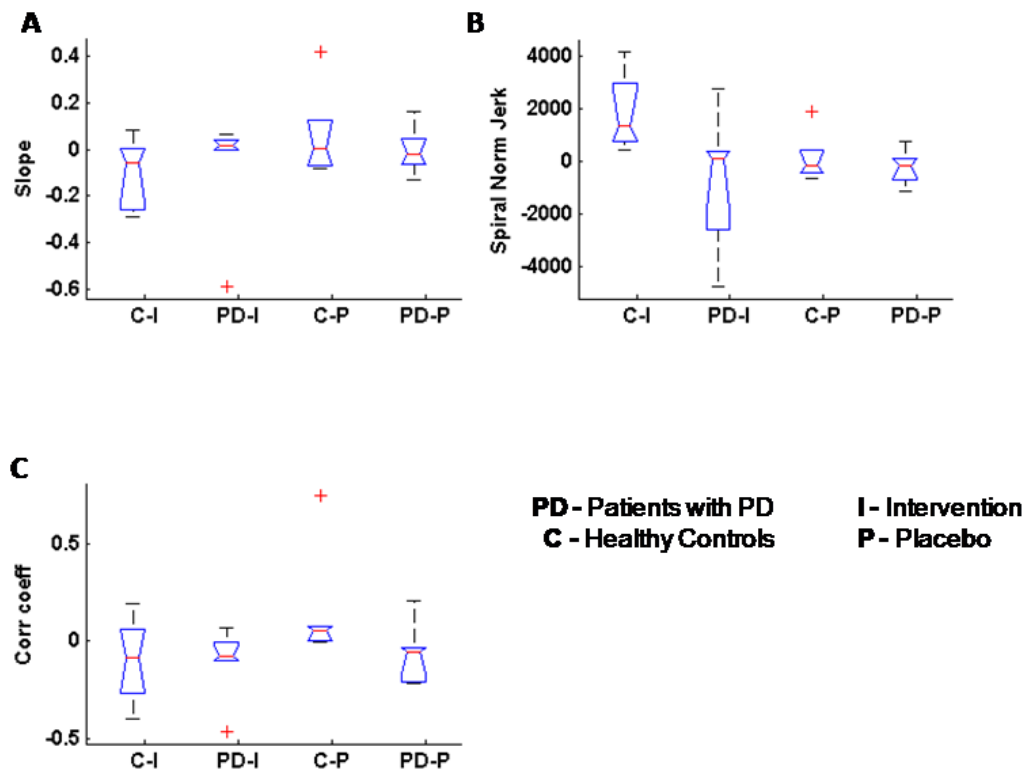
Fig 4.6: Box plots showing differences in (A) linear regression slope and (C) correlation coefficient (r^2) between polar coordinates (angle of revolution and radius for spirals) and (B) normalized jerk scored for spirals and across the 4 groups, C-I, PD-I, C-P and PD-P for baseline corrected measures at post-testing (transfer) after 1 week. There were no significant group differences except for correlation coefficient.

There were no significant differences across groups for baseline corrected spiral normalized jerk scores and slope measures ($p > 0.15$) (fig 4.6). There were no differences between any 2 groups in pair-wise comparisons ($p > 0.05$). However, there was a significant difference in spiral correlation coefficient (r^2) ($\chi^2 = 9.45$ (df 3); $p = 0.0239$) and post-hoc pair-wise comparisons revealed significantly lower r^2 in C-I as compared to other 3 groups ($p < 0.05$). C-I slope median deviated significantly from zero ($p = 0.0313$); all other dependent measures for all groups were not significantly different from zero ($p > 0.05$, Wilcoxon Sign Rank test). Thus, the changes in transfer conditions for writing and drawing are suggestive of the fact that the single visuomotor training session did not produce significant improvements in the paper-pen context.

Chapter V

Discussion

The results from this study suggest that the experimental intervention of gradual reduction in visual display gain promoted comparable adaptive changes in handwriting in the healthy and PD intervention groups. Moreover, these adaptive changes appeared to be retained for at least one week post-training in both the groups; to our knowledge, retention of such sensorimotor learning has not been demonstrated in PD, which is the novel finding of this study. Moreover, the retention of the novel visuomotor gain appears to be specific to the context in which it was acquired, as these adaptive changes did not transfer to a paper-pen context. However, it must be noted that the lack of transfer to a new context may have been due to the limited exposure to the novel gain change as that patients and controls experienced a single training session only.

Visuomotor adaptation of handwriting size

Adaptive increase in handwriting size is validated by the finding that in late adaptation, the stroke lengths for the PD-I group did not differ significantly from the C-I group. Further, the PD-I group maintained their quality of handwriting (i.e., smoothness) through the adaptation while the PD-P group showed a breakdown in movement smoothness as seen in significantly higher normalized jerk scores in the last block of adaptation. This intact ability to adapt to gradual visuomotor gain distortions in PD, particularly in the context of handwriting is consistent with the findings of Contreras-Vidal et al (2002). There are two possible factors mediating this acquisition of a new sensorimotor association in PD: dissociated/indirect visual feedback of handwriting and gradually

changing visuomotor gain distortions, i.e., a ramp decrease in display size of handwriting. Indirect visual feedback of handwriting trajectories projected on the screen display is proposed to recruit different transformational mechanisms between proprioceptive and visual feedback arising from a movement (Norris et al, 2001). This may be particularly amenable to handwriting size modulation in PD owing to their impaired proprioceptive hand position estimation (Contreras-Vidal & Gold, 2004). The dissociated visual feedback may minimize conflict from errors in hand estimation owing to distorted visual feedback of handwriting. Additionally, the strong reliance of patients with PD on visual feedback and cues, in the context of movement aided by a dissociated hence, non-conflicting visual feedback of handwriting movement, may have helped patients adaptively scale their handwriting size in this study. Interestingly, we found progressive increases in normalized jerk scores in the PD-P group concomitant with relative preservation of handwriting size, which were significantly higher in the last block of the visuomotor adaptation phase. Normalized jerk scores in the context of handwriting are reflective of coordination between the wrist and finger joints and these are increased in PD due to sub optimally functioning basal-ganglia thalamocortical networks (Teulings et al, 1997). This impaired coordination is most likely associated with an irregularity in the force scaling or modulation of the muscles at the wrist and fingers during handwriting. Our finding is particularly interesting in light of new findings about functional dissociation for force control in the basal ganglia (Spraker et al, 2007; Vaillancourt et al, 2007). These findings suggest a differential role for anterior basal ganglia nuclei in selection of force amplitude and posterior basal ganglia nuclei in scaling and sustenance of a selected force impulse. The latter functions are mainly seen in Globus Pallidus interna (GPi), subthalamic nucleus (STN), posterior putamen (Vaillancourt et al, 2007) and also in the ventral (posterior, lateral and medial) nuclei of the thalamus,

which form the basal ganglia outflow to the motor cortical areas (Spraker et al, 2007). In addition, the pre-supplementary motor cortical area (pre-SMA) is associated with both selection and production of force and is tightly coupled to the Globus Pallidus externa (GPe) in this integrative function for appropriately selecting, generating and modulating any movement.

These findings are particularly relevant to our handwriting task since it requires selection and production of appropriate amplitudes of force in a series; these strongly require optimal basal ganglia functioning with appropriate input to the primary motor and supplementary motor cortical areas. Predictably patients with PD have impairments in force modulation. However, it is particularly interesting to note that the placebo in our study highlighted a specific impairment in the balance between selection and production/sustenance of force amplitudes in PD. On the contrary, when the task requirements changed, as in requiring adaptive changes in scaling handwriting size due to the intervention, these impairments in balancing scaling and producing force were seemingly attenuated in PD.

It is proposed that the use of the gradually changing gain distortions in this study engaged trial-by-trial error correcting mechanisms plausibly mediated by the cerebellum (Robertson & Miall, 1999; Kagerer et al, 1997) which may have modulated the input to the motor cortical areas favorably to mask this impairment in PD. This could be potentially associated with some interaction between the cerebellar and basal ganglia input to the cortex relaying at the thalamus. This finding is very relevant from a functional perspective because it suggests that such task demands may actually aid in maintaining quality of performance in PD on a trial-by-trial basis; future research can delve deeper in to more specific task needs and their applicability to functional contexts.

Retention and transfer of sensorimotor learning in PD

The PD-I group showed comparable retention or savings in performance to the C-I group, as evidenced by significantly higher stroke lengths in retention testing 1 week post-training (day 8). Evidence of retention of this new sensorimotor association is provided by the finding that the PD-I demonstrated significantly higher stroke lengths than the PD-P on day 8. This confirms that the PD-I did not merely re-adapt to the visual gain reduction on day 8, rather, they recalled a seemingly acquired sensorimotor representation for this movement gain modulation.

Previous research has shown difficulty or even absence of retention of skill learning in PD (Mochizuki-Kawai et al, 2004). On the contrary, patients with PD demonstrated savings in performance after a lapse of one week in this study; this is most likely due to the visuomotor adaptation promoted by the gradually changing gain distortions. As previously described, these are more likely to engage cerebellar error corrective mechanisms than the context recalibrating basal ganglial networks, thus plausibly making it favorable for the neurophysiological status in PD. In fact, the use of gradually varying visuomotor distortions as against sudden ones, leads to better movement adaptation in elderly (Buch et al, 2003) and even PD for a center-out pointing task (Venkatakrishnan et al, 2008). This also corroborates with neurophysiological evidence for these sensorimotor associations and computations in the cerebellum (Kawato, 1999). Thus, the demonstration of ability to retain a sensorimotor association for a complex and sequential, functional task such as handwriting, from one session of training is a novel finding that certainly warrants further research. Since long term retention of at least one year of such acquired internal models of a novel environment has been demonstrated in non-human primates and humans (Yamamoto

et al, 2006), it would be very interesting to investigate the extent of the duration for such retention in PD.

In this study, however, we did not find any significant changes in paper-pen writing and drawing, particularly in movement size, on day 8 as compared to baseline; this is most likely due to the fact that a single session of visuomotor training may have been insufficient to mediate transfer of acquired movement amplitude increases to a functional context such as paper-pen writing. Besides, a gain reduction greater than 50 % could act as a stronger stimulus for learning that may have some carryover to a different context, i.e. paper-pen writing. Further, paper-pen writing is a highly over-learned motor skill and hence making it much harder to transfer any positive gains from an experimental context to it. Alternatively, it is also likely that visuomotor adaptation leads to acquisition of internal models that are analogous to learning use of a new tool, which can coexist with representations for other tools, i.e., paper-pen writing context, in this case. Hence, the possibility of transfer of acquired handwriting changes in visuomotor adaptation context (tool B), may not necessarily transfer to a pre-learned handwriting performance in paper-pen writing context (tool A).

Interestingly, it must be noted that we found a greater reduction in normalized jerk scores for paper-pen writing post-training in the PD as compared to healthy intervention group ($p<0.05$); however this difference between pre- and post-training scores was not significantly different from zero for the PD intervention group. Nevertheless, it is a trend that supports our earlier hypothesis about preservation of movement quality across trials mediated by adaptation to gradually introduced sensorimotor errors. It would be interesting to see if this effect persists in paper-pen writing following training and if so, for how long,

since it could find potential application in designing therapeutic interventions and functional aids for patients with PD.

Future Directions

Patients with PD commonly present with handwriting deficits such as micrographia and the results of this study thus, could provide new direction for developing novel therapies for the management of fine motor skill deficits and advance understanding of adaptive sensorimotor control in PD. Specifically, investigation of retention of experimentally acquired improvements in movement size over longer periods of times could be instrumental in developing novel therapies. This also emphasizes the importance of studying neural mechanisms underlying potential transfer of performance changes from the visuomotor adaptation paradigm to different movement categories and body segments. Also, manipulation of task demands or environmental contexts could prove to be an interesting alternative to maintain or even improve quality of performance. These manipulations could potentially enable clinical translation of research findings using virtual environments and/or training in a broader context to alleviate motor deficits in persons with movement disorders.

APPENDIX I

Health Status Questionnaire

HEALTH CHECKLIST

Page 1 of 1

Cognitive Motor Behavior Laboratory
Department of Kinesiology
University of Maryland College Park

Subject No: _____ Age: _____ Sex: M / F

Date of Birth: ____/____/_____ Date Form Completed: ____/____/_____

Directions: circle y (yes) or n (no) for each question. Please fill in blanks if you answer yes.

Y N 1. Have you ever suffered a stroke in the past?
     If yes, when? _____
     How does it affect you now? _____

Y N 2. Do you feel weakness in your limbs at times?
     If so, describe how often: _____
     How severe is the weakness? _____

Y N 3. Have you ever suffered a head injury (from a sports injury, car accident, etc.)?
     If yes, when? _____
     How does it affect you now? _____

Y N 4. Have you ever lost consciousness?   If yes, when? _____

    5. Do you suffer from any of the following:
      Y N a. High blood pressure?   If yes, since when? _____

      Y N b. Infarct Myocardium?   If yes, when? _____

      Y N c. Heart attacks?   If yes, when? _____

      Y N d. Heart operation?   If yes, when? _____

      Y N 6. Do you suffer from diabetes?   If yes, since when? _____

      Y N 7. Have you ever broken a bone?   If yes, since when? _____

      Y N 8. Do you suffer from arthritis?   If yes, since when? _____
           What part(s) of your body are affected? _____
           _____

    9. When were you first diagnosed with Parkinson's disease?_____

    10. Please list any medications (name and dosage) you currently take (use back of form, if needed).
       _____
       _____
       _____

APPENDIX II

Mini Mental State Examination

MMSE   1

Subject No: _____

Date: _____ Tester's Name: _____

Reason not asked:

1. Not administered according to criterion
2. Attempted test but discontinued because proband couldn't do it
3. Didn't attempt because seemed unlikely proband could do it
4. Proband refused
5. Tried but discontinued because proband refused
6. Sensorimotor reason made it impossible (write reason)
7. Time pressure due to proband limiting time available for testing
8. Time pressure due to proband's lack of stamina
9. Other reason (write why) _____

Test battery not done: _____

MMSE   2

	Correct	Incorrect	Not asked
1. What year is this?	1	2	3 _____
Answer:_____			
2. What season is this?	1	2	3 _____
Answer:_____			
3. What month of the year is this?	1	2	3 _____
Answer:_____			
4. What is today's date? ($\pm$ 1 day)	1	2	3 _____
Answer:_____			
5. What day of the week is this?	1	2	3 _____
Answer:_____			
6. What county are we in?	1	2	3 _____
Answer:_____			
7. What country are we in?	1	2	3 _____
Answer:_____			
8. What city/town are we in?	1	2	3 _____
Answer:_____			
9. IF AT HOME: **What is the street address of this home?** (or equivalent, e.g., name of farm) IF IN INSTITUTION: **What is the name of this hospital/building?** (or equivalent, e.g., service house)	1	2	3 _____
Answer:_____			
10. IF AT HOME: **What room are we in?** IF IN INSTITUTION: **What floor/ward of the building are we on?**	1	2	3 _____
Answer:_____			

MMSE

3

11. I am going to name three objects. After I have said all three objects, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.
"Key, toothbrush, lamp". Please repeat the 3 items for me.

	Correct	Incorrect/ Unable	Not asked
Key	1	4	5 _____
Toothbrush	2	4	
Lamp	3	4	

(Repeat as necessary until all 3 are registered, up to 5 times, but do not award points for correct responses after the first trial.)

ı **Number of Repetitions:** _____

12. **Spell the word KONST:**

(correct spelling if necessary) Yes	No	Not asked	
Correct with or without assistance?	1	2	3 _____

Now spell it backwards, please.

Write answers: 1_____ 2_____ 3_____ 4_____ 5_____   6 _____

13. **Subtract 7 from 100 and keep subtracting from what's left until I tell you to stop.**   Not asked

Write answers: 1_____ 2_____ 3_____ 4_____ 5_____   6 _____

14. **Now what were the three objects that I asked you to remember?**

	Correct	Incorrect	Not asked
Key	1	4	5 _____
Toothbrush	2	4	
Lamp	3	4	

15. **What is this called?** (Point to watch)	1	2	3 _____
16. **What is this called?** (Point to pencil)	1	2	3 _____

MMSE

	Correct	Incorrect	Not asked
17. I would like you to repeat after me: **"the students solved a demanding task".** (Allow only one trial. Write down what respondent says.)	1	2	3 _____

Answer:_____

	Correct	Incorrect	Not asked
18. Read the words on this card and then do **what it says.** (POINT TO THE DOOR) (Repeat instructions up to 3 times. If more appropriate, use POINT TO THE WINDOW)	1	2	3 _____

19. Take this paper in your left/right hand, fold the paper in half once with both hands, and put the paper down on your lap. (Do not repeat instructions. If right handed, ask to take in left hand, and vice versa.)

	Correct	Incorrect	Not asked
Takes paper	1	4	5 _____
Folds paper	2	4	5 _____
Sets paper on lap	3	4	5 _____

	Correct	Incorrect	Not asked
20. Write any complete sentence on that **piece of paper.** (Sentence must make sense. Ignore misspelling.)	1	2	3 _____

Answer:_____

	Correct	Incorrect	Not asked
21. Copy this design please. Pentagons	1	2	3 _____

	Not asked
Behavioral Observations:	2 _____

_____

_____

_____

_____

APPENDIX III

Hoehn & Yahr Rating Scale for Parkinson's disease

SUBJECT No.   DATE:

Table 2.
Modified Hoehn and Yahr Scale[11]

Stage	Description
0.0	No signs of disease
1.0	Unilateral disease
1.5	Unilateral and axial involvement
2.0	Bilateral disease, without impairment of balance
2.5	Mild bilateral disease, with recovery on pull test
3.0	Mild to moderate bilateral disease; some postural instability; physically independent
4.0	Severe disability; still able to walk or stand unassisted
5.0	Wheelchair bound or bedridden unless aided

Hoehn & Yahr Scale
Select one that describes the stage:

  0: No visible symptoms of Parkinson's disease.
  1: Symptoms confined to One-side of the body.
  2: Symptoms on Both-sides of the body-NO difficulty walking.
  3: Symptoms on Both-sides of the body-minimal difficulty walking.
  4: Symptoms on Both-sides of the body-moderate difficulty walking.
  5: Symptoms on Both-sides of the body-unable to walk.

APPENDIX IV

Unified Parkinson's disease Rating Scale

Unified Parkinson's Disease Rating Scale

	SUBJECT No:				Unit Number													
Date																		
DOPA mg/day	hrs DOPA lasts																	
		On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off
1	Mentation																
2	Thought Disorder																
3	Depression																
4	Motivation/Initiative																
	Subtotal 1–4 (maximum=16)																
5	Speech																
6	Salivation																
7	Swallowing																
8	Handwriting																
9	Cutting food																
10	Dressing																
11	Hygiene																
12	Turning in bed																
13	Falling																
14	Freezing																
15	Walking																
16	Tremor																
17	Sensory symptoms																
	Subtotal 5–17 (maximum=52)																
18	Speech																
19	Facial expression																
20	Tremor at rest: face, lips, chin																
	Hands: right																
	left																
	Feet: right																
	left																
21	Action tremor: right																
	left																
22	Rigidity: neck																
	Upper extremity: right																
	left																
	Lower extremity: right																
	left																

© WE MOVE

UPDRS 1/2

	Date	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off	On	Off
23	Finger taps: right																
	left																
24	Hand grips: right																
	left																
25	Hand pronate/supinate: right																
	left																
26	Leg agility: right																
	left																
27	Arise from chair																
28	Posture																
29	Gait																
30	Postural stability																
31	Body bradykinesia																
	Sub-total: 18–31 (maximum=108)																
	Total points: 1–31 (maximum=176)																
32	Dyskinesia (duration)																
33	Dyskinesia (disability)																
34	Dyskinesia (pain)																
35	Early morning dystonia																
36	"Offs" (predictable)																
37	"Offs" (unpredictable)																
38	"Offs" (sudden)																
39	"Offs" (duration)																
40	Anorexia, nausea, vomiting																
41	Sleep disturbance																
42	Symptomatic orthostasis																
	Blood Pressure: seated																
	supine																
	standing																
	Weight																
	Pulse: seated																
	standing																
	Name of Examiner ▶																

		Best	Worst	Best	Worst	Best	Worst	Best	Worst	Best	Worst	Best	Worst	Best	Worst	Best	Worst
	Hoehn & Yahr Stage																	
	% ADL Score (PD)																	
	% ADL (with dyskinesia)																	

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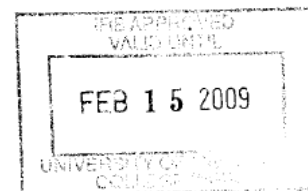
UPDRS 2/2

APPENDIX V

Informed Consent Form

INFORMED CONSENT FORM

Project Title	*Motor Adaptation in Parkinson's disease*
Why is this research being done?	*This is a research project being conducted by Dr. Jose Contreras-Vidal and Anusha Venkatakrishnan (Graduate student at the Department of Kinesiology) at the University of Maryland, College Park. We are inviting you to participate in this research because you are at least 18 years of age and/or suffer from Parkinson's disease. The purpose of this research is to investigate how aging and Parkinson's disease affect movement production and movement adaptation to changing movement conditions. The experiment is designed in a way that makes it possible to determine the influence of different task conditions on arm movements, and how these conditions are affected by Parkinson's disease and aging.*
What will I be asked to do?	*The experiment will begin with a written questionnaire that will review your health history. Participants with Parkinson's disease will be asked to provide information about your medications; and your movement abilities and disease progression will be assessed using standardized scales. After completing the questionnaire, an assessment of your cognitive and mental abilities will be performed by asking you simple questions that will test your orientation, memory, attention and language. Then, you will be seated comfortably in front of a table, and up to six surface sensors will be positioned in the following locations: between the thumb and index finger on the back of your hand, forearm, front and back of your arm and shoulder. The sensors will be attached to your skin with double-sided tape to measure the electrical activity in your arm muscles as you move the arm. Next, you will be asked to perform handwriting, drawing, and pointing movements with your dominant hand (the hand that you use for handwriting) while looking at your hand and/or at the movement of your hand linked to a cursor in a computer screen or display in front of you. Occasionally, the screen cursor may disappear as you write/draw. You will use a pen to perform the following drawing-like movements on a digitizing tablet:* ☐ *Archimedes' spiral* ☐ *Handwriting* ☐ *Controlling a screen cursor using a digitizing pen and/or computer trackball.* *A computer will store information about the position of your hand and/or arm as it is executing the motor tasks. You will be asked to come to the Cognitive Motor Neuroscience laboratory at the University of Maryland, College Park 3 times on separate days and spend about an hour for the experimental procedure in the first session and about 30 minutes in each of the following 2 sessions. The first session is training/practice for performing hand movements in a computer-based (or virtual) environment and the subsequent sessions will help us study your movement abilities in this environment. You will be provided with a compensation of $20.00 per session for your participation in this study.*

Project Title	*Motor Adaptation in Parkinson's disease*
What about confidentiality?	*We will do our best to keep your personal information confidential. To help protect your confidentiality: (1) your name will not be included on the surveys or other collected data; (2) a code will be placed on the collected data; (3) through the use of an identification key, we will be able to link your survey to your identity; and (4) only we will have access to the identification key that will be locked up in the cabinets in the 2237, HHP Building at the Department of Kinesiology. If we write a report or article about this research project, your identity will be protected to the maximum extent possible.* *This research involves making videotapes and/or taking photographs of you that can be shown at scientific meetings and for teaching purposes. (Please check whatever applicable)* *__You agree to be videotaped/photographed during your participation.* *__You do not agree to be videotaped/photographed during your participation.* *Your information may be shared with representatives of the University of Maryland, College Park or governmental authorities if you or someone else is in danger or if we are required to do so by law.*
What are the risks of this research?	*You may experience a modest degree of fatigue from the concentration required during the performance of the task and a slight discomfort from the removal of the adhesive tape. You are free to take breaks if you feel tired before continuing with the task.*
What are the benefits of this research?	*This research is not designed to help you personally, but the results may have a substantial impact in understanding the mechanisms of motor control and learning in Parkinson's disease and this will allow for providing better care to patients in the future.*
Do I have to be in this research? Can I stop participating at any time?	*Your participation in this research is completely voluntary. You may choose not to take part at all. If you decide to participate in this research, you may stop participating at any time. If you decide not to participate in this study or if you stop participating at any time, you will not be penalized or lose any benefits to which you otherwise qualify.*
Is any medical treatment available if I am injured?	*The University of Maryland does not provide any medical, hospitalization or other insurance for participants in this research study, nor will the University of Maryland provide any medical treatment or compensation for any injury sustained as a result of participation in this research study, except as required by law.*

Project Title	*Motor adaptation in Parkinson's disease*
What if I have questions?	*This research is being conducted by Dr. Jose Contreras-Vidal and Anusha Venkatakrishnan (Graduate student in the Department of Kinesiology) at the University of Maryland, College Park. If you have any questions about the research study itself, please contact Dr. Jose Contreras-Vidal at: The University of Maryland, 2363, HHP Building, 301-405-2495 or pepeum@umd.edu* *If you have questions about your rights as a research subject or wish to report a research-related injury, please contact:* **Institutional Review Board Office, University of Maryland, College Park, Maryland, 20742; (e-mail)** irb@deans.umd.edu; **(telephone) 301-405-0678** *This research has been reviewed according to the University of Maryland, College Park IRB procedures for research involving human subjects.*
Statement of Age of Subject and Consent	*Your signature indicates that:* *you are at least 18 years of age;,* *the research has been explained to you;* *your questions have been answered; and* *You freely and voluntarily choose to participate in this research project.*
Signature and Date	**NAME OF SUBJECT**	
	SIGNATURE OF SUBJECT	
	DATE	

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