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Using visual feedback to guide movement: Properties of adaptation in changing environments and Parkinson's disease

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USING VISUAL FEEDBACK TO GUIDE MOVEMENT: PROPERTIES OF ADAPTATION IN CHANGING ENVIRONMENTS AND PARKINSON'S DISEASE

by

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ABSTRACT OF THE DISSERTATION

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On a day-to-day basis we use visual information to guide the execution of our movements with great ease. The use of vision allows us to guide and modify our movements by appropriately transforming external sensory information into proper motor commands. Current literature characterizes the process of visuomotor adaptation, but fails to consider the incremental response to sensed errors that comprise a fully adaptive process. We aimed to understand the properties of the trial-by-trial transformation of sensed visual error into subsequent motor adaptation. In this thesis we further aimed to understand how visuomotor learning changes as a function of experienced environment and how it is impacted by Parkinson's disease.

Recent experiments in force learning have shown that adaptive strategies can be flexibly and readily modified according to the demands of the environment a person experiences.

In Chapter 2, we investigated the properties of visual feedback strategies in response to environments that changed daily. We introduced visual environments that could change as a function of the likelihood of experiencing a visual perturbation, or the direction of the visual perturbation bias across the workspace. By testing subjects in environments with changing statistics across several days, we were able to observe changes in the visuomotor sensitivity across environments. We found that subjects experiencing changes in visual likelihood adopted strategies very similar to those seen in force field learning. However, unlike in haptic learning, we discovered that when subjects experienced different environmental biases, adaptive sensitivity could be effected both within a single training day as well as across training days.

In Chapter 3, we investigated the properties of visuomotor adaptation in patients with Parkinson's disease. Previous experiments have suggested that patients with Parkinson's disease have impoverished visuomotor learning when compared to healthy age-matched controls. We tested two aspects of visuomotor adaptation to determine the contribution of visual feedback in Parkinson's disease: visual extent – thought to be mediated by the basal ganglia, and visual direction – thought to be cortically mediated. We found that patients with Parkinson's disease fully adapted to changes in visual direction and showed more complete adaptation compared to control subjects, but adaptation in Parkinson's disease patients was impaired during changes of visual extent. Our results confirm the idea that basal ganglia deficits can alter aspects of visuomotor adaptation. However, we have shown that part of this adaptive process remains intact, in accordance with hypotheses that state visuomotor control of direction and extent are separable processes.

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I want to dedicate this work to my dad Robert Semrau, who is one of the kindest, most understanding people I know. His continued love, friendship, and support have been so important to me, especially now in my adult life.

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Introduction

Chapter 1.

We possess the ability to generate seemingly simple movements to interact with our environment on a daily basis. While movement may seem effortless, it is in fact far more complicated, requiring the integration of information from multiple sensory modalities to achieve the desired outcome. Human motor learning is characterized by a unique flexibility that allows us to perform an infinite number of movements. We can learn to drive a car, learn to play baseball, or learn to use a computer mouse, all with relative ease. To produce these skilled movements, we depend on the integration of visual information with bodily information to plan, compute and execute movement.

When we are using a computer to run a specific program, we must navigate the mouse cursor to the appropriate desktop icon, our desired location or target. This movement requires calibration of our visual sense of the speed and position of the mouse cursor with internal motor programming that generates and guides hand and arm movements (Ghez et al., 1995). If you are using a computer and mouse that you use everyday, you are well adapted to this visuomotor relationship. When you replace the familiar mouse with a new one; the visuomotor dynamics of the new mouse may be different. For example, the ratio of cursor speed to physical mouse movement (gain) may be dissimilar from your original mouse. This can cause initial difficulty using the new mouse, resulting in increased reaction and movement time during operation. This difficulty is the result of a visuomotor mismatch between expected (old mouse) and experienced (new mouse) sensory feedback.

Conveniently, our visuomotor system is highly flexible and allows for quick learning of this new association, allowing us to become highly adept at using the new computer mouse with minimal practice. However, if you have difficulty with movement production, learning these new eye-hand coordinations may present significant difficulty. The purpose of this thesis is to investigate visuomotor relationships resulting from environmentally induced errors requiring adaptation and recalibration of the visuomotor system.

VISUOMOTOR CONTROL OF MOVEMENT

When we reach for an object in our environment it requires the visual identification of the desired target. These visual coordinates are subsequently transformed to hand-centered space in order to be translated and executed by internal motor programming (Ghez et al., 2000; Ghez et al., 2007). All of these neural computations are necessary before we can interact with our environment; without access to visual information we are unable to complete accurate and timely movements (Ghez et al., 1995). During movement execution we receive feedback from multiple sensory sources that indicates the success or failure of the movement (Wolpert et al.,1995; Paz and Vaadia, 2009). These sensory feedback errors inform future iterations of movement to the adjustments that need to be made in order to accurately execute a movement. This feedback can be proprioceptive, such as hitting your arm on a table, or visual, as in the previous computer mouse example. Each of these modes of sensory feedback provides unique information to the

production of movement. However, with the elimination of either input (Ghez et al. 1995) or a mismatch in sensory feedback (Block and Bastian 2011), movement becomes difficult.

Reaching movements require the integration of proprioception and vision; however, the properties of visual control are distinctly different from that of proprioceptive control. Proprioception relies on muscle and receptor based feedback to gauge limb position as well as input from external visual information (Goodbody and Wolpert 1999; Graziano 1999), while vision relates environmentally driven position information about limb state and object control (Sober and Sabes 2003, Sarlegna and Sainburg 2009). It has been shown that with elimination of proprioception, movement can be compensated through vision, while the reverse is not true (Ghez et al. 1995a, Ghez et al. 1995b).

PROPERTIES OF VISUOMOTOR ADAPTATION

Our ability to adapt to new visuomotor conditions allows us to acquire new skills on a short-term basis (Martin et al. 1996a, Martin et al. 1996b, Pine et al. 1997, Krakauer et al. 2000, Seidler et al. 2006), or longer term through consistent practice (Richter et al. 2002, Marinelli et al. 2010, Trempe and Proteau 2010). This adaptation is highly flexible and mediated by the nature of the visual errors that we experience in our environment (Ghahramani and Wolpert 1997, Kagerer et al. 1997). Early studies of visuomotor control utilized prism lenses to distort visuomotor relationships. These lenses acted to displace the visual world from executed motor action, typically in a lateral direction.

These studies found that when people face a new visuomotor relationship they make large initial errors, but quickly adapt over time and can accurately hit a target under the new conditions. The most profound result of these studies was that after subjects adapted and the prisms were removed, the experimenters saw significantly large errors in the opposite direction of the initial error, referred to as after-effects (Martin et al. 1996a; Martin et al. 1996b). Researchers have used visuomotor after-effects to their advantage, because they are a cardinal sign of adaptation resulting from recalibration of the visuomotor system (Hamilton and Bossom 1964).

While studies using prism glasses were introduced in the early 1960's, techniques have advanced to utilize computerized virtual environments that allow researchers to displace bodily movement from what a participant sees on a computer monitor (Ghilardi et al. 1995, Krakauer et al. 2000, Seidler et al. 2001). This new methodology has been a powerful tool for examining the integration of visual and motor information. Operating on the same scientific principles as prism glasses, computerized methods allow for greater experimental control and flexibility of visuomotor perturbations and parameters. We can now test a variety of visuomotor perturbations types (Kagerer et al. 1997, Pine et al. 1997, Gowen and Miall 2007, Messier et al. 2007) as well as change the visual perturbation on a trial-by-trial basis (Wei and Kording 2009).

TRIAL-BY-TRIAL ADAPTATION

When people learn new skills or experience novel perturbations, adaptation to these new conditions is not a discrete process. Rather, adaptation is a process that increments over time, each prior experience adding to the resulting adaptation. This idea of trial-by-trial motor adaptation is an effective way to not only examine incremental motor learning, but it also allows us to determine the magnitude of effect that single error inducing trials can have on the subsequent movements (Thoroughman and Shadmehr 2000, Scheidt et al. 2001, Thoroughman and Taylor 2005). The process of trial-by-trial adaptation has been extensively investigated in the field of haptic motor control (Thoroughman and Shadmehr 2000, Thoroughman and Taylor 2005, Fine and Thoroughman 2007), whereas little attention has been focused on this type of error transformation in the field of visuomotor control and adaptation. Recent studies have focused on the neural correlates of trial-by-trial visuomotor learning (Grafton et al. 2007), visuomotor response to random perturbations (Wei et al. 2010), and the weighting of relative visual responses and subsequent dependence on the error magnitude (Wei and Kording 2009). None of these studies have been able to make direct comparisons between properties of motor adaptation in visuomotor and proprioceptive control of movement. Importantly, visual feedback is not only used for the programming of movements, it also provides feedback regarding limb state conditions (Sober and Sabes 2003, Scheidt et al. 2005).

In Chapter 2 of this thesis, a visuomotor correlate of Fine and Thoroughman (2007), we investigate the trial-by-trial properties of visuomotor adaptation when subjects experience environments with changing statistics across several days. We were interested in the transformation of experienced visual error into adaptive sensitivity. We discovered that not only does the environment in which a person learns affect the resulting adaptive sensitivity, but that adaptive information learned in one environment can affect the outcome of adaptation in a subsequently experienced environment.

THE BASAL GANGLIA, PARKINSON'S DISEASE, AND VISUOMOTOR CONTROL

For another subject population, the ability to move and interact with their daily environments not taken for granted. Patients with Parkinson's disease (PD) have significant difficulty with movement on a daily basis that is marked by several symptoms: bradykinesia (slowness of movement), tremor, muscular rigidity, and instability of posture. These difficulties are the result of a specific loss of dopamine producing neurons within the substantia nigra, *pars compacta*; one of the nuclei comprising the basal ganglia (Albin et al. 1989, Mink 1996).

The basal ganglia are traditionally thought of as structures necessary for the production and maintenance of movement. Motor behavior is thought to be modulated by activity within the basal ganglia by allowing wanted signals through, while suppressing unwanted motor signals (Mink 1996). Changes to the balance of this gating mechanism can be seen

most profoundly in movement disorders resulting from abnormalities in the basal ganglia such as PD and Huntington's disease that exhibit hypokinesia (too little movement) or hyperkinesia (too much movement), respectively (Albin et al. 1989).

In addition to being involved in the production and maintenance of movement, the basal ganglia have been shown to have significant involvement in motor sequence learning (Lehericy et al. 2005), procedural learning (Hikosaka et al. 1999), and the processing of visuomotor control and adaptation (Graybiel et al. 1994, Nakahara et al. 2001, Contreras-Vidal et al. 2003, Krakauer et al. 2004, Seidler et al. 2006). Researchers have speculated that the basal ganglia are involved in the trial-by-trial processing of sensorimotor error (Brown et al. 2006, Kempf et al. 2007). This speculation has lead to the belief that learning new visuomotor transformations can be impaired in PD as a result of deficient basal ganglia function (Contreras-Vidal et al. 2003, Fernandez-Ruiz et al. 2003, Paquet et al. 2008, Venkatakrishnan et al. 2011).

Learning these new visuomotor transformations for the production and execution of movements relies on the integration of two independent components of movement planning (Ghez et al. 1991, Pine et al. 1997, Desmurget et al. 2003). These movement components are a separable vectorial process in which movements are planned as a function of movement direction and a function of movement extent. The idea that reaching movements require independent calculation of extent and direction is a widely accepted idea, and is supported by behavioral data (Pine et al. 1996, Krakauer et al. 2000), as well as neuroanatomical data (Krakauer et al. 2004). Differences in adaptation

to each component manifest behaviorally as differences in time scales of adaptation (Pine et al. 1996), differences in generalization patterns after adaptation (Krakauer et al. 2000), and differences in movement variability (Gordon et al. 1994).

The neuroanatomical correlates of visuomotor adaptation reinforce the belief that planning of extent and direction are separable processes. During the early phase of adaptation neural activation has correlated to separate neuroanatomical structures depending on what type of visual perturbation subjects experience. Cortical areas have been correlated to adaptation to changes in visual direction, while subcortical areas including the basal ganglia, have been correlated to adaptation to changes in visual extent (Ghilardi et al. 2000, Krakauer et al. 2006). However, another group studying neural correlates of visuomotor adaptation has observed neural activation of the basal ganglia in response to learning visuomotor perturbations of direction (Seidler et al. 2006). Substantial evidence exists to suggest that the basal ganglia play a major role in adaptation to new visuomotor environments; however it is unclear whether or not that role is specific to particular types of visual perturbations.

Current studies suggest that patients with PD have difficulty with sensorimotor integration requiring the combination of motor control with other sensory signals. Difficulties utilizing proprioceptive feedback to maintain posture (Brown et al. 2006), estimate limb and joint position (Zia et al. 2000, Contreras-Vidal and Gold 2004), as well as incorporating proprioceptive feedback into visual tasks (Schettino et al. 2006) have specifically been noted as sensorimotor deficits.

These sensorimotor integration deficits have been thought to specifically affect visuomotor adaptation in PD patients. However, the range of visuomotor impairments is not agreed upon. These impairments have been described as overall difficulty with adaptation with impaired after-effects (Contreras-Vidal and Buch 2003), less robust after-effects post-adaptation (Fernandez-Ruiz et al. 2003) or no impairment during the adaptation process whatsoever (Agostino et al. 1996, Marinelli et al. 2009). It is obvious that a large disparity exists in the current literature that fails to characterize how neurodegeneration in PD affects visuomotor ability to adapt to new visuomotor environments.

In Chapter 3 of this thesis, we investigate the trial-by-trial properties of visuomotor control and adaptation in patients with Parkinson's disease. Additionally we aimed to determine if PD patients exhibited deficits in adaptation to visual perturbations of extent and direction. We discovered that PD patients have intact adaptation for perturbations of direction, with more complete adaptation than control subjects. However, adaptation to changes in visual extent were impaired. Our results suggest that basal ganglia functionality is imperative to intact visuomotor adaptation to perturbations that affect reach magnitude.

REFERENCES

Agostino R, Sanes JN, and Hallett M. Motor skill learning in Parkinson's disease. J Neurol Sci 139: 218-226, 1996.

Albin RL, Young AB, and Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 12: 366-375, 1989.

Block HJ, and Bastian AJ. Sensory reweighting in targeted reaching: effects of conscious effort, error history, and target salience. J Neurophysiol 103: 206-217, 2011.

Brown LA, Cooper SA, Doan JB, Dickin DC, Whishaw IQ, Pellis SM, and Suchowersky O. Parkinsonian deficits in sensory integration for postural control: temporal response to changes in visual input. Parkinsonism Relat Disord 12: 376-381, 2006.

Brown P, Chen CC, Wang S, Kuhn AA, Doyle L, Yarrow K, Nuttin B, Stein J, and Aziz T. Involvement of human basal ganglia in offline feedback control of voluntary movement. Curr Biol 16: 2129-2134, 2006.

Contreras-Vidal JL, and Buch ER. Effects of Parkinson's disease on visuomotor adaptation. Exp Brain Res 150: 25-32, 2003.

Contreras-Vidal JL, and Gold DR. Dynamic estimation of hand position is abnormal in Parkinson's disease. Parkinsonism Relat Disord 10: 501-506, 2004.

Desmurget M, Grafton ST, Vindras P, Grea H, and Turner RS. Basal ganglia network mediates the control of movement amplitude. Exp Brain Res 153: 197-209, 2003.

Fernandez-Ruiz J, Diaz R, Hall-Haro C, Vergara P, Mischner J, Nunez L, Drucker-Colin R, Ochoa A, and Alonso ME. Normal prism adaptation but reduced after-effect in basal ganglia disorders using a throwing task. Eur J Neurosci 18: 689-694, 2003.

Fine MS, and Thoroughman KA. Trial-by-trial transformation of error into sensorimotor adaptation changes with environmental dynamics. J Neurophysiol 98: 1392-1404, 2007.

Ghahramani Z, and Wolpert DM. Modular decomposition in visuomotor learning. Nature 386: 392-395, 1997.

Ghez C, Gordon J., Ghilardi M.F., Sainburg R. Contributions of vision and propriocepton to accuracy in limb movements. Cambridge, MA: MIT Press, 1995a.

Ghez C, Krakauer JW, Sainburg R, Ghilardi MF. Spatial representations and internal models of limb dynamics in motor learning. Cambridge, MA: MIT Press, 2000.

Ghez C, Gordon J, and Ghilardi MF. Impairments of reaching movements in patients without proprioception. II. Effects of visual information on accuracy. J Neurophysiol 73: 361-372, 1995b.

Ghez C, Hening W, and Gordon J. Organization of voluntary movement. Curr Opin Neurobiol 1: 664-671, 1991.

Ghez C, Scheidt R, and Heijink H. Different learned coordinate frames for planning trajectories and final positions in reaching. J Neurophysiol 98: 3614-3626, 2007.

Ghilardi MF, Alberoni M, Rossi M, Franceschi M, Mariani C, and Fazio F. Visual feedback has differential effects on reaching movements in Parkinson's and Alzheimer's disease. Brain Res 876: 112-123, 2000.

Ghilardi MF, Gordon J, and Ghez C. Learning a visuomotor transformation in a local area of work space produces directional biases in other areas. J Neurophysiol 73: 2535-2539, 1995.

Goodbody SJ, and Wolpert DM. The effect of visuomotor displacements on arm movement paths. Exp Brain Res 127: 213-223, 1999.

Gordon J, Ghilardi MF, and Ghez C. Accuracy of planar reaching movements. I. Independence of direction and extent variability. Exp Brain Res 99: 97-111, 1994.

Gowen E, and Miall RC. Differentiation between external and internal cuing: an fMRI study comparing tracing with drawing. Neuroimage 36: 396-410, 2007.

Grafton ST, Schmitt P, Van Horn J, and Diedrichsen J. Neural substrates of visuomotor learning based on improved feedback control and prediction. Neuroimage 39: 1383-1395, 2008.

Graybiel AM, Aosaki T, Flaherty AW, and Kimura M. The basal ganglia and adaptive motor control. Science 265: 1826-1831, 1994.

Graziano MS. Where is my arm? The relative role of vision and proprioception in the neuronal representation of limb position. Proc Natl Acad Sci U S A 96: 10418-10421, 1999.

Hamilton CR, and Bossom J. Decay of Prism Aftereffects. J Exp Psychol 67: 148-150, 1964.

Hikosaka O, Nakahara H, Rand MK, Sakai K, Lu X, Nakamura K, Miyachi S, and Doya K. Parallel neural networks for learning sequential procedures. Trends Neurosci 22: 464-471, 1999.

Kagerer FA, Contreras-Vidal JL, and Stelmach GE. Adaptation to gradual as compared with sudden visuo-motor distortions. Exp Brain Res 115: 557-561, 1997.

Kempf F, Brucke C, Kuhn AA, Schneider GH, Kupsch A, Chen CC, Androulidakis AG, Wang S, Vandenberghe W, Nuttin B, Aziz T, and Brown P. Modulation by dopamine of human basal ganglia involvement in feedback control of movement. Curr Biol 17: R587-589, 2007.

Krakauer JW, Ghilardi MF, Mentis M, Barnes A, Veytsman M, Eidelberg D, and Ghez C. Differential cortical and subcortical activations in learning rotations and gains for reaching: a PET study. J Neurophysiol 91: 924-933, 2004.

Krakauer JW, Pine ZM, Ghilardi MF, and Ghez C. Learning of visuomotor transformations for vectorial planning of reaching trajectories. J Neurosci 20: 8916-8924, 2000.

Lehericy S, Benali H, Van de Moortele PF, Pelegrini-Issac M, Waechter T, Ugurbil K, and Doyon J. Distinct basal ganglia territories are engaged in early and advanced motor sequence learning. Proc Natl Acad Sci U S A 102: 12566-12571, 2005.

Marinelli L, Crupi D, Di Rocco A, Bove M, Eidelberg D, Abbruzzese G, and Ghilardi MF. Learning and consolidation of visuo-motor adaptation in Parkinson's disease. Parkinsonism Relat Disord 15: 6-11, 2009.

Martin TA, Keating JG, Goodkin HP, Bastian AJ, and Thach WT. Throwing while looking through prisms. I. Focal olivocerebellar lesions impair adaptation. Brain 119 (Pt 4): 1183-1198, 1996a.

Martin TA, Keating JG, Goodkin HP, Bastian AJ, and Thach WT. Throwing while looking through prisms. II. Specificity and storage of multiple gaze-throw calibrations. Brain 119 (Pt 4): 1199-1211, 1996b.

Messier J, Adamovich S, Jack D, Hening W, Sage J, and Poizner H. Visuomotor learning in immersive 3D virtual reality in Parkinson's disease and in aging. Exp Brain Res 179: 457-474, 2007.

Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 50: 381-425, 1996.

Nakahara H, Doya K, and Hikosaka O. Parallel cortico-basal ganglia mechanisms for acquisition and execution of visuomotor sequences - a computational approach. J Cogn Neurosci 13: 626-647, 2001.

Paquet F, Bedard MA, Levesque M, Tremblay PL, Lemay M, Blanchet PJ, Scherzer P, Chouinard S, and Filion J. Sensorimotor adaptation in Parkinson's disease: evidence for a dopamine dependent remapping disturbance. Exp Brain Res 185: 227-236, 2008.

Paz R, and Vaadia E. Learning from learning: what can visuomotor adaptations tell us about the neuronal representation of movement? Adv Exp Med Biol 629: 221-242, 2009.

Pine ZM, Krakauer JW, Gordon J, and Ghez C. Learning of scaling factors and reference axes for reaching movements. Neuroreport 7: 2357-2361, 1996.

Richter H, Magnusson S, Imamura K, Fredrikson M, Okura M, Watanabe Y, and Langstrom B. Long-term adaptation to prism-induced inversion of the retinal images. Exp Brain Res 144: 445-457, 2002.

Sarlegna FR, and Sainburg RL. The roles of vision and proprioception in the planning of reaching movements. Adv Exp Med Biol 629: 317-335, 2009.

Scheidt RA, Conditt MA, Secco EL, and Mussa-Ivaldi FA. Interaction of visual and proprioceptive feedback during adaptation of human reaching movements. J Neurophysiol 93: 3200-3213, 2005.

Scheidt RA, Dingwell JB, and Mussa-Ivaldi FA. Learning to move amid uncertainty. J Neurophysiol 86: 971-985, 2001.

Schettino LF, Adamovich SV, Hening W, Tunik E, Sage J, and Poizner H. Hand preshaping in Parkinson's disease: effects of visual feedback and medication state. Exp Brain Res 168: 186-202, 2006.

Seidler RD, Bloomberg JJ, and Stelmach GE. Context-dependent arm pointing adaptation. Behav Brain Res 119: 155-166, 2001.

Seidler RD, Noll DC, and Chintalapati P. Bilateral basal ganglia activation associated with sensorimotor adaptation. Exp Brain Res 175: 544-555, 2006.

Seidler RD, Noll DC, and Chintalapati P. Bilateral basal ganglia activation associated with sensorimotor adaptation. Exp Brain Res 175: 544-555, 2006.

Sober SJ, and Sabes PN. Multisensory integration during motor planning. J Neurosci 23: 6982-6992, 2003.

Thoroughman KA, and Shadmehr R. Learning of action through adaptive combination of motor primitives. Nature 407: 742-747, 2000.

Thoroughman KA, and Taylor JA. Rapid reshaping of human motor generalization. J Neurosci 25: 8948-8953, 2005.

Trempe M, and Proteau L. Distinct consolidation outcomes in a visuomotor adaptation task: Off-line leaning and persistent after-effect. Brain Cogn 73: 135-145, 2010.

Venkatakrishnan A, Banquet JP, Burnod Y, and Contreras-Vidal JL. Parkinson's disease differentially affects adaptation to gradual as compared to sudden visuomotor distortions. Hum Mov Sci 2011.

Wei K, and Kording K. Relevance of error: what drives motor adaptation? J Neurophysiol 101: 655-664, 2009.

Wei K, Wert D, and Kording K. The nervous system uses nonspecific motor learning in response to random perturbations of varying nature. J Neurophysiol 104: 3053-3063, 2010.

Wolpert DM, Ghahramani Z, and Jordan MI. An internal model for sensorimotor integration. Science 269: 1880-1882, 1995.

Zia S, Cody F, and O'Boyle D. Joint position sense is impaired by Parkinson's disease. Ann Neurol 47: 218-228, 2000.

Chapter 2.

Environmental experience within and across training days determines the strength of human visuomotor adaptation

This chapter contains the manuscript:

Semrau JA, Daitch AL, and Thoroughman KA. Experienced environmental dynamics influence both immediate and eventual adaptive strategy to visuomotor perturbations.

ABSTRACT

The use of vision allows us to guide and modify our movements by appropriately transforming external sensory information into proper motor commands. We investigated how people learned visuomotor transformations in different visual feedback environments. These environments presented perturbations of visual sense of movement direction. Across experiments and training days, we altered the likelihood of visual perturbation occurrence and the distribution of sign and magnitude of visual perturbation angles. We then observed how transformation of sensed error into incremental adaptation depended on visual perturbation angle and on environmental experience. We found that environmental context affected adaptive responses within a day and across days. The across-day effect was profound enough that people exhibited very weak or very strong adaptive sensitivity to identical stimuli, dependent solely on prior days' experience. We conclude that trial-by-trial adaptation to visual feedback is not fixed, but dependent on environmental experiences on both short and long time scales.

INTRODUCTION

Human subjects can easily adapt to changing visual feedback and task demands in motor behavior. We make constant adjustments to eye-hand coordination when we drive a car, play sports or reach for objects in our environment. Previous studies have investigated the mechanisms behind visuomotor adaptation using prism glasses to displace vision from hand position (Hamilton and Bossom 1964; Fernandez and Ruiz 1999; Fiorentini et al. 1972). These studies demonstrated that subjects were very good at adapting to the new visual feedback conditions while wearing prism glasses, but when the glasses were removed, subjects overthrew the target in the opposite direction of the initial error (Martin et al. 1996). More recent experiments have used computers to produce a greater variety of visual perturbations. In order to examine the effects of altered feedback, experimenters rotated the displacement of cursor feedback from the true hand path (Ghilardi et al. 1995; Pine et al. 1996; Krakauer et al. 2004). Subjects that adapted to the rotated feedback generated substantial aftereffects after removal of the perturbation (Krakauer et al. 2000; Seidler et al. 2006). While these studies elucidate how altered feedback of the visuomotor system can lead to short-term recalibration of eye-hand coordination, they failed to consider how the visuomotor system compensates on a shorter trial-by-trial time scale.

Trial-by-trial learning has generated a useful and unique perspective that allows for examination of how sensorimotor error is transferred from one movement to the next (Thoroughman and Shadmehr 2000; Scheidt et al. 2001; Thoroughman and Taylor 2005).

Examining adaptation on a trial-by-trial basis allows for understanding how individually sensed errors are transformed into an incrementally adaptive process. In addition, these trial-by-trial processes are far closer to real-time neurophysiological signals than adaptation across hundreds of movements. By investigating these properties of the visuomotor system, we can come closer to understanding how the brain computes error and how that error is transferred across individual movements.

Recently, we have found that people are capable of changing their adaptive strategy depending on the type of environment that they experience (Fine and Thoroughman 2007; Thoroughman et al. 2007). These studies induced adaptation using robotic manipulanda that exert force pulses (Fine and Thoroughman 2006) and viscous forces (Fine and Thoroughman 2007). In order to gain a better understanding of how visuomotor adaptation occurs, we aim to characterize trial-by-trial sensorimotor transformations used to incrementally reduce visuomotor error.

We studied how visuomotor learning changes as a function of environment in human subjects. In these experiments, we hypothesized that, as in our haptic learning studies, visuomotor learning strategies would change as a function of the statistics of visual feedback perturbations that subjects experienced. Twenty-four subjects (two groups of 12 subjects) made 10 cm reaching movements in a virtual reality environment where visual feedback could be varied on a trial-by-trial basis. Subjects performed one of two experiments: the first experiment changed the likelihood of experiencing a visual rotation across days; the second experiment changed the directional bias of visual rotations across

days. We analyzed the trial-by-trial behavior for each experiment and determined that visuomotor trial-by-trial adaptation was dependent on the characteristics of the environment in which the subject was learning on a particular day and on previous days. The latter result surprisingly suggests that the elemental transformation of error into adaptation is sensitive to experience on short and long time scales.

METHODS

Twenty-four right-handed young adult subjects made free, unsupported movements in two separate experiments. In both experiments, subjects experienced a virtual reality environment, in which hand movement was monitored through a Flock of Birds position sensor (Ascension Technology Corporation, Milton, VT) grasped in the right hand by the subject (Fig. 2.1). In the Likelihood Experiment, we altered the likelihood of the visual rotations (Fig. 2.2, *A*-*C*), and in the Bias Experiment, we changed the distribution of the visual rotations (Fig. 2.2, *D*-*F*).

Subjects

Twelve participants for the Likelihood Experiment ranged in age from 18 to 35 years old with an average and standard deviation (SD) of 23.25 ± 6.18 (8 male, 4 female); twelve participants for the Bias Experiment ranged in age from 22 to 33 with an average and SD

of 25.75 ± 2.77 (2 male, 10 female). All protocols were approved by the Washington University Human Research Protection Office (HRPO).

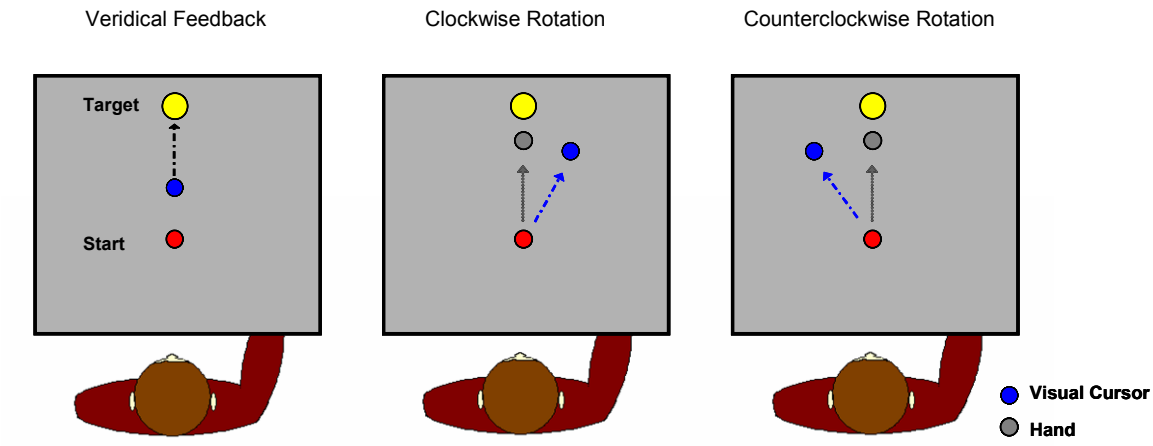

Figure 2.1: Schematic of the virtual reality set up used to generate visual feedback. Subjects experienced veridical feedback where the visual cursor directly represented the position of the hand, a clockwise visual rotation where the visual cursor is rotated off the subjects' hand trajectory to the right, and a counterclockwise visual rotation where the visual cursor is rotated off the subjects' hand trajectory to the left.

Task

Subjects viewed the virtual environment through a half-silvered mirror that reflected a monitor display of the environment. The mirror and the dark room obstructed the subjects' vision of their hand and arm, so subjects received visual feedback solely from the monitor (Fig. 2.1). Subjects stood on a platform and stabilized their head with a chin rest mounted on the mirror. The platform was set to a height where subjects could hold their arm, elbow bent, at a comfortable 90° angle. Subjects performed 6 sets of 60 (total

360) unsupported arm movements on each day, allowing for rest time between sets to counter arm fatigue.

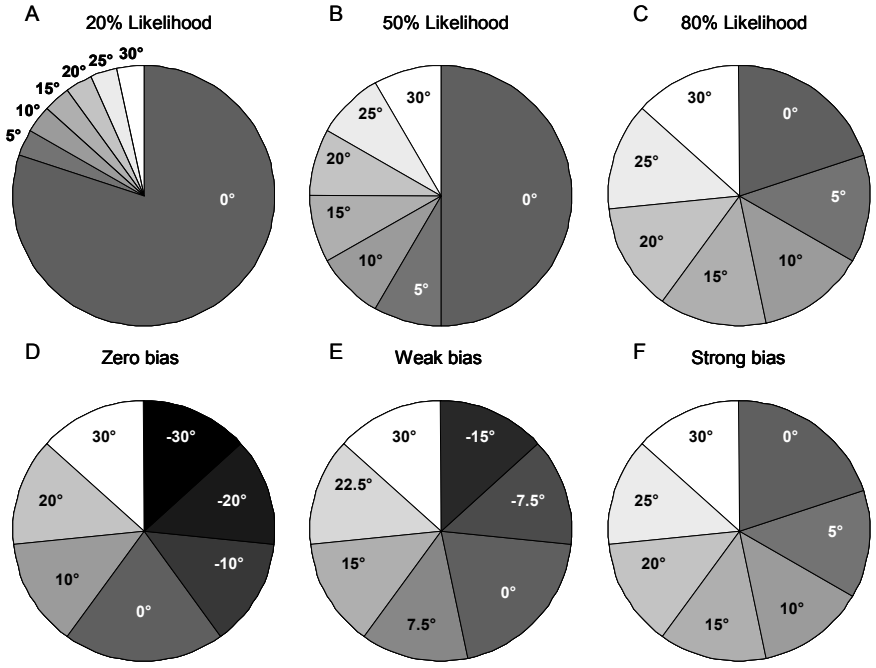

Figure 2.2: Distribution of rotations for the Likelihood Experiment (*A*-*C*), and the Bias Experiment (*D*-*F*). Subjects in the Likelihood Experiment experienced variations in the likelihood of experiencing a visual rotation across days, so that subjects experienced rotations, *A*: 20%, *B*: 50%, *C*: 80% of the time. Subjects in the Bias Experiment experienced changes in the distribution of visual rotations across the workspace that varied from *D*: unbiased (zero bias), *E*: weakly biased to the left (weak bias), or *F*: strongly biased to the left (strong bias).

The task was to begin at a start position (a red sphere) and make a 10 cm reach, directly away from the torso in the horizontal plane, to a second sphere (yellow). A movement of this size is akin to everyday tasks, such as using a hair brush or making movements with a computer mouse. Subjects were to make outward reaching movements within 500 ms ± 50 ms. If subjects satisfied this condition, the yellow sphere would turn green; if subjects moved slower than 550 ms, the target turned blue; and if the subject moved faster than

450 ms, the target would turn red. The experimenter instructed the subject to "get as many green targets as possible." After the outward reach, subjects returned to the start position at their own pace. Subjects had full visual feedback throughout the outward portion of the movement, but during the return, visual feedback was eliminated until subjects were within a 3 cm radius of the start target, where visual feedback was presented as experienced initially in that particular trial.

All subjects performed a four day experiment. On the first day of the experiment, subjects experienced a baseline training condition where they received veridical feedback, where visual cursor position displayed true hand position. On the three subsequent days, subjects received altered visual feedback, where the position of the visual cursor was rotated with the following positional displacement:

$$\begin{aligned} x' &= x\cos\theta - y\sin\theta \\ y' &= x\sin\theta + y\cos\theta \end{aligned} \tag{2.1}$$

where x and y are hand coordinates, θ is the angle of rotation, and x' and y' are the resulting transformed visual coordinates. The center of rotation coincided with the start position. For both experiments the perturbation angle (θ) changed on a trial-by-trial basis, beginning with the presentation of the target sphere.

In the Likelihood Experiment, subjects experienced the baseline condition on day 1, followed by three subsequent test days. On each of the test days, the likelihood of experiencing a visual rotation was varied across test days. The test conditions on the three test days presented subjects with visual rotations [$\theta \in \{30^\circ, 25^\circ, 20^\circ, 15^\circ, 10^\circ, 5^\circ,$

0º}]. For each of the tests (days 2-4), subjects were trained in visually perturbing environments where they experienced non-zero cursor rotations during 20%, 50%, or 80% of the trials (Fig. 2.2, *A*-*C*). The order of visual rotations for each test day was chosen pseudo-randomly and presented identically to all subjects.

In the Bias Experiment, subjects experienced the veridical baseline condition on day 1, followed by three subsequent test days. Test conditions on the three subsequent test days presented subjects with visual environments that all had equal likelihood of experiencing a rotation (80%), but varied in the bias of the rotation distribution. The three test days were unbiased (zero bias), weakly biased to the left side of the workspace (weak bias), or strongly biased to the left side of the workspace (strong bias). In the zero bias condition each of the angles of visual cursor rotation was drawn from a distribution [$\theta \in$ {30º, 20º, 10º, 0º, -10º, -20º, -30º}], where there was an equal chance that a subject received a clockwise cursor rotation or a counterclockwise cursor rotation. The distribution of the weak bias condition [$\theta \in$ {30º, 22.5º, 15º, 7.5º, 0º, -7.5º, -15º}] was weakly biased towards counterclockwise rotations; and the distribution of the strong bias condition (identical to the 80% likelihood condition) [$\theta \in$ {30º, 25º, 20º, 15º, 10º, 5º, 0º}] was strongly biased towards counterclockwise rotations and contained no clockwise rotations (Fig. 2.2, *D*-*F*). The order of visual rotations for each test day in both experiments was chosen pseudo-randomly and presented identically to all subjects.

The order of presentation of test days was shuffled in each experiment using a Latin square approach in order to counterbalance any across day learning effects. This ensured that each possible test day combination was represented twice in each experiment.

Analysis

In each of our experiments, our goal was to understand how single trial errors influenced predictive control of subsequent movements. The overall movement generated by subjects resulted from a combination of feedback and predictive control. In order to analyze these movements we employed two techniques, subtraction of full movement trajectories (Triplet analysis) and state space modeling, to identify and remove feedback components to isolate and quantify predictive control. We used perpendicular displacement at position at peak speed as a scalar metric to evaluate visuomotor adaptation. This measure is a quantitative assessment of the feedforward or predictive control of movement (Thoroughman and Shadmehr, 2000).

Triplet Analysis

Our first analysis implemented a qualitative metric for full trajectory adaptation. The goal of this analysis was to determine how feedback obtained from the previous movement was applied to the next movement. To complete this analysis we averaged full cursor trajectories across all subjects, and computed a subtraction to examine the predictive portion of the trajectory: $triplet_n = movement_{n+1} - movement_{n-1}$. To remove

the effect of feedback control induced by individual rotation strengths (Fig. 2.3, *A*), we subtracted the mean cursor response corresponding to the rotation strengths experienced on movement *n-1* and movement *n+1*, (Fig. 2.3, *B*). Lastly, we subtracted the mean adjusted movement *n-1* from mean adjusted movement *n+1* to identify the effect of the perturbation in movement *n* on movement *n+1*.

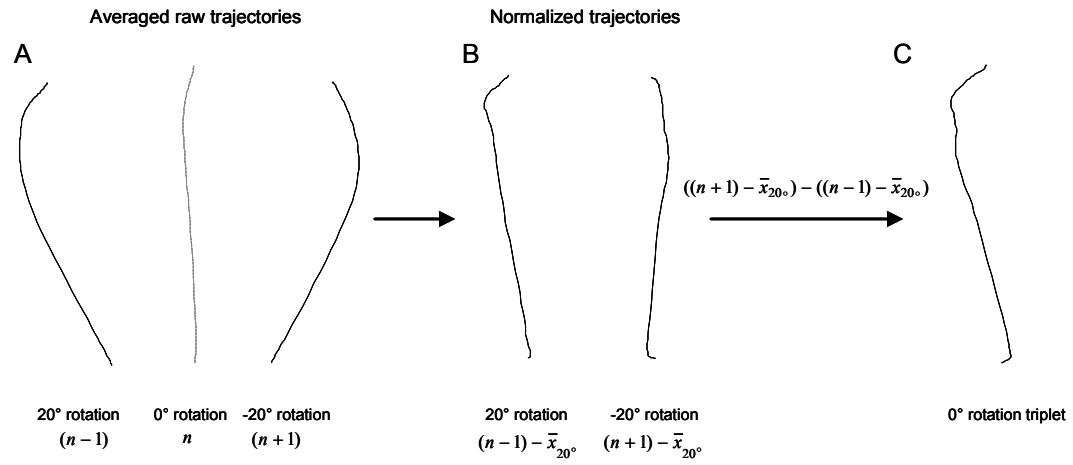

Figure 2.3: Triplet analysis: *A*: Cursor trajectories as viewed by the participant, *B*: mean subtracted trajectories, *C*: Resulting trajectories after (*n*+1)-(*n*-1) triplet subtraction.

We reduced the data and tested hypotheses by examining adaptation of mid-movement hand position; which was identified as displacement of the hand position perpendicular to the target direction at the time of peak speed. These scalars were averaged and subtracted as described above to calculate the dependence of adaptation on perturbation strength. Linear fits were performed to calculate slope of perpendicular displacement change as a function of rotation strength. Slopes were calculated for each of these adaptation functions and tested for significance across bias and likelihood conditions.

State-space Analysis

We also analyzed adaptation using a state-space model (similar to the one described in Fine and Thoroughman 2007). The two equations of the state-space model parameterize how error within a movement and how adaptation across movements depend on perturbation strength.

$$\begin{aligned} x_n &= D(R_n - \hat{R}_n) \\ \hat{R}_{n+1} &= A * \hat{R}_n + \vec{S}(i) \end{aligned} \tag{2.2}$$

The hidden state of the model, $\hat{R}$, represents the subjects' expectation of the visual rotation. The model output (x) represents the movement error and depends on the scalar parameter D and the difference between the actual rotation value on a single trial (R_n) and the subjects' expectation of rotation $(\hat{R}_n)$. The updated expectation of rotation $(\hat{R}_{n+1})$ on the next movement depended on two terms: multiplying the previous modeled estimation by a scalar "forgetting" factor A, and a sensitivity vector $\vec{S}$ (1 x 7) which parameterizes how adaptation depends on each visual rotation strength. Each component of the sensitivity vector corresponded to a rotation strength; for each particular movement, i indexes a particular perturbation type, including a component for the zero degree (veridical) condition.

We used the Gauss-Jordan method to optimize for *D, A,* and $\bar{S}$ that minimized the square-difference between predicted and actual participant performance (Fine and Thoroughman 2007). The model-generated response to perturbations relied on all of these parameters, so we used the best-fitting parameters to construct a generative model. We used this model to transform a time-series of perturbation strengths into movement error (as in Scheidt et al. 2001). We then repeated our triplet analysis (detailed above) on this generated movement error to create a sensitivity metric. We then bootstrapped (described below) triplets of model output (*x*) to determine significance.

Model performance was evaluated by computing variance accounted for (VAF). VAF was calculated as a function of the residual error (model – data) to original data error.

$$VAF = 1 - \frac{\sigma^2_{residual}}{\sigma^2_{data}} \tag{2.3}$$

We observed that our model accounted for over 98% of the variance observed in each of the six original data conditions, with small amounts of residual error (RE). (Residuals error (cm) Likelihood: 20% = 0.0121, 50% = 0.0109, 80% = 0.0119; Bias: zero = 0.0195, weak = 0.0217, strong = 0.0121).

Statistical significance

We tested statistical significance using standard t-tests, repeated measures ANOVA, mixed effects ANOVA, and bootstrapping (to calculate significance within a group or across conditions). A repeated measures ANOVA was used to analyze statistical significance between experienced test conditions. A mixed effects ANOVA was used to

analyze interactions between test day experienced and the order in which subjects experienced test days. Tukey post-hoc tests were completed for all ANOVAs to determine level of significance.

The bootstrap was used to identify whether a single group had a summary metric significantly different than zero. To compute the bootstrap we randomly selected a subject from a pool of 12 subjects, then replaced that subject and selected again to build a resampled group of 12 subjects. We then averaged the magnitude of subject response across our resampled group. From this resampled group data we then computed sensitivities ($\vec{S}$) as described above for our state-space model. In order to calculate adaptation, we subtracted the movements before and after each perturbation type to obtain a value of the strength of induced adaptation. These calculations were then repeated 1,000 times and performed linear fits on the resulting sensitivities to calculate 1,000 slope values. With these 1,000 slope values we then sorted the distributions of the resulting slope values to obtain our p values and 95% confidence intervals (Efron and Tibshirani 1998).

All metric ranges indicate 95% confidence intervals of the mean.

RESULTS

We observed that subjects experiencing changes in likelihood distribution adopted adaptive strategies that scaled with the magnitude and likelihood of the experienced rotation. In contrast when we varied the distribution of bias across testing days, we observed that adaptive sensitivity not only depended on what type of visual environment the subject experienced on that immediate testing day, but could also be influenced by adaptive strategies learned in prior days' environments.

Likelihood Experiment Results – Effects of Likelihood

The first group of 12 subjects experienced visual perturbations of the same counterclockwise rotation but with varying likelihoods (Fig. 2.2, *A*-*C*). We averaged individual cursor trajectories across all subjects for each visual rotation strength to characterize the central tendency for group behavior during each test day (Fig. 2.4, *A*-*C*). This average revealed that subjects experienced kinematic errors that scaled with the magnitude of the visual rotation. We then calculated full trajectory triplet adaptation by subtracting the full trajectory before and after a single movement. These responses were then averaged across subjects and rotation strengths for each experimental day (Fig. 2.5, *A*-*C*). We observe that a change in counterclockwise rotations elicited a change of response in the clockwise direction from subjects in all three conditions, but as we increased likelihood from 20% to 80%, subjects became more sensitive to individual rotation strengths, as shown by the clustering of adaptive hand trajectories in the 20% likelihood condition and the splaying of hand trajectories in the 80% likelihood condition (Fig. 2.5, *A*-*C*).

Mid-movement adaptation was calculated using triplet analysis of perpendicular displacement at peak speed (Fig. 2.6). By performing a linear fit for each likelihood condition (mean slope ± CI: 20%: 0.0049 ± 0.0015; 50%: 0.0061 ± 0.0017; 80%

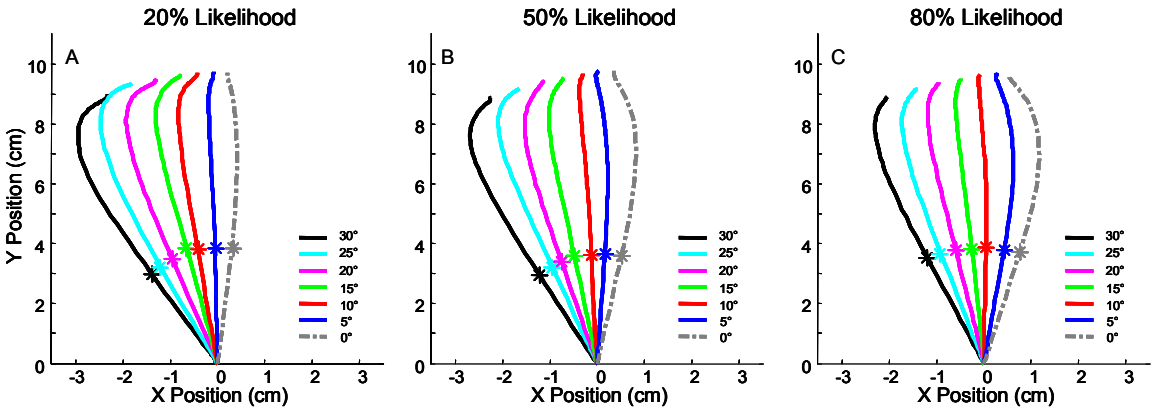

Figure 2.4: Visual cursor trajectories averaged across all movements and subjects for individual visual rotation strengths as a function of likelihood. Asterisks indicate the average position at peak speed for each visual rotation strength.

likelihood: 0.0089 ± 0.0021) we found that the slope changed significantly as a function of test day experienced (repeated measures ANOVA, $p = 0.004$). A tukey post-hoc analysis revealed a significant difference between 20% and 80% likelihood ($p < 0.05$) and non-significant differences between 50% and 80% likelihood ($p > 0.05$), and 20% and 50% likelihood ($p > 0.05$).

To increase the sensitivity of our measurements we utilized a state-space model to quantify trial-by-trial adaptation. The main advantage of using this model is that this method of system identification utilizes the full history of trial-by-trial movements experienced by subjects, taking into account all movements that subjects experienced up to that time point. Processing the full history of movements through the state-space equation allows for precise identification of sensitivity.

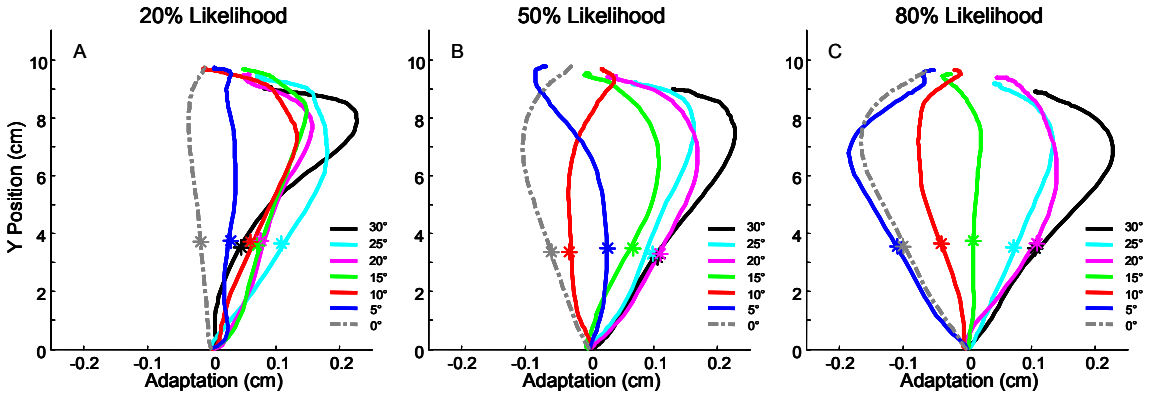

Figure 2.5: Full trajectory adaptation for subjects experiencing visual rotations. Adaptation was calculated as the difference in displacement before and after a single movement. Adaptation is shown to be increasingly proportional as subjects experience a greater likelihood of visual rotations from 20% likelihood to 50% to 80% of the time. Asterisks indicate the location of the average position at peak speed.

We found the parameters *D, A,* and $\vec{S}$ that best fit our data. Since the evolution of error depended on all three parameters (*Eq.* 2.2), we generated a time series of error using the intact model and calculated a triplet analysis parallel to our analysis of the subject data. When we performed this analysis across all 12 subjects, we observed significant differences between 20% (slope: 0.0050 ± 0.0014) and 80% likelihood (slope: 0.0077 ± 0.0021), and 50% (slope: = 0.0060 ± 0.0016) and 80% likelihood (bootstrap: p = 0.009, p = 0.008, respectively). We did not observe a significant difference between 20% and 50% likelihood.

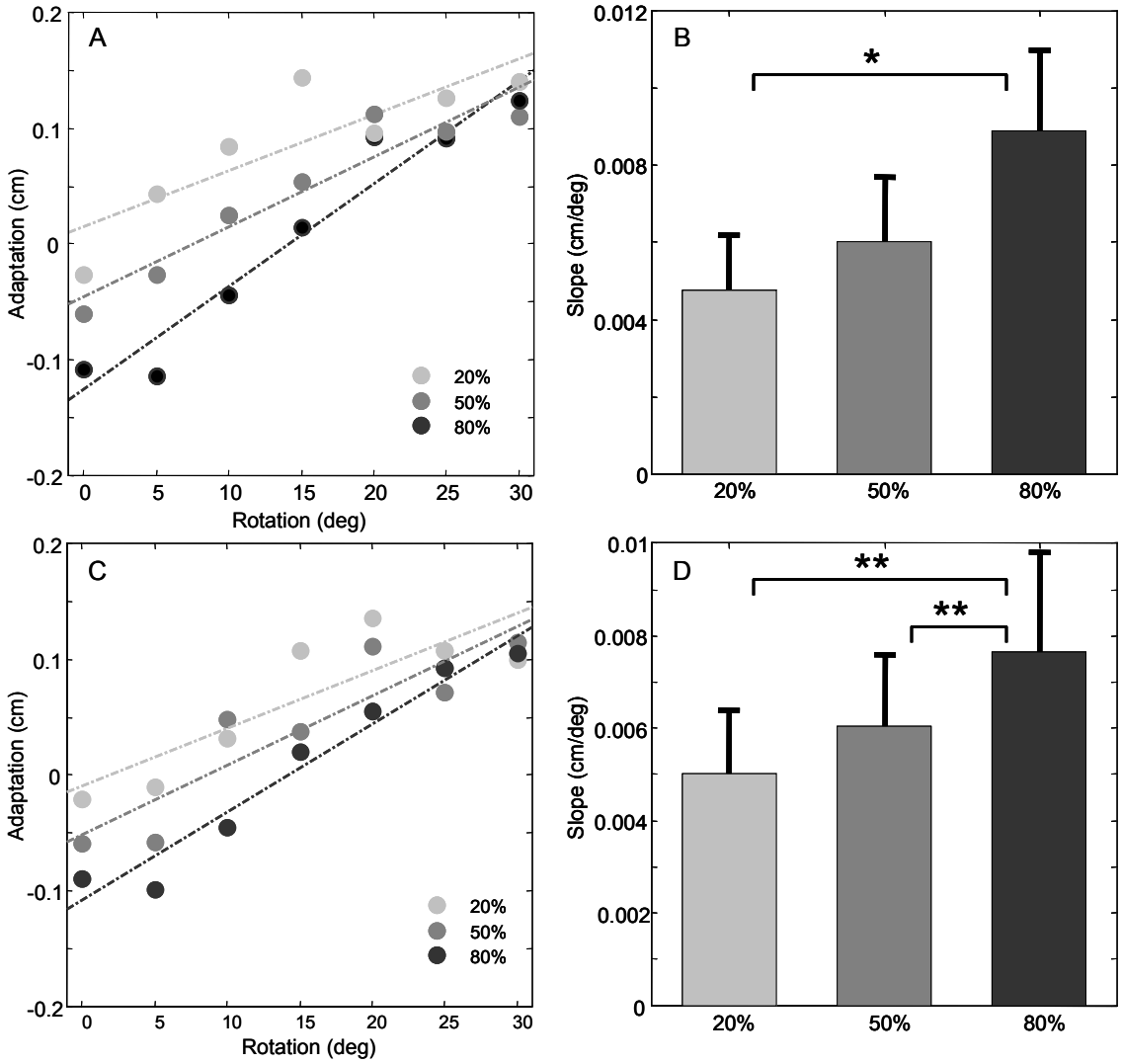

Figure 2.6: *A* and *B*: Triplet adaptation result for subjects experiencing 20%, 50%, and 80% likelihoods. We observed significant differences between the slopes of 20% (0.0049 ± 0.0014) and 80% (0.0089 ± 0.0020) likelihood (repeated measures ANOVA, p = 0.0004, tukey $p < 0.05$). No significant differences were observed between 20% and 50% (0.0061 ± 0.002) or 50% and 80% likelihood. The difference in these slopes indicates increased adaptive sensitivity with increased exposure to rotations. *C* and *D*: Triplet adaptation using state-space quantification for subjects experiencing 20%, 50% and 80% likelihoods. We observe significant differences between the slopes of 20% (0.0050 ± 0.0014) and 80% likelihood (0.0077 ± 0.0021), and 50% (0.0060 ± 0.0016) and 80% likelihood (bootstrap: $p = 0.009$, $p = 0.008$, respectively). Error bars indicate 95% CI of the mean (*$p < 0.05$, **$p < 0.01$).

Bias Experiment Results – Effects of Bias

The second group of 12 subjects experienced visual rotations that always occurred with 80% likelihood, but with varying directional biases (Fig. 2.2, *D-F*). We averaged individual cursor trajectories across all subjects for individual visual rotation strengths (Fig. 2.7). The average of all cursor trajectories revealed that subjects experienced kinematic errors that scaled with the magnitude of the visual rotation.

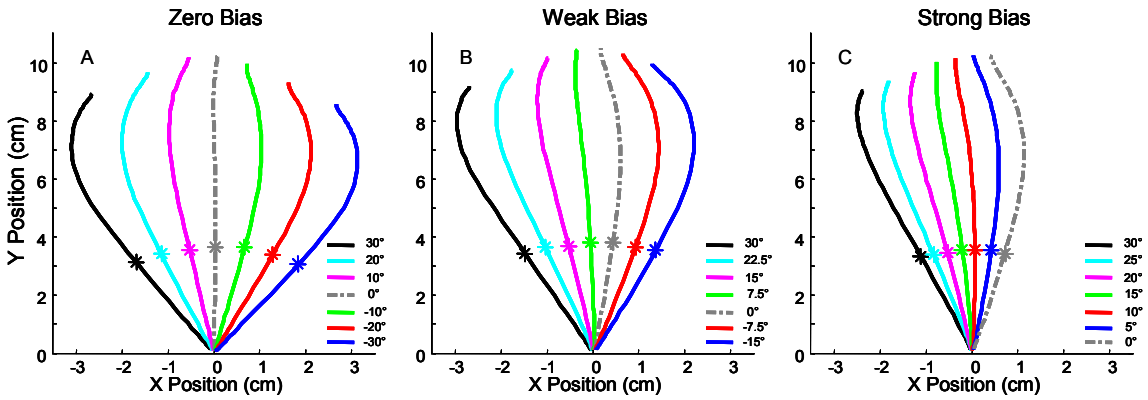

Figure 2.7: Visual cursor trajectories averaged across all movements and all subjects for individual visual rotation strengths as a function of bias. Asterisks indicate the position at peak speed for each visual rotation strength.

Just as in our analysis for the Likelihood Experiment (Fig, 2.4), we calculated adaptation by subtracting the full trajectory before and after a single movement. These responses were then averaged across subjects and rotation strengths for each experimental day (Fig. 2.8). We found that the adaptive response to each perturbation was complexly dependent on both perturbation strength and within-day perturbation bias. Subjects adapting to the zero bias condition and the weak bias condition elicited large errors with large rotation strengths and smaller errors with small rotation strengths (Fig. 2.8, *A-B*). However, the

adaptive trajectories of strong bias appeared to be relatively insensitive to rotation strength, as shown by a clustering of adaptive responses independent of visual rotation magnitude (Fig. 2.8, *C*).

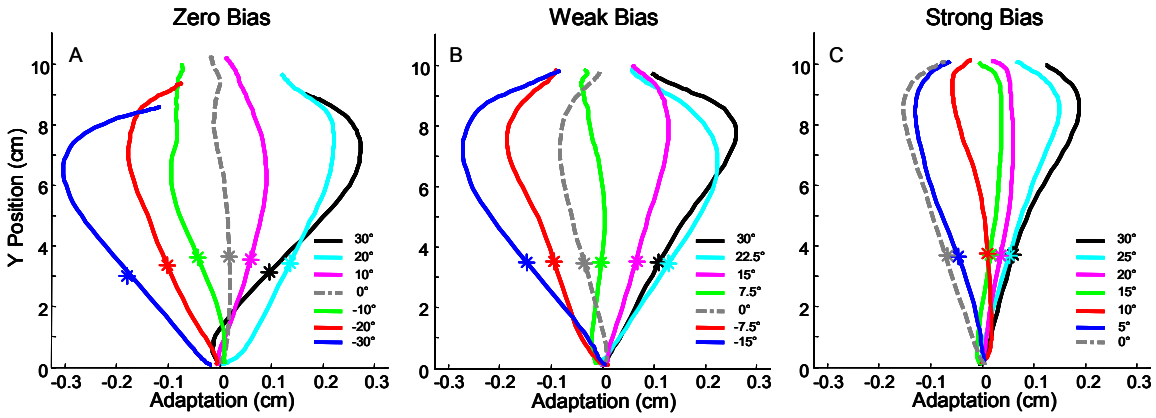

Figure 2.8: Full trajectory adaptation for subjects experiencing visual rotations. Adaptation was calculated as the difference in the amount of positional error experienced before and after a single movement. Adaptation is shown to be highly proportional in the zero bias and weak bias conditions, but less so in the strong bias condition. Asterisks indicate the location of the average position at peak speed.

In order to more closely investigate our observations in Fig. 2.8, we examined adaptive behavior at perpendicular displacement at peak speed across all movements. We calculated adaptation by averaging over triplets of movements: for each instance of rotation strength, we subtracted movement error in the previous movement (m-1) from the subsequent movement (m+1). When we calculated the linear fit for adaptation (mean slope ± CI: zero bias = 0.0048 ± 0.0013, weak bias = 0.0063 ± 0.0012, strong bias = 0.0045 ± 0.0025), we observed non-significant effects of bias (repeated measures ANOVA, $p = 0.3110$, Fig. 2.9, *A-B*).

To increase the sensitivity of our measurements we utilized a state-space model to quantify trial-by-trial adaptation. We found the parameters for *D, A,* and $\vec{S}$ that best fit our data. Since the evolution of error depended on all three parameters (*Eq.* 2.2), we generated a time series of error using the intact model and calculated a triplet analysis

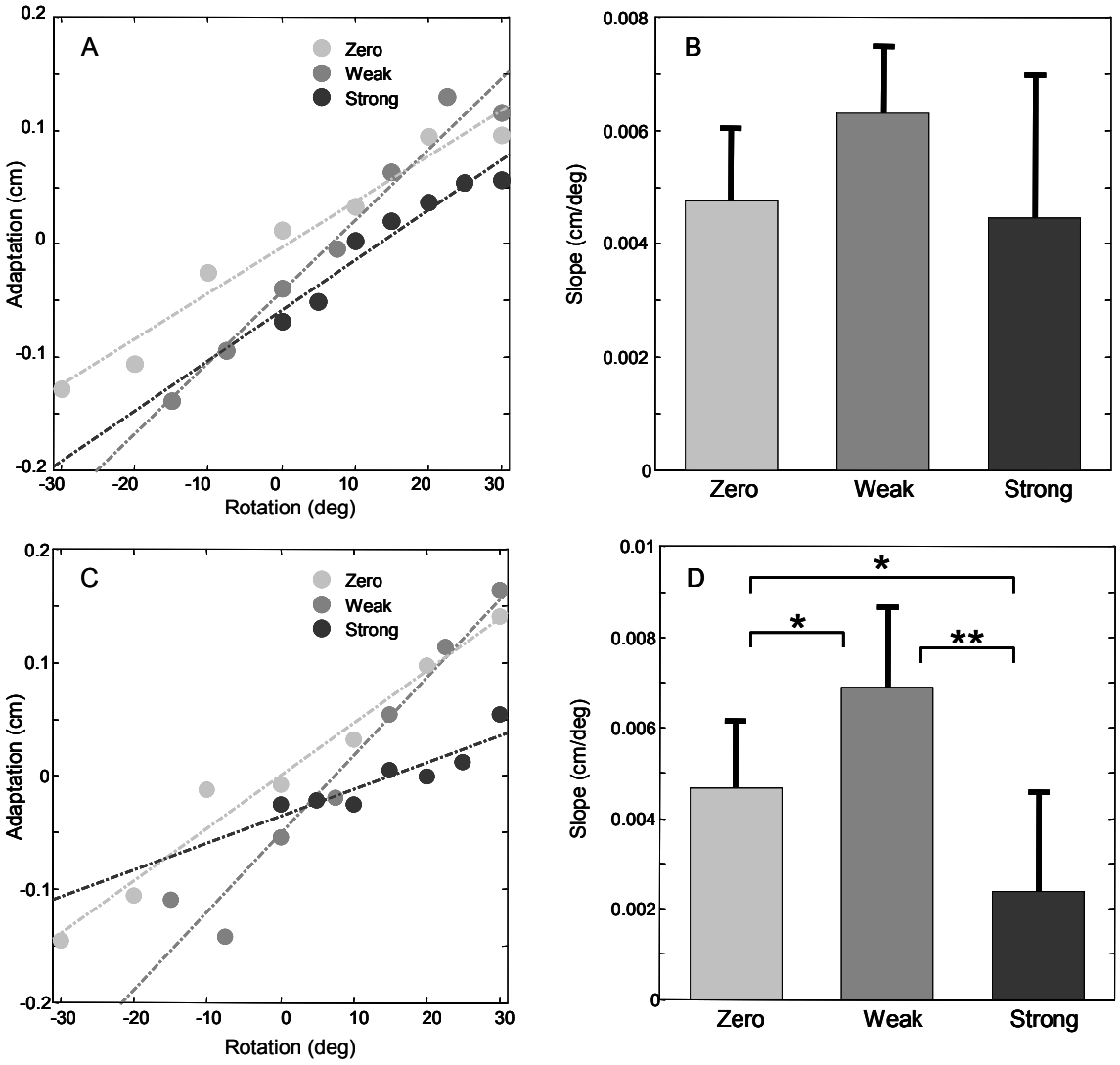

Figure 2.9: *A* and *B*: Triplet adaptation results for subjects experiencing zero, weak, and strong biases. We observed non-significant differences between slopes of the Bias Experiment (zero slope = 0.0041 ± 0.0012, weak slope = 0.0063 ± 0.0012, strong slope = 0.0043 ± 0.0025). *C* and *D*: Triplet adaptation using state-space quantification for subjects experiencing zero, weak and strong biases. We observed significant differences between the slopes of all three conditions: zero (0.0047 ± 0.0015), weak (0.0063 ± 0.0018), and strong (0.0024 ± 0.0020) (bootstrap: zero-weak, $p = 0.0127$, zero-strong, $p = 0.0464$, weak-strong, $p = 0.003$). Error bars indicate 95% CI of the mean (*$p < 0.05$, **$p < 0.01$).

parallel to our analysis of the subject data. When we performed this analysis across all 12 subjects, we observed significant differences across all three bias conditions (mean slope ± CI: zero: 0.0047 ± 0.0015, weak: 0.0063 ± 0.0018, strong: 0.0024 ± 0.0020; bootstrap: zero vs. weak bias, $p = 0.0127$, zero vs. strong bias, $p = 0.0464$, and weak vs. strong bias, $p = 0.003$, Fig. 2.9, *C-D*). Our results show that the adaptive strategies that subjects adopt are dependent on environmental statistics, despite experiencing some of the same magnitude of visual rotations across days.

Compared to the zero and weak bias conditions, we see a marked flatness of slope in the strong bias condition. This suggests that subjects adopt different adaptation strategies across days, and are least sensitive to individual visual rotations within the strong bias condition than compared to the zero and weak bias conditions (Fig. 2.9, *C-D*). The decreased sensitivity in the strong bias condition is unusual in its inversion of our previous findings in haptic learning: strong bias in force perturbations induced heightened, not lessened, sensitivity (Fine and Thoroughman 2007).

These results led us to consider the post-hoc establishment of a hypothesis that different daily experiences could influence adaptive strategy on a subsequent day. Comparing results from our two experiments we observed a discrepancy in behavior exhibited by two groups of subjects experiencing the same condition: the 80% likelihood condition in the likelihood and the strong bias condition in the Bias Experiment. Both of these conditions presented subjects with identical pseudo-random sequences of visual rotations.

To investigate this discrepancy we separated our subjects into subgroups based on order of bias and likelihood presentation to investigate possible across day effects.

Across day effects

In our two experiments, the conditions of the 80% likelihood day of the Likelihood Experiment and the strong bias day of the Bias Experiment were identical; both groups of subjects experienced the same sequence of the same perturbations. The observed cursor trajectories of the two experiments are qualitatively similar (Figs. 2.3, *C* and 2.6, *C*), but when we assess full trajectory adaptation to individual rotation strengths, we see a strongly sloped adaptive profile in the 80% likelihood condition, compared to a far shallower adaptive profile in the strong bias condition, suggesting that subjects participating in the strong bias condition display reduced adaptation (Figs. 2.4, *C* and 2.7, *C*).

To draw across experiment comparisons, we compared our prior triplet analyses across 80% likelihood and the strong bias condition (Figs. 2.6, *A* and 2.9, *A*). When we directly compare the slopes of the adaptation responses from the Likelihood Experiment (Fig. 2.6, *A-B*), to those from the Bias Experiment (Fig. 2.9, *A-B*) we see subjects adopt a more strongly sloped error response during the 80% likelihood day (slope = 0.0089 ± 0.0020), while subjects de-emphasized rotation strength in their adaptation response shown by a decrease in adaptive slope during the strong bias day (slope = 0.0045 ± 0.0025, t-test p = 0.0056) (Fig. 2.10). This was a striking result, because the sole difference between these

two conditions was the perturbations experienced in other training days. This suggested that the adaptive strategy that subjects were using was being altered across days.

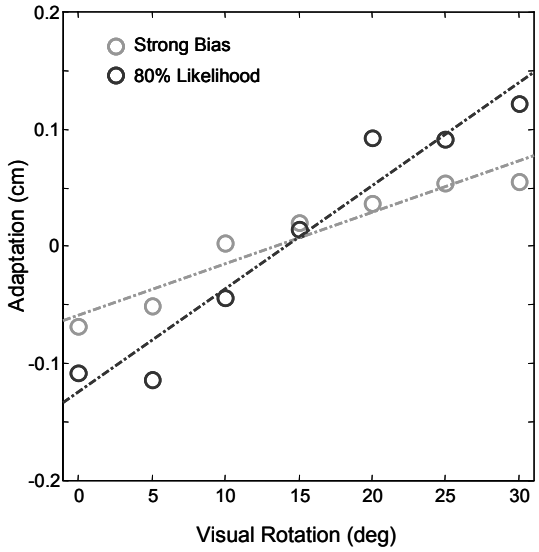

Figure 2.10: Adaptation response for subjects experiencing strong bias and 80% likelihood conditions. We observed a significant difference (t-test, $p = 0.0056$) between the slopes of these two identical days, suggesting that their adaptive responses were context driven in these two separate experiments.

The difference between strong bias and 80% likelihood demonstrates that adaptive behavior could be influenced by previous days' experience. We suspected that the flatness in the adaptive response of our strong bias condition was due to across day effects resulting from adaptive processes being transferred beyond a single day of learning. We then investigated our results from Fig. 2.10 by separating our subjects from the Bias Experiment into two groups of four subjects based on the order that they experienced the test days. The first group of four subjects experienced the strong bias day on the first test day, and the second group of four subjects experienced the strong bias day on the last test day. We performed a triplet analysis and linearly fit adaptation mapped to experience rotation and compared slopes across groups (Fig. 2.11). We found

a significant interaction of testing condition (zero, weak, strong) and the order in which test days were presented (strong first vs. strong last) (mixed effects ANOVA, $p = 0.0026$). Additional post-hoc analyses revealed a significant interaction of the steeply sloped strong bias condition for subjects that experienced strong bias first (slope: 0.0086 ± 0.0015, Fig. 2.11, *A*) when compared to the shallowly sloped strong bias condition for subjects that experienced strong bias last (slope: 0.0017 ± 0.0026, $p < 0.05$, Fig. 2.11, *B*).

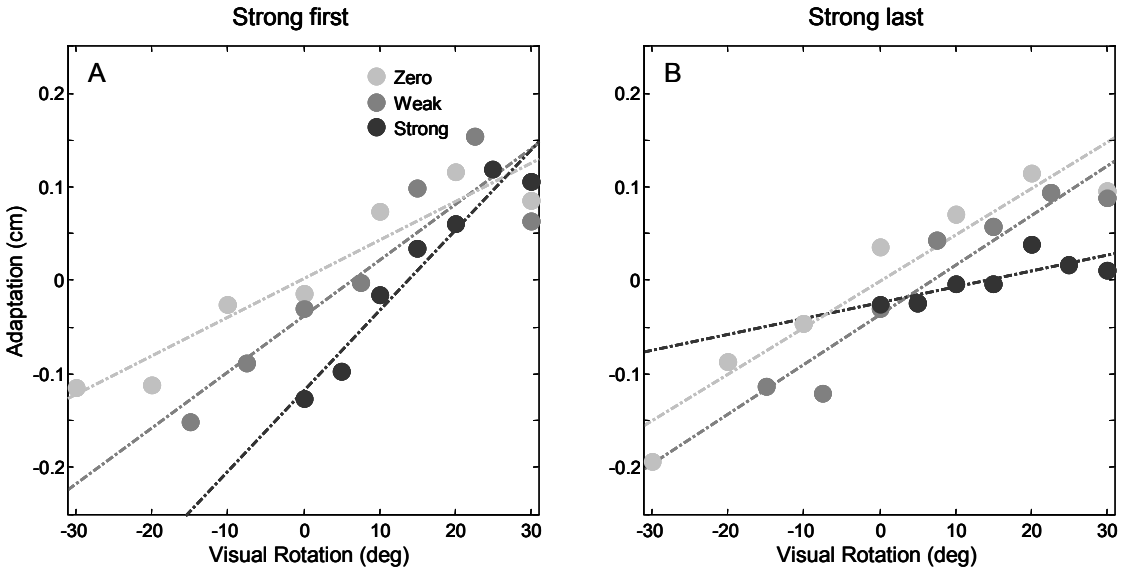

Figure 2.11: Triplet adaptation for subject groups experiencing strong bias on the first experimental day (*A*) and on the last experimental day (*B*). We found significant decreases in adaptation to the strong bias condition when subjects experienced strong bias on the last day (mixed effects ANOVA, $p = 0.0026$, tukey $p < 0.05$).

Our results demonstrate that adaptation to changes in bias can be affected by across day experience. We see a significant decrease in adaptive sensitivity for the strong bias condition when subjects experience the strong bias day on the last day of their testing experience (Fig. 2.11, *A*). However, when we examine adaptive responses for subjects experiencing the strong day on the first day of testing, we see that the strong bias

condition demonstrates a highly sloped adaptive response, similar to that observed for 80% likelihood in the Likelihood Experiment (Figs. 2.11, *B* and 2.6, *A*).

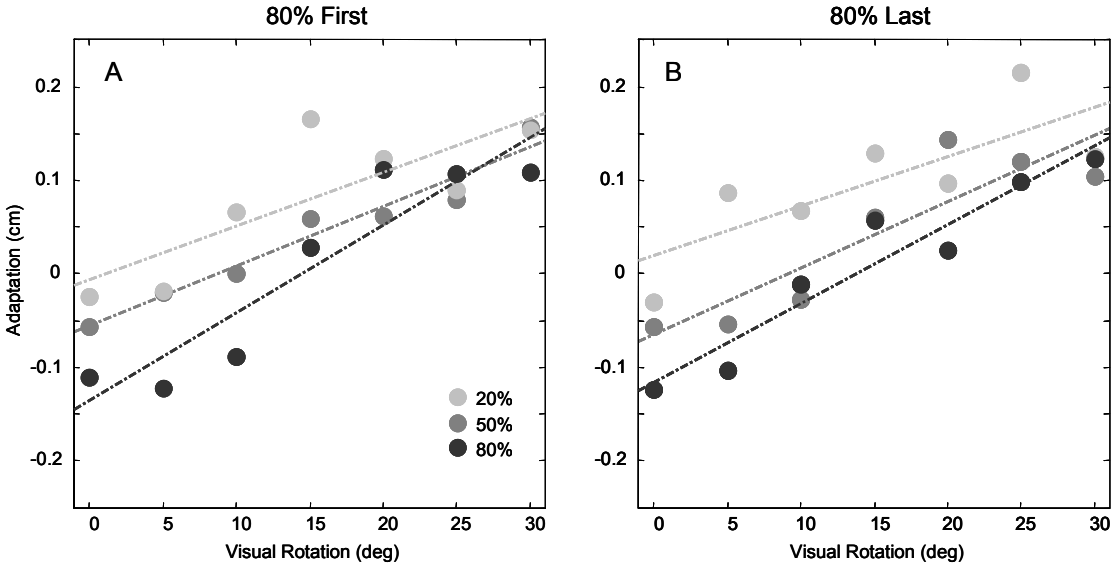

Figure 2.12: Triplet adaptation for subject groups experiencing 80% likelihood on the first day of experimental training (*A*) and 80% likelihood on the last day (*B*). We found no significant interaction of day order and likelihood condition (mixed effects ANOVA, $p = 0.7827$), but observed a significant effect of likelihood condition, $p = 0.0488$, tukey > 0.05).

We also investigated the presence of across day effects during the 80% likelihood day in the Likelihood Experiment by separating our subject groups into two four subjects groups based on the order they experienced the experimental days. One group of four experienced the 80% likelihood on the first experimental day and the second group experienced 80% likelihood on the last experimental day. We found no significant effects of day order when we compared adaptive slope responses for 20%, 50%, and 80%, but a significant effect of likelihood condition (mixed effects ANOVA, $p = 0.7827$, $p = 0.0488$, respectively, Fig. 2.12). We conclude that subjects experiencing differences in environmental biases adopt visuomotor strategies highly susceptible to across day

effects, whereas subjects adapting to changes in environmental likelihood do not change their adaptive strategy according to across-day experiences.

DISCUSSION

In order to adapt to new visuomotor experiences it is necessary to integrate error responses from both vision and proprioceptive signals. In our current study we have established that, as in learning with haptic perturbations (Fine and Thoroughman 2007), the neural processes underlying these adaptive changes are not fixed, but instead change rapidly with the demands of the environment. However, we see that the visuomotor task demands can quickly influence not only adaptation within a day, but across days. We found in the Likelihood Experiment that when subjects experienced an increase in the likelihood of forces we saw a stronger mapping of sensed error into incremental adaptation. The analysis of all subjects in our Bias Experiment revealed unusual results, including reduced sensitivity when subjects experienced the strong bias condition. In our similar study using haptic perturbations (Fine and Thoroughman, 2007), we found that in both the bias and likelihood manipulations, the environments with larger average deviation from baseline induced larger sensitivity. We term "saliency" this magnitude of deviation. Here, in our visuomotor task, the Likelihood Experiment generated similar results, but the Bias Experiment generated very dissimilar results.

We discovered that our two experimental groups responded differently to identical training sets with very different adaptive sensitivities (Fig. 2.10). This difference suggested that environments experienced on other training days could influence trial-by-trial adaptation. Once we separated our experimental groups into subgroups based on order of training day presentation, we found that subjects who experienced the strong bias condition first responded with highly sloped sensitivities. We interpret the response of rotations experienced on the first experimental day to be a naïve state. This result, coupled with the result from our Likelihood Experiment, now fully correlates with our haptic findings: larger saliency, which induces a larger change in behavior on average, induces stronger trial-by-trial adaptation. The subgroup of subjects who experienced the strong bias perturbations on the last day, however, produced shallowly sloped sensitivities which drove the overall group response (Figs. 2.9, *C-D*) to be shallow. The entirety of our subgroup results reveal that the shallow sensitivity we observe when subjects experience the strong bias condition last arises primarily from prior days' experience, within which subjects have previously experienced both zero and weak perturbations.

Consideration of visuomotor control vs. haptic control

While the adaptation patterns we observed in our experiments closely resemble those described in Fine and Thoroughman (2007), we also observe significant across day effects that were not present in the haptic experiment. This brings to light obvious systemic differences between visuomotor and proprioceptive adaptive processing in

humans. There is evidence that sensory representation of force perturbations and subsequent errors are learned in the natural time scale of spindle afferents acting to encode limb state (Hwang and Shadmehr 2005). In addition, when humans do adapt to these haptic perturbations, the limb faces a host of biomechanical filters that act to transform sensed error into motor output (Valero-Cuevas 2005). When subjects adapt to visuomotor rotations, they do not face the same physiological constraints as when people adapt to haptic perturbations. Instead, in visuomotor tasks, incoming visual signals act to plan and update movement performance in extrinsic coordinates on a moment-by-moment basis (Sarlegna and Sainburg 2009; Sober and Sabes 2003).

Across day effects

We observed significant across day effects for adaptation to the strong bias condition. The adaptive responses for subjects experiencing the strong condition first (Fig. 2.11, *A*) and the strong condition last (Fig. 2.11, *B*) were likely masked by a blurring of response that occurred when we averaged subjects in our triplet analysis (Fig. 2.9, *A*). When we separated our subjects into subjects that experienced strong bias first and subjects that experienced strong bias last, we see a far clearer picture of the magnitude of across day effects in the strong bias condition (Fig. 2.11). We did not observe any across day effects in experiment one (Fig. 2.12), which suggests something particularly significant about the nature of the environmental dynamics presented in the Bias Experiment.

In a single sitting, people have demonstrated a nonlinear mapping of visually sensed reaching error into subsequent adaptation. This nonlinear mapping can be explained by the adoption of a credit assignment strategy by the brain; credit is assigned for self and environmentally generated errors: small errors emerging more naturally from self-generated sensorimotor noise (Wei and Kording 2009). In the Bias Experiment experiment, people generated stronger or weaker adaptation to the same stimuli depending on prior day's experience. We see no evidence of lessened linearity across days, suggesting that credit assignment does not likely change with previous experience.

Implications of across-day effects

In haptic and visuomotor learning, several studies have characterized the quantitative features of motor memory that carry across training days. Some of these studies investigated the "savings" or retained learning (Krakauer et al. 1999; Zarahn et al. 2008; Smith et al. 2006; Joiner and Smith 2008); some investigated the transfer across tasks; and others investigated the fragility or robustness of motor memory when subjects train in opposing tasks (Tong and Flanagan 2003; Donchin et al. 2002; Caithness et al. 2004). Our present finding characterizes not the motor memory carried across days, but alterations to the adaptive process itself. In haptic adaptation we found that environments could, within a training day, induce either categorical or (more traditional) proportional adaptive strategies. Here, we observed noticeably decreased adaptation with an interaction between across-day experiences when the strong bias environment occurred last, but more traditional proportional adaptation when strong occurred on the first

experimental training day. The insight we gained from our haptic studies was that learning processes are not fixed, as postulated by the delta rule and its progeny (Rumelhart et al. 1985, Pouget and Snyder 2000) but rather are fluid and quickly adjusted within environmental demands. Here we have gained the additional insight that learning processes can retain information from prior day's experiences, combine that information with current environmental demands, and shape the real valued transformation of error into adaptation.

Cognitive strategies for behavioral control

Adaptation to visuomotor stimuli may be more susceptible to the use of cognitive strategies by subjects than those who experience haptic perturbations. Sudden visual rotations are highly detectable to the observer, and instead of adopting adaptive strategies that involve motor adaptation, subjects may engage cognitive strategies to combat their new experiences (Kagerer et al. 1997, Malfait and Ostry 2004, Michel et al. 2007, Saijo and Gomi 2010, Taylor and Ivry 2011). When we observe across-day effects, it is possible that when these subjects experience strong bias on the last day, the rotations in the strong bias are less detectable, because they are cognitively less distinct after having already experienced the zero and weak bias day which have larger rotation distributions.

Alternatively, it is possible that these cognitive strategies may be the result of a type of "learned helplessness". Subjects exhibited trial-by-trial learning on the zero bias day, but the lack of bias meant that every small positive learning step was balanced by a negative

one, adding to zero overall memory built. We believe that this experience might relate to cognitive behavior modeled by Huys and Dayan (2009) in which failure to succeed, perform, or learn on one task diminishes effort and processing in subsequent tasks. The lessened sensitivity to perturbation when strong bias is experienced last may reflect a quantitative consequence of "helplessness" avoided when strong bias is experienced first.

Sensorimotor transformations of error require the brain to be predictive in that it requires the use of past knowledge to update and improve new and existing adaptive strategies. However, we see that we can influence the adaptive process itself across days, and that information from one adaptive experience can influence processing on a subsequent day. This effect is dependent on surrounding environmental context, and suggests that the brain is continually modifying adaptive processes dependent on past and current experiences.

REFERENCES

Caithness G, Osu R, Bays P, Chase H, Klassen J, Kawato M, Wolpert DM, Flanagan JR. Failure to consolidate the consolidation theory of learning for sensorimotor adaptation tasks. J Neurosci 24: 8662-8671, 2004.

Donchin O, Sawaki L, Madupu G, Cohen LG, Shadmehr R. Mechanisms influencing acquisition and recall of motor memories. J Neurophysiol 88: 2114-2123, 2002.

Efron B, Tibshirani R. An introduction to the bootstrap. Boca Raton, Fla.: Chapman & Hall/CRC, 1998, p. xvi, 436 p.

Fernandez-Ruiz J, Diaz R. Prism adaptation and aftereffect: specifying the properties of a procedural memory system. Learn Mem 6: 47-53, 1999.

Fine MS, Thoroughman KA. Motor adaptation to single force pulses: sensitive to direction but insensitive to within-movement pulse placement and magnitude. J Neurophysiol 96: 710-720, 2006.

Fine MS, Thoroughman KA. Trial-by-trial transformation of error into sensorimotor adaptation changes with environmental dynamics. J Neurophysiol 98: 1392-1404, 2007.

Fiorentini A, Ghez C, Maffei L. Physiological correlates of adaptation to a rotated visual field. J Physiol 227: 313-322, 1972.

Ghilardi MF, Gordon J, Ghez C. Learning a visuomotor transformation in a local area of work space produces directional biases in other areas. J Neurophysiol 73: 2535-2539, 1995.

Hamilton CR, Bossom J. Decay of Prism Aftereffects. J Exp Psychol 67: 148-150, 1964.

Huys QJ, and Dayan P. A Bayesian formulation of behavioral control. Cognition 113: 314-328, 2009.

Hwang EJ, Shadmehr R. Internal models of limb dynamics and the encoding of limb state. J Neural Eng 2: S266-278, 2005.

Joiner WM, Smith MA. Long-term retention explained by a model of short-term learning in the adaptive control of reaching. J Neurophysiol 100: 2948-2955, 2008.

Kagerer FA, Contreras-Vidal JL, and Stelmach GE. Adaptation to gradual as compared with sudden visuo-motor distortions. Exp Brain Res 115: 557-561, 1997.

Krakauer JW, Ghilardi MF, Ghez C. Independent learning of internal models for kinematic and dynamic control of reaching. Nat Neurosci 2: 1026-1031, 1999.

Krakauer JW, Ghilardi MF, Mentis M, Barnes A, Veytsman M, Eidelberg D, Ghez C. Differential cortical and subcortical activations in learning rotations and gains for reaching: a PET study. J Neurophysiol 91: 924-933, 2004.

Krakauer JW, Pine ZM, Ghilardi MF, Ghez C. Learning of visuomotor transformations for vectorial planning of reaching trajectories. J Neurosci 20: 8916-8924, 2000.

Malfait N, Ostry DJ. Is interlimb transfer of force-field adaptation a cognitive response to the sudden introduction of load? J Neurosci 24: 8084-8089, 2004.

Martin TA, Keating JG, Goodkin HP, Bastian AJ, Thach WT. Throwing while looking through prisms. II. Specificity and storage of multiple gaze-throw calibrations. Brain 119 (Pt 4): 1199-1211, 1996.

Michel C, Pisella L, Prablanc C, Rode G, and Rossetti Y. Enhancing visuomotor adaptation by reducing error signals: single-step (aware) versus multiple-step (unaware) exposure to wedge prisms. J Cogn Neurosci 19: 341-350, 2007.

Pine ZM, Krakauer JW, Gordon J, Ghez C. Learning of scaling factors and reference axes for reaching movements. Neuroreport 7: 2357-2361, 1996.

Pouget A, Snyder LH. Computational approaches to sensorimotor transformations. Nat Neurosci 3 Suppl: 1192-1198, 2000.

Rumelhart DE, Hinton GE, Williams RJ. Learning internal representations by error propogation. In: *Parallel Data Processing*, edited by D. E. Rumelhart, and J. McClelland Cambridge, MA: MIT Press, 1986, vol. 1, chap. 8, p. 318-362.Cambridge, Mass.: MIT Press, 1986.

Saijo N, and Gomi H. Multiple motor learning strategies in visuomotor rotation. PLoS One 5: e9399, 2010

Sarlegna FR, Sainburg RL. The roles of vision and proprioception in the planning of reaching movements. Adv Exp Med Biol 629: 317-335, 2009.

Scheidt RA, Dingwell JB, Mussa-Ivaldi FA. Learning to move amid uncertainty. J Neurophysiol 86: 971-985, 2001.

Seidler RD. Differential effects of age on sequence learning and sensorimotor adaptation. Brain Res Bull 70: 337-346, 2006.

Smith MA, Ghazizadeh A, Shadmehr R. Interacting adaptive processes with different timescales underlie short-term motor learning. PLoS Biol 4: e179, 2006.

Sober SJ, Sabes PN. Multisensory integration during motor planning. J Neurosci 23: 6982-6992, 2003.

Taylor JA, and Ivry RB. Flexible Cognitive Strategies during Motor Learning. PLoS Comput Biol 7: e1001096.

Thoroughman KA, Fine MS, Taylor JA. Trial-by-trial motor adaptation: a window into elemental neural computation. Prog Brain Res 165: 373-382, 2007.

Thoroughman KA, Shadmehr R. Learning of action through adaptive combination of motor primitives. Nature 407: 742-747, 2000.

Thoroughman KA, Taylor JA. Rapid reshaping of human motor generalization. J Neurosci 25: 8948-8953, 2005.

Tong C, Flanagan JR. Task-specific internal models for kinematic transformations. J Neurophysiol 90: 578-585, 2003.

Valero-Cuevas FJ. An integrative approach to the biomechanical function and neuromuscular control of the fingers. J Biomech 38: 673-684, 2005.

Wei K, Kording K. Relevance of error: what drives motor adaptation? J Neurophysiol 101: 655-664, 2009.

Zarahn E, Weston GD, Liang J, Mazzoni P, Krakauer JW. Explaining savings for visuomotor adaptation: linear time-invariant state-space models are not sufficient. J Neurophysiol 100: 2537-2548, 2008.

Chapter 3.

Trial-by-trial Visuomotor Adaptation in Parkinson's disease

ABSTRACT

In order to perform simple everyday tasks, we use visual feedback from our external environment to effortlessly generate and guide our movements. However, the effects of a disease resulting in motor impairment, like Parkinson's disease (PD), can make everyday tasks like reaching for a cup extremely difficult. It is unclear what the effects of PD are on sensorimotor integration, specifically the integration of visual and proprioceptive signals. We tested adaptation to changes in visual feedback in patients with PD and age-matched controls to determine the effects of PD on the visual control of movement. Subjects were tested on two classes of visual perturbations: visual rotations and visual gains, allowing us to test adaptive sensitivity to changes in different types of visual feedback. In addition, we also tested trial-by-trial error learning via pseudo-randomly introduced catch-trials, designed to induce transient visual errors. We found that PD subjects more completely adapted to visuomotor rotations compared to controls. In contrast, we discovered that PD subjects display significantly reduced adaptation to changes in visuomotor gain when compared to control subjects. We conclude that damage to the basal ganglia can negatively impact ability to adapt to visuomotor gains, while adaptation to rotations remains intact. Our results support the theory that adaptation to visual gains and rotations are separable processes.

INTRODUCTION

Everyday we use visual information to inform the planning and production of movement. Human motor control can be disrupted in a variety of neurodegenerative disease, which can have deleterious effects on motor production and maintenance. Parkinson's disease (PD) is the second most prevalent neurodegenerative disease, affecting approximately 1 million individuals across the United States (Lees et al. 2009, de Lau and Breteler 2006). The cause of PD is largely unknown, but deficits in motor control manifest due to significant loss of dopaminergic neurons in the substantia nigra, *pars compacta* (Albin et al. 1989, Mink, 1996).; one of the nuclei comprising the basal ganglia. The basal ganglia are a set of deep brain nuclei involved in the production and execution of movement (Horak and Anderson 1984a, 1984b), motor learning (Graybiel et al. 1994, Vaillancourt et al. 2001), motor sequence learning (Lehericy et al. 2005), and visuomotor control of movement (Turner et al. 2003, Vaillancourt et al. 2003, Krakauer et al. 2004, Nixon et al. 2004, Seidler et al. 2006). The motor symptoms that characterize PD are often only partially alleviated by traditional dopamine replacement therapies. Additionally, these medications have negative side effects on movement time (Kwak et al. 2010), tracking ability (Au et al. 2010), and motor learning (Mongeon et al. 2009). Aversive side-effects and incomplete understanding of PD pathophysiology make it imperative to understand the underlying mechanisms that govern motor learning and adaptation in people with PD.

The basal ganglia are thought to contribute to sensorimotor transformations necessary for integrating information across multiple sensory domains (Graybiel et al. 1994, Jobst et al.

1997, Doyon et al. 2003, Desmurget et al. 2003, Contreras-Vidal and Gold 2004, Nowak and Hermsdorfer 2006). These transformations are necessary for the combination of sensory signals received from visual and motor feedback. It is believed that these sensorimotor integration mechanisms can be impaired in patients with PD (Abbruzzese and Berardelli 2002, Messier et al. 2007, Paquet et al. 2008), specifically affecting adaptation to changes in visual feedback (Contreras-Vidal et al. 2003, Fernande-Ruiz et al. 2003, Messier et al. 2007). While these studies suggest that the integration of visual feedback with motor information is impaired in PD, it is unclear what area of the brain mediates the moment-to-moment update of these signals to drive visuomotor adaptation. Current literature suggests that the basal ganglia are essential to updating these types of sensory errors on a trial-by-trial basis (Brown et al. 2006, Kempf et al. 2007, den Ouden et al. 2010).

While these studies attribute visuomotor adaptation and function to the modulation of activity in the basal ganglia, it is unclear whether there is a direct contribution of the basal ganglia to visuomotor adaptation. Current literature does not consistently characterize impairment of visuomotor learning in PD. Visuomotor adaptation has been ill-defined in PD, and has been described in a variety of ways ranging from completely intact during continuous visual feedback (Inzelberg et al. 2008, Marinelli et al. 2009); intact adaptation, but with impaired after-effects during prism learning (Fernandez-Ruiz et al. 2003), and with completely impaired adaptation and subsequent after-effects during continuous visual feedback (Contreras-Vidal and Buch 2003). While these studies were designed to ask questions about visuomotor function in PD they fail to ask how these

visuomotor transformations take place, or what neural mechanisms are responsible for behavioral output. Additionally, these studies have all evaluated patients with PD on their daily levodopa medication. We feel that by testing patients off medication, we will observe a truer representation of visuomotor adaptation and degeneration in the basal ganglia. In total, these studies fail to paint a cohesive story of the ability or impairments present in visuomotor adaptation in PD patients. We believe that by observing how subjects with PD learn these perturbations and then experience unexpected errors, we can better understand the mechanisms by which learning occurs, while observing error responses that are more ecologically valid. By utilizing people with PD as a model to investigate problems of visuomotor control we will be better able to understand the underlying mechanisms of visuomotor error control and the contribution of the basal ganglia to visuomotor adaptation.

Performing a reaching movement while using visual feedback requires the vectorized planning of two components of the visual target: direction (angle of reach) and extent (amplitude of reach) (Ghez et al. 1991, Gordon et al. 1994, Pine et al. 1996, Krakauer et al. 2000). This theory has been well-characterized and supported via the discovery of differences in rates of adaptation to visual perturbations of extent and direction, as well as differences in the generalization of motor behavior for each of these modalities of visuomotor information across multiple targets (Pine et al. 1996, Krakauer et al., 2000). Visuomotor extent and direction can also be distinguished by their neuroanatomical differences, which can be seen through separate neural activation patterns (Krakauer et al. 2004). These activation patterns are differentially characterized by cortical activations in

response to changes in visuomotor direction (rotations), and subcortical activations in the basal ganglia in response to changes in visuomotor extent (visual gain). Alternatively, activation of the basal ganglia has also been found for adaptation to visuomotor rotations (Seidler et al. 2006); suggesting that the underlying neural mechanisms governing these separate elements of visuomotor planning are not well-defined.

Overall, there is a host of evidence that characterizes both impaired and intact visuomotor adaptation in PD, but several aspects are unclear: 1.) whether the basal ganglia are directly involved in the process of visuomotor adaptation, 2.) whether or not visuomotor adaptation mediated via the basal ganglia would result in impaired visuomotor processing in patients with PD, and 3.) whether the planning aspects of visuomotor control are differentially affected due to basal ganglia mediated visuomotor control.

In order to investigate the properties of visuomotor adaptation in patients with PD, we examined reaching kinematics in the presence and subsequent absence of unexpected visual perturbations of rotation (direction) and gain (extent). We hypothesized that patients with PD will show impaired adaptation to visuomotor perturbations compared to their age-matched counterparts, with these deficits being more pronounced during adaptation to perturbations of extent due to behavioral and neural separability of visuomotor extent and direction.

To test our hypotheses, we trained patients with PD on visuomotor perturbations and subsequently presented them with pseudorandomly interspersed trials where the

perturbation was removed. We aimed to characterize adaptation, magnitude of error and unlearning from prior adaptation. These techniques and methods allow us to elucidate differences in the mechanisms driving visuomotor adaptation and the ability or impairments stemming from PD.

METHODS

Subject Groups

Our experiment tested visuomotor adaptation in two groups of participants: Group 1, patients with PD off levodopa therapy (N = 8); Group 2, age-matched control subjects (N = 9) with no prior history of neurological deficits. All subjects were required to have normal or corrected-to-normal vision, as well as the ability to make a 10 cm reaching movement. Subjects in the PD group made reaching movements with the arm that corresponded to the side of the body of initial motor symptom manifestation; all subjects tested had symptoms that presented unilaterally. Subjects in the control group were matched for handedness and side of task performance for our PD group (Table 3.1).

All patient participants were referred by the Neurology department at the Washington University School of Medicine. Inclusion criteria required that all patient subjects have mild to moderate Parkinson's disease (Hoehn and Yahr, stage 2-3), as diagnosed by their referring neurologist.

	Control (*n=9*)	PD OFF (*n=8*)
Age	71.1 ± 5.4	71.4 ± 7.4
Sex	5 Male/4 Female	4 Female/4 Male
Disease duration (years)	----------	11.1 ± 4.4
Side of disease onset	----------	6 Right/2 Left
Side of task performance	7 Right/2 Left	6 Right/2 Left
Handedness	8 Right/ 1 Left	7 Right/1 Left
UPDRS exam score	----------	24 ± 6.5
MMSE score	29.4 ± 0.7	29.5 ± 0.9

Table 3.1: Demographics from both subject groups. PD subjects performed the reaching task on the side where their Parkinson's began. UPDRS scores demonstrate impairment in motor performance for the PD group. Cognitive ability (MMSE) was normal in both groups ($p > 0.6$). Values are mean ± standard deviation.

Subjects in the PD group had motor impairments evaluated on each of two study visits by a certified clinical evaluator. Motor impairments were rated by the Unified Parkinson's Disease Rating Scale (UPDRS), motor evaluation section. Patients in the PD group were taking daily levodopa or carbidopa therapy and were required to abstain from their therapy 12 hours prior to each testing session for purposes of the study (Khor and Hsu 2007). Subjects in both groups were evaluated for cognitive impairments using the mini-mental state exam (MMSE). Inclusion criteria required that study participants score at least a 24 out of 30 possible points. All subjects tested scored at least 28 out of 30 (Table 3.1).

All protocols were approved by the Washington University Human Research Protection Office (HRPO), and all subjects provided signed consent. Subject demographics are listed in Table 3.1.

Apparatus and task

Subjects performed horizontal reaching movements in a virtual environment. Reaching movements were performed and recorded using a digitizing tablet and pen (Wacon Intuous; Wacom Company Ltd. Tokyo, Japan). Subjects were seated with their elbow level to the digitizing tablet and viewed the visuomotor environment through a horizontally mounted half-silvered mirror. Testing was completed in a darkened room so that vision of the hand and arm was completely obstructed by light-level and the mirror.

The task required subjects to make ballistic reaching movements from a starting target located in the middle of the tablet to an end target 10 cm away from the body. A movement this size is akin to everyday movements, such as using a hairbrush or controlling a computer mouse. Subjects were to make outward reaching movement with a time specification of 650 ± 100 ms in order to maintain duration consistency across all subjects. During the task, if the subject satisfied this condition, the end target would turn green to signify a "correct" reach. If the subject moved slower than 750 ms, the end target would turn blue, and if the subject moved faster than 550 ms, the end target would turn red. The experimenter instructed each subject to make outward reaching movements upon target appearance and that the end target would change color according to the above parameters. Subjects were encouraged to get as many green targets as possible.

Subjects made outward movements and were instructed to pause at the end target until it disappeared, which signified they could return to the start target. Visual feedback was eliminated during the return portion of the movement until subjects were within 3 cm of the start target, where visual feedback was experienced as it had been initially presented in that trial.

Participants experienced a variety of perturbations that altered visual feedback by either direction (visual rotations) or extent (visual gains) of movement. All subjects performed a two day experiment, where they experienced all of the following visual perturbations: clockwise rotation (-30°), counterclockwise rotation (30°), minifying gain (0.5), and a magnifying gain (1.5). Positional displacement was generated using the following equation:

$$\begin{aligned} x' &= x\cos\theta - y\sin\theta \\ y' &= x\sin\theta + y\cos\theta \end{aligned} \tag{3.1}$$

where x and y correspond to values of x and y hand position, θ is angle of rotation, and x' and y' are the transformed visual coordinates. Gain displacements were multiplicative of hand position and either increased (magnifying) or decreased (minifying) the hand to cursor ratio. The center of both rotational and gain displacements coincided with the initial start position (Fig. 3.1).

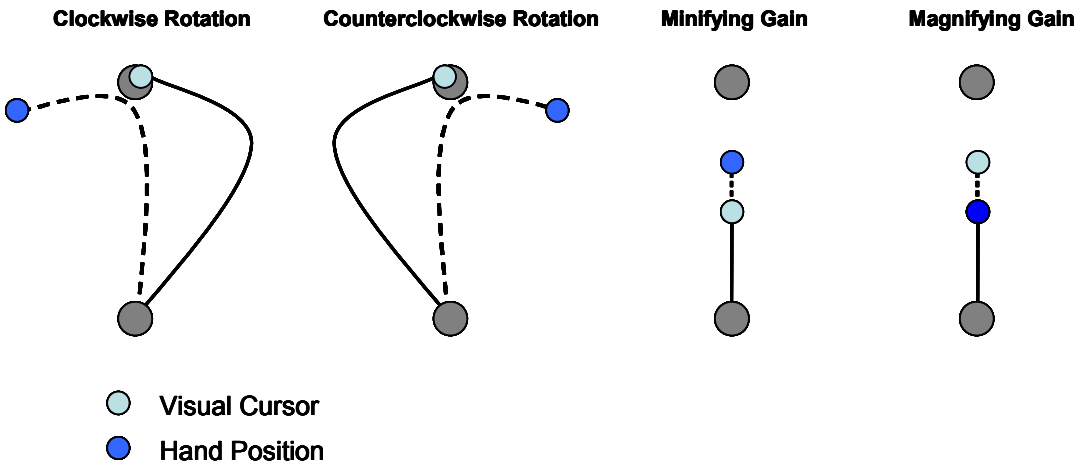

Figure 3.1: Depiction of hand paths with the corresponding visual cursor rotations and visual gains as seen on the monitor display. Clockwise cursor rotations rotated trajectories in a clockwise direction, counterclockwise cursor rotations rotated trajectories in a counterclockwise direction. Minifying gains decreased the cursor to hand ratio, requiring longer reaches, magnifying gains increased the cursor to hand ratio, requiring shorter reaches.

On each testing day, all subjects performed 600 reaching movements that consisted of reaching in a baseline condition, a visual rotation, and visual gain. During testing on Day A, subjects first performed 100 baseline reaching movements where visual feedback matched hand position. Subjects then experienced 200 movements in a clockwise rotation environment. Presentation of the second half of all visually perturbing trials contained 20% catch-trials where the visual perturbation was pseudorandomly removed so that the subjects experienced veridical feedback. Subjects then experienced 50 baseline trials to wash-out the effect of the visual rotation, followed by 200 trials in a minifying gain condition that contained 20% catch-trials in the last 100 movements, followed by 50 baseline trials. The structure of Day B was identical to Day A, except for

perturbations experienced. In Day B subjects experienced a magnifying gain followed by a counterclockwise rotation (Fig. 3.2). All movements were performed in 50 trial blocks with a rest between each block of movements to counter arm fatigue.

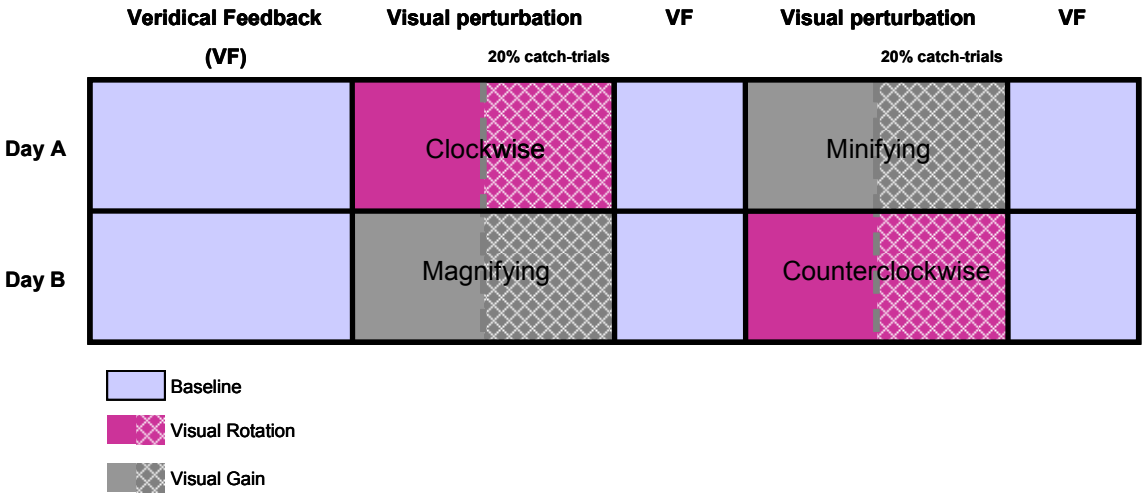

Figure 3.2: Block presentation of visual cursor perturbations across 2 days. Day A, subjects experienced a clockwise rotation and minifying gain. Day B, subjects experienced a magnifying gain and counterclockwise rotation. In all visually perturbing conditions, subjects experienced 20% catch-trials during the second half of perturbation presentation.

Testing of Day A and Day B were completed one week apart. Subjects in each group were counterbalanced to control for effect of day order presentation. Half of the subjects in each group experienced Day A first, and Day B second (Control group: 5 subjects: Day A/Day B, 4 subjects: Day B/Day A; PD group: 4 subjects: Day A/Day B; 4 subjects: Day B/Day A). Due to lack of adaptive signal in both the control group and PD group for the magnifying gain condition, we will focus our results and discussion on the minifying gain condition.

Analysis

Measures of adaptation

In this experiment, our goal was to determine the characteristics of visuomotor learning and trial-by-trial visuomotor adaptation in patients with PD. We aimed to determine differences in adaptation to visual perturbations of extent and direction to characterize how visuomotor error responses influence motor behavior on subsequent movements. We examined characteristics of full-trajectory responses and velocity traces to qualitatively compare averaged movement responses to visual perturbations. For quantitative analyses, we reduced data to lateral displacement at peak speed and peak velocity to analyze the influence of a single movement in a subsequently experienced movement (Thoroughman and Shadmehr 2000).

For all subjects and all movements, we calculated position at peak speed. From these values we calculated baseline performance for individual subjects as an average of baseline experience (movements 90 to 100) during subjects' performance on Day A. For each subject, we normalized all positional data by subtracting the calculated baseline from position at peak speed for all perturbed movements. We examined both x and y displacement at position at peak speed for experienced rotations and gains, respectively. Upon data examination, we determined that x position at peak speed failed to capture the lateral displacement induced by the visual rotation. To more accurately capture the effect of the visual rotation, we converted positional data to polar coordinates, then analyzed angle of position at peak speed from the new line, connecting start to goal.

We observed distinct adaptive differences for asymptote between the PD and control groups for rotation experience. In order to capture the full strength of adaptive performance for individual subjects, we computed the amount of adaptation induced by the visual rotations by calculating the difference between the immediate response to the perturbation (first movement) and the adapted response before the onset of catch-trials (average of movements 90-100). Acquired adaptation for each subject was calculated by computing the difference from initial displacement (movement 1) to the perturbation to adaptation 100 movements later. Percentage change was then calculated as acquired adaptation divided by the amount of initial displacement.

For analyzing responses to the minifying gain, we computed positional and velocity derived adaptation metrics. Metrics for the minifying gain condition utilized y position at peak speed to determine the amount of y positional displacement across movements. Examination of fuller data sets for individual subjects and individual movements indicated that y positional data does not directly capture the true effect of the induced gain displacement. Time series of data revealed velocity-based metrics to capture true adaptive changes in response to displacements of gain. Adaptation was computed as a function of change in velocity breadth (movement time) and peak movement velocity. Our breadth metric was calculated as the time from the beginning to end for each movement. The threshold for the beginning and end of each movement was indicated by the first and last point of the velocity trace where velocity exceeded 0.03 m/s.

Exponential fits

We computed exponential fits to characterize asymptotic behavior of error responses over the first 100 movements experienced in each visual perturbation type (*Eq*. 3.1). Each term in our exponential fit corresponded to a distinct aspect of the adaptive process: *a* was the asymptotic value of the curve, *b* was the learning rate, and $\frac{-1}{c}$ was the time constant. $a = 0.01$, $b = 0.01$, $c = 0.01$, to generate the best fitting exponential to the data. Each curve was fit to the original data by minimizing the square-difference between predicted and actual performance.

$$x(t) = a - b * e^{(\frac{-t}{c})} \tag{3.2}$$

Trial-by-trial metric

We evaluated the influence of single catch-trials on adaptation for each subject by calculating maximum displacement for each movement immediately prior to a catch-trial (pre-catch response) and for each movement immediately subsequent to a catch-trial (post-catch response). We then determined the visuomotor error induced by the catch-trial in the subsequent movement by subtracting the post-catch response from the pre-catch response using the the following equation, where $movement_{(n)}$ is a single catch trial:

$$Induced\text{-}error_n = Movement_{(n+1)} - Movement_{(n-1)} \tag{3.3}$$

Statistical significance

We tested data significance by using standard t-tests and permutation tests. For data derived from exponential fits, we performed permutation tests to test for statistical significance. Due to the highly non-linear nature of fit from the exponential function, parametric tests were no longer appropriate.

Our permutation test performed resampling to analyze the distribution of the null hypothesis to determine whether two groups or conditions had significantly different metrics. In the case of our experiment, we determined asymptotic values for each subject derived from our exponential fits for our two subject groups. The null hypothesis was then examined by randomly assigning 8 subjects to group A and 9 subjects to group B, irrespective of original subject group. Values were shuffled and compared for groups A and B. The distribution of these resampled values created a distribution of the null hypothesis. Where the actual difference between our two groups fell on this distribution determined the p value of our experimental results.

All error bars are reported as 95% confidence interval of the mean.

RESULTS

In this study, we observed that our PD subjects were highly capable of adapting to newly experienced visual rotations when compared to age-matched controls. We observed a large change in the amount of adaptation achieved by the PD group, suggesting they are learning a larger amount of visually derived motor information. Along with observing intact adaptive responses, we also see intact catch-trial responses in PD, characterized by similar error responses to the control group. These results suggest that PD subject are more keenly accessing visual information in response to changes in the direction of movement. In contrast, we see that adaptation to the minifying gain is impaired in PD subjects, characterized by slower adaptation compared to control subjects. These results suggest that not only are the processes of adaptation to visual rotations and gains separable, but they are differentially impaired in PD. The neural machinery necessary for unencumbered adaptation to visual gains does not appear to circumvent impaired basal ganglia circuitry in PD. While certain aspects of adaptation are impaired, we observed intact trial-by-trial learning responses in both types of visual perturbations. This result suggests that visual feedback monitoring of current visuomotor states is intact for sensorimotor error derived from visual information.

Baseline behavior

To determine each groups' response to experiencing the visual environment, we first assessed baseline behavior during veridical movement. We averaged velocity and cursor

trajectories across subjects within each group to characterize baseline behavior (Fig. 3.3). We observed no significant differences between the two groups for peak speed ($p = 0.6751$, t-test) or movement breadth ($p = 0.6600$, t-test) during baseline performance.

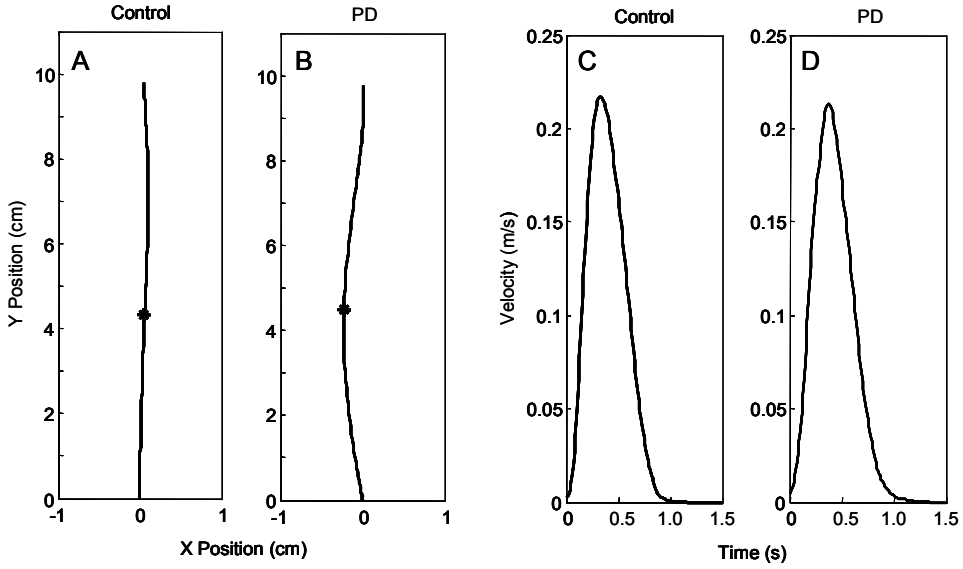

Figure 3.3: Average baseline response for cursor trajectories (*A* and *B*), and velocity profiles (*C* and *D*). No significant differences were observed between baseline profile of control (*A* and *C*) and the PD group (*B* and *D*). In *A* and *B*, asterisks indicate the average position at peak speed.

Adaptation to visual rotations

We characterized average kinematic reaching behavior for initial and adaptive responses in the rotation environments (Fig. 3.4). Across all subjects, we averaged the first exposure to the rotation (Fig. 3.4, *A* and *C*) and the last 10 movements before experiencing a catch-trial (Fig. 3.4, *B* and *D*). This qualitative analysis allows us to determine trends across all subjects. We observed similar initial responses for PD and control for the first exposure to the rotation (Fig. 3.4, *A* and *C*). However, we see that our

PD group achieves a straighter cursor trajectory during adaptation compared to the control group, suggesting more complete adaptation in PD (Fig. 3.4, *B* and *D*).

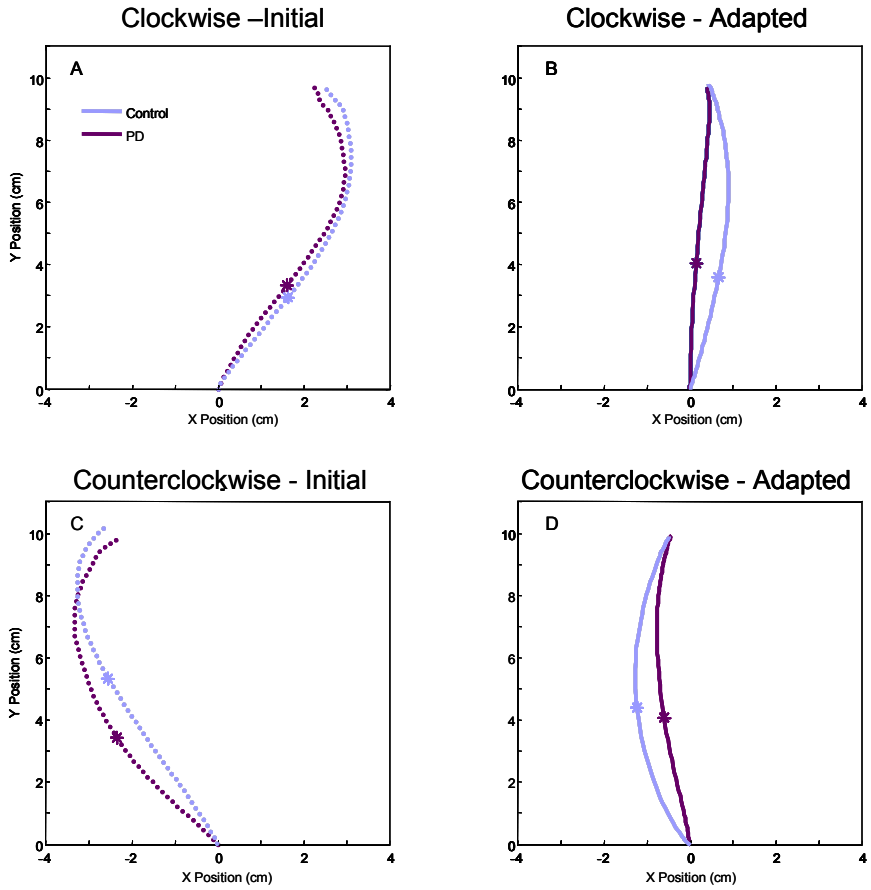

Figure 3.4: Average cursor trajectories for the initial and adapted response to clockwise (*A* and *B*), and counterclockwise (*C* and *D*) visual rotations. The initial rotation experience similarly displaces cursor trajectories for both control and PD (*A* and *C*). After 90 movements in the environment, both groups display straighter cursor trajectories in response to the rotation environment. We see that PD displays more complete adaptation than control (*B* and *D*).

In order to quantify and characterize adaptive rates and amount of adaptation achieved by each of our subject groups, we reduced data to lateral coordinate displacement (theta) at peak speed to determine adaptation across the first 100 movements. We fit an exponential function (*Eq*. 3.2) to this data to derive asymptotic values. We then calculated differences in the asymptotic behavior of our two groups (Fig. 3.5). By examining difference in asymptote magnitude, we observed no significant effect of asymptotic value for the clockwise rotation (control: -0.1652 ± 0.08994; PD: -0.0491 ± 0.0760, permutation test: $p = 0.079$, Fig. 3.5*B*), or the counterclockwise rotation (control: 0.2320 ± 0.1431; PD: 0.1329 ± 0.1178, permutation test: $p = 0.1510$, Fig. 3.5*D*).

It was noted that the PD group consistently displayed asymptotic values closer to idealized adaptation (zero). We then calculated the magnitude of change from initial rotation exposure on the first movement to the asymptotic value calculated from the last 10 movements before experiencing a catch-trial. Calculating adaptation as a percentage change of adaptation from initial exposure allowed us to capture true induced adaptation for each subject. We observed a significant difference in the percent magnitude of adaptation for the clockwise rotation (control: 55.6% ± 21.07%, PD: 96% ± 23.63%, $p < 0.05$, Fig. 3.6*A*). For the counterclockwise rotation we observed a non-significant change in the magnitude of adaptation (control: 34.92% ± 46.23%, PD: 74.79% ± 26.67%, $p = 0.27$, Fig. 3.6*B*). However, the observed difference in the counterclockwise rotation for PD and control follows a similar trend to that observed for the clockwise rotation, where we see a larger magnitude of adaptive change for the PD group. We believe these trends

indicate that PD patients have intact use of visual information to inform motor control when experiencing changes in visual direction.

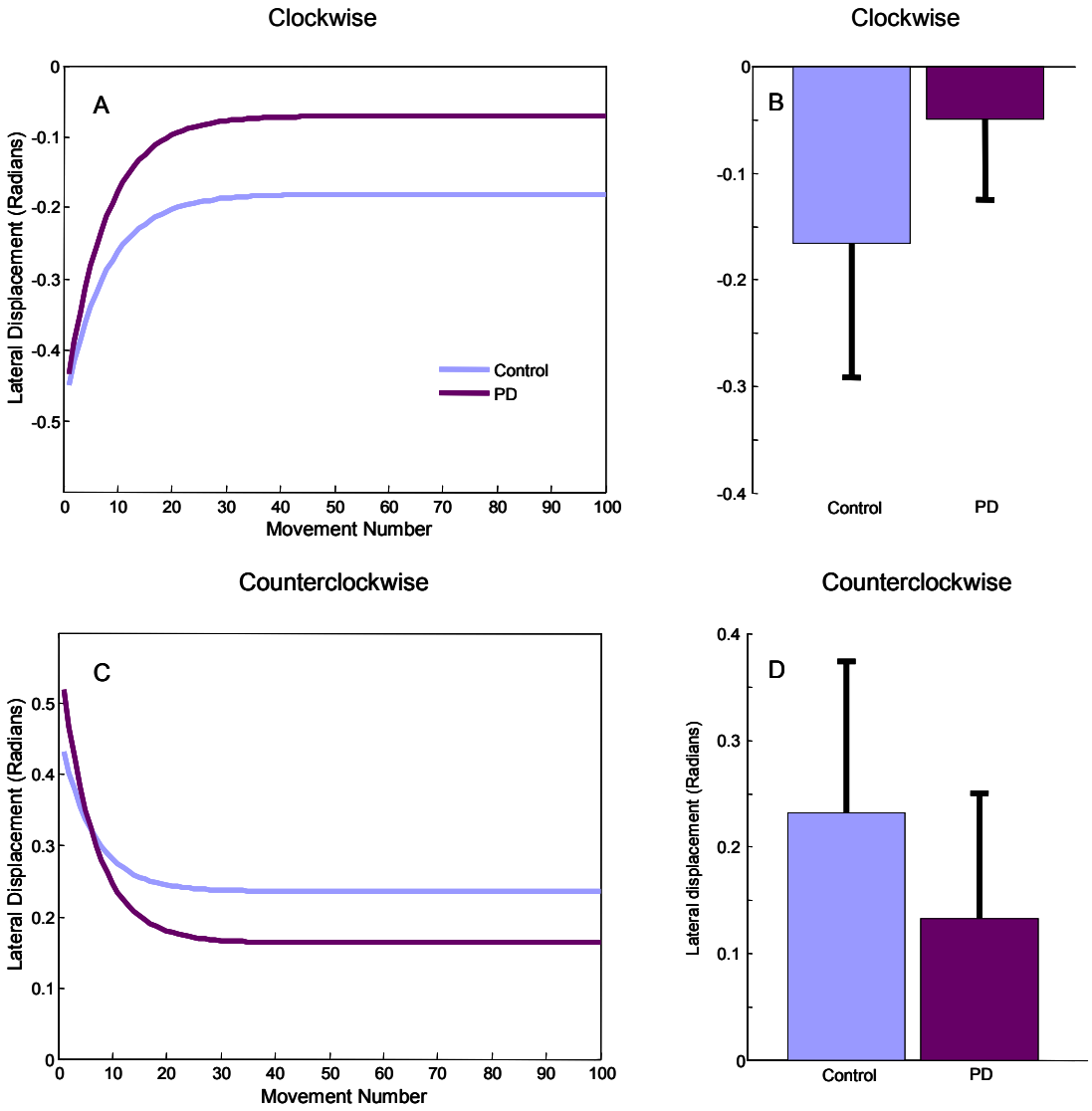

Figure 3.5: Exponentials fits of lateral displacement prior to catch-trial experience, for subjects experiencing clockwise (*A-B*) and counterclockwise (*C-D*) visual rotations. We saw non-significant changes in asymptote for clockwise ($p = 0.079$, permutation test) and counterclockwise ($p = 0.151$, permutation test).

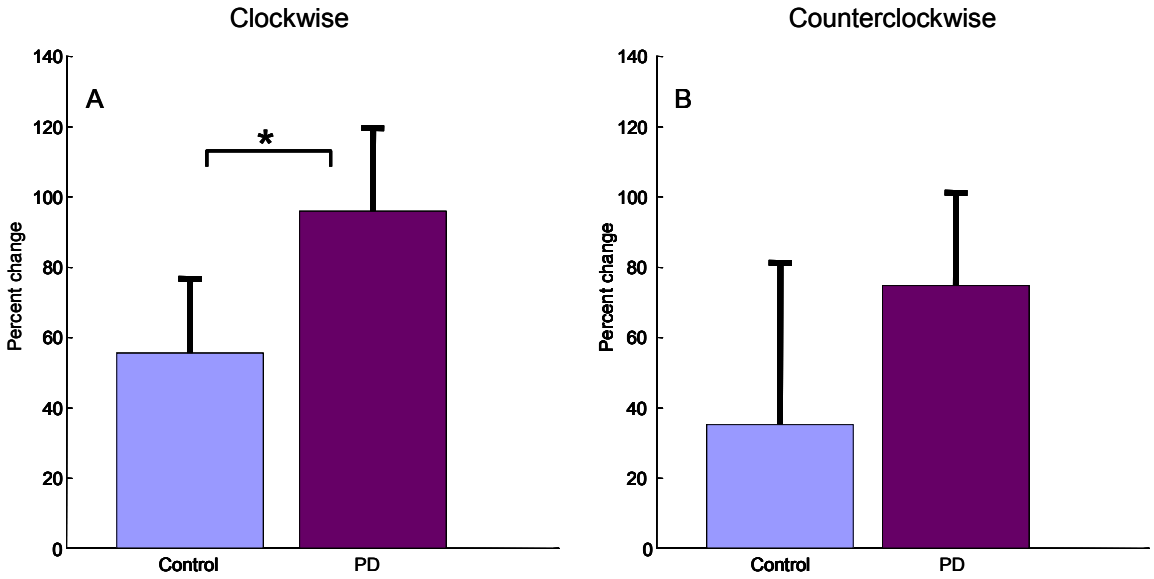

Figure 3.6: Average percent change from initial exposure to visual rotation to adapted behavior achieved over 100 movements. Clockwise rotation (*A*): we observe a significant change in adaptive behavior in the clockwise condition, with the PD group gaining a larger percentage of adaptive information over 100 movements ($p < 0.05$, t-test). Counterclockwise rotation (*B*): we observe a non-significant change between control and PD that trends similarly to the observation in clockwise rotation.

Trial-by-trial adaptation to rotations

We observed the effect of catch-trials by subtracting the average x cursor trajectories as described in (*Eq.* 3.3). We plotted these error responses against the average y cursor trajectory for all subtracted movements to depict the strength of unlearning induced by catch-trials (Fig. 3.7, *A* and *B*). We observe that the PD group performs similarly to the control group when presented with unexpected visuomotor errors in both the clockwise and counterclockwise rotations.

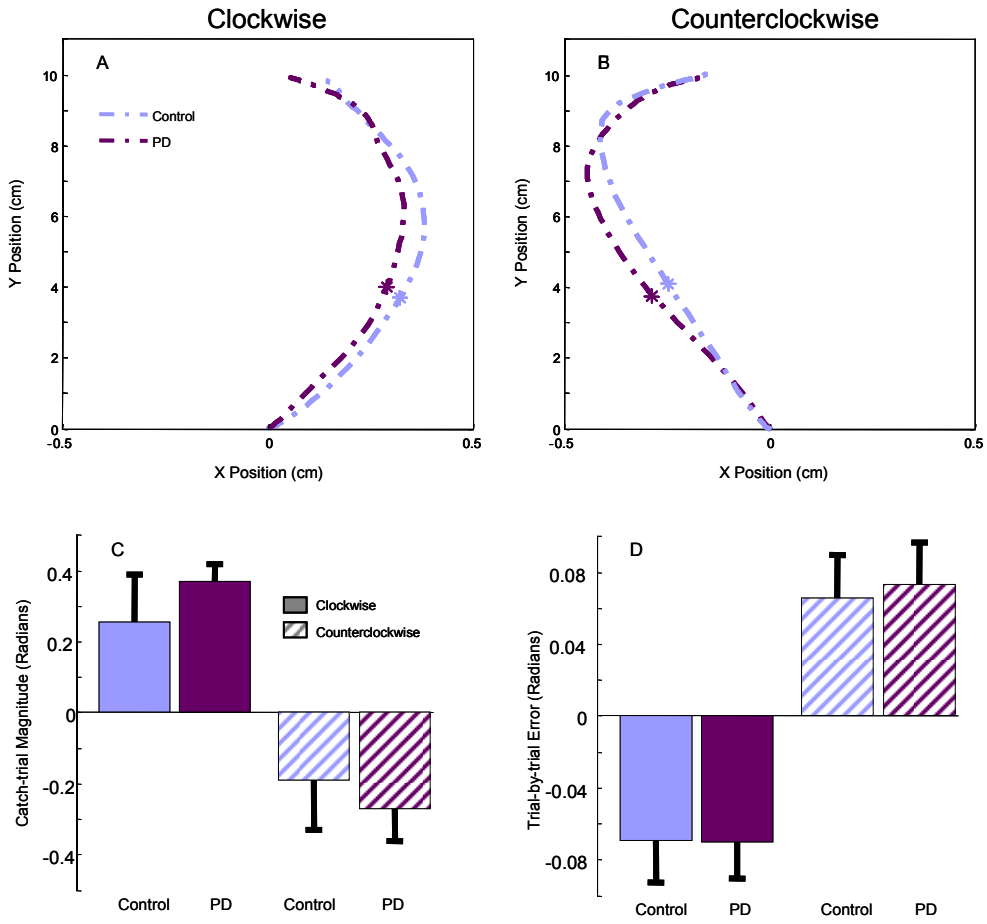

Figure 3.7: Average trial-by-trial cursor trajectory responses for clockwise (*A*) and counterclockwise (*B*), asterisks indicate the position at peak speed. The magnitude of the error response for control and PD was similar for catch-trial induced unlearning (*C* and *D*). *C*: Average lateral displacement at peak speed for catch-trial experiences; *D*: average trial-by-trial error response. We observed no significant difference between our two groups for the magnitude of catch-trial response (*C*), or the resulting error response due to experiencing a catch-trial (*D*).

We quantified this error by calculating the average amount of polar theta displacement at peak speed during the catch-trial (Fig. 3.7*C*) and as a result of catch-trial experience (Fig. 3.7*D, Eq.* 3.3). We observed that catch-trial responses were similar in magnitude for PD and control, for both clockwise and counterclockwise rotations (clockwise: control = 0.2552 ± 0.1347; PD = 0.3696 ± 0.0506, t-test; p = 0.1585; counterclockwise: control = -

0.1896 ± 0.1391; PD = -0.2715 ± 0.0909, t-test; p = 0.3624, Fig. 3.8*A*). The subsequent trial-by-trial error responses as a result of experiencing a catch-trial were also similar between the two groups (clockwise: control = -0.0691 ± 0.0237; PD = -0.0701 ± 0.0204, t-test; p > 0.5; counterclockwise: control = 0.0659 ± 0.0237; PD = 0.0735 ± 0.0236, t-test; p > 0.5, Fig. 3.7*D*).

Adaptation to changes in visual extent

We initially assessed adaptation to minifying gain using y position at peak speed. We fit each subjects' data using an exponential fit to derive asymptote of adaptation (Fig. 3.8, *Eq*. 3.2). We observed non-significant effects of asymptote (control = -0.0079 ± 0.3485; PD = -0.2802 ± 0.3696, permutation test; p = 0.18, Fig. 3.8*B*), but observed that the control group asymptotes more closely to zero, where zero would be ideal adaptation.

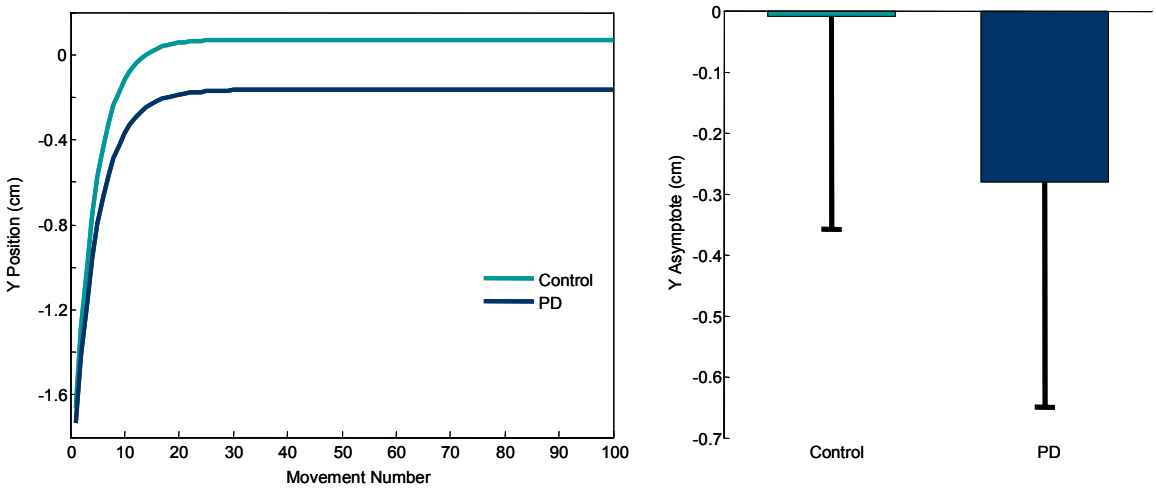

Figure 3.8: *A*: Exponential fits to y position at peak speed across the first 100 movements performed in the minifying gain. *B*: We observed non-significant differences in asymptotic response between PD and control (p = 0.18).

While we saw no significant effect of adaptation derived from exponential fits in the minifying gain condition, we suspected that this error metric did not fully capturing the adaptive elements during exposure to minifying gain. We explored time series of velocity traces to calculate velocity dependent metrics. We evaluated the properties of the velocity profiles in our two groups, and derived two metrics to characterize behavior in the gain condition: breadth of movement and peak velocity. We observed velocity properties across the first five movements to evaluate initial characteristics during the first phase of exposure to the minifying gain (Fig. 3.9).

We observed similar baseline velocity behavior in both groups (Fig. 3.3 and 3.9), suggesting that patients in the PD group had no difficulty performing the task without the presence of a gain modulation. However, we do observe differences in the velocity profile of the PD group when they are faced with the minifying gain. Qualitatively, we see a wider breadth of movement, as well as a reduction in peak velocity in the PD group when contrasted with the performance of the control group (Fig. 3.9*B*).

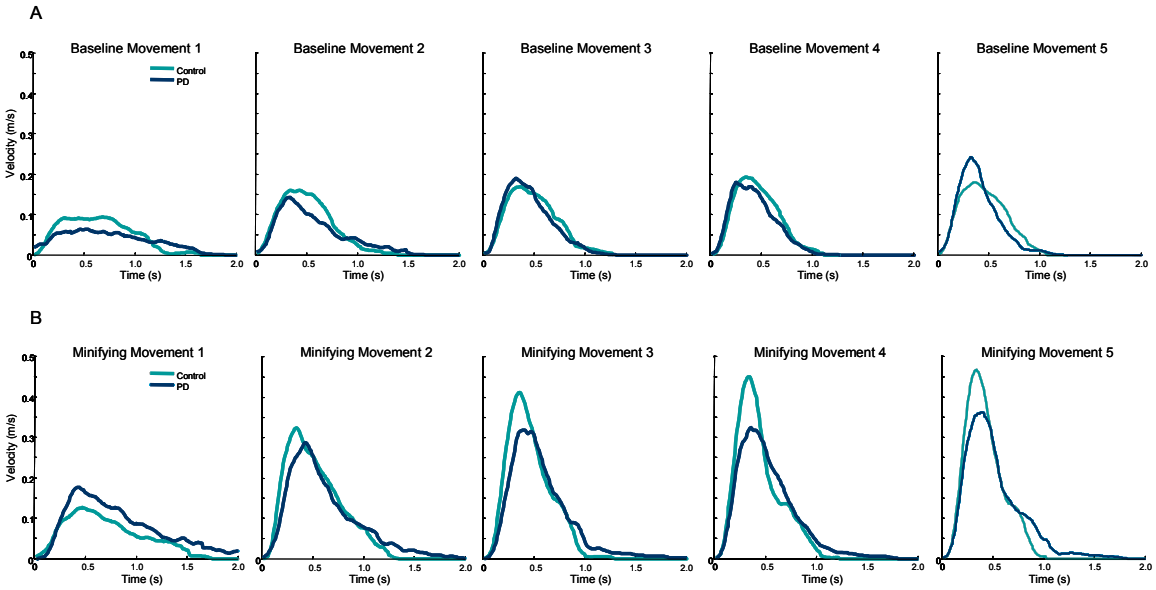

Figure 3.9: Average velocity traces for the first 5 movements of the baseline condition on day 1 (*A*), and the first 5 movements during the minifying gain condition (*B*). We find no baseline differences between control and PD, but observe a lower max velocity and a wider breadth of movement in the PD group indicating initial difficulty with learning the minifying gain.

From our velocity traces we reduced data to examine individual subject values of breadth and peak velocity. We evaluated movement breadth across the first ten movements (Fig. 3.10*A*), and averaged across 10 movement groupings for all 100 movements (Fig. 3.10*B*). We observe that initial exposure to minifying gain results in significantly longer breadth of movement across the average of the first ten movement in PD compared to control (Control: 85.31 ± 2.89; PD: 108.22 ± 16.68; t-test: $p = 0.0131$; Fig. 3.10, *A* and *C*). We did not observe this same difference in breadth during the last ten movements before the onset of catch-trials (Control: 74.21 ± 2.91; PD: 75.55 ± 4.57; t-test: $p = 0.6275$; Fig. 3.10*C*). The rate of adaptation was significantly different between PD and control when we compared each set of ten movements, demonstrating that it took PD subjects over 20 movements to achieve adaptation (movement sets 1-10, 11-20, $p < 0.02$, t-test, Fig

3.10*B*). This indicates that PD adapts at a slower rate, but is able to achieve similar adaptation to controls.

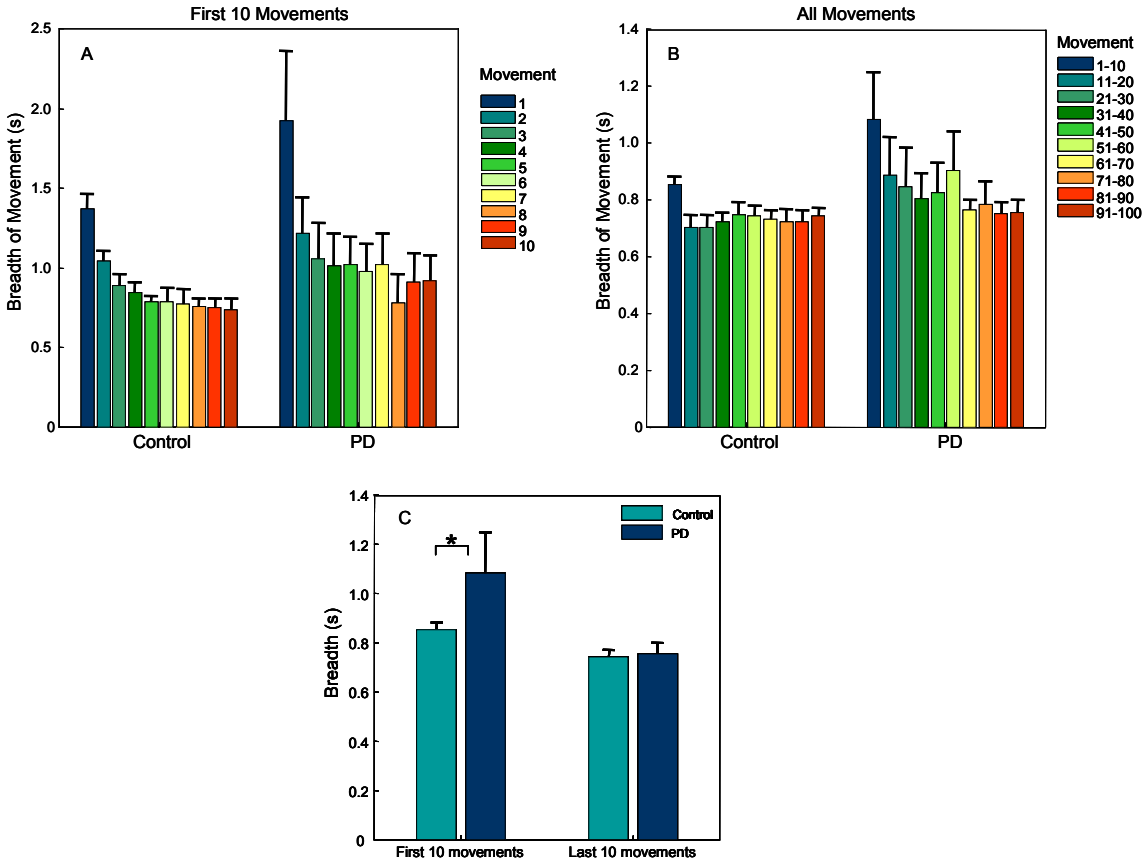

Figure 3.10: Breadth calculations for subjects experiencing the minifying gain. Average subject responses across the first 10 movements (*A*) shows that control subjects quickly adapt to the induced gain while PD subjects respond more slowly. *B*: Breadth profiles across all 100 movements. *C*: We observed a significant difference in the breadth responses for control and PD during the first 10 movements. By adaptation (last 10 movements), PD subjects reach similar breadth responses when compared to control.

In addition to changes in breadth between PD and control we also observe differences in peak velocity behavior between control and PD (Fig. 3.11). We calculated peak velocity similarly to the breadth measurements, to evaluate behavior during the initial phase of adaptation (first 10 movements, Fig. 3.11*A*) and across all movements (10 movement

subsets, Fig. 3.11*B*). We observe that it takes longer for PD to achieve peak velocity associated with adapted movement (Fig. 3.11, *A* and *C*), but that the peak velocity response achieves similar magnitudes at the end of adaptation (Fig. 3.11*B*). We see a significant difference in the amount of change from initial exposure, the average of the first ten movements, to adapted exposure, the average of the last ten movements between control (First 10: 0.4318 ± 0.0308; Last 10: 0.3751 ± 0.0568, p = 0.6648) and PD (First 10: 0.4492 ± 0.0206; Last 10: 0.4827 ± 0.0307, p = 0.0056, Fig. 3.11).

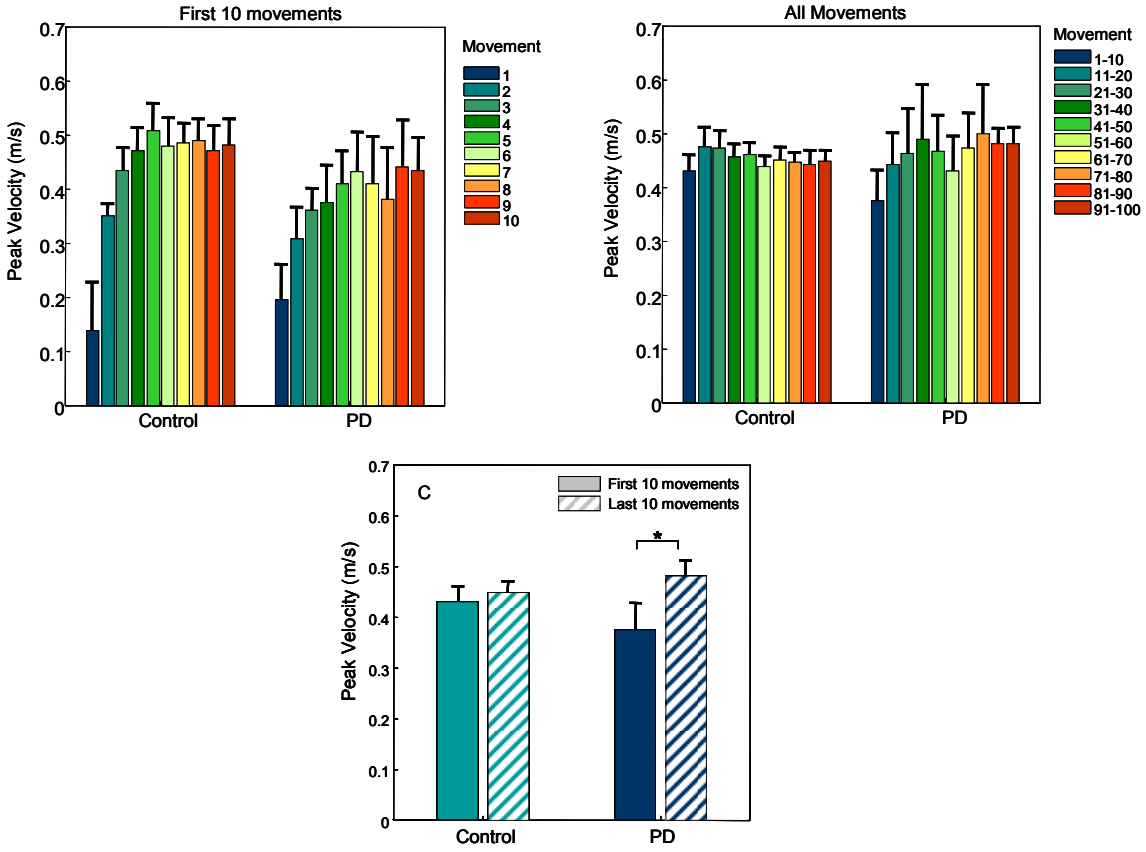

Figure 3.11: Peak velocity calculations for subjects experiencing minifying gains. Average subject response across the first 10 movements (*A*) shows that PD subjects display lower peak velocity magnitudes, but they achieve similar magnitudes of peak velocity near the end of adaptation (*B*). We observe a significant difference in the peak velocity between the average first and last 10 movements in the PD group, which is absent in controls (*C*), suggesting that it takes the PD group longer to reach adaptation during gain experiences.

We observe that the trial-by-trial response to catch-trials during minifying gain was intact (Fig. 3.12). We determined magnitude of catch response (Fig. 3.12*A*) as well as trial-by-trial error (Fig. 3.12*B*, *Eq*. 3.3). We observed no significant differences between our two groups for catch magnitude (Control: 2.29 ± 0.69; PD: 2.20 ± 0.74, p = 0.86), or trial-by-trial error (Control: -0.29 ± 0.18; PD: -0.18 ± 0.31, p = 0.54).

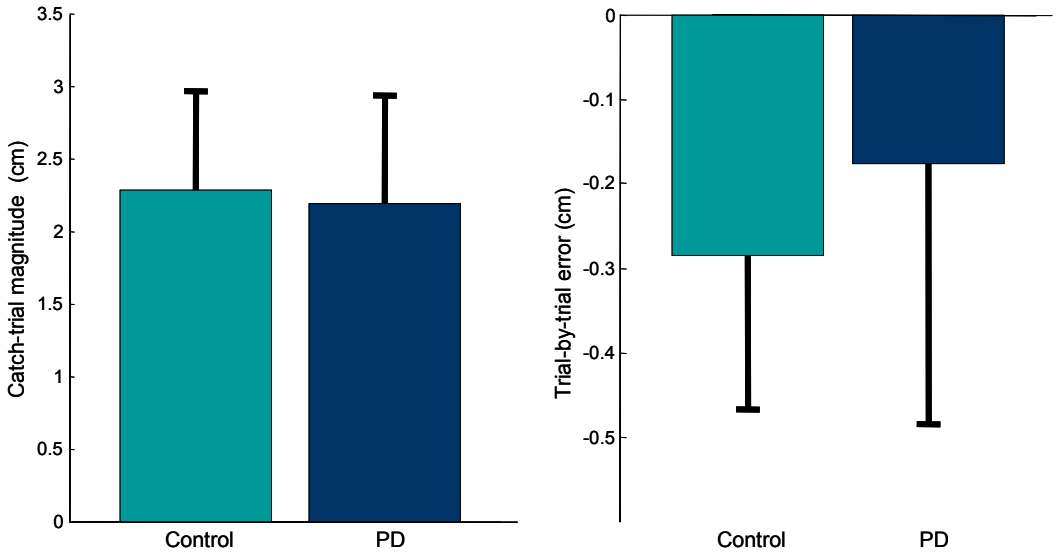

Figure 3.12: (*A*): Average subject response to the presentation of catch-trials in the minifying gain condition. (*B*): Average trial-by-trial error response to the presentation of catch-trials, we see that the error effect is smaller, but not significant in PD.

DISCUSSION

Our original hypotheses were designed to test visuomotor adaptation in Parkinson's disease from a mechanistic viewpoint. We believe that due to basal ganglia impairment, visuomotor adaptation as a whole would be impaired in PD. Additionally, we believe

that this impairment would be more profound for adaptation to visual changes of extent than to changes in direction. We see that PD subjects can possess both intact and impaired visuomotor adaptation depending on the type of task they are presented.

Effects of visual rotation and visual gain

Despite significant motor impairments, we discovered that PD subjects have intact visuomotor adaptation to visual rotations, and show stronger adaptation than our control subjects, marked by an overall larger magnitude of acquired adaptive information (Fig. 3.6). In contrast we observed significant deficits in adaptation to visuomotor gains, marked by decreases in movement time and velocity during the adaptive process (Fig. 3.9-3.11). Not only do our results highlight the behavioral separability of adaptation to changes in extent and direction, but they provide evidence that intact basal ganglia circuitry is necessary for intact adaptation to visuomotor gains.

In a patient population that has marked difficulty with production and maintenance of movement, it is surprising to see such strong adaptive effects in response to visual rotations. In other tablet experiments, adaptation to changes in visual direction have described PD ability to adapt to changes in direction as impaired (Contreras-Vidal et al. 2003, Paquet et al. 2008, Venkatakrishnan et al. 2011). Although these studies used similar methods to test and perturb visual feedback to a rotated cursor, we believe that we more accurately characterize adaptation to rotations by evaluating multiple rotation exposures and testing visuomotor error on a trial-by-trial basis. In our experiment, we

observe that PD is highly capable of learning new visuomotor rotations, as indicated by more ideal movement trajectories (Fig. 3.4), and a larger magnitude of adaptive change compared to controls (Fig. 3.6).

In contrast to the positive results observed for adaptation to rotations, we see that adaptation to changes in visual gain is impaired. While it has been suggested that gain adaptation is intact in PD (Contreras-Vidal et al. 2002), we determined that while subjects with PD and control subjects achieve similar adaptive plateaus, the adaptive process needed to reach adaptation differs. We see that PD made longer and slower movements during early phases of the movement. We believe that this impairment exists because neural machinery necessary for visuomotor adaptation to gains does not circumvent the basal ganglia, as is the case in visuomotor rotations. This idea is supported by previous evidence from gain modulated drawing studies (Fucetola and Smith 1997, Teulings et al. 2002).

The separation of adaptive effects that we see for rotations and gains in our PD subjects act to support the original theory of vectorized planning of reaching movements (Ghez et al. 1991, Gordon et al. 1994). Additionally, the deficits we observe in PD during gain adaptation confirm that basal ganglia circuitry is necessary for proper visuomotor adaptation to changes in gain (Krakauer et al. 2004). We believe that our experiment provides a model of visuomotor adaptation that is differentially affected depending on whether visual feedback is accessing cortical circuitry (rotations) or basal ganglia circuitry (gains).

Trial-by-trial visuomotor learning

We observed no impairments in PD trial-by-trial responses to catch-trials in any of our visuomotor perturbations. The consistency of intact trial-by-trial learning across all conditions suggests that the ability of PD subjects to apply feedback from previous movements is not impaired, as indicated by similar magnitudes of visuomotor error and unlearning responses as a result of catch-trial experience in both of our groups. This result suggests that the ability to extract useful feedback information from ongoing movement performance is not impaired in our PD group, despite observing deficits in the adaptive process.

Importance of visual feedback in PD

The idea that patients with PD utilize visual information to their benefit is well-known. The use of visual feedback has been associated with facilitation of postural response, (Brown et al. 2006b), exercise (Sage and Almeida 2010), visually guided reaching (Myall et al. 2008), in response to visuomotor perturbations that modulate movement amplitude during drawing tasks (Fucetola and Smith 1997) and modulation of reaching movements in response to visuomotor feedback (Ghilardi et al. 2000). In our experiment, we observed that in response to visual rotations, PD subjects adapt more fully than our control group. This result suggests that they may be using an increased amount of visual information to guide their movements.

In contrast, we see that PD subjects display deficits in response to adaptation of visuomotor gains. While this deficit is noticeable, PD subjects achieve similar levels of adaptation compared to controls, but at a slower rate. It is likely that in both types of perturbing environments PD subjects are utilizing visual information to their advantage. In the case of gain adaptation, it is likely that impairment in visuomotor adaptation is severely impaired, but is improved due to the presence of continual visual feedback. It has been suggested that visual guidance aids in tasks requiring movement amplitude (Fucetola and Smith 1997); however, visual feedback is not enough to overcompensate for the damaged basal ganglia circuitry and deficits in the adaptive process are evident.

We suspect that PD patients are able to amplify the use of visual information in order to combat internally noisy motor production. Typically, these aspects of sensorimotor noise are integrated in a statistically optimal fashion (Ernst and Banks 2002). When we consider how our PD subjects respond to visual perturbations we believe that the input they receive from external visual signals is intact and similar to that of control subjects. However, we assume that internal motor control in PD is very noisy due to degeneration of circuitry involved in movement maintenance and production. This noisy input from motor control forces PD patients to rely more heavily on less variable external visual input.

In order to produce movements being informed by visual feedback, it is necessary to process movement via the basal ganglia (Graybiel et al. 1994). When we consider

adaptation to visuomotor stimuli, we must receive external visual information, compute the visual error feedback signals, and then plan and produce the movement. For adaptation to visuomotor rotations, we see this error feedback signal represented cortically while for changes in visual gains it is represented in the basal ganglia (Krakauer et al. 2004). The computations occurring during adaptation to rotations allow visuomotor error signals to guide movement production. While movement production may be mediated via the basal ganglia, the adaptive mechanisms governing learning are mediated cortically and not accessing the basal ganglia in response to visually derived errors, allowing for amplified usage of visual information to drive movement. In the case of the gain condition, both movement production and the underlying adaptive mechanism utilize basal ganglia circuitry (Krakauer et al., 2004). While gain adaptation may in fact utilize more externally guided feedback to guide movement, the internal processing of this information is faulty, leading it to be less reliable. This impairment comes through during the adaptive phase of gain perturbations, where we see decreases in adaptive ability suggesting that the use of external visual information cannot override the impaired visuomotor machinery.

A mix of circuitry and neural plasticity likely result in the increased amounts of adaptation we see in our PD group to visual rotations. Cortical reorganization resulting in an increased reliance on visual control of movement in PD is likely. These types of cortical plasticity have been seen as compensatory behavior in other sensory deficits; such as deafness, where unused or defunct cortical territories are overtaken by visual sensory information processing (Finney et al. 2003). It has been suggested that in PD

patients, cortical remapping takes place in response to Parkinsonian changes of the brain (Helmich et al. 2010), and has been seen specifically to affect remapping of visual cortical areas (Helmich et al. 2007). Remapping of some motor information to visual areas in PD is possible, suggesting that the amplification of visual error signals we see during adaptation to visual rotations results from additional recruitment of cortical areas responsible for processing visual information. This similar mode of cortical remapping to visual areas is possible for PD patients to utilize and rely more on visual information than noisy internal motor control. It may be more difficult for gain error signals to recruit information from visual areas to aid adaptation due to the localization of visual feedback error signals to the basal ganglia

Conclusions

We have shown evidence that suggests that the separation of visuomotor adaptation to direction and extent can be mechanistically modeled via Parkinson's patients. We see that PD patients display intact adaptation to visual rotations that is amplified via visual information; while adaptation to gains may be impaired due to degenerated basal ganglia circuitry. These results suggest that visuomotor movement planning requires the specification of direction and extent, as well as a distinct ability in PD to use visual information to their advantage when visuomotor error mechanisms do not rely on basal ganglia circuitry. Tailoring therapeutic techniques to avoid the use of gain modulation for learning in PD may provide assistance and alleviation of some of the motor symptoms that characterize PD.

REFERENCES

Abbruzzese G, and Berardelli A. Sensorimotor integration in movement disorders. Mov Disord 18: 231-240, 2003.

Albin RL, Young AB, and Penney JB. The functional anatomy of basal ganglia disorders. Trends Neurosci 12: 366-375, 1989.

Au WL, Lei N, Oishi MM, and McKeown MJ. L-dopa induces under-damped visually guided motor responses in Parkinson's disease. Exp Brain Res 202: 553-559, 2010.

Brown LA, Cooper SA, Doan JB, Dickin DC, Whishaw IQ, Pellis SM, and Suchowersky O. Parkinsonian deficits in sensory integration for postural control: temporal response to changes in visual input. Parkinsonism Relat Disord 12: 376-381, 2006.

Brown P, Chen CC, Wang S, Kuhn AA, Doyle L, Yarrow K, Nuttin B, Stein J, and Aziz T. Involvement of human basal ganglia in offline feedback control of voluntary movement. Curr Biol 16: 2129-2134, 2006.

Contreras-Vidal JL, and Buch ER. Effects of Parkinson's disease on visuomotor adaptation. Exp Brain Res 150: 25-32, 2003.

Contreras-Vidal JL, and Gold DR. Dynamic estimation of hand position is abnormal in Parkinson's disease. Parkinsonism Relat Disord 10: 501-506, 2004.

Contreras-Vidal JL, Teulings HL, Stelmach GE, and Adler CH. Adaptation to changes in vertical display gain during handwriting in Parkinson's disease patients, elderly and young controls. Parkinsonism Relat Disord 9: 77-84, 2002.

de Lau LM, and Breteler MM. Epidemiology of Parkinson's disease. Lancet Neurol 5: 525-535, 2006.

DeLong MR, and Wichmann T. Circuits and circuit disorders of the basal ganglia. Arch Neurol 64: 20-24, 2007.

den Ouden HE, Daunizeau J, Roiser J, Friston KJ, and Stephan KE. Striatal prediction error modulates cortical coupling. J Neurosci 30: 3210-3219.

Desmurget M, Grafton ST, Vindras P, Grea H, and Turner RS. Basal ganglia network mediates the control of movement amplitude. Exp Brain Res 153: 197-209, 2003.

Doyon J, Penhune V, and Ungerleider LG. Distinct contribution of the cortico-striatal and cortico-cerebellar systems to motor skill learning. Neuropsychologia 41: 252-262, 2003.

Ernst MO, and Banks MS. Humans integrate visual and haptic information in a statistically optimal fashion. Nature 415: 429-433, 2002.

Fernandez-Ruiz J, Diaz R, Hall-Haro C, Vergara P, Mischner J, Nunez L, Drucker-Colin R, Ochoa A, and Alonso ME. Normal prism adaptation but reduced after-effect in basal ganglia disorders using a throwing task. Eur J Neurosci 18: 689-694, 2003.

Fucetola R, and Smith MC. Distorted visual feedback effects on drawing in Parkinson's disease. Acta Psychol (Amst) 95: 255-266, 1997.

Galvan A, and Wichmann T. Pathophysiology of parkinsonism. Clin Neurophysiol 119: 1459-1474, 2008.

Ghez C, Hening W, and Gordon J. Organization of voluntary movement. Curr Opin Neurobiol 1: 664-671, 1991.

Ghilardi MF, Alberoni M, Rossi M, Franceschi M, Mariani C, and Fazio F. Visual feedback has differential effects on reaching movements in Parkinson's and Alzheimer's disease. Brain Res 876: 112-123, 2000.

Gordon J, Ghilardi MF, and Ghez C. Accuracy of planar reaching movements. I. Independence of direction and extent variability. Exp Brain Res 99: 97-111, 1994.

Graybiel AM, Aosaki T, Flaherty AW, and Kimura M. The basal ganglia and adaptive motor control. Science 265: 1826-1831, 1994.

Hamilton CR, and Bossom J. Decay of Prism Aftereffects. J Exp Psychol 67: 148-150, 1964.

Helmich RC, de Lange FP, Bloem BR, and Toni I. Cerebral compensation during motor imagery in Parkinson's disease. Neuropsychologia 45: 2201-2215, 2007.

Helmich RC, Derikx LC, Bakker M, Scheeringa R, Bloem BR, and Toni I. Spatial remapping of cortico-striatal connectivity in Parkinson's disease. Cereb Cortex 20: 1175-1186.

Horak FB, and Anderson ME. Influence of globus pallidus on arm movements in monkeys. I. Effects of kainic acid-induced lesions. J Neurophysiol 52: 290-304, 1984a.

Horak FB, and Anderson ME. Influence of globus pallidus on arm movements in monkeys. II. Effects of stimulation. J Neurophysiol 52: 305-322, 1984b.

Inzelberg R, Schechtman E, and Hocherman S. Visuo-motor coordination deficits and motor impairments in Parkinson's disease. PLoS One 3: e3663, 2008.

Jobst EE, Melnick ME, Byl NN, Dowling GA, and Aminoff MJ. Sensory perception in Parkinson disease. Arch Neurol 54: 450-454, 1997.

Kempf F, Brucke C, Kuhn AA, Schneider GH, Kupsch A, Chen CC, Androulidakis AG, Wang S, Vandenberghe W, Nuttin B, Aziz T, and Brown P. Modulation by dopamine of human basal ganglia involvement in feedback control of movement. Curr Biol 17: R587-589, 2007.

Khor SP, and Hsu A. The pharmacokinetics and pharmacodynamics of levodopa in the treatment of Parkinson's disease. Curr Clin Pharmacol 2: 234-243, 2007.

Krakauer JW, Ghilardi MF, Mentis M, Barnes A, Veytsman M, Eidelberg D, and Ghez C. Differential cortical and subcortical activations in learning rotations and gains for reaching: a PET study. J Neurophysiol 91: 924-933, 2004.

Krakauer JW, Pine ZM, Ghilardi MF, and Ghez C. Learning of visuomotor transformations for vectorial planning of reaching trajectories. J Neurosci 20: 8916-8924, 2000.

Kwak Y, Muller ML, Bohnen NI, Dayalu P, and Seidler RD. Effect of dopaminergic medications on the time course of explicit motor sequence learning in Parkinson's disease. J Neurophysiol 103: 942-949, 2010.

Lees AJ, Hardy J, and Revesz T. Parkinson's disease. Lancet 373: 2055-2066, 2009.

Lehericy S, Benali H, Van de Moortele PF, Pelegrini-Issac M, Waechter T, Ugurbil K, and Doyon J. Distinct basal ganglia territories are engaged in early and advanced motor sequence learning. Proc Natl Acad Sci U S A 102: 12566-12571, 2005.

Marinelli L, Crupi D, Di Rocco A, Bove M, Eidelberg D, Abbruzzese G, and Ghilardi MF. Learning and consolidation of visuo-motor adaptation in Parkinson's disease. Parkinsonism Relat Disord 15: 6-11, 2009.

Messier J, Adamovich S, Jack D, Hening W, Sage J, and Poizner H. Visuomotor learning in immersive 3D virtual reality in Parkinson's disease and in aging. Exp Brain Res 179: 457-474, 2007.

Mink JW. The basal ganglia: focused selection and inhibition of competing motor programs. Prog Neurobiol 50: 381-425, 1996.

Mongeon D, Blanchet P, and Messier J. Impact of Parkinson's disease and dopaminergic medication on proprioceptive processing. Neuroscience 158: 426-440, 2009.

Myall DJ, MacAskill MR, Anderson TJ, and Jones RD. Submovements in visually-guided and memory-guided reaching tasks: changes in Parkinson's disease. Conf Proc IEEE Eng Med Biol Soc 2008: 1761-1764, 2008.

Nixon PD, McDonald KR, Gough PM, Alexander IH, and Passingham RE. Cortico-basal ganglia pathways are essential for the recall of well-established visuomotor associations. Eur J Neurosci 20: 3165-3178, 2004.

Nowak DA, and Hermsdorfer J. Predictive and reactive control of grasping forces: on the role of the basal ganglia and sensory feedback. Exp Brain Res 173: 650-660, 2006.

Paquet F, Bedard MA, Levesque M, Tremblay PL, Lemay M, Blanchet PJ, Scherzer P, Chouinard S, and Filion J. Sensorimotor adaptation in Parkinson's disease:

evidence for a dopamine dependent remapping disturbance. Exp Brain Res 185: 227-236, 2008.

Pine ZM, Krakauer JW, Gordon J, and Ghez C. Learning of scaling factors and reference axes for reaching movements. Neuroreport 7: 2357-2361, 1996.

Prager AD, and Contreras-Vidal JL. Adaptation to display rotation and display gain distortions during drawing. Hum Mov Sci 22: 173-187, 2003.

Sage MD, and Almeida QJ. A positive influence of vision on motor symptoms during sensory attention focused exercise for Parkinson's disease. Mov Disord 25: 64-69, 2010.

Seidler RD, Noll DC, and Chintalapati P. Bilateral basal ganglia activation associated with sensorimotor adaptation. Exp Brain Res 175: 544-555, 2006.

Teulings HL, Contreras-Vidal JL, Stelmach GE, and Adler CH. Adaptation of handwriting size under distorted visual feedback in patients with Parkinson's disease and elderly and young controls. J Neurol Neurosurg Psychiatry 72: 315-324, 2002.

Thoroughman KA, and Shadmehr R. Learning of action through adaptive combination of motor primitives. Nature 407: 742-747, 2000.

Turner RS, Desmurget M, Grethe J, Crutcher MD, and Grafton ST. Motor subcircuits mediating the control of movement extent and speed. J Neurophysiol 90: 3958-3966, 2003.

Vaillancourt DE, Slifkin AB, and Newell KM. Visual control of isometric force in Parkinson's disease. Neuropsychologia 39: 1410-1418, 2001.

Vaillancourt DE, Thulborn KR, and Corcos DM. Neural basis for the processes that underlie visually guided and internally guided force control in humans. J Neurophysiol 90: 3330-3340, 2003.

Venkatakrishnan A, Banquet JP, Burnod Y, and Contreras-Vidal JL. Parkinson's disease differentially affects adaptation to gradual as compared to sudden visuomotor distortions. Hum Mov Sci 2011.

Zia S, Cody F, and O'Boyle D. Joint position sense is impaired by Parkinson's disease. Ann Neurol 47: 218-228, 2000.

Chapter 4

Discussion and Future Directions

Chapter 4: Discussion and Future Directions

The goal of this thesis was to characterize trial-by-trial use of visual feedback during visuomotor learning in young adults, older adults, and in Parkinson's disease. In Chapter 2 we determined that in normal young adults, current adaptive strategies can be influenced by environmental experience within a single day and on prior days. Our discovery provides important insights into visual control of movement as well as presenting a direct correlate to existing haptic literature (Fine and Thoroughman 2007). Not only do these results suggest similarly flexible adaptation as seen in the force learning study, but they suggest inherent differences in the way that these two types of adaptation occur. While we see some similarities between the force learning and visuomotor learning, it is likely that visuomotor adaptation is influenced by more cognitively salient experiences within the constraints of the environment to drive the adaptive strategy (Kagerer et al. 1997, Michel et al. 2007, Taylor and Ivry 2011).

In Chapter 3 we discovered that visuomotor adaptation is differentially impaired in Parkinson's disease (PD), providing a mechanistic model by which the basal ganglia interacts with and controls visuomotor adaptation. In addition to providing evidence for the separation of visuomotor extent and direction (Gordon et al. 1994, Pine et al. 1996, Krakauer et al. 2000), we surprisingly discovered that our PD patients displayed more complete adaptation to visuomotor rotations. This result contradicts several other studies that describe aspects of visuomotor adaptation in PD as impaired (Contreras-Vidal et al. 2003, Fernandez-Ruiz et al. 2003, Messier et al. 2007, Marinelli et al. 2009). However,

in the majority of these studies, PD subjects remained on their levodopa treatment. To us this suggests that these studies are not a true representation of visuomotor behavior in PD. Levodopa treatment in PD has been suggested to result in visuomotor deficits during visually guided reaching (Au et al. 2010) and sequence learning (Kwak et al. 2010). This suggests that the normal usage of levodopa therapy during experiments may in fact mask the true underlying behavior of basal ganglia activity in PD driving visuomotor adaptation, as well as altering the process of visuomotor control. We feel that the ability to accurately identify abilities and disabilities present during the control of movement are important to not only discerning the mechanisms by which visuomotor adaptation operates, but to provide and identify appropriate rehabilitative and therapeutic interventions that may be able to help these patients in everyday tasks.

FLEXIBLE VISUOMOTOR LEARNING

Our discoveries of across-day visuomotor effects in Chapter 2 have shown that visuomotor adaptation is a highly flexible process that be influenced by immediate environmental conditions and previously learnt adaptive information. More importantly, this experiment also characterizes distinct differences between motor adaptation processes that engage visuomotor adaptation mechanisms and proprioceptive adaptation mechanisms.

Fine and Thoroughman (2007) discussed the flexibility of adaptive strategies in terms of being able to adapt to particular environmental conditions. The results that we see in

Chapter 2 suggest that not only are the mechanisms by which visuomotor adaptation operate flexible, they remain modifiable to account for previously learned information. While we see similarities between our study and Fine and Thoroughman (2007), we also see fundamental differences that highlight and emphasize that in each of these studies feedback informing motor control is derived from different mechanisms. Visuomotor tasks rely solely on visual information to drive motor planning and behavior, while response to force feedback requires an integration of vision and proprioception to drive behavior. This dissociation has been seen by eliminating proprioceptive signaling and testing adaptation to both force and visual feedback tasks (Bock and Thomas 2011).

VISUOMOTOR LEARNING: EFFECT OF DISEASE

We have also identified important aspects of visuomotor adaptation in Parkinson's disease. We see that PD patients can easily adapt to newly experienced visuomotor perturbations. We have observed that this process is highly dependent on the type of visual feedback experience PD subjects receive. Surprisingly when adapting to visuomotor rotations, we saw a greater amount of change in the amount of adaptation, suggesting that despite basal ganglia injury, these subjects could reliably use visual information to guide their movements. In contrast, when experiencing visual gains, we observed a diminished ability to adapt compared to control subjects. This result supports theory for the separation of visual and extent and direction necessary for planning of visually guided movements (Gordon et al. 1994, Pine et al. 1996, Krakauer et al. 2000).

It is known that PD patients have significant difficulties with slowness and freezing of gait; however, it has been shown that visual cues can improve gait performance (Brown et al. 2006, Sidaway et al. 2006). We find that similar properties of visual guidance are present when we examine the visual control of reaching movements. Our results from adaptation to visual rotations and evidence from gait studies suggest that some forms of visuomotor adaptation are able to circumvent the basal ganglia through use of alternative neural pathways. It is likely that adaptation to visual rotations and certain forms of visual feedback during gait access neural signals not impacted by damaged basal ganglia circuitry. It has been suggested that in patients with PD, visuomotor signals are rerouted to the cerebellum via cerebral cortex (Glickstein and Stein 1991). While this is a plausible idea, it only explains our result from adaptation to rotation. We believe that this plasticity may be minimal, and that the visual error feedback mechanisms for rotation and gain reside in cortical and subcortical areas, respectively (Krakauer et al. 2004). If PD subjects were able to use plasticity to reroute their signals, we would see overall improvement of visuomotor behavior.

FLEXIBLE ADAPTATION FOR DISEASE

We have shown in Chapter 2 that visuomotor control can be a flexible, fluid process; while in Chapter 3 we have shown clear ability during visuomotor control for PD subjects with significant movement difficulties. These results combined suggest that if we better understand the strategies by which people learn and continue to learn beyond the initial session, we may be able to customize adaptive processes to optimize transfer of

visuomotor information. While we have shown that PD patients have certain forms of intact adaptation, Marinelli et al. (2009) has shown that while forms of PD adaptation can be intact, motor consolidation across days is impaired. Using adaptive strategies to initially improve movement performance without inducing a formal change in motor behavior are a disservice to improve patient stability. Long-term cues have been shown to be useful in ameliorating gait behavior (Sidaway et al. 2006), but will similar mechanisms work for visually guided reaching? We believe that using customizable adaptive strategies with real-world visual feedback paradigms aimed at accessing PD patient ability to use visually guided movement may help with environmental navigation and everyday tasks. Many PD patients are uncomfortable doing everyday tasks even on levodopa therapy, such as driving, due to movement difficulties leading to reduced reaction times for foot operated pedals (Rascol et al. 2003). To make tasks as these utilize additional sources of visual guided movement may allow for greater freedom for these patients.

FUTURE DIRECTIONS

We have discovered two important factors that influence the visual control of movement. The first shows us that environments can be tailored to adaptive outcome. This suggests that if we better understand the strategies by which people learn and continue to learn beyond an initial session, we may be able to customize the adaptive process to optimize transfer of visuomotor information. This framework is useful when we think about rehabilitation and therapeutic intervention for patients with motor difficulties. PD is a

degenerative disease that affects each person differently. Differences in presentation of motor symptoms in the clinic often make PD hard to diagnose, but even harder to treat residual motor symptoms that are not treated via medication (Rao et al. 2003). By utilizing and exploiting intact aspects of functional sensory modalities in these patients, it is possible to reinforce and aid motor performance.

We have currently characterized kinematic behavior of adaptation in patients with Parkinson's disease. However, we do not know if these adaptive mechanisms transfer from the experimental setting to the real world. While using a computer mouse or pen is fairly ecological from an experimental standpoint, it still does not replicate the interactions these patients have in the real-world. In home feedback tasks can be used to better assess abilities and disabilities, and improve movement performance. Such tasks have been recently used to show improvement in PD patient gait (Espay et al. 2010).

In order for feedback based therapy to be effective, it is necessary to consider the dominant motor symptom or symptoms in each subject. It is likely that a subject with large amounts of tremor and smaller amounts of bradykinesia will respond to therapies differently than a patient who exhibits large amount of bradykinesia and stiffness. Through clearer identification of ability and disability in these patients we can tailor rehabilitative strategies to disease sub-symptoms.

REFERENCES

Au WL, Lei N, Oishi MM, and McKeown MJ. L-dopa induces under-damped visually guided motor responses in Parkinson's disease. Exp Brain Res 202: 553-559.

Bock O, and Thomas M. Proprioception plays a different role for sensorimotor adaptation to different distortions. Hum Mov Sci.

Brown LA, Cooper SA, Doan JB, Dickin DC, Whishaw IQ, Pellis SM, and Suchowersky O. Parkinsonian deficits in sensory integration for postural control: temporal response to changes in visual input. Parkinsonism Relat Disord 12: 376-381, 2006.

Contreras-Vidal JL, and Buch ER. Effects of Parkinson's disease on visuomotor adaptation. Exp Brain Res 150: 25-32, 2003.

Espay AJ, Baram Y, Dwivedi AK, Shukla R, Gartner M, Gaines L, Duker AP, and Revilla FJ. At-home training with closed-loop augmented-reality cueing device for improving gait in patients with Parkinson disease. J Rehabil Res Dev 47: 573-581.

Fernandez-Ruiz J, Diaz R, Hall-Haro C, Vergara P, Mischner J, Nunez L, Drucker-Colin R, Ochoa A, and Alonso ME. Normal prism adaptation but reduced after-effect in basal ganglia disorders using a throwing task. Eur J Neurosci 18: 689-694, 2003.

Fine MS, and Thoroughman KA. Trial-by-trial transformation of error into sensorimotor adaptation changes with environmental dynamics. J Neurophysiol 98: 1392-1404, 2007.

Glickstein M, and Stein J. Paradoxical movement in Parkinson's disease. Trends Neurosci 14: 480-482, 1991.

Gordon J, Ghilardi MF, and Ghez C. Accuracy of planar reaching movements. I. Independence of direction and extent variability. Exp Brain Res 99: 97-111, 1994.

Kagerer FA, Contreras-Vidal JL, and Stelmach GE. Adaptation to gradual as compared with sudden visuo-motor distortions. Exp Brain Res 115: 557-561, 1997.

Krakauer JW, Ghilardi MF, Mentis M, Barnes A, Veytsman M, Eidelberg D, and Ghez C. Differential cortical and subcortical activations in learning rotations and gains for reaching: a PET study. J Neurophysiol 91: 924-933, 2004.

Krakauer JW, Pine ZM, Ghilardi MF, and Ghez C. Learning of visuomotor transformations for vectorial planning of reaching trajectories. J Neurosci 20: 8916-8924, 2000.

Kwak Y, Muller ML, Bohnen NI, Dayalu P, and Seidler RD. Effect of dopaminergic medications on the time course of explicit motor sequence learning in Parkinson's disease. J Neurophysiol 103: 942-949.

Marinelli L, Crupi D, Di Rocco A, Bove M, Eidelberg D, Abbruzzese G, and Ghilardi MF. Learning and consolidation of visuo-motor adaptation in Parkinson's disease. Parkinsonism Relat Disord 15: 6-11, 2009.

Messier J, Adamovich S, Jack D, Hening W, Sage J, and Poizner H. Visuomotor learning in immersive 3D virtual reality in Parkinson's disease and in aging. Exp Brain Res 179: 457-474, 2007.

Michel C, Pisella L, Prablanc C, Rode G, and Rossetti Y. Enhancing visuomotor adaptation by reducing error signals: single-step (aware) versus multiple-step (unaware) exposure to wedge prisms. J Cogn Neurosci 19: 341-350, 2007.

Pine ZM, Krakauer JW, Gordon J, and Ghez C. Learning of scaling factors and reference axes for reaching movements. Neuroreport 7: 2357-2361, 1996.

Rao G, Fisch L, Srinivasan S, D'Amico F, Okada T, Eaton C, and Robbins C. Does this patient have Parkinson disease? Jama 289: 347-353, 2003.

Rascol O, Payoux P, Ory F, Ferreira JJ, Brefel-Courbon C, and Montastruc JL. Limitations of current Parkinson's disease therapy. Ann Neurol 53 Suppl 3: S3-12; discussion S12-15, 2003.

Sidaway B, Anderson J, Danielson G, Martin L, and Smith G. Effects of long-term gait training using visual cues in an individual with Parkinson disease. Phys Ther 86: 186-194, 2006.

Taylor JA, and Ivry RB. Flexible cognitive strategies during motor learning. PLoS Comput Biol 7: e1001096.

Jennifer Anne Semrau – *Curriculum Vitae*

Education

August 2005 – May 2011	**Washington University in Saint Louis**, Saint Louis, MO Ph.D. in Neuroscience
September 1999 – May 2003	**University of Rochester**, Rochester, NY B.A. in Brain and Cognitive Sciences, Psychology

Research Experience

February 2006 – present: Doctoral research

Laboratory of Dr. Kurt Thoroughman, Washington University, Saint Louis, MO, USA

Research Emphasis: Visuomotor adaptation in human subjects. Investigating adaptive strategies in normal humans and patients with Parkinson's disease.

Fall 2005: Research rotation

Laboratory of Dr. Dora Angelaki, Washington University, Saint Louis, MO, USA

Research Emphasis: Investigating properties of smooth pursuit eye movements during activation of vestibulo-ocular reflex.

May 2003 – July 2005: Research Technician

Laboratory of Dr. Jonathan Mink, University of Rochester, Rochester, NY, USA

Research Emphasis: Pathophysiology of movement disorders in human and animal models

May 2003 – May 2004: Research Assistant

Laboratory of Dr. Mary Hayhoe, University of Rochester, Rochester, NY, USA

Research Emphasis: Properties of eye kinematics during natural tasks

September 2001 – September 2003: Undergraduate Research Assistant

Laboratory of Dr. Jonathan Mink, University of Rochester, Rochester, NY, USA

Research Emphasis: Properties of human kinematics in movement disorders

Awards and Fellowships

Neural Control of Movement Travel Scholarship, Society for the Neural Control of Movement, awarded April 2010

NSF Integrative Graduate Education and Research (IGERT) Training Award, awarded September 2006 – September 2008

5th Neuro-IT and Neuroengineering School, July 2007

Publications

Experienced environmental dynamics influence both immediate and eventual adaptive strategy to visuomotor perturbations. **Semrau JA**, Daitch AL, Thoroughman KA. [in revision].

Scaling of the fore-aft vestibulo-ocular reflex by eye position during smooth pursuit **Semrau JA**, Wei M, Angelaki DE, *Journal of Neurophysiology* (2006); **96**, 936-940.

Media Publications

An eye to the future: training the next generation of researchers
Laura Bonetta, *NCRR Reporter,* Winter/Spring 2009; **33**(1)

Brain, behavior, & performance unit aids neuroscience researchers
Gwen Ericson, *ICTS News*, **1**(7)

Abstracts/Presentations

Presentations

2007 **Semrau JA**, Thoroughman KA
Adaptive processes underlying visuomotor learning change with the statistics of the environment
2007 Washington University Neuroscience Retreat

Abstracts

2010 **Semrau JA**, Thoroughman KA
Adaptation to altered visuomotor feedback in Parkinson's disease: Dependence on external signals
20th Annual Meeting of the Society for the Neural Control of Movement, April 2010

2009 **Semrau JA**, Thoroughman KA
Trial-by-trial visuomotor learning in Parkinson's disease
39th Annual Meeting of the Society for Neuroscience, October 2009

2007 **Semrau JA**, Fine MS, Thoroughman KA
Adaptive processes underlying visuomotor learning change with the statistics of the environment
37th Annual Meeting of the Society for Neuroscience, November 2007

Mink JW, Levy EJ, Newhouse N, **Semrau JA**
Kinematic and EMG patterns in chorea
37th Annual Meeting of the Society for Neuroscience, November 2007

Mink JW, **Semrau J**, Guillet A
Globus pallidus activity in a bimanual reaching task in monkeys
International Basal Ganglia Society 9th Triennial Meeting, 2007

Mink JW, **Semrau J**, Levy E, Newhouse N
Kinematics and EMG in human chorea
International Basal Ganglia Society 9th Triennial Meeting, 2007

2006 **Semrau JA**, Taylor JA, Dajles D, Thoroughman KA
Error generalization in trial-by-trial adaptation to visuomotor perturbations
36th Annual Meeting of the Society for Neuroscience, October 2006

2005 Mink JW, **Semrau J**
Globus pallidus activity in a bimanual reaching task
35th Annual Meeting of the Society for Neuroscience, November 2005

2004 Mink JW, **Semrau J**, Moerlein S, Antenor J, Perlmutter JS
Globus pallidus activity in a primate model of dystonia and parkinsonism
8th Meeting of the International Basal Ganglia Society, 2004

2003 Levy EJ, **Semrau J**, McDonough TL, Mink JW
Kinematics of chorea in Huntington disease
33rd Annual Meeting of the Society for Neuroscience, November 2003

Teaching and Mentoring Experience

FIRST Robotics Conference – *Today's Girls in Tomorrow's Workplace*, Invited panelist, April 2011

Neuroday11 – Saint Louis Science Center, Mar 2011

Saint Louis Brain Bee – Saint Louis Science Center, January 2011
Demonstrated brain-relevant experiments and techniques for the community

SciFest10 – Saint Louis Science Center, October 2010
Demonstrated brain-relevant experiments and techniques for the community

NeuroDay10 – Saint Louis Science Center, March 2010

SciFest09 – Saint Louis Science Center, October 2009
Demonstrated brain-relevant experiments and techniques for the community

NeuroDay09 – Saint Louis Science Center, March 2009

SciFest08 – Saint Louis Science Center, October 2008
Developed and led an all-day brain science event with 7 other graduate students

Undergraduate Mentoring – Washington University, Summer 2008 – current
Supervision of research projects conducted by students, providing feedback and discussion on scientific work

Neurophysiology Teaching Assistant – Washington University, August – December 2006
Supervision of rotating groups of undergraduate students performing electrophysiological recordings from the optic tectum of a frog. Responsibilities included a short lecture covering the neurophysiological principles being covered that week as well as instructing groups in dissection and experimental techniques. Students were provided feedback in scientific writing and data presentation techniques through evaluations of group lab reports.

Lecturer, Rochester Summer Scholars – University of Rochester, Summer 2004
Lectured gifted high school students on the topics of basic neuroanatomy, neuroscience, and neurodegenerative diseases.

Lecturer, Rochester Summer Scholars – University of Rochester, Summer 2003
Lectured gifted high school students on the topics of basic neuroanatomy, neuroscience, and neurodegenerative diseases.

Practicum in Developmental Disabilities – University of Rochester, Fall 2003
Supervision of teenagers with developmental disabilities in classroom lessons aimed at teaching life skill lessons (e.g. balancing a checkbook). Responsibilities included general classroom lessons as well as one-on-one lessons.

Professional Affiliations
Society for Neuroscience
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Service Committees

Washington University Neuroscience Steering Committee, 2007-2009
Student representative to voice student questions and concerns to faculty regarding classes, qualifying exams, as well as serving as a student mentor and fostering a sense of community throughout the neuroscience student community

Washington University Neuroscience Retreat Committee, 2007-2009
Student representative