May 2015

Maximizing the Effects of Passive Training on Visuomotor Adaptation By Incorporating Other Motor Learning Strategies

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MAXIMIZING THE EFFECTS OF PASSIVE TRAINING ON VISUOMOTOR ADAPTATION BY INCORPORATING OTHER MOTOR LEARNING STRATEGIES

by

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A Dissertation Submitted in

Partial Fulfillment of the

Requirements for the Degree of

Doctor of Philosophy

in Health Sciences

at

University of Wisconsin-Milwaukee

May 2015

ABSTRACT

MAXIMIZING THE EFFECTS OF PASSIVE TRAINING ON VISUOMOTOR ADAPTATION BY INCORPORATING OTHER MOTOR LEARNING STRATEGIES

by

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The University of Wisconsin-Milwaukee, 2015
Under the Supervision of Professor Jinsung Wang

Passive training has been shown to be an effective rehabilitation approach for stroke survivors, especially for those who suffer from severe control loss or complete paralysis. However, the effectiveness of the treatments that utilize passive assist training is still low. The goal of this dissertation was to develop a training condition that can maximize the effects of passive training on motor learning by combining its effect with other motor learning strategies. To achieve this goal, two specific aims were pursued: one aim was to determine the effects of passive training on learning a visuomotor adaptation task; and the other aim was to determine the effects of passive training in combination with other strategies on learning a visuomotor adaptation task. Experimental results indicated that passive training has a positive effect on visuomotor learning. Furthermore, it was confirmed that a training condition consisting of action observation and passive training leads to significant performance gains beyond what either intervention alone can do. This suggests that passive training could elicit motor representational changes, inducing instance-reliant learning process (use-dependent plasticity) that encodes motor instances associated with specific effectors and task conditions. The findings from this study show great potential for developing specific rehabilitation protocols that utilize passive training and action observation together for severely impaired stroke patients in the future.

I dedicate this work to my parents and my wife

Thank you for your encouragement, support and love.

TABLE OF CONTENTS

LIST OF FIGURES VIII

ACKNOWLEDGMENTS XI

CHAPTER 1: INTRODUCTION 1
Statement of Purpose 7
Specific Aims and Hypotheses 7
Delimitations of the Study 8
Assumptions of the Study 8
Significance of the Study 9

CHAPTER 2: EFFECTS OF PASSIVE TRAINING ON MOTOR GENERALIZATION 10
Introduction 10
Experiment 1 13
Materials and Methods 13
Data analysis 22
Results 23
Experiment 2a 30
Materials and Methods 30
Data analysis 34
Results 35
Experiment 2b 40
Materials and Methods 40
Data analysis 43
Results 45
Discussion 48

CHAPTER 3: EFFECTS OF A TRAINING CONDITION THAT COMBINES PASSIVE TRAINING AND ACTION OBSERVATION ON VISUOMOTOR ADAPTATION 53
Introduction 53
Experiment 3 55
Materials and Methods 55
Data analysis 61
Results 63
Discussion 72

CHAPTER 4: EFFECTS OF A TRAINING CONDITION THAT INCORPORATES THE MANIPULATION OF VISUAL FEEDBACK INTO PASSIVE TRAINING ON VISUOMOTOR ADAPTATION 75

Introduction ... 75
Experiment 4 ... 78
Materials and Methods ... 78
Data analysis ... 83
Results ... 87
Discussion ... 88

CHAPTER 5: SUMMARY AND CONCLUSIONS ... 93

REFERENCE LIST ... 97

APPENDIX A: LITERATURE REVIEW ... 106
Stroke ... 106
Post-stroke neuroplasticity ... 107
Rehabilitation approaches ... 108
Robotic rehabilitation ... 109
End-effector and exoskeletal robotic systems ... 113
Robotic rehabilitation and motor learning principles ... 113
Motor adaptation and after-effects ... 114
Mechanisms underlying Motor Learning ... 116
Model-based and Model-free Learning ... 120
Generalization of Motor Learning ... 124
Motor Learning by Observation ... 127
Motor learning by passive training ... 128
Reference List ... 131

APPENDIX B: INFORMED CONSENT FORM ... 139

APPENDIX C: HANDEDNESS QUESTIONNAIRE ... 145

APPENDIX D: RECRUITMENT FLYER ... 147

LIST OF FIGURES

Figure 1: Motor learning mechanism underlying active training, passive training and action observation 6

Figure 2: Experimental device. A: KINARM Exoskeleton robot. B: 2D virtual reality 16

Figure 3: A: Experimental setup. B: Subjects reached toward 30-deg clockwise target relative to the training target passively (where they reached toward following complete visuomotor adaptation 19

Figure 4: A: Hand-path without visual rotation (left) and hand-path with visual rotation (right). B: Diagram of initial direction error. C: Diagram of velocity profile 20

Figure 5: Protocols for Experiment 1. Group 1 trained with passive movements. Group 2 trained without passive movements 21

Figure 6: Tangential hand velocities from representative subjects observed at the last trial during the baseline session (A), and those observed at the first trial (B) and last trial (C) during the training session 24

Figure 7: Each column shows hand-paths of reaching movement. Column 1 shows performance upon initial exposure to the visual rotation. Column 2 shows improved performance at the end of the training session. Column 3 shows performance at the beginning of the generalization session 27

Figure 8: Mean performance measure. Every data point shown on X axis represents the average of 5 consecutive trials (block) across all subjects within each group (mean ± SE) 28

Figure 9: The extent of generalization from the training to generalization session (left panel), and slope values during the generalization session (right panel). Slope values obtained from nonlinear logarithmic regression equation were used to calculate the adaptation rate 29

Figure 10: A: Experimental setup. B: Subjects reached toward 30-deg clockwise target relative to the generalization target passively (where they reached toward following complete visuomotor adaptation 32

Figure 11: Protocols for Experiment 2a. Group 1 trained with passive movements. Group 2 trained without passive movements 33

Figure 12: Each column shows hand-paths of reaching movement. Column 1 shows performance upon initial exposure to the visual rotation. Column 2 shows improved performance at the end of the training session. Column 3 shows performance at the beginning of the generalization session 37

Figure 13: Mean performance measure. Every data point shown on X axis represents the average of 5 consecutive trials (block) across all subjects within each group (mean ± SE) 38

Figure 14: The extent of generalization from the training to generalization session (left panel), and slope values during the generalization session (right panel) 39

Figure 15: A: Experimental setup. B: Subjects reached toward 30-deg clockwise target relative to the training target passively (where they reached toward following complete visuomotor adaptation. C: Protocols for Experiment 2b 42

Figure 16: Each column shows hand-paths of reaching movement. Column 1 shows performance upon initial exposure to the visual rotation. Column 2 shows improved performance at the end of the training session. Column 3 shows performance at the beginning of the generalization session........ 44

Figure 17: Mean performance measure. Every data point shown on X axis represents the average of 5 consecutive trials (block) across all subjects within each group (mean ± SE) 47

Figure 18: A: Experimental setup. B: An illustration of the targets presented on the display. C: Still frame taken from a video shown to observer 57

Figure 19: Protocols for Experiment 60

Figure 20: Each row shows hand-paths of reaching movement from each group at the first cycle of the testing session. 62

Figure 21: A: Mean performance measure for group TD, PP, and AP. Every data point shown on X axis represents the average of 4 consecutive trials (cycle) across all subjects within each group (mean ± SE). 65

Figure 22: A: Mean performance measure for group TD, PP, and AP. Every data point shown on X axis represents the average of 4 consecutive trials (cycle) across all subjects within each group (mean ± SE). B: Direction errors at the very first cycle (left panel), and slope values during the testing session (right panel). 65

Figure 23: A: Mean performance measure for group TD, AO, and AP. Every data point shown on X axis represents the average of 4 consecutive trials (cycle) across all subjects within each group (mean ± SE). B: Direction errors at the very first cycle (left panel), and slope values during the testing session (right panel). 67

Figure 24: A: Mean performance measure for group TD, AO+PP, and AP. Every data point shown on X axis represents the average of 4 consecutive trials (cycle) across all subjects within each group (mean ± SE). B: Direction errors at the very

first cycle (left panel), and slope values during the testing session (right panel) 69

Figure 25: A: Mean performance measure for group PP, AO, and AO+PP. Every data point shown on X axis represents the average of 4 consecutive trials (cycle) across all subjects within each group (mean ± SE). B: Direction errors at the very first cycle (left panel), and slope values during the testing session (right panel).. 71

Figure 26: A: Experimental setup. B: An illustration of the targets presented on the display. C: In VE group, a cursor representing fingertip location was shown throughout movement. In BE group, no cursor was shown; instead, target color changed to red (success) or blue (failure) upon completion of reaching movement.. 80

Figure 27: Protocols for Experiment 82

Figure 28: Hand-paths at the very first block of the testing session from the three groups. 84

Figure 29: Mean performance measure. Every data point shown on X axis represents the average of 5 consecutive trials (block) across all subjects within each group (mean ± SE) 85

Figure 30: Direction error at the very first cycle (left panel), and slope values during the testing session (right panel)... 86

Figure 31: Forward model receives a copy of motor command and generates a predicted sensory consequence at a short latency. The predicted sensory consequence is integrated with true sensory feedback to optimize state estimate. 118

ACKNOWLEDGMENTS

Foremost, I would like to express an extensive amount of gratitude to my advisor Dr. Jinsung Wang, for his continued encouragement and advice to help me through this process. It is my great honor to be his first Ph.D. student. I would like to thank my committee members, Dr. Kristian M. O'Connor, Dr. Kevin G. Keenan, Dr. Susan E. Cashin, and Dr. Amol D. Mali for providing their invaluable suggestions and insightful comments to the dissertation. I wish to thank my parents, Jianping Lei and Dongjiao Liu for their constant encouragement, inspiration and love. Finally, I am grateful for my wife, Yue Li, who helps me in numerous ways.

Chapter 1: Introduction

Stroke (cerebral vascular disease) is a leading cause of permanent disability in the United States (Muntner et al. 2002; Roger et al. 2011). Every year, more than 780,000 people suffer a stroke, with about 500,000 of which being first-time cases (Muntner et al. 2002; Roger et al. 2011). Currently, a stroke is more likely to lead to a long-term disability rather than death because of modern medical advances, implying that there is a growing concern of the cost of the healthcare and assistance for stroke survivors (Roger et al. 2011). It is estimated that among stroke survivors who were 65 years or older, 50% reported some form of hemiparesis and 30% reported limitations in activities of daily living (ADLs) without assistance (Rosamond et al. 2008; Huang et al. 2009). Stroke not only strikes the elderly, it also occurs among children between infancy and toddler age. In fact, stroke is one of the leading causes of death for children (Lloyd-Jones et al. 2009). The rate of stroke occurrence from birth through the age of 18 is nearly 11 in every 100,000, with 50% to 80% having permanent neurological deficits, most commonly hemiparesis or hemiplegia (Roach et al. 2008). With the progressive growth of the elderly (age 65 and over) population due to the aging baby boomers, and the increase in the rate of strokes among children, the concerns of stroke-related disability will increase over time.

Although stroke can result in deficits in a number of neurologic functions based on the locations in the brain where the lesions occur resulting from a stroke, the most commonly affected is the motor functions (Duncan et al. 1992), which encompass motor control and learning abnormalities, muscle weakness, and spasticity (Gresham et al. 1995; Rathore et al. 2002). Approximately 50% of the strokes are accompanied by hemiparesis (weakness on one side of the body) or hemiplegia (paralysis on one side of the body) (Kelley-Hayes et al. 2003). Only about 60% of stroke survivors with hemiparesis regain functional independence; and those suffering from hemiplegia have an even lower rate of recovery. Therefore, it is necessary to develop an effective treatment for stroke rehabilitation.

Rehabilitation approaches that clinicians have typically implemented for stroke patients include impairment-oriented training (Platz et al. 2001), constraint-induced movement therapy (CIMT) (Taub et al. 1993; Dromerick et al. 1999; Mark and Taub, 2004), interactive robotic therapy (Krebs et al., 1998), and virtual reality-based rehabilitation (Deutsch et al. 2004; Holden, 2005). These approaches improve motor function by forcing the repetitive exercise with the affected limb to reestablish muscle activity. As a result of the active engagement of the affected limb, the brain stimulates neural pathways and activates the motor cortex, thus inducing cortical reorganization and motor learning.

There is an increasing interest in using interactive robotic devices for stroke rehabilitation (van Vliet and Wing, 1991; Hesse et al. 2003; Hogan et al. 2004; Reinkensmeyer et al. 2004; Nef and Riener, 2005). Compared to other rehabilitation approaches, robotic therapy is attractive because of its programmable ability to alter task dynamics, its high measurement reliability, and its ability to deliver high-level intensity therapy than that with conventional therapy (Huang and Krakauer, 2009; Reinkensmeyer and Patton, 2009; Kitago and Krakauer, 2013). Active assist exercise, which uses external assistance to aid patients to accomplish intended movements, is the primary paradigm that has been used in robotic therapy (Marchal-Crespo and Reinkensmeyer, 2009). Active assist exercise can be grouped into three modes in terms of the dose of robotic assistance (Takahashi et al., 2008): (1) active non-assist mode, in which patients do all work without the robot's help, (2) active assist mode, in which patients actively exert effort to move and the robot supplements its effort, (3) passive assist mode, in which patients relax while the robot do all work. Interventional studies demonstrate that active assist mode can achieve greater behavioral gains for stroke patients who can exert efforts on their own to move (Lotze et al., 2003; Perez et al., 2004), since robotic devices, in active assist mode, provide assistance for patients to move their paretic limb in desired patterns during reaching, grasping, or walking to provoke motor plasticity (Marchal-Crespo and Reinkensmeyer, 2009).

While active assist training is certainly more beneficial than passive assist training for the majority of stroke patients, passive assist training may still be beneficial for those who can hardly move on their own, because passive repetitive movements can also lead to a change of cortical network (Lotze et al., 2003). In addition, another intervention which may be beneficial for the severely impaired stroke patients involves an action observation. Evidence exists that the observation of action and the actual execution of the observed action involve the same cortical motor representation (Fadiga et al., 1995; Iacoboni et al., 1999; Mattar and Gribble, 2005). Recently, action observation has been demonstrated to have a positive effect on rehabilitation of motor deficits after stroke through reactivating motor representation relevant to the observed action (Pomeroy et al., 2005; Buccino et al., 2006; Ertelt et al., 2007; Celnik et al., 2008).

The content of stroke rehabilitation is built upon the principle of motor learning. In order to optimize stroke rehabilitation, it is important to understand how motor learning principle can be applied to functional recovery following a given intervention (Krakauer, 2006; Wolpert et al., 2011; Kitago and Krakauer, 2013). The motor learning literature suggests that when an individual learns a motor task, more than one learning process is involved. For example, it has been suggested that motor learning involves two distinct, yet complementary processes: model-based learning and model-free learning (Huang et al., 2011; Haith and Krakauer, 2013). In the model-based learning system, an internal map or a model of the environment is built, which describes the relationship between the state of the body and environment. The model-free learning system, in contrast, learns action directly through trial and error. Unlike model-based learning, in the model-free learning system there is no intermediate internal model and no explicit error calculation required to correct for systematic biases (Haith and Krakauer, 2013). Instead, in the model-free learning system, improvements in performance are driven through exploring possible actions until an optimal solution is found. Manipulation of online visual feedback provided during motor learning has been shown to effectively differentiate the contribution of these two learning processes (Schmuelof et al., 2012). Another process that may be involved in motor learning, called instance-reliant learning, deals with effector- or movement-specific instances that are accrued during repeated performances of a task (Wang and Sainburg, 2004; Lei and Wang, 2015). According to this idea, the motor instances are later retrieved from the memory to allow fast and automatized performances of the learned task. Collectively, a given learning condition may involve all these processes or only one of them depending on specific characteristics of the learning condition.

It is, then, plausible that different stroke interventions may involve different motor learning processes. For example, active training is likely to involve multiple motor learning processes (model-based, model-free and instance-reliant learning process) (Figure 1), while passive training may only involve instance-reliant learning, which occurs through accruing motor instances of goal movement and build a template of expected sensory consequence (Kovacs et al., 2011). Similarly, observational learning may only be associated with model-based learning, which is driven by sensory prediction errors. Like the actor, the observer predicts the consequence of the movements, and updates the internal model by comparing prediction errors to actual outcomes. It is possible that the facilitative effects of these interventions for motor recovery may be associated with the underlying motor learning processes. If so, a proper understanding of their associations may enable us to maximize the potential benefits of these rehabilitation interventions, especially for severely impaired stroke patients who cannot move their paretic arm on their own.

Therefore, this study attempts to determine how to maximize the effects of passive training on learning a visuomotor adaptation task by combining it with other motor learning mechanisms (i.e., model-based, model-free, instance-reliant learning) in healthy young adults. Given that the current selection of stroke rehabilitation overlooks the significant population of stroke survivors suffering from severe control loss or complete paralysis, findings from this study may prove valuable for developing specific rehabilitation protocols targeted for severely impaired stroke patients in the future.

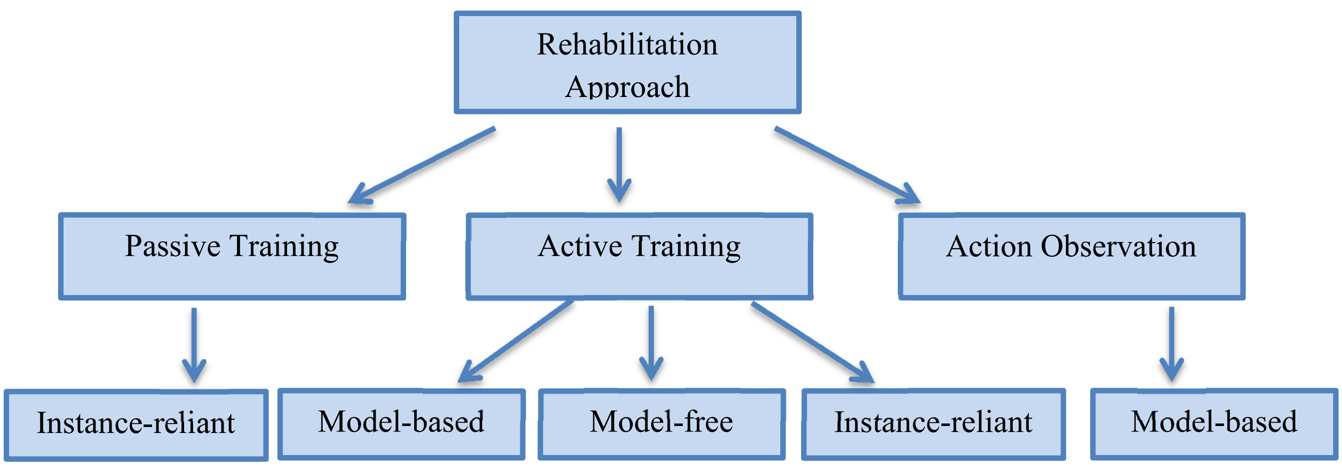


Figure 1: Motor learning mechanisms underlying active training, passive training and action observation.

Statement of Purpose

The main purpose of this dissertation is to develop a training condition that can maximize the effects of passive training on visuomotor adaptation by combining its effects with other motor learning strategies.

Specific Aims and Hypotheses

Aim 1: To determine the effects of passive training on learning a visuomotor adaptation task.

In aim 1a: Determine the effects of passive training on generalization of visuomotor adaptation across the two limbs.

Working hypothesis: There would be a complete generalization of visuomotor adaptation across limbs when inducing motor instances associated with motor effector by performing a motor task passively.

In aim 1b: Determine the effects of passive training on generalization of visuomotor adaptation across movement directions within the same arm.

Working hypothesis: There would be a complete generalization of visuomotor adaptation across movement directions within the same arm when inducing motor instances associated with specific directions by performing a motor task passively.

Aim 2: To determine the effects of passive training in combination with other strategies on learning a visuomotor adaptation task.

In aim 2a: Determine the effects of a training condition that combines passive training and action observation on visuomotor adaptation.

Working hypothesis: Action observation combined with passive assist training would enhance the effects of motor training relative to plain observational learning, as reflected by formation of motor memories.

In aim 2b: Determine the effects of a training condition that incorporates the manipulation of visual feedback into passive training on visuomotor adaptation.

Working hypothesis: The effects of passive training would be improved when robotic devices manipulate visual feedback in ways that provoke multiple motor learning mechanisms.

The remainder of this dissertation is outlined as follows: Chapter 2 describes experiments 1 and 2 (a and b) that were conducted to achieve Aims 1a and 1b, respectively. Chapter 3 describes experiment 3 that was conducted to achieve Aim 2a. Chapter 4 describes experiment 4 that was conducted to achieve Aim 2b. Finally, Chapter 5 describes summary and major conclusions.

Delimitations of the Study

1. Data were collected on young healthy adults and, therefore, any generalizations made from the findings will be limited to such a population.
2. This study looks at the contributions of active assist training, passive assist training and action observation to visuomotor adaptation. Therefore, findings from the present study should be generalized to other types of motor learning tasks with caution.

Assumptions of the Study

1. Participants honestly answered the questions consent form.
2. Participants do not have any known neurological damage.

3. Participants are right-handed.

Significance of the Study

Stroke is a leading cause of permanent disability to date. The rates of strokes in the United States are high, especially in the elderly (age 65 and over) population. Most stroke rehabilitative treatments that have been identified in the literature and clinical setting are only effective if the stroke survivor retains some residual motor ability in the affected limb. There are very few selections of stroke rehabilitative approaches that aim at the population of stroke survivors suffering from severe control loss or complete paralysis.

Passive assist training and action observation therapy have been shown to be effective rehabilitation approaches, however the effectiveness of the treatments that utilize these interventions is still low. This study provided substantial insights into our understanding of the motor learning mechanisms that underlie passive training and action observation, which in turn would help us to understand why there is limited treatment effectiveness in passive assist training and action observation in rehabilitation settings, and how to develop a training condition that can maximize the potential benefits of these training methods. Given that passive training and action observation therapy could be a valuable rehabilitation strategy for the severely impaired stroke patients, findings from this research may prove valuable for the development of more efficient rehabilitation protocols in the future.

Chapter 2: Effects of Passive Training on Motor Generalization

Introduction

Generalization of motor learning is an important aspect of motor learning, which refers to the extent to which the acquired learning transfers to novel situations not encountered during training. For example, can an individual apply what learned from table tennis to playing tennis? Studies on generalization have provided considerable insight into the specificity of learning and how learning is represented in the central nervous system (Imamizu et al. 1995; Krakauer et al. 2000; Mattar and Ostry, 2010). Motor generalization is also thought as an important topic in rehabilitation, as therapy-induced changes should occur over time and settings, and sometimes spread to a variety of related behaviors (Stokes and Baer, 1977). A low degree of generalization might demonstrate the limitations of the impact of certain rehabilitation interventions (Stokes and Baer, 1977; Page, 2003; Huxlin and Pasternak, 2004; Krakauer, 2006; Van Peppen et al., 2006).

Patterns of generalization have been studied widely by examining transfer of learning across movement directions (Bedford 1993; Ghilardi et al. 1995; Gandolfo et al. 1996; Vetter et al. 1999; Sainburg et al. 1999; Krakauer et al. 2000; Thoroughman and Shadmehr 2000; Thoroughman and Taylor 2005; Mattar and Ostry 2007), movement amplitudes (Goodbody and Wolpert 1998; Krakauer et al. 2000), movement speeds (Goodbody and Wolpert 1998), workspace locations ((Hwang et al. 2003; Malfait et al. 2002; Lei et al. 2013), and the effectors (Criscimagna-Hemminger et al. 2003; Dizio and Lackner 1995; Krakauer et al. 2006; Wang and Sainburg 2004a,b; Lei and Wang 2014).

Previous studies have shown that the extent of generalization varies in terms of task conditions. For example, adaptation to a novel visuomotor transformation in one part of the workspaces can generalize broadly to different parts of the workspaces that have not been experienced during training (Bedford 1993; Krakauer et al. 2000; Vetter et al. 1999; Lei et al. 2013), whereas learning in one direction of movement results in the extent of generalization to other directions that decays with increased angular distance from the learned direction (Gandolfo et al. 1996; Sainberg et al. 1999; Krakauer et al., 2000), especially when the angular difference between the training and testing directions over 45 degrees, the generalization could fall to zero (Krakauer et al., 2000). Similarly, the extent of generalization across effectors is also limited, only ranging from 10 to 60% (Morton et al., 2001; Sainburg and Wang, 2002; Taylor et al., 2011; Wang et al., 2011; Joiner et al., 2013). These findings suggest that the extent of generalization highly depends on the nature of the task, but it remains unclear why learning generalizes broadly in some tasks, but narrowly in others.

Previous accounts of generalization of motor learning have focused on the idea that the internal model, a representation of how the central nervous system predicts the outcome of motor commands, generalizes between different tasks (Shadmehr and Mussa-Ivaldi 1994). A typical experiment demonstrates that generalization is consistent with the idea of internal model is that generalization no longer occurs if internal model is extinguished (washout). However, this idea could not account for why the acquired learning in movement direction broadly generalizes across limb configurations and workspaces, but partly generalizes across directions and effectors. Internal models should have no option but to generalize under all circumstances using estimated changes in the limb (Berniker and Kording, 2008).

The variation in the extent of generalization suggests that generalization might not be purely guided by an internal model of the environment that is updated based on prediction. Our lab recently introduced a second learning mechanism, which is independent of an internal model, leading to changes in the extent of generalization (Wang et al. 2015). We refer to this mechanism as instance-reliant learning, in which effector-specific instances are accrued during repeated performances of a task and automatically retrieved later to allow fast and automatized performances of the task (Wang and Sainburg, 2003, 2004; Lei and Wang, 2014; Wang et al. 2015). In that study, we showed that in adaptation to visuomotor rotation, in which subjects adapt to a rotated display with the left arm while repeatedly performing the reaching task with the right arm without providing performance feedback, training with the left arm completely generalizes to the right arm (Wang et al., 2015). This suggests that the absence of motor instances associated with specific effectors and task conditions might be the major reason for limited generalization of motor learning.

In the present study, we induced instance-reliant learning by passively guiding movements in a specific direction or with a specific effector, and investigated how instance-reliant learning mechanism could account for the phenomenon of limited generalization in motor adaptation across movement directions and effectors. We hypothesized that if limited generalization across movement directions and effectors because of the absence of motor instances, a greater extent of generalization would occur in the condition in which subjects were provided motor instances passively.

Experiment 1

The purpose of experiment 1 was to investigate generalization of visuomotor adaptation during reaching movements across limbs when movement instances associated with one arm were provided while visuomotor adaptation occurred with the other arm.

Materials and Methods

Subjects

16 neurologically intact right-handed individuals participated in this study. Handedness was assessed using the 10-item version of the Edinburgh inventory (Appendix C) (Oldfield, 1971). The participants were recruited on University of Wisconsin-Milwaukee's campus through word of mouth and posted flyers (Appendix D). Participants are between the ages of 18-30 years old. The participants were paid for their participation. Informed consent approved by the Institutional Review Board of the University of Wisconsin – Milwaukee (Appendix B) was solicited prior to participation. The participants were randomly assigned to one of two groups (8 subjects per group). Sample size estimations were based on previous studies conducted in our lab. These analyses have established that 8 subjects are sufficient to show significant differences.

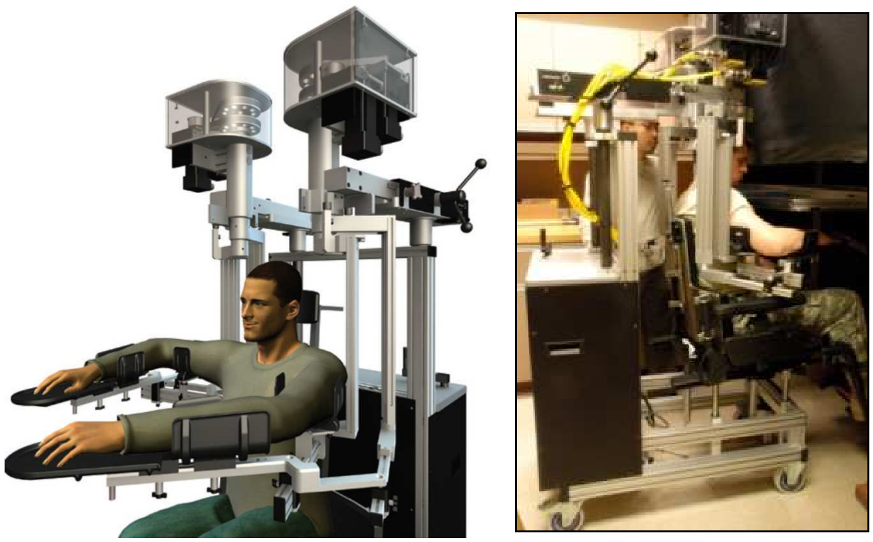
Exclusion criteria for this study were: 1) a major psychiatric diagnosis (e.g., schizophrenia), 2) hospital admission for substance abuse, 3) peripheral disorders affecting sensation or movement of the upper extremities (e.g., peripheral neuropathy), or 4) if they are left-handed. Also, any participant who is pregnant was excluded from participation.

Apparatus

The BKIN Dexterit-E system (BKIN Technologies Ltd, Kingston, ON, Canada) was used to collect kinematic data in this study, which consists of two KINARM Exoskeleton robots for the upper limbs, a 2D virtual reality display and Dexterit-E^{TM} experimental control and data acquisition software (Figure 2A). Each KINARM robot can be used as an exoskeleton for each arm; and the 2D virtual reality display is used to present visual stimuli in such a way that the stimuli (e.g., targets for reaching movements) appear at the same horizontal level as the hand (Figure 2B). Dexterit-E^{TM} experimental control and data acquisition software are designed to run on a multi-computer system. Dexterit-E itself runs on a Windows-based computer, in which it effectively acts as a user-interface for choosing task protocols, providing visual feedback to the operator, and saving data. The chosen task protocol is associated with a real-time computer, which is used to control the task. The real-time computer runs an operating system from the Mathworks Corporation called xPC Target. During the execution of a task, the communication from the real-time computer to the Windows-based computer allows the Windows-based computer to offer online feedback to the operator.

The KINARM robot is a motorized exoskeleton for the arm that allows manipulation of the arm in the horizontal plane. The KINARM's joints are aligned with the subject's shoulder and elbow joints. Therefore, subject does not experience the KINARM inertia adversely. Position feedback is acquired through incremental encoders that are integral to the motors, with a feedback resolution of 20,000 per revolution at the motor, which at the joint angles is equal to 80,000 per revolution because of the 4x gear ratio in the KINARM robot.

A



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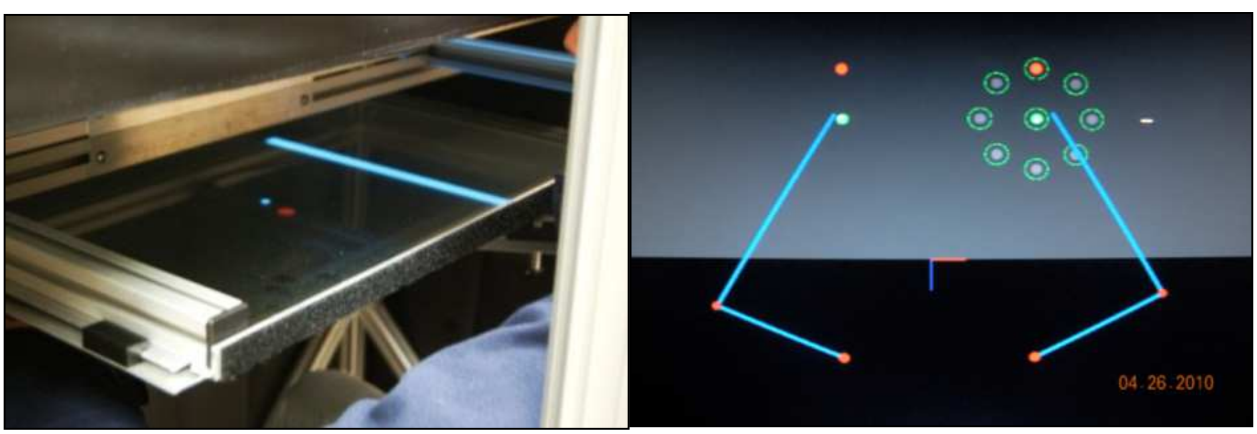

Figure 2: Experimental device. A: KINARM Exoskeleton robots. B: 2D virtual reality

Experimental Design

Subjects were seated on the KINARM chair with the arms supported by exoskeletons that provided full gravitational support of the entire arm; and the chair was moved to bring the arm under the horizontal display. The KINARM was incorporated with a virtual reality system that projected visual targets on the display to make them appear in the same plane as the arm. Direct vision of the subjects' arm was blocked and a cursor representing their index finger tip was provided to guide reaching movement. This system was used to collect the 2D hand-position data, which was sampled at 1,000 Hz, low pass filtered at 15 Hz, and differentiated to yield resultant velocity and acceleration values. Movement onset and offset were defined by the last minimum (below 5% maximum tangential velocity) prior to and the first minimum (below 5% maximum tangential hand velocity) following the maximum in the tangential hand velocity profile, respectively (Figure 4C). Data were processed and analyzed using MATLAB.

In general, subjects were asked to perform rapid reaching movement through a cursor indicating the location of the index finger tip from a start circle to a target (2 cm in diameter, 10 cm away from the start circle) repeatedly (Figure 3A). They were instructed to move their index finger to the target rapidly and as straight as possible in response to the appearance of the target, and stop without correcting their movement. Subjects were tested with or without cursor feedback of hand position. The experiment consisted of four sessions: baseline with the left arm and with the right arm, visuomotor adaptation with the left arm (training) and with the right arm (generalization). In the baseline sessions, the subjects were familiarized with the general reaching movement with each arm. In the training and generalization sessions, they adapted to visual display that was rotated 30 degrees counterclockwise about the start circle with the left and the right arm (Figure 4A) (i.e., hand movement made in the “12 o’clock” direction resulted in cursor movement made in the “11 o’clock” direction). During the training session, subjects were divided into two groups. The first group experienced passive movement with the right arm in the 30-degree clockwise direction relative to the training target for 10 trials after every 20 adaptation trials with the left arm (Figure 3B). Visual feedback was provided for adaptation trials, but not for passive trials, during the training session. This allowed specific instances associated with the task to be performed later with the right arm in the generalization session to be accrued in advance, without generation of motor command. In the second group, subjects took a short break (1 min) each time the first group performed right arm passive movements for 10 trials. During the generalization session, all subjects received visual feedback. Each of the sessions consisted of 40 (20 for the left, 20 for the right arm), 150 (100 for the adaptation trials, 50 for the passive trials) and 80 trials, respectively (Figure 5).

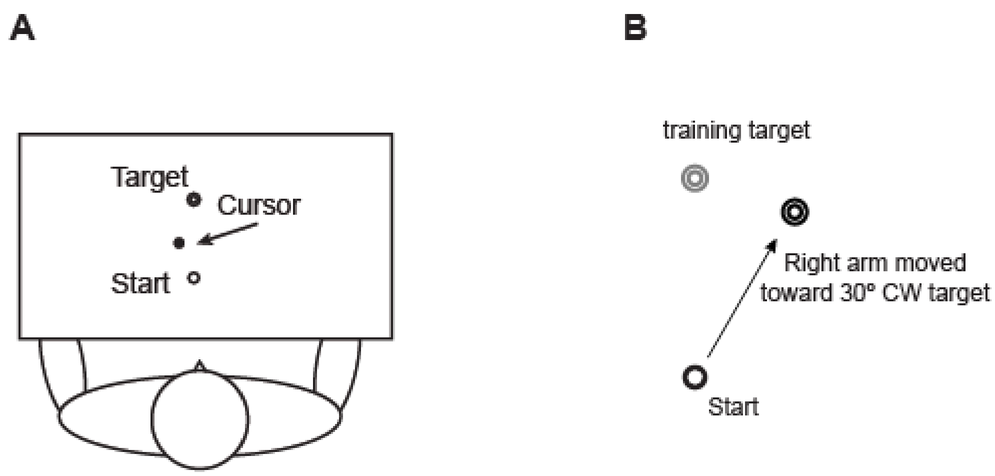

Figure 3: A: Experimental setup. B: Subjects reached toward 30-deg clockwise target relative to the training target (where they reached toward following complete visuomotor adaptation) passively

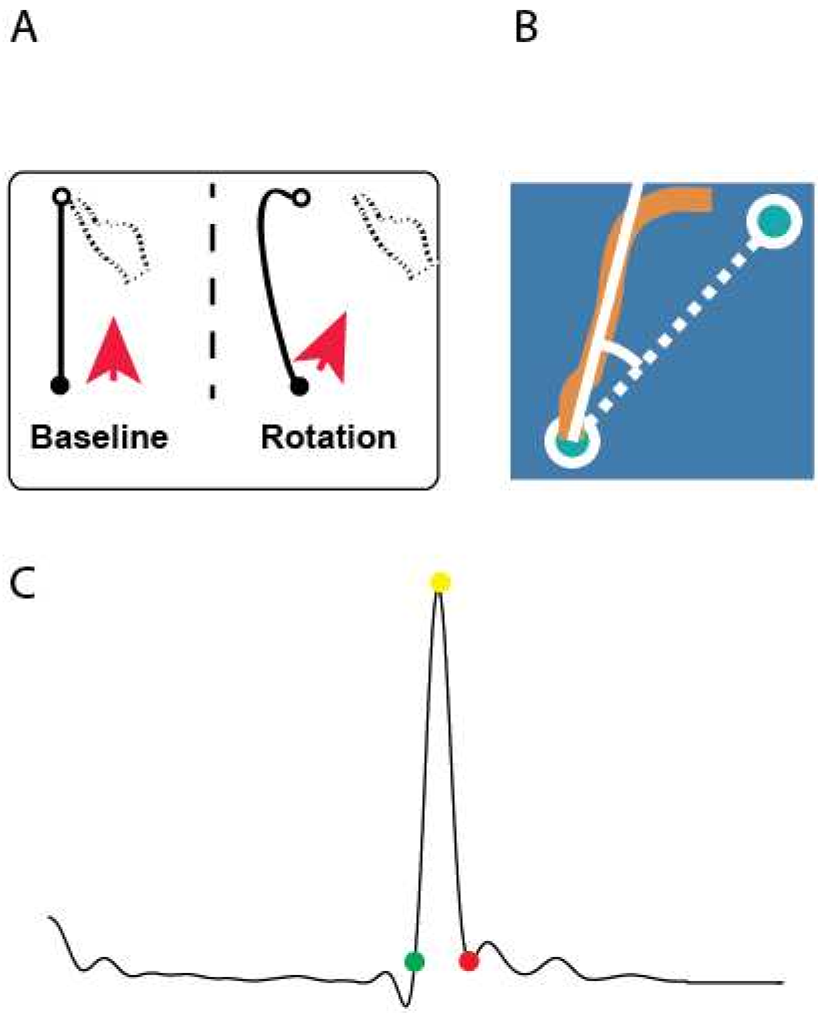

Figure 4: A: Hand-path without visual rotation (left) and hand-path with visual rotation (right). B: Diagram of initial direction error. C: Diagram of velocity profile

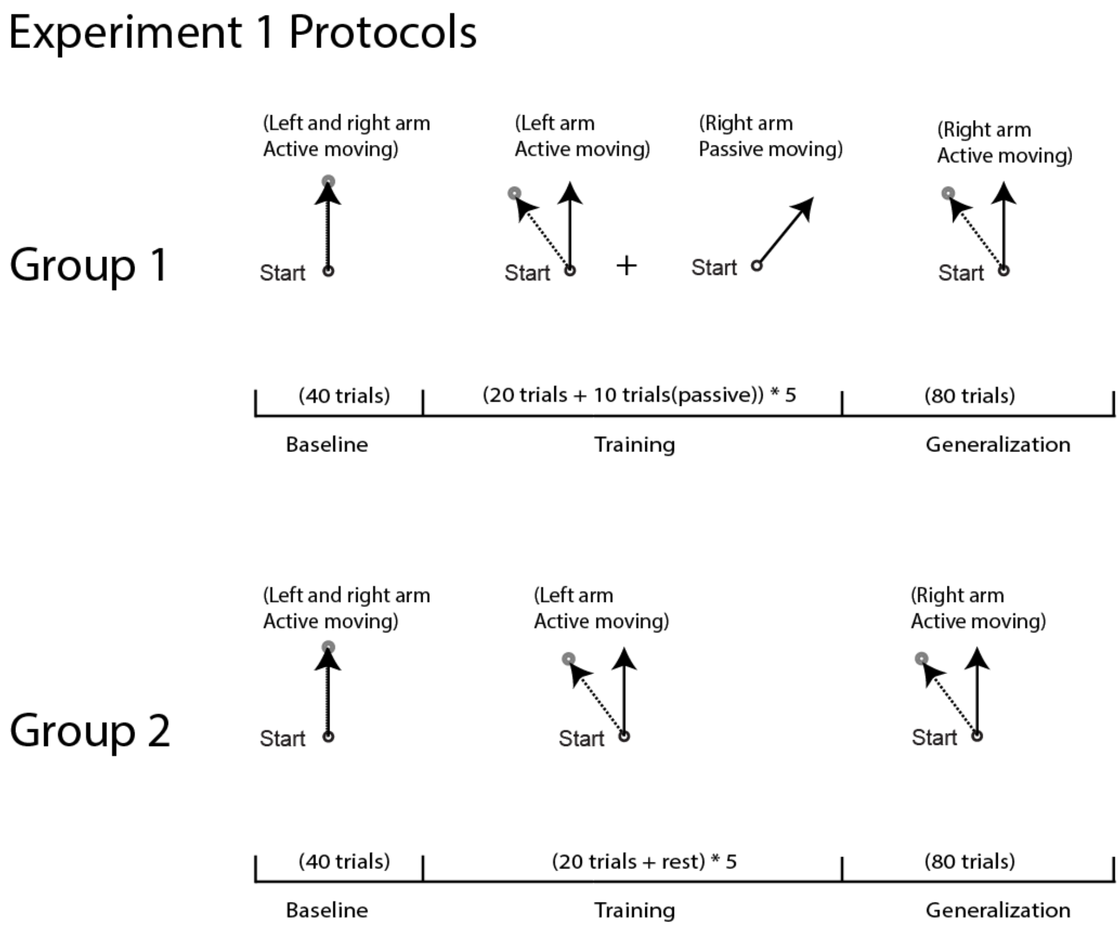

Figure 5: Protocols for Experiment 1. Group 1 trained with passive movements. Group 2 trained without passive movements

Data analysis

To examine performance accuracy, I calculated initial direction error (DE), which was the angular difference between a vector from the start circle to the target and another vector from the hand position at movement start to that at peak arm velocity. Using this measure, the extent of generalization was computed for each subject based on the following equation: [(DE at the first block of the training session –DE at the first block of the generalization session) / (DE at the first block of the training session –DE at the last block of the training session)] × 100 (%). A block represents the mean of 5 consecutive trials.

Initial direction errors from the adaptation sessions were subjected to a repeated-measures ANOVA with group as a between-subject factor and block (the first and the last blocks of the training session, the first and the last blocks of the generalization session) as a within-subject factor to determine if there was any difference between the subject groups throughout the training and the generalization sessions.

Following this, two independent t-tests were conducted. The first t-test was conducted to determine if the extent of generalization was different between the subject groups. For the second t-test, a line of approximation was constructed for each subject in the groups by fitting a logarithmic regression line to the arm performance data in the generalization sessions; and the slope values were used to determine if the adaptation rates in the generalization sessions following initial training were different between the groups. Statistical power analysis has been performed based on our previous studies that employed the identical tasks and performance measures (Wang and Sainburg, 2004), and indicated that 6 subjects (for each experimental group) are needed to reach the conventional power level of 80% and a medium effect size ($d = .50$). We tested 8 subjects for each group. This met the most stringent statistical requirements, and allowed room for possible attrition. The alpha level was set at 0.05. Post hoc comparisons, using dependent t-tests, were made between the first block of the training session and the first block of the generalization session, as well as between the last block of the training session and the first block of the generalization session, within each experimental condition.

Results

Figure 6A shows the hand tangential velocity obtained when the hand was moving without visual perturbation. The velocity profiles observed on the first trial and last trial when the visuomotor rotation was introduced were shown in Figure 6B and Figure 6C.

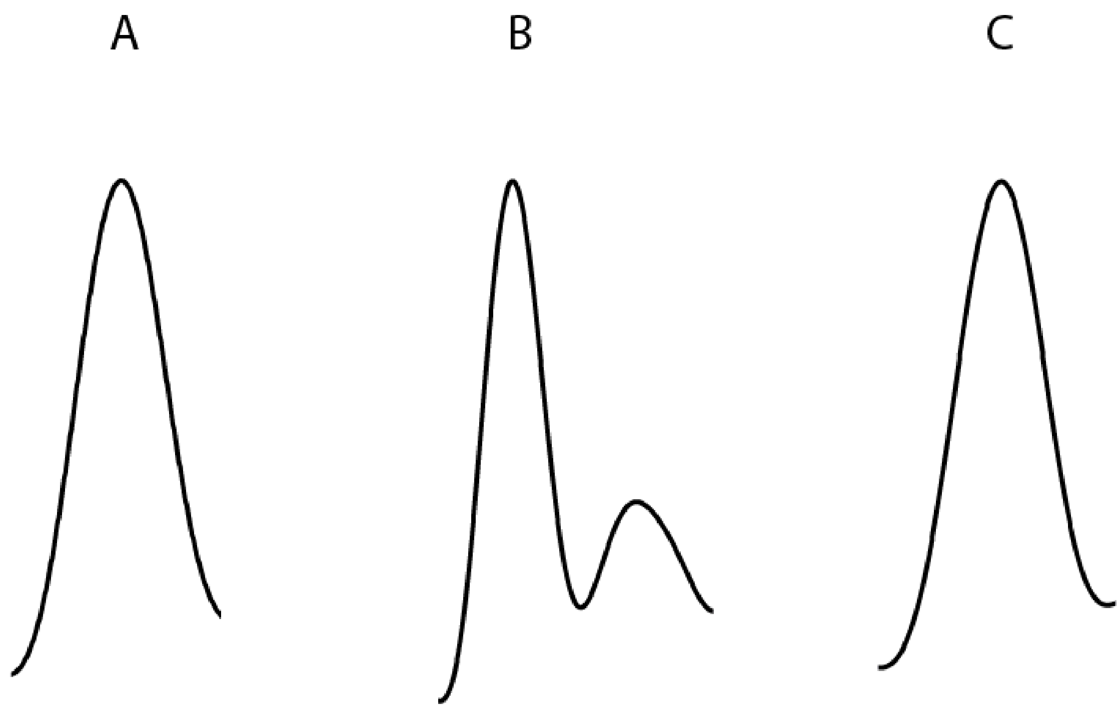

Figure 6: Tangential hand velocities from representative subjects observed at the last trial during the baseline session (A), and those observed at the first trail (B) and last trial (C) during the training session.

Figure 7 illustrates the hand-paths of a representative subject from each of the two subject groups. The hand-paths during the training session were similar for both of the groups, in that they were largely deviated from the target lines during the initial phase of the training session (Figure 7, column 1), but became relatively straight and more accurate at the last cycle of the session (Figure 7, column 2). During the generalization session, the hand-paths upon initial exposure to the visual rotation appeared different across the groups, in that the subjects in group 1 who performed reaching movements toward the 30-degree target with the right arm passively during the initial training showed relatively straight hand-paths from the beginning of the generalization session (Figure 7, column 3, row 2), whereas the subjects' hand-paths in group 2 were more curved. These hand-paths suggest that the extent of generalization across limbs following visuomotor adaptation may differ across the subject groups.

We quantified the difference by subjecting direction error measures to a repeated-measures ANOVA, which revealed a significant interaction effect between group and block ($p = 0.016$; Figure 8). Our post hoc analyses indicated that the direction errors at the first block of the generalization session were significantly smaller than those at the first block of the training session in both subject groups. The errors at the first block of the generalization session were significantly lower in the group who performed reaching movements toward the 30-degree target during initial training than that observed in the other group. Independent t-tests indicated that the extent of generalization observed in the group who performed reaching movements toward the 30-degree target passively during the initial training was significantly higher than that observed in the other group (p=0.044); and the mean slope value obtained from the former group was significantly lower than that of the other group (p=0.031). This indicates that the extent of generalization across limbs can increase substantially when movement instances directly associated with the task to be learned (i.e., 30-deg. target direction) can be accrued during the initial training.

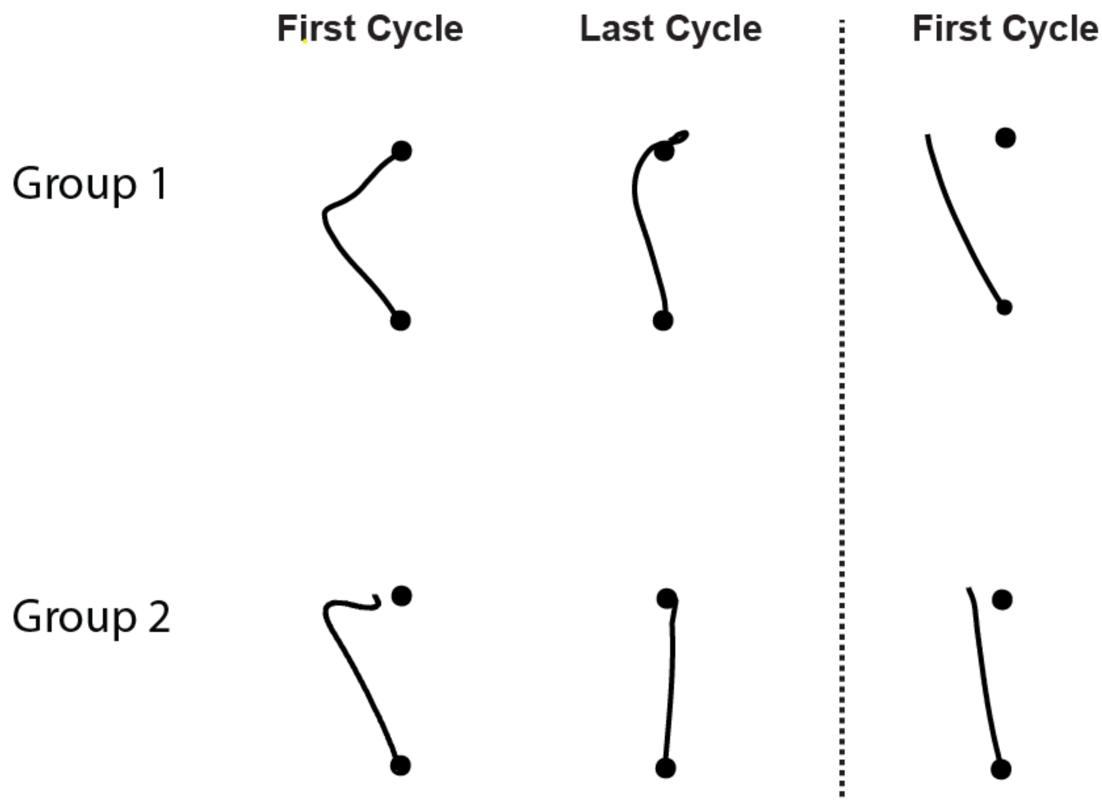

Figure 7: Each column shows hand-paths of reaching movement. Column 1 shows performance upon initial exposure to the visual rotation. Column 2 shows improved performance at the end of the training session. Column 3 shows performance at the beginning of the generalization session.

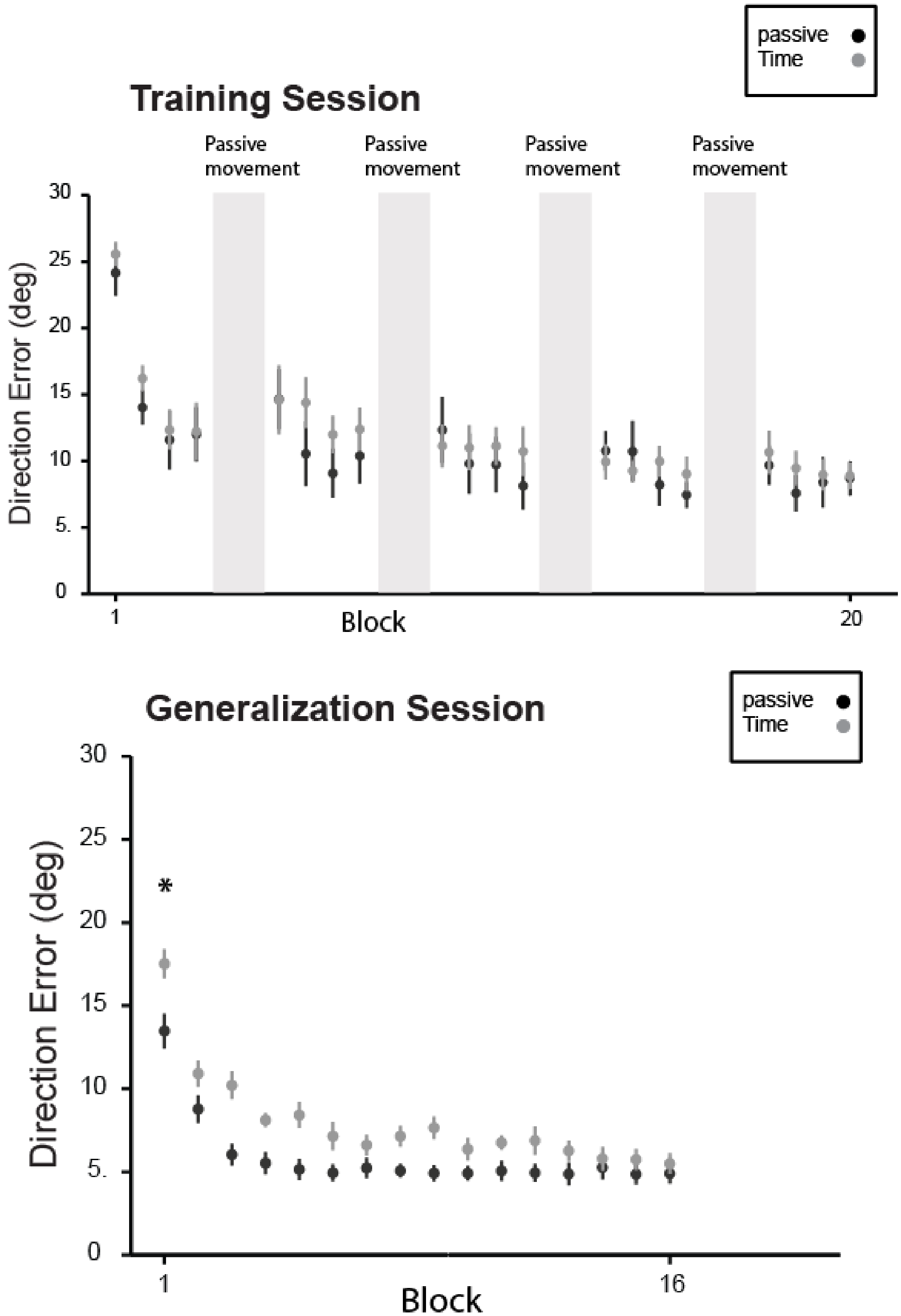

Figure 8: Mean performance measure. Every data point shown on X axis represents the average of 5 consecutive trials (block) across all subjects within each group (mean ± SE).

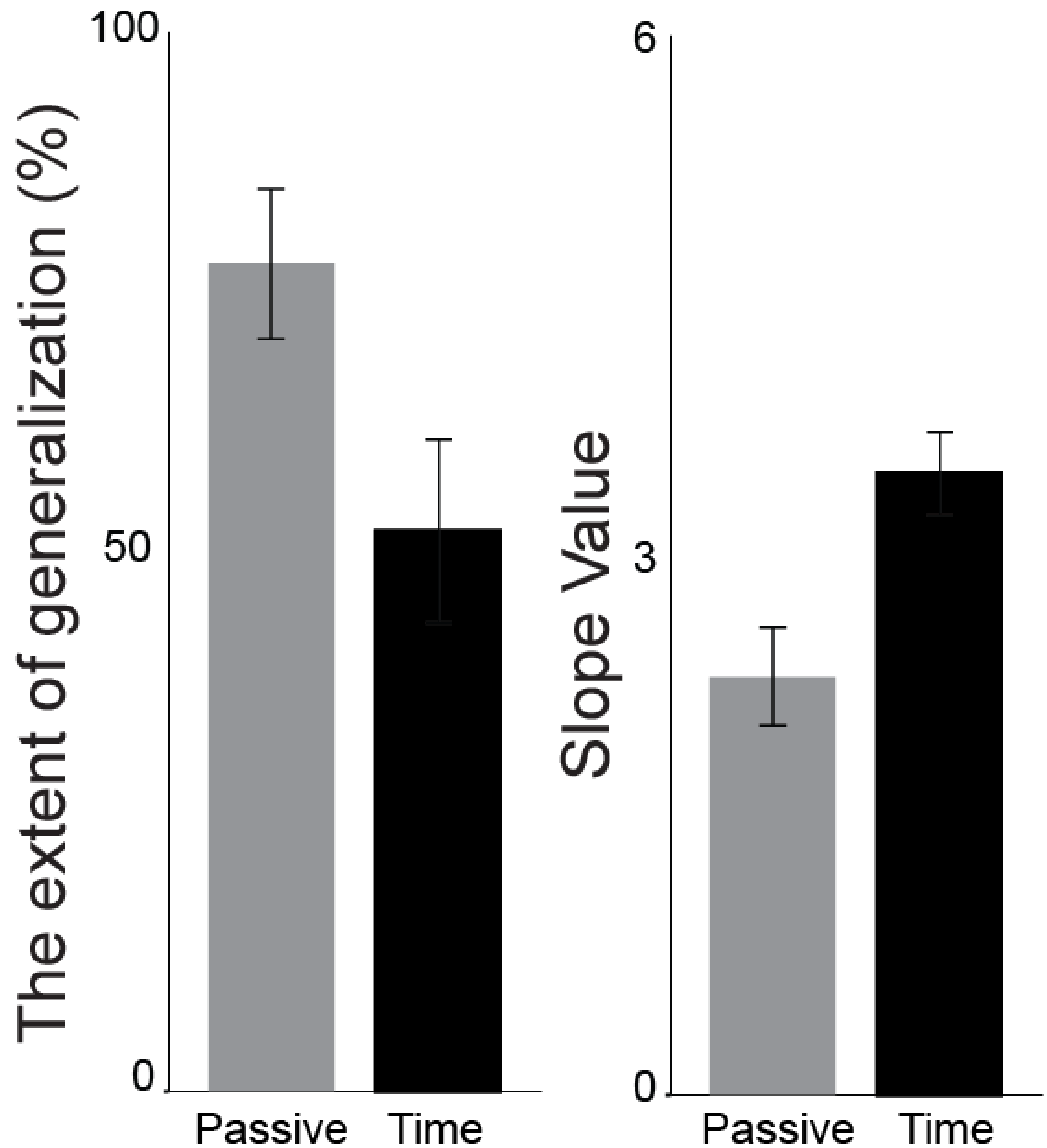

Figure 9: The extent of generalization from the training to generalization session (left panel), and slope values during the generalization session (right panel). Slope values obtained from nonlinear logarithmic regression equation were used to calculate the adaptation rate.

Experiment 2a

The results from experiment 1 indicated substantial generalization across limbs when movement instances directly associated with the task to be leaned later can be accrued during the initial training. The purpose of experiment 2a was to investigate generalization of visuomotor adaptation during reaching movements across two different movement directions when movement instances directly associated with one direction (i.e., one to be experienced later during the generalization session) can be accrued during the initial training associated with the other direction.

Materials and Methods

Subjects

16 healthy young adults (18-30 old, right-handed) volunteered to participate in this experiment. A questionnaire for handedness and an informed consent form were read and signed by all subjects prior to the beginning of the study. The protocol was approved by the University of Wisconsin-Milwaukee Institutional Review Board. Subjects were randomly assigned to one of two groups (8 subjects per group). No subject tested in this experiment participated in Experiment 1.

Apparatus

The same apparatus used in Experiment 1 was used in this experiment.

Experimental Design

Subjects were instructed to perform rapid reaching movement through a cursor indicating the location of the index finger tip from a start circle to a target

(2 cm in diameter, 10 cm away from the start circle) as straight as possible with the right arm (Figure 10A). The experiment consisted of three sessions: baseline, training, generalization. In the baseline session, the subjects were familiarized with the general reaching task. In the training and generalization sessions, they adapted to a visual display rotated 30 degrees counterclockwise about the start circle with the right hand (i.e., hand movement made in the “12 o’clock” direction resulted in cursor movement made in the “11 o’clock” direction). For the arrangement of the training and generalization targets, the generalization target was 180-degree relative to the training target (Figure 10B). During the training session, the subjects were divided into two groups. In one group, they experienced passive movement, with velocity and movement duration comparable with those in the active movement, in the 30-degree clockwise direction relative the generalization target for 10 trials after every 20 adaptation trials with the right hand. Visual feedback was provided for adaptation trials, but not for passive trials, during the training session. This allowed specific instances associated with the task to be performed later in the generalization session to be accrued in advance, without generation of motor command. In the other group, subjects took a short break (1 min) each time the first group performed passive movements for 10 trials. During the generalization session, all subjects received visual feedback. Each of the three sessions consisted of 40, 150 (100 for the adaptation trials, 50 for the passive trials) and 80 trials, respectively (Figure 11).

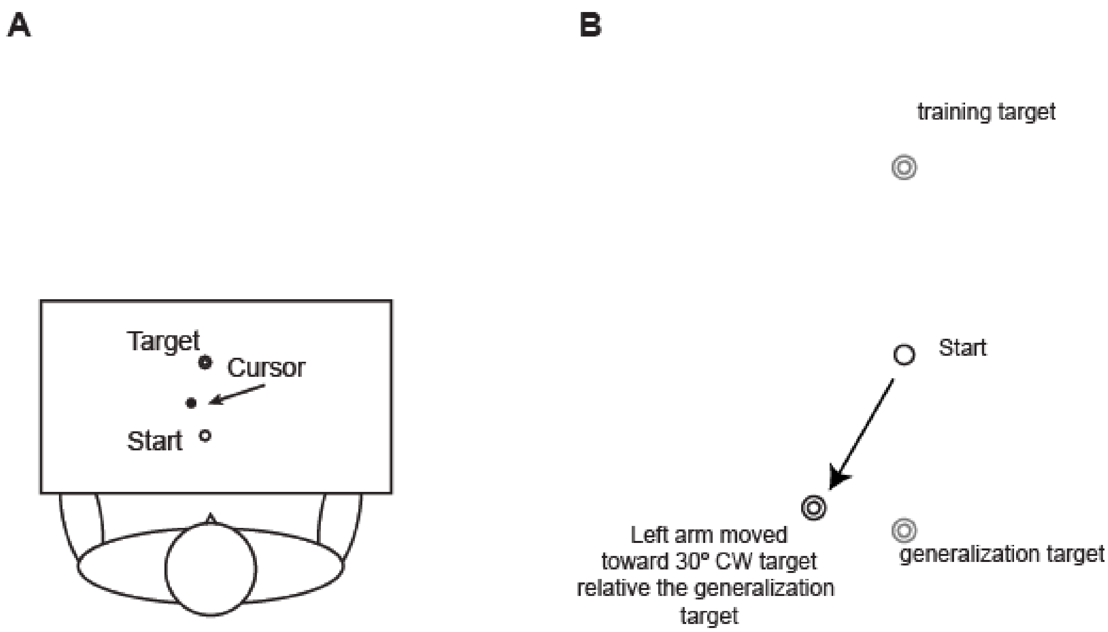

Figure 10: A: Experimental setup. B: Subjects reached toward 30-deg clockwise target relative to the generalization target passively (where they reached toward following complete visuomotor adaptation)

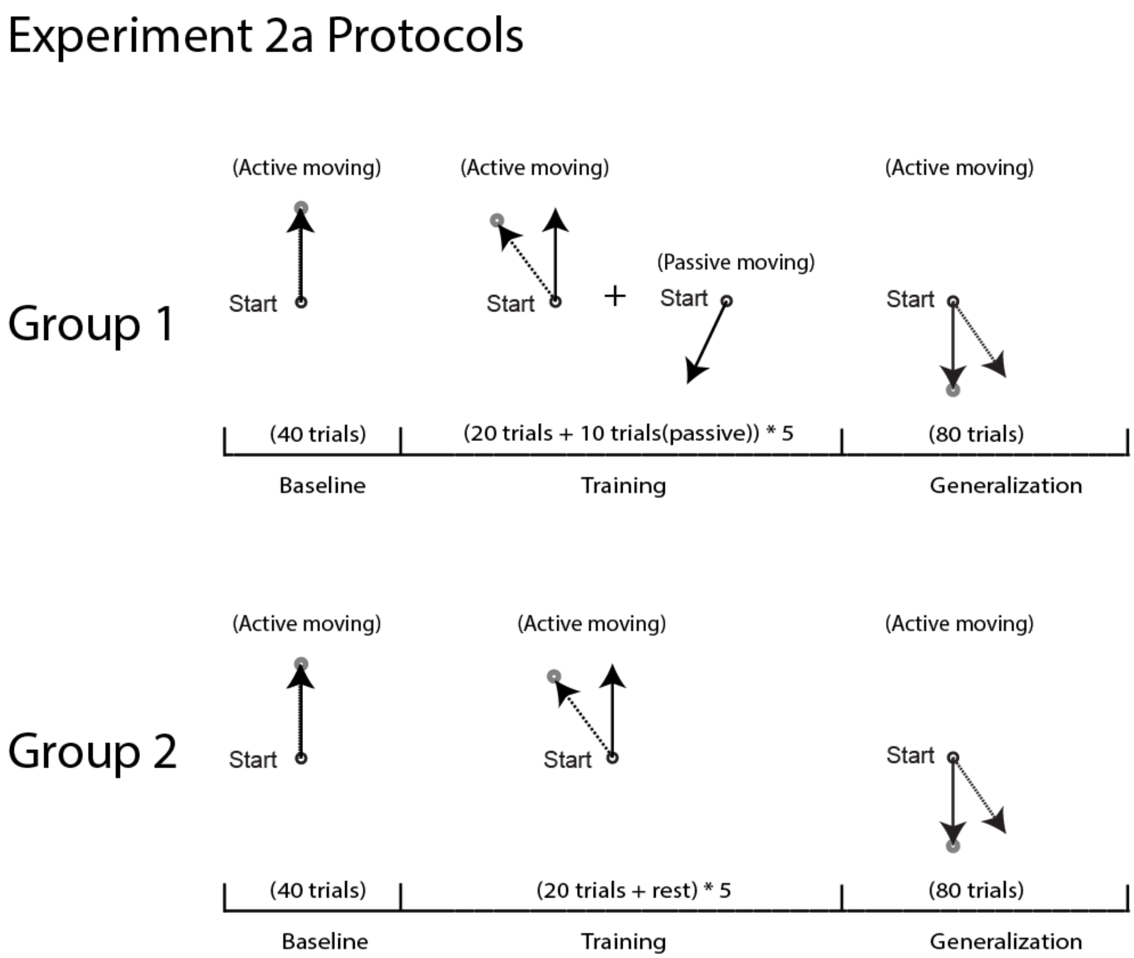

Figure 11: Protocols for Experiment 2a. Group 1 trained with passive movements. Group 2 trained without passive movements

Data analysis

As in Experiment 1, initial direction error (DE) was calculated. Using this measure, we also computed the extent of generalization for each subject. Initial direction errors from the adaptation sessions were subjected to a repeated-measures ANOVA with group as a between-subject factor and block (the first and the last blocks of the training session, the first and the last blocks of the generalization session) as a within-subject factor to determine if there was any difference between among the subject groups throughout the training and the generalization sessions. Following this, we conducted two independent t-tests. The first t-test was conducted to determine if the extent of generalization was different between the subject groups. For the second t-test, a line of approximation was constructed for each subject in the groups by fitting a logarithmic regression line to the arm performance data in the generalization sessions; and the slope values were used to determine if the adaptation rates in the generalization sessions following initial training were different between the groups. The alpha level was set at 0.05. Post hoc comparisons, using dependent t-tests, were made between the first block of the training session and the first block of the generalization session, as well as between the last block of the training session and the first block of the generalization session, within each experimental condition.

Results

Figure 12 illustrates typical hand-paths of representative subjects during the initial and final phases of the training session, and during the initial phase of the generalization session for both of two groups. Two groups demonstrated largely curved hand-paths at the beginning of the training session (Figure 12, column 1), which became relatively straight by the end of the session (Figure 12, column 2). The hand-paths at the beginning of the generalization session (Figure 12, column 3) were substantially straighter than those observed at the beginning of the training session, although not as straight as those shown at the end of the training session. These hand-paths suggest substantial, though incomplete, generalization of visuomotor adaptation from the training to the generalization session in both subject groups.

With respect to DE, the repeated-measures ANOVA showed a significant main effect of block ($p = 0.001$). The post hoc analyses indicated that the direction errors at the first block of the generalization session were significantly smaller than those at the first block of the training session, and significantly greater than those at the last block of either the training or generalization session (Figure 13). Neither the main effect of group nor the interaction effect between group and block was significant ($p = 0.346$ and 0.212, respectively). This indicates that the extent of generalization following visuomotor adaptation across movement directions was not significantly different between the two subject groups.

The lack of difference between the two subject groups was further confirmed by calculating the extent of generalization from the training to generalization session (Figure 14, left panel), as well as the rate of the generalization session (i.e., slope value) (Figure 14 right panel), neither of which indicated a significant difference between the two groups ($p = 0.957$ and 0.171, respectively). Overall, these results suggest that the extent of generalization across movement direction cannot increase substantially when movement instances directly associated with the task to be leaned can be accrued during initial training.

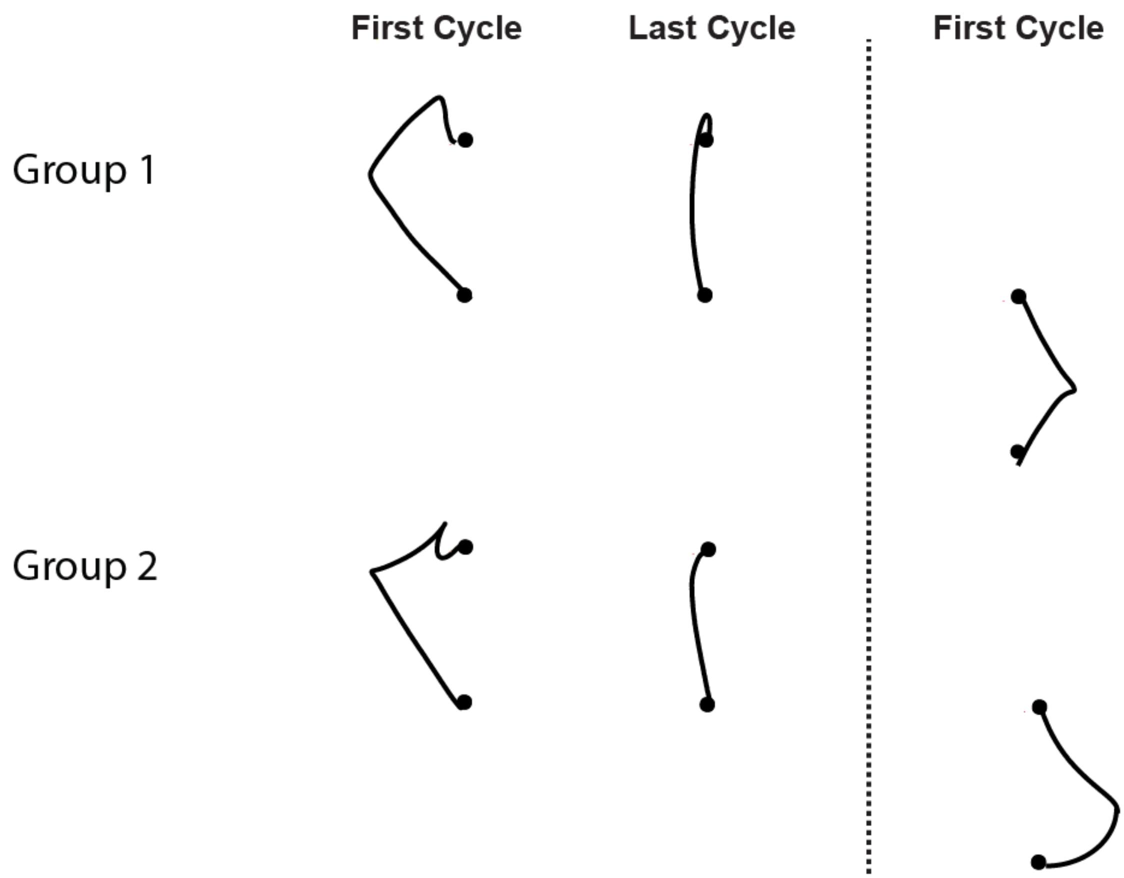

Figure 12: Each column shows hand-paths of reaching movement. Column 1 shows performance upon initial exposure to the visual rotation. Column 2 shows improved performance at the end of the training session. Column 3 shows performance at the beginning of the generalization session.

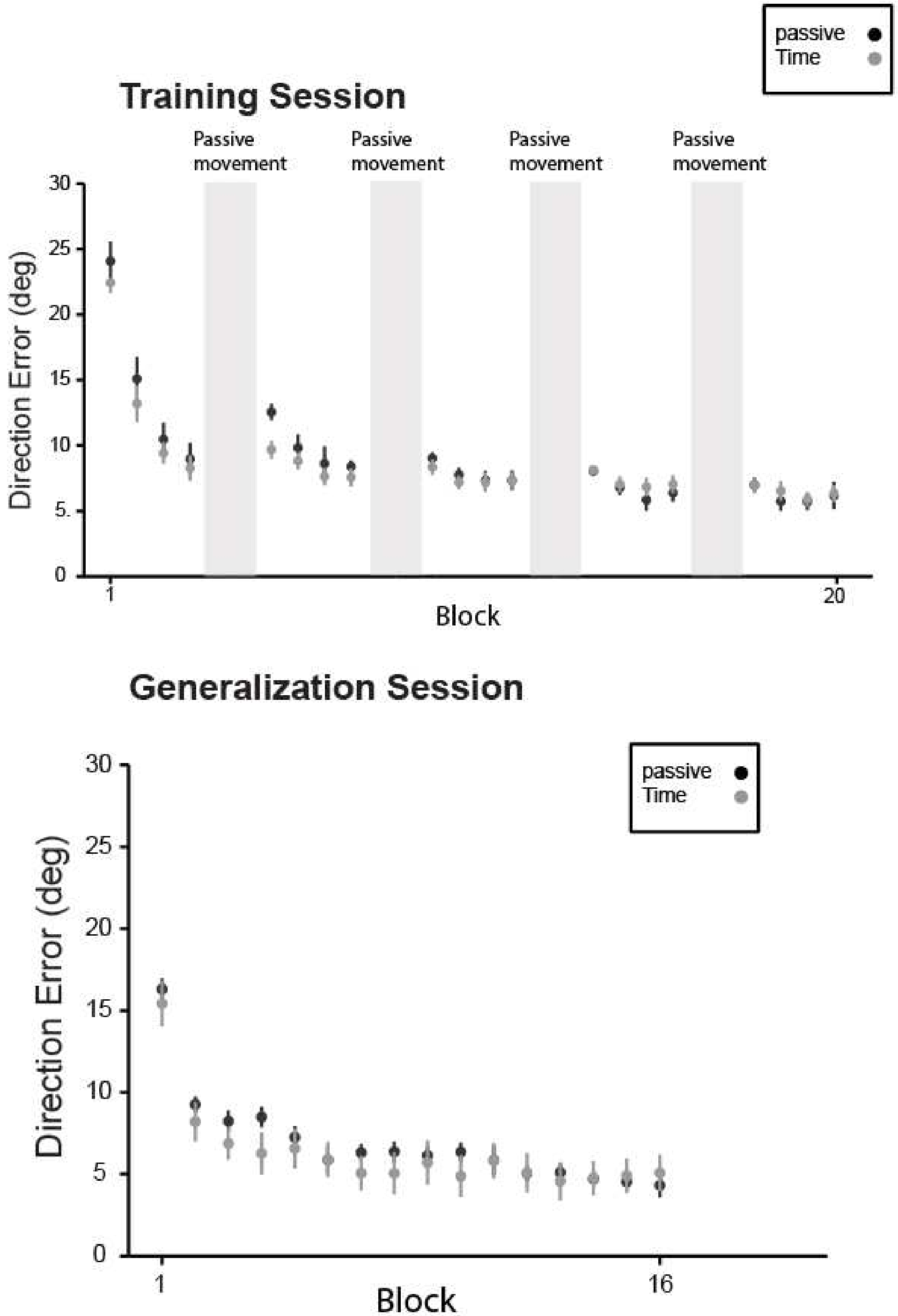

Figure 13: Mean performance measure. Every data point shown on X axis represents the average of 5 consecutive trials (block) across all subjects within each group (mean ± SE).

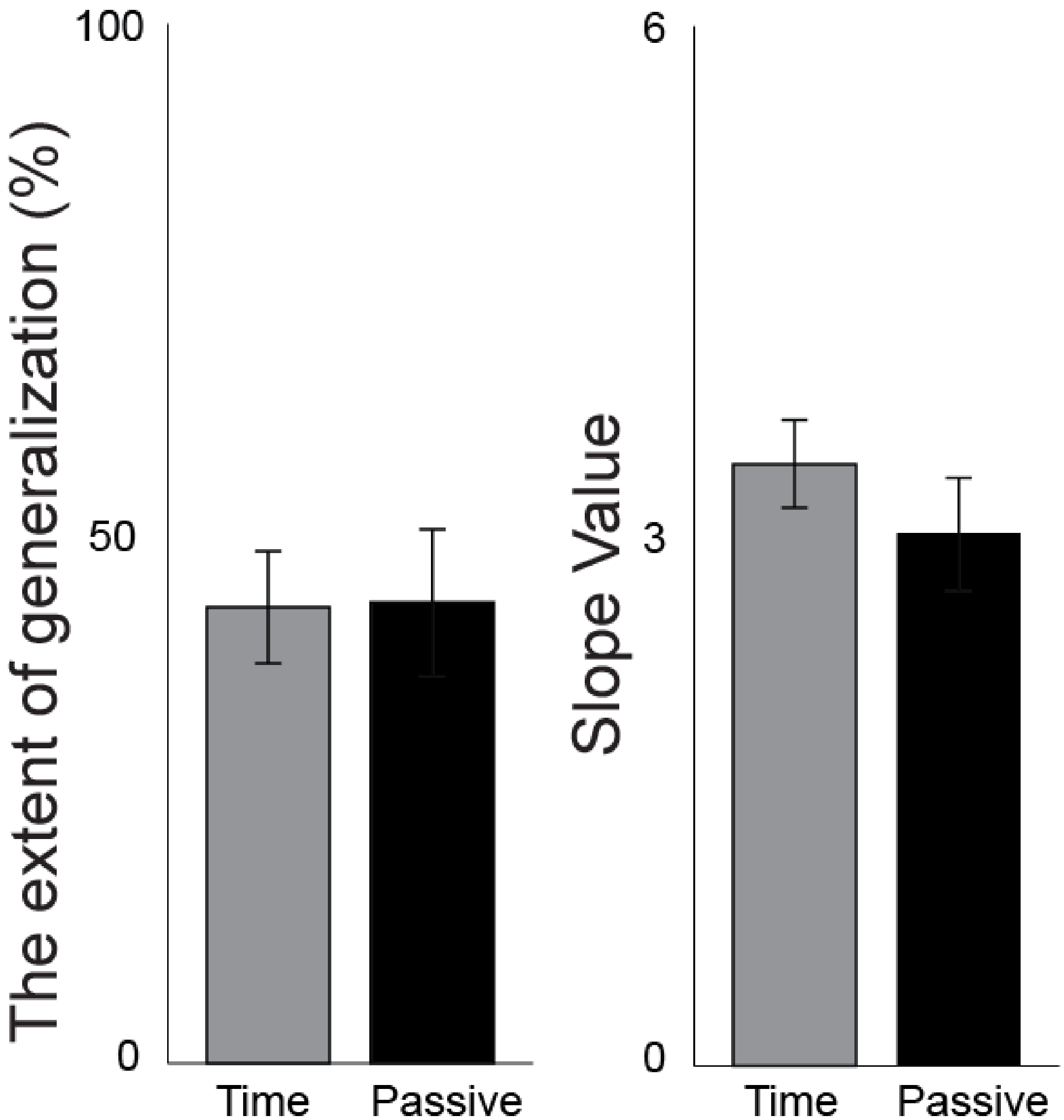

Figure 14: The extent of generalization from the training to generalization session (left panel), and slope values during the generalization session (right panel). Slope values obtained from nonlinear logarithmic regression equation were used to calculate the adaptation rate.

Experiment 2b

The results from experiment 1 and 2a indicated substantial generalization across limbs, but limited generalization across movement directions within the same limb, when movement instances directly associated with the direction to be experienced later can be accrued during initial training. It seems plausible that the extent of generalization within the same arm was limited probably due to the fact that the amount of instances associated with the new task to the learned later was also limited. Thus, I added a new condition to test this idea in this part of experiment 2a. The purpose of experiment 2b was to investigate generalization of visuomotor adaptation across movement directions within the same limb when a substantially greater amount of movement instances were provided during initial training.

Materials and Methods

Subjects

Subjects were 5 neurologically intact young adults (aged between 18 and 30) who were right-handed. A questionnaire for handedness and an informed consent form were read and signed by all subjects prior to the beginning of the study. The protocol was approved by the University of Wisconsin-Milwaukee Institutional Review Board. No subject participated in the other experiment.

Apparatus

The same apparatus used in experiment 1 and 2a was used in this experiment.

Experimental Design

This experiment employed the same reaching tasks described in experiment 2a, and also consisted of three sessions: baseline, training, generalization. In the baseline session, the subjects were familiarized with the general reaching task. In the training and generalization sessions, they adapted to a visual display rotated 30 degrees counterclockwise about the start circle (i.e., hand movement made in the “12 o’clock” direction resulted in cursor movement made in the “11 o’clock” direction). For the arrangement of the training and generalization targets, the generalization target was 180-degree relative to the training target (Figure 15A). During the training session, all subjects experienced passive movement, with velocity and movement duration comparable with those in the active movement, in the 30-degree clockwise direction relative the generalization target for 50 trials after every 20 adaptation trials with the right hand (Figure 15B). Visual feedback was provided for adaptation trials, but not for passive trials, during the training session. This allowed specific instances associated with the task to be performed later in the generalization session to be accrued in advance, without generation of motor command. During the generalization session, all subjects received visual feedback. Each of the three sessions consisted of 40, 350 (100 for the adaptation trials, 250 for the passive trials) and 80 trials, respectively (Figure 15C).

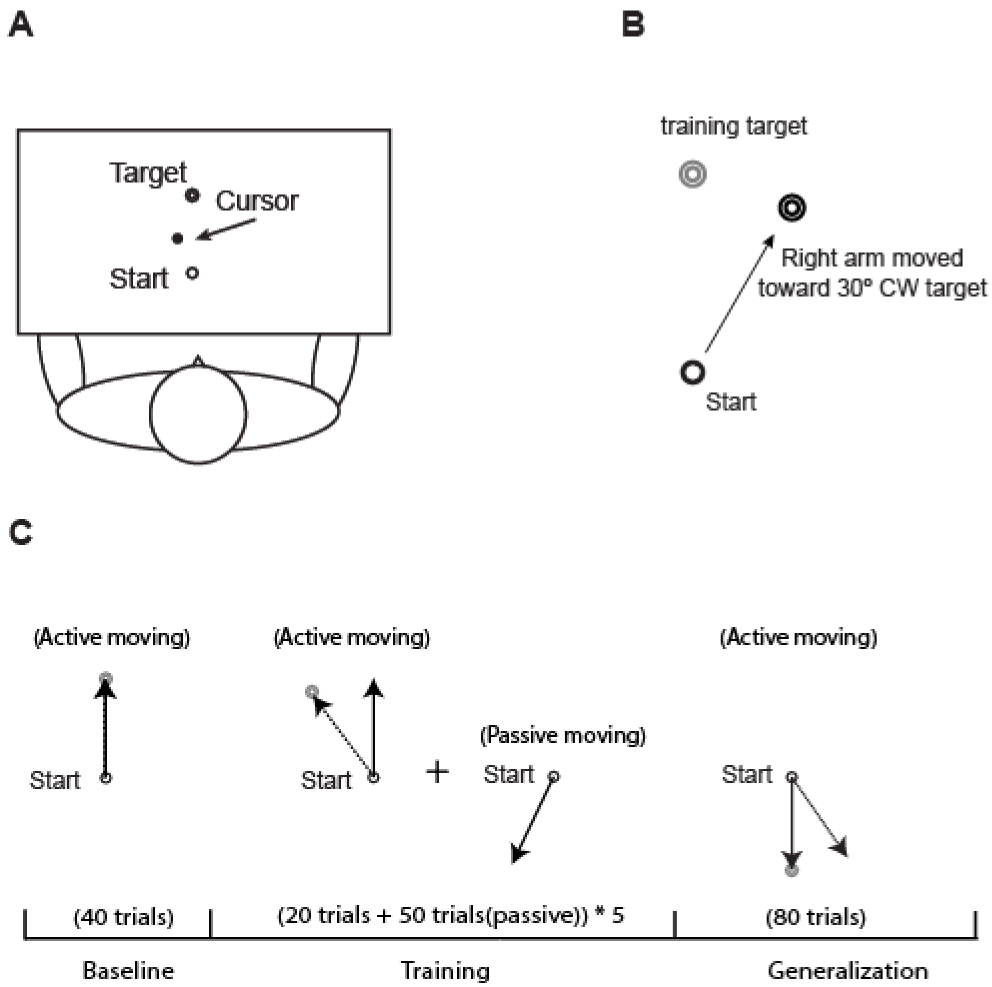

Figure 15: A: Experimental setup. B: subjects reached toward 30-deg clockwise target relative to the training target (where they reached toward following complete visuomotor adaptation) passively. C: Protocols for Experiment 2b

Data analysis

For statistical analysis, direction errors from the aforementioned group were compared with those groups from experiment 2a. A 3×4 repeated-measures ANOVA with group as a between-subject factor and block (the first and the last blocks of the training session, the first and the last blocks of the generalization session) as a within-subject factor to determine if there was any difference among the subject groups throughout the training and the generalization sessions. Following this, two simple ANOVAs with group as a between-subject factor were conducted: one, using the percentage of transfer, to determine if the extent of generalization across movement directions was different among the subject groups: and the other, using the slope values from regression lines, to determine if the rate of visumotor adaptation during the generalization session was different among the groups. The alpha level was set at 0.05. Post hoc comparisons, using dependent t-tests, were made between the first block of the training session and the first block of the generalization session, as well as between the last block of the training session and the first block of the generalization session, within each experimental condition.

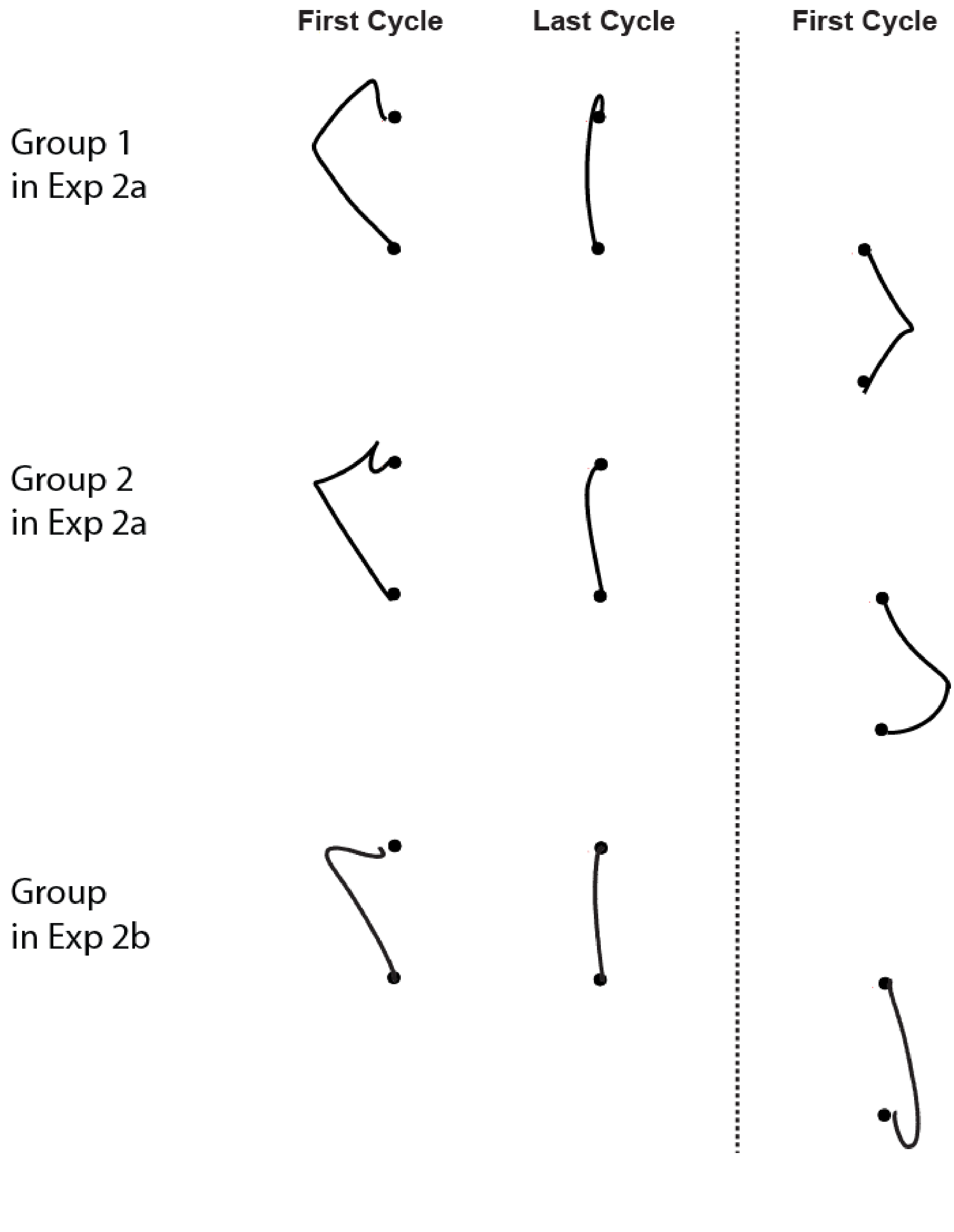

Figure 16: Each column shows hand-paths of reaching movement. Column 1 shows performance upon initial exposure to the visual rotation. Column 2 shows improved performance at the end of the training session. Column 3 shows performance at the beginning of the generalization session.

Results

Figure 16 illustrates the hand-paths of a representative subject from each of the three subject groups in experiment 2a and 2b. The hand-paths during the training session were similar across the subjects, in that they were largely curved at the beginning (Figure 16, column 1), but became relatively straight by the end of the session (Figure 16, column 2). During the generalization session, the hand-paths upon initial exposure to the visual rotation appeared different across the subjects, in that the subject who experienced more passive movements toward the 30-degree target during initial training showed relatively straight hand-paths from the beginning of the generalization session (Figure 16, column 3, row 3), whereas the other subjects' hand-paths were noticeably more curved. These hand-paths suggest that the extent of generalization across movement directions following visuomotor adaptation may differ across the subject groups.

We quantified the difference by subjecting direction error measures to a repeated-measures ANOVA, which revealed a significant interaction effect between group and block ($p = 0.027$; Figure 17). Our post hoc analyses indicated that the direction errors at the first block of the generalization session were significantly smaller than those at the first block of the training session in all subject groups. However, the errors at the last block of the training session and those at the first block of the generalization session were not significantly different in the group who experienced more passive movements toward the 30-degree target during the initial training, whereas they were significantly different in the other two groups. Simple ANOVAs also revealed a significant effect of group for the extent of generalization and the slope value ($p = 0.031$ and 0.012, respectively). Post hoc comparisons indicated that the extent of generalization observed in the group who experienced more passive movements toward the 30-degree target with the right arm during initial training was significantly higher than that observed in the other two groups; and the mean slope value obtained from the former group was significantly lower than that of the other two groups. This indicates that the extent of generalization can increase substantially when more motor instances were applied on arm during the initial training.

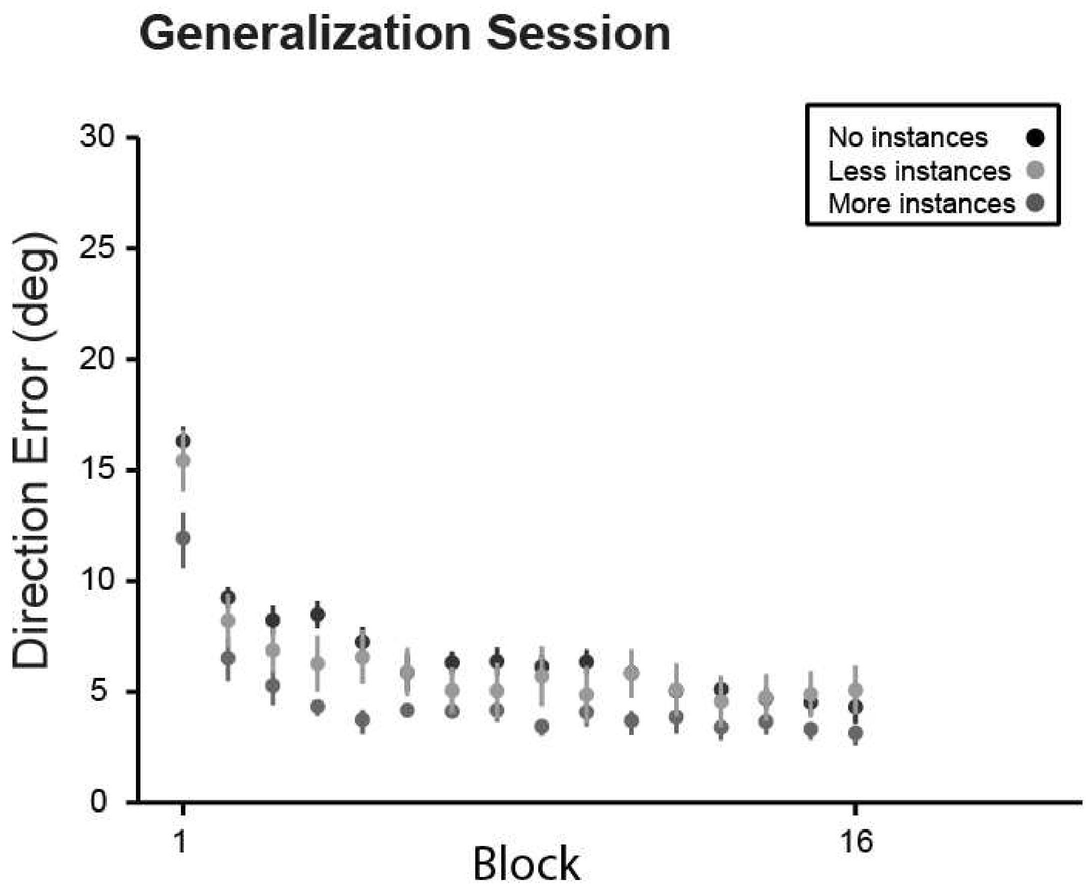

Figure 17: Mean performance measure. Every data point shown on X axis represents the average of 5 consecutive trials (block) across all subjects within each group (mean ± SE).

Discussion

In this study, we investigated how instance-reliant motor learning mechanism could explain the phenomenon of limited generalization in motor adaptation across movement directions and effectors. For this aim, we executed three experiments. In experiment 1, we predicted based on the instance-reliant learning hypothesis that providing movement-specific instances (i.e., by experiencing passive training without providing performance feedback) would increase the extent of generalization across effectors. Here, we assumed that visuomotor adaptation would not occur with the right arm during the initial training with the left arm because visual feedback was not available when the subjects experienced passive movements with the right arm. Following the training session, our data revealed substantially greater extent of generalization in the subject group who reached toward the 30-degree target with the right arm passively during the training session, as compared with the other group. The extent of generalization in the former group was over 80%, while that in the other group was below 50%. This is consistent with the findings reported by Wang et al. (2015), who demonstrated ~90% of transfer from the left to the right arm following visuomotor adaptation when subjects performed reaching movements actively with the right arm, without visual feedback, during the left-arm training session.

In experiment 2a, we focused on the effects of instance-reliant learning processes on motor generalization across movement directions. We expected that we would be able to confirm a greater extent of generalization from the passive training group. As previously described, we observed no difference between the two groups in terms of motor generalization. This suggests that providing motor instances using passive training seems to have no benefit for generalization of visuomotor adaptation across movement directions. However, because instance retrieval occurs within the same arm, it is possible that movement-specific instances provided by active movements interfere with the retrieval of the motor memory for passive training. In fact, the extent of generalization is even worse in passive training group in which subjects only experienced passive movements for only 50 trials during the training session, rather subjects performed active movement for 100 trials.

In experiment 2b, we investigated whether prolonged passive training would increase the extent of generalization across movement directions. We hypothesized that the instances accrued by active movements inhibits the expression of the recently acquired motor memory for passive movements, because the former instances are more than the instances accrued by passive movements. Instances from active movements would already be available while those from passive movements were being accrued; and a competition might occur between the two sets of instances in such a way that the instances associated with active movements would be automatically retrieved, thus causing inhibition of the expression of instances associated with passive movements, until the instances associated with passive movements were accrued sufficiently. This explanation is consistent with an idea that multiple motor memories, or instances can compete with each other for retrieval. For example, one study

(Billalta et al (2013)), in which researchers applied repetitive transcranial magnetic stimulation (rTMS) over the primary motor cortex following initial motor adaptation, and prior to washout trials to depress corticospinal excitability, demonstrated increased amount of savings by preventing a competition between motor memories at recall, one associated with the motor adaptation and the other associated with the washout trials. Therefore, it is possible that if a substantially greater amount of movement instances are provided in passive training, motor instances associated with passive training would prevail over that provided by active movements. Therefore, we prepared a group in which subjects performed passive movements for 250 trials. For the results, this group demonstrated a greater extent of generalization compared with the two groups in experiment 2a. These results suggest that prolonged passive training would consolidate the expression of the recently acquired motor memory.

As an alternative explanation for these results, it is possible that the extent of generalization across the movement directions is limited for experiment 2a due to the uncertainty of the properties of the motor memory acquired during the passive training. Human subjects can preserve the motor memory after significant periods of time, but the act of another motor behavior could have adverse effects on recalling a previously acquired motor memory. A Bayesian analysis of motor adaptation has demonstrated that the nervous system combines multiple pieces of information to achieve optimal motor outcome, and the nervous system weights each pieces of information with respect to its likelihood (Kording and Wolpert, 2004; Ma et al. 2006). Thus, prolonged training with a motor behavior may increase the certainty in its properties, so as to translate this certainty into strong priors, making the acquired motor memory relatively unsusceptible to expression.

Our findings demonstrated that motor generalization can be improved by passive training. Previous studies suggested that passive training can improve motor learning by providing proprioceptive information of the desired movement. For example, subjects who were provided additional proprioceptive information of circular hand movement trajectories passively were better able to learn this new motor skill (Beets et al., 2010; Wong et al., 2012). We suggest that process leading to motor learning through passive training is considered as the instance-reliant learning. Instance-reliant learning is thought to be associated with specific movement performed by specific effectors. Prescriptive proprioceptive information provided by passive practice helps accrue motor instances of the goal movement and build a template of expected sensory consequence (Kovacs et al., 2011).

What are motor instances? The theory of instance was originally proposed by Logan (1988), a cognitive psychologist who suggests that instances are specific solutions to specific stimuli; and each solution is encoded and stored to, and retrieved from, memory separately. Here, instances are associated with repetition of physical movements, and that are associated with specific movement directions and effectors. Instance-reliant learning can also be thought as a form of use-dependent plasticity (Diedrichsen et al. 2010), being driven through encoding the specific kinematic aspects of the repetitive movement even without any outcome information (Wolpert et al., 2011). The neural substrates of these instances may be similar with those suggested to underlie use-dependent plasticity, mainly involving the primary motor cortex (Classen et al., 1998; Diedrichsen et al., 2010; Sanes, 2000).

Chapter 3: Effects of a training condition that combines passive training and action observation on visuomotor adaptation

Introduction

Although it is commonly held that motor learning is acquired through physical practice, observation alone or passive practice alone have also been shown to be benefit to specific motor performance gains (Vogt, 1995; Black and Wright, 2000; Edwards et al. 2003; Petrosini et al. 2003; Mattar and Gribble, 2005; Badets et al. 2006; Haith et al. 2008; Brown et al. 2009; Cressman and Henriques, 2009; Wong et al. 2012). As such, through action observation, participants can form physiological motor memories by learning high-level information about the form of movement such as the movement kinematics (Hayes et al., 2010), coordination pattern (Hodges et al., 2007), as well as spatial-temporal goals (Vogt, 1995). These motor memories are coded in a neural representation similar to that underlie motor execution. Whereas passive practice augments motor learning through delivering proprioceptive information of the goal movement, which helps build a template of expected sensory consequences (Schmidt RA 1975) or forward models (Kawato and Gomi, 1992; Wolpert et al. 1995; Wong et al. 2012; Beets et al. 2012).

Compared to motor learning via physical practice, motor skills acquired through the mere observation of actions or passive practice alone often results in limited performance gains in motor training. For example, it has been recently shown that observers who watched an actor performing reaching movements in a novel dynamic environment performed better than non-observing control subjects, but worse than those who actively experienced this environment, when later adapting to the same environment (Wanda et al. 2013). Similarly, it has been reported that passive training activates cortical regions similar to those activated by active training (Weiller et al. 1996; Carel et al. 2000; Lotze et al. 2003), but active training is more effective in eliciting performance gains and cortical reorganization than passive training (Lotze et al. 2003).

Learning a motor task is associated with changes in sensory system (Bernardi et al. 2013), such that motor learning involving arm movements is accompanied with changes in sensed limb position (Cressman and Henriques, 2009) and perceptual acuity (Wong et al. 2011). Given that repetitive passive movements elicit cortical motor representational changes, inducing use-dependent plasticity that encodes the specific kinematic aspects of the practiced movement, and the mere observation of actions yields motor learning through enhancing the effect of visual perception on action, it is therefore possible that when action observation is combined with passive practice, the training effects would be quantitatively enhanced relative to mere action observation or passive practice alone.

To investigate the effect of action observation in combined with passive practice on motor learning, we compared the learning performance of five different groups: action observation alone, passive practice alone, action observation combined with passive practice, the passage of time, and active practice. We hypothesized that these five different interventions would result in quantitatively different performance gains.

Experiment 3

Materials and Methods

Subjects

Subjects were recruited via word of mouth and flyers posted on University of Wisconsin-Milwaukee's campus. Upon arrival to the Neuromechanics laboratory subjects completed an informed consent form previously approved by the UWM Internal Review Board before participation in the study (Appendix A). Testing for this study was completed in one session and took no more than an hour to complete. A total of 40 neurologically intact right-handed individuals aged from 18 to 30 years old were recruited. They had normal or corrected-to-normal vision. Handedness was assessed using the 10-item version of the Edinburgh inventory (Oldfield, 1971). The participants were paid for their participation. Exclusion criteria for this study were: 1) a major psychiatric diagnosis (e.g., schizophrenia), 2) hospital admission for substance abuse, 3) peripheral disorders affecting sensation or movement of the upper extremities (e.g., peripheral neuropathy), or 4) if they are left-handed. Also, any participant who is pregnant was excluded from participation. All subjects were naïve to the purpose of the experiment. Each subject was randomly assigned to one of five groups.

Apparatus

KINARM was used as the experimental apparatus. Subjects sat on the KINARM chair with the right arm supported on the exoskeleton that provided full gravitational support of the entire arm (Figure 18A); and the chair was moved to bring the arm under a horizontal display. The KINARM was incorporated with a virtual reality system that projected visual stimuli (starting and target circles) on the display to make them appear in the same plane as the arm. Direct vision of the subject's hand was blocked by the horizontal display; and a cursor representing subjects' index finger tip was provided to guide their reaching movement. The visual stimuli consisted of a central starting circle (2 cm in diameter) and four target circles (2 cm in diameter) positioned 10 cm away from the starting circle (Figure 18B). The 2-D position data of the hand, elbow and shoulder were sampled at 1000 Hz, low-pass filtered at 15 Hz, and differentiated to yield resultant velocity. Computer algorithms for data processing and analysis were written in MATLAB (The Mathworks Inc., Natick, MA, USA).

Video Recording

Video recording was made using Dexterit-E Explorer, which provided observers with a top-down view of an actor's right arm movement, together with the visual targets and a cursor representing the position of the hand (Figure 18C). Recording was approximately 8 min in duration and demonstrated a series of 120 movements. The recording depicted a representative subject moving to target in a novel visual rotated environment, which showed the progression from highly perturbed to relative straight movements associated with motor learning.

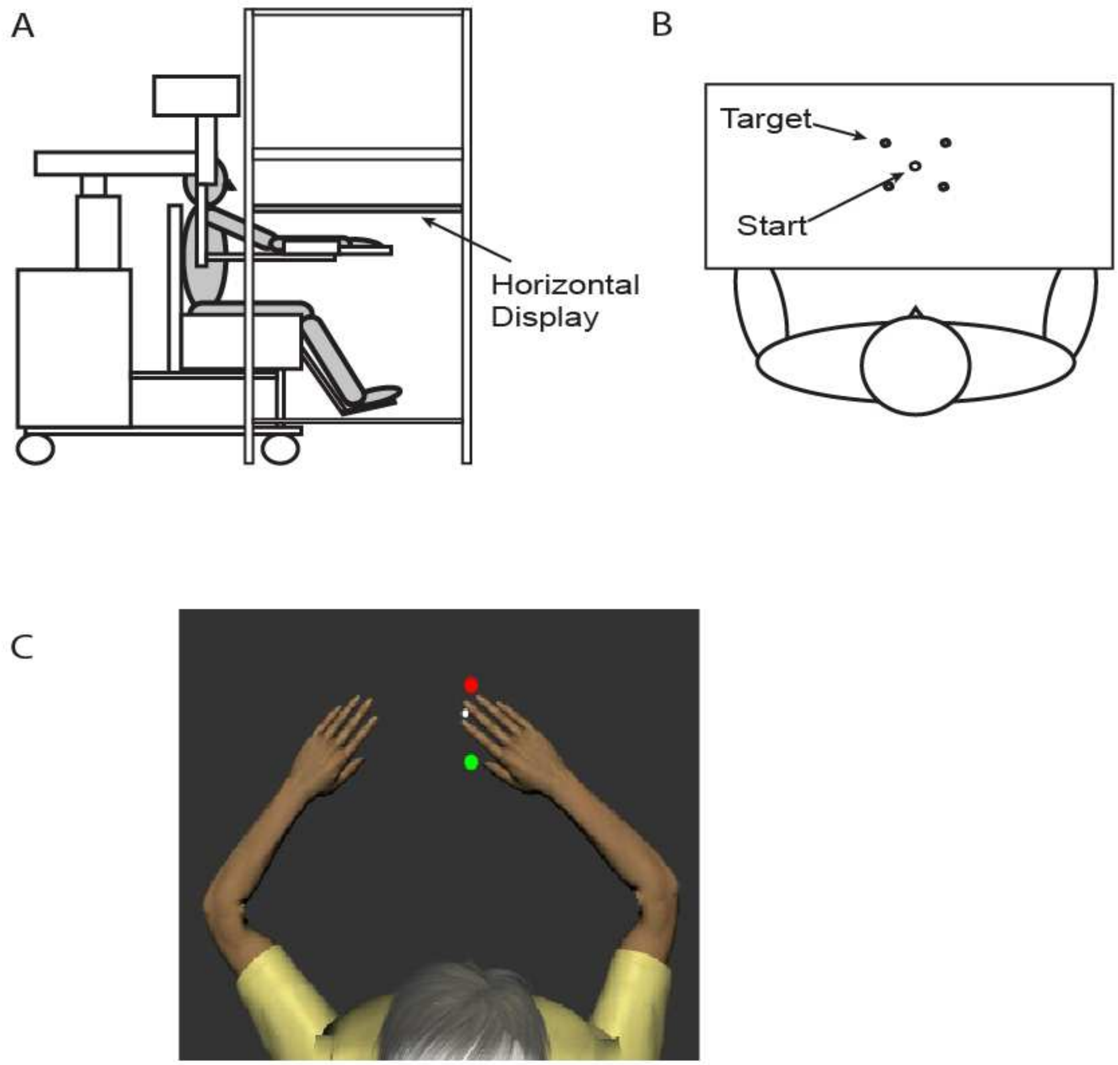

Figure 18: A: Experimental setup. B: An illustration of the targets presented on the display. C: Still frame taken from a video shown to observer.

Experimental Design

Prior to movement, each of the four radial targets was presented in a pseudorandom manner during a cycle of four trials. Subjects were instructed to move their index finger rapidly from the start circle to the target as straight and accurately as possible in response to the appearance of the target. They were also told not to make corrections at the end of reaching movements within each trial. Subjects were assigned to one of five groups (8 subjects per group): passive practice only (PP), time delay (TD), action observation only (AO), active learning (AL), and action observation combined with passive practice (AO+PP). The experiment task was divided into three sessions: baseline, training, testing. In the baseline sessions, all subjects performed 60 reaching movements without manipulations of their visual feedback to be familiarized with the general reaching task. All movements were presented in a pseudorandom sequence across four target directions. During the training sessions, subjects underwent each of the following five interventions. The PP subjects group experienced passive movement in the 30-degree clockwise direction relative to the training targets for 120 trials. The TD subjects group sat on the robotic chair without moving their arm. The AO subjects group was instructed to remain motionless sitting on the robotic chair, and watch a movie of a naïve actor performing 120 reaching movements under the visual rotation environment described above. The AL subjects group performed 120 reaching movements under a novel visual rotation environment, in which a visual display about the start circle will be rotated 30 degrees counterclockwise (i.e., hand movement made in the “12 o’clock” direction resulted in cursor movement made in the "11 o'clock" direction). The AO+PP group experienced passive movement in the 30-degree clockwise direction relative to the training targets for 20 trials after every 30 observation trials. During the testing sessions, all subjects performed 60 reaching movements under the 30 degree counterclockwise visual rotation environment (Figure 19).

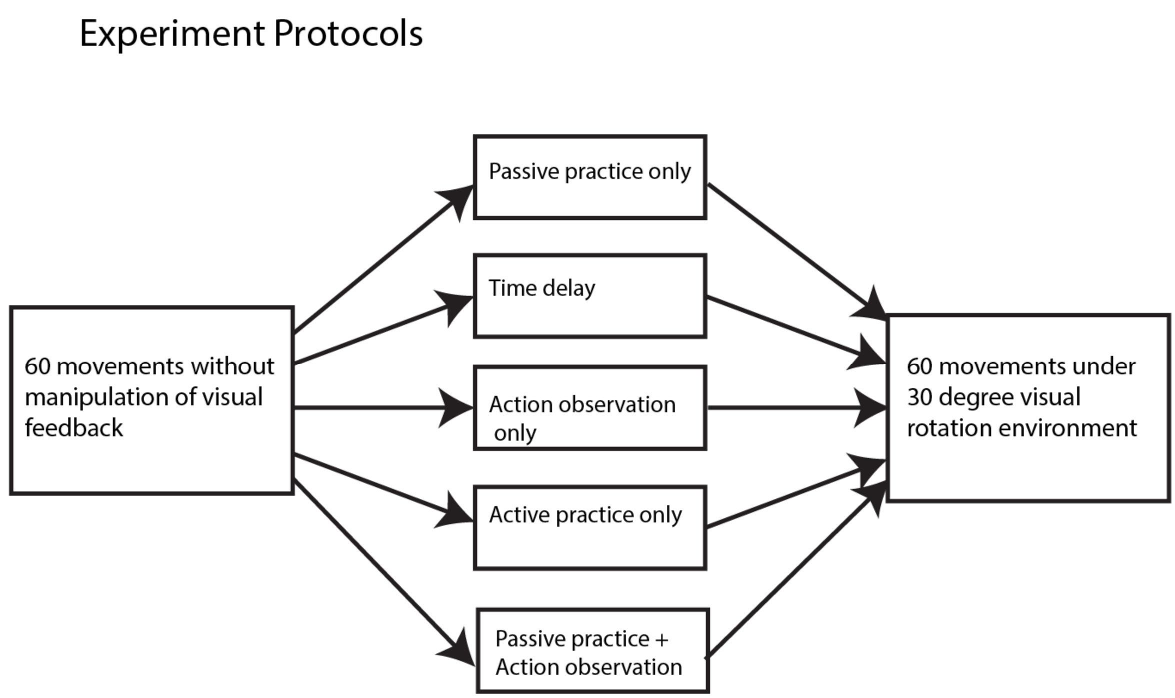

Figure 19: Protocols for Experiment

Data analysis

The performance measure used in this study was initial direction error (DE), which was the angular difference between a vector from the start circle to the target and another vector from the hand position at movement start to that at peak arm velocity. A cycle represents the mean of 4 consecutive trials.

For statistical analysis, two simple ANOVAs with group as a between-subject factor were conducted: one, using initial direction errors from the first cycle of the testing session, to determine if there was any difference among the five groups during the testing session: and the other, using the slope values from regression lines, to determine if the rate of visumotor adaptation during the testing session was different among the groups. The alpha level was set at 0.025 (i.e., 0.05/2) for the analyses after a Bonferroni correction was made, and at 0.05 for post hoc comparisons (Tukey's tests for between-group comparisons).

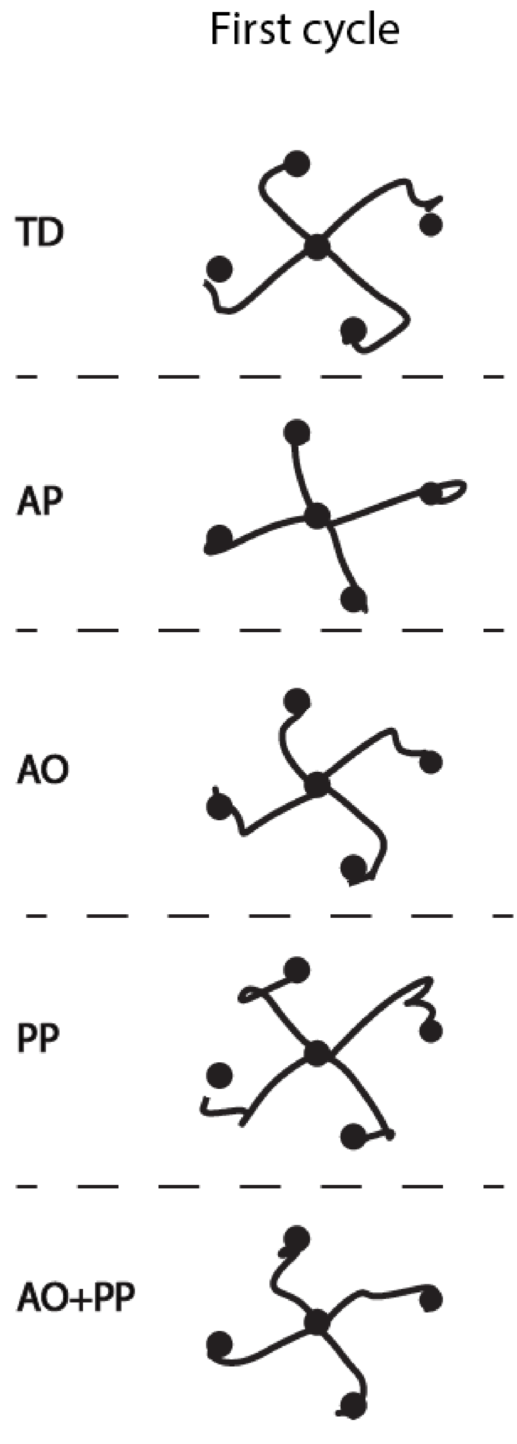

Figure 20: Each row shows hand-path of reaching movement from each group at the first cycle of the testing session.

Results

In this experiment, all subjects adapted to the rotated visual display with the right arm during the testing session. Figure 20 illustrates the hand-paths of a representative subject from each group during the initial phase of visuomotor adaptation in the testing session. In the TD group, the hand-path was largely curved to the target (Figure 20, row 1), whereas the AO and PP groups demonstrated relatively straight hand-paths at the beginning of the testing session (Figure 20, row 3, 4). The hand-path in the AO+PP group (Figure 19, row 5) was substantially straighter than those observed from the aforementioned groups, although not as straight as the hand-path shown from the AP group (Figure 20, row 2). Figure 21 illustrates the changes in performance across the cycles in terms of initial direction error for all groups.

The data regarding hand direction errors (DE) at the very first cycle of performance from the testing session were subjected to a one-way ANOVA, which showed a significant difference ($p<0.01$) among the five groups in terms of DE at the first cycle of the testing session. The difference among the five groups was further confirmed by calculating the rate of adaptation (i.e., slope value). All the fit slopes were significantly among the five groups ($p<0.01$). With regard to the post-doc tests, the comparisons for all groups were shown below.

TD vs. PP vs. AP group

Figure 21A illustrates the changes in performance across the cycles in terms of initial direction error for group TD, PP, and AP.

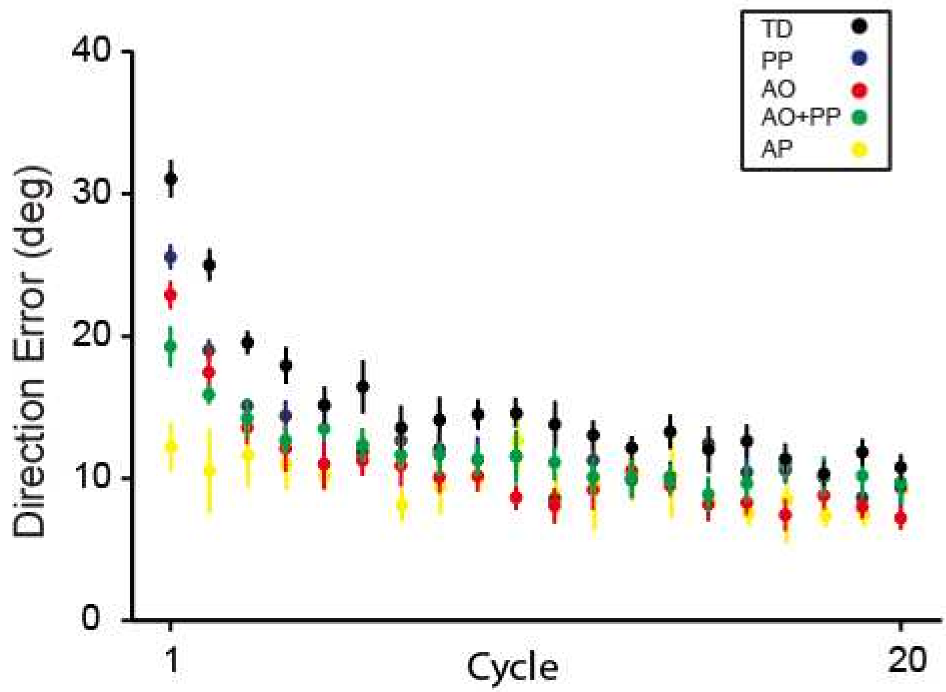

Figure 21: A: Mean performance measure for all groups. Every data point shown on X axis represents the average of 4 consecutive trials (cycle) across all subjects within each group (mean ± SE).

Direction errors at the very first cycle of performance during the testing session were substantially larger in the TD and PP groups than in the AP group. The post hoc analyses indicated that the direction errors in group AP were significantly smaller than those at the first cycle during the testing session in group TD and PP (Figure 21B). The average slope values over eight subjects are shown in Figure 21B. The error bars represent the SE across subjects. A post hoc analysis revealed that the slopes in the PP group were significantly larger than that in the AP group, but smaller than that in the TD group. Overall, these results suggest that subjects performed substantially better in the PP group than those in the TD group, although not as good as those from the AP group.

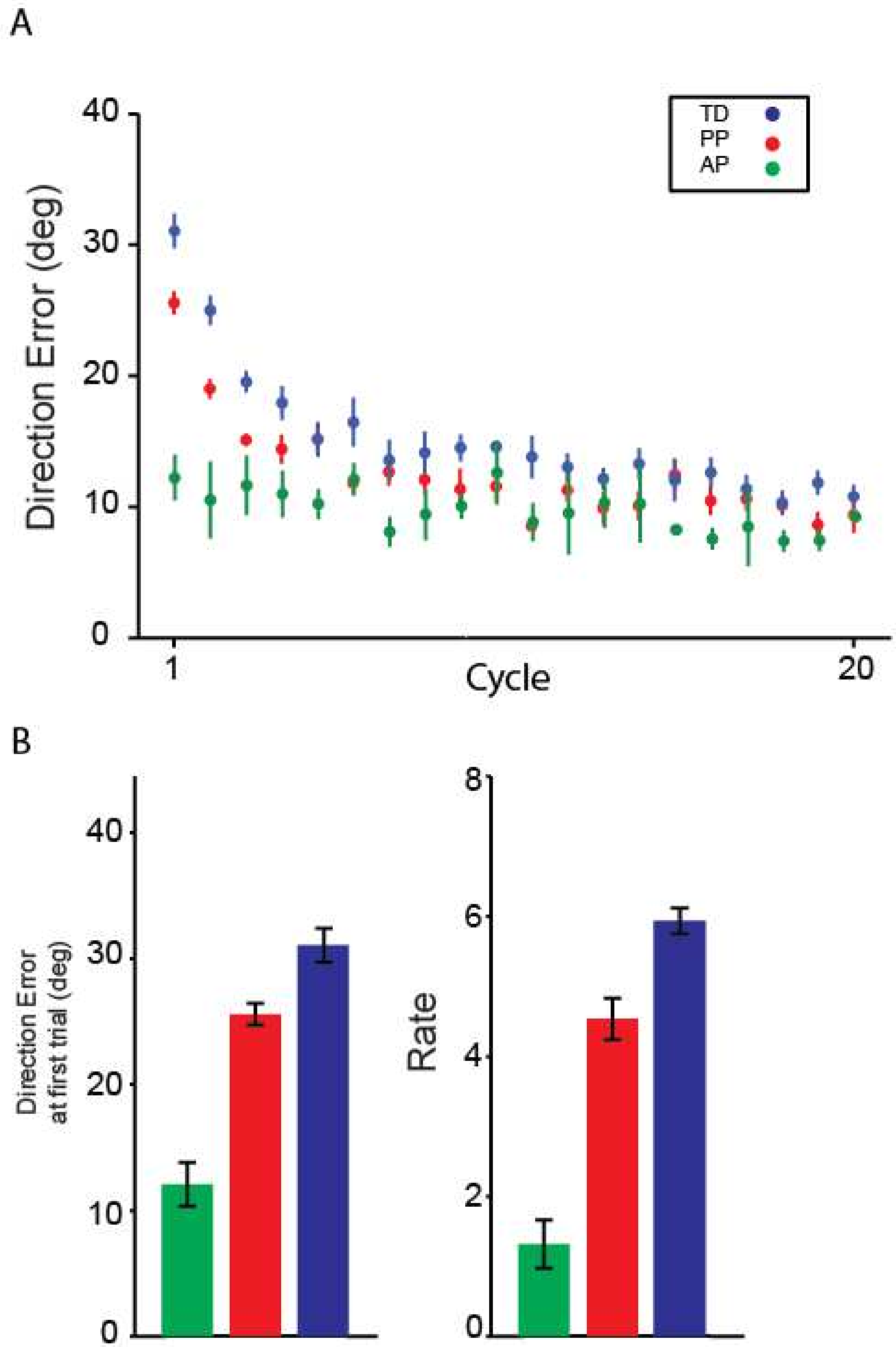

Figure 21: A: Mean performance measure for group TD, PP, and AP. Every data point shown on X axis represents the average of 4 consecutive trials (cycle) across all subjects within each group (mean ± SE). B: Direction errors at the very first cycle (left panel), and slope values during the testing session (right panel).

TD vs. AO vs. AP group

Figure 22A depicts the changes in performance across the cycles in terms of initial direction error for group TD, AO, and AP. The results show that direction errors decreased at a decelerating rate across the cycles regardless of the groups. Direction errors at the very first cycle of the performance in the AO group were substantially larger than that in the PP group, but smaller than that in the TD group. The average fit parameter (the rate of adaptation) over the eight subjects is shown in Figure 22B. The rate differed significantly among the three groups. Specifically, the rates in the TD group were significantly larger than for the AO and AP groups. Overall, these results suggest that subjects performed substantially better in the AO group than those in the TD group, although not as good as those from the AP group.

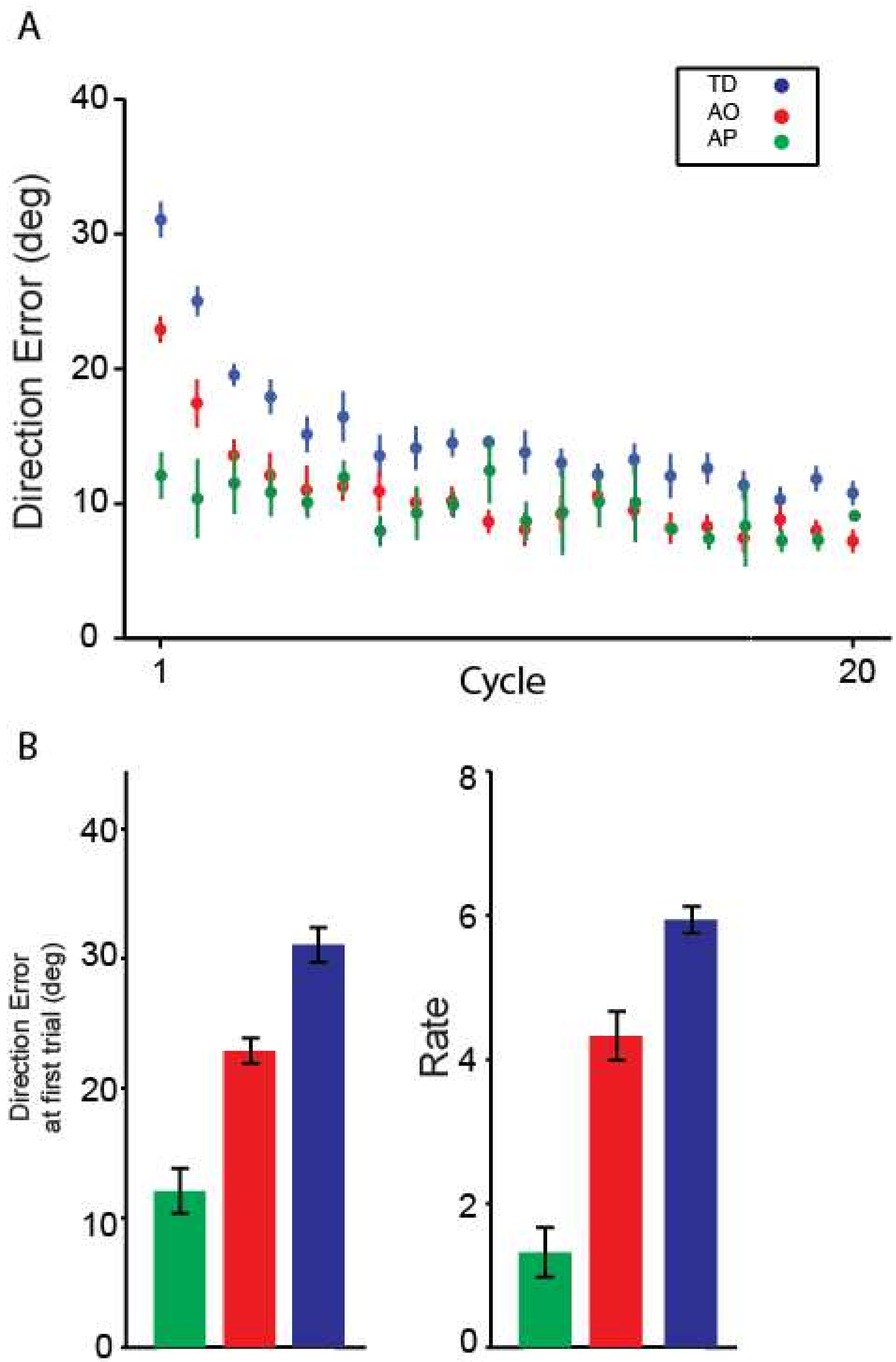

Figure 22: A: Mean performance measure for group TD, AO, and AP. Every data point shown on X axis represents the average of 4 consecutive trials (cycle) across all subjects within each group (mean ± SE). B: Direction errors at the very first cycle (left panel), and slope values during the testing session (right panel).

TD vs. AO+PP vs. AP group

Figure 23A shows direction errors as a function of the cycle for the group TD, AO+PP, and AP. Direction errors decreased across the cycles, indicating again that adaptation occurred regardless of groups. The direction errors at the very first cycle during the testing session and fit slopes are shown in Figure 23B. The post hoc analyses indicated that the direction errors in group AP were significantly smaller than those at the first cycle during the testing session in group TD and AO+PP. Similarly, the slopes in the AO+PP group were significantly larger than that in the AP group, but smaller than that in the TD group.

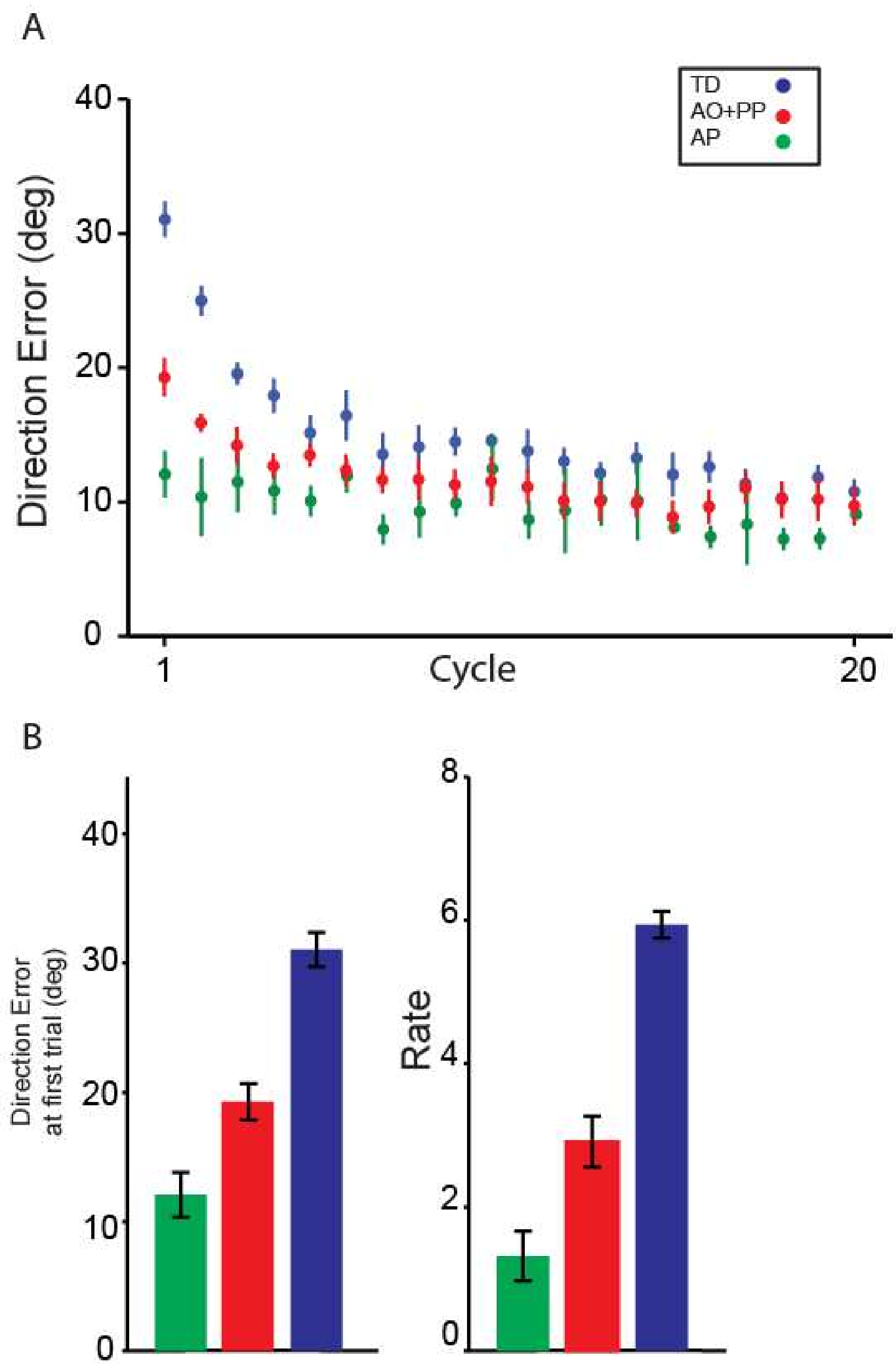

Figure 23: A: Mean performance measure for group TD, AO+PP, and AP. Every data point shown on X axis represents the average of 4 consecutive trials (cycle) across all subjects within each group (mean ± SE). B: Direction errors at the very first cycle (left panel), and slope values during the testing session (right panel).

AO vs. PP vs. AO+PP group

Figure 24A shows direction errors as a function of the cycle for the group AO, PP, and AO+PP. Our post hoc analyses indicated that the direction errors at the first block of the testing session in group AO+PP were significantly smaller than those at the first block of the testing session in all subject groups. Post hoc comparisons also indicated that the mean slope value obtained from the AO+PP group was significantly lower than that of the other two groups (Figure 24B). This indicates that subjects performed substantially better in the AO+PP group than those in the other two groups during the testing session.

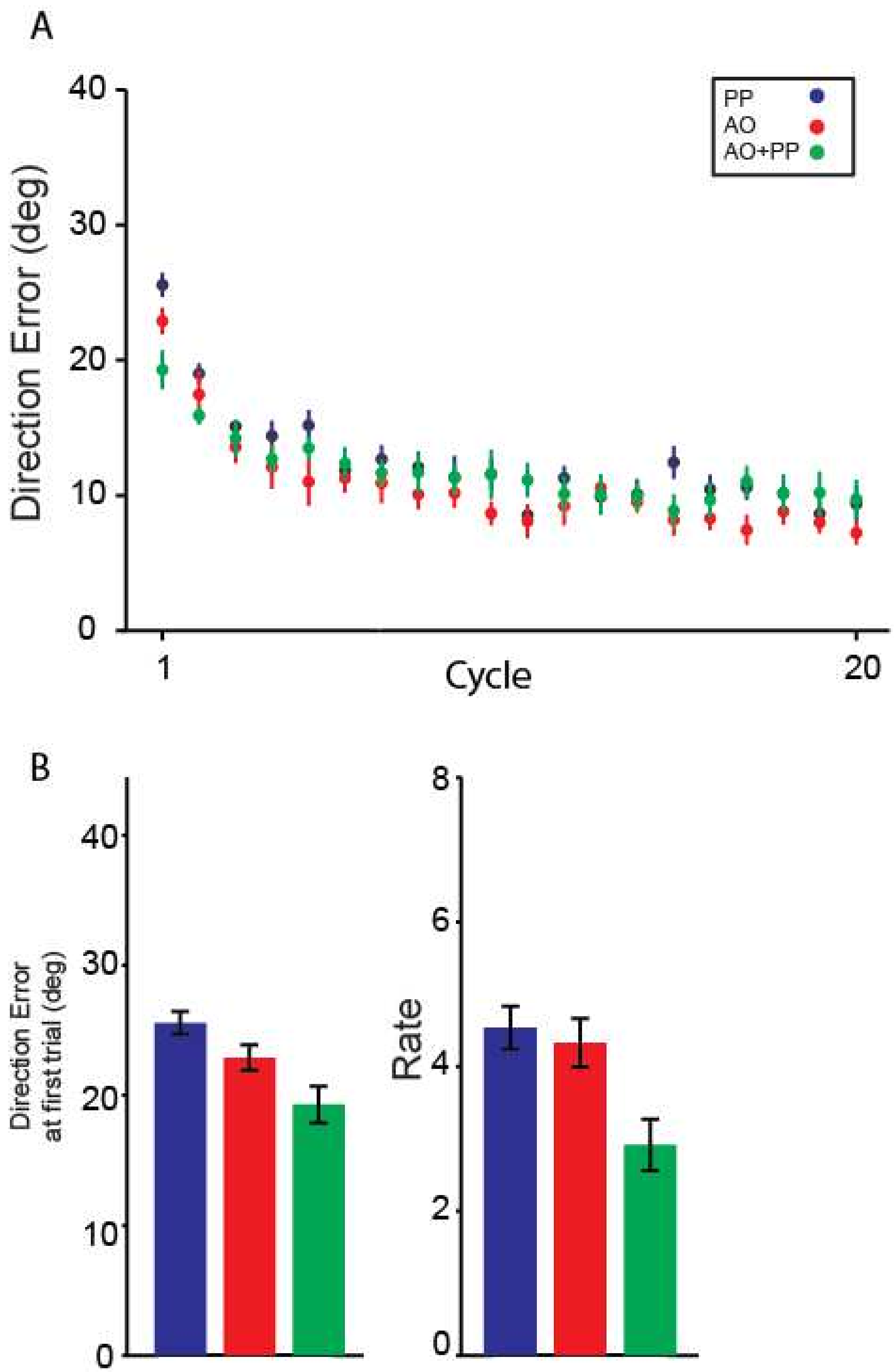

Figure 24: A: Mean performance measure for group PP, AO, and AO+PP. Every data point shown on X axis represents the average of 4 consecutive trials (cycle) across all subjects within each group (mean ± SE). B: Direction errors at the very first cycle (left panel), and slope values during the testing session (right panel).

Discussion

In this study, we investigated how the mere observation of action, passive practice alone, and action observation combined with passive practice could contribute to the formation of specific memory trace for motor performance gains. We demonstrated a decrease in direction error following the mere observation of an actor learning to adapt in a novel, rotated environment. This suggests that subjects can acquire neural representation of visual rotated environment on the basis of visual information. This is consistent with the findings reported by Hodges et al (2007), who demonstrated that subjects who viewed videos that were congruent with subsequent visuomotor adaptation performed well on direct tests of learning in the same environment. Similarly, we indicated that the passive practice alone has a positive effect on motor learning. As previously described, we were able to confirm that the passive practice (PP) group exhibited a significant decrease in angular error compared with the control group (TD). This is well consistent with previous passive practice studies (Cressman and Henriques, 2009, 2010; Sakamotor and Kondo, 2012), which show that passive motor experience imparts a positive effect on visuomotor learning task.

Furthermore, we tested hypothesis that action observation of movements in synchrony with passive practice would enhance training effects relative to the mere observation of action or passive training alone. We found that action observation combined with passive practice leads to significant improvements in motor performance relative to mere action observation or passive practice alone. This may suggest that subjects could form a specific motor memory depending on the kinematic features of the observed movement; and passive training helps to consolidate this motor memory by delivering proprioceptive information of the observed movement.

The motor learning literature suggests that when an individual learns a motor task, more than one learning process is involved, including model-based, model-free and instance-reliant learning (use-dependent plasticity). Learning mechanism underlying passive practice is considered as the instance-reliant mechanism or use-dependent plasticity (Classen et al. 1998; Butefisch et al. 2004; Stefan et al. 2005, 2008; Celnik et al. 2006, 2008; Lei and Wang, 2014; Wang et al. 2015). This form of mechanism encodes the specific kinematic aspects of passive movement (Wolpert et al., 2011). Prescriptive proprioceptive information by means of passive practice can help accrue motor instances of the goal movement and build a template of expected sensory consequence (Kovacs et al., 2011). The benefits of proprioceptive experience are likely due to provision of a reference of correctness that can be used to guide motor output. Similarly, learning mechanism underlying observational learning may only be associated with model-based learning, which is driven by sensory prediction errors. Action observation combined with passive training can involve both of model-based and instance-reliant learning processes, thus resulting in significant improvements in motor performance relative to mere action observation or passive practice alone.

An alternative view explaining the different intervention effects in terms of motor performance gains would be that each intervention induces its own motor memory in different sites of the nervous system. In this way, the mere observation of action induces a movement memory associated with visual perception on action, whereas passive practice alone induces a movement memory associated with proprioceptive information. The intervention combined with action observation and passive practice would result in two interacting simultaneous memory processes: one elicited by action observation and the other elicited by passive practice. This hypothesis is supported by a study showing action observation alone may generate a motor memory in M1, which is much smaller than that induced by physical practice (Stefan et al. 2005). Action observation facilitates accurate performance of motor task through the activity of the same neuronal substrate generated in the subsequence active movements. This idea is in line with previous studies showing that observation of congruent movements facilitates motor performance, while viewing non-congruent movements inhibits motor performance by competing neural activity (Kilner et al., 2003; Dijkerman and Smit, 2007). This idea is further supported by evidence that shows action observation influences the excitability of connections between PMv and M1 (Koch et al. 2010; Lago et al. 2010).

Our findings demonstrate, for the first time, that training periods consisting of action observation and passive practice lead to significant performance gains beyond what either intervention alone can do. Even though action observation in combined with passive training is effective in motor learning, the active training group is more successful in eliciting performance improvements, because the active training group involves error detection and correction processes, amplifying the perception-action interplay.

Chapter 4: Effects of a training condition that incorporates the manipulation of visual feedback into passive training on visuomotor adaptation

Introduction

Human subjects adapt rapidly to unfamiliar kinetic or kinematic transformations through an error-based learning (model-based) mechanism, in which the motor system builds an internal model of the state of body and/or environment that is used for planning of movements (Haith and Krakauer, 2013). If an expected perturbation is experienced, the motor system adapts the next motor command to minimize the prediction error, the difference between predicted and observed sensory consequence. This learning mechanism can be mathematically described with state-space model, which assumes that learning occurs through penalizing the deviations from the desired goal based on gradient descent on the squared movement errors (Thoroughman and Shadmehr, 2000; Donchin et al., 2003; Cheng and Sabes, 2006; Zarahn et al., 2008). Model-based learning is robust phenomenon that leads to fast improvements in performance in a changing environment.

However, model-based learning mechanism cannot be instrumental in reducing the variability of the movement outcome, because it can only achieve zero performance error on average. In this case, a second learning mechanism that not only results in performance gains under a perturbation, but also leads to a lower variance is introduced. We refer to this mechanism as success-based learning mechanism or reinforcement learning rule, because it assesses actions on the basis of experiences to maximize rewards and minimize punishments

(Sutton and Barto, 1998). in success-based mechanism the learners don't know a signed error signal regarding the movement, but an unsigned signal about the relative success and failure of the movement, so they don't have any information about the direction required to correct the movement. Thus, they have to explore possible actions to gradually improve their movement until an optimal solution is found.

Manipulation of online visual feedback provided during motor learning has been shown to effectively differentiate the contribution of these two learning processes (Izawa and Shadmehr, 2011; Schmuelof et al. 2012). In visuomotor adaptation paradigm, for example, learning from full vector error regarding movements involves primarily model-based mechanism. In contrast, learning from binary feedback about the success or failure of movements relies on model-free mechanism (Izawa and Shadmehr, 2011).

Recently, a similar but somewhat different view of motor learning mechanism has emerged, which suggests that motor learning also involves instance-reliant learning, in which effector- or movement-specific instances are accrued during repeated performances of a task to be learned and later retrieved to allow fast and automatized performances of the learned task (Wang and Sainburg, 2004; Lei and Wang, 2014). Instance-reliant learning can be thought as a form of use-dependent plasticity (Diedrichsen et al. 2010), being driven through encoding the specific kinematic aspects of the repetitive movement even without any outcome information (Wolpert et al., 2011).

The aforementioned learning mechanisms are associated with active motor experience. In terms of motor rehabilitation, training consisting of passive motor experience is believed to play a crucial role in rehabilitative medicine, particularly when patients are too weak to perform voluntary movements. It has been suggested that passive practice activates cortical regions akin to those activated by voluntary movements. We refer this phenomenon as use-dependent plasticity that encodes the specific kinematic aspects of the practiced movement, which has been interpreted as being indicative of a formation of a motor memory.

Although it is known that passive training can contribute to motor learning, it often results in less improvement compared to active learning. According to the former view of motor learning mechanisms (model-based learning vs. model-free learning), it is possible that the absence of model-based and model-free learning processes is the major reason for the limited improvement. Therefore, we hypothesized that the learning effect of passive training would improve when provoking model-based learning by providing vector error feedback regarding spatial information such as movement direction and amplitude, or eliciting model-free learning by providing binary error feedback regarding task success or failure (Shmuelof et al., 2012) during passive training.

Experiment 4

Materials and Methods

Subjects

Subjects were recruited via word of mouth and flyers posted on University of Wisconsin-Milwaukee’s campus. Subjects were 24 healthy young adults (18-30 old, right-handed). Handedness was assessed using the 10-item version of the Edinburgh inventory (Oldfield, 1971). Informed consent approved by the Institutional Review Board of the University of Wisconsin-Milwaukee was solicited prior to participation. The subjects were paid for their participation. Exclusion criteria for this study are: 1) a major psychiatric diagnosis (e.g., schizophrenia), 2) hospital admission for substance abuse, 3) peripheral disorders affecting sensation or movement of the upper extremities (e.g., peripheral neuropathy), or 4) if they are left-handed. Also, any participant who is pregnant was excluded from participation. All subjects were naïve to the purpose of the experiment. Each subject was randomly assigned to one of five groups.

Apparatus

We used experimental setup as shown in Figure 25A for experiments described in the study. Movement data were obtained with a bilateral robotic exoskeleton called KINARM (BKIN Technologies, Kingston, ON, Canada). Subjects sat on the KINARM chair with the right arm supported on the exoskeleton that provided full gravitational support of the entire arm; and the chair was moved to bring the arm under a horizontal display. The KINARM was incorporated with a virtual reality system that projected visual stimuli (starting and target circles) on the display to make them appear in the same plane as the arm. Direct vision of the subject's hand was blocked by the horizontal display; and a cursor representing subjects' index finger tip was provided to guide their reaching movement. The visual stimuli consisted of a central starting circle (2 cm in diameter) and four target circles (2 cm in diameter) positioned 10 cm away from the starting circle (Figure 25B). The 2-D position data of the hand, elbow and shoulder were sampled at 1000 Hz, low-pass filtered at 15 Hz, and differentiated to yield resultant velocity. Computer algorithms for data processing and analysis were written in MATLAB (The Mathworks Inc., Natick, MA, USA).

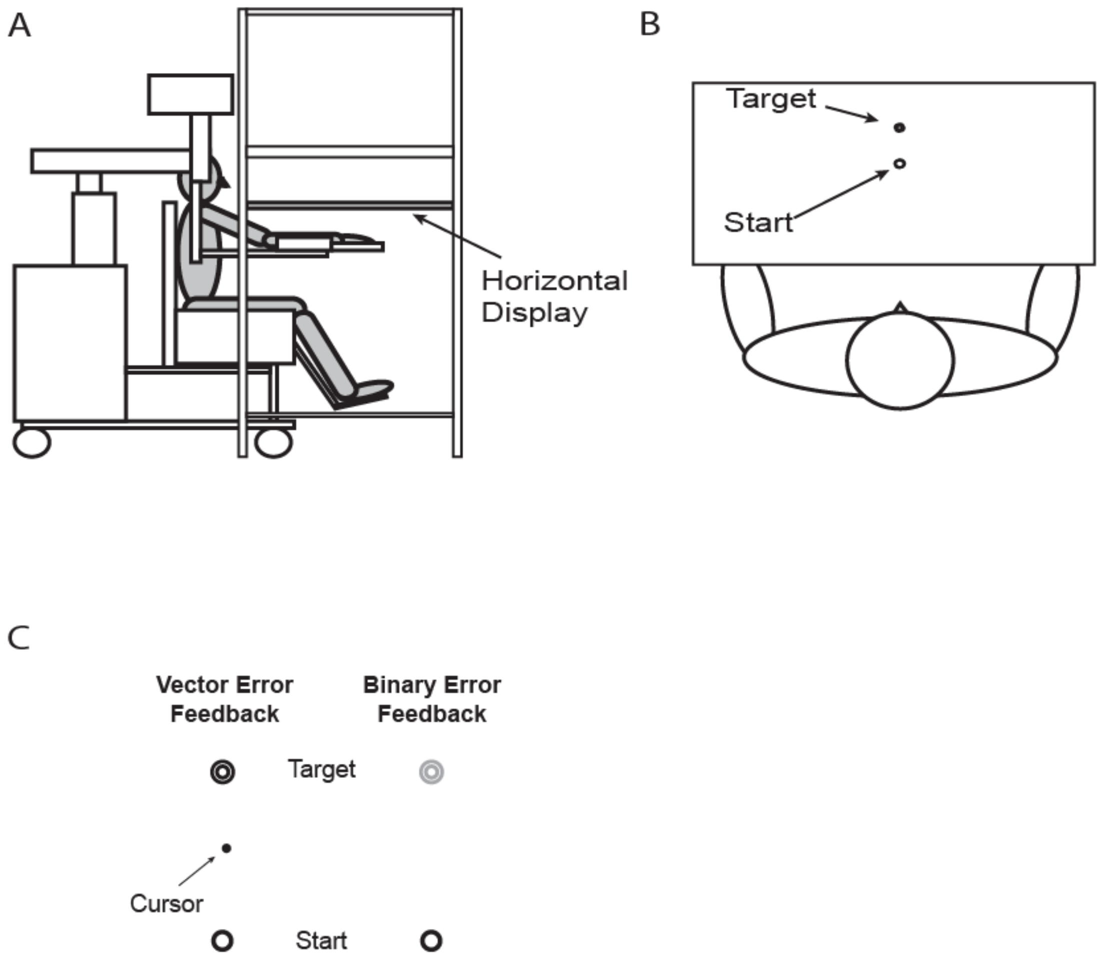

Figure 25: A: Experimental setup. B: An illustration of the targets presented on the display. C: In VE group, a cursor representing fingertip location was shown throughout movement. In BE group, no cursor was shown; instead, target color changed to red (success) or blue (failure) upon completion of reaching movement.

Experimental Protocol

In general, subjects were instructed to perform rapid targeted-reaching movements from a start circle to a target (2 cm in diameter, 10 cm away from the start circle) repeatedly with the right arm. They were instructed to move their index finger to the target rapidly and as straight as possible in response to a ‘go’ signal, and stop without correcting their movement. The experiment consisted of 3 sessions: (1) 40 trials active movements with unperturbed visual feedback (baseline), (2) 100 trials passive movement in the 30-degree clockwise direction relative to the target (training), (3) 80 trials active movements with perturbed feedback in which visual feedback will be rotated 30 degree counterclockwise (testing). During the passive-training session, subjects were randomly divided into three groups based on types of visual feedback: no feedback (Null), vector error feedback (VE), binary error feedback (BE). In the Null group, subjects received no visual feedback about their passive movements. In the VE group, they received continuous vector error feedback that was rotated 30 degrees counterclockwise about the direction of passive movement. Visual feedback was provided in form of a cursor representing the fingertip location throughout the movement, which provided detailed spatial information such as movement direction and amplitude. In the BE group, they received binary error feedback about task success or failure. This type of visual feedback was provided in such a way that the color of the target changed to red or blue upon completion of the movement depending on whether the subject hit the target successfully or not (Figure 25C)

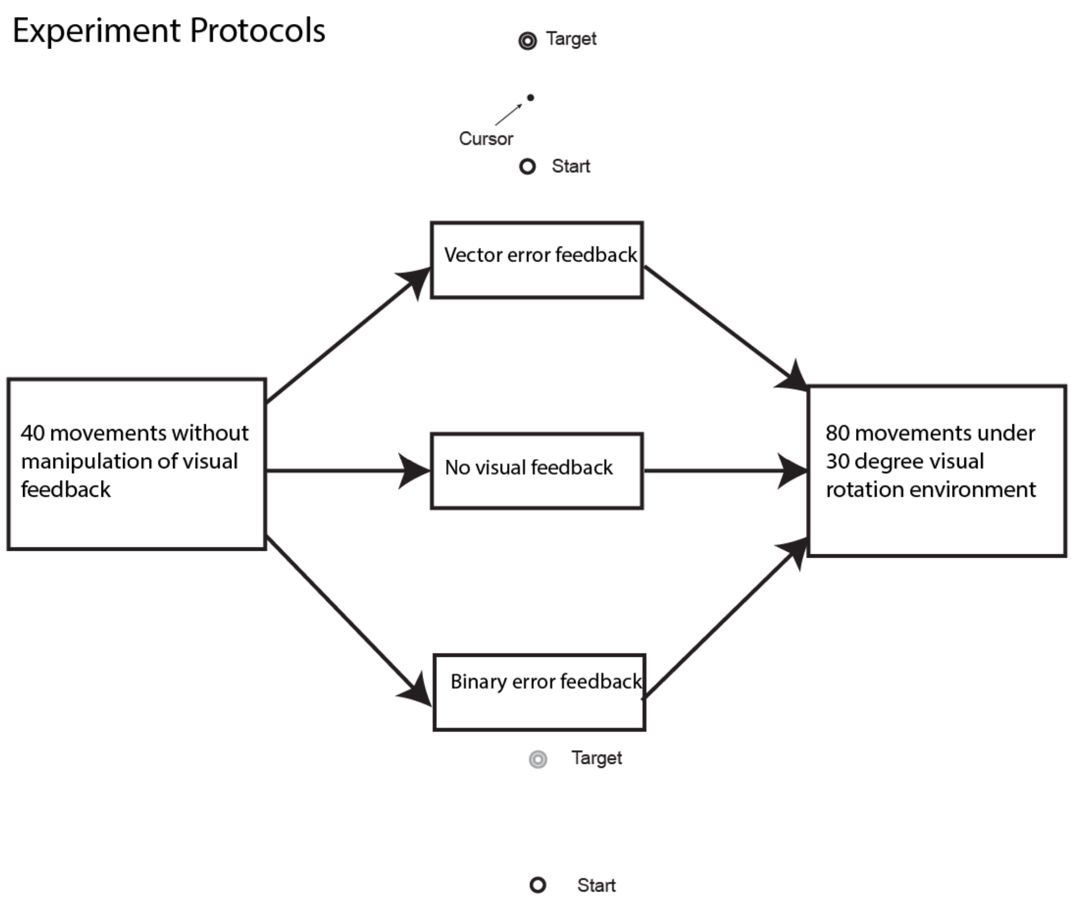

Figure 26: Protocols for Experiment

Data analysis

The performance measure used in this study was initial direction error (DE), which was the angular difference between a vector from the start circle to the target and another vector from the hand position at movement start to that at peak arm velocity. A block represents the mean of 5 consecutive trials.

For statistical analysis, initial direction errors from the first cycle of the testing session from were subjected to a one-way ANOVA, with group as a between-subject factor, to determine if there was any difference among the three groups during the testing session. Following this, we fitted a logarithmic regression line to the arm performance data in the testing session; and the slope values were used to conduct another one-way ANOVA to determine if the rate of visumotor adaptation during the testing session was different among the groups. The alpha level was set at 0.025 (i.e., 0.05/2) for the analyses after a Bonferroni correction was made, and at 0.05 for post hoc comparisons (Tukey's tests for between-group comparisons).

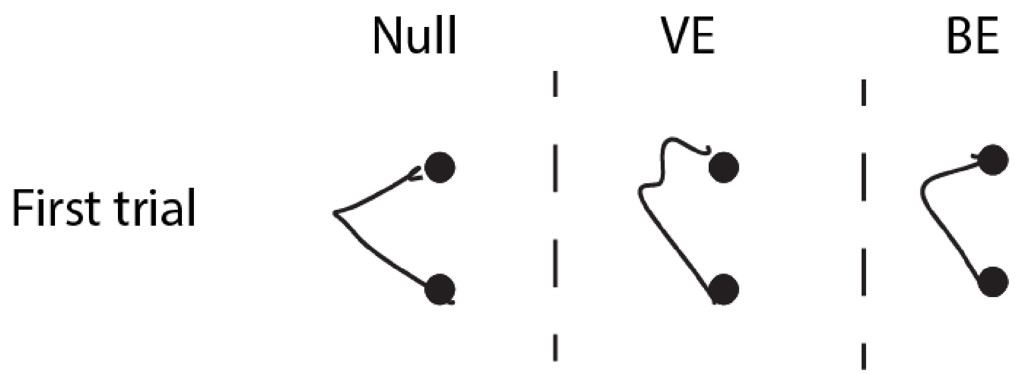

Figure 27: Hand-paths at the very first block of the testing session from the three groups.

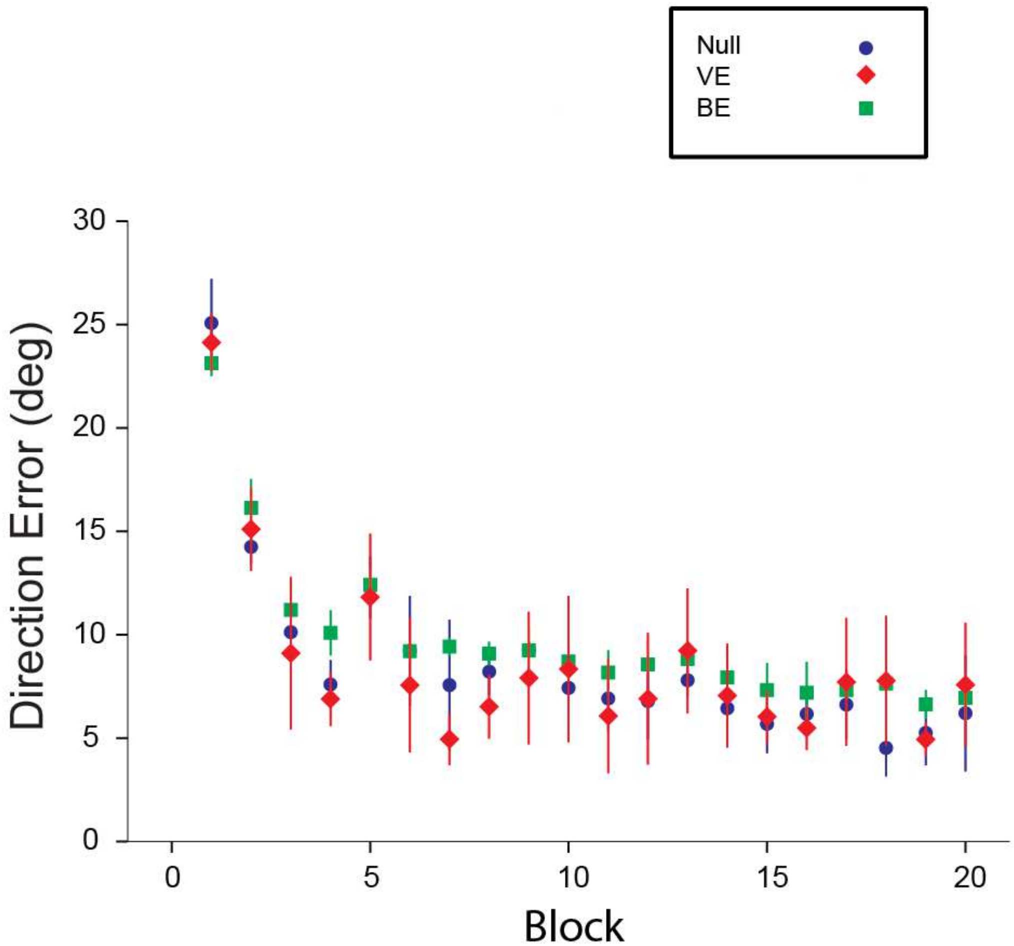

Figure 28: Mean performance measure. Every data point shown on X axis represents the average of 5 consecutive trials (block) across all subjects within each group (mean ± SE)

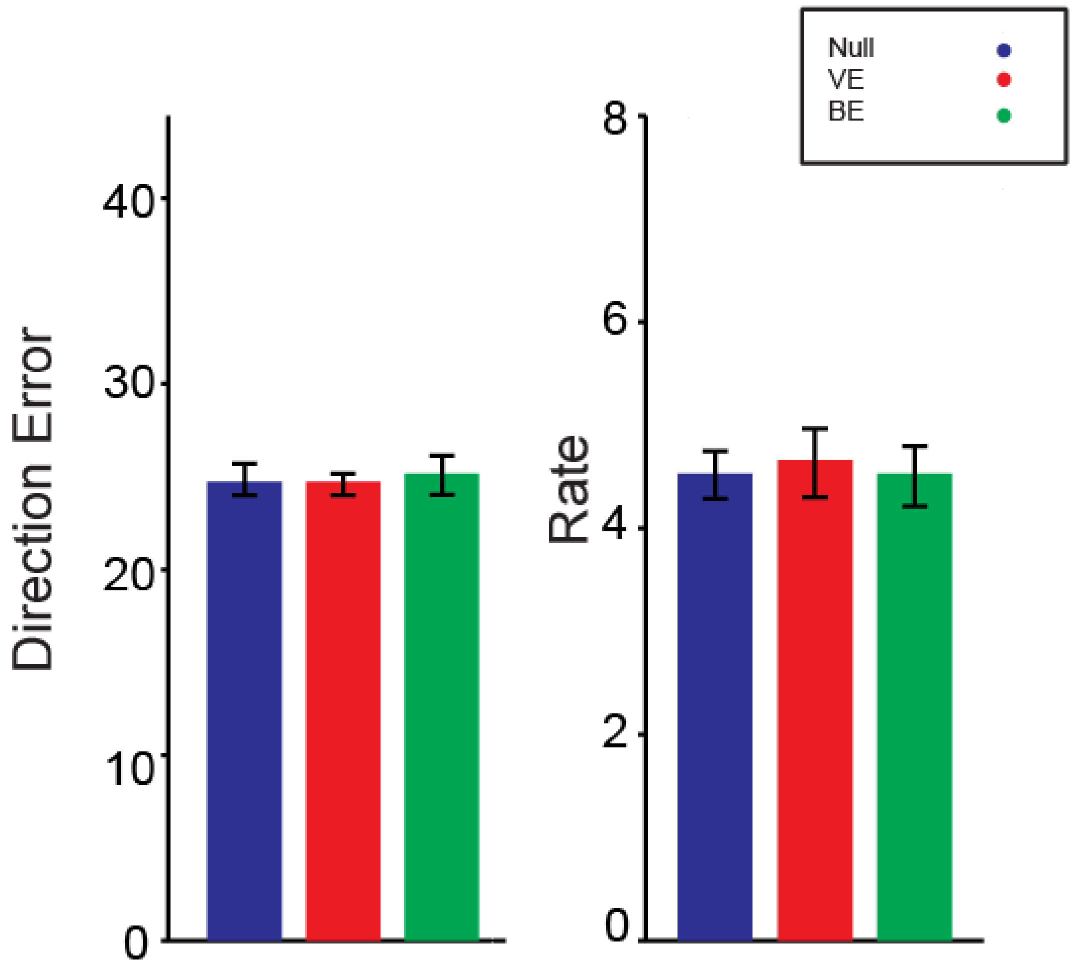

Figure 29: Direction error at the very first cycle (left panel), and slope values during the testing session (right panel).

Results

Figure 27 illustrates the hand-paths of a representative subject from the no feedback group, vector error feedback group, and the binary error feedback group, all of whom demonstrated a largely curved hand-path at the beginning of the testing session. Figure 28 depicts the changes in performance across the blocks in terms of initial direction error for the three groups. The one-way ANOVAs showed no significant main effect of group ($p = 0.759$) for the direction error and the slope value ($p=0.425$) (Figure 29). Overall, these results suggest that neither providing binary error feedback nor vector error feedback has beneficial effects on motor learning.

Discussion

In this study, we investigated whether the two motor learning hypotheses (one that involves model-based learning, the other that involves model-free learning) could lead to improvements in motor learning. In experiment, we predicted based on the hypothesis that reinforcement of successful actions would improve motor learning. To reinforce successful actions, we provided binary error feedback. Shmuelof et al. (2012) suggested that providing binary error feedback once visuomotor adaptation would promote reinforcement learning. Our subjects were provided with the vector error or binary error feedback, yet the performance gains were similar among the subject groups.

In experiment, we focused on the effects of visual feedback on the formation of motor memories during a passive motor experience. It has been reported that manipulation of online visual feedback would induce different learning processes. For example, learning from full vector error regarding movements involves primarily model-based mechanism. In contrast, learning from binary feedback about the success or failure of movements is associated with model-free mechanism (Izawa and Shadmehr, 2011). We hypothesized that forming a specific motor memory regarding a motor learning mechanism would be crucial for sensorimotor adaptation even in the passive motor learning. We designed a protocol in which the subjects were randomly divided into three groups based on types of visual feedback: no feedback (Null), vector error feedback (VE), binary error feedback (BE). For results, there was no significant difference among the groups. These results suggest that manipulation of visual feedback during passive training has no additional benefit on visuomotor learning, and model-based and model-free learning processes are only elicited through active movement.

Our data appears to suggest that passive movements accompanied with visual feedback cannot generate internal models, and the motor system cannot learn from error detection or correction without active execution. This finding is consistent with neurophysiological evidence that efference copies or internal models are required through active movements. However, the subjects experiencing passive training performed better than those who experienced no passive movement. It suggested that passive motor experience imparts a positive effect on visuomotor learning task. Passive practice leading to motor improvements is associated with instance-reliant learning mechanism or use-dependent plasticity (Classen et al. 1998; Butefisch et al. 2004; Stefan et al. 2005, 2008; Celnik et al. 2006, 2008; Lei and Wang, 2014; Wang et al. 2015). This form of mechanism encodes the specific kinematic aspects of passive movement (Wolpert et al., 2011).

There is evidence to support the existence of two motor systems for guiding motor learning: (1) a model-based learning system and (2) a model-free learning system (Huang et al., 2011; Haith and Krakauer, 2013). In a model-based learning system, motor improvements are driven by sensory prediction error, which reports discrepancies between the observations and the current internal model. In the mode-free learning system, by contrast, motor improvements are driven by the reward prediction error, which reports a difference between an actual and expected reward in a given action (Glascher et al. 2010). In other words, model-based system learns through building an internal model from actions to outcome and invert that model to map desired outcomes to action. By contrast, model-free learning is driven by a scalar measure of task success. An example of model-free learning can be provided by such “reaching under risk” studies, in which subjects reach for reward and penalty zones. It widely believed that two motor systems are conceived as acting in parallel, interacting at the motor planning stage (Haith and Krakauer, 2013), which provides the motor system with robustness and redundancy, such that one type of learning still enable the motor system to maintain the overall performance if the other type of learning fails for any reasons.

Our lab, recently, argued that visuomotor adaptation involves two types of motor learning processes, algorithmic learning process, which is effector independent, and instance-reliant learning process, which is effector dependent. The idea of algorithmic is analogous to the idea of model-based learning, in that algorithmic learning and model-based learning both occur through building an internal model. However, Instance-reliant learning is somewhat different from that of model-free learning, in which effector-specific instances are accrued during repeated performances of a motor task and automatically retrieved later to allow fast and automatized performances of the task (Wang and Sainburg, 2003; Lei and Wang, 2014; Wang et al. 2015). Here, the idea of instance-reliant learning is in line with the idea of use-dependent learning (Classen et al. 1998; Diedrichsen et al. 2010), which refers to a phenomenon that current movements are often biased to become similar to previously experienced movements. The ideas of algorithmic and instance-reliant learning can account for the phenomenon of limited transfer across the effectors, in that learning can transfer across the effectors mainly by utilizing algorithmic learning, which is effector independent; but the extent of transfer across the effectors is limited because instance-reliant learning process cannot transfer across the effectors, which is effectors dependent. This argument has been supported by our recent study, in which subjects adapt to a rotated display with the left arm while repeatedly performing the reaching task with the right arm without providing performance feedback: training with the left arm completely generalizes to the right arm (Wang et al., 2015). This suggests that the absence of instance-reliant learning process is the major reason for limited generalization of motor learning.

A large amount of neural evidence supported the existence of different neural substrates identified for distinct learning systems. For example, the neural activity in the cerebellum only reflects the kinematics of movement rather than the motor commands required to achieve the kinematics, which indicates that the cerebellum is not clearly associated with motor output, instead it appears that the cerebellum implements an internal model that predicts the kinematic of motor commands before that information finally become available from the periphery (Haith and Krakauer, 2013). Furthermore, patients with cerebellar ataxia or lesions have consistently been demonstrated to have difficulties in motor adaptation that mainly involves model-based learning or algorithmic learning process (Lewis and Zee, 1993; Maschke et al., 2004; Mortan and Bastian, 2006;

Smith and Shadmehr, 2005; Rabe et al. 2009). In addition, motor adaptation can be sped up through transcranial magnetic stimulation of the cerebellar (Galea et al., 2011). Together with the above-mentioned findings, these studies strongly suggest that model-based learning or algorithmic learning process is likely to be cerebellar-dependent. Surprisingly, patients with cerebellar ataxia can still learn in motor adaptation tasks in the condition that the perturbation is introduced sufficiently gradually (Criscimagna-Hemminger et al. 2010; Izawa et al. 2011). Learning in this case is not associated with model-based learning processes due to the inability to update an internal model. It is believed, instead, that cerebellar ataxia patients learn by engaging the model-free processes that rely solely on the degree of task success. The phasic firing of dopamine neurons has been consistently linked with reward prediction error (Montague et al. 1996; Schultz et al. 1997). Substantial work in degenerative diseases of the basal ganglia, in which there is widespread death of dopamine cells, shows that a decrease in dopamine release results in learning deficits in motor tasks that rely on reward prediction error signal. This finding clearly suggests that the basal ganglia may play a key role in model-free learning.

Chapter 5: Summary and Conclusions

The goal of this investigation was to develop a training condition that can maximize the effects of passive training on visuomotor adaptation by combining its effect with other motor learning strategies. The motivation of this study stemmed from the need to address the population of stroke survivors who suffer from severe control loss or complete paralysis, and have few or no options for therapy.

Stroke is a leading cause of long-term disability to date. Approximately half of stroke survivors suffer from some form of hemiparesis, and 30% of which reported limitations in activities of daily living (ADLs) without assistance (Rosamond et al., 2008; Huang et al., 2009). Most stroke rehabilitative treatments that clinicians have typically implemented are active training techniques, such as constraint induced movement therapy (CIMT). These treatments require stroke survivors retain some residual motor activity in the affected limb. There are very few selections of stroke rehabilitative approaches that aim at the population of stroke survivors suffering from severe control loss or complete paralysis. Passive assist training has been shown to be an effective rehabilitation approach; however the effectiveness of the treatments that utilize passive assist training is still low.

A total of 104 neurologically intact right-handed individuals (18-30 years old) participated in this study. Participants were tested to pursue two specific aims: aim 1 to determine the effects of passive training on a visuomotor adaptation task, and aim 2 to determine the effects of passive training in combination with other strategies on learning a visuomotor adaptation task.

In aim 1, we tested whether a greater extent of generalization in motor adaptation across effectors and movement directions would occur by providing subjects with passive training. For this aim, we executed three experiments. The results from the experiment 1 and 2a indicated substantial generalization across effectors, but limited generalization across movement direction within the same effectors, when motor instances directly associated with the direction to be experienced later can be accrued during initial passive training. We suggested that the extent of generalization within the same effector was limited probably due to the fact that the amount of instances associated with the new task to be learned later was limited. Thus, we conducted experiment 2b to test whether motor generalization could be improved when a substantially greater amount of motor instances were provided during initial passive training. Results indicated substantial generalization across movement directions. These findings support the idea that passive training can augment motor learning by inducing instance-reliant learning processes, and that this benefit is greater when prolonged passive training (i.e., sufficient instances) was provided.

In aim 2a, we investigated the effects of action observation in association with passive training on motor learning, as reflected by formation of motor memories. We compared the learning performance of five different groups: action observation alone, passive practice alone, action observation combined with passive practice, the passage of time, and active practice. Results indicated that action observation combined with passive training enhances training effects relative to the mere observation of action or passive training alone. In aim 2b, we tested whether the effects of a training condition could be improved by incorporating the manipulation of visual feedback into passive training. We compared with the learning performance of three different groups, which were divided based on types of visual feedback: no feedback, vector error feedback, and binary error feedback. For results, there was no significant difference among groups. This suggested that manipulation of visual feedback during passive training has no additional benefit on visuomotor learning.

These findings are significant because they are the first to demonstrate that a training condition consisting of action observation and passive training together can lead to significant performance gains beyond what either intervention alone can do. The results of the study show great potential for developing specific rehabilitation protocols that utilize passive training and action observation together for severely impaired stroke patients in the future.

We have contrasted three distinct, yet complementary processes regarding motor learning: (1) a model-based learning system, in which an internal model is updated via sensory prediction errors, (2) a model-free learning system, in which learning occurs directly through trial and error, and (3) a instance-reliant learning system, in which effector-specific instances are accrued during repeated performances of a motor task and automatically retrieved later to allow fast and automatized performances of the task. (Huang et al., 2011; Haith and Krakauer, 2013; Wang et al. 2015). We have argued that different stroke interventions may involve different motor learning processes. For example, active training is likely to involve multiple motor learning processes (model-based, model-free and instance-reliant learning process), while passive training may only involve instance-reliant learning, which occurs through accruing motor instances of goal movement and build a template of expected sensory consequence (Kovacs et al., 2011). Similarly, observational learning may only be associated with model-based learning, which is driven by sensory prediction errors. It is possible that the facilitative effects of these interventions for motor recovery may be associated with the underlying motor learning processes. If so, a deeper understanding of their associations may enable us to advance the efficacy of rehabilitation following stroke patients, and to maximize the potential benefits of these rehabilitation interventions, especially for severely impaired stroke patients who cannot move their paretic arm on their own.

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Appendix A: Literature Review

Stroke

Stroke (cerebral vascular disease) is a leading cause of permanent disability in the United States and many other countries (Muntner et al., 2002; Ingall et al., 2004; Smith et al., 2004; Roger et al., 2011). From 2000 to 2010, trends in the United States have shown that the relative rate of stroke death fell by 35.8% and the actual number of stroke deaths declined by 22.8%, yet more than 790,000 people continue to suffer a new or recurrent stroke per year, with approximately 610,000 of these being first events and 180,000 being recurrent stroke events ((Muntner et al., 2002; Ingall et al., 2004; Smith et al., 2004; Roger et al., 2011; Go et al., 2014). Internationally, the rates of strokes are comparable to those of the United States (Ingall et al., 2004; Smith et al., 2004; Roger et al., 2011; Go et al., 2014).

Among stroke survivors who were 65 years or older, 50% reported some form of hemiparesis and 30% reported limitations in activities of daily living (ADLs) without assistance (Rosamond et al., 2008; Huang et al., 2009). The average yearly health care services, medication, and lost productivity that directly attributable to stroke vary greatly according to severity of injury. In 2011, it was estimated that the costs of stroke, not including any indirect costs such as losses in wages and fringe benefits, is approximately 38.5 billion in the United States (Heidenreich et al., 2011). Stroke not only strikes the elderly, it also occurs among children between infancy and toddler age. In fact, stroke is one of the leading causes of death for children (Lloyd-Jones et al., 2009). The rate of stroke occurrence from birth through the age of 18 is nearly 11 in every 100,000, with 50% to 80% having permanent neurological deficits, most commonly hemiparesis or hemiplegia (Roach et al., 2008). With the progressive growth of the elderly (age 65 and over) population due to the aging baby boomers, and the increase in the rate of strokes among children, the concerns of stroke-related disability will increase over time.

A stroke happens due to a disturbance in the blood supply to the brain. This disturbance is due to either ischemia, which occurs as a result of an obstruction within a blood vessel, or hemorrhage occurring when a weakened blood vessel ruptures. A stroke results in partial destruction of cortical tissue. The symptoms of stroke depend on how severe the stroke is and which part of the brain is damaged, which may include numbness or weakness of face, arm or leg (especially on one side of the body), confusion, severe headache, or loss of balance or coordination. Although stroke can result in deficits in a number of neurologic functions, the most commonly affected is the motor functions, which encompass motor control and learning abnormalities, muscle weakness, and spasticity (Gresham et al., 1995; Rathore et al., 2002).

Post-stroke neuroplasticity

Neuroplasticity refers to physiological changes in neural pathways and synapses in response to new situation or to changes in environment. Neuroplasticity results in functional changes on a variety of levels, ranging from cellular changes due to learning to cortical reorganization in response to brain injury. Cortical reorganization occurs through mechanisms in which undamaged axons grow new nerve endings to reconnect neurons whose links were injured, or sprout nerve endings to connect with other undamaged neurons to form new neuronal circuits. Neuroplasticity is the scientific basis for treatment of acquired brain injury, such as stroke. Rehabilitation studies involving neuroplasticity principles have shown that the brain following stroke demonstrates a capability to reorganize itself to counterbalance the effect of the lesion, however cortical plasticity can also result in an overcompensation of unaffected limb and a decreased cortical representation of affected limbs without professional interventions (Liepert et al., 1995; Rossini et al., 2003, 2004). Such intervention requires limb-associated sensory input to influence cortical plasticity while using task specific practice to take advantage of post-stroke plasticity (Jenkins et al., 1987; Kaas, 1991; Johansson, 2000).

Rehabilitation approaches

Rehabilitation approaches that target stroke patients across the spectrum from mild to severe hemiparesis include impairment-oriented training (Platz et al., 2001), constraint-induced movement therapy (CIMT) (Taub et al., 1993; Dromerick et al., 1999; Mark and Taub, 2004), interactive robotic therapy (Krebs et al., 1998), and virtual reality-based rehabilitation (Deutsch et al., 2004; Holden, 2005). These approaches improve motor function by limiting the use of the unaffected limbs and forcing the repetitive exercise with the affected limb to reestablish muscle activity. As a result of the active engagement of the affected limb, the brain stimulates neural pathways and activates the motor cortex, thus inducing cortical reorganization and motor learning. CIMT is the most common approach for stroke rehabilitation, which increases activity in areas of motor cortex surrounding lesions to induce the plasticity of the brain and possibly reinstating the neural motor control. With CIMT therapy, the therapist constrains the patients' unaffected arm with a sling or other means of inhibition. The patients are required to use their affected arm repetitively and intensively for a preset time period, ranging from 1 to 10 weeks. While most studies have reported that CIMT therapy results in improved function in stroke patients, CIMT therapy has its limitations. First of all, CIMT requires patients to have residual motor ability in the affected limb, which excludes patients with more severe stroke. Second, the lack of specific instruction in CIMT therapy leads to the patients developing compensating movement. In addition, the cost needed to conduct CIMT therapy is high. Because of these limitations, we are seeking to replace CIMT with other rehabilitative trainings.

Robotic rehabilitation

Robotic therapy has grown as a complement to CIMT, and hold promise for improving traditional stroke therapy. As we know, rehabilitation process is labor-intensive, requiring therapists to spend significant time working with a single patient. Unlike conventional rehabilitation therapy, robotic technology is attractive because of its ability to provide efficient therapies with less direct supervision, its ability to allow for safe interactions between robotic devices and patients, and its ability to deliver therapy at dosages higher than that with conventional therapy (Huang and Krakauer, 2009). Robotic devices not only provide measurement reliability and movement controllability to be programmed to perform in multiple functional modes for a long time periods, but also can implement novel forms of mechanical manipulation, which help neurologists and therapist address the challenges that impossible for them due to limited speed, sensing, and strength (Kahn et al., 2006; Huang and Krakauer, 2009). In addition, robotic devices can provide insights in the recovery process, in terms of movement kinematics and dynamics, from initial impairment to impairment changes after treatment, such that through investigating stroke patients' ability to apply novel force assistance patterns (Patton and Mussa-Ivaldi, 2004). To date, many studies have shown that robot-assisted technology is effective to restore locomotion and upper extremity function (Reinkensmeyer et al., 2004).

There have been a few clinical studies that have investigated the effects of robotic-aided therapy on stroke rehabilitation in a clinical setting (van Vliet and Wing, 1991; Hesse et al. 2003; Hogan et al. 2004; Reinkensmeyer et al. 2004; Nef and Riener, 2005). In studies with a robot-trained group and a control group, for example, robot-aided therapy had more short-term effects, such as muscle activation patterns and speed of movement, than conventional therapy in stroke patients (Volpe et al., 2000; Krebs et al., 2000; Fasoli et al., 2003; Ferraro et al., 2003). There also has been a study to support the long-term beneficial effects of robot on stroke rehabilitation. For example, Prange and colleagues reported that robotic rehabilitation lead to long-term improvement in motor functions (Prange et al., 2006).Given that only one study examined long-term effects, no firm conclusion can be draw. One interesting aspect regarding robotic rehabilitation is that moderately affected patients seem to be more responsive to robot-aided therapy than severely affected patients (Ferraro et al., 2003). For example, stroke patients with the highest initial motor function achieved more behavioral gains after robot-aided therapy than the patients with the lowest initial motor function (Stein et al., 2004). Robotic technology has also been used extensively to study motor learning in healthy subjects, which allows researchers to investigate the mechanisms underlying motor learning so as to help us design more effective rehabilitation protocols.

Robotic rehabilitation is multifold, including active assist training, passive assist training, and action observation therapy (Seitz et al., 2002; Ertelt et al., 2007). Active assist exercise, which uses external assistance to aid patients to accomplish intended movements, is the primary paradigm that has been used in robotic therapy (Marchal-Crespo and Reinkensmeyer, 2009). Active assist exercise can be grouped into three modes in terms of the dose of robotic assistance (Takahashi et al., 2008): (1) active non-assist mode, in which patients do all work without the robot’s help, (2) active assist mode, in which patients actively exert effort to move and the robot supplements its effort, (3) passive assist mode, in which patients relax while the robot do all work. Interventional studies demonstrate that active assist mode can achieve greater behavioral gains for stroke patients who can exert efforts on their own to move (Lotze et al., 2003; Perez et al., 2004), since robotic devices, in active assist mode, provide assistance for patients to move their paretic limb in desired patterns during reaching, grasping, or walking to provoke motor plasticity (Marchal-Crespo and Reinkensmeyer, 2009).

While active assist training is certainly more beneficial than passive assist training for the majority of stroke patients, passive assist training may still be beneficial for those who can hardly move on their own. Another intervention which may be beneficial for the severely impaired stroke patients involves an action observation. Evidence exists that the observation of action and the actual execution of the observed action involve the same cortical motor representation (Fadiga et al., 1995; Iacoboni et al., 1999; Mattar and Gribble, 2005). Recently, action observation has been demonstrated to have a positive effect on rehabilitation of motor deficits after stroke through reactivating motor representation relevant to the observed action (Pomeroy et al., 2005; Buccino et al., 2006; Ertelt et al., 2007; Celnik et al., 2008).

Most robotic treatment protocols implement active assist training. For example, Fasoli et al. and Stein et al.'s studies suggest that robot-aided therapy that incorporates active assist training is beneficial for upper-limb recovery (Fasoli et al., 2003; Stein et al., 2004). However, the effectiveness of the treatments that utilize passive assist training and action observation therapy is still unknown. This study will provide substantial insights into our understanding of treatment effectiveness in passive assist training and action observation in rehabilitation settings, and how to develop a training condition that can maximize the potential benefits of these training methods. Given that passive training could be a valuable rehabilitation strategy for the severely impaired stroke patients, findings from this research may prove valuable for the development of more efficient rehabilitation protocols in the future.

End-effector and exoskeletal robotic systems

Current robotic devices that are being used in clinical trials can be grouped into two types: end-effector and exoskeleton. MIT-Manus is an end-effector system, which is the first robotic device that undergoes clinical tests. With MIT-Manus, patients hold a two-joint manipulandum that experiences robot-imposed force. An initial study involving MIT-Manus showed that robotic rehabilitation has a positive effect on cortical reorganization (Krebs et al., 1998). For exoskeletal system, patients' limbs are enclosed in robotic suit, which provides full specification of limb configuration and allows for forces to be applied and measured at each joint independently (Huang and Krakauer, 2009). KINARM is exoskeletal robotic system, which has been used in the clinical trials to quantify impairments related stroke (Coderre et al., 2010; Dukelow et al., 2010).

Robotic rehabilitation and motor learning principles

The goal in rehabilitation, for patients, is to relearn motor skills that stroke may have taken away, indicating the fact that the content of rehabilitation rests on two basic assumptions: (1) practice can lead to improvement in motor functions after stroke; (2) motor learning principles can be applied to recovery (Krakauer, 2006; Wolpert et al., 2011; Kitago and Krakauer, 2013). Given that motor learning can occur at different level of the motor hierarchy, one key issue must be paid much attention in rehabilitation based on motor learning principles: whether and to what extent processes of motor learning may be impaired in stroke patients, and which type(s) of motor learning are most relevant to stroke patients (Kitago and Krakauer, 2013). In other words, there may be several types of motor learning processes and representations through which learning is achieved, and they may be affected based on lesion location (Krakauer, 2006; Wolpert et al., 2011). The rehabilitation strategy for stroke must be planned based on a sound knowledge of what processes may be involved in motor learning, and what the effects of stroke on motor learning process would be. Unfortunately, we have not reached this point yet.

Motor adaptation and after-effects

Everyday usage of the term “motor learning” in the minds of most people is usually defined as skill learning, which refers to a relatively permanent change in the capability for responding due to practice or a novel experience (Schmidt, 1988). It often involves the acquisition of new spatiotemporal muscle-activation patterns associated with complicated movements such as learning to play the piano, drive a car, or climb trees (Sanes and Donoghue, 2000; Shadmehr and Wise, 2005). In this kind of tasks, the progress of learning from initial incompetence to proficiency is often very slow, typically requiring days or even months of practice. This slow improvement is not only attributable to the unfamiliarity of the task, but also due to the redundancy inherent in the task and in human biomechanics (Manley et al. 2014). For example, you play the game of darts. The outcome (the location where the dart hits the board) is determined by a large number of variables, such as the posture of the trunk, the orientation of the wrist, the distance between the dart and board, the position and velocity of the elbow and shoulder joints. The outcome can be achieved through multiple combinations of these variables.

Not all motor learning falls under the concept of motor skill learning. Another form of motor learning, called motor adaptation, involves the acquisition of associations between sensory cues and motor actions in an altered environment (Shadmehr and Wise, 2005). The key difference between motor adaptation and motor skill learning is that the former adjusts the motor system for only one context (Shadmehr and Wise, 2005). In general, there is no new capability to emerge after motor adaptation. To better understand motor adaptation, consider a scenario in which you need to reach for a coin that is in the water, the air-water interface results in a defection of the coin position falling on your retina. In order to reach for the coin accurately, the motor system needs to take into account for changes in the environment (i.e., the mismatch between the actual location of the coin and the coin position sensed through your eye) when planning the reaching movement. The process of correcting the reaching errors induced by this distortion is called motor adaptation. Motor adaptation is viewed as a crucial capability of the nervous system as well as a prerequisite for skill learning (Shadmehr and Wise, 2005). Skill learning would be impossible without motor adaptation.

In laboratory settings, motor learning has been studied extensively in the context of motor adaptation tasks, in which subjects adapt their movements to overcome a perturbation, either as a rotation of movement direction, or as a deflecting force on the arm (Bernier, 2007; Shadmehr and Mussa-Ivaldi, 1994; Wang and Sainburg, 2005). Here I will focus on the visuomotor adaptation paradigm. Visuomotor adaptation has served as a well-established paradigm for studying the capability of the CNS adapting altered visual feedback (Abeele and Bock 2001a, 2001b, 2003; Imamizu and Shimojo 1995; Krakauer et al. 2000). Typically, the main paradigm is to distort visual information about initial hand position by the use of either optical prisms or virtual reality environments. For example, in a visuomotor adaptation study conducted in 1867 by Hermann von Helmholtz, subjects who made pointing movement toward targets while wearing prism lenses that displaced the visual field laterally initially experienced leftward direction errors during pointing movements, but could compensate for the errors after some practice. As soon as the prisms were removed, they made rightward direction errors (called ‘after-effect’).This motor after-effect demonstrates that subjects not only react to changes in environment but also predict the expected dynamics of the new environment. Therefore, after-effect is considered strong evidence that a new internal model has been developed as a result of motor adaptation. In motor adaptation paradigms, the performance of motor learning is measured on the time course of the kinematics and dynamics of motion that involves arm movement. Learning is thought to occur via incremental reduction in errors caused by a perturbation over successive movements. Improvements in performance are initially rapid, and then reach slowly to asymptote close to the baseline level of performance (Haith and Krakauer, 2013).

Mechanisms underlying Motor Learning

Motor adaptation was thought to involve two distinct, yet complementary processes: (1) a model-based learning system and (2) a model-free learning system (Huang et al., 2011; Haith and Krakauer, 2013). In a model-based learning system, an internal map or a model of the environment is built, which describes the relationship between the state of the body and environment (Figure 30). The driving force for model-based learning is the sensory prediction error, which reports discrepancies between the observations and the current model. If a prediction made by the internal model results in an accurate movement outcome, the internal model is maintained in a stable state. However, a movement results in a prediction error due to an unexpected perturbation, the internal model starts a calibration process based on currently available information until the prediction error is minimized.

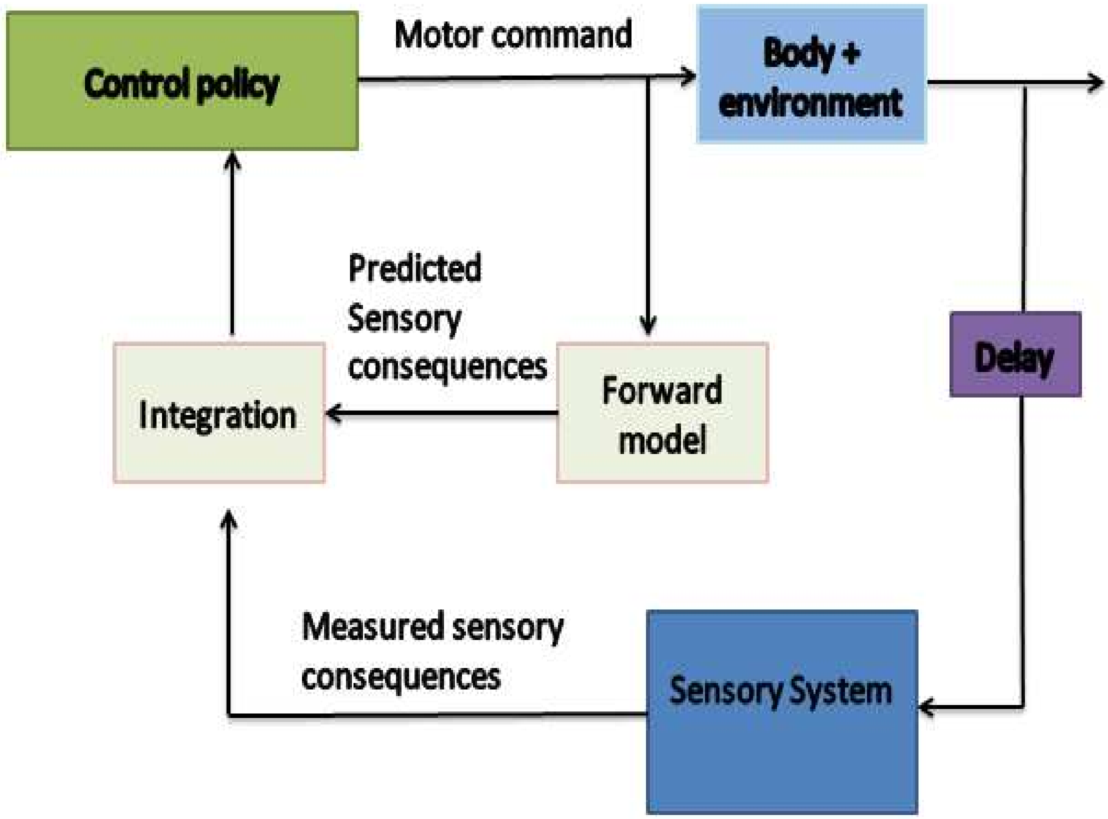

Figure 30: Forward model receives a copy of motor command and generates a predicted sensory consequence at a short latency. The predicted sensory consequence is integrated with true sensory feedback to optimize state estimate.

The model-free learning system, in contrast, learns action directly through trial and error. Unlike model-based learning, in the model-free learning system there is no intermediate internal model and no explicit error calculation required to correct for systematic biases (Haith and Krakauer, 2013). Instead, in the mode-free learning system, improvements in performance are driven through exploring possible actions until an optimal solution is found. The reward prediction error was thought of as the engine of model-free learning, which reports a difference between an actual and expected reward in a given action (Glascher et al. 2010). This error signal is used to learn the value of executing a given action on the basis of trial and error experience to update expectations in order to maximize future reward (Sutton and Barto, 1998) Thus, model-free learning system updates the control policy directly based on reward prediction errors.

Recently, a similar but somewhat different view of motor learning mechanisms has emerged, which suggests that motor adaptation involves algorithmic learning, in which one successively improves a rule-based method of control, and instance-reliant learning, in which effector- or movement-specific instances are accrued during repeated performances of a task to be learned and later retrieved to allow fast and automatized performances of the learned task (Wang and Sainburg, 2004; Lei and Wang, 2014). Instance-reliant learning can be thought as a form of use-dependent plasticity, being driven through encoding the specific kinematic aspects of the repetitive movement even without any outcome information (Wolpert et al., 2011). While the ideas of model-based learning and algorithmic learning are in line with each other, the ideas of model-free learning and instance-reliant learning are different, in that reinforcement of successful actions is considered necessary only for the former idea, while effector-specific instances are thought to be necessary only for the latter idea.

Model-based, model-free and instance-reliant learning processes provide the motor system with robustness and redundancy, such that if one type of learning fails for any reason (e.g., a cerebellar disease affecting model-based learning), the other type of learning still enables the motor system to improve overall performance (e.g., Izawa et al., 2011). A comprehensive understanding of the relative contribution of each mechanism to motor learning and the optimal balance between them is paramount to advance the efficacy of neurorehabilitation (Huang and Krakauer, 2009; Haith and Krakauer, 2013).

Model-based and Model-free Learning

The terminology of model-based and model-free learning comes from the field of reinforcement learning. Reinforcement learning agent learns by interacting with an environment, and assesses actions on the basis of experiences to maximize rewards and minimize punishments (Sutton and Barto, 1998). Reinforcement learning is used to learn a value function for a given control policy, which reflects how much future reward can be expected when performing actions given the current state and time. Model-based and model-free learning are expressed as two different forms of reinforcement learning, and differ in how to use experience to update the value function. At root, the key distinction between model-based and model-free learning is the use of information in building representation of the environment that involves the different computational processes and their substrates in the CNS (Khamassi and Humphries 2012).

Model-based learning uses experience indirectly, building a model of the state of body and/or environment that is used for planning of movements (Haith and Krakauer, 2013). Action in each state is assigned a value, and action selection depends on those values. The current state is the root, and the control policy with the highest value is determined by updating the model based on action errors, either forward from the root state to each next state or backward from each possible state to the root state to compare all possible actions and identify the best ones (Dolan and Dayan, 2013). In model-based learning, all value of all states and actions can be computed exactly, which imposes a huge burden on motor control. This learning process can be mathematically described with state-space model, which assumes that learning occurs through penalizing the deviations from the desired goal based on gradient descent on the squared movement errors (Thoroughman and Shadmehr, 2000; Donchin et al., 2003; Cheng and Sabes, 2006; Zarahn et al., 2008). A state-space model is defined below:

$$X_{n+1} = A * X_n + B * e_n + \varphi_n$$

$$Y_n = X_n + \delta_n$$

X_n: The state of the internal model on trial n

Y_n: The hand position on trial n

e_n: Error on trial n

A: Trial-to-trial retention rate

B: learning rate

φ, δ: Independent noise terms

By contrast, model-free learning is computationally efficient, since experience directly leads to changes in a control policy in the form of a reward prediction error. No model is built and instead the value of an action of a given state is learned through a process of trial and error-explore possible actions that lead to success. Given that the model-free learning system simply relies on repetition of actions that lead to reward, irrespective of noisy computations each time a movement must be made, it tends to deliver superior performance. The major disadvantage of model-free learning is that although it replaces computation with memory, it can be statistically inefficient due to the forward-looking nature of the prediction error (Daw et al., 2005).

In model-based learning system the learner senses the movement outcome and compares this to the predicted outcome. In this case, the learner not only knows whether s/he misses the goal but also identifies how s/he misses it. Thus model-based learning often leads to fast improvements in performance through calibrating and reducing the average performance error. Although model-based learning can reduce the average performance error to zero, it cannot be instrumental in improving performance further. Take, for example, the game of darts, the location where the dart strikes to the board is determined by a large amount of variables, such as the orientation of the trunk, the position and velocity of the wrist or arm. This task is redundant because multiple combinations of these variables can achieve the goal. Model-based learning can achieve zero performance error on average, but cannot reduce the variability of the final outcome. However, unlike model-based learning, in model-free learning the learner does not know a signed error signal regarding his/her movement, but an unsigned signal about the relative success and failure of the movement, so s/he does not have any information about the direction required to correct his/her movement. Thus, s/he has to explore possible actions to gradually improve his/her movement until an optimal solution is found. A recent study (Izawa and Shadmehr, 2011), which showed that subjects can learn to adapt the perturbation when given only the success and failure of the movement, demonstrated that model-free learning system drives learning via task success feedback.

Manipulation of online visual feedback provided during motor learning has been shown to effectively differentiate the contribution of these two learning processes (Izawa and Shadmehr, 2011; Schmuelof et al. 2012). In visuomotor adaptation paradigm, for example, learning from full vector error regarding movements involves primarily model-based mechanism. In contrast, learning from binary feedback about the success or failure of movements relies on model-free mechanism (Izawa and Shadmehr, 2011).

Generalization of Motor Learning

Generalization of motor learning is an important aspect of motor learning. Generalization of motor learning refers to the degree to which the acquired learning can be effectively used across motor tasks, workspaces, effectors, and limb configurations. For example, if one is an expert in the game of table tennis, and now s/he is going to learn tennis, can s/he apply what s/he has learned from table tennis to playing tennis? In the rehabilitation domain, can rehabilitative training received under a specific physical therapy setting transfer to facilitate movement under an unconstrained environment? These questions can be addressed by studying the generalization of motor learning. Generalization of motor learning is thought as an important topic in rehabilitation, as therapy-induced changes should occur over time and settings, and sometimes spread to a variety of related behaviors (Stokes and Baer, 1977). A low degree of generalization might demonstrate the limitations of the impact of certain rehabilitation interventions (Stokes and Baer, 1977; Page, 2003; Huxlin and Pasternak, 2004; Krakauer, 2006; Van Peppen et al., 2006). For example, therapy-induced changes in task A must lead to changes in performance not just for task A, but also generalize to other tasks (Huang and Krakauer, 2006).

The amount of generalization could be used to infer whether the acquired learning is task specific, condition specific, effector specific, etc. A high degree of generalization indicates that components of learning are represented at abstract or task-level, while a low degree of generalization indicates that components of learning are represented at an effector or response-level (Imamizu and Shimojo, 1995). Motor generalization studies have also been used to determine the extent to which model-based, model-free and instance-reliant learning systems control behavior by examining the extent to which learning system should transfer across tasks within the same workspace. Each learning mechanism is expected to exhibit some degree of generalization. However, it is widely accepted that model-based learning tends to generalize more broadly across tasks than model-free learning (Izawa and Shadmehr 2011). For example, subjects trained to compensate for a rotation given vector error (engaging primarily model-based learning) generalize more broadly than those trained to compensate the same perturbation but only given binary feedback regarding the success or failure of task (engaging primarily model-free learning) (Izawa and Shadmehr 2011).

Motor learning is not simply the memory of specific motor acts. Central to motor learning is the ability to generalize what has been learned in one movement condition to another movement condition (Poggio and Bizzi, 2005). A large number of studies using sensorimotor adaptation paradigms are frequently used to study the mechanisms underlying generalization of motor learning, indicating that adaptation can generalize, to varying degrees, across the limb configurations, the workspace, and effectors. To test whether generalization can occur across the workspaces, for example, we asked subjects to perform targeted-reaching tasks across different workspace locations under a novel visuomotor condition in which the visual display of the movement was rotated 30 degrees counterclockwise (Lei et al., 2013). As we found, generalization across different workspaces could reach 100%. Some studies have also indicated that generalization is not restricted to the same arm configuration in which adaptation took place (Baraduc and Wolpert, 2002; Krakauer et al., 2000). Adaptation to a novel visuomotor transformation in one initial arm configuration can completely generalize to different initial arm configurations that have not been experienced during training.

However, the extent of generalization appears to be task dependent. Previous research examining generalization across movement directions, for example, showed that generalization fell to zero as the angular difference between the training direction and the testing directions over 45 degrees (Krakauer et al., 2000). Some studies showed that generalization can also occur across effectors, but its extent is very limited, ranging from 10 to 60% (Morton et al., 2001; Sainburg and Wang, 2002; Taylor et al., 2011; Wang et al., 2011; Joiner et al., 2013). Although various neural mechanisms underlying generalization of motor learning have been suggested (Taylor and Heilman, 1980; Anguera et al., 2007; Perez et al., 2007; Block and Celnik, 2013), it remains unknown why their extents are so limited.

Motor Learning by Observation

The brain utilizes multiple forms of learning, not restricted to the learning mechanisms described above. The learning strategies that I have focused on are usually involved in executing motor tasks, whereas the mere observation of others performing the same motor tasks can also facilitate motor learning by conveying high-level information about the form of movement such as the movement kinematics (Hayes et al., 2010), coordination pattern (Hodges et al., 2007), as well as spatial-temporal goals (Vogt, 1995). There have been a number of studies to support that motor learning occurs by observation without actual execution. For instance, rats can learn a novel task by observing other rats engaged in the same task (Petrosini et al., 2003). Human subjects who observe an actor learning a motor task perform better when they subsequently learn the same task (Kelly et al., 2003; Brown et al., 2009; Mattar and Gribble, 2005; Ong and Hodges, 2010). These studies are further supported by several imaging studies that demonstrate the common neural areas are activated when performing a specific action and observing others performing a similar action (Rozzolatti and Craighero, 2004).

It is widely accepted that motor skill can be learned through observing the actions of others. For example, naïve observers can learn finger-tapping sequences by watching others (Kelly et al., 2003). Similarly, naïve observers who watch an actor learning to adapt in a novel visuomotor or dynamic environment perform better when later adapting to the same environment themselves (Brown et al., 2009; Mattar and Gribble, 2005; Ong and Hodges, 2010). Moreover, there is evidence that motor learning from observation is not based on explicit, conscious strategies but instead is mediated by implicit, motor-related processes (Mattar and Gribble, 2005). For example, a similar neural network is involved when executing a motor task and observing others performing the same task (Iacoboni et al., 1999). By watching an actor grasping an object, motor potentials evoked from the stimulation of the motor cortex is altered (Fadiga et al., 1995). In addition, the cerebellum seems to be involved in procedural learning as well as observational learning (Petrosini et al., 2003). Taken together, these findings suggest that observational and physical learning may involve similar learning processes.

Motor learning by passive training

Unlike active and observational learning, passive training can improve motor learning by providing proprioceptive information of the desired movement. Proprioception is the sense of the position and movement of the body. Muscle spindles which encode information on muscle length and its rate of change are believed to play a large role in proprioception. In passive training, improvements in performance are often associated with cortical reorganization (Nudo et al., 1996; Shadmehr and Holcomb, 1997; Classen et al., 1998; Muellbacher et al., 2001). Several imaging studies have demonstrated that passive training could be as effective as active learning in eliciting cortical reorganization so as to result in behavioral gains (Alary et al., 1998; Carel et al., 2000). In rehabilitation settings, patients with brain lesions, such as stroke patients, are too weak to perform voluntary movements are often guided passively to acquire proprioceptive information associated with the correct movement.

For motor learning to occur, the process in which information regarding the actual movement (what was done) can be compared to the goal movement (what should be done) is very important (Beets et al., 2012). It is generally agreed that visual and proprioceptive information are the critical inputs for this motor learning process. While it has been supported that visual information contributes to motor learning significantly, much less is known about the effect of provision of proprioceptive information for learning. Previous studies have shown that passive training can improve motor learning by providing proprioceptive information of the goal movement. For example, subjects who were provided additional proprioceptive information of circular hand movement trajectories passively were better able to learn this new motor skill (Beets et al., 2010; Wong et al., 2012). Similarly, a study investigating the effect of passive arm movements on the motor learning showed that passive motor experience has a positive effect on the improvement of motor learning of visuomotor adaptation even without conscious motor intention (Cressman and Henriques, 2009, 2010; Sakamoto and Kondo, 2012). Taken together, these findings suggest that motor conscious, motor planning, and experience of proprioceptive sensation may influence the learning of a motor skill independently.

Process leading to motor learning through passive movement is considered as the instance-reliant learning. Instance-reliant learning is thought to be associated with specific movement performed by specific effectors, and driven through encoding the specific kinematic aspects of that specific movement without any outcome information (Wolpert et al., 2011). Prescriptive proprioceptive information provided by passive practice helps accrue motor instances of the goal movement and build a template of expected sensory consequence (Kovacs et al., 2011).

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Appendix B: Informed Consent Form

UNIVERSITY OF WISCONSIN – MILWAUKEE
CONSENT TO PARTICIPATE IN RESEARCH

THIS CONSENT FORM HAS BEEN APPROVED BY THE IRB FOR A ONE YEAR PERIOD

1. General Information

Study title: Maximizing the effects of passive training on visuomotor adaptation by incorporating other motor learning strategies

Person in Charge of Study (Principal Investigator):

My name is Dr. Jinsung Wang. I am an associate professor in the Department of Kinesiology at University of Wisconsin -- Milwaukee.

2. Study Description

You are being asked to participate in a research study. Your participation is completely voluntary. You do not have to participate if you do not want to.

Study description:

The purpose of this study is to develop training conditions that can maximize the effects of passive training and action observation on motor learning. We know that passive training and action observation therapy are effective rehabilitation approaches, but the effectiveness of these trainings is still low. We are now investigating why there is limited treatment effectiveness in passive assist training and action observation in rehabilitation settings, and how to develop training conditions that can maximize the potential benefits of these training methods.

This study will be conducted in the Neuromechanics Laboratories at UWM. Approximately 80 volunteers will participate in this study. Your participation in this study will take approximately one and a half hours, over the course of one day.

Eligibility:

If you are a healthy individual, defined as a person who does not have any neurological damage, and are right handed and aged between 18 and 30, you are eligible to participate in this study. You will be excluded for following criteria: 1) a major psychiatric diagnosis (e.g., schizophrenia), 2) hospital admission for substance abuse, 3) peripheral disorders affecting sensation or movement of the upper extremities (e.g., peripheral neuropathy), or 4) if they are left-handed.

3. Study Procedures

What will I be asked to do if I participate in the study?

If you agree to participate you will be asked to come to the Neuromechanics Laboratories, located on the first floor of Enderis Hall at UWM. Upon your arrival, an experimenter will first describe the task to you. You will then sit at a table, and a computer game will be projected on a computer display in front of you. Though you may not see your hand, you will see the position of your hand as a cursor, projected on the screen. You will be asked to position this cursor in a start circle located in the middle of the screen. At computer-generated tones, you will be asked to move your hand toward targets presented on the screen. You may be asked to use your right arm, left arm, or both at the same time, depending on the condition you are assigned to. It will take approximately one and a half hours for you to complete an experiment.

Your arm movements will be recorded using a non-invasive, 2-dimensional robotic system where you will rest your arms on robotic armrests. No audio/video/photographic recordings will be made.

4. Risks and Minimizing Risks

What risks will I face by participating in this study?

This research involves minimal risk, that is, no risks to physical or mental health beyond those encountered in the normal course of everyday life. During the experiment, however, some minor discomfort associated with remaining seated for over an hour may be experienced. When that happens, you may request a break to stretch, move about the room, and visit the lavatory.

5. Benefits

Will I receive any benefit from my participation in this study?

Participation in this research has no direct benefit you, beyond that of an opportunity to participate in research that may prove valuable for the development of more efficient rehabilitation protocols for stroke patients.

Are subjects paid or given anything for being in the study?

In return for your participation, you may receive extra credit for your class (please confirm with your instructor who offers extra credit for participating in faculty research), after completing the experiment. If you are not a student of the PI, extra credit cannot be guaranteed.

6. Study Costs

Will I be charged anything for participating in this study?

You will not be responsible for any of the costs from taking part in this research study.

7. Confidentiality

What happens to the information collected?

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. We may decide to present what we find to others, or publish our results in scientific journals or at scientific conferences. Information that identifies you personally will not be released without your written permission. Only the PI, and other personnel assigned by the PI, will have access to the information. However, the Institutional Review Board at UW-Milwaukee or appropriate federal agencies like the Office for Human Research Protections may review your records.

The only records that maintain your identity will be this consent form; this form will be kept locked in the PI's laboratory. The collected data will be saved with your initial (e.g., jw for Jinsung Wang) as part of the data file name (e.g., jw0001). This is necessary to process and analyze the data from each participant separately. These data cannot be associated with you without access to your consent form that is kept locked in the PI's laboratory. Only the PI and specific personnel assigned by the PI will have access. After the study is complete, the data will be kept in the PI's password-protected computer for up to six years; it will be destroyed afterwards.

8. Alternatives

Are there alternatives to participating in the study?

If you are currently a student of the PI, you may choose to complete an extra reading assignment, which requires approximately the same time to complete it; and the same extra credit will be given for that assignment. You are not allowed to participate in this study AND complete the reading assignment. If you are not a student of the PI, you should ask your instructor for alternative methods of earing extra credit.

9. Voluntary Participation and Withdrawal

What happens if I decide not to be in this study?

Your participation in this study is entirely voluntary. You may choose not to take part in this study. If you decide to take part, you can change your mind later and withdraw from the study. You are free to not answer any questions or withdraw at any time. Your decision will not change any present or future relationships with the University of Wisconsin Milwaukee. And we will destroy all information we collect about you.

10. Questions

Who do I contact for questions about this study?

For more information about the study or the study procedures or treatments, or to withdraw from the study, contact:

Dr. Jinsung Wang

Department of Kinesiology

College of Health Sciences

University of Wisconsin -- Milwaukee

492 Enderis Hall

Milwaukee, WI, 53201

(414) 229-3226

Who do I contact for questions about my rights or complaints towards my treatment as a research subject?

The Institutional Review Board may ask your name, but all complaints are kept in confidence.

Institutional Review Board

Human Research Protection Program

Department of University Safety and Assurances

University of Wisconsin – Milwaukee

P.O. Box 413

Milwaukee, WI 53201

(414) 229-3173

11. Signatures

Research Subject's Consent to Participate in Research:

To voluntarily agree to take part in this study, you must sign on the line below. If you choose to take part in this study, you may withdraw at any time. You are not giving up any of your legal rights by signing this form. Your signature below indicates that you have read or had read to you this entire consent form, including the risks and benefits, and have had all of your questions answered, and that you are 18 years of age or older.

____

Printed Name of Subject/ Legally Authorized Representative

______________________________________ __________________

Signature of Subject/Legally Authorized Representative Date

Principal Investigator (or Designee)

I have given this research subject information on the study that is accurate and sufficient for the subject to fully understand the nature, risks and benefits of the study.

______________________________________ __________________

Printed Name of Person Obtaining Consent Study Role

______________________________________ __________________

Signature of Person Obtaining Consent Date

Appendix C: Handedness Questionnaire

Handedness Questionnaire

This questionnaire is designed to thoroughly evaluate one's degree of handedness. Please place a check mark in the appropriate box for each task. If you use both hands, check both, but indicate the one used more often or that you feel is more controlled. If you have any questions, do not hesitate to ask.

	R	L		R	L
Signing			Throwing		
Writing			Broom (upper hand)		
Drawing			Striking Match		
Scissors			Opening Box		
Toothbrush			Foot to kick with		
Knife			Bat (swing)		
Spoon					

1. Do you consider yourself:

   Right-Handed Left-Handed Ambidextrous (Both Hands)

2. Is there anyone in your family who is Left-handed? Yes or No

   If yes, then who ______________________________

3. Did you ever change handedness? Yes or No

If yes, please explain ____

4. Is there any activity not in this list that you do consistently with your Left Hand?

If yes, please explain

Appendix D: Recruitment Flyer

Subjects Needed

The Neuromechanics Laboratory is seeking subjects for research to study the motor learning mechanisms underlying passive training.

Subjects must be **18 to 30 years of age** and must be **right hand** dominant.

As a subject, your arm movements will be recorded while you play a computer game. The entire procedure is non-invasive and comfortable. The session will last for approximately one hour.

You may receive extra credit for participating in this research. (Please confirm with your course instructor(s))

Please send me an email at **ylei@uwm.edu**

for more information or to schedule a time.

CURRICULUM VITAE

SCIENTIFIC EDUCATION

Ph.D. in **Health Professions and Related Clinical**, 2015
University of Wisconsin, Milwaukee, WI, USA
Research Advisor: Jinsung Wang

M.S. in **Biomedical Engineering**, 2013
Marquette University, Milwaukee, WI, USA
Research Advisor: Michelle J. Johnson

B.S. in **Biomedical Engineering**, 2009
Nanchang HangKong University, China
Research Advisor: Kaiqiong Sun

RESEARCH INTERNSHIP

Research Intern in **Single Motor Unit Laboratory**, 02/2014 – 09/2014
Rehabilitation Institute of Chicago/Northwestern University, Chicago, IL, USA
Research Advisor: W. Zev Rymer

PROFESSIONAL EXPERIENCE

Graduate Research Assistant, 2012-2015
Department of Kinesiology, University of Wisconsin, Milwaukee, WI, USA
Research Regarding multi-joint pointing movements, sensorimotor adaptation, and motor learning

Graduate Teaching Assistant, 2013-2014
Department of Kinesiology, University of Wisconsin, Milwaukee, WI
Assisted/taught lab activity for Motor development class
Graduate Research Assistant, 2009-2012
Department of Biomedical Engineering, Marquette University, Milwaukee, WI
Research regarding functional MRI

Graduate Research Assistant, 2009-2011
Eye Institute, Medical College of Wisconsin, Milwaukee, WI
Research regarding medical imaging segmentation and registration

TEACHING EXPERIENCE

Lecturer for graduate course, 2014 –2015
Department of Kinesiology, University of Wisconsin, Milwaukee, WI
HMS 703 Survey of Research in the Human Movement Sciences (Co-Instructor)

Graduate Teaching Assistant/Lab Instructor, 2013-2014
Department of Kinesiology, University of Wisconsin, Milwaukee, WI
HMS 460 Life Span Motor Development (Assisted/taught lab activity for Motor development class)

HORNORS AND AWARDS

Chancellor's Graduate Student Award 2012-2015, University of Wisconsin, Milwaukee, WI
College of Health Sciences Scholarship 2012-2015, University of Wisconsin, Milwaukee, WI
Chancellor's Graduate Student Award 2014 summer term, University of Wisconsin, Milwaukee, WI
Graduate Student Travel Support 2013, University of Wisconsin, Milwaukee, WI
Department of Kinesiology Scholarship 2012-2013, University of Wisconsin, Milwaukee, WI
Graduate Student Research Award 2012, University of Wisconsin, Milwaukee, WI
Honorable Mention in Mathematical Contests in Modeling 2008
Nanchang Hangkong University Academic Scholarship 2005-2008
Nanchang Hangkong University Cadre Honor Award 2007-2008

PUBLICATIONS

NL Suresh, **Lei Y**, WZ Rymer. Muscles within muscles: Do spationeural mechanisms underpin force production (in preparation)

Lei Y, Wang J. Savings and aftereffects observed during visuomotor adaptation involves distinct motor learning mechanisms (in preparation)

Wang J, **Lei Y**. Performing, but not learning, a task with one arm during initial training with the other arm can lead to complete transfer of motor learning across the arms (Submitted to Journal of Neuroscience). 2014

Lei Y, Wang J. Prolonged training does not result in a greater extent of interlimb transfer following visuomotor adaptation. **Brain Cognition**, 91: 95-9, 2014.

Lei Y, Johnson MJ, and Wang J. Separation of visual and motor workspaces during targeted reaching results in limited generalization of visuomtor adaptation. **Neurosci Lett** 541: 234-7, 2013

Wang J, **Lei Y**, Xiong K, and Marek K. Substantial Generalization of Sensorimotor Learning from Bilateral to Unilateral Movement Conditions. **PLOS ONE** 8: e58495, 2013.

Lei Y. The Effect of Separation Visual and Motor Workspaces on the Generalization of Visuomotor Adaptation across Movement Conditions. M.S. Thesis, 2013.

Wang J, Joshi M, and **Lei Y**. The extent of interlimb transfer following adaptation to a novel visuomotor condition does not depend on awareness of the condition. **J Neurophysiol** 106:259-64, 2011.

Melissa Wagner-Schuman, Adam M. Dubis, Rick N. Nordgren, **Lei Y**, Daniel Odell, Hellen Chiao, Eric Weh, William Fischer, Yusufu Sulai, Alfredo Dubra and Joseph Carroll. Racial and Gender Differences in Retinal Thickness and Foveal Pit Morphology. **Invest Ophthamlmol Vis Sci** 52: 625-634, 2011.

Zhou X, Wang Y, Yu Z, Zhou B and **Lei Y**. Collection of ECG signal based on LabVIEW. **Science and Technology Innovation Herald** 4: 38-39, 2008.

PUBLISHED ABSTRACTS

Lei Y, Wang J. (2014) Performing, but not learning, a reaching task with one arm while learning the same task with the other leads to complete transfer of visuomotor adaptation across the arms: Society for Neuroscience. Online

Bao S, **Lei Y**, Wang J. (2014) Performing a reaching task with one arm passively while learning the same task with the other leads to substantial transfer of visuomotor adaptation across the arms: Society for Neuroscience

Wang J, **Lei Y**. (2013) Prolonged training during visuomotor adaptation does not result in a greater extent of interlimb transfer: Society for Neuroscience. Online

Wang J, **Lei Y**. (2012) Complete generalization of sensorimotor learning from bilateral to unilateral movement conditions. Program No. 88.05, Neuroscience Meeting Planner. New Orleans: Society for Neuroscience. Online

Lei Y, Wang J. (2012) Dissociation of visual and motor workspace locations during targeted reaching results in lack of generalization of visuomotor adaptation. Program No. 679.02, Neuroscience Meeting Planner. New Orleans: Society for Neuroscience. Online

FUNDED GRANT APPLICATIONS (Lei Y as PI)

The effect of motor and visual workspace dissociation on sensorimotor learning

Goals: To investigate the roles of vision and proprioception in sensorimotor learning in healthy young adults by dissociating motor and visual workspaces during reaching movement.
Student Principal Investigator: **Lei Y**
Graduate Student Research Award
Funded for 1 year ('11-'12)

OTHER FUNDED GRANT APPLICATIONS

Association between physical activity and hemispheric lateralization in elderly
Principal Investigator: Wang J (**Lei Y**, Research Associate)
UWM Graduate School Research Award
Funded for 2 years ('13-'15)

Hemispheric motor lateralization in elderly
Principal Investigator: Wang J (**Lei Y**, Research Associate)
UWM College of Health Sciences SEED grant
Funded for 1 year ('13-'14)

Neural mechanisms underlying functional laterality of the intact arm of amputees
Goals: To understanding the relation between cortical reorganizations following amputation and functional laterality of the intact arm.
Principal Investigator: Wang J (**Lei Y**, Research Associate)
Research Grant by Clinical and Translational Science Institute
Funded for 1 year ('12-'13)

Hemispheric Lateralization and Interlimb Transfer of Motor Learning
Principal Investigator: Wang J (**Lei Y**, Research Associate)
NIH NICHD (NCMRR) Research Scientist Development Award K01 HD050245
Funded for 5 years ('07-'12)

INVITED PRESENTATIONS (ORAL)

Lei Y (2014) Cross-hemispheric transfer of motor learning. Rehabilitation Institute of Chicago (Biodynamics Lab), Chicago.

INVITED PRESENTATIONS (POSTERS)

Lei Y, Wang J. (2014) Performing, but not learning, a reaching task with one arm while learning the same task with the other leads to complete transfer of visuomotor adaptation across the arms, Society for Neuroscience, Washington, DC.

Bao S, **Lei Y**, Wang J. (2014) Performing a reaching task with one arm passively while learning the same task with the other leads to substantial transfer of visuomotor adaptation across the arms, Society for Neuroscience, Washington, DC.

Lei Y, Wang J. (2014) Performing, but not learning, a reaching task with one arm while learning the same task with the other leads to complete transfer of visuomotor adaptation across the arms, UWM Neuroscience Minisymposium, Milwaukee, WI

Wang J, Bao S, **Lei Y**, Binder J (2014) Savings in Visuomotor Adaptation following Unlearning Session with or without visual feedback. Cognitive Neuroscience Society Conference, Boston, MA

Wang J, **Lei Y**. (2013) Prolonged training during visuomotor adaptation does not result in a greater extent of interlimb transfer, Society for Neuroscience. San Diego, CA

Lei Y, Johnson MJ, Wang J. (2013) Separation of visual and motor workspaces during targeted reaching results in limited generalization of visuomotor adaptation, 2013 Meeting of the Milwaukee Chapter of the Society for Neuroscience, Milwaukee, WI

Lei Y, Wang J. (2012) Complete generalization of sensorimotor learning from bilateral to unilateral movement conditions, CHS Research Symposium, University of Wisconsin, Milwaukee, WI.

Wang J, **Lei Y**. (2012) Complete generalization of sensorimotor learning from bilateral to unilateral movement conditions. Society for Neuroscience, New Orleans, LA

Lei Y, Wang J. (2012) Dissociation of visual and motor workspace locations during targeted reaching results in lack of generalization of visuomotor adaptation. Society for Neuroscience, New Orleans, LA

Lei Y, Wang J. (2012) Dissociation of visual and motor workspace locations during targeted reaching results in lack of generalization of visuomotor adaptation. Federation of European Neuroscience Societies, Barcelona, Spain

Lei Y, Wang J. (2012) Dissociation of visual and motor workspace locations during targeted reaching results in lack of generalization of visuomotor adaptation. CHS Research Symposium, University of Wisconsin, Milwaukee, WI

Lei Y, Johnson MJ, Wang J. (2012) Combined contributions of visual and proprioceptive information to adaptation to novel visuomotor conditions. Biomedical symposium, Marquette University, Milwaukee, WI

Lei Y, Johnson MJ, Wang J. (2012) Combined contributions of visual and proprioceptive information to adaptation to novel visuomotor conditions. Physical Medicine and Rehabilitation Research Symposium, Medical College of Wisconsin, Milwaukee, WI

MEMBERSHIP IN PROFESSIONAL AND SCIENTIFIC ORGANIZATIONS

Society for Neuroscience 2012 – Present
American Kinesiology Association 2012-Present

ACTIVITES AND SERVICE

Research volunteer in U.S. Department of Veterans Affairs, Milwaukee 2009 – 2011

TECHNICAL SKILLS

C/C++/VB
MATLAB/SIMULINK/STATEFLOW/
AFNI (fMRI data processing software)
LABVIEW
VISUAL 3D