PROPRIOCEPTIVE TRAINING AND MOTOR TRANSFER IN PATIENTS WITH PARKINSON'S DISEASE

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Last, but not the least, my parents and my brother must be a part of this page, but not definitely limited to this page. Their encouragement and best wishes made me come this far.

Dedication

This thesis is dedicated to

My parents

For boundless love and affection,

For always inspiring me to push the boundaries of my capabilities, and

For making sure that I always get the best in my life.

Abstract

Parkinson's disease (PD) is a neurodegenerative disorder that affects the motor system, but is also associated with sensory impairments, such as anosmia or proprioceptive dysfunction. Recent research on healthy individuals shows that a sensorimotor training which challenges the proprioceptive system improves both proprioceptive and motor function. However, it is unknown whether proprioceptive function can be enhanced in PD. It is further unclear, if an improved proprioceptive-motor function after learning leads to general improvements in motor performance. That is, the extent of transfer to other motor tasks is unknown. To fill this knowledge gap, this study employed a robot-aided visuo-proprioceptive motor training to people with PD with the following objectives: First, to identify whether proprioceptive function in Parkinson's disease (PD) can be enhanced by a visuo-proprioceptive training that emphasizes precise, small amplitude continuous wrist movements. Second, to determine if proprioceptive improvements after training are associated with improvements in an untrained discrete wrist movement task, i.e. demonstrating a sensorimotor transfer within the same joint degree of freedom. Third, to identify if the training transferred to improvements in a functional writing task that relied on multi-joint wrist-hand motion, i.e. showing a sensorimotor transfer for additional joint degrees of freedom.

METHOD: 13 participants presenting with mild to moderate PD were tested in their ON medication state. Training involved tilting a virtual table projected on a screen with the aim to position a virtual ball on a target by making continuous and precise small amplitude wrist flexion/extension movements. Wrist position sense acuity, spatial errors for the untrained, goal-directed wrist pointing movement (local transfer) and the more functional hand writing task were assessed before and after training.

RESULTS: First, proprioceptive function was improved after training. As a group, PD participants showed a statistically significant reduction in position sense acuity thresholds (mean: pre/post = 1.6° / 1.1°). Second, significant evidence for

a localized sensorimotor transfer was found. In the untrained discrete wrist pointing movement, 10 out of 13 participants (77%) recorded improvements in spatial movement precision error (mean: pre/post = 2.4° / 1.8°). Third, spatial error measured in handwriting based tracing and tracking tasks did not show statistically significant training related improvements.

CONCLUSION: Wrist proprioceptive function in PD patients can be enhanced with a brief specialized sensorimotor training that emphasizes proprioceptive acuity. Sensorimotor training involving continuous small-amplitude wrist movements improved movement accuracy in an untrained discrete non-visuomotor task. This transfer of spatial motor precision was evident for the same joint degree of freedom, but not in a multiple-joint-degrees-of-freedom handwriting task. These initial findings provide evidence that visuo-proprioceptive training can enhance proprioceptive function in PD. Moreover, they reveal that somatosensory-based training may generalize to other motor tasks using the same trained joint degrees of freedom.

Table of Contents

Contents

List of Tables

List of Figures

Introduction:

Parkinson's disease – more than a basal ganglia disorder

Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by the cardinal motor signs including tremor, rigidity, akinesia and postural instability (Jankovic, 2008). The prevalence of Parkinson's disease in the United States is estimated to be 1588 per 100,000 people above 65 years of age, which is about 1.6% of the elderly population (Wright-Willis, Evanoff, Lian, Criswell, & Racette, 2010). It is well established that PD affects the basal ganglia. Motor impairments in PD such as bradykinesia of upper and lower limbs, freezing, shuffling gait and postural instability PD coincide with a degeneration of nigrostriatal dopaminergic neurons (Cahn et al., 1998; Chapuis, Ouchchane, Metz, Gerbaud, & Durif, 2005; Gómez-Esteban et al., 2007; Rahman, Griffin, Quinn, & Jahanshahi, 2008). However, numerous other neuroanatomical areas also show signs of degeneration in PD. For example, cholinergic neurons in the pedunculopontine nucleus (Hirsch, Graybiel, Duyckaerts, & Javoy-Agid, 1987; Pahapill & Lozano, 2000; Zweig, Jankel, Hedreen, Mayeux, & Price, 1989), norepinephrinergic neurons in the locus ceruleus (Del Tredici, Rüb, de Vos, Bohl, & Braak, 2002; Gibb, Scott, & Lees, 1991; Zarow, Lyness, Mortimer, & Chui, 2003), serotoninergic neurons in the raphe nuclei (Halliday et al., 1990), substance P-containing neurons in lateral reticular formation and dorsal motor vagal nucleus (Halliday et al., 1990), cholinergic neurons in the nucleus basalis of Meynert (Arendt, Bigl, Arendt, & Tennstedt, 1983; Candy et al., 1983) and neurons in frontal and temporal lobes (Burton, McKeith, Burn, Williams, & O'Brien, 2004) show degenerative changes in PD. In summary, the available neuroanatomical evidence indicates that PD is a neurodegenerative disease which affects several regions of the cerebrum and brainstem and is not restricted to the basal ganglia.

Parkinson's disease - more than a movement disorder

Aside from the cardinal motor impairments, PD patients also experience somatosensory impairments. Although somatosensory deficits in PD may not be clinically obvious in the early stages of the disease, recent research provides extensive evidence for somatosensory abnormalities in people with PD. People with PD show abnormalities in shape discrimination tasks when compared to healthy adults (Weder et al., 2000; Weder et al., 1999). PD patients exhibit increased thresholds for detecting grating orientation (Shin, Kang, & Sohn, 2005), tactile perception (Cao, Xu, Zhao, Long, & Zhang, 2011), and somatosensory temporal discrimination (Fiorio et al., 2008). Thermal sensation and pain perception are altered in people with PD demonstrated by increased thermal perception thresholds and a reduction in mechanical pain perception when compared to healthy controls (Nolano et al., 2008). Abnormalities in proprioception has also been extensively reported (discussed below). Behavioral alterations in somatosensory perception has been shown to be associated with altered activity in several cortical areas. When PD patients performed an object discrimination task, Weder et al (2000) found cerebral blood flow to show unilateral reduction in the contralateral sensorimotor cortex, bilateral reduction in the premotor area, supplementary motor area and in the parietal lobule, and abnormally increased activation in the cerebellum. Along with these changes, Cao et al (2011) found reduced activity in contralateral striatum and reduced connectivity in ipsilateral supplementary motor area. These studies demonstrate that somatosensory abnormalities in PD are more pronounced than previously considered. In the following, research evidence on proprioceptive dysfunction in PD will be discussed in detail as this dysfunction is central to the current study.

Proprioceptive receptors

The term *proprioception* refers to active motion sense, passive motion sense, limb position sense and sense of heaviness (Goldscheider, 1898). Proprioception is encoded by receptors such as muscle spindles, Golgi tendon organs and

mechanoreceptors in the ligaments and capsules of the joints. These muscle and joint receptors encode different aspects of proprioception such as muscle length, contractile speed, muscle tension and joint position as discussed below.

Muscle spindles

Muscle spindles are small encapsulated sensory receptors that have a spindle-like or a fusiform shape and are located within the fleshy part of a muscle (Pearson & Gordon, 2012). Muscle spindles are most sensitive to changes in muscle length. Muscle spindles have three main components: 1) intrafusal muscle fibers with polar contractile regions and a central non-contractile region, 2) sensory fibers that innervate the central non-contractile region of the intrafusal fibers and 3) motor fibers that innervate the polar contractile region of the intrafusal muscle fibers (Hulliger, 1984). Furthermore (Boyd, 1980), the intrafusal muscle fibers are of two types – nuclear bag fibers and nuclear chain fibers. Nuclear bag fibers can be divided into two sub-groups – static nuclear bag fibers and dynamic nuclear bag fibers. Intrafusal muscle fibers are innervated by the sensory large diameter Ia afferent fibers (primary muscle spindle afferent flow). Nuclear chain fibers and static nuclear bag fibers are innervated by type II sensory afferent nerves (secondary muscle spindle afferent flow). The polar contractile regions of the dynamic nuclear bag fibers are innervated by dynamic gamma motor neuron, whereas those of static nuclear bag fibers and nuclear chain fibers are innervated by static gamma motor neuron (Brown & Matthews, 1966). This motor innervation ensures optimal sensitivity of the muscle spindles to stretch during voluntary muscle contraction. When the extrafusal muscle fibers stretch, the intrafusal muscle fibers in the muscle spindle also stretch resulting in action potentials in the sensory afferent fibers. Intensity of firing frequency in sensory fibers is directly proportional to the intensity of stretch in the intrafusal muscle fibers. This tonic discharge of muscle spindle afferents signal steady-state length of the muscle.

Golgi tendon organs

Golgi tendon organs are slender encapsulated structures located at the junction between skeletal muscle fibers and tendon (Pearson & Gordon, 2012). They are approximately 1mm long and 0.1 mm in diameter. The capsules comprise several braided collagen fibers which are in series with extrafusal muscle fibers. Each tendon organ is innervated by a single Ib sensory afferent axon which divides into many fine endings and intertwines with the collagen fibers. Whenever there is a contraction of the muscle, the collagen fibers in the Golgi tendon organs are stretched. The stretch in the collagen fibers causes a compression of the Ib sensory afferent axons which increases their firing rate (Schmidt, 1983). The sensor nerve endings are highly sensitive to changes in muscle tension. The discharge rate of a population of Golgi tendon organs signals the force exerted by the muscle (Crago, Houk, & Rymer, 1982). The greater the force, the greater the discharge rate of the Golgi tendon organs.

Joint mechanoreceptors

Mechanoreceptors found in the ligaments and capsules of joints serve as an important source of information about limb position and motion. These receptors morphologically resemble Golgi-like endings and Pacinian corpuscles and are innervated by type I afferent fibers. Other unencapsulated free nerve endings in the joints are innervated by type II afferent fibers (Newton, 1982). These receptors show activation at specific joint positions (Boyd & Roberts, 1953). Some receptors sense mid-range joint positions whereas others are mostly active at end-range joint positions.

These receptors encode several aspects of proprioception and ultimately all the information encoded by these receptors reach primary somatosensory areas in the parietal lobe (Ageranioti-Bélanger & Chapman, 1992; Chapman & Ageranioti-Bélanger, 1991; Rincon-Gonzalez, Warren, Meller, & Tillery, 2011). Several cortical areas process the proprioceptive information so that it can be used in generation of motor command. Posterior parietal cortex integrates

somatosensory information from the periphery along with vision based object recognition and visuospatial perception. This integration of visual and somatosensory information in the posterior parietal and in the premotor cortical areas is essential for motor control (Rizzolatti & Kalaska, 2012). Lack of integrity in these pathways result in altered proprioception and movement accuracy in different clinical conditions such as deafferentation, sensory neuropathy and Parkinson's disease (Ghez, Gordon, Ghilardi, Christakos, & Cooper, 1990; Maschke, Gomez, Tuite, & Konczak, 2003; Mongeon, Blanchet, & Messier, 2009; Putzki et al., 2006; Rothwell et al., 1982).

The evaluation of proprioceptive function

Proprioception can be evaluated using psychophysical methods that are known to provide reliable and valid measures of proprioceptive function (Cappello et al., 2014; Elangovan, Herrmann, & Konczak, 2014). Psychophysical methods typically use a *forced-choice paradigm* to obtain a threshold. Forced-choice paradigm is a method in which the subjects are forced to identify an odd stimulus from two different stimuli. A threshold is defined as the smallest amount of stimulus energy necessary to produce a sensation (Gescheider, 1985). Detection threshold is defined as the smallest change in position that a person can consciously identify whereas discrimination threshold will be the critical difference between two positions that can be identified. Discrimination threshold is a psychophysical measure of the proprioceptive acuity whereas detection threshold is a measure of proprioceptive sensitivity. Proprioceptive acuity is usually evaluated in terms of discrimination thresholds and/or position sense error (Elangovan et al., 2014; Goble, 2010). Position sense error is the angular error that occurs during active/passive reproduction of a perceived position.

Proprioception in Parkinson's disease

As discussed earlier, people with PD manifest abnormalities in somatosensation including proprioception. PD patients demonstrate increased active and passive

joint position sense error than healthy controls (Klockgether, Borutta, Rapp, Spieker, & Dichgans, 1995; Shagufta Zia, Cody WJ, & O'Boyle J, 2002). PD patients show increased proprioceptive discrimination thresholds than healthy age matched controls (S. Zia, Cody, & O'Boyle, 2000). Konczak et al. (2007) found PD patients to have a 92-166% increase in motion detection times compared to the healthy controls (Konczak, Krawczewski, Tuite, & Maschke, 2007). While these studies demonstrated impairment in proprioceptive acuity, some studies show altered cortical processing of proprioceptive afferents in PD (Contreras-Vidal & Gold, 2004; Lewis & Byblow, 2002; Seiss, Praamstra, Hesse, & Rickards, 2003). Transcranial magnetic stimulation studies on PD patients showed reduced intra-cortical inhibition in the flexor carpi radialis and extensor carpi radialis areas with changes in static wrist position and also during passive wrist movement (Lewis & Byblow, 2002). Similarly, studies on proprioception based EEG-potentials, elicited by passive index finger flexion have shown altered sensory cortex activation at longer latencies in PD (Seiss et al., 2003). These results suggest that proprioceptive afferents have an abnormal influence on corticomotor excitability in PD patients. Behavioral studies have also suggested that PD patients have deficits in the central processing and integration of kinesthetic signals, which will result in the incorrect assembly of multiple sensorimotor inputs into a motor plan (Contreras-Vidal & Gold, 2004). All these studies clearly demonstrate proprioceptive impairment in PD. This proprioceptive impairment may in turn further influence the motor impairments.

Effects of levodopa medication on proprioception

Patients with Parkinson’s disease typically receive dopamine replacement therapy as an established standard of care. The effects of anti-parkinsonian medications on proprioceptive and haptic acuity has been tested before (Konczak et al., 2007; Li, Pickett, Nestrasil, Tuite, & Konczak, 2010; Maschke et al., 2003). Maschke et al. (2003) found in a passive position sense discrimination task that patients with PD do not show significant correlation between the

number of correct responses and the daily levodopa-equivalent dose. In a different study, Konczak et al (2007) found similar effects of levodopa-equivalent dose in passive motion sense discrimination task. The angular displacement required to detect passive motion had an insignificant correlation with levodopa-equivalent dose. The differences on haptic perception between the medication ON state and medication OFF state was tested in PD patients by Li et al (2010). They found anti-parkinsonian medications reduced haptic detection thresholds by approximately 15% in the ON state compared to OFF state indicating an improvement in haptic perception with medications. Although, they found PD patients to have more sensitivity to haptic detection with dopamine replacement therapy, it was still reduced when compared to healthy subjects. Based on these studies, it is evident that PD medications may have an ameliorating effect of proprioceptive function, but still there is room of improvement in proprioceptive function.

Training the proprioceptive sense

Proprioceptive function can be enhanced in healthy humans and stroke survivors

Proprioceptive training is a form of intervention that targets the improvement of proprioceptive function, focusing on the somatosensory signals such as proprioceptive or tactile afferents in the absence of inputs from other modalities such as vision (Aman, Elangovan, Yeh, & Konczak, 2014). Such somatosensory training while enhancing proprioceptive function can result in concurrent motor learning. This concurrent motor learning will manifest as motor performance improvements (Beste & Dinse, 2013). Several studies have evaluated the effects of proprioceptive training in improving proprioceptive function as well as motor performance. Proprioceptive training employed by means of active limb movements are shown to be more effective in improving proprioceptive function in healthy adults than those that utilizes passive limb movements (Aman et al., 2014; Beets et al., 2012; Wong, Kistemaker, Chin, & Gribble, 2012). In a

systematic review, Aman et al (2014) found proprioceptive training to improve proprioceptive function by about 26% on average across 14 studies. Proprioceptive training in stroke patients showed improvements in movement accuracy during a tracking task indicating a somatosensory training can transfer improvements to a motor task (Cordo et al., 2008). Long term proprioceptive training in stroke (Dechaumont-Palacin et al., 2008) has been shown to alter cortical activity in somatosensory and sensorimotor processing areas. Dachaumont-Palacin et al (2008) found changes in the supplementary motor area, prefrontal cortex and contralesional inferior parietal cortex, secondary sensory cortex and ventral premotor cortex after 4 weeks of proprioceptive training in stroke patients indicating behavioral improvements are associated with functional changes in the cortex. These studies show that proprioceptive training results in both behavioral improvements such as enhanced proprioceptive and motor function, and physiological improvements such as cortical plasticity.

The term proprioceptive training has been used for a diverse range of behavioral treatments in the literature (Aman et al., 2014). Most often the term is used for any form of training that is even remotely associated with improving proprioceptive function. In a strict form of the definition, proprioceptive training should involve isolated activation of somatosensory afferents such as proprioceptive and tactile afferents. But activation of proprioceptive afferents requires limb movement as proprioception is innately linked with motor control. One must be mindful that proprioceptive training is actually a proprioceptive-motor training as it requires limb movements. In this study, proprioceptive training includes active limb movements with the use of visual feedback through virtual environment and it is a form of *visual proprioceptive motor training*. While the term visuo-proprioceptive training is used throughout the dissertation, it actually refers to visuo-proprioceptive motor training.

Proprioceptive training in Parkinson's disease

Given the beneficial effects of proprioceptive training in healthy adults and in

stroke population (for a review see Aman et al.; 2014), and the extensive evidence for proprioceptive deficits in PD (for a review see Konczak et al, 2009), people with PD are suitable candidates for proprioceptive training.

Somatosensory training in the form of whole body vibration to improve posture has been studied in PD. However, results demonstrate inconsistent effects of whole body vibration on postural control in PD patients (Chouza, Arias, Viñas, & Cudeiro, 2011; Ebersbach, Edler, Kaufhold, & Wissel, 2008; Haas, Buhlmann, Turbanski, & Schmidtbleicher, 2006). While vibration on limb segments may influence proprioceptive function, whole body vibration may also target additional sensory systems such as the vestibular apparatus. Ebersbach et al (2008) found improvements in balance after 3 weeks of whole body vibration training. In contrast, Haas et al (2006) did not find any significant improvements in balance after whole body vibration training.

A sensory training with the focus on proprioception of the upper limb has not been studied in PD, although upper limb function and fine motor control is also compromised in PD. There are no current data indicating whether and to what extent proprioceptive function can be restored through somatosensory training in PD. Moreover, we have no knowledge if a training-induced improvement in somatosensory function translates to improved motor function. While research on healthy humans has established that adaptive motor learning induces plastic changes in somatosensory as well as motor cortical areas (for a review see Ostry and Gribble (2016)), we do not know this for patients with PD. Finally, and important from clinical point of view, we have no knowledge, if learning effects transfer or generalize to other functional tasks. Therefore, this dissertation seeks to address the following questions:

1. Does visuo-proprioceptive training enhance proprioceptive function in people with PD?
2. Does visuo-proprioceptive motor training of small-amplitude continuous movements requiring spatial precision generalize to control of discrete movement within the same joint-degree of freedom? That is, is there

evidence for a local sensorimotor transfer?

3. Does such visuo-proprioceptive motor training improve control in a functional hand writing task requiring multiple joint degrees of freedom of the wrist/hand complex? That is, is there evidence for a more global sensorimotor transfer?

Specific aims

Aim 1: To document that people with PD will show evidence of visuomotor learning and improved spatial accuracy of volitional wrist movements. Using a wrist robotic exoskeleton, people with PD will receive training in a continuous movement task that requires wrist flexion-extension. A virtual-visual environment coupled to the robot provides relevant visual feedback. Showing a significant decrease in the cumulative spatial error and related kinematic measures before and after training will verify this aim.

Aim 2: To test the hypothesis that visuo-proprioceptive training can enhance proprioceptive function in people with PD. Wrist position sense acuity will be evaluated using a passive position sense discrimination task before and after training. Showing a significant decrease in wrist position sense acuity after training as measured by psychophysical just-noticeable difference thresholds will verify this aim.

Aim 3: To test the hypothesis that visuo-proprioceptive training shows local transfer to an untrained motor task requiring the same joint degree of freedom. The spatial accuracy during the execution of untrained discrete wrist pointing movements will be evaluated. Vision will be blocked to facilitate use of proprioceptive feedback and feedforward control. Showing a significantly decreased spatial motor precision error in people with PD will verify this aim.

Aim 4: To test the hypothesis that visuo-proprioceptive training will generalize to

a functional handwriting task that requires the use of multiple joint degrees of freedom of the wrist/hand complex. Spatial accuracy of tracing a line and tracking a cursor moving on a line will be evaluated in a battery of handwriting tests both before and after training. Showing that training led to a significant decrease in the spatial error with respect to tracing and tracking will verify this aim.

Methods:

Research participants

Thirteen patients with idiopathic PD (primary Parkinsonism) were identified and recruited for the study. Research protocol was reviewed and approved by Institutional Review Board at University of Minnesota. All patients were informed and voluntarily consented to participate in the study. Patients were recruited based on the following selection criteria. *Inclusion criteria:* 1) patients with primary Parkinsonism, 2) modified Hoehn and Yahr rating of 3 or below, 3) Mini Mental Status Exam score of 24 or above and 4) able to walk. *Exclusion criteria:* 1) Severe arm rigidity, 2) Severe resting tremor of the arm, 3) “on-off” fluctuations with PD medications, 4) Levodopa induced dyskinesias, 5) depression, 6) action tremor, 7) dystonia, 8) cognitive deficits, 9) history of neurological disorders other than PD, 10) any musculoskeletal disorders involving the upper limb and 11) visual deficits. All patient demographic data are shown in Table 1.

Research protocol and design

All patients visited Human Sensorimotor Control Lab twice within 7 days to complete the study requirements (see **Figure 1**). All PD patients were tested “*on*” medications as PD medications enhance proprioception and any behavioral treatment would supplement medication effects. On Day 1, all research participants were evaluated for disease severity using the *motor examination* sub section of *Unified Parkinson’s Disease Rating Scale* (UPDRS), and for cognitive functions using *Mini Mental Status Exam* (MMSE). To allow for consistency,

Table 1. Patient demographic data

ID	Age (in years)	Gender	Disease duration (in years)	UPDRS score III (Motor evaluation)	MMSE score	Most affected side	Dominant side	Levodopa equivalent dosage (in mg)
1	65	F	5.0	26	28	Left	Right	300
2	55	M	3.4	13	29	Right	Right	300
3	66	M	2.9	10	25	Right	Left	300
4	49	F	0.8	5	30	Left	Left	200
5	74	M	0.4	36	28	Right	Right	0
6	54	F	0.9	16	29	Right	Right	0
7	61	M	10.0	28	26	Left	Right	550
8	64	F	2.3	9	30	Right	Right	225
9	67	F	2.4	11	29	Right	Right	300
10	67	F	2.3	8	30	Right	Right	300
11	55	F	5.4	9	28	Right	Right	800
12	63	F	3.3	8	29	Right	Right	300
13	62	M	2.9	13	30	Left	Right	450

UPDRS and MMSE evaluations were performed on all participants by the same researcher who is a physical therapist. Immediately after the clinical evaluations, participants were evaluated for baseline proprioceptive acuity and motor performance. All these evaluations took approximately about 2 hours for completion in all participants. All participants were encouraged to plan for a second visit to the lab within 1-7 days for completing the research requirements.

On their second visit, participants were evaluated for proprioceptive acuity, motor performance, visuomotor performance, and handwriting, both before and after proprioceptive training. The whole procedure on day 2 took about 3 hours for completion in all participants. A separate age-matched healthy control group [Age (mean ± SD): 66.7 ± 6.3 years; 4 males and 8 females] completed the proprioceptive training task and was evaluated only in proprioceptive acuity and motor performance before and after training.

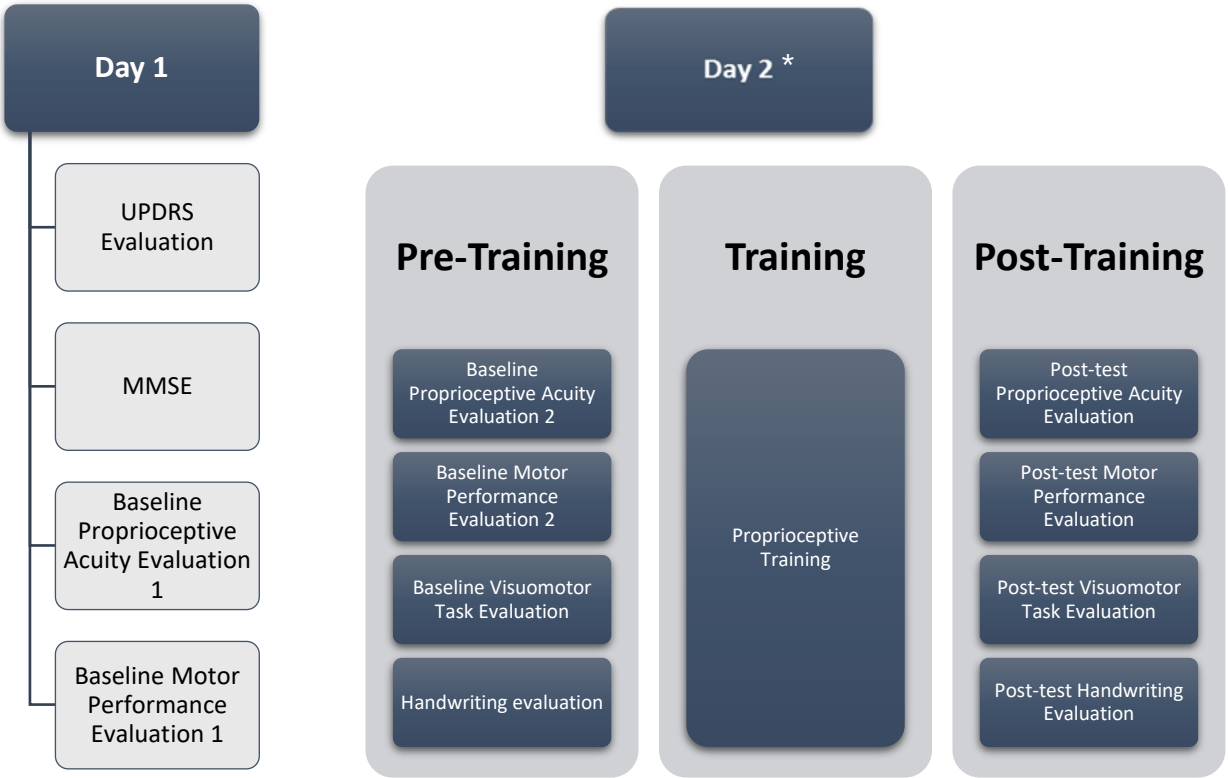

Figure 1. Research protocol. * - Day 2 represents the second visit which was within 1-7 days of Day 1.

Wrist robotic device

The wrist robot (**Figure 2**) is a three degree-of-freedom exoskeleton robot described elsewhere (Masia, Casadio, Sandini, & Morasso, 2009). This wrist robotic device allows for full range of motion of the human wrist. It consists of a hand grip and a forearm splint with Velcro straps to secure the forearm of the participant in constant position. This haptic robot is a fully backdriveable system with capability to deliver torque levels comparable to maximum human torque levels in at the human wrist. The range of motion (ROM) allowed by robot in all three degrees of freedom matches the ROM of human wrist: 65°/70° of Flexion/Extension (FE), 15°/30° of Adduction/Abduction (AA), 90°/90° of Pronation/Supination (PS), in a typical human subject, vs. ±72° of FE, 45°/27° of AA and ± 80° of PS, in the wrist robot. 4 brushless motors powered the robot to provide a wide haptic rendering and compensate for the weight and inertia of the device. It can deliver precise haptic, position, and velocity stimuli at the wrist joint while being able to accurately encode the wrist position. Angular rotations on the all three axes can be measured by means of digital encoders with a resolution of 4000 quadrature-counts/turn.

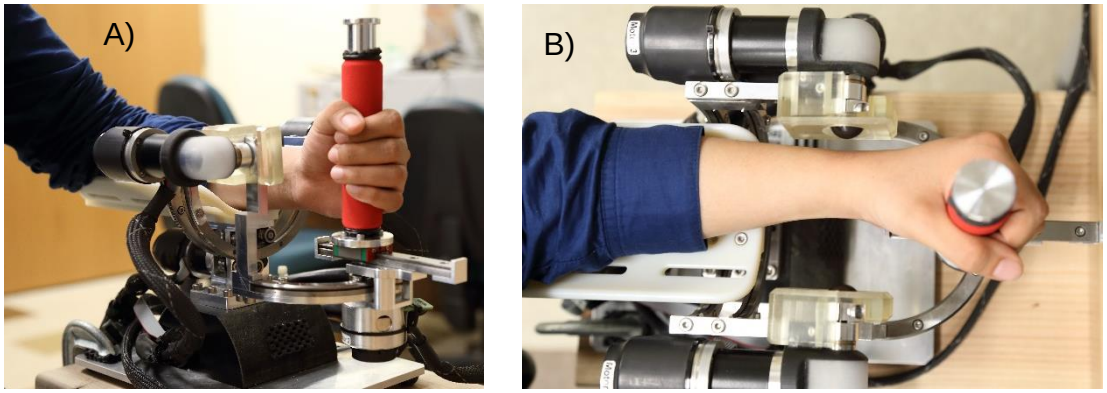

Figure 2. Wrist robot. **A**) Antero-medial view of the wrist robot with a participant's forearm positioned in the support splint, their hand holding the hand grip. **B**) Superior view of the wrist robot with participant's forearm supported on the forearm splint.

The system is integrated with a virtual reality environment (VR) to provide visual

feedback to the user about his/her wrist position during the execution of training task. A custom-written software routine using SIMULINK in MATLAB controlled the wrist robot. The control architecture is based on three control loops: 1) an inner loop, running at 7 kHz in the motor servos; 2) an intermediate loop running at 1 kHz on a real-time kernel that updates the current reference of each motor; 3) an external loop running at 100 Hz for the visual virtual reality and user interface. The desktop computer is equipped with an Analog and Digital I/O PCI card (Sensoray, model 626), in which the following channels were used: a) Four 14-bit D/A channels for commanding the reference values of the motor currents; b) Four 24-bit counters for receiving the repetition signals of the digital encoders.

Procedure

Wrist visuo-proprioceptive training

Using the virtual reality environment in combination with the wrist robot, the visuo-proprioceptive training required participants to use vision and proprioception to balance a virtual ball on a virtual table by making precisely controlled, small amplitude wrist flexion/extension movements based on visual and haptic feedback received. During training, participants sat comfortably in a chair with the forearm of their most affected side resting on the support splint of the wrist robot (**Figure 3**). When participants flexed or extended their wrist on their most affected side, the virtual table tipped either to the left or to the right respectively, resulting in the virtual ball moving as it would happen in real world. In each training trial, the goal for the participant was to halt the ball within a circular target and to hold it there for 5 seconds. A training trial is considered complete, when the participant balances the ball inside the target for about 5 targets. On completion of the trial, a new virtual target was shown in the monitor. A training trial is considered as a successful trial when the participant can hold the ball inside the target for about 5 seconds within 45 seconds from the start of the trial. In a training block (here referred to as a particular level of task difficulty), a trial would have a balanced wrist position of either 10°, 15° or 20° flexion from

the neutral joint position correspond to a fully balanced, horizontal position of the virtual board where the ball would not move. When a participant accomplishes a successful trial in each of these three balanced wrist flexion positions for a particular level of task difficulty, the training will progress to the next level of difficulty.

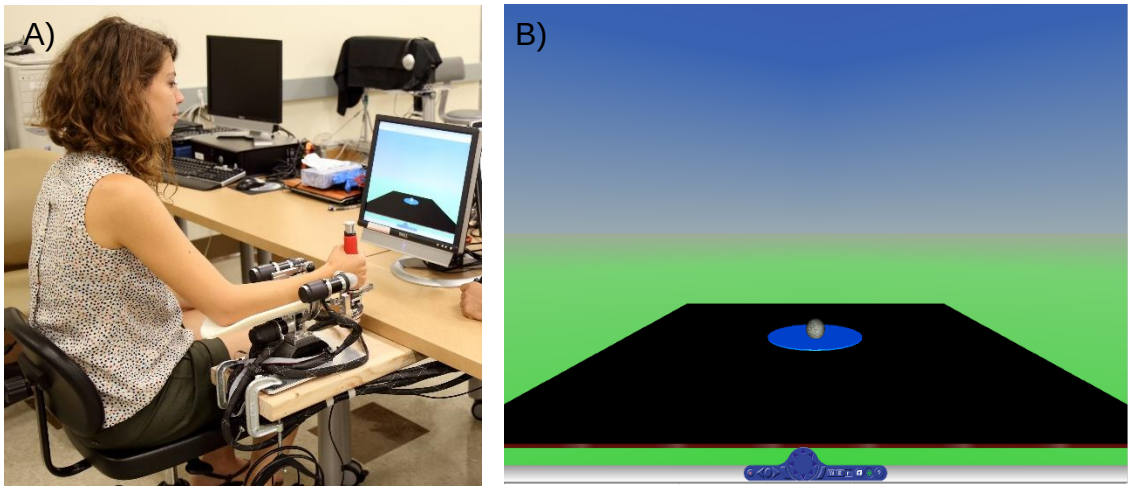

Figure 3. A) A research participant using the wrist robot to complete the training task. The participant's forearm is rested on the forearm support splint during the training task. **B)** A screenshot of the virtual reality environment as seen by the participant. When the participant moves their wrist to the left, the black surface tips to the left, and the gray ball on top of the virtual table tips to the left.

The level of difficulty was defined by manipulating mass of the ball, ball velocity, dampening force on the ball velocity and gravity in the virtual environment. A single unit advance in the difficulty level is constituted by the following changes: 1) 25% increase of gains in virtual ball mass, 2) 20% increase of gains in ball velocity, 3) 60% increase of gains in gravity of the virtual environment, and 4) 8% decrease of gains in dampening force. Every participant completed a total of 60 training trials. Total number of training trials was the same for all participants, but the level of task difficulty they could achieve and experience, would vary between participants depending on their performance in each trial. Participants took about 30 minutes (Range: 13 – 53 minutes) to complete the 60 training trials. If the

participant was successful in every single trial, he/she would have achieved a maximum of difficulty level 20. Conversely, if the participant was unsuccessful in every single trial, he or she would have stayed at level 1 at the first wrist position. Participants were allowed a 5-minute break after every 30 trials.

Assessment of sensorimotor learning and motor transfer

Evaluation of visuomotor learning in the training task

Visuomotor performance was evaluated using the training trials to identify the improvements achieved by each participant during training. The participants completed 3 trials of the virtual reality based visuo-proprioceptive training task at a difficulty level of 15. Participants were instructed to hold the ball in the target by moving the wrist to a balanced position, until a new target is seen in the virtual reality monitor. All participants performed the visuomotor assessment trials in a fashion similar to performance of training trials. Participants wrist angular displacement and time taken to complete the trials were recorded. Participants were given instruction and demonstration of the task by the researcher before the beginning of evaluation.

Evaluation of proprioceptive learning

A *psychophysical forced-choice paradigm* employed using the wrist robot determined the wrist proprioceptive acuity, i.e. the ability of participants to discriminate two wrist positions. During proprioceptive acuity evaluation, participants were instructed to sit in an upright position with their forearm in mid-prone position on the support splint and their hand loosely holding the hand grip of the wrist robot. Participants wore a pair of opaque glasses and headphones to minimize extraneous sensory cues. In each trial, the robot passively moved the participants' wrist to a 15° flexion position (standard stimulus), hold it there for 2 seconds, moved back the starting position and then to another flexion position always greater than 15° (comparison stimulus) (**Figure 4**). After every trial, the participants were asked to identify the stimulus that was farthest from the starting position.

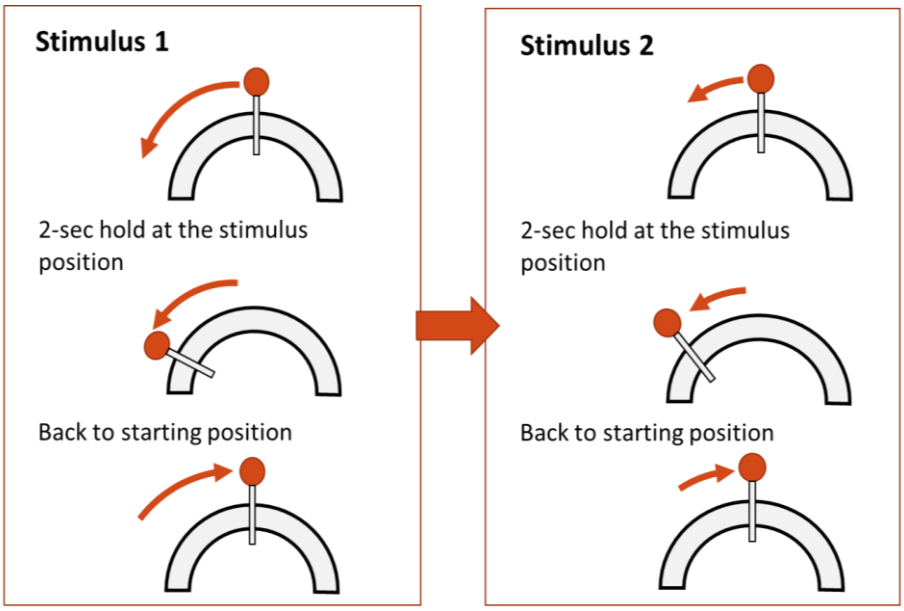

Figure 4. Schematic description of wrist position stimulus presentation for proprioceptive acuity evaluation.

Based on the participant's response, the difference (*stimulus difference size*) between the standard and the comparison stimulus for the subsequent trial was determined using the *psi marginal method* (Prins, 2013), an adaptive psychophysical algorithm. The adaptive algorithm increased or decreased the stimulus difference size for the subsequent trial, in such a way that stimulus difference size monotonically converges to the position sense *just-noticeable difference (JND) threshold*. The order of the standard and comparison stimuli presentation was randomized. In all the trials, the wrist robot moved the wrist at a constant velocity of 6°/s. The participants were given rest periods of 1-2 minutes after 15 trials to ensure an active focus on the task. The procedure was repeated for 30 trials with subject responses and the stimulus difference sizes being recorded for every trial. Participants were provided with a couple of familiarization trials at the beginning of evaluation.

Evaluating transfer of learning in a wrist pointing task

Motor performance was evaluated in a discrete wrist movement pointing task in the absence of visual feedback. For this task, the wrist robot passively moved the participants' wrist to a 15° target position, held it for 2 seconds and moved back

to the starting position. The participant is instructed to actively move their wrist to the previously presented target position. They were allowed back and forth movements, until they feel they have reached the target position. On reaching the target position, the participants were instructed to hold on to that position, until the robot records the position and moves their wrist back to the starting position. All participants wore a pair of headphones that played pink noise and a pair of opaque glasses, as they did in proprioceptive acuity evaluation. This procedure was repeated for 20 trials. The angular wrist position was recorded during the target position and participant replicated position. Participants were provided with a couple of familiarization trials at the beginning of evaluation.

Evaluating transfer of learning in a functional handwriting task

To evaluate the transfer of learning effects to a functional task, participants were evaluated in a battery of handwriting tasks, that includes tracing an arc, straight and spiral lines, and tracking a cursor moving on an arc, straight line and spiral line. A Cintiq® Companion 2 tablet (manufactured by Wacom Co., Ltd., Japan) paired with an active stylus was used for the handwriting task. All participants used their most affected side to complete the task, irrespective of whether their most affected side is their dominant side or not. In the tracing task, participants were required to trace the shape seen in the monitor at their own pace using the active stylus, whereas tracking task required the participants to track the cursor that moved at a specific rate of 0.5 Hz. Arc and straight line tasks required back and forth movements of six repetitions. The first and last repetitions were removed from further analysis to avoid any inconsistencies at the beginning of the movement. Spiral line task required tracing or tracking a cursor moving in a concentric spiral line starting at the outer edge and moving all the way in to the core of the spiral. In all these tasks, the contact point of the stylus with respect to the tablet screen was recorded. It took about 5-7 minutes for the participants to complete this task. Participants were provided with clear instruction and demonstration by the researcher before the beginning of evaluation.

Measurements

Spatiotemporal measures of visuomotor training

Participants' wrist displacement was recorded during the visuomotor performance task. This task is aimed to evaluate the direct effects of training on the training task. Participant's angular displacement during the assessment trials were used to compute spatial measure of their performance. Absolute angular displacement across time was used to determine the area under the curve across time for each trial. Mean displacement area under the curve across the trials served as *cumulative spatial error (CSE)*. This CSE represented the total angular displacements required to achieve the target. CSE represented spatio-temporal measure of the extent of displacements. Greater the extent of displacements, greater CSE and lesser the efficiency. To understand the temporal and spatial effects irrespective each other, the *time for trial completion* and *task-related functional range of motion (F-ROM)* were also computed.

Proprioceptive just-noticeable difference thresholds

Participant responses recorded after each trial during the proprioceptive acuity evaluation was used to determine the correct response rate for various stimulus difference intervals. The correct response rate and the stimulus difference sizes were fitted using a logistic Weibull function. Based on these fitted values, the smallest stimulus difference required to discriminate the standard stimulus position from the comparison stimulus position was computed. This smallest stimulus difference was used as *Just-noticeable Difference* (JND) thresholds (Prins, 2013). In this study, JND threshold for each participant indicated the minimum difference in wrist flexion position required to discriminate a stimulus from the standard stimulus of 15° wrist flexion. This JND threshold served as a measure of the participant's position sense acuity.

Spatial errors during wrist pointing movements

In the motor precision test, wrist flexion angles were recorded during the target stimulus presentation and the participant replicated position. Absolute angular

difference between the target position and the patient replicated position were calculated for each trial. Mean absolute angular difference across trials were computed for each participant. This mean of absolute angular difference across trials served as *Motor Precision Error* for each participant. Motor precision error represented the participant's ability to motorically replicate a perceived position in the absence of visual feedback. This motor precision error will serve as a measure to evaluate transfer of learning from a continuous, visuomotor learning task designed to challenge proprioceptive system to a discrete non-visuomotor task.

Spatiotemporal errors in functional handwriting

During the tracing and tracking tasks, the stylus contact positions achieved by the participant with respect to the target was recorded. Using the stylus contact position data and the target tracing or tracking trajectory, resultant *root mean-squared error* measures were derived based on horizontal (x) and vertical (y) displacement ($RMSE_{Track}$, $RMSE_{Trace}$). These RMSE measures represent the ability to accurately move the stylus over the required trajectory either at a self-generated pace (tracing task) or at a required pace (tracking task). Furthermore, the *time-to-completion* was evaluated to identify any systematic differences in frequency of tracing before and after training.

Results:

Patients with PD demonstrate learning related motor performance changes after training

Cumulative spatial error decreased with training

Performance in the continuous visuo-proprioceptive motor task was evaluated on two instances: at baseline and after training. One of the participants was unable to complete the visuomotor assessment trials. Since the assessment was performed at a higher difficultly level compared to the training, this patient was

unable to hold the ball in the target position even after 607.9 seconds. The data collected from this patient was omitted from further analysis. Mean CSE during baseline (**Figure 5**) across 12 participants was 1.45 rad*sec (SD: 0.61 rad*sec; Range: 0.89 – 2.89 rad*sec). Mean CSE across 12 participants after training (**Figure 5**) was 0.86 rad*sec (SD: 0.50 rad*sec; Range: 0.49 – 2.21 rad*sec). As shown in **Figure 5**, the CSE shows a reduction with training indicating training related improvements. A repeated measures ANOVA was performed to understand the effects of training on CSE. Repeated measures ANOVA showed that CSE (**Figure 7**) significantly reduced with training ($F_{1,11} = 19.14$, $p = 0.001$). These results indicate show that training related enhancements in the spatio-temporal measure.

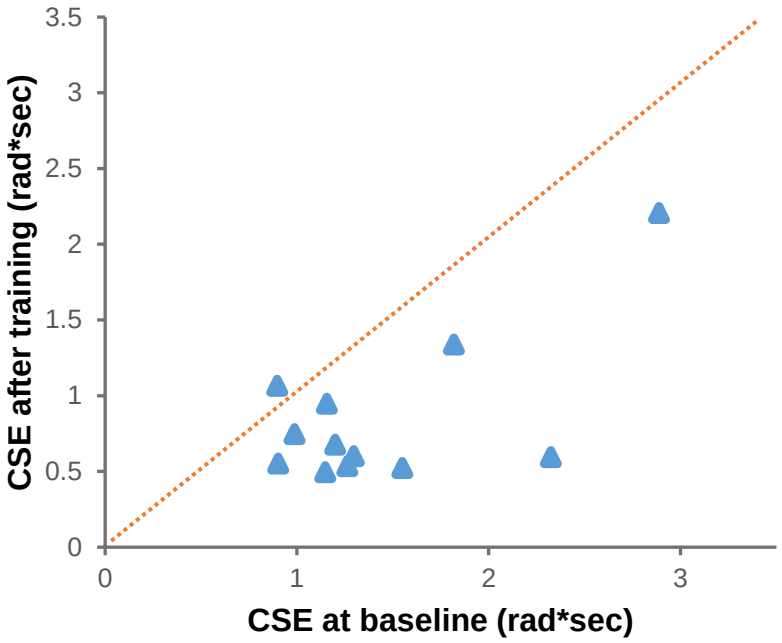

Figure 5. Cumulative spatial error across during baseline testing and after training. Each data point represents each participant's CSE at baseline and after training. The orange dotted line represents the line of equality indicating no change due to training. The black dashed line represents the linear regression fit. Note that most participants show a decrease in CSE indicating an improvement in wrist motor performance. One of the participants retained the baseline spatial error after training.

Functional range of motion increased with training

Functional range of motion (F-ROM) was measured during the baseline and after training visuomotor assessment trials. Mean F-ROM across 12 participants in the baseline condition (**Figure 6**) was 9.83° (SD: 2.11°; Range: 6.05° - 13.27°). Mean F-ROM across 12 participants after training (**Figure 6**) was 12.93° (SD: 2.83°; Range: 9.49° - 19.43°). As seen in **Figure 6**, F-ROM increased in all participants with training. To understand the effects of training on F-ROM, a repeated measures ANOVA was performed. F-ROM (**Figure 7**) significantly increased with training ($F_{1,11} = 10.28$, $p = 0.008$). These results indicate that training resulted in an increase in F-ROM across all participants by about 31.5%.

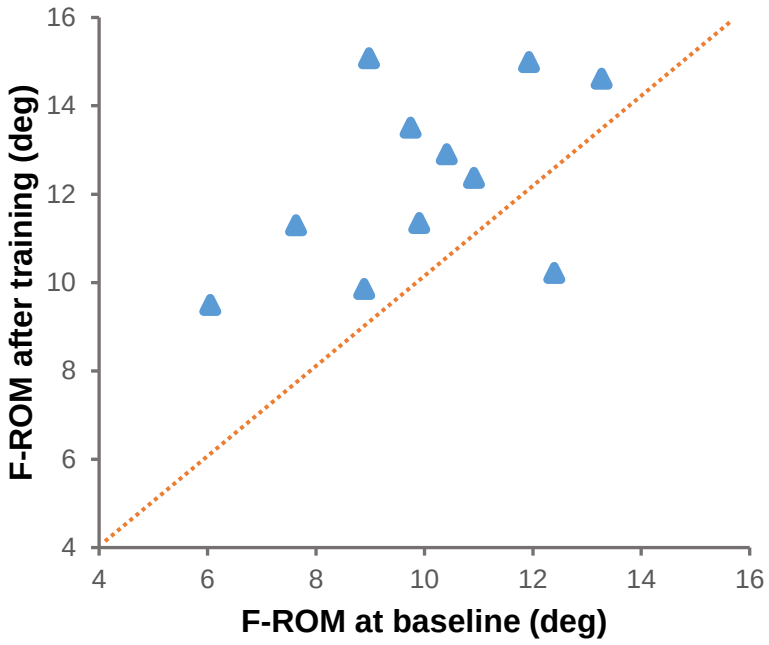

Figure 6. Functional range of motion during visuomotor assessment trial at baseline and after training. Each data point represents each participant's F-ROM at baseline and after training. The orange dotted line represents the line of equality indicating no change due to training and the black line represents linear fit. Except one participant, most participants show an increase in F-ROM with training.

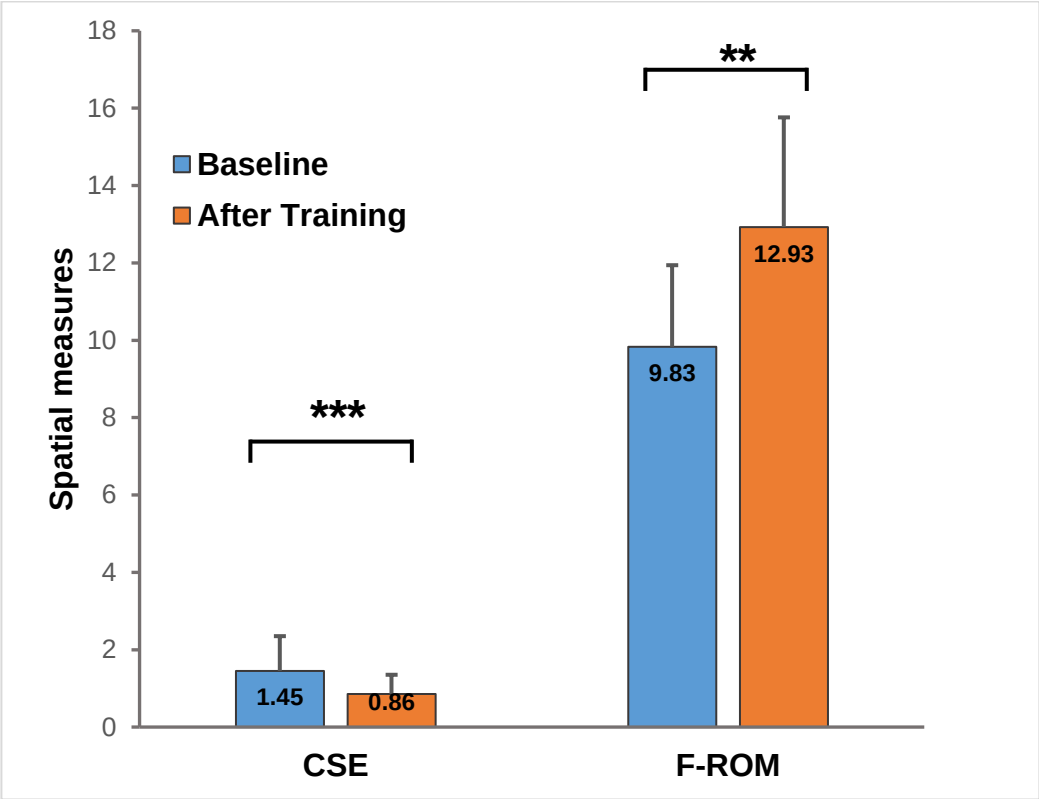

Figure 7. Group means in cumulative spatial error and functional range of motion in visuomotor assessment trials before and after training. CSE is expressed in rad*s and F-ROM is expressed in deg. Error bars indicate one standard deviation. *** - p=0.001, ** - P < 0.01.

Time-to-trial completion reduced with training

The time taken for visuomotor assessment trial completion was evaluated to understand the temporal effects of training. On average, all participants took about 63.89 s to complete the assessment trials (**Figure 8**) before training (SD: 37.74 s; Range: 20.55 s – 151.16). After training, the time-to-completion across all participants (**Figure 8**) reduced to an average of about 29.25 s (SD: 18.18 s; Range: 9.3 – 66.81 s). **Figure 8** shows systematic differences in time taken for trial completion across all participants. A repeated measures ANOVA between the time duration taken for completion before and after training showed significant decrease in time-to-completion after training ($F_{1,11}$ = 13.33, p = 0.004).

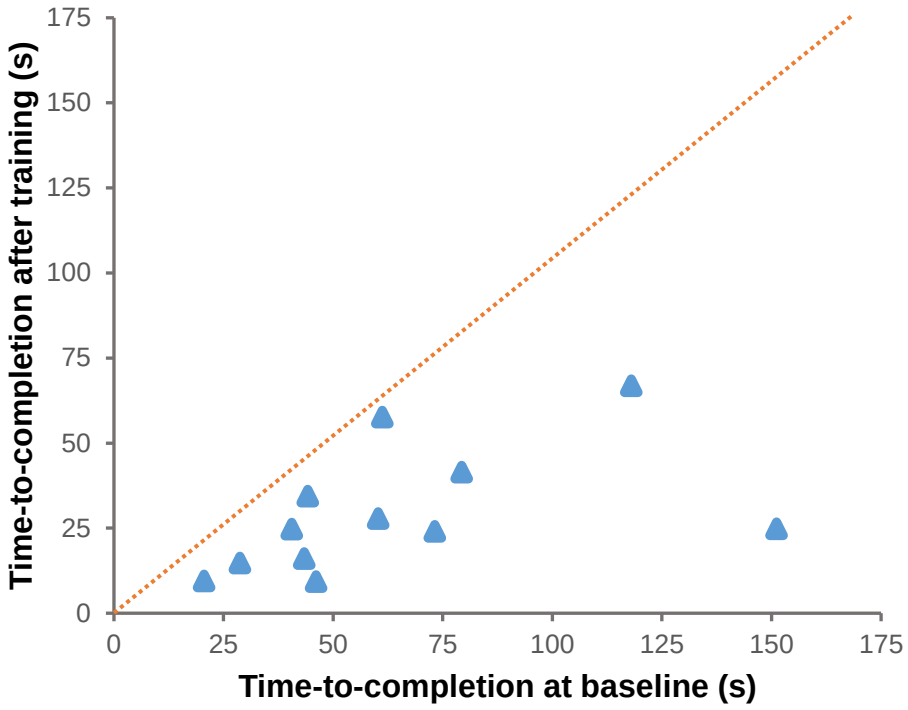

Figure 8. Time to trial completion in visuomotor assessment at baseline and after training. Each data point represents each participant's trial completion time before and after training. The orange dotted line represents line of equality indicating no change due to training and the black dashed line represents linear regression fit. Note how all participants show a decrease in time for trial completion after training. One of the participants remain close to the baseline value but they show a decrease in the time-to-completion compared to the baseline.

In summary, visuomotor performance measures show training related enhancements in all the variables. With training, participants took less time to complete the assessment trials, and moved their wrist with larger F-ROM, resulting in a lesser CSE, demonstrating specific improvements in the training task.

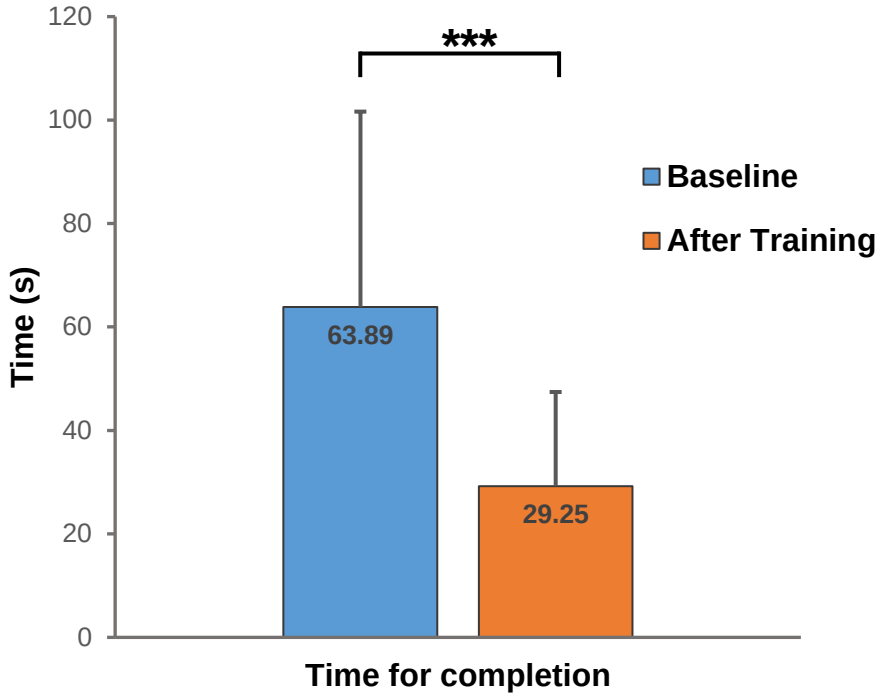

Figure 9. Group means in time to completion of visuomotor assessment trial completion before and after training. Error bars indicate standard deviation. *** - p = 0.004.

Visuo-proprioceptive training improved proprioceptive function

Just noticeable difference thresholds were measured at three distinct times: baseline 1, baseline 2 and after training. The mean JND threshold of all participants at baseline 1 was 1.61° (SD: 0.50°; Range: 1.01° - 2.70°) and 1.56° (SD: 0.42°; Range: 1.12° - 2.68°) at baseline 2 (**Figure 10**). A repeated measures ANOVA performed between the two baseline measures found no statistically significant difference between the JND measures at baseline 1 and baseline 2 ($F_{1,12} = 0.294$, $p = 0.598$). Because there were no systematic differences between the two baseline measures, an average of the two baseline JND threshold was computed for each participant to serve as a baseline JND threshold to evaluate the effects of training on proprioceptive acuity.

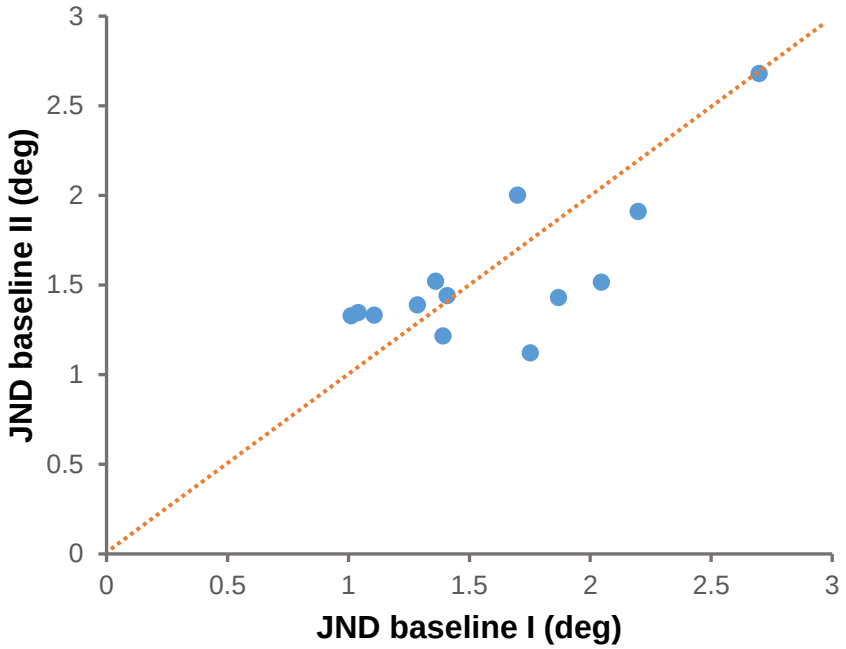

Figure 10. Just-noticeable difference thresholds across all participants during the two baseline evaluations. Each data point indicates each participant's JND threshold during baseline 1 and baseline 2. The orange dotted line indicates the line of equality indicating no change due to training. Note how all the participants are centered around the line of equality indicating no systematic differences in thresholds occurring between the two baseline evaluations.

Mean of the average baseline JND thresholds (**Figure 11**) for all participants was 1.58° (SD: 0.43°; Range: 1.17° - 2.69°). Mean of the JND thresholds after training for all participants (**Figure 11**) was 1.14° (SD: 0.30°; Range: 0.70° - 1.99°). As seen in **Figure 11**, all participants show a decrease in JND thresholds after training. A decrease in JND thresholds indicate an improvement in proprioceptive function. To further understand the training related improvements in JND thresholds, a repeated measures ANOVA was performed between the average baseline JND threshold and JND threshold after training. JND thresholds after training (**Figure 14**) was significantly smaller and different from the average baseline thresholds ($F_{1,12} = 26.49$, $p < 0.001$). On average, JND

thresholds across all participants improved with training by about 27.7%. To understand the effects of baseline JND thresholds on the degree of improvement, a Pearson's product-moment correlation analysis was performed contrasting the average baseline JND against the absolute improvements in JND after training. The average baseline JND measure has a strong positive correlation with absolute improvements in JND with training ($R = 0.71$, $p = 0.006$). This demonstrates that a participant with a larger JND threshold at baseline shows the greatest improvements in the proprioceptive function. In summary, these results indicate the training resulted in highly significant improvements in the proprioceptive domain with larger gains in individuals with poor proprioception at baseline.

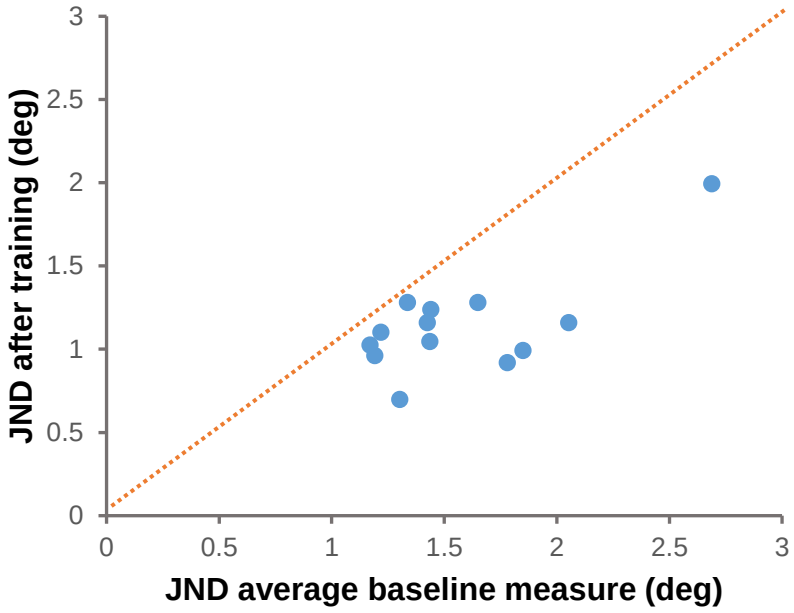

Figure 11. Just-noticeable difference thresholds across all participants during baseline and after training. Each data point indicates each participant's JND threshold during baseline and after training. The orange dotted line indicates the line of equality indicating no change due to training and the black dashed line indicates a linear regression fit. All participants are below the line of equality indicating training related improvements in JND thresholds.

Training generalized to untrained wrist pointing

The motor precision error was measured in three instances: baseline 1, baseline 2 and after training. Mean MPE across all participants in baseline 1 (**Figure 12**) was 2.50° (SD: 1.31°; Range: 1.29° - 5.46°). Mean MPE across all participants in baseline 2 (**Figure 12**) was 2.30° (SD: 1.17°; Range: 1.12° - 5.43°). As seen in **Figure 12**, there was no systematic difference in MPE between the two baseline evaluations, which was confirmed by a repeated measures ANOVA on the two baseline measures ($F_{1,12} = 1.96$, $p = 0.187$). An average of the two baseline MPE measures for each participant was used for comparison with MPE after training.

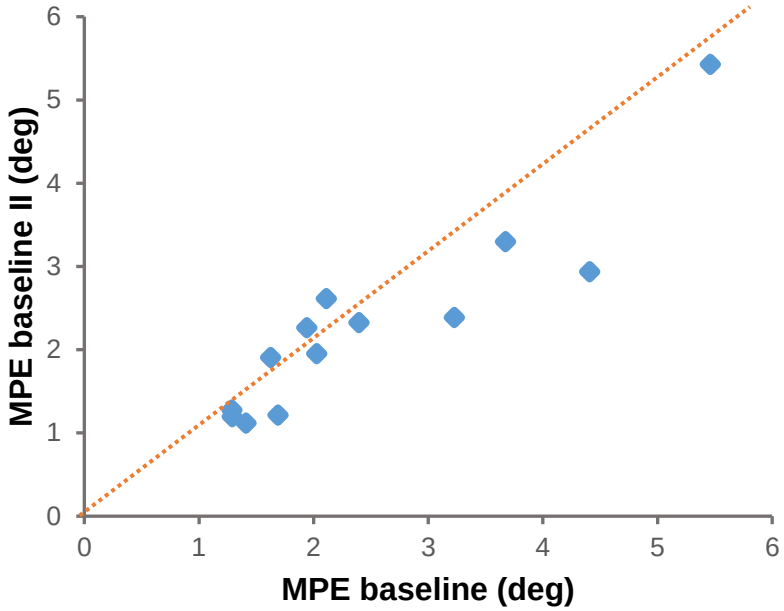

Figure 12. Motor precision error for both baseline conditions. Each data point represents each participant's MPE during baseline 1 and baseline 2. The orange dotted line indicates the line of equality indicating no change due to training. Note how most of the participants are clustered around the line of equality.

Mean of the average baseline MPE (**Figure 13**) across all participants was 2.40° (SD: 1.21°; Range: 1.24° - 5.44°). Mean MPE after training (**Figure 13**) across all participants was 2.40° (SD: 1.86°; Range: 0.86° - 3.53°). As seen in **Figure 13**, most of the participants improve in motor precision error. In order to

systematically evaluate the effects of training in motor performance, a repeated measures ANOVA was performed with the two variables – Average baseline MPE and MPE after training. MPE after training (**Figure 14**) was found to be significantly different and lower than the average MPE across all participants ($F_{1,12} = 5.38$, $p = 0.039$). On average across all participants, MPE improved by about 22.3%. On those participants who show improvements, MPE improved by about 31.4%. In order to understand the effects of baseline MPE on improvements in MPE, a Pearson's product-moment correlation analysis was performed. Average baseline MPE measure had a strong positive correlation with absolute improvements in MPE after training ($R = 0.78$, $p = 0.002$). This correlation shows that a participant with higher MPE at baseline benefits with largest improvements in MPE after training. These results indicate that training resulted in transfer of improvements in the sensorimotor performance with larger gains in individuals with poor motor performance at baseline.

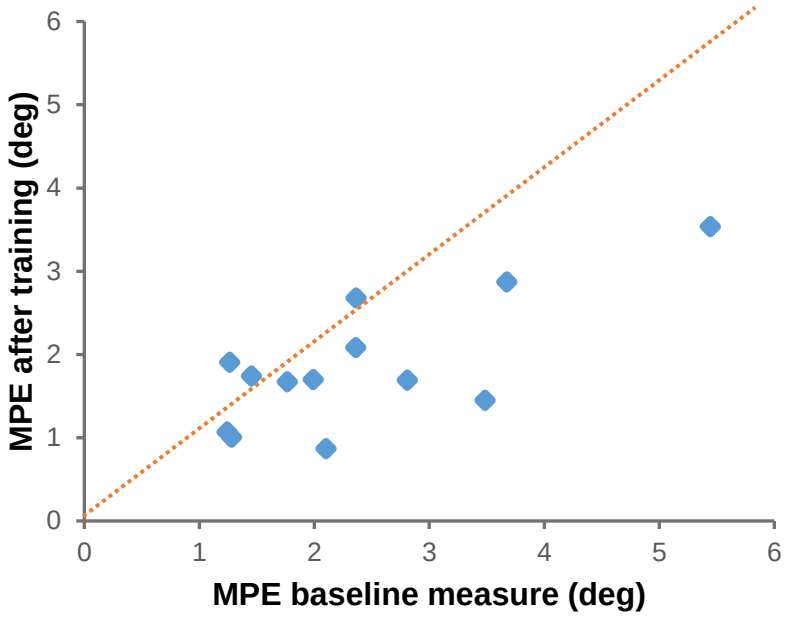

Figure 13. Motor precision error during the baseline and after training. Each data point indicates each participant's MPE during baseline and after training. The orange dotted line indicates the line of equality indicating no change due to training and the black

solid line indicates a linear fit. Note how most participants are below the line of equality indicating improvements in motor performance measure.

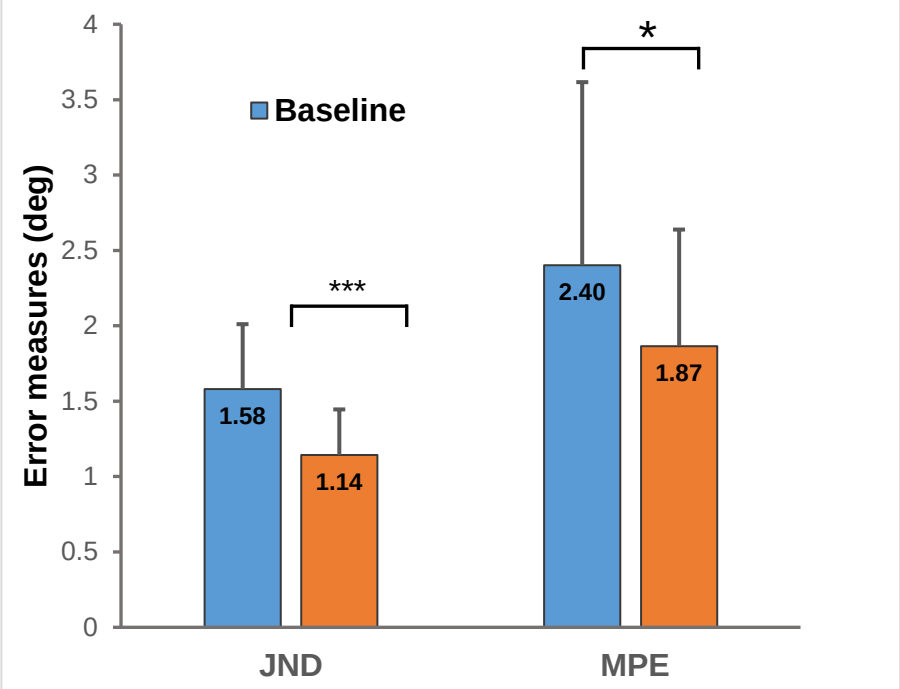

Figure 14. Group means for the just-noticeable threshold and the motor precision error before and after training. Error bars indicate standard deviation. *** - $p < 0.001$; * - $p < 0.05$.

Training does not transfer to the functional handwriting task

In the tracing tasks, RMSE of tracing and time taken for completion was evaluated in all participants at baseline and after training. Mean values across all participants are shown in the tables below. There were no systematic differences found in RMSE values and time-to-completion in all the tracing tasks with training. Repeated measures ANOVA was performed to identify any differences and yielded non-significant results in all the variables. On close observation, there are some participants who show differences in some variables but they do not show similar differences in all variables in all the tasks. Tracing tasks were

performed in participant generated pace. Since all the participants are clustered around the line of equality (Figures included in Appendix), it shows that there were no systematic differences in the rates at which these tasks were performed by each participant between baseline and after training. Overall, the participants do not show training related enhancements in the performance of the tracing tasks.

Table 2. Measures of accuracy in the tracing tasks.

Arc	(mean ± SD)	
	Baseline	After Training
$RMSE_{Trace}$ (mm)	0.36 ± 0.24	0.27 ± 0.13
Time-to-completion (s)	3.64 ± 1.64	3.23 ± 1.54
Straight line		
$RMSE_{Trace}$ (mm)	0.80 ± 0.32	0.89 ± 0.31
Time-to-completion (s)	1.63 ± 0.70	1.49 ± 0.63
Spiral line		
$RMSE_{Trace}$ (mm)	0.12 ± 0.06	0.13 ± 0.07
Time-to-completion (s)	41.93 ± 13.49	37.64 ± 10.07

In tracking tasks, RMSE with respect to the trace as well as to tracking cursor was evaluated along with the time taken for completing the tracking task. Mean values of all tracking task measurements across all participants are shown in the table below. Similar to tracing task measurements, tracking task measurements did not show any systematic differences across all participants or any systematic training related enhancements in the performance measures. Repeated measures ANOVA of all the variables contrasting the baseline values against the after training measurements did not show any significant differences in all the variables. Time taken for completion in all the tracking tasks were more clustered around the line of equality compared to the tracing tasks, given that the tracking tasks were performed at a constant rate of 0.5 Hz. Overall, participants do not

show any systematic training related enhancements in both tracing and tracking tasks.

Table 3. Measures of accuracy in the three tracking tasks.

Arc	(mean ± SD)	
	Baseline	After Training
$RMSE_{Trace}$ (mm)	0.35 ± 0.25	0.34 ± 0.28
$RMSE_{Track}$ (mm)	12.43 ± 11.98	8.89 ± 3.19
Time-to-completion (s)	2.73 ± 0.48	2.70 ± 0.56
Straight line		
$RMSE_{Trace}$ (mm)	1.05 ± 0.66	1.11 ± 0.93
$RMSE_{Track}$ (mm)	79.92 ± 1.17	80.62 ± 0.70
Time-to-completion (s)	3.81 ± 0.83	3.78 ± 0.87
Spiral line		
$RMSE_{Trace}$ (mm)	0.10 ± 0.04	0.13 ± 0.10
$RMSE_{Track}$ (mm)	3.87 ± 1.05	4.76 ± 3.82
Time-to-completion (s)	41.64 ± 2.31	42.78 ± 1.46

Relationship between proprioceptive and motor learning

Training resulted in enhancements of both proprioceptive function as well as motor performance in an untrained non-visuomotor task. In order to understand the relationship between the improvements in proprioceptive acuity and motor performance, a Pearson's product-moment correlation analysis was performed between the absolute improvements in JND threshold and MPE as a result of training. This analysis showed a medium correlation (R = 0.46) between the absolute improvements, but failed to reach significance (p = 0.11). A vector plot (**Figure 15**) of the absolute improvements in MPE and JND threshold contrasts

the individual variability in improvements in both these measures. Although most participants showed improvements in MPE, some participants did not improve in motor performance, which may influence the group correlation analysis. Improvements in JND threshold relative to the baseline contrasted against changes in MPE relative to the baseline also showed similar correlation results ($R = 0.36$, $p = 0.22$).

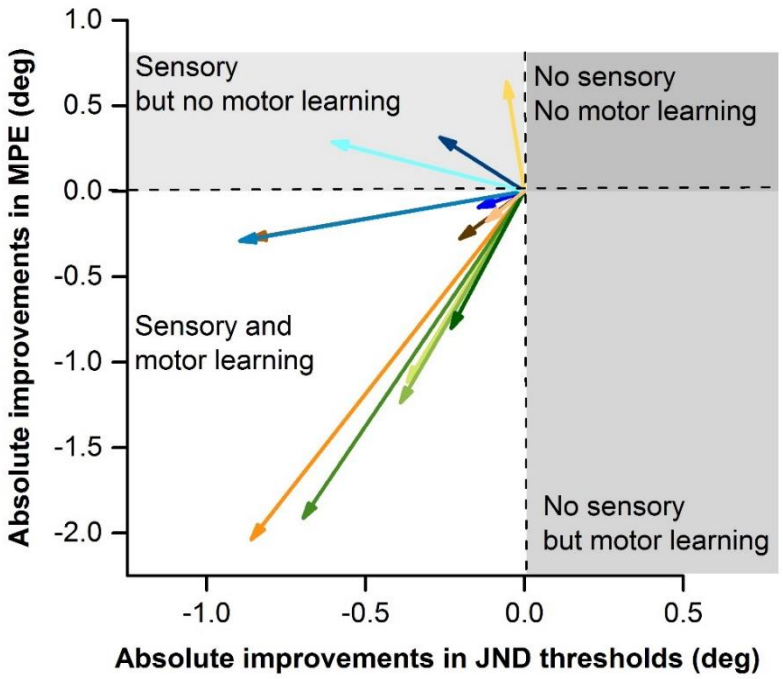

Figure 15. Vector plot showing absolute improvements in just-noticeable difference threshold and motor precision error in all participants. Each vector represents a participant's training-related change in JND threshold in the x-axis and their training-related change in MPE in the y-axis. A negative value represents improvement and a positive value represents a decrement. Note how all participants demonstrate sensory learning and most participants show motor learning.

Effects of disease duration, disease severity and medication on sensorimotor outcome measures

Age and gender did not systematically confound sensory, motor, visuomotor or

functional domain variable in the PD participants. Pearson's product-moment correlation analyses contrasting age and gender with dependent variables in this study yielded no statistically significant correlations.

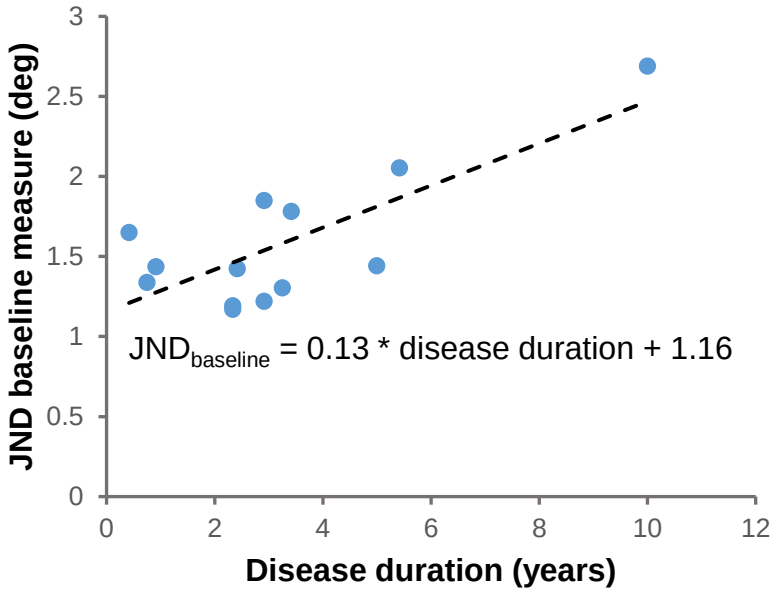

Figure 16. Effect of PD disease duration on just-noticeable difference threshold at baseline. Each data point represents a single participant's disease duration mapped against their JND threshold at baseline. Participant's disease duration had a strong positive and highly significant correlation with their JND threshold at baseline (R = 0.77, p = 0.002).

To understand the effects of disease duration on the evaluation measures, Pearson's product-moment correlation analyses were performed. Disease duration had a strong positive and significant correlation with JND threshold (**Figure 16**) at baseline (R = 0.77, p =0.002). Similarly, MPE at baseline (**Figure 17**) had a moderate positive and significant correlation with disease duration (R = 0.58, p = 0.05). This shows that the longer the participant's disease duration, the larger their JND thresholds and MPE were. A PD patient with longer disease duration had poor proprioceptive acuity and motor performance compared to someone with shorter disease duration. Training-related enhancements in JND

threshold and MPE did not yield significant correlations with disease duration. Disease duration did not show a significant correlation with any of the motor learning variables collected during the visuomotor training.

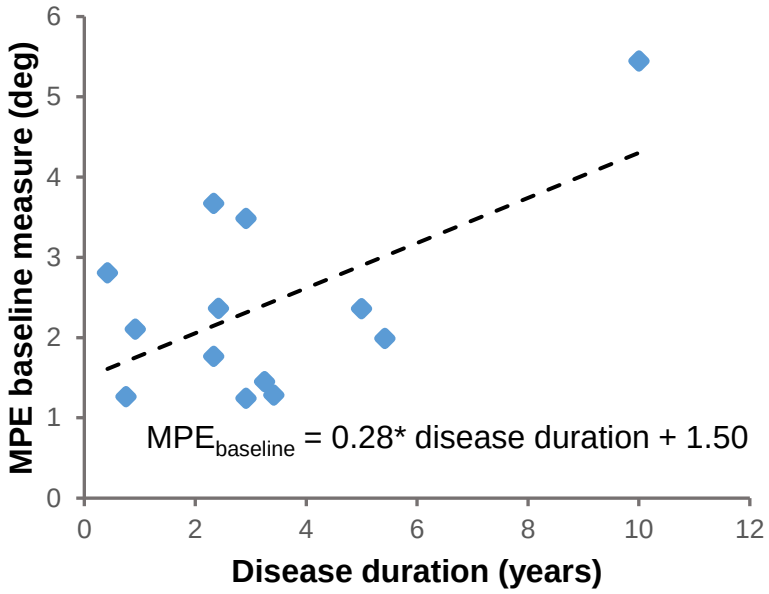

Figure 17. Effect of PD disease duration on motor precision error at baseline. Each data point represents a single participant's disease duration mapped against their MPE at baseline. Participant's disease duration had a moderate positive and significant correlation with their MPE at baseline (R = 0.58, p = 0.05).

The effects of UPDRS motor score and levodopa equivalence dosage on proprioceptive and motor performance was evaluated. Pearson's product-moment correlation analyses were performed to understand the effects of UPDRS motor score and levodopa equivalent dosage on proprioceptive and motor performance measures. Across all participants, there were no systematic effects or significant correlations of UPDRS motor score and levodopa equivalence dosage on any of these measures either at the baseline, or after training, or with the relative and absolute improvements in individual variables. The only variable levodopa equivalence dosage had significant correlations with disease duration (R = 0.73, p = 0.005).

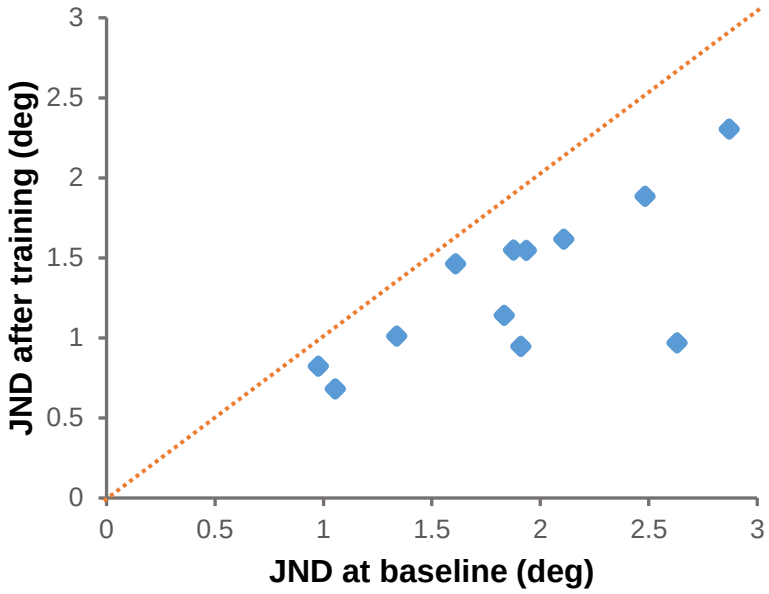

Figure 18. Just-noticeable difference thresholds in *healthy controls* before and after training. Each data point represents a participant's JND before and after training. The orange dotted line represents the line of equality indicating no change due to training. The black dashed line represents the linear regression fit. Note that all participants show improvements in JND thresholds.

Comparing PD group learning outcomes to healthy controls

Healthy control participants were evaluated for improvements in proprioceptive acuity (**Figure 18**) and motor precision error (**Figure 19**). All healthy controls improved in proprioceptive acuity (*Baseline:* Mean -1.88°, SD - 0.59°, Range - 0.97° - 2.87°; *After training:* Mean -1.32°, SD - 0.48°, Range - 0.68° - 2.30°). Nine out of the twelve control participants showed improvements in MPE (*Baseline:* Mean -2.66°, SD - 0.91°, Range - 1.69° - 4.13°; *After training:* Mean -2.30°, SD - 0.68°, Range – 1.20° - 3.41°). On average, all healthy controls (**Figure 20**) improved by about 29.5% in JND thresholds (n = 12) and by about 20.2% in MPE (n = 9). These improvements in healthy adults are comparable to those recorded in PD patients.

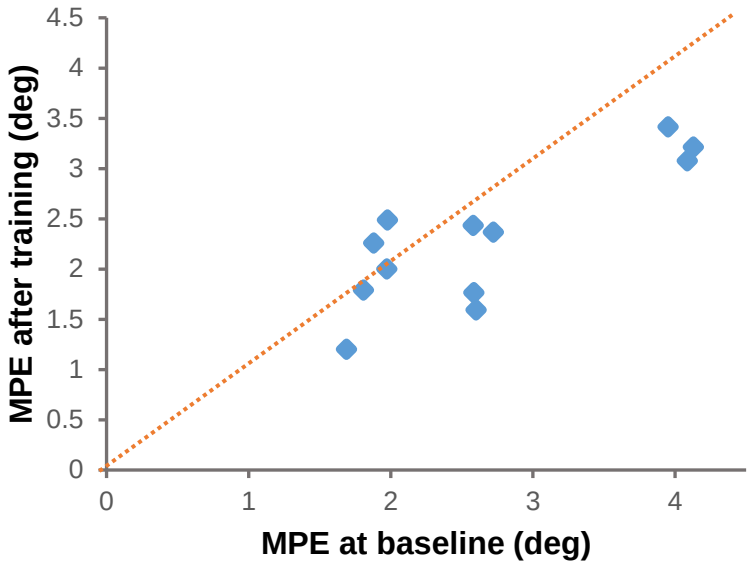

Figure 19. Motor precision error in *healthy controls* before and after training. Each data point represents a participant's MPE before and after training. The orange dotted line represents the line of equality The black dashed line represents the linear regression fit. Note that most participants show improvements in MPE.

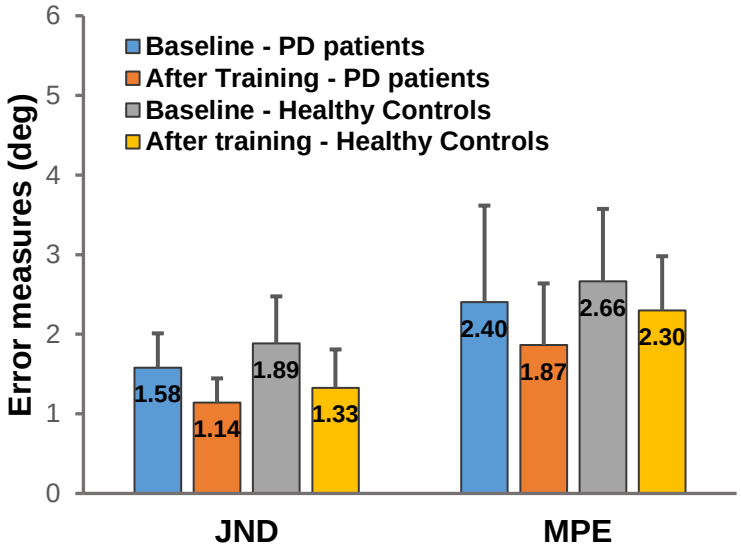

Figure 20. Just-noticeable difference threshold and motor precision error compared between PD patients and healthy controls. Error bars indicate standard deviation. Note that improvements in PD patients are similar to that in healthy controls.

Discussion:

This study administered a robot-aided visuo-proprioceptive motor training to people with PD. The research objectives were the following: First, to document that the tested PD sample population learned and improved their task-related motor performance (aim 1). Second, to identify whether proprioceptive function in PD can be enhanced by a visuo-proprioceptive training that emphasizes precise, small amplitude continuous wrist movements (aim 2). Third, to determine if proprioceptive improvements after training are associated with improvements in an untrained discrete wrist movement task, i.e. showing a sensorimotor transfer within the same joint degree of freedom (aim 3). Fourth, to identify if the training transferred to improvements in a functional writing task that relied on multi-joint wrist-hand motion, i.e. showing a sensorimotor transfer for additional joint degrees of freedom (aim 4).

The principal findings of this study are as follows: First, PD patients showed direct training related improvements in the visuo-proprioceptive training task. Second, the training improved proprioceptive acuity across all patients by 28%. Third, there was evidence of a motor transfer within the same joint degree of freedom. Participants trained on a continuous visuomotor task showed improved movement precision on an untrained discrete non-visuomotor task within the same degree of freedom. The magnitude of the training related changes in the non-visuo motor task was approximately 31% in those who showed improvements. Lastly, there was no evidence for transfer of training related changes to the multiple degree-of-freedom functional handwriting task.

The wrist robot used in this study delivered accurate passive movements and precisely encoding wrist joint position during the tasks (Masia et al., 2009). This device also facilitated the provision of a virtual environment to provide visual feedback during training. Employing this device in this study provided a means to evaluate proprioception using previously established, reliable and valid methods (Cappello et al., 2014; Elangovan et al., 2014).

All PD patients showed consistent improvements in the training trials. An improvement in the performance of these trials demonstrated the direct effects of visuomotor performance. Training allowed the use of visual inputs and integration of visual inputs with other somatosensory modalities including proprioception for the task performance. Training related effects of proprioceptive improvements and generalization of training within and beyond the trained workspace are discussed below.

Training results in proprioceptive improvements in PD

All PD patients who participated in the study showed signs of somatosensory improvemnets. Specifically, PD participants improved their proprioceptive acuity by about 28%. These improvements in PD participants were comparable to the improvements seen in the healthy elderly adult control group recruited for this study. In a different study using the same protocol, healthy young adults showed improvements in JND threshold by about 34% (Elangovan, Cappello, Masia, Aman, & Konczak). Thus, the improvements in proprioceptive acuity seen in PD patients are consistent with other studies on healthy adults. One should be mindful that the improvements seen in this study were attained after a brief 30-minute proprioceptive training. The training task involved the use of visual feedback about current wrist position from the virtual environment and required integration of visual with proprioceptive and tactile information. However, improvements in proprioceptive function were measured using a passive position discrimination task evaluated in the absence of visual feedback. Thus, the absence of visual joint position information during this evaluation extracted the effects of proprioceptive learning, while learning could have occurred in multiple areas of motor processing such as somatosensory, visual, and motor networks in the cerebral cortex.

Previous literature has evaluated the perceptual changes on various visuomotor adaptation tasks such as force-field learning (Haith, Jackson, Miall, & Vijayakumar, 2009; Krebs, Hogan, Hening, Adamovich, & Poizner, 2001), and

prism adaptation (Harris, 1963). Such studies demonstrate a shift in the integration of multiple sensory modalities. Force field adaptation studies show a directional shift in the somatosensory perceptual boundary with respect to the limb position depending upon the direction of force field perturbation (Haith et al., 2009; Krebs et al., 2001). Prism adaptation studies demonstrate misalignment in the somatosensory perceptual boundary and the visual feedback after adaptation trials (Cressman & Henriques, 2010; Harris, 1963). Current study establishes perceptual change by means of an increase in proprioceptive acuity, specifically in the PD population. Furthermore, the double baseline assessments of proprioceptive acuity before training yielding insignificant differences indicated that there is multiple testing effect on the measurements. This study provided reliable behavioral evidence for proprioceptive learning in PD patients.

Training generalizes to untrained motor task within workspace

There was solid evidence that sensorimotor learning transferred to the untrained motor domain within the same joint degree of freedom. Healthy controls improved their motor precision error during wrist pointing by about 20%, whereas PD patients improved by about 31%. The nature of this untrained pointing task differed from the training task in multiple ways. First, wrist pointing task involved a discrete active wrist movement to a target flexion position presented passively. The training task involved continuous active wrist flexion and extension around a target wrist flexion position. Second, wrist pointing task was performed in the absence of vision necessitating the reliance on proprioception, whereas training task involved visual feedback to accurately control wrist positions. Third, training task involved utilization of visual feedback to constantly align the proprioceptive feedback in accordance with visual feedback by performing continuous wrist movements. Wrist pointing task requires transformation of proprioceptive information into a motor command, and comparison of internally generated predicted sensory feedback and actual sensory feedback from the periphery are required to complete the task. Wrist pointing task required utilization of

proprioceptive information in the somatosensory perceptual and motor cortical areas for accurate performance. The results in the study demonstrated the generalizability of the training effects in an untrained discrete pointing task. Previous literature has found various effects of motor transfer in healthy adults. While a group of healthy adults demonstrated transfer of effects from a discrete somatosensory training task to discrete motor transfer task (Vahdat, Darainy, & Ostry, 2014), another study found no effect of transfer from a continuous somatosensory training task to discrete motor transfer task (Cuppone, Squeri, Semprini, Masia, & Konczak, 2016). In a bimanual coordination study, healthy adults were found to show improvements in discrete rhythmic tasks after a continuous training task (Chiou & Chang, 2016). After continuous bimanual tracking training, Chiou and Chang (2016) found healthy adults to show greater transfer to discrete rhythmic tracking task than to a continuous tracking task. The differences between the two transfer tasks are the availability of visual feedback in a discrete form or in a continuous form. These studies show a clear transfer of learning from a continuous to continuous or a discrete to discrete tasks. However, transfer of continuous visuomotor training task to a discrete non-visuomotor pointing task has been established in the current study. Furthermore, the similarity of the double baseline assessments of motor precision error demonstrated the reliability of the motor precision error measures. Current study provides evidence that training has generalized to an untrained motor task within the same degree of freedom in the PD patient population.

Training does not generalize to hand writing movements

It is intriguing that visuo-proprioceptive training did not show any changes in the tracing and tracking tasks that involves multiple degrees of freedom. This shows that visuo-proprioceptive training does not generalize to untrained planes of movements. It is quite reasonable to question the sensitivity of the measurements, when a desired effect is not achieved. But the battery of handwriting tasks used in the study are quite relevant and often used in the

literature. As micrographia is a common clinical symptom in patients with PD and handwriting is commonly evaluated in both clinics and laboratory settings. Straight line tracing and spiral line tracing tasks are routinely performed in a clinical setting. The variables evaluated in this study have been identified as a standardized measure for evaluating handwriting in PD (Smits et al., 2014). The sensitivity of this task and variables are well established in PD. However, handwriting being a functional task requires higher order processing than the tasks used for evaluating sensory and motor learning in this study. Although, handwriting relies more on visual information in comparison with proprioceptive information, it is the most relevant functional task to evaluate wrist function in patients with PD, owing to the fact that micrographia is a common motor symptom in PD affecting the quality of life in patients with PD. A lack of training related changes in tracing and tracking tasks could be interpreted in multiple ways. One possibility is that proprioceptive training is highly specific to the sensorimotor domain that it may not get transferred to a complex task such as handwriting which requires higher order processing in the form of visual-somatosensory integration, one degree of freedom movement to multiple degrees of freedom movements. It could also be argued that training was employed for about 30 minutes, that it is not enough to induce an effect in an unrestrained functional task such as handwriting. It is also likely that the sample patient population included in this study did not have disease related changes in handwriting. They may have been at their best handwriting performance that they did not have any room for improvements. Considering these factors, it is safe to say that a longer training program and a diverse and larger sample size is warranted before completely rejecting the possibility of generalizing the effects of visuo-proprioceptive training in a specific joint workspace to a functional handwriting that requires movement in multiple joint degrees of freedom.

Disease duration relates to sensorimotor performance

Disease duration is the only measure of disease severity that had a strong and

significant correlation with baseline proprioceptive acuity and baseline motor precision error measure. The longer the duration, the larger the proprioceptive discrimination threshold and the motor precision error. This showed that PD patients have worse proprioceptive deficits and movement accuracy in more advanced stages of the disease. This finding is consistent with previous findings (Alves, Wentzel-Larsen, Aarsland, & Larsen, 2005; Schrag & Quinn, 2000). Disease duration did not reliably correlate with training-related improvements in any of the variables. However, the training-related improvements in proprioceptive discrimination threshold and motor precision error had strong correlations with the baseline values. Based on these two findings, it can be inferred that an individual with longer PD duration, has poor proprioception, and a person with poor proprioception gains larger benefits from the training. It would require further evaluation to derive any conclusions regarding the effect of disease duration on training-related improvements in proprioception and motor performance.

It is not surprising that UPDRS motor scores and levodopa equivalent dosage do not correlate with any of the baseline measures or with training related improvements. Previous studies have found the levodopa equivalent dosage to not correlate with proprioceptive thresholds (Konczak et al., 2007; Maschke et al., 2003). Since, levodopa is known to enhance haptic perception (Li et al., 2010) and the dosage is adjusted to produce better symptomatic control (Tomlinson et al., 2010), levodopa equivalent dosage may not correlate with baseline proprioceptive or motor performance measures or with training-related improvements. UPDRS motor score subjectively evaluates motor symptoms such as tremor, rigidity, finger tapping, and postural stability, but it does not include aspects of proprioceptive acuity, or movement accuracy. UPDRS scores has an inherent limitation that they are subjectively evaluated, which may result in high intrarater variability. While the current study evaluated motor precision in a sensorimotor task and proprioceptive acuity, these measures may not exactly attribute the factors represented in the UPDRS motor score. Collectively, these

factors explain the lack of correlation of UPDRS scores with the dependent variables.

Limitations and outstanding questions

In this study, a brief visuo-proprioceptive training resulted in proprioceptive learning, and generalization of learning to an untrained discrete wrist pointing task. However, this study did not address avenues such as retention of learning effects, optimal training duration and dosage to achieve maximal training effects. Also, to strictly adhere to the definition of proprioceptive training as discussed earlier, virtual reality based visual feedback in the training can be replaced with other somatosensory forms of feedback such vibrotactile feedback and haptic feedback. However, such studies would still require use of limb movements limiting the ability to strictly be termed as proprioceptive training. As this study demonstrated behavioral improvements in proprioceptive and motor function, neural correlates of training can be identified in the future. Understanding the neural correlates of these behavioral improvements can facilitate optimization of training for specific clinical population. Furthermore, the effect of proprioceptive training in various phenotypes of PD needs to be evaluated. It is also unclear why three of the participants improved only in sensory function and not in motor function. Addressing these outstanding questions will benefit the application of such training programs in clinics to achieve maximal sensorimotor performance and fine motor control in the PD population.

Conclusion

In summary, this study establishes evidence for proprioceptive learning in PD patients. This has never been shown in the literature. PD patients show transfer of learning from a continuous visuomotor training task to a discrete non-visuomotor pointing task within the trained joint degree of freedom. Generalization of learning to the multi-joint functional handwriting task is not evident from the current study. This study empirically confirms previous findings

in the literature that disease duration is an indicator of sensorimotor impairments. Being the first study, to provide evidence for proprioceptive learning and associated transfer to fine motor control in Parkinson's disease, this study provides a basis to apply visuo-proprioceptive training in clinics to improve fine motor control in PD patients.

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Appendix I (Figures 21 – 32)

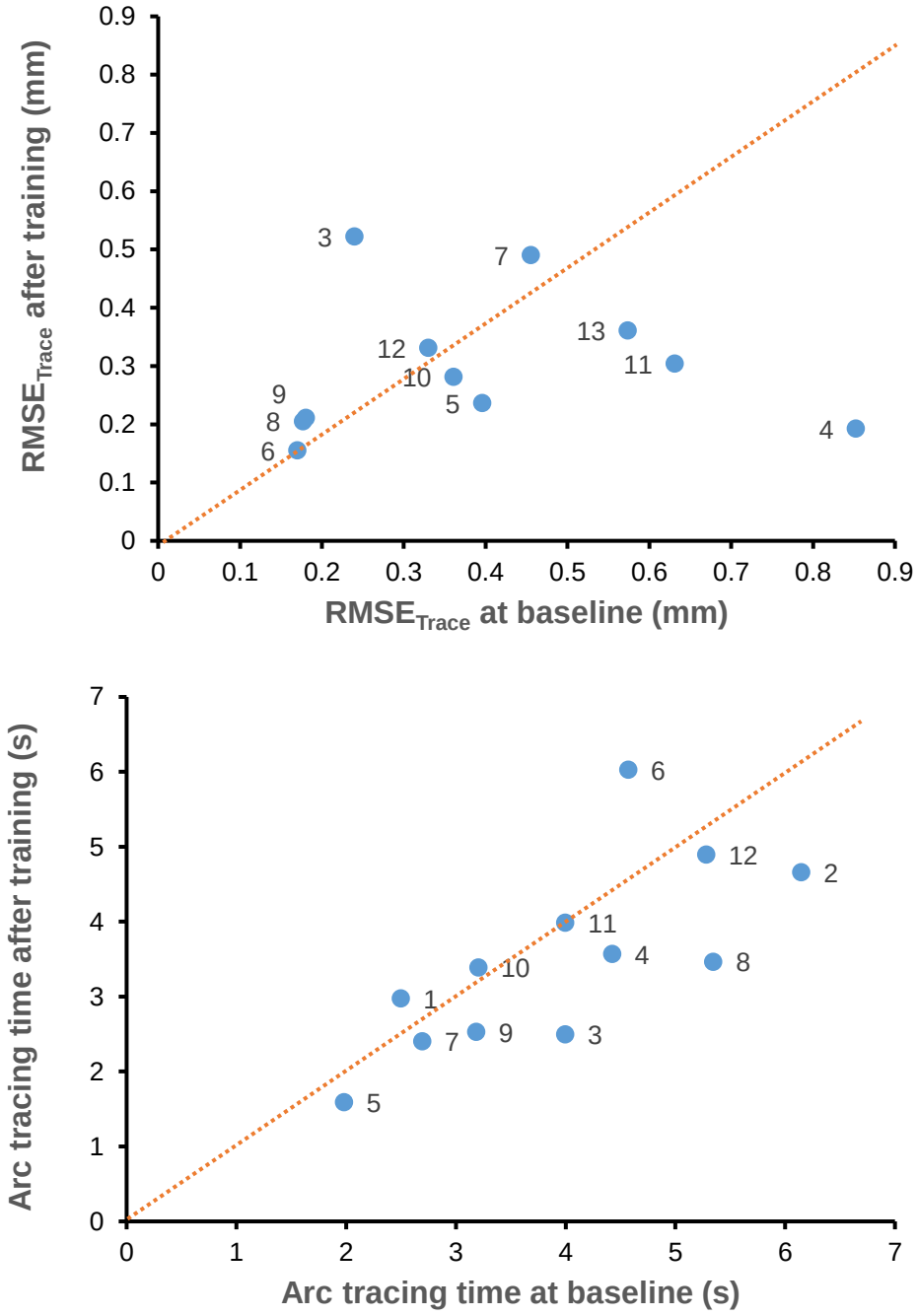


Figure 21. Arc tracing measurements. Top figure shows the RMSE with respect to the *trace* in arc tracing across all participants during baseline and after training. Note the variability of RMSE across all participants. Bottom figure shows the time taken for completion by all participants at baseline and after training. Note that all data points are

clustered around the line of equality (orange dotted line) indicating that there are no systematic differences in the time taken for completion across all participants. Data labels on all data points indicate the participant numbers.

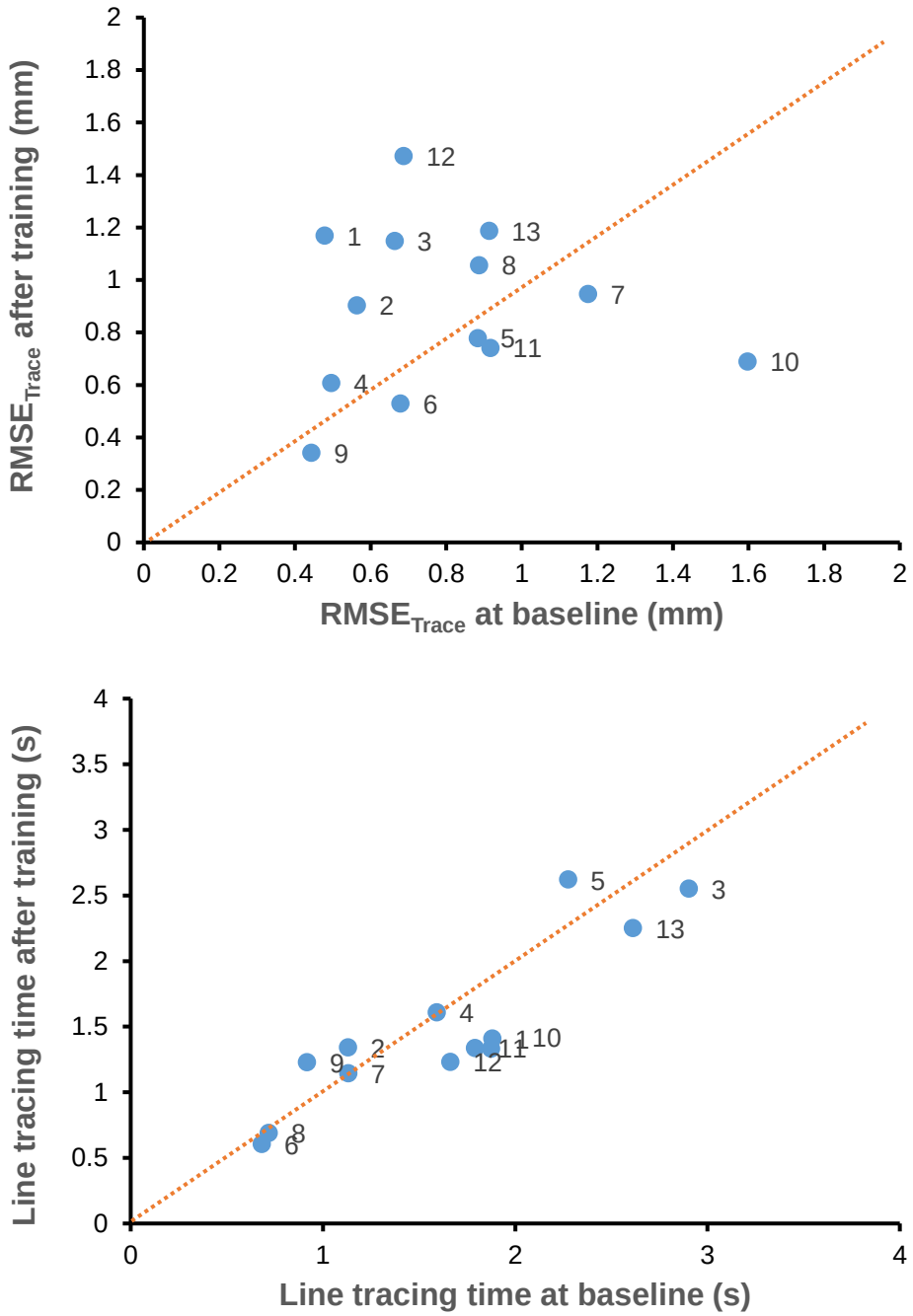
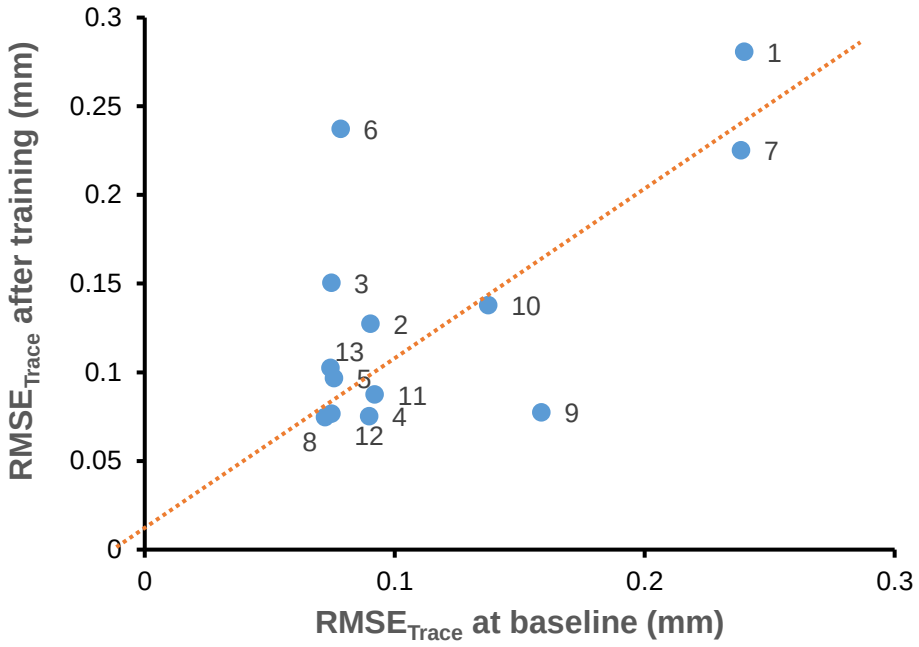


Figure 22. Line tracing measurements. Top figure shows the RMSE with respect to the *trace* in line tracking task across all participants during baseline and after training. Note

the variability of RMSE across all participants and that there were no systematic differences in RMSE with training. Bottom figure shows time taken by all participants for line tracing trial completion. Note that all data points are clustered around the line of equality (orange dotted line) there were no systematic differences in time taken for trial completion across all participants. Data labels on all data points indicate the participant numbers.



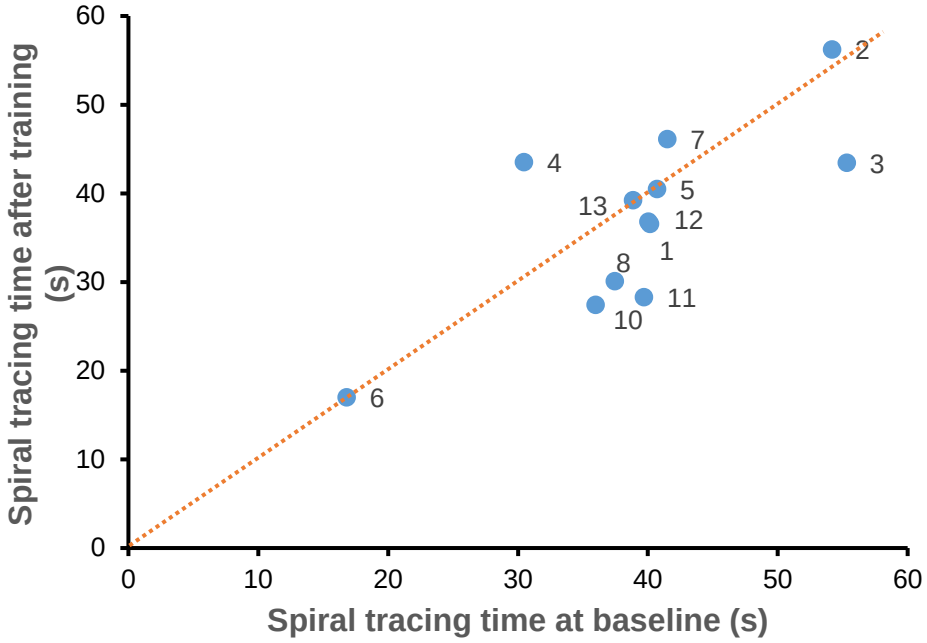


Figure 23. Spiral tracing measurements. Top figure shows the RMSE with respect to *trace* in spiral tracing task across all participants at baseline and after training. Note that there were no systematic differences in RMSE with training. Bottom figure shows the time taken by all participants for completion before and after training. All data points are clustered around the line of equality (orange dotted line). Data labels on all data points indicate the participant numbers.

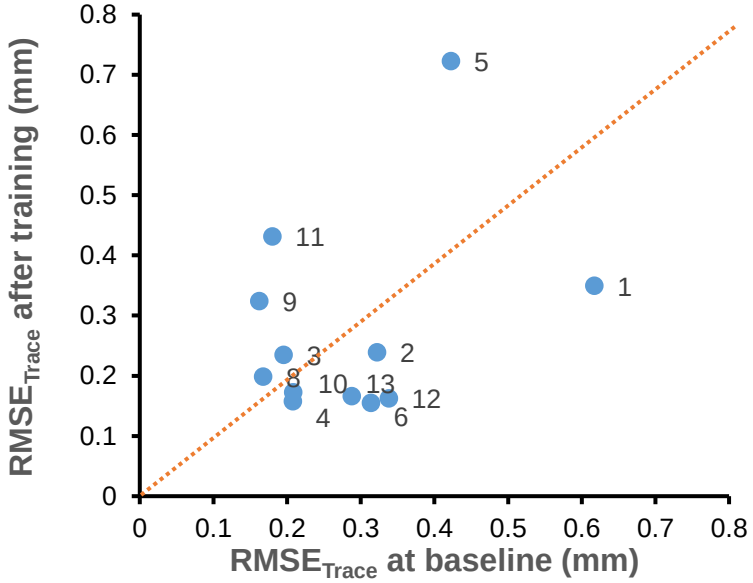


Figure 24. RMSE with respect to the *trace* in arc tracking task before and after training. Each data point represents each participant's RMSE before and after training. Data labels indicate participant ID.

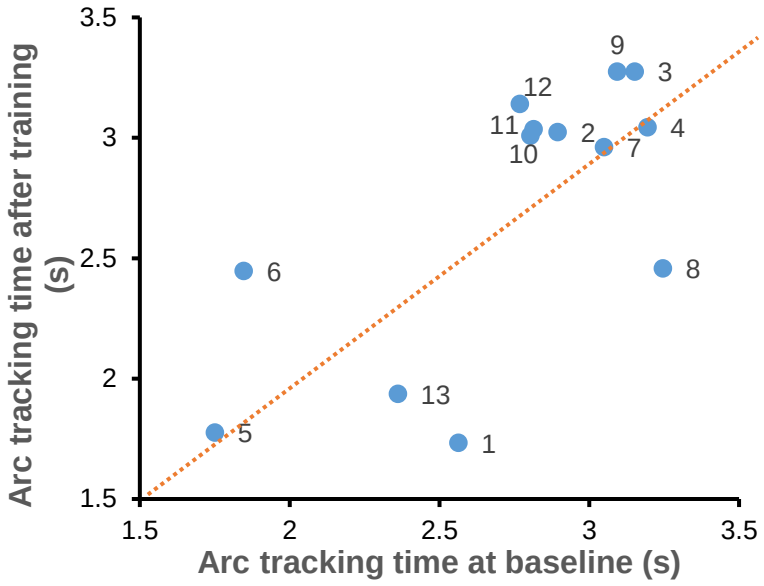


Figure 25. Arc tracking time. Each data point shows the time taken for completing the arc tracking task by each participant before and after training. Note that all participants are clustered around the line of equality. Data labels indicate participant ID.

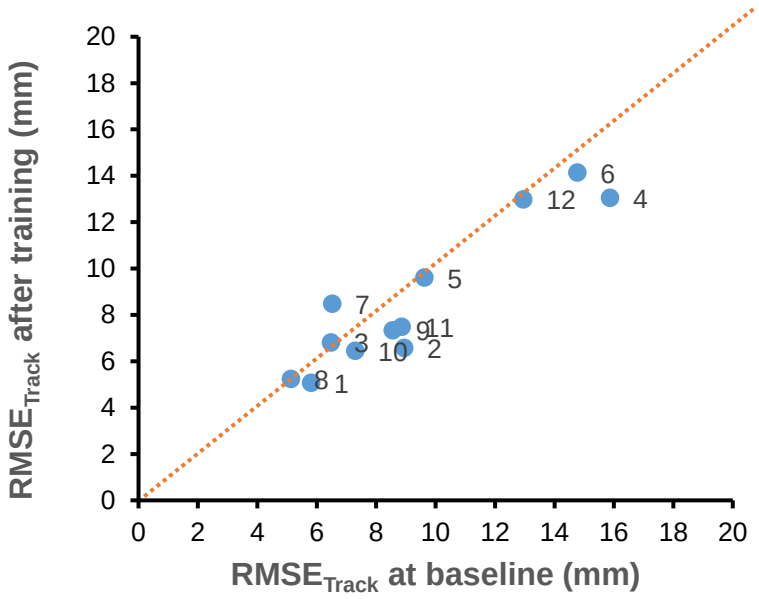


Figure 26. RMSE with respect to *tracking cursor* in arc tracking task. Each data point

represents each participant's RMSE with respect to the tracking cursor before and after training. Note that all data points are clustered around the line of equality showing no training related changes in RMSE. Data labels indicate participant ID.

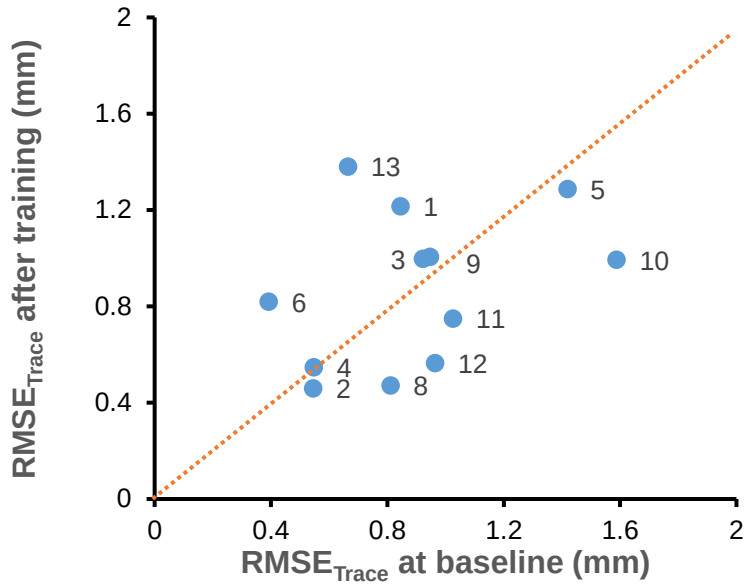


Figure 27. RMSE with respect to the *trace* in a line tracking task. Each data point represents each participant's RMSE with respect to the trace before and after training. Note the variability in RMSE before and after training indicating that there are no systematic changes in RMSE with training. Data labels indicate participant ID.

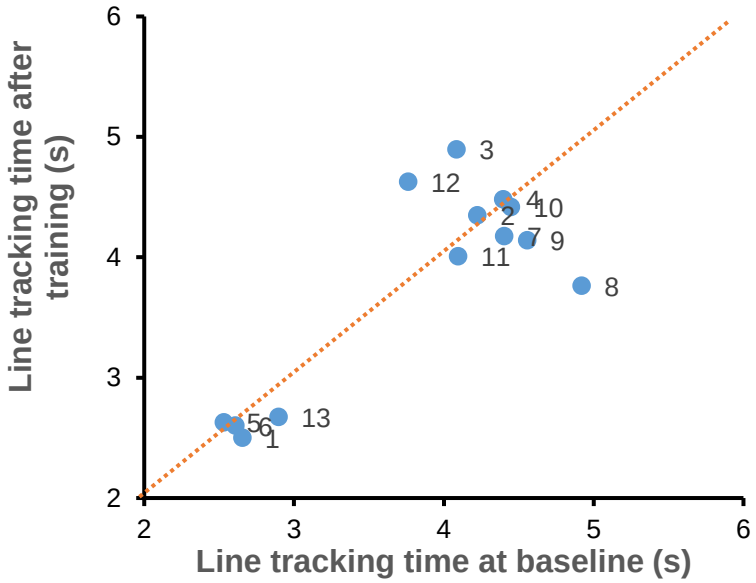


Figure 28. Line tracking time. Each data point represents the time taken by each participant to complete the line tracking task before and after training. Note the variability in the time taken for completion each participant. Data labels indicate participant ID.

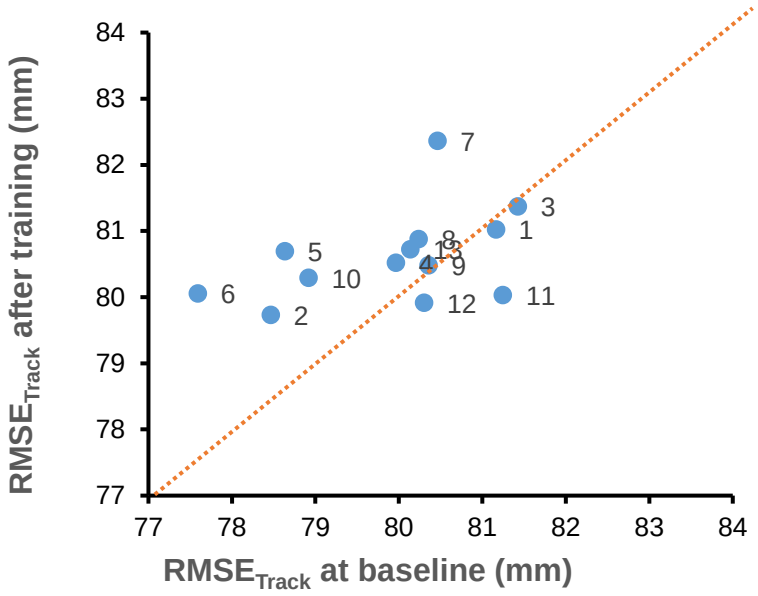


Figure 29. RMSE with respect to the *tracking cursor* in line tracking task. Each data point represents each participant's RMSE before and after training. Data labels indicate participant ID.

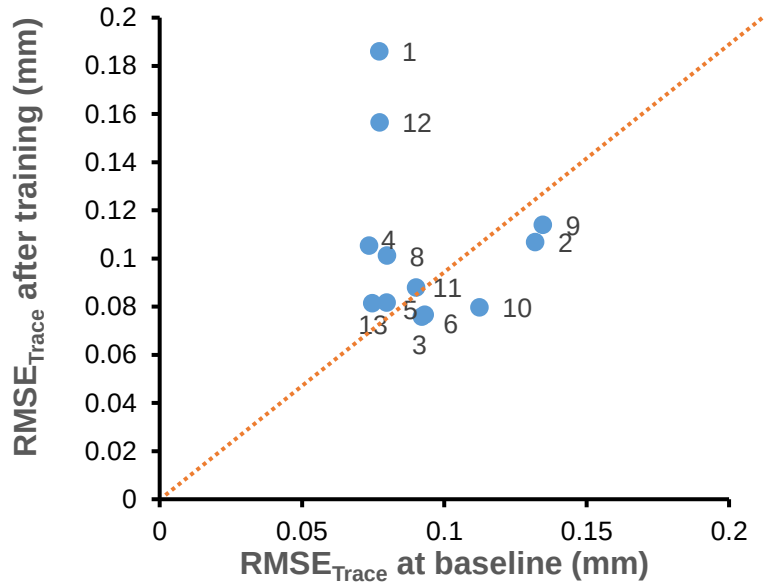


Figure 30. RMSE with respect to the *trace* in spiral tracking task. Each data point represents each participant's RMSE before and after training. Note that most participants are clustered around the line of equality. Data labels indicate participant ID.

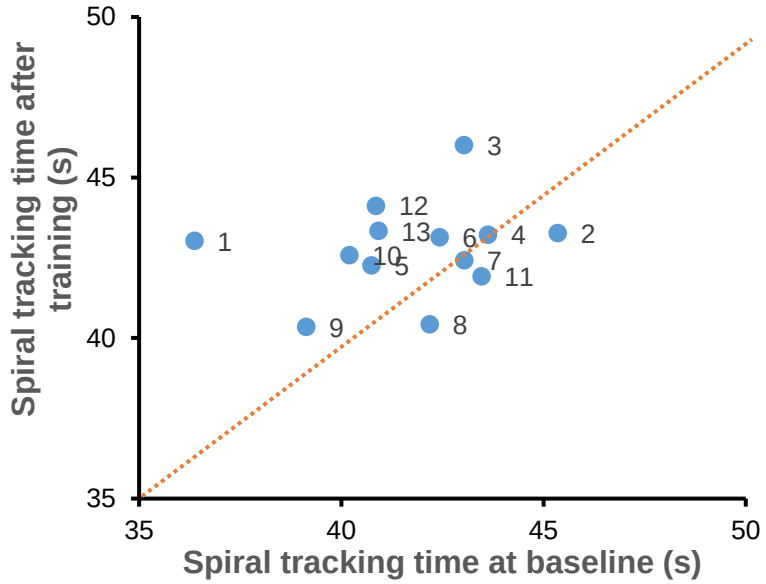


Figure 31. Spiral tracking time. Each data point represents the time taken by each participant to complete the spiral tracking task before and after training. Data labels indicate participant ID.

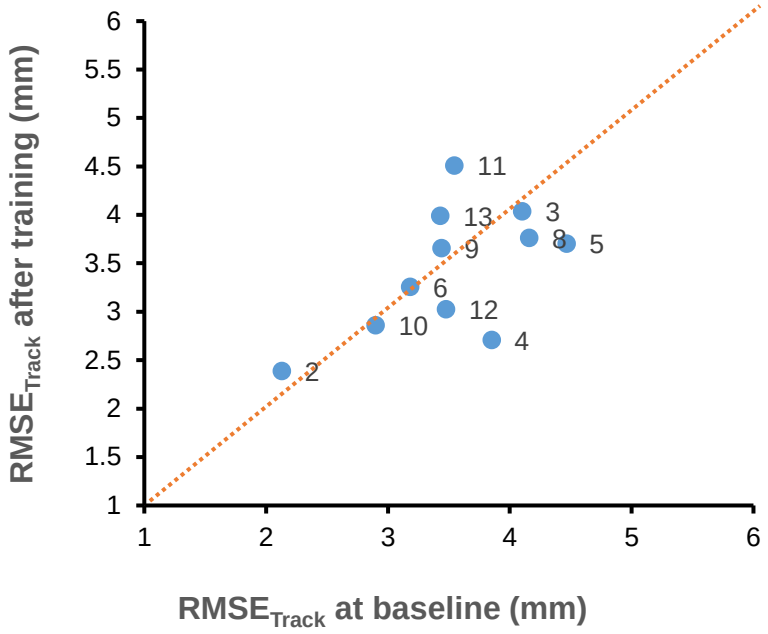


Figure 32. RMSE with respect to the *tracking cursor* in spiral tracking task. Each data point represents each participant's tracking RMSE before and after training. Note that there are no systematic changes in RMSE before and after training across all participants. Data labels indicate participant ID.