Effects of a robot-assisted sensorimotor training program with vibro-tactile feedback on proprioception and motor function in people with chronic stroke

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Dedication

This dissertation is dedicated to my clients and their loved ones who I had the honor to provide care as an occupational therapist. Your resilience and support for each other has been my inspiration to pursue research in neurorehabilitation and a personal reminder on why research in this field is necessary and worth the time and effort invested.

Abstract

Proprioceptive deficits are exhibited in nearly 50% of all stroke survivors and is associated with poor upper limb motor function and impaired activities of daily living function. Improving proprioception enhances motor learning and improves motor performance in non-stroke populations. Thus, improving proprioception could serve as an additional route to enhance motor recovery after stroke. The aims of this study were to examine whether a robot-aided sensorimotor training regimen requiring active wrist movements administered without vision would improve the proprioceptive acuity, proprioception-related somatosensory evoked potential (SEP) measures and motor performance in adults with chronic stroke. METHODS: Twelve adults with chronic stroke were recruited (Median age: 63 years, 42 – 74 years; median time after stroke: 12 months; median Fugl-Meyer Assessment – UE: 65 points). Participants completed two training sessions in two consecutive days (total training time: 1 hour). Users grasped the robot handle and performed wrist adduction/abduction movements to tilt a virtual board on which a virtual ball rolled. Users were tasked to roll the ball to a target area on the board. Real-time, vibro-tactile feedback about ball position and speed was provided to the forearm. The task difficulty increased as the user continued training. Assessments were conducted before, immediately after, and two days after the intervention. Outcome measures were wrist proprioceptive acuity indicated by the just-noticeable-difference (JND) threshold, spatial errors of wrist tracing tasks, movement time and endpoint error of a wrist pointing task and short-latency SEPs induced by median nerve stimulation. RESULTS: The stroke group significantly reduced JND thresholds at posttest and retention in comparison to the pretest (Medians: pretest: 1.8°, posttest: 1.4°, retention: 1.3°; $W = 10$, $p = 0.0042$ for both comparisons). Higher reduction in the JND threshold was associated with a higher increase in the P27-N30 peak-to-peak SEP amplitude at retention compared to pretest. Changes in SEP measures and motor measures across visits did not reach statistical significance. DISCUSSION: This exploratory, proof-of-concept study documented that proprioceptive function of adults with chronic stroke improved after a brief active proprioceptive-motor training. If proven effective, such interventions or elements could be employed in clinical practice in addition to existing rehabilitation approaches.

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Introduction

Stroke is one of the leading causes of long-term disability in adults in the United States (Go et al., 2014). Approximately 50% of stroke survivors require assistance for activities of daily living (ADL) at three months after the stroke (Bernhardt et al., 2015). Proprioception refers to the perception of limb motion or position and the orientation of one's body in space (Stillman, 2002). Approximately 20-60% of stroke patients exhibit forms of proprioceptive impairment (Connell, Lincoln, & Radford, 2008; Kessner, Bingel, & Thomalla, 2016). It is related to longer length-of-stay in hospitals (Sommerfeld & Von Arbin, 2004), higher severity in upper limb impairment, upper limb fine motor performance and ADL function (Coupar, Pollock, Rowe, Weir, & Langhorne, 2012; Meyer, Karttunen, Thijs, Feys, & Verheyden, 2014; Meyer et al., 2016; Tyson, Hanley, Chillala, Selley, & Tallis, 2008). The negative impacts of proprioceptive impairment on motor function and activity participation in adults with stroke were expected based on studies from patients with exclusive loss of somatosensation reported their incoordination even when their motor system was not affected (Ghez, Gordon, & Ghilardi, 1995; Sainburg, Ghilardi, Poizner, & Ghez, 1995). Similarly, monkeys showed motor impairment after the destruction of peripheral afferents to the spinal cord but with intact motor pathways, a phenomenon referred to as "learned non-use" (Taub, Uswatte, & Elbert, 2002). Considering the critical role of proprioception in motor performance, restoring the proprioceptive function is expected to enhance motor recovery after stroke. This concept was supported by a study with healthy middle-aged adults which showed that the improvement in the proprioceptive acuity correlated with enhanced motor performance in an unfamiliar reaching task after one session of proprioceptive training (Vahdat, Darainy, & Ostry, 2014).

Proprioceptive training refers to therapies that target improvement of proprioceptive functions to improve sensorimotor function. It can be categorized into three major types. (1) Repetitive sensory or sensorimotor stimulation aims to enhance the excitability of the central sensorimotor network by applying stimulation to the affected limb. Examples

include cutaneous electrical stimulation (Kattenstroth, Kalisch, Peters, Tegenthoff, & Dinse, 2012; Peurala, Pitkänen, Sivenius, & Tarkka, 2002) and passive limb movement (Dechaumont-Palacin et al., 2008). These interventions were usually applied to stroke survivors with limited motor function. (2) Somatosensory discrimination approach is based on principles of perceptual learning and neuroplasticity. Participant receive feedback on their correctness of somatosensory discrimination without vision to recalibrate their impaired somatosensory system with other less-affected function, such as vision or the less-affected hand (Carey, Macdonell, & Matyas, 2011; Yekutiel & Guttman, 1993). (3) Active motor training requires participants actively moved their limbs or body. Interventional motor tasks are often performed without visual feedback of the limb position to maximize the use of proprioceptive feedback (Casadio, Giannoni, Morasso, & Sanguineti, 2009; De Santis et al., 2014). Performance feedback is often provided through somatosensory modalities (Casadio et al., 2009; De Santis et al., 2014; Kita et al., 2013). One example is vibro-tactile feedback (VTF) generated by light-weight vibratory motors secured on the user's skin surface. In one study, this mode was employed in conjunction with haptic feedback in a wrist pointing training with young healthy adults with their vision occluded (Cuppone, Squeri, Semprini, Masia, & Konczak, 2016). VTF indicated the magnitude and direction of the deviation of the user's wrist position from the ideal, straight reaching trajectory. The additional use of VTF resulted in more improvement in wrist proprioception compared to using only haptic feedback. Overall, the effectiveness of proprioceptive training are mixed due to widely varying definitions of proprioceptive training, use of outcome measures and few high-quality experimental studies(Aman, Elangovan, Yeh, & Konczak, 2014; Doyle, Bennett, Fasoli, & McKenna, 2010). Comparing the three types of proprioceptive training, somatosensory discrimination approach and active movement training showed better effectiveness on proprioception and motor performance in the stroke population (Aman et al., 2014; Carey & Matyas, 2005; Casadio et al., 2009).

To examine underlying neural mechanisms following proprioceptive interventions, use of neurophysiological measures is recommended (Sullivan & Hedman, 2008). One

neurophysiological measure of somatosensory processing is to examine somatosensory evoked potentials (SEPs). SEPs induced by median nerve stimulation have been well documented in healthy subjects (Allison, Mccarthy, Wood, & Jones, 1991; Papadelis, Eickhoff, Zilles, & Ioannides, 2011; Srisa-an, Lei, & Tarkka, 1996). In typical waveforms of SEPs induced by median nerve stimulation, N30 peak is a negative peak observed at approximately 30 ms after the stimulation from pre-central and central electrodes. N30 is believed to reflect early processing of proprioceptive information because it can be observed with intramuscular stimulation (Gandevia, BURKE, & MC KEON, 1984) and absent with cutaneous anesthesia (Restuccia et al., 2002). Lower N30 peak amplitude or longer N30 peak latency compared to normative values has been well documented in stroke survivors (e.g. (Meyer et al., 2016; Yamada, Kimura, Wilkinson, & Kayamori, 1983)). SEPs are also used as outcome measures to reflect neuroplastic changes of the somatosensory function in interventional studies, mostly in the healthy population (Nasir, Darainy, & Ostry, 2013; Pellicciari, Miniussi, Rossini, & De Gennaro, 2009; Tinazzi, Rosso, Zanette, Fiaschi, & Aglioti, 2003). Two studies with the stroke population had used SEPs as their outcome measures. The number of participants with re-emerged or normal SEPs increased significantly in a group of 32 chronic stroke participants after a 3-week intervention program of repetitive cutaneous stimulation in addition to intensive inpatient rehabilitation (Peurala et al., 2002). A case study reported one participant with severe sensory deficits showed re-emerging SEPs resembling typical waveforms after 22 weeks of daily 20-minute cutaneous stimulation (Kattenstroth et al., 2012). However, it is worth noting that both focused on tactile function recovery instead of proprioception.

To date, effectiveness of proprioceptive training after stroke on proprioception and motor function remains unclear and the scarcity of neurophysiological measures in interventional studies slows understanding on underlying mechanisms. Therefore, the research question of this study was whether a robot-assisted sensorimotor training program could improve wrist proprioception, motor function and proprioception-related

SEP measures in adults with chronic stroke. Derived aims and hypothesis were as follows:

Aims

1. Determine if the wrist proprioceptive training improves wrist proprioceptive acuity in adults with chronic stroke. Wrist proprioceptive acuity (i.e. the ability to discriminate the smallest possible difference in limb position) was objectively measured by the just-noticeable-difference (JND) threshold in a wrist position discrimination test. A significant reduction in the JND threshold in the posttest or retention test compared to the pretest would verify this aim.

2. Determine if the wrist proprioceptive training program improves the spatial accuracy of wrist motor performance of the affected arm in untrained tracing tasks in adults with chronic stroke. This would elucidate the possible transfer of proprioceptive training gains on fine motor function. The spatial error between the trace and the reference was used to indicate wrist tracing performance. A significant reduction in spatial error in the posttest or retention test compared to pretest would verify this aim.

3. Determine if the wrist proprioceptive training program improves the functional performance in an untrained functional wrist movement task of the affected arm in adults with chronic stroke. This aim sought to demonstrate the transfer effect of proprioceptive training gains on functional motor performance, measured by time and endpoint pointing error in a wrist pointing task with a regular computer mouse. A significant reduction of the task completion time or spatial error in the posttest or retention test compared to pretest would verify this aim.

4. Determine if the training program is associated with changes in somatosensory evoked potentials of the affected wrist in adults with chronic stroke. Time-to-peak amplitude (latency) and peak-to-peak amplitude of the N30 wave following median nerve stimulation on the trained wrist were extracted. A significant changes in the N30 measures in the posttest or retention test compared to pretest would verify this aim.

Hypotheses

1. Adults with chronic stroke would demonstrate an improvement in the wrist proprioceptive acuity after the proposed wrist proprioceptive training compared to the pretest.
2. Adults with chronic stroke would demonstrate a more precise wrist movement control in untrained motor tasks after the proposed wrist proprioceptive training compared to the pretest.
3. Adults with chronic stroke would demonstrate a reduction of time to complete a functional motor task after the proposed wrist proprioceptive training compared to the pretest.
4. Adults with chronic stroke would show changes in somatosensory evoked potentials of the affected wrist in adults with chronic stroke after the proposed wrist proprioceptive training compared to the pretest.

Significance

Achieving Aim 1 would indicate wrist proprioception can be improved in adults with chronic stroke. Then this training program would have the potential to be applied in clinical practice to improve proprioception. Achieving Aim 2 and 3 would indicate the program could improve untrained motor function in adults with chronic stroke, verifying that proprioceptive training could be an augmented therapeutic route to enhance motor recovery after stroke. Achieving Aim 4 would verify the training program could induce neuroplastic changes related to proprioceptive processing.

Method

Participants

Twelve adults were recruited in the Twin Cities area from January 2016 to April 2017. The inclusion criteria for stroke participants were (1) a cerebral stroke occurring three months prior to data collection; (2) presence of a minimum of 20° active range of motion (ROM) at the wrist of the more-affected side; (3) the ability to resist minimal resistance

in the gravity-eliminated position at the wrist indicated by 2+/5 in the manual muscle testing(Hislop, Avers, & Brown, 2013). Potential participants were excluded if (1) they scored less than 23 points on Mini Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975); (2) they showed markedly increased muscle tone through most of the ROM of wrist, indicated by being rated higher than 1+ on Modified Ashworth Scale (Bohannon & Smith, 1987)); (3) they were diagnosed with other medical conditions that may affect upper limb sensorimotor function by the time of data collection; (4) they cannot perceive 60-to-100 Hz vibro-tactile stimulus on either arm; or (5) they did not have no magnetic resonance imaging (MRI) records available to confirm the diagnosis of the stroke. Participants were recruited via convenience sampling, primarily from the following three venues (Figure 1): (1) outpatient clinics of Neurology and Physical Medicine and Rehabilitation at University of Minnesota Medical Center. Potential participants were first identified by research coordinators and then were screened for medical fitness before enrolling in the study; (2) stroke support groups in the Twin Cities area and local stroke patient groups through recruitment flyers or in-person informative sessions. Interested potential participants initiated contact with the researcher and then were screened for eligibility; and (3) eligible potentials retrieved and identified from Clinical Data Depository supported by Clinical and Translational Science Institute at the University of Minnesota in May 2016. Recruitment materials were mailed to invite them to join the study. The study protocol was approved by the Institutional Review Board of University of Minnesota. Data was collected in a laboratory setting at the University of Minnesota.

To describe the clinical characteristics of the stroke participants, the following information was collected prior to the intervention: 1) stroke lesion characteristics, 2) upper limb motor impairment by Fugl-Meyer Assessment (FMA) (motor section for upper limb)(Fugl-Meyer, Jääskö, Leyman, Olsson, & Steglind, 1975) and 3) Somatosensory function assessed by commonly-used clinical tools: a) wrist position sense by Erasmus MC-modified Nottingham Sensory Assessment (NSA) on a 3-point scale: 0, *Absent ("Patient does not detect the movement taking place"*; 1, *Impaired*

("Patient detects the movement taking place but the direction is no correct on all three occasions"; 2, *Normal ("Patient correctly detects the direction of the movement taking place on all three occasions"*). Both inter-rater and intra-rater reliability were 0.63 based on a sample of 18 neurological adults(Stolk-Hornsveld, Crow, Hendriks, Van Der Baan, & Harmeling-Van Der Wel, 2006). (b) vibration sensitivity of the affected arm using a 64 Hz Rydel-Seiffer tuning fork at a scale of 0 – 8 that indicates the strength of the vibration. Participant indicates verbally when the vibration can no longer be perceived. Normative values from neurologically intact elderly has been documented (Martina, van Koningsveld, Schmitz, Van Der Meché, & Van Doorn, 1998) (Hilz et al., 1998). (c) light touch sensitivity was assessed with a 6-set Semmes-Weinstein monofilament test kit (0.07g, 0.4g, 2g, 4g,10g, 300g from North Coast Medical Inc.)(Bell-Krotoski, Fess, Figarola, & Hiltz, 1995).

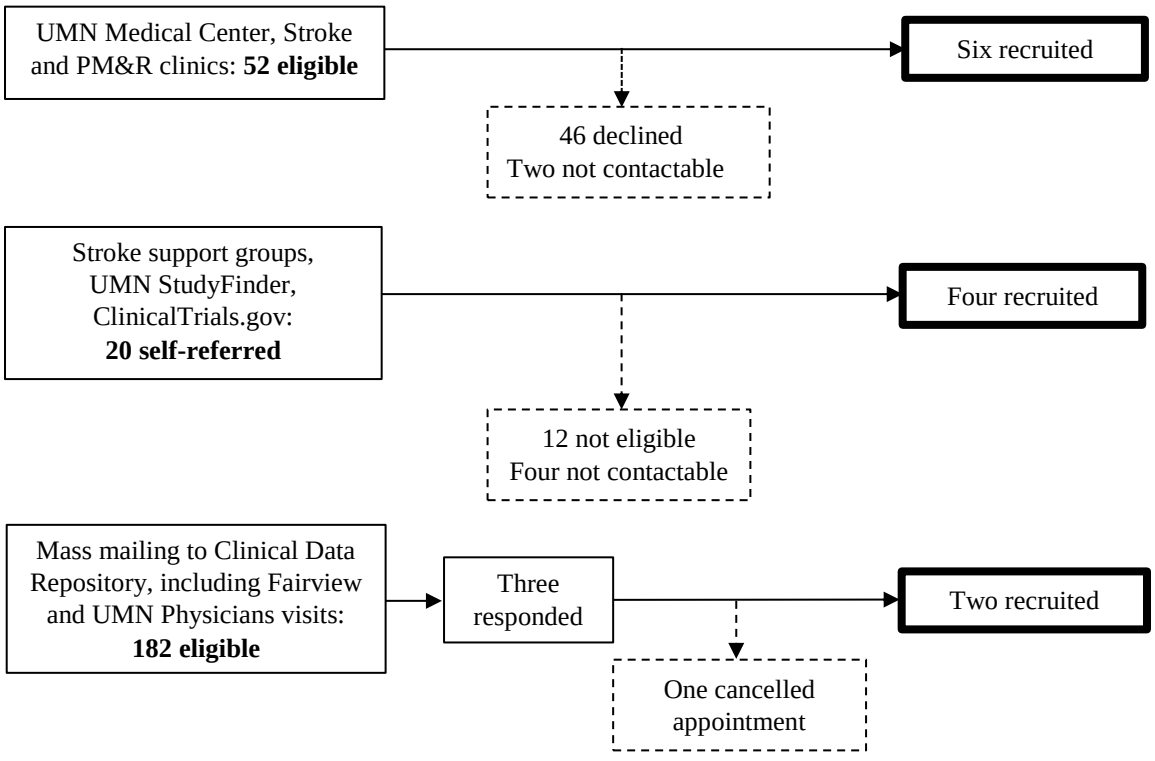

Figure 1. Recruitment flowchart. UMN, University of Minnesota. PM&R, Physical Medicine and Rehabilitation.

Twelve adults with stroke aged 42 to 73 years had completed in the study (Table 1). All had at least one cerebral stroke more than 3 months prior to data collection. All had unilateral lesion except for S10, who was tested on their more affected side (right). Time since stroke ranged from 4 to 55 months with a median of 12 months. Their FMA-UL score ranged from 42 to 66 points with a median of 64.5 points out of a maximum of 66 points. This showed that most participants had mild upper limb function impairment or no impairment at all. Likewise, most participants can engage their affected side in daily life activities. On clinical somatosensory measures, most stroke participants showed comparable function to the control group and normative values except for S10 and S11. S10 was rated as *absent* wrist position sense in both wrist flexion/extension and abduction/adduction. S11 was rated *impaired* wrist position sense in wrist abduction/adduction. In addition, ten adults with no neurological condition (6 women and 4 men, aged from 44 to 79 years, median age: 71 years) were recruited to match the gender and age with the stroke participants as possible. Control participants performed the training and assessment tasks with the side that their matched stroke participant used.

Study design

This study was an exploratory, proof-of-concept study, designed with one experimental treatment and repeated measures. Both stroke group and non-stroke group completed the same intervention protocol (Figure 2). Participants completed the pretest and then one intervention session in Visit 1 (Day 1). During Visit 2 on the following day (Day 2), they completed the second intervention session and the posttest. Visit 3 was scheduled two days after Visit 2. Participants completed the outcome measures as the retention test.

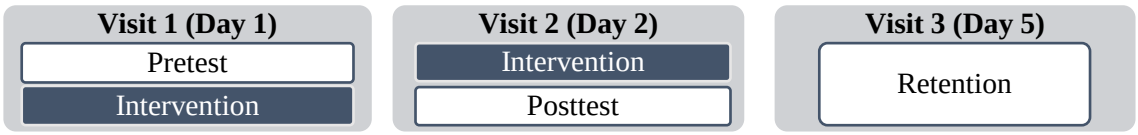

Figure 2. Study protocol.

Table 1. *Demographics and clinical evaluation for the stroke group*

ID	Gender	Age (years)	Time since stroke (months)	Lesion side	Lesion location	Type	FMA-UL (0 – 66)	NSA (FE/AA) (0 – 2)
S03	F	57	27	L	Cortical and subcortical parietal lobe	ischemic	66	2/2
S04	M	73	11	L	EC, putamen, PVWM	ischemic	66	2/2
S05	M	47	4	L	Posterior subcortical frontal, BG, posterior limb of IC	ischemic	65	2/2
S06	F	74	6	R	Thalamus, putamen	hemorrhagic	64	2/2
S07	M	63	7	L	Corona radiata	ischemic	65	2/2
S08	F	42	13	R	Superior thalamus, cortical and subcortical temporal and occipital lobe	ischemic	64	2/2
S09	F	63	5	R	Frontal (precentral gyrus), parietal (postcentral gyrus), occipital lobe	ischemic	66	2/2
S10	M	65	26	L & R	Cortical and subcortical occipital lobe, L & R thalamus	ischemic	46	0/0
S11	M	71	55	R	Thalamus	hemorrhagic	42	2/1
S12	F	68	6	L	Frontal (precentral gyrus)	ischemic	65	2/2
S13	M	60	49	L	Subcortical frontal and parietal	ischemic	58	2/2
S14	F	56	14	L	Frontal (precentral gyrus), parietal (postcentral gyrus)	ischemic	64	2/2
Ave.	**6F/6M**	**62**	**18**	**4 R/ 7 L / 1 both**	**3 cortical / 7 subcortical/ 2 both**	**10 ischemic**	**61**	**-**

Note. FMA-UL, Fugl-Meyer Assessment Upper Limb. NSA, Erasmus MC modified Nottingham Sensory Assessment, 0, *Absent*, 1, *Impaired*, 2, *Normal*. FE, flexion/extension. AA, abduction/adduction. EC, external capsule. PVWM, periventricular white matter. BG, basal ganglia. IC, internal capsule.

Apparatus

The customized wrist system ("*WristBot*") allows full ROM at the wrist and forearm in three degrees of freedom (DOF) (wrist flexion/extension, wrist abduction/adduction and forearm pronation/supination) (Figure 3). Torques generated by motors in each DOF could block movement in undesired DOFs as needed. Optical encoders housed in the *WristBot* measure angular displacement in the three DOFs in real time. The encoder resolution is 0.0065° in the direction of wrist abduction/adduction and 0.0075° in the direction of wrist flexion and extension (Cappello et al., 2015).

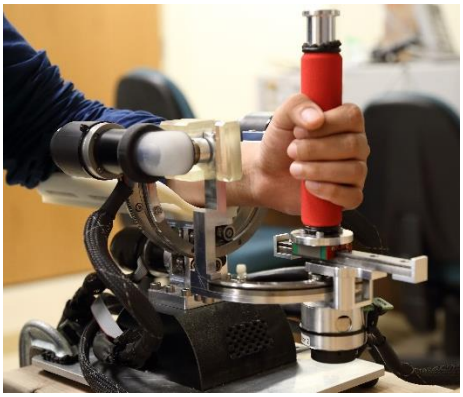

Figure 3. WristBot. Participant grasped onto the handle with the forearm supported, the wrist axes of rotation aligning with the axes of rotation of motors of the *WristBot*.

Intervention

Participant sat on a height-adjustable chair at a height that participant's shoulders were a similar height when relaxed. Stroke participants used their affected side and the non-stroke participants used either the dominant or non-dominant side with which their matched stroke participant used. The axes of rotation of wrist were visually inspected to ensure alignment with the axes of rotation of the *WristBot* in respective DOFs. In the intervention task, participant grasped the handle of the *WristBot* and use wrist abduction and adduction to tilt a virtual board to move a virtual ball on the board move toward a target. One degree of wrist adduction/adduction translated to one degree of tilt angle of the virtual board. Movement of wrist flexion/extension and forearm pronation/supination were blocked. A trial was completed when the ball stayed within the target area for 5

seconds (Figure 4) and followed by the beginning of the next trial. Three target locations were rotated in the following order: left, center and right of the tilt board. The difficulty level increased after every 6 trials. The physical properties of the virtual ball changed with the difficulty level by increasing ball momentum, ball speed gain and decreasing the friction force on the board.

Incorporating existing evidence and the recommended principles, feedback about the task performance was provided through the somatosensory modality. The position and speed of the virtual ball were provided through three light-weight vibratory motors (9 mm in diameter, 25 mm in length, 4.6 g in weight; Model 307-100, Precision Microdrives Ltd., London, United Kingdom). The motors were placed at distances sufficient for the participant to differentiate the locations of vibration to assure effective perception of direction-specific feedback from each motor. Two motors placed along the long axis of the performing forearm signaled the distance between the ball position and the target. The vibration frequency increased in three levels with the distance with respect to the length of the screen: 0 – 15%: 2 Hz trains of 100-Hz pulses; 15 – 40%: 80 Hz; >40%: 90 Hz. The motor placed distally was switched on when the ball was on the right side of the target while the proximal motor was switched on when the ball was the left side of target. In cases where participants could not correctly use the information in the designed motor placement (S03 and S12), these two motors were reversely placed for two participants. In this way, the VTF indicated the direction of desired ball movement direction instead of signaling the distance between target and the ball position. The 3rd motor was placed on the other forearm that reflected ball speed. The vibration frequency indicated the ball speed regardless of the direction in four levels (75 Hz, 82 Hz, 90 Hz and 98 Hz). S10 could not sense the VTF on the performing arm (i.e. the more-affected arm) and therefore the two motors indicating the ball position were then placed on the less-affected arm, straddling the vibratory motor indicating the ball speed was placed. Placing the VTF on the contralateral arm to the trained wrist showed a comparable training effect on wrist proprioception as placing the VTF on the ipsilateral arm after a wrist proprioceptive training in healthy young adults(Cuppone et al., 2016).

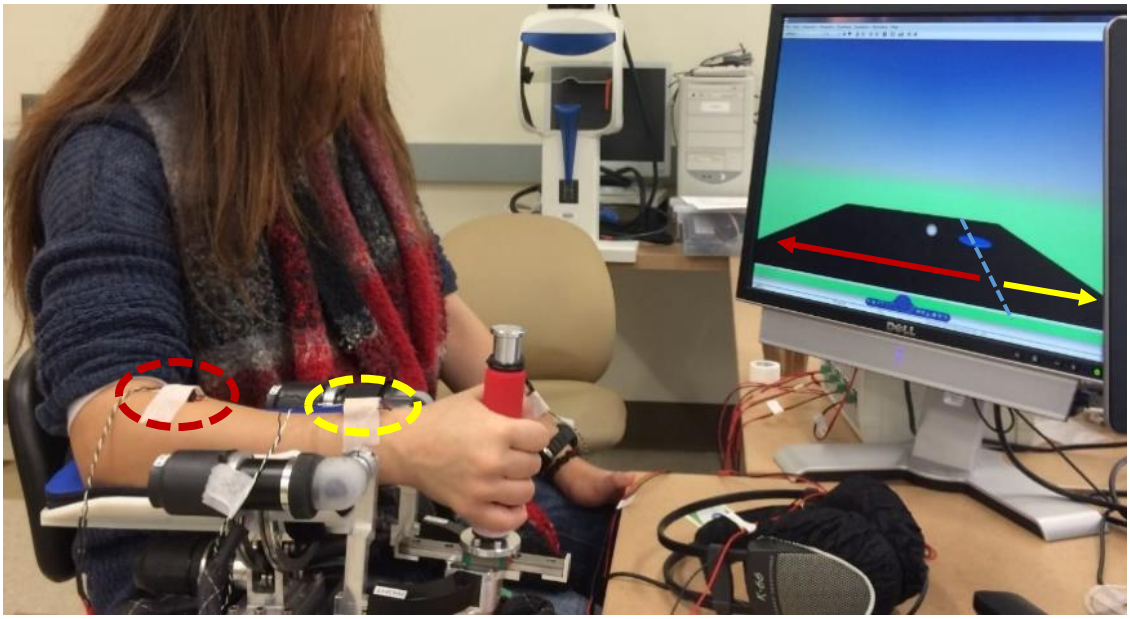

Figure 4. Intervention task. The participant adducted the wrist so the board tilted toward the further end so the ball rolled toward the target circle. The two motors on the performing arm indicated the respective ball position relative to the target, shown as the blue circle. The distal motor (indicated by the yellow circle) was switched on when the ball was on the right side of the target, indicated by the yellow arrow. The proximal motor (indicated by the red circle) was switched on when the ball was in the area indicated by the red arrow.

Participants completed one 24-minute session on Visit 1 and another one on Visit 2. Both sessions began with a familiarization phase and then continue with three 8-minute training blocks. During the familiarization phase, participant first learned about how to interact with the *WristBot* and how their wrist movement controlled the virtual board tilt. Then the vibratory motors were placed on their forearms and respective information of each motor were explained. Participant were instructed to pay attention to associate the feedback with the ball-target distance with vision available. Once the participant could perform the task with vision comfortably, they were asked to perform the task with eyes closed and were encouraged to formulate strategies to complete the task. The familiarization phase was capped at 10 minutes. Then the participant began the three 8-minute intervention blocks. At the beginning of each block, the participant performed three trials with vision available to familiarize with the physical properties of the virtual reality environment. Then they performed the rest of the block with vision occluded. When the participant spent considerable time in one trial, they would be asked to

verbalize their challenges and may be asked to perform the task with eyes open to review their strategies.

The total time that participants performing the intervention task was approximately one hour, including approximately 10 minutes of familiarization with vision available and 48 minutes with vision occluded. This was relatively shorter than most sensorimotor interventions for chronic stroke survivors. The rationale that an improvement in the proprioceptive acuity after the intervention can be expected was based on previous studies from our laboratory employing the virtual balance board task with visual feedback in healthy elderly (Elangovan, Cappello, Masia, Aman, & Konczak, 2017) and patients with Parkinson's diseases (Elangovan, 2016). After a 10 – 35 minutes of the intervention, participants showed an average of approximately 25% reduction in their wrist proprioceptive acuity. Therefore, with more than double of the intervention time in this study, an improvement in proprioceptive acuity was expected.

Outcome measures

Just-noticeable difference (JND) threshold

Participant sat in the height-adjustable chair at a comfortable height with the tested forearm secured with Velcro strap to minimize movement during testing and vision occluded. Pink noise was provided via headphones to obscure sounds generated by motor movement to prevent additional information about wrist position. The participant's wrist was displaced from the resting position (10° wrist adduction, i.e. ulnar deviation) at a constant angular velocity (6°/s) to the stimulus position. Two stimuli were presented in each trial. One was the reference position of 5° wrist abduction. The other one was the comparison position based on the non-zero stimulus difference generated from the psi-marginal adaptive method. Therefore, the comparison position was always more abducted than the reference position. The order of the two stimulus positions were randomized. In each trial, participant verbally identified the stimulus with the larger amplitude by answering the following question: *"Which position was farther from the starting position?"* The algorithm selected the next stimuli difference based on the participant's response. A correct response was followed by a smaller stimulus difference than the

previous trial. Breaks were scheduled every 10 to 15 trials, upon request or when the participant demonstrated clear signs of inattention. 30 trials in total were administered.

The psi-marginal adaptive method (Prins, 2013) selects the stimulus difference for each trial based on the participant's response to the previous stimulus difference and estimates the JND threshold based on the fitted performance function every trial. The JND threshold used in the study was the estimate at the last (30^{th}) trial. As a psychophysical method, this method infers the performance of an underlying sensory mechanism from participant's pattern of responses, a performance function that describes the probability of observing a correct response as a logarithmic Weibull function of the stimulus difference. In this study JND threshold was defined as the smallest stimulus intensity that the participant can discriminate based on the fitted performance function. The method aims to minimize the expected uncertainty of the posterior distribution generated from the current performance function across all threshold and slope values, which were selected for the next trial. The selected threshold and slope generates the next stimulus difference using the psychometric function. Stimulus difference was initiated at 1.92°, slightly higher than the normative threshold of 11 young adults with no signs of neurological condition for easy detection (Cappello et al., 2015). The stimulus difference of the following trial depended on the participant's response – the stimulus difference decreased after a correct response and vice versa. Test-retest reliability indicated by Pearson correlation coefficient $r = 0.99$ between 1^{st} test and 2^{nd} test, $r = 0.97$ between 1^{st} test and 3^{nd} test. The average within-subject variability was 0.09° (Cappello et al., 2015). The method was executed with customized MATLAB scripts (MathWorks, Inc., Natick, MA) that primarily employs Palamedes toolbox (Prins & Kingdom, 2009).

Movement accuracy in 1-DOF and 2-DOF tracing tasks

Participant traced templates on a computer monitor involving both wrist abduction/adduction and flexion/extension with the *WristBot* handle. Angular positions of wrist flexion/extension and abduction/adduction were recorded by optical encoders housed in the Wrisbot at 100 Hz. Wrist flexion/extension angular position was translated to linear horizontal cursor movement while wrist abduction/adduction angular position

was translated to linear vertical cursor movement. This task was to examine the transfer effect of the proposed wrist proprioceptive training on the untrained motor task. The task consisted of five shapes: horizontal line, vertical line, triangle, figure of eight and ellipse, which were sized to the 60% of the participant's active ROM in the respective DOF except for the triangle (Figure 5). The triangle template was sized solely based on the ROM of the abduction/adduction to prevent the slope of the two-DOF sides from being biased by the participant's ROM in the flexion/extension direction. The width of the triangle was 30% of abduction/adduction ROM. During the task, the reference template was always available and a target circle indicated the direction of the movement. Participants always started tracing with a wrist flexion movement, which means right-handers started from the right end of the shape and left-handers started with the left end of the figure. For each visit of each participant time series angular position data obtained from the wrist tracing tasks were filtered with a low-pass 4th-order Butterworth filter with a cut-off frequency of 2.5 Hz. Spatial error was indicated by computing the minimal distance of each sample point of the tracing cursor to the reference template in respective tasks using customized MATLAB scripts (MathWorks, Inc., Natick, MA). This teste was designed to verify Aim 2: the wrist proprioceptive training program improves the spatial accuracy of wrist motor performance of the affected arm in untrained tracing tasks in adults with chronic stroke. A decrease in the spatial error at the posttest compared to the pretest indicates an improvement in spatial accuracy of the tracing performance. Independent from computing spatial error, individual traces were normalized to the range of the target template to create visualization for average group performances.

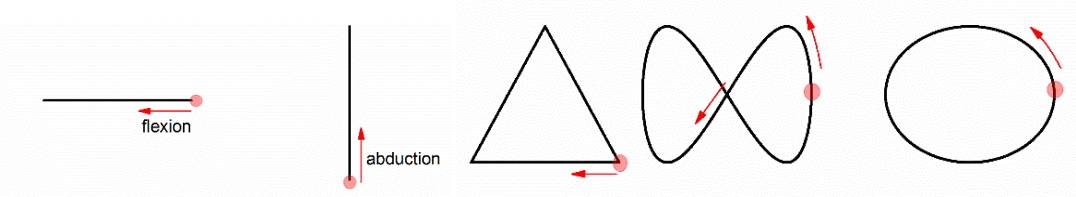

Figure 5. Wrist tracing figures. Red circles indicate the starting pointing for right-handed users.

Movement time to complete a wrist functional task

Participant performed a pointing task with a computer mouse to verify the transfer effect of the proposed proprioceptive training to functional unconstrained wrist motor performance. The participant sat in a height-adjustable office chair in front of a 13-inch monitor with a resolution of 1600 x 900 pixels. They held the computer mouse with the same hand that they performed the wrist training task. They could choose whether to use a mouse pad. If a mouse pad was used, the pad was secured with adhesive tapes on the desk with the position indicated by the participant. On the monitor, two blue circles with a radius of 50 pixels (0.9 cm) on a black background were presented at 20% of the screen width from the midline, approximately 11.5 cm apart. The positions were chosen to be in the midrange of the wrist ROM. The task began with the cursor appeared in the center of the monitor and the participant was instructed to move between the two target circles as fast as possible. The color of the target circle changed when participant moved the cursor within the target circle. A pointing attempt was considered successful when the cursor stayed within the circle radius for 0.2 s. The task finished when 10 successful attempts were achieved. Before the task began, familiarization of 1 to 2 practice trials were given for the participant to optimize the physical environment, such as their arm placement on the desk, the distance to the monitor or how they would hold the mouse. Position data of the computer mouse were recorded at 50 Hz. The data was then filtered by a filtered with a low-pass 4^{th}-order Butterworth filter with a cut-off frequency of 5 Hz offline. The outcome measures of this task were 1) time required to complete 10 successful repetitions and 2) spatial accuracy in horizontal and vertical directions indicated by the endpoint pointing error, the distance between every endpoint pointing attempt and the target center in the respective directions. Post-processing was performed in customized MATLAB scripts (MathWorks, Inc., Natick, MA). Movement time indicates the global motor performance while the spatial error indicates the process of movement.

Measures of SEPs

Participant sat in a height-adjustable chair with a back support (Figure 6). They were instructed to minimize bodily movement, fixate their gaze at the target straight ahead on

an object throughout the electroencephalography recording. Median nerve stimulation was applied to the training side. Electrical stimulation was generated by Grass S88 stimulator (Grass Technologies, West Warwick, RI) with SIU 5 stimulus isolation unit (Grass Technologies, West Warwick, RI). Two surface electrodes were placed along the longitudinal axis of the forearm near the wrist crease. The cathode placed proximal to the anode by 2 cm center-to-center. Square-wave pulses of 0.2 ms duration were delivered at 2 Hz and at the voltage just sufficient to induce a noticeable thumb adductor twitch. The stimulation voltage of the first SEP recording was used for recordings in subsequent visits unless it was not sufficient to elicit a visible response or the participant requested to lower the intensity while a visible response was still observable. 1200 stimuli were delivered in two blocks, with a break at 600^{th} stimuli when participants could move in their seat.

EEG data was recorded continuously from nine Ag/AgCl electrodes mounted on an elastic cap (Waveguard EEG cap, eemagine Medical Imaging Solutions GmbH, Berlin, Germany) using ANT Neuro eego system (eemagine Medical Imaging Solutions GmbH, Berlin, Germany). The montage used covered the primary sensorimotor cortical area (Fz, F3/4, FC1/2, FC3/4, Cz, C3/4, CP3/4, CP5/6, P3/4) on the contralateral hemisphere of the stimulated wrist and bilateral mastoid processes based on the standard international 10–20 system. Signals recorded from bilateral mastoid processes were used to re-reference the scalp recording offline. All signals were sampled at either 2 kHz or 4 kHz with a 24-bit A/D-converter.

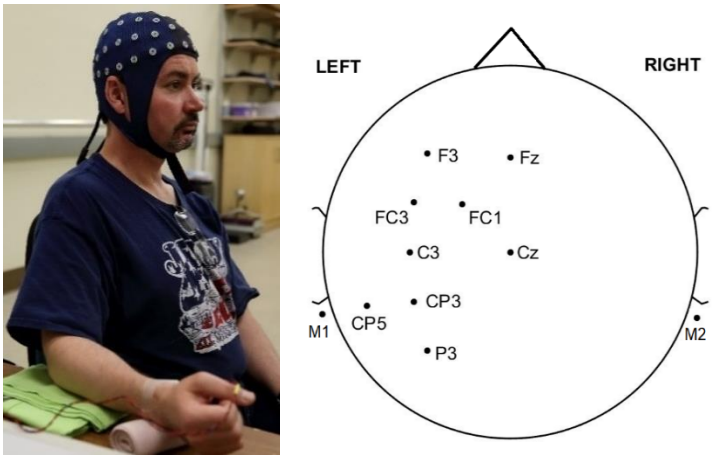

Figure 6. Setup of the SEP recording. *Left*, participant was seated in a height-adjustable chair with the tested arm rested on the table in a dimmed, quiet room, with gaze fixated straight ahead on an object. The stimulation electrode was secured on the wrist with a hypoallergenic, adhesive medical-grade tape, shown on the right wrist. *Right*, SEP montage used for testing the right side. The figure was created with EEGLAB Toolbox (Delorme & Makeig, 2004).

EEG data was then processed with EEGLAB toolbox (Delorme & Makeig, 2004) and ERPLAB toolbox(Lopez-Calderon & Luck, 2014) in MATLAB (MathWorks, Inc., Natick, MA). First, continuous EEG signals were visually inspected to remove clear electromyography (EMG) or movement artifacts. Second, the data was resampled to 1000 Hz to allow subsequent analysis across participants whose data were sampled at different sampling rates due to equipment updates. Third, the average values of the continuous EEG signals were subtracted from the signal to remove the DC offset and then the data was filtered with a high-pass 2^{nd}-order Butterworth filter with a cut-off frequency of 0.1 Hz and a low-pass with a cut-off frequency of 200 Hz in series. Signals were then re-referenced to the average of signals recorded from bilateral mastoid processes as a common practice to allow for optimal signal magnitude obtained at frontal electrodes. Lastly, the continuous signals were segmented into 300-ms epochs with 100 ms before and 200 ms after the onset of the peripheral stimulus. Artifact rejection was performed through a moving average method that flagged epochs that contained any peak-to-peak amplitude higher than 100 μV in 200-ms moving window in a 100-ms step in ERPLAB. All artifact-free epochs were then averaged to generate the grand average for each visit for each participant. On average 89% of total epochs were accepted after artifact

rejection. The acceptance percentage ranged from 58% (666 epochs) to 99.5% (1416 epochs) of total number of stimuli applied. Two measures were extracted from to characterize the temporal and spatial features of N30 based on individual grand SEP waveforms for each participant: (1) peak latency of N30, defined as the first negative peak from the frontal electrodes (F3/4, FC1/2, FC3/4) after 28 ms (Cruccu et al., 2008). (2) peak-to-peak amplitude of P27-N30: P27 referred to as the positive peak prior to N30, typically occurring from 22 to 28 ms after the stimulus (Longo, Pernigo, & Haggard, 2011). Peak-to-peak amplitude was used to indicate the amplitude of N30 to account for different noise levels across visits and subjects instead of the absolute peak amplitude.

Lesion-behavior mapping

To identify what lesion sites influenced intervention-related outcome measures, voxel-based lesion symptom mapping (VLSM) was performed based on MRI images of all stroke participants acquired at the acute phase in various clinical sites. The pretest measurements of JND threshold, N30 latency and P27-N30 peak-to-peak amplitude at pretest indicated baseline proprioceptive impairment while the change from pretest to posttest of the measurements indicated intervention-related changes. First, lesions were manually traced in MRIcroGL (Rorden & Brett, 2000) primarily from T2-weighted images or fluid-attenuated inversion recovery (FLAIR) images. Lesion tracing was aided with reports by attending radiologists or neurologists from medical records. For each slice, the lesion area was identified by a change in brightness compared to the analogous site in the contralateral hemisphere. Subsequently, the manual trace, T2-weighted image where the lesion tracing was based and associated T1-weighted image(s) were then normalized to the standard MNI (Montreal Neurological Institute) 152 template using enantiomorphic normalization (Nachev, Coulthard, Jäger, Kennard, & Husain, 2008) in the Clinical Toolbox incorporated in SPM 12 (Rorden, Bonilha, Fridriksson, Bender, & Karnath, 2012). Images of four participants with right lesions were mirrored to the left hemisphere before generation group overlay plots.

Statistical analysis

Nonparametric tests were employed for all variables for the small sample size and likely non-normal distributions of some outcome variables. Mann-Whitney rank-sum tests were used to compare the pre-intervention performance of the stroke and the control group. Wilcoxon signed-rank tests were applied to test for the differences between pretest and posttest and between pretest and retention. In additional, to quantify the effect sizes across visits, Cohen's *d* were computed from Wilcoxon's statistics as $d = 2r/\sqrt{1-r^2}$, where $r = \mathrm{z}/\sqrt{n}$, z as the *z* score of Wilcoxon statistics (Fritz, Morris, & Richler, 2012; Ivarsson, Andersen, Johnson, & Lindwall, 2013). Conventionally, $d = 0.20$ is considered as a small effect, $d = 0.50$ as medium and $d = 0.80$ as large (Fritz et al., 2012) (Cohen, 1988). One caveat that warrants caution of interpreting the effect size is when $n < 10$, the normal distribution on which the *z* score of the *W* statistics relies may not be appropriate (Fritz et al., 2012). The other note of caution is that this conversion method tend to generate higher *d* values than a parametric method, as much as 0.1 for a 0.79 effect size (Ivarsson et al., 2013). Post hoc power analysis was performed for pretest-posttest comparisons of the stroke group that did not reach statistical significance. Subsequently, sample size required to reach statistical significance was computed for future reference. Spearman correlation coefficients (r_s) were used as measures for bivariate correlations. The significance level was set at $\alpha = 0.05$. Statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY: IBM Corp.). Power analysis was performed in G* Power 3.1, using Lehman method with Laplace distribution where power is interpreted as the probability of Wilcoxon test to detect the effect size found in this study (Faul, Erdfelder, Lang, & Buchner, 2007).

Results

All participants tolerated the intervention session well. No discomfort was reported after the intervention. Three stroke participants completed the intervention with the setup adjusted. One participant (S10) could only perform the intervention with vision on the first visit but then able to perform pars of the intervention task without vision on the second visit. Excluding S10, stroke group completed a similar number of trials (median:

82 trials) as the control group (median: 78 trials). Following sections were organized by assessment tasks. In each section comparisons at pretest between the stroke and control groups were presented first to document their baseline performance, followed by presentation on changes across the three visits to document intervention-related effects. Descriptive statistics were reported in medians and interquartile range (IQR) unless otherwise stated. Individual data were provided in the Supplementary Information.

Wrist proprioception indicated by JND threshold

Eleven of twelve stroke participants completed JND threshold testing across the three visits. S10 was unable to complete the test because of no passive movement could be perceived when vision was occluded. Nine of ten control participants completed all three JND threshold testing. Data of C06's posttest was excluded from further analysis because the participant had fallen asleep during the testing. At pretest, seven stroke participants had a JND threshold higher than the median JND threshold of the control group (Control: 1.4° (1.0°), Stroke: 1.8° (1.1°)) (Figure 7). The group difference in JND threshold at pretest did not reach statistical significance ($U = 38$, $p = 0.25$). At posttest, eight of 11 stroke participants lowered their JND thresholds, reducing the group median by 0.5° (1.3° (0.4°)), comparable to the median of the control group at pretest. The change translated to a group average of 16% reduction of individual pretest JND threshold, reaching statistical significance ($W = 10$, $p = 0.0042$, $d = 1.57$) and indicating an improvement in proprioceptive acuity of the stroke group at posttest. At the two-day retention test, seven stroke participants showed mild reduction in thresholds from posttest (average 2% reduction with respect to the posttest) and the median group JND threshold at retention stayed at 1.3° (0.4°), same as the pretest group median, which was still significantly lower than the pretest ($W = 10$, $p = 0.0042$, $d = 1.70$). This indicates the improvement in JND threshold persisted two days after the intervention. In comparison, control group showed only an average of 2% reduction in JND threshold from pretest to posttest. The group median JND threshold reduced by 0.2° to 1.2° (0.9°) ($W = 13$, $p = 0.30$, $d = 0.81$) at posttest and maintained at the same level at retention (1.2° (0.6°), $W = 19$, $p = 0.43$, $d = 0.57$). Overall the control group showed improvement but did not reach significant

change in the JND threshold after the intervention at either posttest or retention. In summary, the findings supported the hypothesis in Aim 1: proprioceptive acuity in the stroke group improved significantly after the intervention.

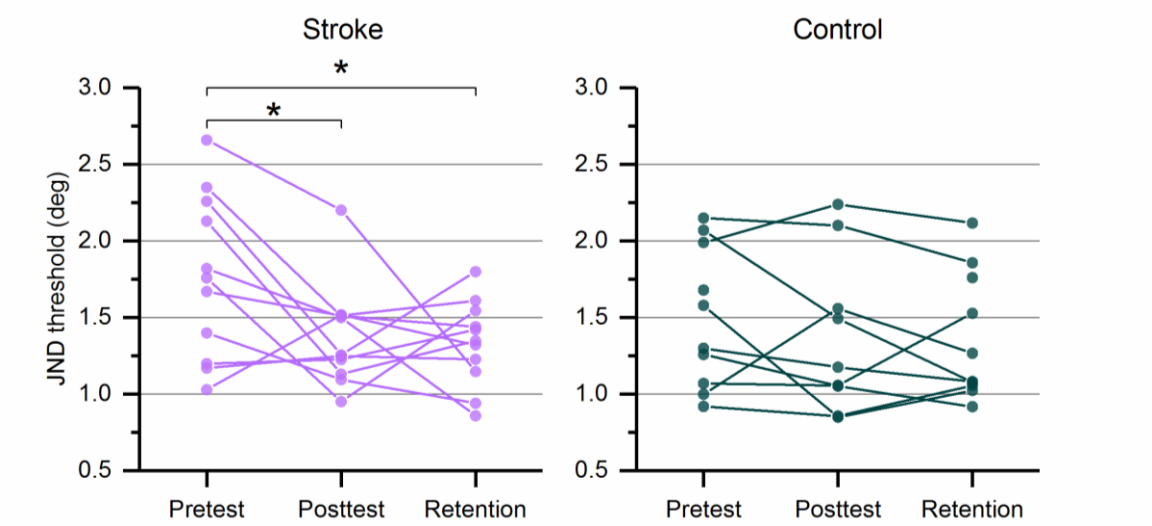

Figure 7. JND thresholds across the three visits. C06's posttest data was excluded while the pretest threshold (1.7°) and posttest threshold (1.8°) were shown. *$p < 0.05$.

Spatial performance of wrist tracing in 1-DOF and 2-DOF tasks

All twelve stroke participants and ten control participants completed tracing tasks at three visits. The average of the radial deviation from the target template were computed as the constant error of the tracing performance. At the of one-DOF tasks, stroke and control groups performed comparably. In comparison, tracing two-DOF figures resulted in larger errors for both groups, especially for the stroke group (Table 2). Figure 8 shows the traces of one high-performing (S07) and one low-performing (S10) stroke participants in comparison with the average trace of the control group at pretest. S07 traced the template as well as the average control group trace and in fact had a constant error lower than the median of the control group. On the other hand, S10 could barely keep their trace on the reference template, resulting a constant error of ~ 1° (0.017 rad), more than twice as high as the control group median. It is worth noting that S10 also had the most impaired proprioceptive function in the sample of stroke participants, who could not perceive any passive movement. What is also interesting is that for the most impaired performers (S11,

S10 and S13), their tracing performance seemed to reflect their upper limb impairment level indicated by their FMA scores (42, 48 and 58 points respectively, see Table 1), lowest among the stroke participants. In tracing the ellipse, both groups showed a similar level of errors (Table 2). In fact, the low-performing stroke participants (S11, S10 and S13) had 20 to 45% less error. Among the two-DOF tracing tasks, the largest errors were observed with tracing figure of eight. The control group on average had a 50% higher error than the triangle tracing task while the stroke group had a 23% higher error. In summary, stroke group performed comparably to the control in the one-DOF tasks but showed higher constant errors in the two-DOF tasks prior to the intervention.

Table 2. *Medians and IQRs of tracing errors of the wrist tracing task*

	Horizontal line	**Vertical line**	**Triangle**	**Figure of eight**	**Ellipse**
Pretest					
Stroke	4.03 (3.03)	6.37 (3.30)	11.26 (6.75)	14.67 (3.04)	10.20 (3.88)
Control	4.88 (1.10)	5.08 (3.17)	7.79 (1.82)	12.24 (2.40)	7.80 (1.88)
U	52	39	17	22	22
p	0.60	0.17	0.005[A]	0.012[A]	0.012[A]
Posttest					
Stroke	4.09 (5.75)	5.11 (3.58)[C]	9.30 (6.71)[C]	14.36 (2.28)	11.80 (3.78)
Control	4.64 (3.16)[B]	5.87 (4.65)[C]	7.70 (2.71)	12.10 (2.54)	7.66 (2.13)[C]
Retention					
Stroke	3.12 (3.03)	5.39 (3.58)	10.69 (4.50)[C]	14.16 (3.05)	10.85 (3.17)
Control	3.21 (0.72)[C]	3.24 (5.41)	7.85 (2.04)	12.60 (2.49)	7.18 (3.13)

Note. Unit is 10^{-3} rad. [A], $p < 0.05$ for between-group comparisons at pretest. [B], $p < 0.05$ for pretest vs. posttest comparison. [C], $d \geq 0.8$ for comparisons across visits (i.e. pretest vs. posttest or pretest vs. retention).

With respect to tracing performance across visits, the stroke group showed changes varying vastly across tasks: 17% and 20% reductions in the group medians of constant error were observed in the triangle tracing and vertical line tracing at posttest with the improvement of nine stroke participants in both tasks. The differences were large effects but did not reach statistical significance ($W = 16$ & 15, $p = 0.08$ & 0.06, $d = 1.15$ & 1.30 respectively). On the other hand, in the ellipse tracing, eight participants showed an increase in constant error at the posttest, which yielded a 16% increase in the group median ($W = 24$, $p = 0.27$, $d = 0.72$). When looking at changes at the individual level

across five tracing tasks, S08, S09 and S13 showed improvement in four tasks, the highest number of tasks with improvement found in the stroke group. Across tasks where they showed improvements, the average reduction was 2.42 $x10^{-3}$ rad, which was 26.0 % with respect to individual pretests. At retention, the most reduction with respect to the pretest error observed in the stroke group was in the horizontal line tracing, 23% of the pretest median ($W = 35$, $p = 0.57$, $d = 0.37$). The largest effect size was observed in the triangle tracing ($W = 18$, $p = 0.11$, $d = 1.08$). However, neither reached statistical significance. As a reference, the control group showed less than 1 x 10^{-3} rad change at posttest and less than 2 x 10^{-3} rad change at retention overall (Posttest vs pretest: Ws = 12 – 26, ps = 0.064 – 0.92, d = 0.097 – 1.49; Retention: Ws = 18 – 39, ps = 0.014 – 1, d = 0.50 – 2.32). The difference in the horizontal tracing (1.6 x 10^{-3} rad) from pretest to retention reached statistical significance in the control group. In summary, the results did not support the hypothesis of Aim 2, that is, the wrist tracing performance did not change as a function of the intervention.

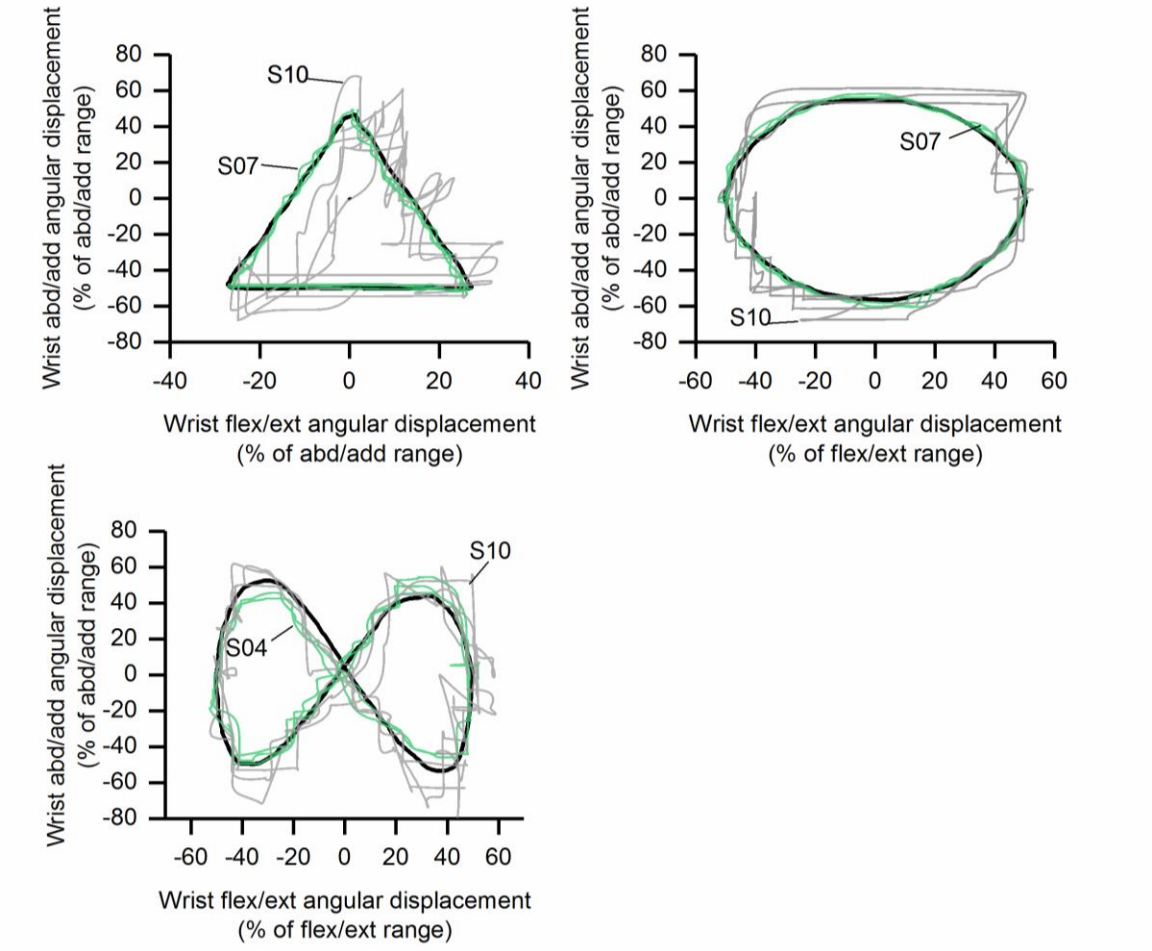

Figure 8. Exemplar wrist tracing performance at pretest. Shown was the average control group trace (black line) and two exemplar stroke participants, one with comparable performance to the control group and the other with large error.

Functional performance in a wrist pointing task

First, using the movement time required to complete 10 successful pointing attempts as a global temporal measure of performance, at pretest movement time of the stroke participants was 11.4 (7.6 s), significantly longer than that of the control group 8.2 (1.7 s) (U = 19.5, p = 0.0083). Looking at the resultant endpoint error indicating the spatial measure of the performance, nine stroke participants had errors higher than the control group median (10.3 (8.4) pixels) which four were outside the maximum of the control group (S03, S08, S09, S10) (Figure 9). Overall, the median of the stroke group (12.4 (18.6) pixels) was not significantly different from the control group. Movement time and

spatial error showed significant correlation across all participants (r_s = 0.47, p = 0.03) and similar magnitude of correlation found when analyzed by group (stroke: r_s = 0.49, p = 0.15; control: r_s = 0.48, p = 0.12).

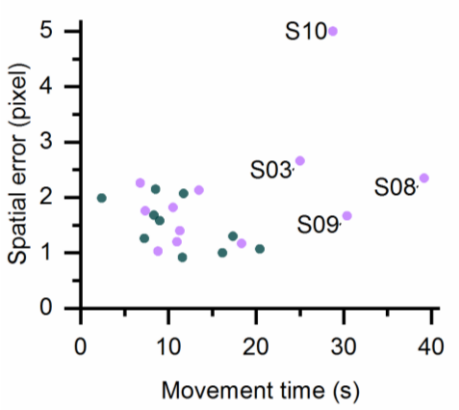

Figure 9. Pointing performance at pretest

At posttest, eight stroke participants reduced their movement time by an average of 2.5 s, 14% of individual pretest movement time while the remaining four participants increased their time by an average of 0.8 s and 9% of individual pretest time (Figure 10). Overall the group median of the stroke group reduced to 10.7 (4.6) s and remained a similar level at retention (10.9 (4.3) s). Despite the large effect sizes, changes across visits was insufficient to reach statistical significances for both pretest vs. posttest and pretest vs. retention (W = 15, p = 0.064, d = 1.30 for both comparisons). In comparison, the control group maintained their performance across the three visits, with their group medians ranging from 8.2 – 8.5 s and IQRs ranging from 1.3 – 1.7 s (W = 23 & 21, p = 0.70 & 0.56, d = 0.29 & 0.43 respectively). Eight stroke participants lowered their endpoint error and the group median reduced to 9.3 (4.7) pixel at posttest, a similar level to median of the control group at pretest (W = 20, p = 0.15, d = 0.95). At retention, only half continued improving their endpoint error compared to their posttest (W = 27, p = 0.38, d = 0.57). Their group median at retention (10.1 (15.9) pixel) was comparable to their posttest median and the control group's pretest and posttest medians. Taking changes in both temporal and spatial measures together, six stroke participants improved on both measures and maintained the improvement at retention. Control group maintained their

performance at posttest (10.0 (10.5) pixel) and retention (13.3 (12.8) pixel) (W = 23 & 26, p = 0.92 & 0.70, d = 0.097 & 0.29). In summary, stroke participants showed slower movement than the control group at pretest and showed large effects of improvement in time and endpoint errors. However, the improvements did not reach statistical significance. This rejects the hypothesis of Aim 3 that wrist pointing performance would change as a function of the intervention.

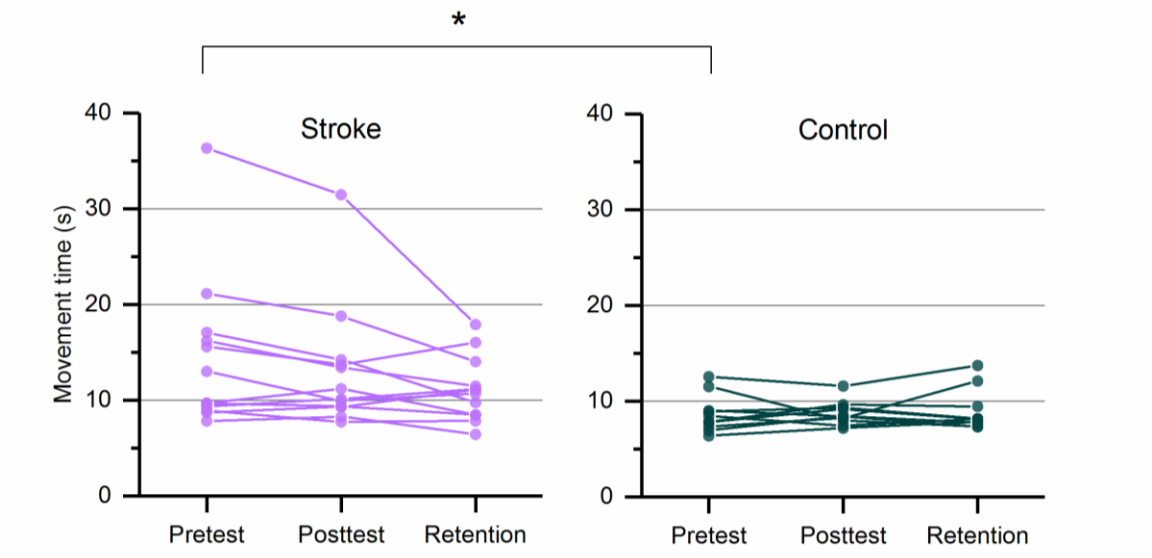

Figure 10. Changes of movement time of the pointing task across visits. The stroke group was significantly slower than the control group at pretest (U = 19, p = 0.008).

SEPs measures

Nine stroke participants and seven control participants completed all three SEP measures. S10 completed the SEP testing at posttest and retention but their data was excluded from the analysis because of involuntary, irregular muscle contractions at both recording sessions. The incompletion was because the SEP testing was skipped to keep the time the participants spent in the laboratory reasonable and prevent excessive exhaustion from prolonged testing. Figure 11 shows the grand average of SEP waveforms of the control group. Recordings from the frontal electrodes (F3, FC1 and FC3) showed comparable waveforms so the proprioception-related SEP waveforms were examined from signals recorded from FC1. Two measures were extracted from SEP waveforms to characterize the temporal and spatial features of the N30 component respectively, N30 peak latency

and P27-N30 peak-to-peak amplitude. Peak-to-peak amplitude was used to account for different baseline noise level across recording sessions. At pretest, stroke group median (39 (9.5), 30 – 64 ms) was higher than the control group median (32 (7), 30 – 40 ms) but only three stroke participants (S05, S06, S08) showed latencies longer than the maximal N30 peak latency of the control group (Figure 12). Overall the two groups had similar medians (Stroke: 51 (12), 46 – 126 ms; Control: 50 (6), 46 – 55 ms)). Expectedly, the group comparisons of N30 peak latency did not reach significant differences ($U = 17.5$, $p = 0.14$). Regarding the spatial measure, the median amplitude of the stroke group was 46% of that of the control group, significantly lower P27-N30 peak-to-peak amplitude (2.07 (2.94), 1.07 – 6.02 μV) compared to the control group (4.47 (3.84), 2.92 – 8.10 μV, $U = 11$, $p = 0.03$).

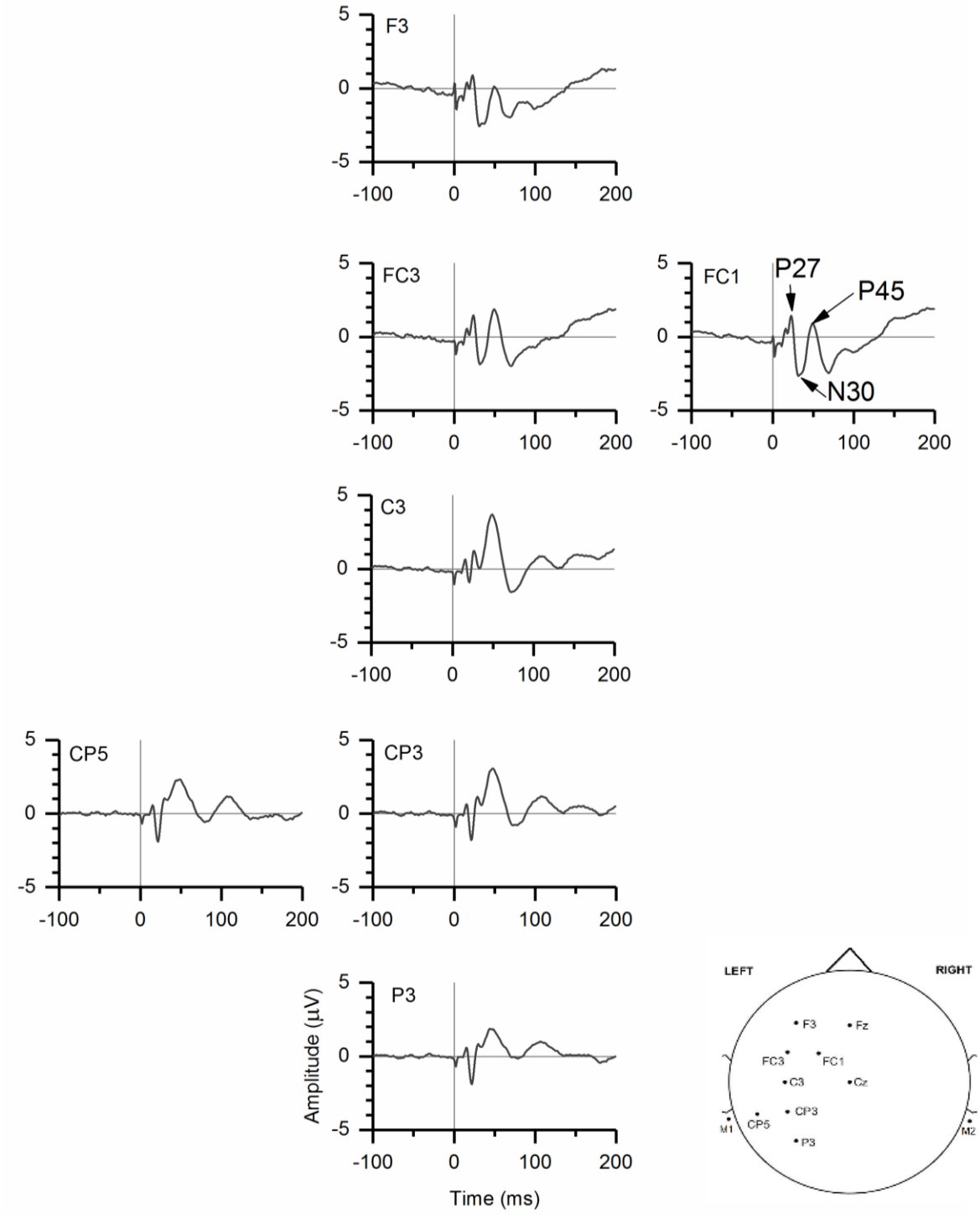

Figure 11. SEP waveforms of the grand average of control group at pretest. Complete axis titles are shown in the figure of P3 electrode.

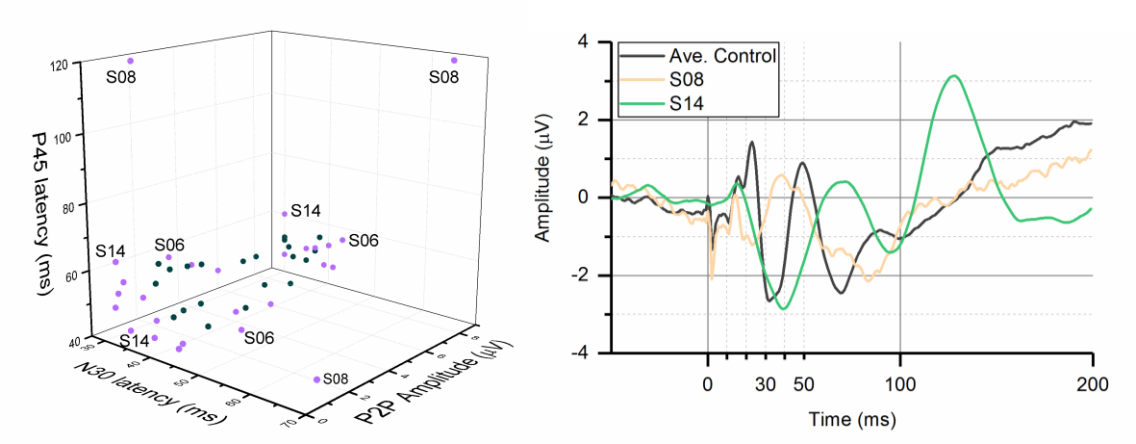

Figure 12. SEP measures at pretest. *Left*, SEP measures at pretest. *Right*, exemplar stroke participants showing delayed N30 peak or decreased overall SEP amplitudes in comparison to the average waveform of the control group.

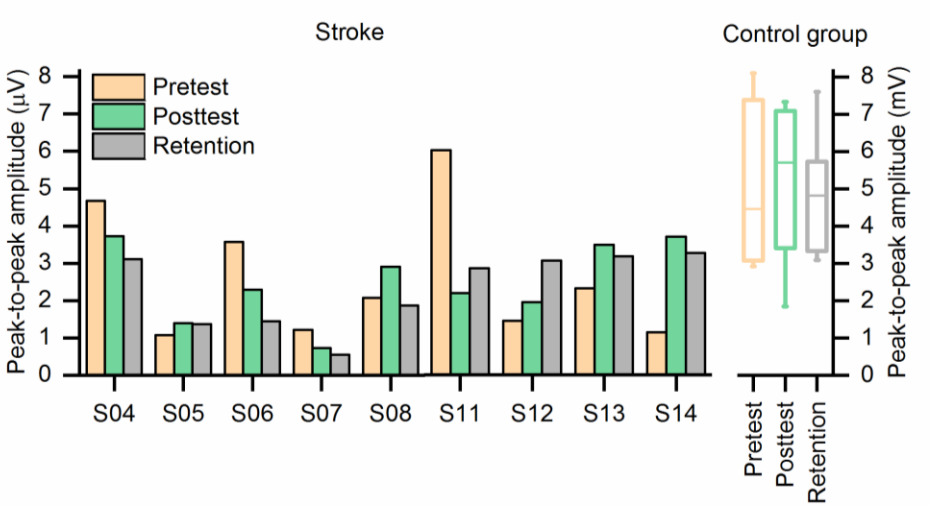

Figure 13. P27-N30 peak-to-peak amplitude across visits. Data of individual stroke participants and the summary statistics of the control group were shown: medians (lines), IQR (box boundary) and 5th - 95th percentiles (whiskers).

Moving on to examine the effects of intervention, the two SEP measures showed minimal change after the intervention. The medians of N30 latency did not change for either group (Stroke: posttest: 39 (10) ms, d = 0.24; retention: 39 (12) ms, d = 0.14; Control: 32 (5) ms for both posttest and retention). Cohen's *ds* for the SEP measures of the control group

were not showed because of the small sample size (n = 7). Regarding the peak-to-peak amplitude, five of the stroke group showed an increase at posttest and four maintained the increase at the retention, yielding comparable group medians (2.3 (1.9) μV, d = 0.08 at posttest and 2.9 (1.7) μV, d = 0.24 at retention. See Figure 12). While the control group showed an increase in amplitude form 4.47 (3.84) – 5.71 (3.50) μV at posttest and 5.64 (3.84) μV at retention, the difference was not sufficient to reach statistical significance (W = 12 and 13, p = 0.81 and 0.94 respectively). In summary, the findings in SEP measures suggested that SEP measures did not change as a function of the intervention, rejecting the hypothesis of Aim 4.

Post-hoc power analysis

Post-hoc power analyis was performed only for the stroke group on comparisons with the highest effec size among those which did not reach statistical differences within each task. In the wrist tracing task, the posttest-pretest difference in the tracing error of vertical line tracing reached p = 0.06, d = 1.30 and therefore was selected for analysis. The post-hoc power analysis revealed a power of 0.96, suggesting the probability of detecting an effect size of 1.30 was 96%. It allowed for achieving $p < 0.05$ with a sample size of 12. This contradicted with our finding of p = 0.06, which might be contributed by the inflation of d values via the employed approach. Further exploratory analysis was performed to examine how much the d value affected the number of sample size required for achieving $p < 0.05$ given a power of 0.96. It was found that n = 13 was required to achieve the statistical significance with an effect size of d = 1.293. In brief, the pretest-posttest difference could be expected to reach statistical significance with n = 13, given the same effect size. In the mouse pointing task, same p and d values were observed for the movemen time at pretest v.s posttest and therefore a sample size of 13 should yield a statistical significance. As for the difference in the endpont error at pretest v.s posttest, it achieved a power of 0.78 and a sample of 20 would be required to reach the statistical significance. For SEP measures, the overall effect sizes were small (d = 0 – 0.24), which achieved a power of 0.11 and required n = 264 to reach the statistical difference in the N30 peak latency.

Examining performance across measures in the stroke group

In this section, 1) relationships between measures at pretest were examined to verify if JND threshold, a behavioral measure of proprioception was related to SEP measures, indicators of proprioceptive processing and if proprioceptive function was related with motor function measures at pretest. 2) Relationships between improvements in JND threshold and baseline were examined to identify characteristics of responders, stroke participants who showed improvements after the intervention. 3) Relationships between JND threshold improvement and changes of other measures to verify if proprioceptive improvement was associated with SEP measures or motor performance measures.

At pretest, four out of five stroke participants who had JND thresholds equal or higher than 1.8° showed either delayed N30 peak latency or P45 peak latency (S05, S06, S08, S14) (See individual data in the Supplementary Information). P45 was the positive peak following N30 obtained from the same electrode (Figure 11) and was not included in the initial analysis. However, by examining individual waveforms, P45 latency may be a complementary measure to N30 latency as the neural correlates for proprioceptive acuity function and therefore was included for subsequent analysis. The pretest JND thresholds of the stroke group showed a moderate correlation with P45 peak latency (r_s = 0.66, p = 0.053, n = 9), N30 peak latency (r_s = 0.53, p = 0.15, n = 9) and peak-to-peak amplitude (r_s = -0.42, p = 0.27, n = 9). When examining proprioceptive measures were associated with motor performance, stroke participants with higher JND threshold at pretest showed higher error of ellipse tracing (r_s = -0.62, p = 0.043, n = 11). The correlations with other motor measures did not reach significance. The next strongest correlation was with movement time of the pointing task (r_s = -0.40, p = 0.22). In summary, before the intervention, higher JND threshold was associated with a longer P45 peak latency and a higher error of ellipse tracing.

Second, changes in the JND threshold from pretest to posttest was used as an indicator to identify responders vs. non-responders. Preliminary observation of the changes of JND threshold across visits suggested that stroke participants who had a pretest threshold

higher than 1.4° improved at posttest while participants who had a pretest threshold no larger than 1.2° showed an increase in threshold. This was confirmed by significant correlations between pretest JND threshold and change from pretest to posttest (r_s = -0.86, p = 0.001, n = 11) in the stroke group (Figure 14). This suggests that stroke participants with higher JND threshold at pretest showed more reduction at posttest. With respect to the temporal SEP measures, stroke participants with 0.8° or more reduction (S06, S08, S12 and S14) at posttest all showed N30 or P45 peak latency longer than the maximum of the control group at pretest except for S12. Confirming the observation, stroke participants with higher P45 peak latency at pretest showed more JND threshold reduction at posttest (r_s = -0.68, p = 0.045, n = 9). On the other hand, N30 peak latency and the peak-to-peak amplitude showed low correlations (r_s = -0.37 & 0.38, p = 0.33 & 0.31 respectively, n = 9). At retention, higher JND threshold at pretest was still associated with more reduction in JND threshold from pretest to retention (r_s = -0.90, p < 0.001, n = 11). Different from the change at posttest, the reduction in the JND threshold from pretest to retention did not show significant correlations with SEP measures (p = 0.13 – 0.48). The strongest correlation was found with peak-to-peak amplitude (r_s = 0.55, p = 0.13). Moving to examining if baseline motor performance could characterize responders, the constant error of ellipse tracing (r_s = 0.55, p = 0.077) showed the highest correlation while pointing performance showed weak association with the JND threshold changes. In brief, participants with higher pretest JND threshold and longer pretest P45 peak latency showed higher reduction in JND threshold at posttest. Participants with higher pretest JND threshold showed higher reduction in JND threshold at retention.

Last, correlations between proprioceptive improvement and changes in SEP measures or motor performance measures were examined. At posttest, JND threshold changes showed weak to moderate correlations with SEP measure changes (r_s = -0.40 – 0.49, p = 0.18 – 0.29), pointing performance change (r_s = -0.21 – 0.08, p = 0.54 – 0.8) or tracing error changes (r_s = -0.17 – 0.13, p = 0.46 – 0.61). At retention, findings for changes in JND threshold with other measures were similar as that at posttest. One finding worth noting was that four stroke participants who showed an increase in the peak-to-peak amplitude

from pretest to retention all had an reduction in the JND threshold (r_s = -0.42, p = 0.27, n = 9) (Figure 14) while all three participants who had an increase in the JND threshold all showed a reduction in the peak-to-peak amplitude. It suggests that that change in the peak-to-peak amplitude could be a neural correlation of the change in the JND threshold. To summarize, JND threshold improvement at posttest was not associated with changes in SEP or motor measures but JND threshold changes at retention were associated with the change in the peak-to-peak amplitude.

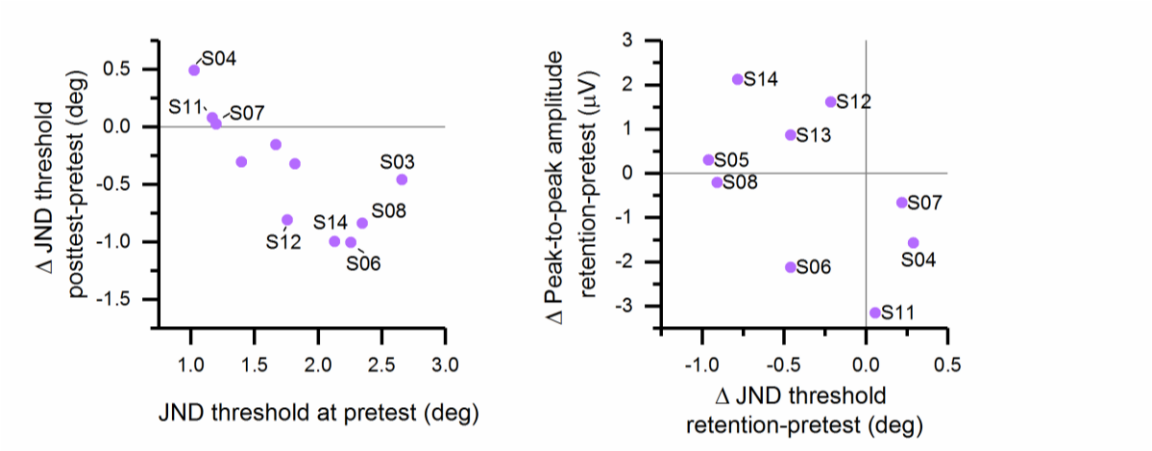

Figure 14. Relationships of changes in the JND threshold with pretest JND threshold (*left*) and with changes in the peak-to-peak amplitude (*right*). A negative change of JND threshold from pretest to posttest (or retention) indicates a reduction in the JND threshold. A positive change of peak-to-peak amplitude from pretest to posttest (or retention) indicates an increase in the peak-to-peak amplitude.

Lesion-behavior mapping

To examine whether lesion locations predict intervention-related changes, stroke participants were further sub-grouped based on (1) the change in the JND threshold from pretest to posttest and (2) the change in the SEP amplitude. Given the high association between JND threshold changes and pretest JND thresholds in the stroke group, regions with overlapping lesions of these participants may either relate to the level of proprioceptive impairment or the amount of intervention-related changes. Figure 15 shows lesions of the five stroke participants who improved the most (S03, S06, S08, S12 and S14) were shown. They showed a reduction in the JND threshold from pretest to

posttest of 0.5° – 1.0° and pretest JND thresholds of 2.1° – 2.7°. They were all females, 42 to 74 years of age, with 14 months or less after stroke onset expect for S03 (27 months) and had a pretest FMA of 64 or higher. Overall, their lesion areas were widely distributed. Two had exclusive cortical lesions (S12 and S14), S06 had exclusive subcortical involvement and two (S08 and S03) had both cortical and subcortical lesions. Superior thalamus and basal ganglia were the overlapping region of more than one participant (S08 and S06). In comparison, the three participants with the least improvement (S04, S07 and S11) who showed either minimal (S07, S11) to an increase (S04) in the JND threshold from pretest to posttest were all males, aging 63 to 73 years old and were 7, 11 and 55 months after stroke respectively. They all had subcortical lesions, overlapping in basal ganglia (Figure 16). Taken together, it suggests proprioceptive impairment could result from lesions of a distributed brain areas, not limited to primary sensorimotor areas or thalamus. It also suggested that lesions in the basal ganglia was not associated with pretest JND thresholds or the changes in the JND threshold.

The other subgrouping for lesion-behavior mapping was the change in the peak-to-peak SEP amplitude for its correlation with changes in the JND threshold from pretest to retention (See Figure 14). A decrease in the amplitude and increase in the JND threshold were found in S04, S07 and S11, whose lesions were shown in Figure 16. The other subgroup (S05, S12, S13 and S14) who showed a decrease in the JND threshold and an increase in the peak-to-peak amplitude had a more widespread lesions, involving cortical and subcortical lesions as well as frontal and parietal lobes (Figure 17). No overlapping in the lesions were found in this subgroup.

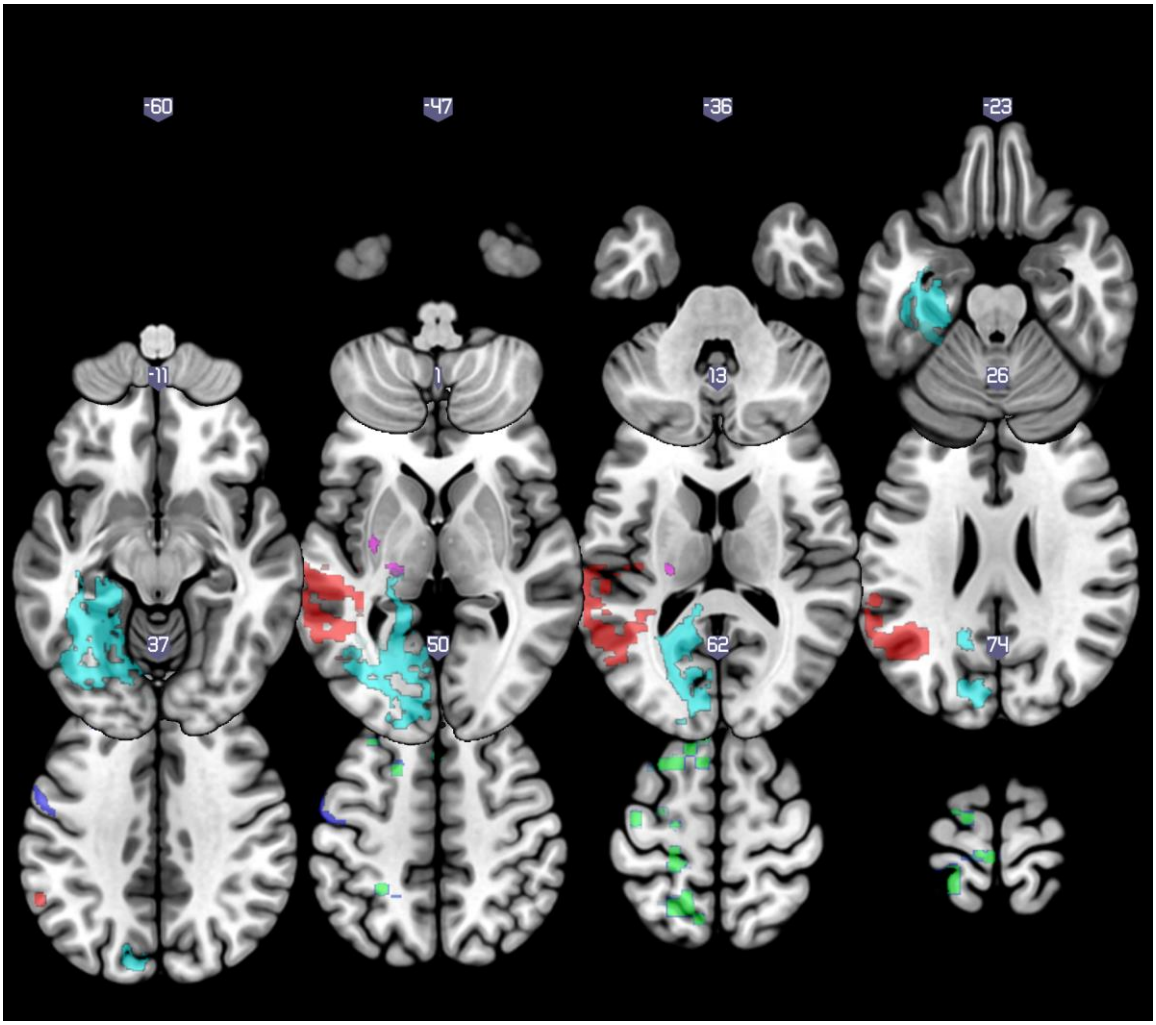

Figure 15. Lesion locations of stroke participants who showed most improvement on the JND threshold from pretest to posttest. Each color represents one participant: S03 (red), S06 (purple), S08 (cyan), S12 (blue) and S14 (green). JND thresholds at pretest and posttest of these participants: S03: 2.7° to 2.2°, S06: 2.3° to 1.3°, S08: 2.4° to 1.6°, S12: 1.8° to 1.0° and S14: 2.1° to 1.0°.

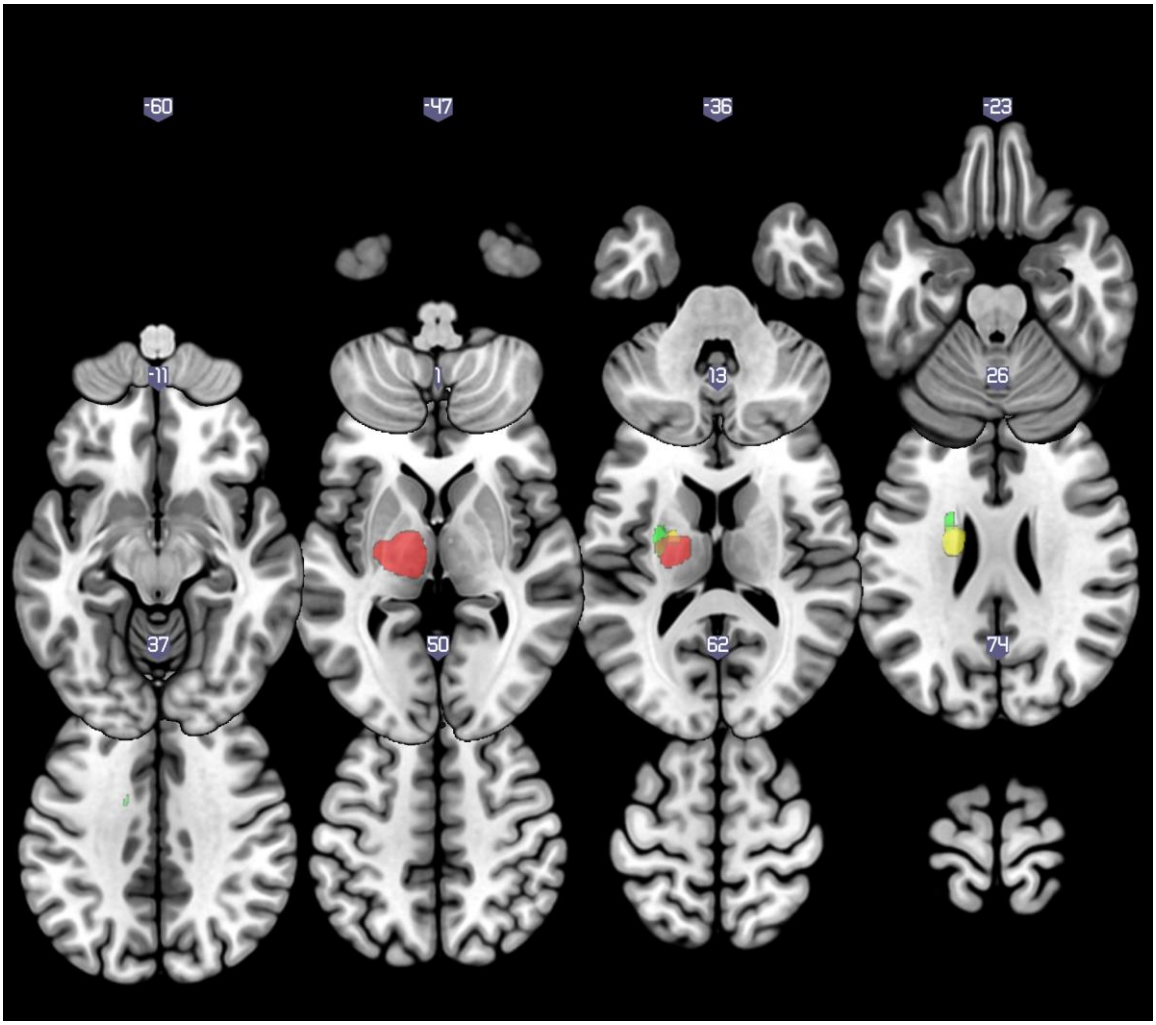

Figure 16. Lesion locations of stroke participants who showed the least improvement on the JND threshold from pretest to posttest. Each color represents one participant: S04 (green), S07 (yellow) and S11 (red).

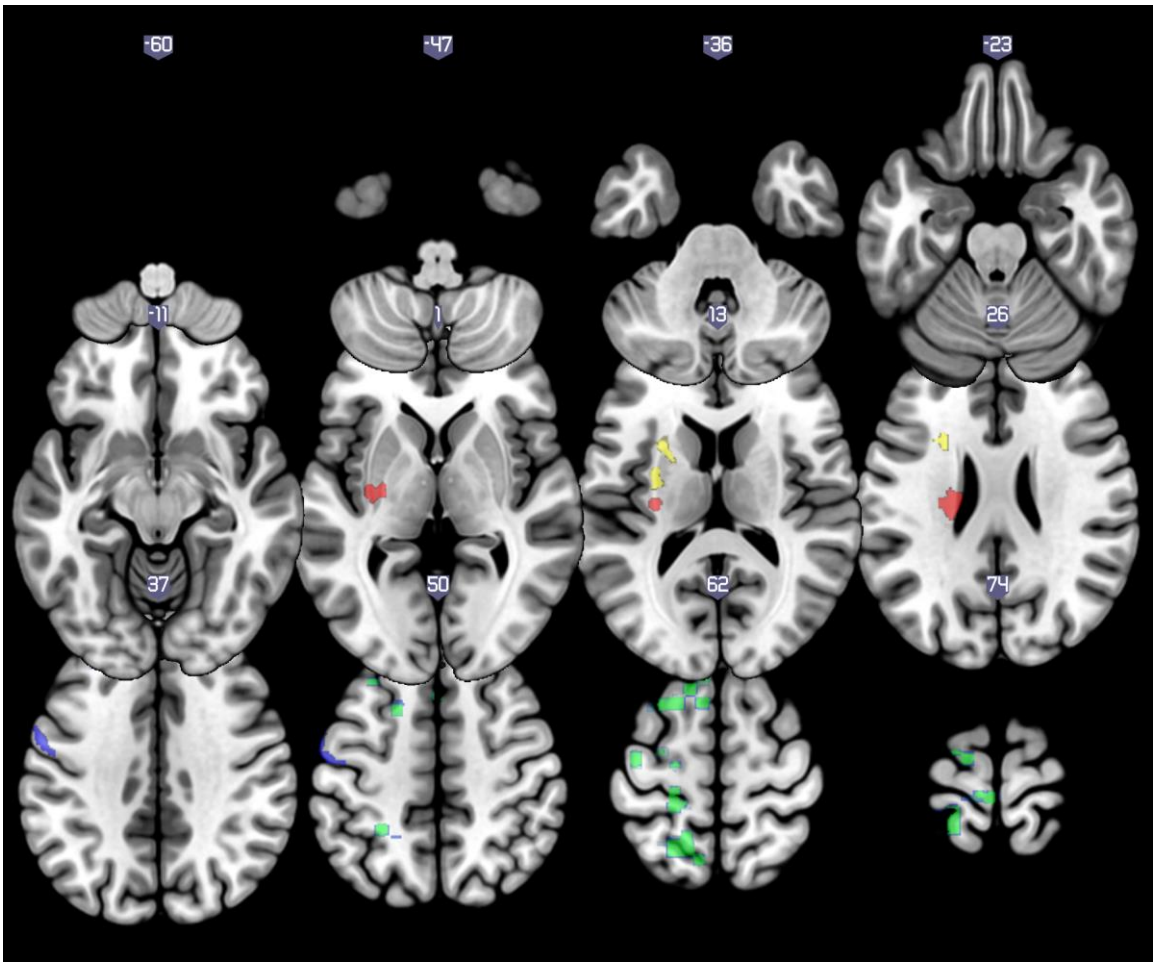

Figure 17. Lesion locations of stroke participants who showed an increase in the peak-to-peak amplitude. Each color represents one participant: S05 (red), S12 (blue), S13 (yellow) and S14 (green).

Discussion

In this study 12 adults with chronic stroke and 10 adults with no neurological conditions completed a brief two-day robot-assisted sensorimotor intervention that aimed to improve proprioceptive and motor function. The stroke participants were functionally independent, with mostly mildly affected upper limb and overall physical function. Before the intervention, compared to the control group, the stroke group had (1) comparable proprioceptive acuity, (2) larger errors in tracing two-dimensional figures, (3) longer movement time for accomplishing the functional wrist pointing task and (4) lower

P27-N30 peak-to-peak amplitudes of SEPs induced by median nerve stimulation. Participants with lower proprioceptive acuity indicated by lower JND threshold showed more delayed P45 peak latencies and larger errors in the ellipse tracing. After intervention, the stroke group showed a significant improvement in their proprioceptive acuity, approaching the pretest median of the control group but did not improve significantly in their SEPs and measures in the tracing and pointing tasks. Participants who showed more improvement in the proprioceptive acuity had a lower proprioceptive acuity and more delayed pretest P45 peak latency. The improvement in proprioceptive acuity at the two-day retention was associated with an increase in the SEP amplitude.

Changes in the proprioceptive acuity after intervention

Here we documented proprioceptive acuity improvement in an untrained perceptual discrimination task after the brief training program in chronic stroke adults with mild impairment. The reduction of 0.5° of the stroke group median from pretest to posttest was a 16% reduction of individual pretest thresholds and 5% of the reference position of 10° wrist abduction. This finding was encouraging for a brief bout of intervention for stroke survivors at minimum three months after their stroke, when functional recovery was minimal (Kwakkel, Kollen, & Twisk, 2006). Furthermore, the proprioceptive improvement from the active sensorimotor intervention was reflected in an untrained, passive joint position discrimination task. Lastly, the improvement observed immediately after intervention was retained two days after intervention, suggesting a relatively long-term behavioral change. On the other hand, it is important to consider any alternative explanations for the observed improvement. The first alternative explanation is the learning effect. It is unlikely to explain the change in proprioceptive acuity for the following reasons: (1) Participants received no feedback of their performance or results of the JND threshold testing. (2) Reliability of the threshold testing was documented in young healthy adults (Cappello et al., 2015) and early Parkinson's disease patients (unpublished work in our laboratory). (3) The lack of continuing improvement of JND threshold from posttest to retention, which should have occurred if there were a learning

effect. Second, one might suspect cognitive impairment would confound the JND threshold testing. Indeed, the participants were only screened for memory impairment and it was possible that executive function impairment was not detected. However, it is unlikely that the intervention task improved executive function and then drove the changes of proprioceptive acuity within such a brief intervention period. In addition, the baseline proprioceptive acuity was associated with the baseline P45 peak latency, which suggests the behavioral proprioceptive acuity measure was likely to be associated with the underlying proprioception-related processes.

A 16% reduction in the proprioceptive acuity at posttest was comparable to another study where a similar rationale of providing task-relevant augmented feedback and vision-occluded sensorimotor training was employed. De Santis et al (De Santis et al., 2014) cued chronic stroke participants the desired reaching direction by providing an assistance force during a center-out whole-arm reaching task. Six out of seven participants improved in the discriminative threshold of movement direction, yielding an average of 25% of improvement and reaching statistical differences compared to the pretest after five intervention sessions over two weeks. However, the improvement was not retained one week after intervention. The rate of improvement of this study and the study by De Santis et al were comparable to interventions primarily employed primarily somatosensory discrimination tasks. They overall reported 21% – 67% improvement on proprioceptive acuity assessed by joint position matching errors after 8 – 40 hours of intervention (Borstad et al., 2013; Byl et al., 2003; Carey & Matyas, 2005; Carey, Matyas, & Oke, 1993). Taken together, it appears that the active sensorimotor interventions coupled with feedback might be more efficient by yielding improvements in proprioception with a shorter time of intervention. What other elements of the intervention employed in this study may contribute to the benefits on proprioception? First, the intervention task was a functional motor task where somatosensory function played a critical role, in contrast to interventions that focused on training somatosensory processing itself, such as discrimination or detection (Carey et al., 2011; Yekutiel & Guttman, 1993). Furthermore, the intervention employed augmented, real-time feedback

relevant to users' movement and the task during learning a new motor task. Augmented feedback has been recommended for somatosensory interventions (Sullivan & Hedman, 2008; Trombly Latham & Bentzel, 2014) and is theorized to lead to "re-calibration" of the sensorimotor system during motor learning in an impaired somatosensory system (Kita et al., 2013; Seitz & Dinse, 2007). VTF in this study signaled the consequences related to the user's wrist movement might have helped with this process. Lastly, the intervention was performed primarily with no visual feedback which may have allowed users to pay attention to the somatosensory information and therefore utilize it, as recommended in rehabilitation literature (Sullivan & Hedman, 2008) and used by somatosensory discriminative interventions (Aman et al., 2014).

Changes in motor performance after intervention

Other than improvement in proprioceptive acuity, in the untrained motor performance, participants showed 14 to 25% improvement with large effects in the pointing performance and up to 22% improvement with large effects in the tracing performance. Despite the large effect sizes, the differences did not reach statistical significance. This suggests that statistical insignificance of motor improvement after the intervention is likely due to insufficient sample size and large between-subject variability indicating unsystematic changes within the group. This might be further improved by a longer, more intensive intervention protocol in future studies. Most interventional studies in stroke physical rehabilitation employed much longer interventions (6 – 60 hours) (Langhorne, Coupar, & Pollock, 2009; Turville, Carey, Matyas, & Blennerhassett, 2017). The other strategy would be to complement the current protocol with interventions focusing on functional motor activities to strengthen the transfer effect to untrained motor performance. A study that pooled 80 chronic survivors with somatosensory impairment from two randomized controlled trials that combined somatosensory discrimination training with active somatosensory-relevant exploration activities reported a significant, approximately 50% improvement (1.8 to 2.7 points) in the group median on the functional arm use by Motor Activity Log (MAL) after participants completed 18 – 27

hours of training over 6 – 9 weeks (Turville et al., 2017). In addition, it is more feasible for clinical practice to incorporate multiple approaches to maximize overall intervention effects than using only one approach at a time. Taken together, a significant change in the motor performance may be expected with increased time and intensity of the intervention and complementary activity-focused interventions.

Changes in proprioception-related neurophysiological measures

In terms of SEP measures, changes across visits in temporal measure were minimal across participants. On the other hand, changes in the amplitude spanned a wide range between participants and were not systematic changes as a group. It is difficult to compare directly with literature in stroke rehabilitation that employed SEP changes as outcome measures for sensorimotor interventions. They usually employed week-long interventions and categorical outcomes for SEP measures. For example, the number of participants with SEP characteristics within normative range increased significantly after a 3-week of repetitive cutaneous stimulation on the affected limb in addition to inpatient rehabilitation (Peurala et al., 2002). A case series also described SEP waveforms re-emerged after 22 weeks of daily cutaneous stimulation (Kattenstroth et al., 2012). Given the intervention here was relatively briefly, it might not be surprising that we did not observe a change in SEP measures in stroke participants. On other hands, for the control group, the findings were not expected based on literature reporting changes in SEPs after a variety of brief sensorimotor interventions. Frontal N30-P40 amplitude was attenuated after 20-mins typing movements for 10 minutes (Murphy, Haavik Taylor, Wilson, Oliphant, & Mathers, 2003) but a later study with a similar protocol found an increase of 13% in the frontal P22-N30 after the typing task (Andrew, Haavik, Dancey, Yielder, & Murphy, 2015). One session of 150-trial of visuomotor reaching with force perturbations resulted in a reduction in the peak amplitude of SEPs recorded at the parietal region approximate 100 ms after the somatosensory stimulus, passive arm displacement (Nasir et al., 2013). The discrepancies of the results compared to previous studies may be from two differences: 1) SEP protocol. Nasir et al (Nasir et al., 2013) employed SEPs induced

by passive movement. 2) the typing task employed Murphy and colleagues (Andrew et al., 2015; Murphy et al., 2003) involved only thumb abduction. It might be possible that frontal SEP changes may require more specific, intensive interventions. Taken together, given the variability in changes of the SEP amplitude across participants, a more specific motor task, movement-induced SEP protocol and longer intervention for the stroke survivors may allow for a systematic change at the group level.

SEPs reflect proprioceptive acuity before and after intervention

The baseline proprioceptive acuity was correlated significant with the P45 peak latency when all participants were pooled. The correlations with N30 peak latency and P27-N30 peak-to-peak amplitude was moderate in strength but did not reach statistical significance. The origin of P45 is debated, potential candidates including primary somatosensory cortex (Allison, McCarthy, & Wood, 1992), beyond the primary somatosensory cortex (Desmedt & Bourguet, 1985). Little is available in the current literature on neurophysiological role of P45 independent from N30. N30 is thought to reflect the input of somatosensory information to the cortex based on the findings that it was induced by intramuscular stimulation (Gandevia & Burke, 1990; Restuccia et al., 2002) and barely induced with cutaneous stimulation (Restuccia et al., 2002). The origin of N30 is also debated, including primary somatosensory cortex(Allison et al., 1992), anterior bank of central sulcus (MacKinnon, Verrier, & Tatton, 2000) and supplementary motor (Kaňovský, Bareš, & Rektor, 2003)area. The changes in N30 in general would suggest changes in the sensorimotor areas. Most research involving stroke survivors focused on the prognostic values of SEPs obtained at acute stage on motor recovery while little research had examined SEPs with upper limb somatosensory function. One study showed that all participants with prolonged N13-N19 or N20-P40 interval recorded from the parietal region showed abnormal position sense indicated by a combined rating scale of finger, toe and trunk position sense (Yokota, Hirose, Tsukagoshi, & Tanabe, 1991). Here we documented that P45 peak latency was a neurophysiological correlate of wrist

proprioception. N30 peak latency and P27-to-N30 peak-to-peak amplitude can potentially be neural correlates if the findings are substantiated in a larger sample.

Despite the lack of significant change in SEP measures across visits, participants who showed higher change in the peak-to-peak amplitude from pretest to position showed more improvement in proprioceptive acuity change from pretest to retention (See Figure 14). A slightly weaker correlation was found between changes from pretest to posttest of the two measures but with no statistical significance. This finding suggests that SEP amplitude change could be a neurophysiological correlate of the change of proprioceptive acuity. A similar correlation has been reported between parietal movement-induced SEP and magnitude of a visuomotor learning in young healthy adults (Nasir et al., 2013). Nasir et al 2013 reported out of 15 young healthy adults, participants with higher magnitude of motor learning showed more reduction in the parietal SEP amplitude induced by passive arm displacement immediately after the intervention (Nasir et al., 2013). With respect of the interpretation of the amplitude, peak amplitude measured via scalp ERP reflects primarily the summation of postsynaptic potentials of cortical pyramidal neurons (Luck, 2014) and therefore an increase in the amplitude imply stronger or more synchronized neuronal activity (Luck, 2014). In this study, the increase in amplitude associated with improvement in proprioceptive acuity may suggest a stronger or more synchronized neuronal activation in the generator of N30.

Limitations

Given that this study is a proof-of-concept, exploratory study in nature, there are limitations prompting cautious interpretation and generalization of the findings. The small sample size affects the statistical power and generalizability. The recruitment was challenging. Despite exploring multiple venues, 5% of the potential participants participated and completed the study in the 15-month recruitment period. At screening for eligibility, the two primary reasons for exclusion were a non-cerebral lesion and insufficient active wrist movement. For eligible potential participants, the transportation to the laboratory was reportedly a barrier for participation, e.g. long commute time and

inconvenience of finding a driver for the frequent visits. Provision of mobile robotic system that allows providing intervention outside of laboratory settings may help recruitment. In addition, the sampled stroke participants were mostly functionally independent and showed no overt cognitive impairment. Therefore, the findings may not appropriate to be generalized to stroke survivors with more severe physical impairment or cognitive impairment. Contributed partly by the recruitment challenges and the study being exploratory in nature, the lack of an attentional control phase or group prevented us from ruling out potential effect from participants or researchers. Apart from recruitment and sampling, psychometric properties of customized motor tracing task, customized mouse pointing tasks and N30 measures were not documented, which may affect the ability to detect intervention-related changes. Lastly, we did not survey participant experiences systematically, such as the usability of the *WristBot* system and the intervention task or the perceived intervention-related changes. This information would be feedback to revise the intervention program when recruiting more participants and providing longer intervention periods in future studies.

Conclusion and implications

This study documented that after a brief robot-assisted sensorimotor training coupled with augmented somatosensory feedback and primarily with no vision, proprioceptive acuity was improved in chronic stroke survivors. Overall the proprioceptive acuity change was associated with the change in a proprioception-related neurophysiological measure. This study provides initial evidence for such interventions to be further substantiated with a longer intervention sessions, a wider range of functional abilities of participants and continued use of proprioception-related neurophysiological measures. If proven effective, such interventions or its elements could be employed in clinical practice in addition to existing stroke rehabilitation approaches.

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