THE SENSING BRAIN: THE ROLE OF SENSATION IN REHABILITATION AND TRAINING

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THE SENSING BRAIN: THE ROLE OF SENSATION IN REHABILITATION AND TRAINING

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Table of Contents

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EDITORIAL
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Editorial: The Sensing Brain: The Role of Sensation in Rehabilitation and Training

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Keywords: sensation, perception, sensorimotor, rehabilitation, multi-modal

Editorial on the Research Topic

The Sensing Brain: The Role of Sensation in Rehabilitation and Training

In the skill acquisition and rehabilitation literature substantial attention is placed on the central and peripheral action systems—the efferent and motor performance side of the behavior. However, there is a quiet but steady interest being expressed in the role of sensation—and the perception of sensation—in improving performance. There is also growing recognition that the primary function of different sensory systems can be trained in clinical populations to improve detection, discrimination, and spatial/object recognition. Moreover, the more hidden function of perception of sensations can improve motor performance by improving feedback and feedforward.

We are delighted that the following selection of 12 papers explores these topics conceptually and empirically in humans. They include a systematic review, randomized controlled trials, pilot reports, imaging, and mechanistic studies; in clinical and non-clinical populations.

Several authors have investigated aspects of sensory function in healthy populations. Zerr et al. have explored multi-sensory processing—in particular the temporal binding window—whereby we build up composite and coherent perception. Their pilot randomized controlled trial (RCT) demonstrates this window of time for binding multiple sensory input is both modifiable with training AND can influence function—in this example fluency of speech. Further, Matsugi et al. elaborate on the role of the cerebellum in modulating specifically vestibulo-spinal function using either transcranial magnetic (repetitive cerebellar) or galvanic (noisy) stimulation. Both authors invite readers to consider future clinical applications.

Yasuda et al. and Zhang et al. both considered the sensory aspects of walking in healthy populations. Yasuda investigated augmenting feedback (vibrotactile) to the feet during gait practice whilst Zhang tested a system that simulates the usual tactile pressures experienced on the soles of the feet during walking. Lopez-Rosado et al. explored these ideas in a pilot clinical trial with people with stroke—finding that increasing tactile input to the affected foot (using a sock that passively stimulates) could improve gait speed.

Other papers also investigated the role of sensory training in people with stroke. To provide an overview of the current literature (Serrada et al.) have reported a systematic review and meta-analyses of RCTs investigating the effect of sensory-based interventions on function after stroke. They confirmed that the literature still supports the effectiveness of more passive modalities—stimulating body parts with afferent (sub-motor-level) devices—with the strongest evidence. There is also emerging evidence for the active retraining of sensory appreciation and its effect on both sensory appreciation and motor performance, however more research in larger, stronger studies is still needed.

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Other studies investigated specific modalities for sensory-based intervention post-stroke. Gandolfi et al. concluded that robotic stair walking (as an example of assisted, task-specific training) improved both postural control and sensory integration in their RCT. Allowing the participants to have a voice in their RCT, Turville et al. reported that people post-stroke found their somato-sensory retraining program (SENSe) to be both challenging and rewarding—believing it helped them to increase their sensation and to improve the way they used their stroke-affected arm. Adding to the quest for robust methodology in sensory training research, Carey et al. validated an objective measure of haptic object identification for researchers and clinicians to use to evaluate change in stroke survivors before and after the same form of somatosensory retraining.

The final stroke-related paper investigated a different form of somato-sensory appreciation. Cai et al. concluded that people with stroke can consistently and accurately perceive force production (torque or effort) at either their affected or less affected elbow if tested unilaterally, but not simultaneously. This confirms we need to further consider the role of cognition and attention in sensory rehabilitation.

The remaining paper leads us back to considering multiple sensory input. Cuppone et al. investigated the idea that people with visual impairments may also have spatial perceptual issues. They used an intact sense (auditory) coupled with movement to improve proprioceptive spatial perception in this group. This furthers our understanding of the way we can use complementary senses to substitute in situations of severe impairment.

We hope you find these studies of interest—we are particularly pleased that the research spans different sensory modalities from vision and audition to somatosensory and vestibular. We look forward to ongoing interest in the training of sensation (and perception) for improvement of skilled performance in non-clinical and clinical populations.

AUTHOR CONTRIBUTIONS

All authors contributed to the editorial and approved the final version.

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ORIGINAL RESEARCH
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Sensory Amplitude Electrical Stimulation via Sock Combined With Standing and Mobility Activities Improves Walking Speed in Individuals With Chronic Stroke: A Pilot Study

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Objective: To determine if sensory amplitude electrical stimulation (SES) delivered via sock electrode combined with standing and mobility activities improved gait speed, sensation, balance, and participation in chronic stroke. It was hypothesized that SES would enhance the effectiveness of exercise, resulting in reduced impairment and improved function.

Design: Case Series.

Setting: Home-based intervention.

Participants: Thirteen adults (56.5 + 7.84 years old) with chronic stroke (8.21 + 4.36 years post) and hemiparesis completed the study. Participants were community ambulators.

Intervention: Participants completed 6 weeks of self-administered SES delivered via sock electrode concurrent with standing and mobility activities for a minimum of 5 days/week for 30-min, twice daily.

Outcome Measures: Berg Balance Scale (BBS), Stroke Rehabilitation Assessment of Movement—LE subscale (STREAM), 10 Meter Walk Test (10 MWT), Activities-Specific Balance Confidence Scale (ABC), Stroke Impact Scale (SIS), Perceptual Threshold of Electrical Stimulation (PTTES), and Monofilament testing were administered at pre-test, post-test, and 3-month follow up.

Results: Baseline sensory scores and change scores on functional outcomes were analyzed using Pearson Product-Movement Correlation Coefficients, Friedman test, and Linear mixed models. There was a significant change with 10 MWT self-selected pace (Friedman's $p = 0.038$). Pre-post intervention changes in other outcome measures were not significant. According to the Cohen's effect size classification, there were medium effect sizes for both the STREAM-LE and Monofilaments.

Conclusion: The use of home-based SES via sock electrode combined with standing and mobility activities may contribute to improve gait speed in chronic stroke.

Keywords: stroke, rehabilitation, lower limb, electrical stimulation, gait, function

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INTRODUCTION

Stroke is a leading cause of disability and the fifth leading cause of death in adults in the United States (Mozaffarian et al., 2015). Approximately 50% of this population regains independent ambulation by the end of rehabilitation; however 73% have some degree of long-term gait disability (Woolley, 2001). The amount of community walking done by individuals post-stroke is considerably less than their healthy peers (Michael and Macko, 2007). Falls are a serious consequence of stroke (Langhorne et al., 2000), with more than half of individuals experiencing a fall (Ashburn et al., 2008; Sackley et al., 2008). Post stroke falling is associated with gait and balance dysfunction (Minet et al., 2015). Post stroke changes in sensory dysfunction (Carey, 1995; Winward et al., 2007; Connell et al., 2008; Tyson et al., 2008) have also been associated with falls following stroke (Yates et al., 2002; Tyson et al., 2006; Wutzkea et al., 2013).

Sensory amplitude stimulation (SES) is electrical stimulation utilized at a threshold to stimulate sensory neurons only without stimulating motor neurons. In healthy adults, SES has been reported to enhance cortical motor excitability (Hamdy et al., 1998; Ridding et al., 2000; Kaelin-Lang et al., 2002; Golaszewski et al., 2004; Tinazzi et al., 2005; Meesen et al., 2010) and produce short-term plastic changes in the motor and sensory cerebral cortices (Ridding et al., 2001; Tinazzi et al., 2005; Wu et al., 2005). The enhanced afferent input provided by SES has been hypothesized to contribute to motor recovery of individuals with neurological conditions (Kwong et al., 2008; Bastos Conforto et al., 2018).

In adults post-stroke, SES use has been associated with body structure/function-domain improvements in force (Ng and Hui-Chan, 2007; Klaiput and Kitisomprayoonkul, 2009; Yan et al., 2009; Conforto et al., 2010; Tyson et al., 2013) and sensation (Ng and Hui-Chan, 2007; Tyson et al., 2013). Positive activity-domain changes such as improved gait speed, walking distance, balance, trunk control, and foot placement have been reported. Use-dependent plastic changes in the sensorimotor cortex following SES intervention have been demonstrated post-stroke. A recent systematic review on SES use following stroke examined 15 studies and concluded that the intervention has beneficial effects on motor recovery, especially when concurrently administered with standing and mobility activities The diverse outcome measures used across studies precluded meta-analysis, but the majority of studies reported significant effects on at least one outcome.

While preliminary positive findings following SES interventions post-stroke have been reported, important gaps in the literature remain. Only a small number of studies have examined retention by conducting follow up testing. The majority of SES studies to date have utilized surface electrodes located either over muscles or nerves corresponding to the target function. This electrode placement might actually interfere with activity. Several recent studies have utilized wearable electrodes (socks, gloves), which enable peripheral stimulation over a broad receptor field concurrent with activity (Ng and Hui-Chan, 2007; Yan et al., 2009; Tyson et al., 2013). Finally, studies have been primarily conducted in a clinic or research lab. Few studies have sought to examine whether beneficial effects can occur with a home-based SES intervention.

The aim of this study was to examine the effects of a 6-week intervention of home-based SES via sock electrode delivered during standing and mobility activities in individuals with chronic stroke. This will be known as "SES plus activity." Our primary hypothesis was that there would be significant improvements in gait speed, balance, and balance confidence, which would be retained at 3-months post-intervention. We also hypothesized that there would be improvements in quality of life and in lower extremity active movement.

METHODS

Participants

Participants were recruited from a university-based stroke database. Inclusion criteria were: (1) diagnosis of chronic stroke (>6 months); (2) able to ambulate in the community; (3) at least 21 years of age; (4) English-speaking. Exclusion criteria were: (1) contraindications to electrical stimulation (such as active local infection, inflammation, or malignancy); (2) positive history of neurologic diagnosis other than stroke; (3) chemodenervation (e.g., *Botox*™) in the more involved lower extremity within the past 6 months. All participants were informed of their rights and the expectations for the study. Participants provided informed consent per the protocol as outlined by the Northwestern University Institutional Review Board Office.

Experimental Design

This study used a case series design with a pre-test, post-test, and follow-up. All assessment sessions were completed in a university setting. Research participants completed the 6-week intervention primarily in their home and community. We used STROBE cohort reporting guides (von Elm et al., 2007).

Intervention

Electrical stimulation for SES plus activity was delivered using a muscle stimulator (EMPI, Inc., St. Paul, MN, USA) through a Silver-Thera sock electrode (Prizm Medical, Inc., Duluth, GA, USA) worn on the more involved foot. A secondary 2 × 2″ pre-gelled electrode was placed over the *Tibialis anterior* muscle belly. Stimulator parameters were as follows: symmetrical biphasic waveform, pulse duration 250 ms, stimulus frequency 50 Hz, duty cycle 10-s ON: 10-s OFF, and amplitude above sensory threshold but below motor threshold. Participants performed standing and mobility activities while receiving SES plus activity for a minimum of 30 min twice a day, 5 days/week for 6 weeks. Participants were not provided with a standard set of upright activities. They were only instructed to be standing and active during the stimulation. Participants reported walking around their home, leaving the house to run errands to the pharmacy and supermarket, attending church services and doctor's appointments. A compliance meter on the stimulator captured stimulation time, but didn't account for movement time. Additionally, all participants completed a daily log sheet and recorded stimulation time and standing and mobility activities. Daily logs were detailed and discussed with all participants during reassessment times; this method proved to be efficacious as our participants reported feeling independent while being accountable recording their activities.

Participants returned to the university setting for a minimum two sessions during the 6-week period. The purpose of the visits was to monitor adherence, answer participant questions, to assess the stimulator, and readjust the sensory threshold if needed.

Outcome Measures

The outcome measures administered at pre-test, post-test, and 3 months follow-up included:

Primary Measures

10 meter walk test (10MWT)

The reliability and responsiveness of this test has been established in chronic stroke, as well as its high correlation with self- reported outcome measures in this population. Lower scores correspond to higher gait speed and lower risk for falls. Both self-selected and fast pace were assessed (Bushnell et al., 2015).

Activities of balance confidence scale (ABC)

This is a self-reported survey that captures participant's perceived balance confidence in a 0–100% range (the higher the score, the better the perceived balance). Reliability and normative scores have been reported for chronic stroke (Salbach et al., 2006).

Berg balance scale (BBS)

The BBS examines static and dynamic balance performance. Reliability and responsiveness data is highly correlated with the ABC for individuals post-chronic stroke. Higher scores are indicative of better balance performance (Salbach et al., 2006).

Secondary Measures

Stroke impact scale (SIS)

This is a multi-dimensional, self-reported health status measure post-stroke. Reliability and validity has been established specifically for individuals post-stroke. Responsiveness and normative data have been reported (Bushnell et al., 2015).

Stroke rehabilitation assessment of movement- lower extremity subscale (STREAM-LE)

The STREAM-LE was used to assess voluntary movement in the lower extremity. It has established reliability and responsiveness and normative data in adults post-stroke, and it is recommended as one assessment for function and strength in the paretic lower extremity (Huang et al., 2015).

Monofilaments

Assessment with monofilaments was conducted with the Semmes-Weinstein monofilaments (SWM) test on the sole of the paretic feet. Reliability of the SWM test was high on the paralyzed side (rs = 0.86, $\kappa = 0.71$–0.79), it was low on the other side without paralysis (rs = 0.33–0.50, $\kappa = 0.33$–0.50; Arakawa et al., 2012).

Statistical Analysis

Friedman tests were used to assess overall change over time. Linear mixed models were used as post-tests to demonstrate between which assessment points a significant change was seen. Due to the small sample size, these models were also fit adjusting for one covariate at a time.

Baseline sensory scores and change scores on functional outcomes were analyzed using Pearson Product-Movement Correlation Coefficients. Effect sizes were calculated for each of the outcome measures, as previous similar studies (Sullivan et al., 2015).

RESULTS

Fifteen participants were enrolled; 13 completed the study. **Table 1** summarizes participants' characteristics. Two participants dropped* from the study because of personal reasons unrelated to the study.

Table 2 illustrates the mean outcome measures over time of those who completed the study. There was a significant change over time with 10 MWT at self-selected pace (Friedman's $p = 0.038$). Using a linear mixed models analysis, there was a significant effect on 10 MWT at self-selected pace, $p = 0.030$, comparing baseline to post-test. This remained significant after adjusting for time from onset of stroke, or the use of an assistive device. The change in other outcome measures between assessment periods was not significant.

To account for sample size, Cohen's effect size classifications were determined (Cohen, 1988). There were medium effect sizes for both the STREAM-LE and Monofilaments in participants from baseline to follow up. A large effect size was also observed for both 10 MWT at self-selected and fast pace (see **Table 3**).

Baseline sensory status of the hemiparetic plantar surface of the foot was assessed via the Perceptual Threshold of Electrical Stimulation (PTTES) and Monofilament testing on three locations. This tool has been shown to be reliable for testing sensation following stroke.

Baseline sensory status (both PTTES & Monofilaments) showed moderate to strong correlation with Baseline SIS 16 scores and change scores on the SIS 16 and ABC, suggesting sensory status may be associated with self- perception of physical performance (refer to **Table 4**).

DISCUSSION

Participants experienced significant group effects changes in self-selected walking speed following SES plus activity in the home and community setting. These effects were maintained after the end of the intervention, but they weren't sustained at follow up.

Moderate to strong correlations with Baseline SIS 16 scores and change scores on the SIS 16 and ABC may suggest that sensory status may be associated with self- perception of physical performance. Greater sensory impairment was associated with lower self- reported baseline status. It remains unclear whether utilizing PTTES and/or Monofilaments to assess sensory status is the optimal approach.

TABLE 1 | Participant demographic and baseline data.

ID	Age (years)	Sex	Years since stroke	Body side involved	Baseline scores					
					10 MWT (m/s) self-selected	10 MWT (m/s) fast	ABC (%)	BBS (/56)	STREAM LE (/20)	Mono filaments
1	65	M	9	L	0.97	2.63	83.75	55	9	4.56
2	47	M	15	L	0.63	0.74	81.88	50	10	7.80
3	45	M	10	R	0.83	1.26	72.50	56	9	4.31
4*	67	M	8	L	0.68	0.81	78.13	51	11	4.0
5	44	M	4	R	0.87	1.27	68.75	56	12	7.8
6	60	M	6	R	0.82	1.17	85.63	55	9	4.31
7*	62	M	5	R	0.66	1.11	80	53	15	4.31
8	53	M	10	R	0.53	0.84	73.13	46	11	4.56
9	49	M	16	R	0.88	1.44	85.63	52	11	4.56
10	63	M	7	L	0.22	0.24	66.88	32	7	6.65
11	56	F	6.5	L	0.76	1.62	77.19	51	10	5.07
12	60	M	0.75	R	0.78	1.07	95	56	8	4.56
13	62	F	7	L	0.65	0.75	71.56	53	8	4.31
14	55	M	13.5	R	0.31	0.5	65	42	8	6.65
15	61	M	7	L	0.54	0.89	46.56	53	8	6.65
Median	60		7		0.68	1.07	77.19	53	9	4.56
Interquantile range	13		4		0.29	0.52	15	5	3	2.34

Participant demographic and baseline data. M, male; F, female; L, left; R, right; 10 MWT, 10 Meter Walk Test; S, Self-Selected Pace; F, Fast Pace; ABC, Activities-Specific Balance Confidence Scale; BBS, Berg Balance Scale; STREAM LE, Stroke Rehabilitation Assessment of Movement, leg subscale.
**Individuals who dropped the study.*

TABLE 2 | Mean (SD) of outcomes measures over time.

	Baseline	Post	Follow Up	Friedman's *p*
10 MWT (m/s) *S**	0.69 (0.22)	0.78 (0.25)	0.76 (0.26)	**0.038**
10 MWT (m/s) *F**	1.05 (0.49)	1.11 (0.44)	1.07 (0.45)	0.066
ABC (%)	75.4 (11.4)	74.3 (18.2)	73.7 (14.7)	0.926
BBS (/56)	50.7 (6.5)	51.1 (7.4)	50.8 (8.1)	0.911
SIS	3.88 (0.39)	3.84 (0.33)	3.76 (0.29)	0.458
STREAM-LE (/20)	9.73 (2.05)	9.92 (1.49)	9.77 (2.12)	0.226
Monofilaments	5.34 (1.357)	5.36 (1.532)	5.38 (1.519)	0.310

**S-self-selected pace; F-fast pace. 10 MWT, 10 Meter Walk Test; S, Self-Selected Pace; F, Fast Pace; ABC, Activities-Specific Balance Confidence Scale; BBS, Berg Balance Scale; SIS, Stroke Impact Scale; STREAM LE, Stroke Rehabilitation Assessment of Movement, leg subscale. Bold value indicates the level of significance.*

TABLE 3 | Effect size of treatment between Baseline and Follow-Up.

	Baseline → follow up
STREAM-LE	0.371
Monofilaments	0.455
10 MWT (m/s) *S*, 1st trial	0.689
10 MWT (m/s) *F*, 1st trial	0.568

The significant improvement in the gait speed of individuals with a more recent stroke and younger age may be related to an enhanced neural plasticity potential. The medium effect sizes in the STREAM-LE supports that possibility. Stimulating the paretic distal lower extremity at the sensory level may have an effect on the motor output level required for self-selected gait speed, suggesting a sensorimotor integration loop. This may potentially influence optimal SES dosage parameters to positively affect self-selected gait speed, which has implications on balance functional levels in individuals post-stroke at a chronic stage.

There were no other changes in other administered outcome measures. Participants scored highly at baseline on the BBS and ABC, so there might have been a ceiling effect. Alternatively, these outcome measures may have been less sensitive to changes with this intervention.

The sock electrode delivered electrical stimulation over the entire surface of the foot and distal leg instead of targeting specific distal lower extremity musculature. Different target areas or affected nerves may have had an impact on performance and outcomes in this study. A control trial would allow a more rigorous comparison of the elements of the intervention.

Participants self-monitored dosage and performed the prescribed intervention independently; therefore, compliance and adherence to the intervention protocol may have had an impact on outcomes. In addition, the variability of activities performed within SES plus activity is a limitation as it was not uniform across all subjects. Other limitations of this study include the small sample size, lack of a control group, and lack of formal measures of adherence to the SES plus activity program. While the results are preliminary, SES plus activity

TABLE 4 | Correlations between outcome measures and sensory data.

Outcome measures and mean scores		Baseline PTTES			Baseline monofilaments		
		Baseline	**Baseline to post Δ**	**Baseline to F/U Δ**	**Baseline**	**Baseline to post Δ**	**Baseline to F/U Δ**
10-Meter Walk Test (10 MWT) with Self-Selected (SSP) and Fast Pace (FP)	SSP: 0.7 m/s (0.28–1.12)	0.278	0.121	0.087	0.340	0.244	0.391
	FP: 1.02 m/s (0.46–1.81)	0.168	0.056	0.121	0.360	0.179	0.383
Activities-Specific Balance Confidence Scale (ABC)	$\bar{x}$: 75.4% (46.5–95/100)	0.183	0.535	0.777**	0.439	0.292	0.044
Stroke Impact Scale (SIS)	$\bar{x}$: 65% (50–85%)	0.679**	0.278	0.222	0.209	0.091	0.137
SIS 16[a]	$\bar{x}$: 82%	0.824**	0.631*	0.560*	0.052	0.065	0.076
SIS mobility[b]	$\bar{x}$: 82%	0.715**	0.526	0.538	0.069	0.151	0.013
SIS participation[c]	$\bar{x}$: 71%	0.359	0.063	0.270	0.649**	0.425	0.314
Berg Balance Scale (BBS)	$\bar{x}$: 50/56 (32–56/56)	0.167	0.138	0.266	0.274	0.033	0.147
Stroke Rehabilitation Assessment of Movement (STREAM)	LE Subscale: $\bar{x}$: 9.67/20 (7–14/20)	0.123	0.065	0.316	0.123	0.459	0.429

Correlations (Explorable.com and Wilson, 2009)

Weak	Moderate	Strong	Significant	Significant
0.2–0.29	0.3–0.39	0.4–0.69	*$p \le 0.05$	**$p \le 0.01$

[a]*SIS 16: a subset of 16 items capturing daily activities from the SIS.* [b]*SIS mobility: a subset of 9 items capturing mobility items from the SIS.* [c]*SIS participation: a subset of 8 items capturing participation and role function from the SIS.*

has the potential for clinical benefit and should be further studied in a large, randomized controlled study that includes a feasibility assessment.

CLINICAL IMPLICATIONS AND CONCLUSIONS

We believe that this is the first study that combines SES with standing and mobility activities in a community setting. In an era with limited sources for formal physical therapy, a home base program that produces beneficial functional outcomes is an attractive therapeutic alternative.

Sensory data is related to both physical performance and perceived physical performance. Future studies may consider stratifying research participants based on baseline functional and chronicity level (how long ago they had the stroke). This may inform patient characteristics most associated with change. Establishing evidence based practice guidelines to determine the appropriate dosing of SES parameters to improve LE motor function had remained a challenge.

ETHICS STATEMENT

This study was approved by the Northwestern University Institutional Review Board Office, Northwestern University, Chicago IL (#STU00097364).

AUTHOR'S NOTE

In our study, adults post-stroke wore a sock electrode, which allowed for concurrent delivery of Sensory Electrical Stimulation (SES) during standing and mobility activities. Our findings suggest that this intervention resulted in a significant improvement in the gait speed of younger individuals with a more recent stroke. We believe that this is the first study that combines SES with standing and mobility activities in a community setting.

AUTHOR CONTRIBUTIONS

RL-R was designated as first author, wrote, edited, and prepared the manuscript for publication. JS conceived the study and participated in its design and coordination and helped to draft the manuscript. RL-R, JS, MB, and AK participated in data collection and analysis. The authors of this study declared no potential conflicts of interest regarding the research conducted, authorship, or publication of this manuscript.

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REFERENCES

Arakawa, T., Otao, H., Okamura, M., Nakao, H., Hachiya, M., Mizokami, A., et al. (2012). Reliability of the Semmes-Weinstein monofilaments test in stroke patients. *Jap. J. Health Promot. Phys. Ther*. 2, 65–68. doi: 10.9759/hppt.2.65

Ashburn, A., Hyndman, D., Pickering, R., Yardley, L., and Harris, S. (2008). Predicting people with stroke at risk of falls. *Age Ageing* 37, 270–276. doi: 10.1093/ageing/afn066

Bastos Conforto, A., Monteiro dos Anjos, S., Marques Bernardo, W., Alves da Silva, A., Conti, J., Machado, A. G., et al. (2018). Repetitive peripheral sensory stimulation and upper limb performance in stroke: a systematic review and meta analysis. *Neurorehabil. Neural Repair*. 10:1177. doi: 10.1177/1545968318798943

Bushnell, C., Bettger, J. P., Cockroft, K. M., Cramer, S. C., Edelen, M. O., Hanley, D., et al. (2015). Chronic stroke outcome measures for motor function intervention trials: expert panel recommendations. *Circulation* 8, S163–S169. doi: 10.1161/CIRCOUTCOMES.115.002098

Carey, L. M. (1995). Somatosensory loss after stroke. *Critic. Rev. Phys. Rehabil. Med*. 7, 51–91. doi: 10.1615/CritRevPhysRehabilMed.v7.i1.40

Cohen, J. (1988). *Statistical Power Analysis for the Behavioral Sciences,* 2nd Edn. South Wellfleet: Routledge.

Conforto, A. B., Ferreiro, K. N., Tomasi, C., Laurenti dos Santos, R., Moreira, V. L., Marie, S. K. N., et al. (2010). Effects of somato-sensory stimulation on motor function after subacute stroke. *Neurorehabil. Neural Repair*. 24, 263–272. doi: 10.1177/1545968309349946

Connell, L. A., Lincoln, N. B., and Radford, K. A. (2008). Somatosensory impairment after stroke: frequency of different deficits and their recovery. *Clin. Rehabil*. 22, 758–767. doi: 10.1177/0269215508090674

Explorable.com and Wilson, L. T. (2009). *Statistical Correlation is a Statistical Technique Which Tells us if Two Variables are Related.* Available online at: https://explorable.com/statistical-correlation (accessed March 14, 2019).

Golaszewski, S. M., Siedentopf, C. M., Koppelstaetter, F., Rhomberg, P., Guendisch, G. M., Schlager, A., et al. (2004). Modulatory effects on human sensorimotor cortex by whole-hand afferent electrical stimulation. *Neurology* 62, 2262–2269. doi: 10.1212/WNL.62.12.2262

Hamdy, S., Rothwell, J. C., Aziz, Q., Singh, K. D., and Thompson, D. G. (1998). Long-term reorganization of human motor cortex driven by short-term sensory stimulation. *Nat Neurosci*. 1, 64–68. doi: 10.1038/264

Huang, Y. J., Chen, K. L., Chou, Y. T., Hsueu, I. P., Hou, C. Y., and Hsieh, C. L. (2015). Comparison of the responsiveness of the long-form and simplified stroke Rehabilitation Assessment of Movement: group- and individual-level; analysis. *Phys. Ther*. 95, 1172–1183. doi: 10.2522/ptj.20140331

Kaelin-Lang, A., Luft, A. R., Sawaki, L., Burstein, A. H., Sohn, Y. H., and Cohen, L. G. (2002). Modulation of human corticomotor excitability by somatosensory input. *J. Physiol*. 540(Pt 2), 623–33. doi: 10.1113/jphysiol.2001.012801

Klaiput, A., and Kitisomprayoonkul, W. (2009). Increased pinch strength in acute and subacute stroke patients after simultaneous median and ulnar sensory stimulation. *Neurorehabil. Neural Repair*. 23, 351–356. doi: 10.1177/1545968308324227

Kwong, P. W., Ng, G. Y., Chung, R. C., and Ng, S. S. (2008). Trasncutaneous electrical nerve stimulation improves walking capacity and reduces spasticity in stroke survivors: a systematic review and meta analysis. *Clin. Rehabil*. 32, 1203–1219. doi: 10.1177/0269215517745349

Langhorne, P., Stott, D. J., Robertson, L., MacDonald, J., Jones, L., McAlpine, C., et al. (2000). Medical complications after stroke: a multicenter study. *Stroke* 31, 1223–1229. doi: 10.1161/01.STR.31.6.1223

Meesen, R. L., Cuypers, K., Rothwell, J. C., Swinnen, S. P., and Levin, O. (2010). The effect of long-term TENS on persistent neuroplastic changes in thehuman cerebral cortex. *Hum. Brain Mapping* 32, 872–882. doi: 10.1002/hbm.21075

Michael, K., and Macko, R. F. (2007). Ambulatory activity intensity profiles, fitness, and fatigue in chronic stroke. *Topics Stroke Rehabil*. 14, 5–12. doi: 10.1310/tsr1402-5

Minet, L. R., Peterson, E., von Koch, L., and Ytterberg, C. (2015). Occurance and predictors of falls in people with stroke. *Stroke* 46, 2688–2690. doi: 10.1161/STROKEAHA.115.010496

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., et al. (2015). Heart disease and stroke statistics-—2015 update a report from the american heart association. *Circulation* 131:e29-322. doi: 10.1161/CIR.0000000000000152

Ng, S. S. M., and Hui-Chan, C. W. Y. (2007). Transcutaneous electrical nerve stimulation combined with task-related training improves lower limb functions in subjects with chronic stroke. *Stroke* 38, 2953–2959. doi: 10.1161/STROKEAHA.107.490318

Ridding, M. C., Brouwer, B., Miles, T. S., Pitcher, J. B., Thompson, P. D. (2000). Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in humans. *Exp. Brain Res*. 2000, 135–143. doi: 10.1007/s002219900269

Ridding, M. C., McKay, D. R., Thompson, P. D., and Miles, T. S. (2001). Changes in corticomotor representations induced by prolonged peripheral nerve stimulation in humans. *Clin. Neurophysiol.* 112, 1461–1469. doi: 10.1016/S1388-2457(01)00592-2

Sackley, C., Brittle, N., Patel, S., Ellins, J., Scott, M., Wright, C., et al. (2008). The prevalence of joint contractures, pressure sores, painful shoulder, other pain, falls, and depression in the year after a severely disabling stroke. *Stroke* 39, 3329–3334. doi: 10.1161/STROKEAHA.108.518563

Salbach, N. M., Mayo, N. E., Hanley, J. A., Richards, C. L., and Wood-Dauphinee, S. (2006). Psychometric evaluation of the original and Canadian French version of the activities-specific balance confidence scale among people with stroke. *Arch. Phys. Med. Rehabil.* 87, 1597–1604. doi: 10.1016/j.apmr.2006.08.336

Sullivan, J. E., Girardi, M., Hensley, M., Rohaus, J., Schewe, C., Whittey, C., et al. (2015). Improving arm function in chronic stroke: a pilot study of sensory amplitude electrical stimulation via glove electrode during task-specific training. *Topics Stroke Rehabil*. 22, 169–175. doi: 10.1179/1074935714Z.0000000007

Tinazzi, M., Zarattini, S., Valeriani, M., Romito, S., Farina, S., Moretto, G., et al. (2005). Long-lasting modulation of human motor cortex following prolonged transcutaneous electrical nerve stimulation (TENS) of forearm muscles: evidence of reciprocal inhibition and facilitation. *Exp. Brain Res*. 161, 457–464. doi: 10.1007/s00221-004-2091-y

Tyson, S. F., Hanley, M., Chillala, J., Selley, A., and Tallis, R. C. (2006). Balance disability after stroke. *Phys. Ther*. 86, 30–38. doi: 10.1093/ptj/86.1.30

Tyson, S. F., Hanley, M., Chillala, J., Selley, A. B., and Tallis, R. C. (2008). Sensory loss in hospital-admitted people with stroke: characteristics, associated factors, and relationship with function. *Neurorehabil. Neural Repair*. 22, 166–172. doi: 10.1177/1545968307305523

Tyson, S. F., Sadeghi-Demneh, E., and Nester C. J. (2013). The effects of transcutaneous electrical nerve stimulation on strength, proprioception, balance and mobility in people with stroke: a randomized controlled cross-over trial. *Clin. Rehabil*. 27, 785–791. doi: 10.1177/0269215513478227

von Elm, E., Altman, D. G., Egger, M., Pocock, S. J., Gotzsche, P. C., and Vandenbroucke, J. P. (2007). The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. *BMJ* 335, 806–808. doi: 10.1136/bmj.39335.541782.AD

Winward, C. E., Halligan, P. W., and Wade, D. T. (2007). Somatosensory recovery: a longitudinal study of the first 6 months after unilateral stroke. *Disabil. Rehabil*. 29, 293–299. doi: 10.1080/09638280600756489

Woolley, S. M. (2001). Characteristics of gait in hemiplegia. *Topics Stroke Rehabil*. 7, 1–18. doi: 10.1310/JB16-V04F-JAL5-H1UV

Wu, C. W. H., van Gelderen, P., Hanakawa, T., Yaseen, Z., and Cohen, L. G. (2005). Enduring representational plasticity after somatosensory stimulation. *NeuroImage* 27, 872–884. doi: 10.1016/j.neuroimage.2005.05.055

Wutzkea, C. J., Mercerab, V. S., and Lewek, M. D. (2013). Influence of lower extremity sensory function on locomotor adaptation following stroke: a review. *Topics Stroke Rehabil*. 20, 233–240. doi: 10.1310/tsr2003-233

Yan, T., Hui-Chan, C. W., Yan, T., and Hui-Chan, C. W. Y. (2009). Transcutaneous electrical stimulation on acupuncture points improves muscle function in subjects after acute stroke: a randomized controlled trial. *J. Rehabil. Med*. 41, 312–316. doi: 10.2340/16501977-0325

Yates, J. S., Lai, S. M., Duncan, P. W., and Studenski, S. (2002). Falls in community-dwelling stroke survivors: an accumulated impairments model. *J. Rehabil. Res. Dev*. 39, 385–394. Available online at: https://pdfs.semanticscholar.org/ee95/98153ee1807571ba5cd534c338465922e00c.pdf

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SYSTEMATIC REVIEW
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Does Sensory Retraining Improve Sensation and Sensorimotor Function Following Stroke: A Systematic Review and Meta-Analysis

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Background: Reduced sensation is experienced by one in two individuals following stroke, impacting both the ability to function independently and overall quality of life. Repetitive activation of sensory input using active and passive sensory-based interventions have been shown to enhance adaptive motor cortical plasticity, indicating a potential mechanism which may mediate recovery. However, rehabilitation specifically focusing on somatosensory function receives little attention.

Objectives: To investigate sensory-based interventions reported in the literature and determine the effectiveness to improve sensation and sensorimotor function of individuals following stroke.

Methods: Electronic databases and trial registries were searched from inception until November 2018, in addition to hand searching systematic reviews. Study selection included randomized controlled trials for adults of any stroke type with an upper and/or lower limb sensorimotor impairment. Participants all received a sensory-based intervention designed to improve activity levels or impairment, which could be compared with usual care, sham, or another intervention. The primary outcomes were change in activity levels related to sensorimotor function. Secondary outcomes were measures of impairment, participation or quality of life.

Results: A total of 38 study trials were included (n = 1,093 participants); 29 explored passive sensory training (somatosensory; peripheral nerve; afferent; thermal; sensory amplitude electrical stimulation), 6 active (sensory discrimination; perceptual learning; sensory retraining) and 3 hybrid (haptic-based augmented reality; sensory-based feedback devices). Meta-analyses (13 comparisons; 385 participants) demonstrated a moderate effect in favor of passive sensory training on improving a range of upper and lower limb activity measures following stroke. Narrative syntheses were completed for studies unable to be pooled due to heterogeneity of measures or insufficient data, evidence for active sensory training is limited however does show promise in improving sensorimotor function following stroke.

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Conclusions: Findings from the meta-analyses and single studies highlight some support for the effectiveness of passive sensory training in relation to sensory impairment and motor function. However, evidence for active sensory training continues to be limited. Further high-quality research with rigorous methods (adequately powered with consistent outcome measures) is required to determine the effectiveness of sensory retraining in stroke rehabilitation, particularly for active sensory training.

Keywords: stroke, rehabilitation, sensory, physiotherapy, occupational therapy, recovery of function

INTRODUCTION

Rationale

Sensation is the means by which we process and interact with the world and our environment (Connell, 2007; Carey et al., 2016). It allows us to detect and discriminate objects and textures, know where our body is in space (proprioception) and accurately perceive and discriminate sensations of pain, temperature, pressure and vibration (Carey, 1995; Schabrun and Hillier, 2009; Doyle et al., 2010; Carey et al., 2011, 2018). As a result, sensation is critical for normal human function and is fundamental for motor behaviors (Doyle et al., 2010). For example, somatosensory input is required for accurate and adaptable motor control and the acquisition of motor skills, suggesting intact sensation may be a critical component to facilitate motor rehabilitation (Carey et al., 1993; Yekutiel and Guttman, 1993; Wu et al., 2006; Celnik et al., 2007).

Reduced sensation is experienced by one in two individuals following stroke (Carey et al., 2018), impacting both the ability to function independently and overall quality of life (Carey et al., 1993, 2018; Yekutiel and Guttman, 1993). Most significantly these deficits contribute to confidence and movement difficulties with an enduring impact on simple everyday activities such as reaching, grasping and manipulating objects or knowing where a foot is positioned during gait without the need to visually observe its position. As expected, reduced sensation following stroke is associated with slower recovery, reduced motor function (in terms of quality of movement control) and lesser rehabilitation outcomes (Wu et al., 2006; Doyle et al., 2010; de Diego et al., 2013; Carey, 2014). These deficits continue to persist for years with many individuals often learning not to use their sensory affected limb (learned non-use) due to uncertainty, lack of confidence of whether to use it and/or vulnerability and fear of safety (Doyle et al., 2010; Turville et al., 2017). This continued disuse leads to a further reduction and deterioration (Carey et al., 1993, 2018; Yekutiel and Guttman, 1993; Doyle et al., 2010). In addition, these sensory deficits have widespread effects not only in predicting poor functional outcomes but increasing length of hospitalization, reduced numbers of discharges to home and increased mortality rates (Yekutiel and Guttman, 1993; Carey, 1995; Doyle et al., 2010; Carey et al., 2011).

Repetitive activation of sensory input (sensory-based interventions) has been shown to enhance adaptive motor cortical plasticity, indicating a potential mechanism which may mediate recovery (Carrico et al., 2016b). As such, sensory input may be integral to facilitate the recovery of function following stroke (Schabrun and Hillier, 2009). Yet despite these findings suggesting an association between sensory and motor function in recovery following stroke, rehabilitation specifically focusing on somatosensory function receives little attention (Carey, 1995; Schabrun and Hillier, 2009; de Diego et al., 2013; Carey et al., 2016).

Objectives/Research Question

The objective of this study was to systematically review and update the literature around somatic sensory-based interventions to improve sensation and sensorimotor function of individuals following stroke. This review is an extension of (Schabrun and Hillier, 2009).

METHODS

Systematic Review Protocol

The protocol was specified a priori and according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols. This study was registered prospectively on November 23, 2018, with the International Prospective Register of Systematic Reviews before commencement (CRD42017078103); http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017078103.

Study Design and Eligibility Criteria

Database searching was conducted based on the predetermined criteria in **Table 1**.

Within sensory training the types of interventions and the mechanism of action differ significantly making it difficult to clearly delineate intervention effects. Sensations of interest were limited to somatic (cutaneous and proprioceptive). Sensory training was separated into three areas; passive (an externally applied sensory stimulation approach, with a purported mechanism of priming the nervous system), active (a sensory retraining approach based on graded re-education using learning principles) and hybrid (a combination of sensory stimulation and retraining) interventions (see **Table 1**) (Schabrun and Hillier, 2009; Doyle et al., 2010).

Search Strategy and Data Sources

The search strategy of medical subject headings and keywords were developed in Ovid Medline database using variations of the term stroke and sensation, "sensory training," "sensory education," "sensory rehabilitation," "sensory practice," "sensory treatment," "sensory awareness," "sensory movement," "sensory intervention," "sensory discrimination," "stimulation therapy," "cutaneous stimulation," "electrical stimulation," "afferent

TABLE 1 | Search criteria.

Variable	Criteria
Population	Adults (>18 years) following a stroke with a sensory and/or motor deficit. Any type (ischemic/ hemorrhage), location and stage (acute, sub-acute, chronic) of stroke.
Intervention	**Inclusion/** Sensations of interest were limited to somatic (cutaneous, and proprioceptive). Any sensory training (active, passive, hybrid) applied to the upper/lower limb or trunk, delivered as stand-alone or an adjunct to usual care and addressing the recovery of sensation and/or sensorimotor function. *Passive: An externally applied sensory stimulation approach, with a purported mechanism of priming the nervous system. Sensory stimulation to produce activation of cutaneous nerves in the absence of muscle contraction (sub-motor) with a clear intent to stimulate only somatosensory afferents (e.g., thermal stimulation, pressure, peripheral nerve stimulation, transcutaneous electrical nerve stimulation, vibration stimulation).* *Active: A sensory retraining approach based on graded re-education using learning principles and augmenting sensory input (e.g., proprioception, tactile recognition, desensitization, stereognosis, localization, discrimination).* *Hybrid: A combination of sensory stimulation (passive) and retraining (active) interventions (e.g., haptic-based augmented reality, feedback devices that augment targeted sensory afferents).* **Exclusion/** Studies which combine sensory training with other forms of therapy or where sensory training is embedded within broader rehabilitation protocols – in either case the effects of the sensory program cannot be isolated from the potential effects of the other approaches. *Passive: Functional/neuromuscular electrical stimulation (targets motor efferents), paired associative, acupuncture or dermatomal stimulation, brain stimulation (transcranial magnetic/peripheral magnetic or transcranial direct current stimulation).* *Active: Mirror therapy, brain computer interface, visual-based robotics/virtual-augmented reality, biofeedback (forceplates), kinematics/whole body vibration, manipulating/varying multi-modal sensation (balance training that includes manipulating vision).*
Comparator	Any inactive (placebo/sham, no treatment) or active control (usual care).
Outcome	Primary outcome: Change in activity levels related to sensorimotor function (measures of mobility, upper/lower limb function and task-specific activities). Secondary outcomes: Measures of motor impairment (range of motion, strength or postural sway), participation and quality of life. Change in sensory impairment as measured by a standardized sensory test (Nottingham Sensory Assessment).
Design	Randomized Controlled Trials.
Publication/Date	No limits applied.
Language	No limits applied. Studies in languages other than English were translated.

stimulation," "sensory stimulation," "stimulation therapy," "somatosensory stimulation" (see **Appendix 1** in Supplementary Material). An academic librarian with experience in health-related systematic reviewing was also consulted. This strategy was adapted for other bibliographic databases, database-specific filters were applied and modifications were restricted to closely reflect the original strategy. Eleven electronic databases were searched from inception to November 27, 2018: AMED, CINAHL, Cochrane Database of Systematic Reviews, Elsevier Scopus, Embase, Medline, OTseeker, Ovid Emcare, PEDRO and Pubmed. Five trial registries were searched with studies documented and followed for published results: Australian New Zealand Clinical Trials Registry, ClinicalTrials.gov, Cochrane Central Register of Controlled Trials, Stroke Trials Registry and World Health Organization International Clinical Trials Registry Platform. A citation-tracking database of Web of Science was used as well as hand searching reference lists of included studies, systematic reviews, clinical guidelines and key reviews in this area to identify individual trials not retrieved from the electronic search. To complete word citation tracking, key references were entered in Science Citation.

Study Selection

Search result records were saved in EndNote X8 and Covidence online software. Duplicate publications were identified and removed. Studies retrieved were screened and assessed by one reviewer for the obviously irrelevant titles. Studies were then assessed for meeting the selection criteria based on title and abstract. Of the eligible studies, full texts were accessed and independently assessed by two reviewers (I.S. and B.H.). Disagreement between reviewers was discussed to reach consensus and/or resolved by a third reviewer (S.H.).

Data Extraction

Data extraction was conducted using the *Cochrane Handbook* version 5.1.0 recommendations, using a predesigned data extraction spreadsheet in Microsoft Excel 2018, version 16.16.5. Extracted data included characteristics of participants, intervention, comparator, and outcome results.

Risk of Bias Analysis

Two reviewers (I.S. and B.H.) independently assessed all the included studies using the standardized domain-based evaluation Cochrane Risk of Bias Tool, the preferred tool of the Cochrane Collaboration (Higgins et al., 2011). Assessments were completed using Covidence online software to blind judgements of reviewers. Disagreement between reviewers was discussed to reach consensus and resolved by a third reviewer (S.H.).

Data Synthesis and Statistical Analysis

Descriptive statistics were used to summarize findings of the included studies. Data including study characteristics/method (study design, participants, intervention, controls and outcome measures) and results (sample size, means and standard deviations) where appropriate were manually extracted by two independent assessors (I.S. and S.H.) and transferred into Microsoft Excel 2018 (version 16.16.5). Review Manager

(RevMan 5.3.5) software was used for data synthesis and to perform meta-analyses with sufficiently homogenous data to calculate effect sizes. In the meta-analyses, data from randomized controlled trials were pooled based on comparable control groups and outcome measures. These were then grouped into the *International Classification of Functioning, Disability and Health* framework outcomes with the primary interest of activity levels (for example Wolf Motor Function Test or Berg Balance Scale) and secondarily impairment (for example range of motion or strength). Two authors (I.S. and S.H.) extracted and entered data and cross-referenced to reduce risk of errors. The mean and standard deviation data from the first post intervention time-point (or first group from crossover studies) were used. Data from time-points other than the first post intervention assessment including follow-up data were not analyzed because of the heterogeneity between studies. When mean and standard deviation data were not available, study authors were contacted for the original data set. Those that could not be contacted but median and interquartile range were available, a formula for the standard deviation (SD) from Hillier and Inglis-Jassiem $SD = 0.75 \times \text{IQR}$ ($SD = 0.75 \times \text{IQR}$) was used and it was assumed the median equated to the mean (Liang et al., 2012). If appropriate data was still not possible, the study was excluded from meta-analyses. Either post-intervention means or mean change scores were included. In the case of dichotomous data, number of participants in both the experimental and control group and the total sample size were identified. The data were generally ordinal and analyzed as continuous data outcomes using the summary statistics recommended by the Cochrane Collaboration. Data were then analyzed to calculate either relative risk, with 95% confidence intervals or individual and group effect sizes. Meta-analyses used the fixed-effect model, analysis of effect sizes used the mean difference (MD). Heterogeneity was assessed with the I^2 test, where >50% was interpreted as substantial heterogeneity. Where data were not available or of unacceptable heterogeneity, a narrative summary of study results was produced using reported effects.

RESULTS

Study Selection and Characteristics

A total of 14,446 trials were identified from preliminary searches, with the summary flow of trials outlined in **Figure 1**. The final analysis included 38 papers, of these 29 passive (20 upper limb and 9 lower limb); 6 active (4 upper limb and 2 lower limb) and 3 hybrid studies (2 upper limb and 1 trunk) (see **Tables 4**–**6**). A total sample of 1,093 participants were included. Total mean age range was 39.9–72.6 years, 657 of these were males and 399 females and 366 were affected on the left-side and 404 right. Total mean time since stroke ranged from 0.87 months to 11.5 years. The most common reasons for exclusion are reported in **Figure 1**.

Synthesized Findings

Meta-Analyses

Where possible, data were pooled based on outcome measures and controls. Meta-analysis of data to determine effectiveness was possible for 13 studies (11 passive, 2 active) (11 upper limb, 2 lower limb) (see **Tables 2**, **3**) with a total sample of 385 participants included. Pooling was not possible for the remaining 25 studies because of the diversity of intervention protocols and outcome measures, the results of these interventions are reported narratively.

Sensory versus usual care

Of the data pooled based on comparisons of sensory versus usual care (see **Table 2**), a significant difference favoring sensory training was found on the Functional Ambulation Category (FAC) from two studies investigating passive lower limb sensory interventions (thermal stimulation) (Chen et al., 2011; Liang et al., 2012) (MD, fixed effects 0.71; 95% CI 0.59, 0.82; $z = 12.35$; $P = 0.00001$). A significantly positive difference was also found for the Motor Assessment Scale (MAS) (MD, fixed effects 6.15; 95% CI 4.91, 7.40; $z = 9.69$; $P = 0.00001$). The Box and Block Test (BBT) did not show a significant effect (MD, fixed effects 2.28; 95% CI −4.62,9.17; $z = 0.65$; $p = 0.52$) with one active upper limb study (Perfetti's method) (Chanubol et al., 2012) showing a slight positive effect while the two passive upper limb studies (somatosensory and afferent stimulation) (Lin et al., 2014a,b) showed no effect (see **Appendix 2** in Supplementary Material for figures). Comparisons of these outcomes FAC ($I^2 = 0\%$), MAS ($I^2 = 0\%$) and BBT ($I^2 = 0\%$) showed no heterogeneity.

The Barthel Index (BI) showed an overall positive significant effect from sensory training (MD, fixed effects 8.27; 95% CI 5.59, 10.95; $z = 6.05$, $p = 0.00001$), the passive lower limb study (thermal stimulation) (Liang et al., 2012) favored sensory training while the active upper limb study (Perfetti's method) was equivocal (Chanubol et al., 2012). The Berg Balance Scale (BBS) meta-analysis showed a significantly negative result, with both passive lower limb studies (thermal stimulation) favoring the control group (Chen et al., 2011; Liang et al., 2012) (MD, fixed effects, −3.78; 95% CI −6.39, −1.18; $z = 2.84$; $p = 0.004$). A significant effect favoring sensory training was found on the Fugl-Meyer Assessment (FMA) (MD, fixed effects 5.93; 95% CI 5.17, 6.70; $z = 15.21$; $P = 0.00001$) with two lower limb passive studies (thermal stimulation) (Chen et al., 2011; Liang et al., 2012) indicating a positive change while the third, an active upper limb study (de Diego et al., 2013) reported a negative effect (see **Appendix 2** in Supplementary Material for figures). Comparisons of these outcomes BI ($I^2 = 95\%$), BBS ($I^2 = 94\%$), and FMA ($I^2 = 91\%$) showed considerable heterogeneity.

Sensory versus sham stimulation

Further meta-analyses were conducted for the comparison of sensory versus sham stimulation (see **Table 3**). For the outcomes of Action Research Arm Test (ARAT) (MD, fixed effects 2.80; 95% CI 2.27, 3.32; $z = 10.46$, $p = 0.00001$), Wolf Motor Function Test (WMFT) (MD, fixed effects −0.13; 95% CI −0.22, 0.04; $z = 2.73$, $p = 0.006$) and FMA (MD, fixed effects 2.75; 95% CI 1.53, 3.96; $z = 4.43$, $p = 0.00001$) all returned a significant effect (see **Appendix 3** in Supplementary Material for figures). Heterogeneity was variable with substantial

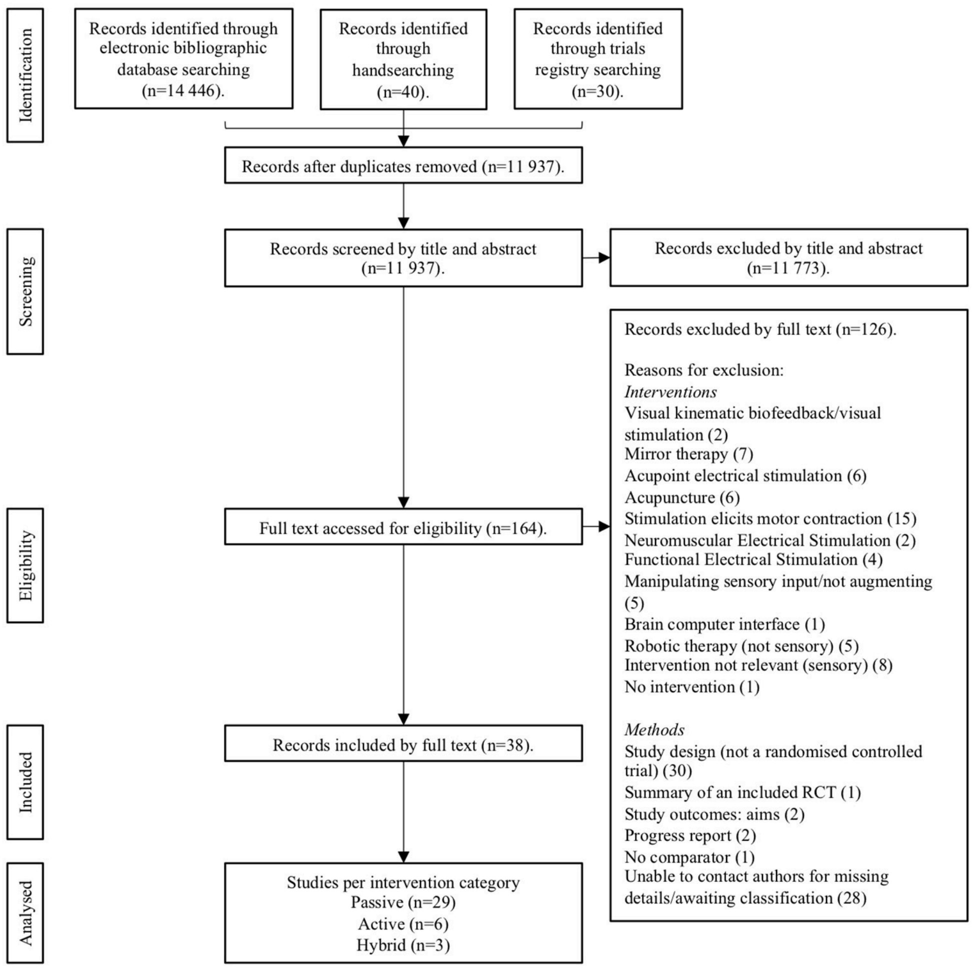

FIGURE 1 | Preferred Reporting for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of the review process.

heterogeneity reported for ARAT ($I^2 = 62\%$), moderate for FMA ($I^2 = 35\%$) and no heterogeneity for WMFT ($I^2 = 0\%$).The MAL (MD, fixed effects 0.01; 95% CI −0.32, 0.34; $z = 0.05$; $P = 0.96$) and Nottingham Sensory Assessment (NSA) (MD, fixed effects 0.59; 95% CI −0.75, 1.93; $z = 0.86$, $p = 0.39$) showed no significant effect on sensory training, while Stroke Impact Scale (SIS) (MD, fixed effects −1.86 (95% CI −5.85, 2.12) $z = 0.92$, $p = 0.36$) returned a negative effect (see **Appendix 3** in Supplementary Material for figures). No heterogeneity was reported for MAL ($I^2 = 0\%$) and SIS ($I^2 = 0\%$), while considerable heterogeneity was indicated for NSA ($I^2 = 84\%$).

Narrative Synthesis

Narrative synthesis was used to summarize the randomized controlled trials that could not be pooled in meta-analyses.

Passive sensory training interventions

Passive sensory training interventions used a variety of frequency parameters and intensities (see **Table 4**). Five studies applied transcutaneous electrical nerve stimulation (TENS), the three lower limb studies indicated positive results for balance and mobility (Tyson et al., 2013; Ng et al., 2016; In and Cho, 2017), while the two upper limb studies showed no change for hemineglect (Polanowska et al., 2009; Seniow et al., 2016). Two studies used sensory amplitude electrical stimulation (SES), both studies showed a slight positive effect with upper limb motor function and sensation (Sullivan et al., 2012) and lower limb spasticity and gait (Yavuzer et al., 2007) however these were not significant. Three upper limb studies applied repetitive peripheral nerve stimulation (RPSS), two of these studies showed positive findings on hand function (dos Santos-Fontes et al., 2013), however for Conforto 2010 this was observed only in the lower intensity group (Conforto et al., 2010). While contradictory results were found for pinch strength (Klaiput and Kitisomprayoonkul, 2009; Conforto et al., 2010) and no effect on arm function (Klaiput and Kitisomprayoonkul, 2009). Five upper limb studies used peripheral nerve stimulation (PNS), two studies showed a slight positive effect on hand function (Wu et al., 2006; Celnik et al., 2007). While three studies showed positive findings on arm function (Ikuno et al., 2012;

TABLE 2 | Effect size (95% CIs) for sensory training compared to usual care.

Study (author, year)	Outcome measure	Total sample size E:C (n)	Mean difference (IV, Fixed, 95% CI)	Heterogeneity (I^2)	Overall effect (P)
ACTIVITY					
Chen et al., 2011; Liang et al., 2012	Functional Ambulation Category	32:31	0.71 (0.59, 0.82)	0%	$P < 0.00001$
Chen et al., 2011; Liang et al., 2012	Motor Assessment Scale	32:31	6.15 (4.91, 7.40)	0%	$P < 0.00001$
Chanubol et al., 2012; Lin et al., 2014a,b	Box and Block Test	42:42	2.28 (-4.62,9.17)	0%	$p = 0.52$
Chanubol et al., 2012; Liang et al., 2012	Barthel Index	35:35	8.27 (5.59, 10.95)	95%	$p < 0.00001$
Chen et al., 2011; Liang et al., 2012	Berg Balance Scale	32:31	−3.78 (-6.39, −1.18);	94%	$p = 0.004$
IMPAIRMENT					
Chen et al., 2011; Liang et al., 2012; de Diego et al., 2013	Fugl-Meyer Assessment	44:40	5.93 (5.17, 6.70)	91%	$P < 0.00001$

TABLE 3 | Effect size (95% CIs) for sensory training compared to sham stimulation.

Study (author, year)	Outcome measure	Total sample size E:C (n)	Mean difference (IV, Fixed, 95% CI)	Heterogeneity (I^2)	Overall effect (P)
ACTIVITY					
Stein et al., 2010; Wu et al., 2010; Fleming et al., 2015; Carrico et al., 2016a,b	Action Research Arm Test	71:70	2.80 (2.27, 3.32)	62%	$p < 0.00001$
Carrico et al., 2016a,b	Wolf Motor Function Test	28:27	−0.13 (−0.22, 0.04)	0%	$p = 0.006$
Stein et al., 2010; Sullivan et al., 2012; Fleming et al., 2015	Motor Activity Log	51:50	0.01 (−0.32, 0.34)	0%	$P = 0.96$
Stein et al., 2010; Sullivan et al., 2012	Stroke Impact Scale	35:33	−1.86 (−5.85, 2.12)	0%	$p = 0.36$
IMPAIRMENT					
Cambier et al., 2003; Stein et al., 2010; Sullivan et al., 2012; Fleming et al., 2015; Carrico et al., 2016a,b	Fugl-Meyer Assessment	90:89	2.75 (1.53, 3.96)	35%	$p < 0.00001$
Cambier et al., 2003; Sullivan et al., 2012	Nottingham Sensory Assessment	31:30	0.59 (0.75, 1.93)	84%	$p = 0.39$

Carrico et al., 2016a,b). Five studies used thermal stimulation, the three upper limb studies showed positive findings on arm function (Wu et al., 2010) and motor function, spasticity, range and sensation (Chen et al., 2005, 2011). Similarly, the two lower limb studies highlighted positive effects on motor function and spasticity (Liang et al., 2012; Hsu et al., 2013). Of the two median nerve stimulation (MNS) studies, both studies indicated positive effects on hand function and pinch force (Conforto et al., 2002, 2007). Two studies using somatosensory stimulation (SS) showed positive improvements on arm and hand function (Lin et al., 2014b; Fleming et al., 2015), while the third study using afferent stimulation in addition also improved in gait and mobility (Lin et al., 2014a). A single upper limb study combined subsensory electrical and vibratory stimulation, no significant effect on arm function was found (Stein et al., 2010). While another upper limb study used a splint connected to an intermittent pneumatic compression device showed positive results on sensation, motor function and spasticity (Cambier et al., 2003). Of two lower limb studies, one provided a vibration stimulus showing improvements in postural sway and gait ability (Lee et al., 2013), while the other study delivered low-amplitude segmental muscle stimulation with positive results on mobility and gait parameters (Paoloni et al., 2010).

Training duration and controls: Training duration varied from 20 to 180 min, 1 to 7 sessions/week over a period of 1–12 weeks, with the number of sessions ranging from 1 to 30. Fifteen studies used sham stimulation without current delivered/turned off as the control (Cambier et al., 2003; Yavuzer et al., 2007; Klaiput and Kitisomprayoonkul, 2009; Polanowska et al., 2009; Stein et al., 2010; Sullivan et al., 2012; dos Santos-Fontes et al., 2013; Lee et al., 2013; Tyson et al., 2013; Fleming et al., 2015; Carrico et al., 2016a,b; Ng et al., 2016; Seniow et al., 2016; In

TABLE 4 | Passive sensory training study characteristics.

Author, year	Study design	Sample size	Age (years) mean (SD)	Gender (M:F)	Stroke duration (time since stroke) mean (SD)	Side of stroke (affected side, L: R)	Frequency, pulse length, intensity	Target duration	Control condition	Outcome measures	Direction of effects (+ positive, – negative, +/– both)
Cambier et al., 2003	RCT (Parallel Group)	11E, 12C	63.9 ± 11.2E, 61.1 ± 12.8C	5:6E, 9:3C	114.1 ± 92.6E, 83.2 ± 44.9C (days)	6:5E, 8:4C	Pneumatic compression (10 cycles of 3 min with a peak of 40 mmHg)	UL 30 min, 5 days/week for 4 weeks, 20 sessions	Sham SWT and standard PT	NSA, FMA-UE, AS, VAS	+
Carrico et al., 2016a	RCT (Parallel Group)	10E, 9C	56.7E, 54.6C	3:7E, 6:3C	29.5 (months)	6:4E, 2:7C	PNS 10 Hz, 1 ms Mild paraesthesias	UL (posterior interosseous, median and ulnar nerves) 10 × 2 h consecutive sessions	Sham PNS paired with/preceding modified constraint induced movement therapy	WMFT, FMA-UE, ARAT	+
Carrico et al., 2016b	RCT (Parallel Group)	18E, 18C	58.7 ± 12.1E, 65.4 ± 10.8C (months)	9:9E, 9:9C	39.2 ± 34.6E, 25.7 ± 17.7C (months)	6:12E, 3:15C	PNS 10 Hz, 1 ms Mild paraesthesias	UL (radial and median nerves) 10 × 2h consecutive sessions	Sham PNS paired with/preceding intensive task oriented training	FMA-UE, WMFT, ARAT	+
Celnik et al., 2007	RCT (Crossover)	9	55.2 ± 14.3	3:6	3.2 ± 1.6 (years)	–	PNS 10 Hz, 1 ms Mild paraesthesias	UL (hand) 1 × 2 h session	No stimulation	JTHFT	+
Chen et al., 2005	RCT (Parallel Group)	15E, 14C	58.5 ± 12.9E, 59.6 ± 12.0C	6:9E, 10:4C	14.3 ± 6.8E, 12.4 ± 6.6 C (days)	10:5E, 8:6C	Thermal stimulation (10×[30s + 30 s]×2 × 2)	UL (wrist and hand) 20–30 min, 5 days/week for 6 weeks, 30 sessions	Standard rehabilitation	Brunnstrom stages, MMAS, MAS, monofilaments, HGS, wrist E/F angles	+/–
Chen et al., 2011	RCT (Parallel Group)	17E, 16C	58.0 ± 11.5E, 62.3 ± 11.3C	13:4E, 9:7C	11 (7.13-9.0)E, 11 (6.98–10.5)C (days)	11:6E, 9:7C	Thermal stimulation (8×[30 s + 30 s] ×2 × 3)	LL (calf or foot) 30–40 min, 5 days/week for 6 weeks, 30 sessions	Standard rehabilitation	FMA-LE, MRC LE scale, MMAS, PASS, BBS, FAC, MAS	+
Conforto et al., 2002	RCT (Crossover)	8	65 (38-81)	7:1	66 (14–84) (months)	n/a	MNS 10 Hz, 1 ms Strong paresthesias	UL (median nerve) 1 × 2 h session	No stimulation	Pinch strength	+
Conforto et al., 2007	RCT (Crossover)	11	39.9 (4.2)	4:7	4.3 (0.7) (years)	9:2	MNS 10 Hz, 1 ms Strong paraesthesias	UL (median nerve) 1 × 2 h session	Subthreshold low-frequency stimulation	Modified JTT	+
Conforto et al., 2010	RCT (Crossover)	11E, 11C	59.3 ± 1.4 (sub), 64.2 ± 3.7 (supra)	6:5 (sub), 5:6 (supra)	53.1 ± 1.8 (sub), 53.5 ± 2.6 (supra) (days)	6:7 (sub), 7:6 (supra)	RPSS 10 Hz, 1 ms Subsensory (below sensory threshold), suprasensory- (strong paraesthesias)	UL (median nerve) 2 h, 3 days/week for 4 weeks, 12 sessions	–	JTT, pinch strength, FIM	+/–
dos Santos-Fontes et al., 2013	RCT (Parallel Group)	10E, 10C	52.2 ± 11.1E, 59.1 ± 11.1C	5:5E, 6:4C	3.8 ± 4.5E, 3.3 ± 2.1C (years)	6:4E, 7:3C	RPSS 31 Hz Strong paraesthesias	UL (median nerve) 2 h, 7 days/week for 4 weeks, 28 sessions	Sham RPSS and motor training at home	JTT	+
Fleming et al., 2015	RCT (Parallel Group)	16E, 17C	62.3 ± 35-82E, 60.6 ± 24-84C	13:3E, 7:10C	28.9 ± (3–130), 26.6 ± (4–126) (months)	6:10E, 8:9C	SS 10 Hz, 1 ms 3× sensory threshold	UL (median, radial and ulnar nerves) 2 h, 3 days/week for 4 weeks, 12 sessions	Sham SS paired with/preceding task-specific training	ARAT, FMA-UE, MAL, GAS	+
Hsu et al., 2013	RCT (Parallel Group)	11E:12C	51.1 ± 14.0E, 52.6 ± 13.3C	8:3E, 6:6C	5.8 ± 4.2 E, 9.4 ± 7.1C (months)	8:3E, 6:6C	Thermal stimulation (10×[15 s + 15 s]×2 × 2)	LL (distal LE and foot) 30 min, 3 days/week for 8 weeks, 24 sessions	Sham/innocuous thermal stimulation with standard rehabilitation	LE-STREAM, mob-STREAM, FAC, BI, PASS, MAS	+/–
Ikuno et al., 2012	RCT (Crossover)	11E (immediate gp), 11C (delayed gp)	68.8 ± 13.9E, 70.1 ± 13.5C	6:5E, 5:6C	91.0 ± 46.5E, 110.3 ± 45.2C (days)	5:6E, 8:3C	PNS 10 Hz, 1 ms Mild paraesthesias	UL (median and ulnar nerve) 1h, 6 days/week for 2 weeks, 12 sessions	Task-oriented training	VAS (level of fatigue), WMFT, BBT, HGS, pinch strength	+/–
In and Cho, 2017	RCT (Parallel Group)	20E, 20C	56.2 ± 10.4E, 56.3 ± 10.2C	11:9E, 12:8C	6.5 ± 2.7E, 6.6 ± 2.5C (months)	10:10E, 11:9C	TENS 100 Hz, 200 ms 2× sensory threshold	LL (peroneal nerve) 30 min, 5 days/ week for 6 weeks, 30 sessions	Sham TENS preceding 30 min sit-to-stand training plus standard therapy	CSI, LL strength, postural-sway distance	+

(Continued)

TABLE 4 | Continued

Author, year	Study design	Sample size	Age (years) mean (SD)	Gender (M:F)	Stroke duration (time since stroke) mean (SD)	Side of stroke (affected side, L: R)	Frequency, pulse length, intensity	Target duration	Control condition	Outcome measures	Direction of effects (+ positive, – negative, +/– both)
Klaiput and Kitisomprayoonkul, 2009	RCT (Parallel Group)	10E, 10C	63.0 ± 11.06E, 64.5 ± 10.98C	8:2E, 6:4C	11.9 ± 10.56E, 38.9 ± 54.06C (days)	–	RPSS 10 Hz, 1 ms Strong paraesthesias	UL (median and ulnar nerve) 1 × 2 h session	Sham stimulation	Pinch strength, ARAT	+/–
Lee et al., 2013	RCT (Parallel Group)	16E, 15C	53.31 ± 8.37E, 55.73 ± 8.27C	13:3E, 11:4C	56.94 ± 25.73E, 49.93 ± 29.97C (months)	8:8E, 7:8C	Vibration stimulation 90 Hz, 15 μm	LL (foot-heel, tibialis anterior and achilles tendon) 30 min, 3 days/week for 6 weeks, 18 sessions	Sham local vibration stimulus and standard rehabilitation	Postural sway velocity and distance, gait ability	+
Liang et al., 2012	RCT (Parallel Group)	15E, 15C	56.1 ± 11.9E, 59.73 ± 11.6C	12:3E, 7:8C	10.9 ± 5.4E, 13.6 ± 6.4C (days)	9:6E, 8:7C	Thermal stimulation (8× [30 s+30 s] ×2 × 3)	LL (calf or foot) 40 min 5days/week for 6 weeks, 30 sessions	Standard rehabilitation and consults	FMA-LE, MRC LE, BBS, MMAS, MAS, FAC, BI	+
Lin et al., 2014a	RCT (Parallel Group)	14 (MT+MG), 14 (MT)E, 15C	55.79 ± 14.59 MT +MG/ 56.01 ± 12.53 MTE 53.34 ± 10.12C	11:3 (MT+MG); 10:4 (MT)E, 11:4C	22.71 ± 13.62(MT+MG)/ 18.50 ± 11.61(MT)E, 17.80 ± 10.56C (months)	6:8 (MT+MG); 8:6 (MT)E, 7:8C	Afferent stimulation subthreshold (80% of conscious sensory threshold), conscious sensory threshold (100%), above conscious sensory threshold (120%)	UL (hand) 1.5 h, 5 days/week for 4 weeks, 20 sessions	Mirror Therapy	FMA, muscle tone (myoton-3), BBT, 10MWT, kinematic parameters, MAL, ABILHAND	+
Lin et al., 2014b	RCT (Parallel Group)	8 (MT+MG)E, 8 (MT)C	56.31 ± 14.79E, 54.97 ± 14.10C	6:2E, 7:1C	18.88 ± 14.78E, 23.38 ± 10.86C (months)	4:4E, 4:4C	SS subthreshold (80% of conscious sensory threshold); conscious sensory threshold (100%); above conscious sensory threshold (120%)	UL (hand) 1.5 h, 5days/week for 4 weeks, 20 sessions	Mirror Therapy	MAS, BBT, ARAT, FIM	+/–
Ng et al., 2016	RCT (Parallel Group)	37E, 39C	72.6 ± 97E, 69.3 ± 100C	24:13E, 24:15C	6.1 ± 2.7E, 6.3 ± 2.9C (weeks)	18:19E, 20:19C	TENS parameters (–)	LL (common peroneal and sural nerve) 60 min, 2 days/week for 8 weeks, 16 sessions	Sham stimulation with task-oriented balance training and standard PT and OT	BBS, 6MWT, MRMI, TUGT, SF-36	+/–
Paoloni et al., 2010	RCT (Parallel Group)	22E, 22C	59.5 ± 13.3E, 62.6 ± 9.5C	86.4:13.6%E, 90.9: 9.1%C	1.85 ± 0.59E, 1.86 ± 0.61C (years)	50:50%E, 45.5:54.5%C	Segmental muscle vibration (stimulates 1a spindle afferents) 120 Hz, 10 mm Subthreshold	LL (tibialis anterior and peroneus longus) 30 min, 3 days/week over 4 weeks, 12 sessions	Standard PT	Gait time-distance and kinematics	+
Polanowska et al., 2009	RCT (Parallel Group)	20E, 20C	61.6 ± 8.3E, 58.3 ± 12.9C	11:9E; 14:6C	44.4 ± 27.3E, 46.6 ± 26.2C (days)	–	TENS 5 kHz, 100 ms Mild paraesthesias	UL (hand) 30 min, 5 days/week for 4 weeks, 20 sessions	Sham stimulation paired with conventional VST	BI, hemineglect severity assessment	–
Seniow et al., 2016	RCT (Parallel Group)	14E, 15C	63.4 ± 7.7E, 60.2 ± 9C	7:7E, 8:7C	40.5 (18.75–105)E, 34.5 (20.25–33.75)C (days)	–	TENS 50 Hz, 300 ms Subthreshold (mild paraesthesias)	UL (hand) 30 min, 5 days/week for 3 weeks, 15 sessions	Sham TENS combined with conventional VST	Hemispatial neglect severity assessment	–

(Continued)

TABLE 4 | Continued

Author, year	Study design	Sample size	Age (years) mean (SD)	Gender (M:F)	Stroke duration (time since stroke) mean (SD)	Side of stroke (affected side, L: R)	Frequency, pulse length, intensity	Target duration	Control condition	Outcome measures	Direction of effects (+ positive, – negative, +/– both)
Stein et al., 2010	RCT (Parallel Group)	15E, 15C	60.8 ± 14.2E; 66.0 ± 9.0C	46.7:53.3%E: 53.3:46.7%C	5.4 ± 3.6 (0.9–12.6)E, 6.8 ± 4.2 (1.7–13.9)C (years)	53.3%E: 46.7%C	Stochastic resonance stimulation (a) mechanical noise (vibration) bandwidth between/near 0 and 100 Hz, with an amplitude of 0.5- to 1-mm (b) electrical signal bandwidth between/near 0 and 1,000 Hz. Low levels of surface electric current, <150 uA max (50 uA root mean square) Below sensory threshold	UL (upper arm and dorsal forearm) 1 h, 3 days/week for 4 weeks, 12 sessions	Sham stimulation and exercise	FMA-UE, WMFT, ARAT, MAS, SIS-16, MAL, RPS, LT (monofilaments), vibration testing, distal proprioception test	–
Sullivan et al., 2012	RCT (Parallel Group)	20E, 18C	61.6 ± (37–88)E, 59.5 ± (41–85)C	13:7E, 14:4C	7.7 ± (1–29)E, 6.6 ± (3–14)C (years)	10:10E, 11:7C	SES 35 Hz, 250 ms Sensory threshold (mild paraesthesias)	UL (forearm) 60 min (2 × 30 min sessions), 5 days/week for 4 weeks, 20 sessions	Sham stimulation (subsensory) during exercise	PTTES, NSA, FMA, AMAT, TS, MAL-14, SIS-16	–
Tyson et al., 2013	RCT (Crossover)	29	64.5 ± 12.6 (28–82)	14:15	–	11:16:2 (bilateral weakness)	TENS 70–130 Hz, 50 us Mild paraesthesias	LL (foot and ankle) 1 × 2 h session	Sham stimulation	DF/PF strength and proprioception detection threshold, FRT, 10MWT	+
Wu et al., 2006	RCT (Crossover)	9	64.5 ± 4.4	5:4	6.5 ± 1.0 (years)	–	PNS 10 Hz, 1 ms Mild paraesthesias	UL (median, ulnar and radial nerves) 1 × 2 h session	No stimulation (sitting and reading)	JTHFT	+
Wu et al., 2010	RCT (Parallel Group)	12E, 11C	59.9 ± 11.4E, 54.3 ± 10.3C	4:8E, 5:6C	10.0 ± 7.3E, 7.2 ± 5.4C (months)	7:5E, 7:4C	Thermal stimulation (10×[15 s + 15 s] ×2 × 2)	UL (hand and distal arm) 30 min, 3 days/week for 8 weeks, 24 sessions	Same thermal stimulation protocol but on LL plus standard therapy	UE-STREAM, ARAT, BI, MAS	+
Yavuzer et al., 2007	RCT (Parallel Group)	15E, 15C	61.9 ± 10.01E, 64.4 ± 9.8C	7:8E, 9:6C	3.5 ± 2.1E, 3.4 ± 2.3C (months)	7:8E, 6:9C	SES 35 Hz, 240 ms Sensory threshold (mild paraesthesias)	LL (common peroneal nerve) 30 min, 5 days/4 weeks, 20 sessions	Sham SES and standard PT and OT	Brunnstrom stages, gait time-distance and kinematic characteristics	–

***Abbreviations:** –, not known; PT/OT, Physio-Occupational Therapy; UL/LL, upper and lower limb. **Outcome measures:** AMAT, Arm Motor Ability Test; ARAT, Action Research Arm Test; AS, Ashworth Scale; BBS, Berg Balance Scale; BI, Barthel Index; BBT, Box and Block Test; CSI, Composite Spasticity Index; FAC, Functional Ambulation Category; FIM, Functional Independence Measure; FMA-UE, Fugl Meyer Assessment-Upper Extremity; FRT, Functional Reach/Forward Reaching Test; GAS, Goal Assessment Scale; HGS, Hand Grip Strength; JTHFT/JTT, Jebsen Hand Function Test; LE-STREAM/Mob-STREAM, Lower Extremity/mobility subscale of Stroke Rehabilitation Assessment of Movement; MAL, Motor Activity Log; MAS, Modified Ashworth Scale; MMAS, Modified Motor Assessment Scale; MRC-LE scale, Medical Research Council scale for Lower Extremity; MRMI, Modified Rivermead Mobility Index; NSA, Nottingham Sensory Assessment; PASS, Postural Assessment Scale for Stroke; PTTES, Perceptual Threshold Test-Electrical Stimulation; RPS, Reaching Performance Scale; SF-36, short form general health questionnaire; TS, tardieu scale; TUGT, Timed Up and Go Test; UE-STREAM, Upper Extremity subscale of Stroke Rehabilitation Assessment of Movement; VAS, visual analog scale; WMFT, Wolf Motor Function Test; 10MWT/6MWT, 10/6 Meter Walk Test. **Interventions:** MNS, Median Nerve Stimulation; PNS, Peripheral Nerve Stimulation; RPSS, Repetitive Peripheral Nerve Stimulation; SS, somatosensory stimulation; SES, Sensory amplitude Electrical Stimulation; SWT, Short Wave Therapy; TENS, Transcutaneous Electrical Nerve Stimulation; TS, thermal stimulation; VST, visual scanning training.*

TABLE 5 | Active sensory training study characteristics.

Author, year	Study design	Sample size	Age (years)	Gender (M:F)	Stroke duration (time since stroke) mean (SD)	Side of stroke (affected side)	Intervention	Target duration	Control condition	Outcome measures	Direction of effects (+ positive, – negative, +/- both)
Byl et al., 2003	RCT (Crossover)	8E, 10C	69.0, 58.5	5:3, 7:3	4.5, 4.8	5:3, 5:5	Sensory discrimination training (and mental imagery, mirror and functional practice at home)	UL 1.5 h/week for 4 weeks, 4 sessions [and HEP CIMT 7 h + 15–90 min functional practice]	–	Sensory discrimination (kinesthesia, graphesthesia, stereognosis), PPT, WMFT, Cal-FCP, UL/LL strength and ROM, gait speed	+
Carey et al., 2011	RCT (Parallel/ Crossover)	25E, 25C	61.08 ± 14.38E, 60.96 ± 11.17C	17:8E, 20:5C	32.57 (12.22–111.22)E, 51.86 (20.57–72.53)C (weeks)	40:60%E, 44:56%C	Somatosensory discrimination training (texture discrimination, limb position sense, and tactile object recognition)	UL 60 min, 3 sessions/week for ~4 weeks, 10 sessions	Exposure to sensory stimuli	Composite index of functional somatosensory discrimination capacity: FMT, WPST, fTORT	+
Chanubol et al., 2012	RCT (Parallel Group)	20E, 20C	63.2 ± 10.1	9:11E, 11:9C	-	1:19E, 1:19C	Perfetti's method (cognitive sensory motor training therapy-perception tasks: sensing and discriminating limb positions)	UL 30 min, 5 times/week for 4 weeks, 20 sessions	Standard OT	ARAT, BI, BBT	–
de Diego et al., 2013	RCT (Parallel Group)	12E, 9C	61.9 ± 9.7E, 60.6 ± 15.6C	-	44.7 ± 24.5E, 60.7 ± 58.2C (months)	–	Sensory stimulation and functional activity training (targeting tactile stimulation, mental imagery and practice of ADL's at home)	UL 1 h, 2 days/week over 8 weeks, 16 sessions [and HEP 30 min/day over 8 weeks total 28 h]	Standard rehabilitation	FMA-UE, MAL, SIS-16, sensory discrimination battery: tactile sensibility (monofilaments), proprioceptive sensibility (passive ROM), consistency and weight discrimination (ordering consistency and weight of objects)	+
Lynch et al., 2007	RCT (Parallel Group)	10E, 11C	61.0 ± 15.8, (21–77)E, 62.0 ± 12.3, (38–82)C	7:3E, 9:2C	48.7 ± 31.1 (19–122)E, 47.8 ± 27.7 (13–112)C (days)	5:5E, 8:3C	Sensory retraining (education, detection, localization, discrimination and proprioception)	LL(foot) 30 min, 10 sessions over 2 weeks	Sham relaxation and standard PT	LT monofilaments, distal proprioception test, BBS, gait time and Iowa	+/–
Morioka and Yagi, 2003	RCT (Parallel Group)	12E, 14C	62.6 ± 13.3 (51–79)E, 61.3 ± 11.0 (56–73)C	9:3E, 8:6C	65.4 ± 18.6 (36–106)E, 61.9 ± 20.8 (31–111)C (days)	6:6E, 5:9C	Perceptual learning exercises (hardness discrimination)	LL 10 trials/session, 10 days over 2 weeks	Standard PT/OT (no perceptual learning exercise)	SBT (postural sway)	+/–

Abbreviations: *–, not known; UL/LL, upper and lower limb;* ***Outcome measures:*** *Cal-FCP, California Functional Capacity Evaluations; FMT, Fabric Matching Test; fTORT, Tactile Object Recognition Test; PPT, Purdue Pegboard Test; SBT, Stabilometer Balance Test; WMFT, Wolf Motor Function Test; WPST, Wrist Position Sense Test;* ***Interventions:*** *ADL's, activities of daily living; CIMT, constraint induced movement therapy; HEP, home exercise program.*

and Cho, 2017). Five studies used conventional rehabilitation (Chen et al., 2005, 2011; Paoloni et al., 2010; Ikuno et al., 2012; Liang et al., 2012), while Conforto used subthreshold low-frequency stimulation (Conforto et al., 2007) and Conforto did not use a control (Conforto et al., 2010). Three studies did not deliver any stimulation (Conforto et al., 2002; Wu et al., 2006; Celnik et al., 2007). Wu used the same thermal stimulation protocol but on the lower limb not upper limb (Wu et al., 2010), Hsu an innocuous thermal stimulation protocol (Hsu et al., 2013), and Lin used mirror therapy (Lin et al., 2014a,b).

Outcome measures: A broad range of measures were used, however the most commonly assessed functional measures were ARAT (Klaiput and Kitisomprayoonkul, 2009; Stein et al., 2010; Wu et al., 2010; Lin et al., 2014b; Fleming et al., 2015; Carrico et al., 2016a,b), JTHFT (Wu et al., 2006; Celnik et al., 2007; Conforto et al., 2007, 2010; dos Santos-Fontes et al., 2013), WMFT (Stein et al., 2010; Ikuno et al., 2012; Carrico et al., 2016a,b) and Barthel Index (Polanowska et al., 2009; Wu et al., 2010; Liang et al., 2012; Hsu et al., 2013). While the most commonly used impairment-based measures were FMA (Cambier et al., 2003; Stein et al., 2010; Chen et al., 2011; Liang et al., 2012; Sullivan et al., 2012; Lin et al., 2014a; Fleming et al., 2015; Carrico et al., 2016a,b), modified Ashworth Scale (Cambier et al., 2003; Chen et al., 2005, 2011; Stein et al., 2010; Wu et al., 2010; Hsu et al., 2013; Lin et al., 2014b) and Brunstromm Stages (Chen et al., 2005; Yavuzer et al., 2007; Paoloni et al., 2010).

Active sensory training interventions

Four studies delivered sensory discrimination training (see **Table 5**). All studies showed positive effects with three upper limb studies indicating improvements on sensation, arm and hand function as well as gait (Byl et al., 2003; Carey et al., 2011; de Diego et al., 2013), while the lower limb study highlighted changes in postural sway (Morioka and Yagi, 2003). Two studies also showed positive results, one lower limb study delivered sensory education and retraining with improvements found on sensation, gait and mobility (Lynch et al., 2007). Another upper limb study investigated Perfetti's method (a cognitive sensory motor training approach) and showed no effect on arm and hand function or mobility (Chanubol et al., 2012).

Training durations and controls: Training duration varied from 30 to 90 min, 1 to 5 days/week over a period of 2–8 weeks, with the number of sessions ranging from 4 to 20. Three studies used standard rehabilitation as the control (Morioka and Yagi, 2003; Chanubol et al., 2012; de Diego et al., 2013), while Lynch used sham relaxation in addition to standard rehabilitation (Lynch et al., 2007). Carey used a comparative control exposure to sensory stimuli (Carey et al., 2011) and Byl did not use a control (Byl et al., 2003).

Outcomes measures: Most common functional outcomes measures included ARAT (Chanubol et al., 2012), WMFT (Byl et al., 2003), MAL and SIS-16 (de Diego et al., 2013). The most common impairment-based measures were FMA (de Diego

TABLE 6 | Hybrid sensory training study characteristics.

Author, year	Study design	Sample size	Age (years)	Gender (M:F)	Stroke duration (time since stroke) mean (SD)	Side of stroke (affected side)	Intervention (active)/(passive-frequency, pulse length, intensity)	Target duration	Control condition	Outcome measures	Direction of effects (+ positive, – negative, +/– both)
(Cameirão et al., 2012)	RCT (Parallel Group)	16 (RGS-vision-based tracking system alone), 14 (RGS exoskeleton), 14 (RGS haptics)	68.7 ± 10.9 RGS, 59.4 ± 9.7 RGS-E, 59.9 ± 13.0 RGS-H	9:7 RGS, 9:5 RGS-E, 7:7 RGS-H	1649 ± 300 RGS, 1598 ± 230 RGS-E, 1334 ± 297 RGS-H (days)	6:10 RGS, 4:10 RGS-E, 6:8 RGS-H	Rehabilitation gaming system (configurations: vision-based tracking, passive exoskeleton or haptics)	UL 35 min/day, 5 days/week for 4 weeks, 20 sessions	No control	BI, MI-UE, MAS, FMA-UE, CAHAI, 9-HPT, BBT	+/–
(Sim et al., 2015)	RCT (Crossover)	11	60.36 ± 12.39	7:4	12.64 ± 11.02 (months)	5:6	SS (no stimulation, vibration, light and rough touches)	UL 1 × 5 min session	No stimulation	BBT, JTHFT, HGS, FRT	+
(Thielman, 2010)	RCT (Parallel Group)	8E (sensor), 8C (stabilizer)	62.9 ± 6.5 sensor, 63 ± 9.2 stabilizer	6:2 sensor, 4:4 stabilizer	26.5 sensor, 22.75 stabilizer (months)	4:4 sensor, 4:4 stabilizer	Auditory feedback sensor to pressure or stabilizer feedback (trunk restraint)	Trunk 40–45 min, 2-3 days/week for 4–6 weeks, 12 sessions	No control	RPS, FMA-UE, AROM, HGS, WMFT, MAL	+/–

Abbreviations: *UL/LL, upper and lower limb.* ***Outcomes:*** *CAHAI, Chedoke arm and hand activity inventory; MI, Motricity Index; 9-HPT, nine-hole peg test.* ***Interventions:*** *SS, somatosensory stimulation.*

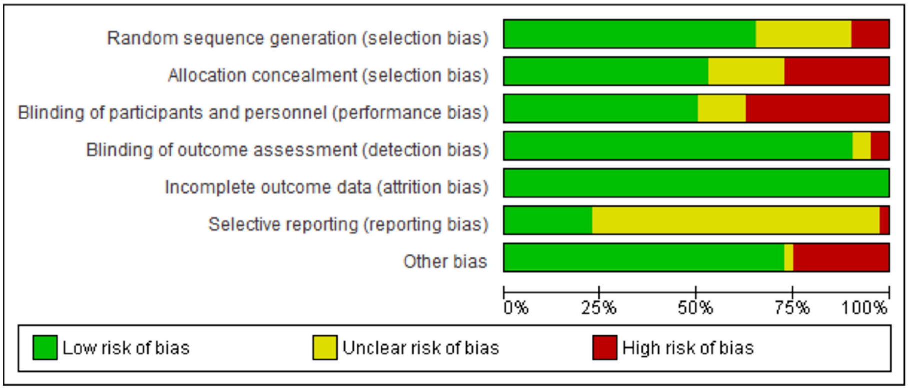

FIGURE 2 | Assessment of risk of bias presented as percentages across all included studies.

et al., 2013) and a varied battery of sensory tests including discrimination (texture, weight, consistency), tactile sensibility (Semmes-Weinstein monofilaments) and object recognition and proprioception (wrist position sense test) (Byl et al., 2003; Lynch et al., 2007; Carey et al., 2011; de Diego et al., 2013).

Hybrid sensory training interventions

Three studies did not fit within the active or passive group alone and were considered hybrid (see **Table 6**). One study focused on sensory-based and stabilizer-based trunk feedback and showed no significant effects on arm function (Thielman, 2010). Another study delivered one of three virtual-reality based rehabilitation configurations: vision-based tracking, haptic feedback (primary interest) or a passive exoskeleton and indicated no significant between-group differences on arm and hand function, spasticity or mobility (Cameirão et al., 2012). While the third study delivered four types of somatosensory stimulation (no stimulation, vibration, and light and rough touches) with improvements on arm and hand function, particularly following vibration (Sim et al., 2015).

Training duration and controls: Training duration varied from 5 to 45 min, 1 to 5 sessions/week over a period of 4–6 weeks, with the number of sessions ranging from 1 to 20. Two studies used no controls and were comparative studies (Thielman, 2010; Cameirão et al., 2012), while one used no stimulation as the control condition (Sim et al., 2015).

Outcome measures: Most commonly used functional outcomes measures were BBT (Cameirão et al., 2012; Sim et al., 2015) and WMFT (Thielman, 2010). While impairment-based measures included FMA (Thielman, 2010; Cameirão et al., 2012), modified Ashworth scale (Cameirão et al., 2012) and range of motion and strength (Thielman, 2010; Sim et al., 2015).

Risk of Bias

Risks to methodological quality were prominent in the assessment of selection, performance and reporting biases. An assessment summary is presented in **Figure 2**, and details for each study are provided in **Figure 3**. High risk of selection biases were most frequent within the domains of performance biases from a lack of participant and/or personnel blinding, however this is a common, and often unavoidable part of physiotherapy and occupational therapy intervention research designs. Further high risk biases were found within the domains of selection bias including inadequate random sequence generation and allocation concealment as well as other biases due to small sample size limiting generalization to the wider population, single session interventions and lack of follow-up testing (reducing the ability to extrapolate results from repeated sessions and increasing the difficulty to understand findings beyond the study procedures). Further, we noted potential biases of control conditions including sham stimulation which may cause central afferent input affecting cortical reorganization and study outcomes, difficulty putting on/setting up equipment (electrode glove) compromising practice, lack of rigorous procedures to monitor subject compliance at home and during passive stimulation, absence of an independent intervention group to delineate effects of standard rehabilitation, potential carryover effects in crossover and study design limited by using only one group or no control group. There was an unclear risk of bias within reporting biases including selective reporting of results due to lack of, or unclear, protocol registration and reporting of randomized controlled trial study designs, and again within the domain of selection biases (random sequence generation and allocation concealment) and performance bias (blinding of participants and personnel). However, detection and attrition biases were generally well reported and of low risk.

DISCUSSION

Summary of Main Findings

The purpose of this review was to evaluate the body of literature around sensory-based interventions to improve sensation and/or sensorimotor function of individuals following stroke. This is an important question as sensory-based interventions have largely been overlooked despite the indication that they are likely to form a critical component of

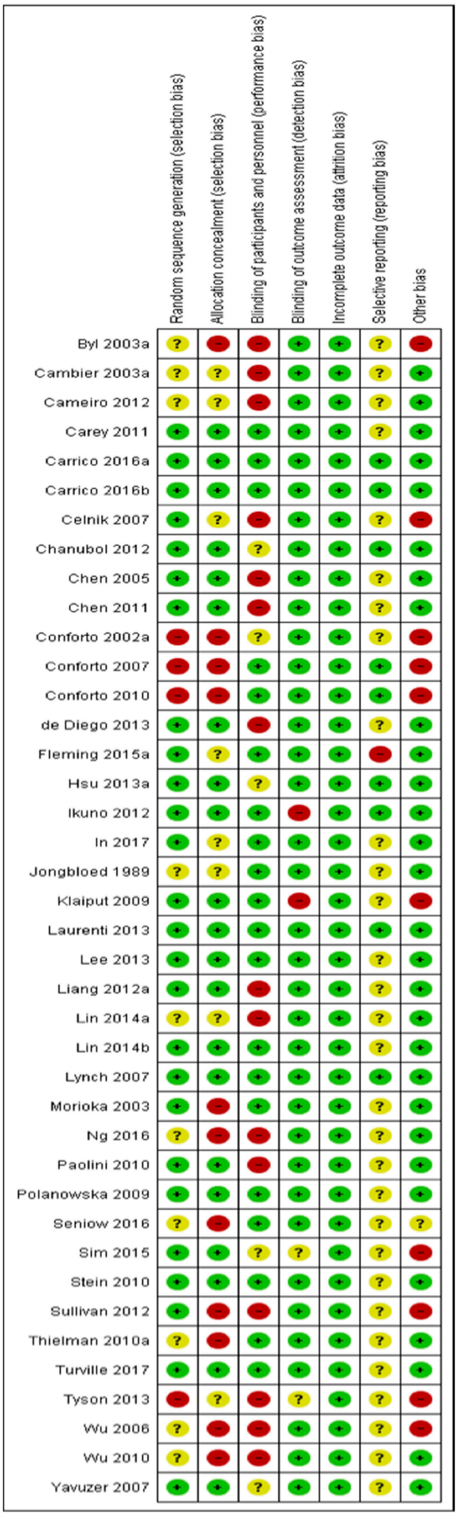

FIGURE 3 | Risk of bias summary for each included study.

stroke recovery. This review found 38 full-text manuscripts that investigated sensory-based interventions in people with stroke. We categorized these interventions into passive, active or hybrid. The key findings from the meta-analyses suggest that there is some evidence to support the use of passive sensory techniques with improved outcomes following thermal stimulation, pneumatic compression and peripheral nerve stimulation. The data for active sensory training was limited with most findings reported narratively, many highlighting positive activity-based outcomes. The large number of techniques reviewed did show promise in addressing sensation and sensorimotor function following stroke however at this stage we continue to not have adequate high quality trials to be able to make clear recommendations regarding the use of passive and active interventions.

Findings continue to suggest passive sensory training may enhance the effects of current task-oriented training and may be a useful adjunct when combined with standard rehabilitation (Schabrun and Hillier, 2009; Doyle et al., 2010). Only two studies reported no effect, one delivering stochastic resonance stimulation and the other sensory amplitude electrical stimulation (Stein et al., 2010; Sullivan et al., 2012). The limited high-quality research for active sensory training continues to neither affirm or negate its use, suggesting it may be effective as a supplemental training program and applied with careful clinical reasoning and measurement of individual effects. Two studies showed improvements following sensory discrimination training (Byl et al., 2003; Carey et al., 2011), with only one study exploring Perfetti's method showing no effect when compared to usual care (Chanubol et al., 2012). Findings from hybrid studies suggest somatosensory stimulation may be beneficial with positive effects found in a single study for vibration stimulation (Sim et al., 2015), however less clear effects were found for somatosensory-based feedback and virtual reality-based haptics (Thielman, 2010; Cameirão et al., 2012). Compared to previous reviews (Schabrun and Hillier, 2009; Doyle et al., 2010), we have found a greater number of studies addressing a broader range of interventions and outcome measures, however the general findings have not changed significantly and similar issues need to be addressed. The lack of sufficient literature to perform meta-analyses and insignificant effect sizes continue to mean it is not possible to determine the effectiveness of sensory retraining, particularly for the active group (Schabrun and Hillier, 2009; Doyle et al., 2010).

Implications for practice: Health professionals may use this evidence to guide clinical decision-making surrounding sensory training following stroke. Few studies mentioned (or evaluated) adverse effects: clinicians need to be conscious of monitoring these effects when using any sensory-based interventions. Careful consideration must also be taken by therapists regarding the suitability of sensory training for the individual prior to clinical application to improve individual functional outcomes particularly when active participation is required.

Implications for research: The significant number of individuals that continue to experience sensory deficits following stroke and the potential benefits of sensory training identified in this review indicate further research is essential. High-quality randomized controlled trials with high statistical power and rigorous methods including consistent and homogenous outcome measures are required to support or refute the effectiveness of sensory training, particularly active sensory training following stroke. Sufficient reporting of the type of intervention and training parameters are required to allow replication of the sensory training protocol.

Limitations

All studies included were randomized controlled trials which are considered the 'gold standard' when determining treatment effectiveness as this robust methodological design minimizes the effects of bias. Methodological quality was reasonable across most studies, however, there were areas where methodological rigor was notably lacking introducing the potential for bias and reducing confidence in the findings. The results may have been influenced by widespread lack of blinding of participants and personnel with the potential for performance biases, lack of concealment with the potential for selection biases and the potential for other biases with seven of the included studies implementing a single treatment session. These were included as they met the selection criteria, however the therapeutic effect of a single session has heightened the risk of biases as these data cannot be extrapolated to results from repeated sessions as would occur in a clinical setting. Of the 38 randomized controlled trials, only nine studies justified the selected sample size while 23 of these sample sizes were relatively small and six only mentioned the total sample size limiting capacity to observe significant effects. This may mean the insufficient evidence in this review may be due to poor statistical power rather than ineffective intervention. Reliability and validity of measures used were strong, however, passive training studies predominantly used measures relating to motor activity (ARAT, WMFT), while active training focused on measures at the impairment level (tactile sensibility, sensory discrimination). The impairment-based measures may be more sensitive to detecting change and any changes are likely to be of a smaller magnitude and not reach statistical significance as easily, while changes in function are generally larger and may be the results of net improvements in sensation, proprioception and motor function rather than one single component (Schabrun and Hillier, 2009; Doyle et al., 2010). This has particularly impacted on forming conclusions in the active group. Seven studies focused on balance and postural control, these were excluded as they were considered to manipulate multi-modal sensory input (particularly vision) rather than augment which was the primary focus of this review. Most studies only reported selective outcomes increasing the potential risk for reporting biases. Most active and passive studies reported standard rehabilitation or sham stimulation as the comparator, however again these were poorly defined which may have resulted in greater variability between studies particularly in the active group. In addition, the high heterogeneity between types of intervention, intervention parameters and outcomes measures made it difficult to produce clear comparisons in the meta-analyses and prevented the ability to perform subgroup analyses.

CONCLUSIONS

This review sought to provide an updated review investigating the effects of sensory training protocols on somatosensory function following stroke. Although a greater number of studies have been published since the previous reviews in 2009 and 2010 (Schabrun and Hillier, 2009; Doyle et al., 2010) only a small number of these studies were of high quality with a greater focus on passive sensory training than active. Findings indicate there is some evidence to support the use of passive sensory techniques and while data for active sensory training is limited it does show promise in improving sensation and sensorimotor function following stroke. The ability of this review to form sound conclusions and develop clear recommendations regarding sensory training in stroke rehabilitation continues to be affected by the limited high-quality studies and the diverse range of interventions and outcome measures.

CLINICAL MESSAGES

- Passive sensory interventions may assist in improving activity following stroke.
- Evidence for active sensory training continues to be limited by research design, small sample size and heterogeneous outcome measures.
- Further high-quality research is required to determine the effectiveness of sensory training in stroke rehabilitation, particularly active-based therapy.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the **Supplementary Files**.

AUTHOR CONTRIBUTIONS

All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2019.00402/full#supplementary-material

REFERENCES

Byl, N., Roderick, J., Mohamed, O., Hanny, M., Kotler, J., Smith, A., et al. (2003). Effectiveness of sensory and motor rehabilitation of the upper limb following the principles of neuroplasticity: patients stable poststroke. *Neurorehabil. Neural Repair*. 17, 176–191. doi: 10.1177/0888439003257137

Cambier, D. C., De Corte, E., Danneels, L. A., and Witvrouw, E. E. (2003). Treating sensory impairments in the post-stroke upper limb with intermittent pneumatic compression. Results of a preliminary trial. *Clin. Rehabil.* 17, 14–20. doi: 10.1191/0269215503cr580oa

Cameirão, M. S., Badia, S. B., Duarte, E., Frisoli, A., and Verschure, P. F. (2012). The combined impact of virtual reality neurorehabilitation and its interfaces on upper extremity functional recovery in patients with chronic stroke. *Stroke* 43, 2720–2728. doi: 10.1161/STROKEAHA.112.653196

Carey, L. (2014). "Core concepts in sensory impairment and recovery after stroke," in *Stroke: Interventions to Support Occupational Performance*, eds T. J. Wolf and G. M. Giles (Annapolis, MD: AOTA Press), 95–118.

Carey, L. M. (1995). Somatosensory loss after stroke. *Crit. Rev. Phys. Rehabil. Med.* 7, 51–91. doi: 10.1615/CritRevPhysRehabilMed.v7.i1.40

Carey, L. M., Lamp, G., and Turville, M. (2016). The state-of-the-science on somatosensory function and its impact on daily life in adults and older adults, and following stroke: a scoping review. *Occupat. Participation Health* 36, 27S−41S. doi: 10.1177/1539449216643941

Carey, L. M., Macdonell, R., and Matyas, T. A. (2011). SENSE: study of effectiveness of Neurorehabilitation on Sensation after Stroke: a randomized controlled trial. *Neurorehabil. Neural Repair*. 25, 304–313. doi: 10.1177/1545968310397705

Carey, L. M., Matyas, T., and Oke, L. (1993). Sensory loss in stroke patients: effective training of tactile and proprioceptive discrimination. *Arch. Phys. Med. Rehabil.* 74, 602–611. doi: 10.1016/0003-9993(93)90158-7

Carey, L. M., Matyas, T. A., and Baum, C. (2018). Effects of somatosensory impairment on participation after stroke. *Amer. J. Occupat. Therapy* 72, 1–10. doi: 10.5014/ajot.2018.025114

Carrico, C., Chelette Ii, K. C., Westgate, P. M., Salmon-Powell, E., Nichols, L., and Sawaki, L. (2016a). Randomized trial of peripheral nerve stimulation to enhance modified constraint-induced therapy after stroke. *Am. J. Phys. Med. Rehabil.* 95, 397–406. doi: 10.1097/PHM.0000000000000476

Carrico, C., Chelette, K. C., Westgate, P. M., Powell, E., Nichols, L., Fleischer, A., et al. (2016b). Nerve stimulation enhances task-oriented training in chronic, severe motor deficit after stroke: a randomized trial. *Stroke* 47, 1879–1884. doi: 10.1161/STROKEAHA.116.012671

Celnik, P., Hummel, F., Harris-Love, M., Wolk, R., and Cohen, L. G. (2007). Somatosensory stimulation enhances the effects of training functional hand tasks in patients with chronic stroke. *Arch. Phys. Med. Rehabil.* 88, 1369–1376. doi: 10.1016/j.apmr.2007.08.001

Chanubol, R., Wongphaet, P., Chavanich, N., Werner, C., Hesse, S., Bardeleben, A., et al. (2012). A randomized controlled trial of Cognitive Sensory Motor Training Therapy on the recovery of arm function in acute stroke patients. *Clin. Rehabil.* 26, 1096–1104. doi: 10.1177/0269215512444631

Chen, J., Liang, C., Shaw, F., Chen, J., Liang, C., and Shaw, F. (2005). Facilitation of sensory and motor recovery by thermal intervention for the hemiplegic upper limb in acute stroke patients: a single-blind randomized clinical trial. *Stroke* 36, 2665–2669. doi: 10.1161/01.STR.0000189992.06654.ab

Chen, J. C., Lin, C. H., Wei, Y. C., Hsiao, J., and Liang, C. C. (2011). Facilitation of motor and balance recovery by thermal intervention for the paretic lower limb of acute stroke: a single-blind randomized clinical trial. *Clin. Rehabil*. 25, 823–832. doi: 10.1177/0269215511399591

Conforto, A. B., Cohen, L. G., dos Santos, R. L., Scaff, M., and Marie, S. K. N. (2007). Effects of somatosensory stimulation on motor function in chronic cortico-subcortical strokes. *J. Neurol.* 254, 333–339. doi: 10.1007/s00415-006-0364-z

Conforto, A. B., Ferreiro, K. N., Tomasi, C., dos Santos, R. L., Moreira, V. L., Marie, S. K. N., et al. (2010). Effects of somatosensory stimulation on motor function after subacute stroke. *Neurorehabil. Neural Repair*. 24, 263–272. doi: 10.1177/1545968309349946

Conforto, A. B., Kaelin-Lang, A., and Cohen, L. G. (2002). Increase in hand muscle strength of stroke patients after somatosensory stimulation. *Ann. Neurol.* 51, 122–125. doi: 10.1002/ana.10070

Connell, L. A. (2007). *Sensory Impairment and Recovery After Stroke*. Nottingham: University of Nottingham.

de Diego, C., Puig, S., and Navarro, X. (2013). A sensorimotor stimulation program for rehabilitation of chronic stroke patients. *Restor. Neurol. Neurosci.* 31, 361–371. doi: 10.3233/RNN-120250

dos Santos-Fontes, R. L., N., FdAK, Sterr, A., and Conforto, A. B. (2013). Home-based nerve stimulation to enhance effects of motor training in patients in the chronic phase after stroke: a proof-of-principle study. *Neurorehabil. Neural Repair*. 27, 483–490. doi: 10.1177/1545968313478488

Doyle, S., Bennett, S., Fasoli, S. E., and McKenna, K. T. (2010). Interventions for sensory impairment in the upper limb after stroke (Review). *Cochr. Database Syst. Rev.* 2010, 1–57. doi: 10.1002/14651858.CD006331.pub2

Fleming, M. K., Sorinola, I. O., Roberts Lewis, S. F., Wolfe, C. D., Wellwood, I., and Newham, D. J. (2015). The effect of combined somatosensory stimulation and task-specific training on upper limb function in chronic stroke: a double-blind randomized controlled trial. *Neurorehabil. Neural Repair*. 29, 143–152. doi: 10.1177/1545968314533613

Higgins, J. P. T., Altman, D. G., Gotzsche, P. C., Juni, P., Moher, D., Oxman, A. D., et al. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *Br. Med. J.* 343, 1–9. doi: 10.1136/bmj.d5928

Hsu, H. W., Lee, C. L., Hsu, M. J., Wu, H. C., Lin, R., Hsieh, C. L., et al. (2013). Effects of noxious versus innocuous thermal stimulation on lower extremity motor recovery 3 months after stroke. *Arch. Phys. Med. Rehabil.* 94, 633–641. doi: 10.1016/j.apmr.2012.11.021

Ikuno, K., Kawaguchi, S., Kitabeppu, S., Kitaura, M., Tokuhisa, K., Morimoto, S., et al. (2012). Effects of peripheral sensory nerve stimulation plus task-oriented training on upper extremity function in patients with subacute stroke: a pilot randomized crossover trial. *Clin. Rehabil*. 26, 999–1009. doi: 10.1177/0269215512441476

In, T. S., and Cho, H. Y. (2017). Effects of sit-to-stand training combined with transcutaneous electrical stimulation on spasticity, muscle strength and balance ability in patients with stroke: a randomized controlled study. *Gait Posture* 54, 183–187. doi: 10.1016/j.gaitpost.2017.03.007

Klaiput, A., and Kitisomprayoonkul, W. (2009). Increased pinch strength in acute and subacute stroke patients after simultaneous median and ulnar sensory stimulation. *Neurorehabil. Neural Repair*. 23, 351–356. doi: 10.1177/1545968308324227

Lee, S. W., Cho, K. H., and Lee, W. H. (2013). Effect of a local vibration stimulus training programme on postural sway and gait in chronic stroke patients: a randomized controlled trial. *Clin. Rehabil.* 27, 921–931. doi: 10.1177/0269215513485100

Liang, C. C., Hsieh, T. C., Lin, C. H., Wei, Y. C., Hsiao, J., and Chen, J. C. (2012). Effectiveness of thermal stimulation for the moderately to severely paretic leg after stroke: serial changes at one-year follow-up. *Arch. Phys. Med. Rehabil*. 93, 1903–1910. doi: 10.1016/j.apmr.2012.06.016

Lin, K.-C., Chen, Y. T., Huang, P. C., Wu, C. Y., L. HW, W. Y. H., et al. (2014b). Effect of mirror therapy combined with somatosensory stimulation on motor recovery and daily function in stroke patients: a pilot study. *J. Formosan Med. Assoc.* 113, 422–428. doi: 10.1016/j.jfma.2012.08.008

Lin, K.-C., Huang, P., Chen, Y., Wu, C., and Huang, W. (2014a). Combining afferent stimulation and mirror therapy for rehabilitating motor function, motor control, ambulation, and daily functions after stroke. *Neurorehabil. Neural Repair*. 28, 153–162. doi: 10.1177/1545968313508468

Lynch, E. A., Hillier, S. L., Stiller, K., Campanella, R. R., and Fisher, P. H. (2007). Sensory retraining of the lower limb after acute stroke: a randomized controlled pilot trial. *Arch. Phys. Med. Rehabil.* 88, 1101–1107. doi: 10.1016/j.apmr.2007.06.010

Morioka, S., and Yagi, F. (2003). Effects of perceptual learning exercises on standing balance using a hardness discrimination task in hemiplegic patients following stroke: a randomized controlled pilot trial. *Clin. Rehabil.* 17, 600–607. doi: 10.1191/0269215503cr654oa

Ng, S. S. S., Lai, C. W. K., Tang, M. W. S., and Woo, J. (2016). Cutaneous electrical stimulation to improve balance performance in patients with sub-acute stroke: a randomised controlled trial. *Hong Kong Med. J.* 22(Suppl. 2), S33–S36.

Paoloni, M., Mangone, M., Scettri, P., Procaccianti, R., Cometa, A., and Santilli, V. (2010). Segmental muscle vibration improves walking in chronic stroke patients with foot drop: a randomized controlled trial. *Neurorehabil. Neural Repair*. 24, 254–262. doi: 10.1177/1545968309349940

Polanowska, K., Seniow, J., Paprot, E., Lesniak, M., and Czlonkowska, A. (2009). Left-hand somatosensory stimulation combined with visual scanning training in rehabilitation for post-stroke hemineglect: a randomised, double-blind study. *Neuropsychol. Rehabil.* 19, 364–382. doi: 10.1080/09602010802268856

Schabrun, S. M., and Hillier, S. (2009). Evidence for the retraining of sensation after stroke: a systematic review. *Clin. Rehabil.* 23, 27–39. doi: 10.1177/0269215508098897

Seniow, J., Polanowska, K., Lesniak, M., and Czlonkowska, A. (2016). Adding transcutaneous electrical nerve stimulation to visual scanning training does not enhance treatment effect on hemispatial neglect: a randomized, controlled, double-blind study. *Top. Stroke Rehabil.*. 23, 377–383. doi: 10.1179/1074935715Z.00000000058

Sim, S., Oh, D. W., and Chon, S. (2015). Immediate effects of somatosensory stimulation on hand function in patients with poststroke hemiparesis: a randomized cross-over trial. *Int. J. Rehabil. Res.* 38, 306–312. doi: 10.1097/MRR.0000000000000126

Stein, J., Hughes, R., D'Andrea, S., Therrien, B., Niemi, J., Krebs, K., et al. (2010). Stochastic resonance stimulation for upper limb rehabilitation poststroke. *Amer. J. Phys. Med. Rehabil.* 89, 697–705. doi: 10.1097/PHM.0b013e3181ec9aa8

Sullivan, J. E., Hurley, D., and Hedman, L. D. (2012). Afferent stimulation provided by glove electrode during task-specific arm exercise following stroke. *Clin. Rehabil*. 26, 1010–1020. doi: 10.1177/0269215512442915

Thielman, G. (2010). Rehabilitation of reaching poststroke: a randomized pilot investigation of tactile versus auditory feedback for trunk control. *J. Neurol. Phys. Therapy* 34, 138–144. doi: 10.1097/NPT.0b013e3181efa1e8

Turville, M., Carey, L. M., Matyas, T. A., and Blennerhassett, J. (2017). Change in functional arm use is associated with somatosensory skills after sensory retraining poststroke. *Amer. J. Occupat. Therapy* 71, 1–9. doi: 10.5014/ajot.2017.024950

Tyson, S. F., Sadeghi-Demneh, E., and Nester, C. J. (2013). The effects of transcutaneous electrical nerve stimulation on strength, proprioception, balance and mobility in people with stroke: a randomized controlled cross-over trial. *Clin. Rehabil*. 27, 785–791. doi: 10.1177/0269215513478227

Wu, C. W., Seo, H., and Cohen, L. G. (2006). Influence of electric somatosensory stimulation on paretic-hand function in chronic stroke. *Arch. Phys. Med. Rehabil.* 87, 351–357. doi: 10.1016/j.apmr.2005.11.019

Wu, H. C., Lin, Y. C., Hsu, M. J., Liu, S. M., Hsieh, C. L., and Lin, J. H. (2010). Effect of thermal stimulation on upper extremity motor recovery 3 months after stroke. *Stroke* 41, 2378–2380. doi: 10.1161/STROKEAHA.110.593673

Yavuzer, G., Oken, O., Atay, M. B., and Stam, H. J. (2007). Effect of sensory-amplitude electric stimulation on motor recovery and gait kinematics after stroke: a randomized controlled study. *Arch. Phys. Med. Rehabil*. 88, 710–714. doi: 10.1016/j.apmr.2007.02.030

Yekutiel, M., and Guttman, E. (1993). A controlled trial of the retraining of the sensory function of the hand in stroke patients. *J. Neurol. Neurosurg. Psychiatr*. 56, 241–244. doi: 10.1136/jnnp.56.3.241

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Using a Vibrotactile Biofeedback Device to Augment Foot Pressure During Walking in Healthy Older Adults: A Brief Report

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Human movement based on sensory control is significant to motor task performance. Thus, impairments to sensory input significantly limit feedback-type motor control. The present study introduces a vibrotactile biofeedback (BF) system which augments information regarding the user's foot pressure to enhance gait performance. The effects of the proposed system on the gait patterns of healthy older adults and on the cognitive load during gait were evaluated; these factors are essential to clarify feasibility of the device in real-life settings. The primary task of our study was to evaluate gait along with a cognitively demanding activity in 10 healthy older adults. Regarding kinematic and kinetic data in the BF condition, the subjects had significantly increased ankle dorsiflexion during the heel contact phase in the sagittal plane and marginally increased foot pressure at the toe-off and stride length. However, such kinematic and kinetic changes were not attributed to the increased walking speed. In addition, cognitive performance (i.e., the number of correct answers) was significantly decreased in participants during gait measurements in the BF condition. These data suggest that the system had the potential for modifying the kinematic and kinetic patterns during walking but not the more comprehensive walking performance in older adults. Moreover, the device appears to place a cognitive load on older adults. This short report provides crucial primary data that would help in designing successful sensory augmentation devices and further research on a BF system.

Keywords: older, sensory augmentation, human-machine interface, gait training, dual task

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INTRODUCTION

Gait performance is important to independently perform activities of daily living, and it is an important measure of functional capacity among the elderly people (Fritz and Lusardi, 2009). Moreover, gait performance can help predict adverse events (Montero-Odasso et al., 2005), disability, and mortality in older adults (Studenski et al., 2011). Aging negatively affects spatiotemporal gait parameters, such as shorter stride length, wider base of support, variability gait duration, and slower walking speed (Aboutorabi et al., 2016). Aging-related variations in gait parameters are associated with body structure and cognitive function changes (Tian et al., 2017).

Therefore, preserving gait performance is important for older adult health and fall prevention (Fritz and Lusardi, 2009).

Sensory augmentation is a technique to enhance or supplement sensory information to improve information processing and performance (Bach-y-Rita et al., 1969). This type of technique provides specific sensory feedback (e.g., visual, auditory, or tactile feedback) of body fluctuation or gait patterns during training. Compared with other methods, rhythmic auditory stimulation (RAS) was found beneficial in enhancing the gait performance of patients with Parkinson's disease (PD) (Thaut et al., 1996; Pau et al., 2016); associated studies have shown that artificial RAS (i.e., metronome or music-sounds) and ecological RAS (i.e., personalized actual footstep sounds) are equally effective in improving gait performance in PD (Murgia et al., 2018). Recently, a multisensory approach established on action observation plus sonification (i.e., auditory feedback acquired by transforming kinematic data of the movements of relevant body parts) was reported to help patients with PD with freezing gait to relearn gait movements (Mezzarobba et al., 2018). Various methods have been established to provide biofeedback (BF) on body fluctuation to older adults or patients with neurological disorders during stance (Dozza et al., 2007) or gait (Verhoeff et al., 2009; Davis et al., 2010) tasks. Moreover, most previous reports have emphasized on the head or trunk positions as representative body movements (Dozza et al., 2007; Horak et al., 2009; Verhoeff et al., 2009; Davis et al., 2010; Wall, 2010). However, proper foot movement is important to progress with the supporting foot during stance. In particular, appropriate heel strike and push off during walking play an important role in the attenuation of impact forces, and assist in forward propulsion (Whittle, 1999). Further, previous studies have reported that compared with young adults, older adults have reduced ankle dorsiflexion at initial contact and reduced plantarflexion at toe-off (Judge et al., 1996; Kerrigan et al., 1998; Arnold et al., 2014). These studies have demonstrated the importance of appropriate foot motion for the maintenance and improvement of gait performance.

It has been recently shown that vibrotactile feedback (VTF) can influence postural and gait performance during dual tasks and cognitive task performance (Verhoeff et al., 2009; Haggerty et al., 2012). This may be attributable to the fact that VTF necessitates participants to engage in higher cognitive processes to deal with the stimulus. In particular, the elderly would be vulnerable to decreased dual-task performance during gait tasks or postural control (Woollacott and Shumway-Cook, 2002; Fraizer and Mitra, 2008). Therefore, such an increase in cognitive load should be taken into account in the application of VTF to real-life situations. In this study, we introduced a vibrotactile BF system that can provide information on the foot pressure pattern to improve optimal foot movements (Judge et al., 1996; Kerrigan et al., 1998; Whittle, 1999; Arnold et al., 2014). First, we examined the influence of the proposed BF system on the gait pattern of 10 healthy older adults in an initial validity study. Thereafter, we aimed to clarify the influence of the developed BF device on cognitive burden during gait because this aspect is necessary to clarify its feasibility in real-life settings.

MATERIALS AND METHODS

System Overview

The biofeedback device consists of a BF unit (four vibrators in the belt), a sensing unit (foot pressure sensor), and a personal computer (PC) (**Figure 1A**). The system was designed for transmitting the timing and strength of heel contact and push off, since ankle dorsiflexion at heel contact, and push off at heel off are important foot motions during walking in older adults (Judge et al., 1996; Kerrigan et al., 1998; Whittle, 1999; Arnold et al., 2014).

Two built-in pressure sensors are found in the sensing unit, and sensor placement is designed to easily understand the timing of heel strike and push off (**Figure 1C**). The proposed system enhances the foot pressure pattern with four vibrators attached to the pelvis. The pelvis was chosen because (a) the anterior-superior iliac spine and posterior-superior iliac spine are large osteophytes and readily detect vibration and (b) stimulation patterns are easy to understand as anterior and posterior parts of the pelvis and anterior and posterior parts of the foot (toe and heel) are in the same horizontal planes, respectively. Four vibrators (**Figure 1B**) in the pelvic belt facilitate the older adult participant to convey foot contact information (i.e., timing and intensity of foot pressure). A vibration at a frequency of 80 Hz was applied to the pelvis in the stance phase in synchronization with the earth connection of the foot pressure sensor. The small number of vibrators helps the users easily understand BF input. The importance of the vibration is comparative to that in the foot pressure sensors in the shoes.

By using the proposed feedback system, our device provides accurate information regarding the trainees' gait pattern. In gait training, the older adults are provided BF to modify the gait patterns properly. The foot pressure sensor should correctly obtain pressure data during gait and send data back to the PC.

Participants

This study included 10 healthy older adults (5 males and 5 females, mean age; 71.9 $\pm$ 2.6 years). Participants were recruited from the Shinjuku-ward, Tokyo, which was facilitated through local advertising by the Human Resources Center in Shinjuku-ward. At the initial visit, screening physical and hearing examination were performed. The inclusion criteria were as follows: age $\geq$65 years, sufficient communication skills to understand the instructions, living independently in the community, able to walk without an aid, free of neurological or musculoskeletal disorders that might influence gait performance or cognition (stroke, brain trauma, PD, acute illness, and significant orthopedic disability), mini-mental state examination score $>$20 (no dementia), and ability to sense vibrations of the BF system (during screening evaluation, vibration was actually applied to the pelvis to confirm reactions). Furthermore, participants were excluded if they had a hearing deficit, nerve

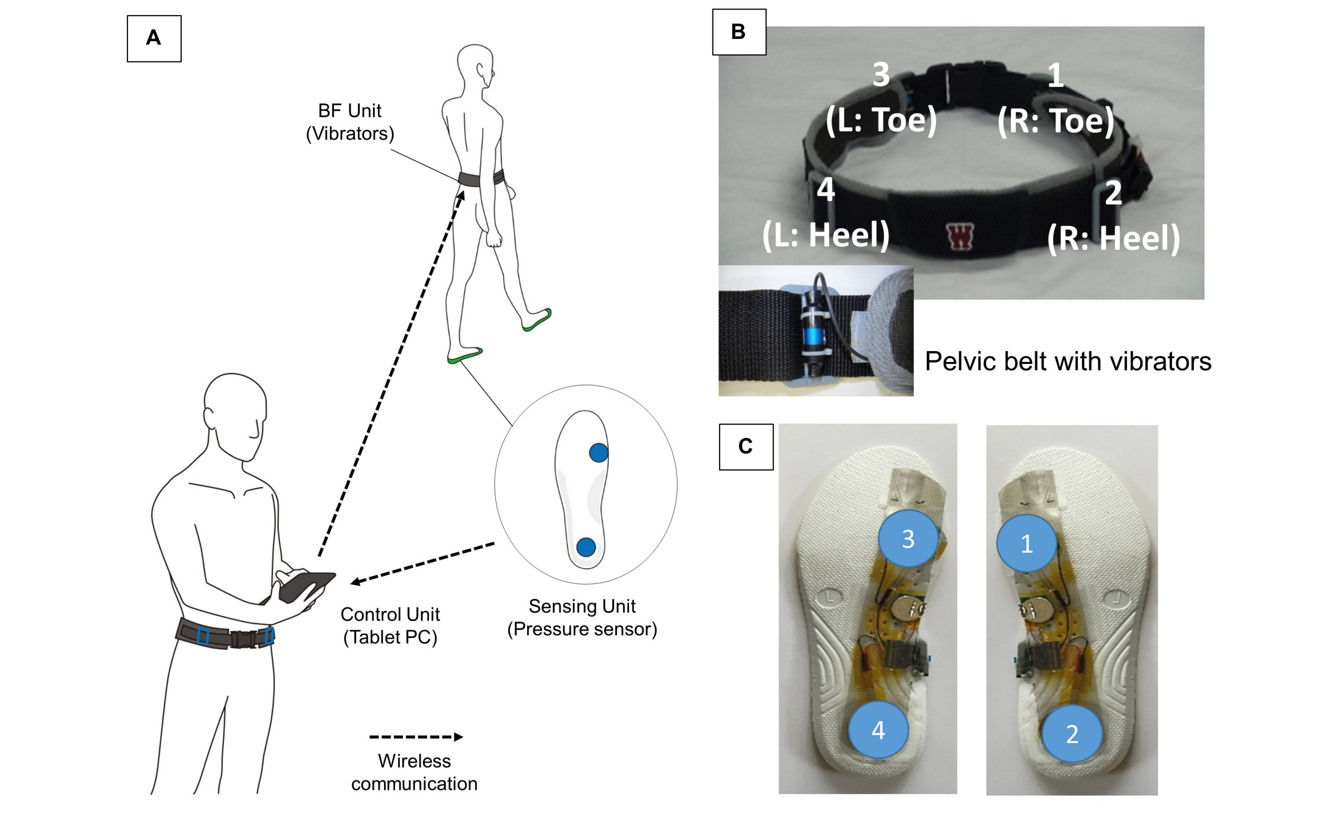

FIGURE 1 | System overview. **(A)** Our devices consist of a shoe insole with a foot pressure sensor, vibrotactile BF device (pelvic belt), and personal computer. The system augments the foot pressure pattern by using the vibratory belt attached to the pelvis. By using the feedback information, our system provides the user with accurate information regarding their gait pattern. **(B)** Vibrators are placed on the anterior and posterior-superior iliac spines to easily understand the tactile stimuli. During gait training, the vibrators on the trainee's pelvic belts are simultaneously activated corresponding to the user's foot presser sensor. **(C)** The sensing unit includes two built-in pressure sensors, and the sensor placement is designed to easily understand heel strike and push off. Using this information from insole sensors, the user can be aware of the timing, and intensity of their heel strike and push off.

damage, body pain, severe visual impairment, a history of fainting, or a body mass index >30 kg/m^2.

Ethics Approval and Consent to Participate and Publication

Procedures in this study were approved by the Waseda University Ethics Committee for Human Research. After a complete description of the procedures and purpose of the study, written informed consent was obtained from all participants.

Procedure

In the validation study, the main task was gait and a cognitive-demanding task (i.e., serial subtraction task) (Ellmers et al., 2016). Participants walked for 1 min along the corridor at the same time performed a serial subtraction task. Before the 1-min walking task, each participant sat down on a chair and received an adequate explanation from the experimenter regarding the relationship between the sensor and the vibrator. Next, participants practiced a 10-m walking task to better understand the relationship between the foot pressure sensor and the vibration.

During the walking task, participants counted backward aloud in increments of seven from a starting number. The initial number was determined from 125 to 250 (Ellmers et al., 2016). Then, for the gait session, a different number was randomly selected while subtracting. Further, in the BF condition, the older adults walked and corrected the gait pattern with BF information while attempting the serial subtracting task. In the control (No-BF) condition, the older adults only walked while subtracting.

Biofeedback conditions and control conditions were measured at a 1-week interval in counterbalanced order among participants for avoiding potential order effect. All measurements associated with walking and cognition tasks in this study were performed by part-time research assistants blinded to the BF or no-BF condition.

Measurements and Analysis

The following were measurements used to examine the participants' walking performance: (a) ankle dorsiflexion at heel strike as kinematic data, (b) maximum foot pressure at the push off as kinetic data, (c) stride length as a measure of performance of walking, and (d) walking speed as the comprehensive evaluation of walking. Inertial sensors was used to measure kinematic data during walking (Rehagait, Hasomed, Germany). During the 1 minute of walking, acceleration, and deceleration data for motion capture in the walking test were excluded from the analyses. The maximum foot pressure at push off, stride length during walking, and walking speed were measured using a force plate (P-walk, BTS, Italy). Data were acquired with a 2-m long reaction force sensor placed 5 m away from the starting point for walking. For data (a), (b), and (c), mean values of the left and right leg were used.

The cognitive performance score was the number of responses and correct verbalized arithmetic calculations (Ellmers et al., 2016). During trials, dual-task scores were calculated when the older adults simultaneously performed the walking and cognitive tasks. The number of responses and correct arithmetic calculations verbalized by participants were calculated for the BF condition and control condition.

Data normality was evaluated with the Shapiro – Wilk test, and a non-parametric test was used if a violation of normality was noted. With respect to ankle dorsiflexion in the sagittal plane, maximum foot pressure at push off, and stride length, multiple *t*-tests with correction for multiple comparison using the Holm–Sidak method were applied using GraphPad Prism software (Streiner, 2015) (Graphpad Prism version 6.0, GraphPad Software Inc., CA, United States). Differences were considered to be significant at $p < 0.05$. As for walking speed and cognitive performance, Student's *t*-test or the Wilcoxon signed-rank test was used for comparing the BF and control conditions with a *p*-value of <0.05 considered to be statistically significant.

RESULTS

Table 1 presents the results of walking and cognitive performance of older adults during the experiment. With respect to ankle dorsiflexion in the sagittal plane, the participants in the BF condition had increased ankle dorsiflexion angle at the heel contact phase than in the control condition [$t(18) = 2.412$, $p = 0.027$]. In the BF condition, participants had marginally higher foot pressure at toe off than the controls [$t(18) = 1.956$, $p = 0.066$]. Participants using BF marginally extended their stride length [$t(18) = 2.072$, $p = 0.053$] compared with the control. However, there were no significant difference between BF and the control conditions for walking speed [$t(9) = 1.462$, $p = 0.177$].

Regarding cognitive performance, no significant difference was observed in the number of answers between BF and control conditions [$t(9) = 0.937$, $p = 0.373$]. The number of correct arithmetic calculations was decreased in the participants during gait in the BF condition [$t(9) = 3.031$, $p = 0.014$] compared with the control condition.

TABLE 1 | Variables for walking and cognitive performance during the experiment.

	BF	Control (No-BF)	*p*-value
Walking performance (*n* = 10)			
Ankle joint angle (degrees)	25.3 ± 1.4	20.1 ± 5.1	0.027*
Foot pressure (hpa)	80.6 ± 4.2	77.1 ± 3.6	0.066†
Stride length (m)	1.2 ± 0.1	1.1 ± 0.1	0.053†
Walking speed (m/s)	1.0 ± 0.2	1.0 ± 0.1	0.177
Cognitive performance (*n* = 10)			
Number of response	12.1 ± 5.1	12.5 ± 5.6	0.373
Correct answers	8.0 ± 4.8	9.9 ± 5.7	0.014*

Values are denoted in mean ± SD. BF, biofeedback; $^{\dagger}p < 0.1$, $^{*}p < 0.05$.

DISCUSSION

A proposed device that augments foot pressure information was introduced in this study. The validation study explores the feasibility (i.e., effects of gait performance and cognitive burden) of the BF system in 10 older participants. In walking ability, the BF system helped participants increase their ankle dorsiflexion angle in the sagittal plane at the heel contact phase and marginally increased foot pressure at the toe-off and stride length. However, these kinematic and kinetic changes have no influence on the increased walking speed required for comprehensive walking performance. Furthermore, cognitive performance (i.e., the number of correct arithmetic calculations) was significantly decreased in the BF condition. Therefore, although there are beneficial kinematic and kinetic changes, the proposed BF system may need higher information awareness from the BF of the participants.

Appropriate foot movements contribute to shock absorption and allow the body to move forward with the supporting foot during walking (Aboutorabi et al., 2016). Proposed BF system may induce positive kinematic and kinetic changes in field trials, as the BF information directly conveys the characteristics of the foot contact pattern. However, these changes did not result in improvements in walking speed. A previous study showed that older adults tend to adopt a conservative gait pattern when they walk in an unfamiliar environment (Menz et al., 2003). This tendency may explain why walking speed did not change under the BF condition in the present study. For addressing this limitation, the effect of habituation after repeated practice must be assessed.

Furthermore, it is necessary to address the points to be improved. Our device only used four vibrators to reduce the cognitive burden during BF training. Nevertheless, the older participants demonstrated a decrease in cognitive performance during gait tasks. This is probably due to the low working memory in older adults (Woollacott and Shumway-Cook, 2002; Fraizer and Mitra, 2008; Lovden et al., 2008). As mentioned in the introduction, previous reports have suggested that VTF can affect gait performance during dual tasks and affect cognitivetask performance (Verhoeff et al., 2009). This may be because VTF requires older adults to perform higher cognitive processes to deal with the information from the BF device. Given that the older adults are susceptible to decreased cognitive performance during gait tasks, the increase in cognitive load with BF device should be considered when attempting to apply VTF.

This feasibility study was performed to examine the feasibility of the proposed BF system. However, the sample size was relatively small. Thus, a more rigorous study with a larger sample size is required. Moreover, future studies should include young participants to clarify the effect of BF gait training on cognitive and motor performance.

Thus, the BF system may have the potential to modify the kinematic and kinetic patterns, but not the walking speed (i.e., comprehensive walking performance) in older adults. Moreover, it is likely that the even four vibratory stimuli placed an increased cognitive load, which could be linked to the limited capacity of working memory in older people. In future trials, this aspect should be considered to establish a cutoff value for age or improve the proposed device. This report provides essential initial data for successfully designing sensory augmentation devices and exploring future academic issues.

ETHICS STATEMENT

All procedures were approved by the Waseda University Ethics Committee for Human Research. After a complete description of the procedures and purpose of the study, written informed consent was obtained from all participants.

AUTHOR CONTRIBUTIONS

KY designed the study, collected and analyzed the data, and drafted the manuscript. YH and AT made contributions toward data development and analyses. HI was involved in the conception of the system. All authors agreed with the final contents of the manuscript.

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REFERENCES

Aboutorabi, A., Arazpour, M., Bahramizadeh, M., Hutchins, S. W., and Fadayevatan, R. (2016). The effect of aging on gait parameters in able-bodied older subjects: a literature review. *Aging Clin. Exp. Res.* 28, 393–405. doi: 10.1007/s40520-015-0420-6

Arnold, J. B., Mackintosh, S., Jones, S., and Thewlis, D. (2014). Differences in foot kinematics between young and older adults during walking. *Gait Posture* 39, 689–694. doi: 10.1016/j.gaitpost.2013.09.021

Bach-y-Rita, P., Collins, C. C., Saunders, F. A., White, B., and Scadden, L. (1969). Vision substitution by tactile image projection. *Nature* 221, 963–964. doi: 10.1038/221963a0

Davis, J. R., Carpenter, M. G., Tschanz, R., Meyes, S., Debrunner, D., Burger, J., et al. (2010). Trunk sway reductions in young and older adults using multi-modal biofeedback. *Gait Posture* 31, 465–472. doi: 10.1016/j.gaitpost.2010.02.002

Dozza, M., Horak, F. B., and Chiari, L. (2007). Auditory biofeedback substitutes for loss of sensory information in maintaining stance. *Exp. Brain Res.* 178, 37–48. doi: 10.1007/s00221-006-0709-y

Ellmers, T. J., Cocks, A. J., Doumas, M., Williams, A. M., and Young, W. R. (2016). Gazing into thin air: The dual-task costs of movement planning and execution during adaptive gait. *PLoS One* 11:e0166063. doi: 10.1371/journal.pone.0166063

Fraizer, E. V., and Mitra, S. (2008). Methodological and interpretive issues in posture-cognition dual-tasking in upright stance. *Gait Posture* 27, 271–279. doi: 10.1016/j.gaitpost.2007.04.002

Fritz, S., and Lusardi, M. (2009). White paper: "walking speed: the sixth vital sign". *J. Geriatr. Phys. Ther.* 32, 46–49.

Haggerty, S., Jiang, L. T., Galecki, A., and Sienko, K. H. (2012). Effects of biofeedback on secondary-task response time and postural stability in older adults. *Gait Posture* 35, 523–528. doi: 10.1016/j.gaitpost.2011.10.359

Horak, F. B., Dozza, M., Peterka, R., Chiari, L., and Wall, I. I. I. C. (2009). Vibrotactile biofeedback improves tandem gait in patients with unilateral vestibular loss. *Ann. N.Y. Acad. Sci.* 1164, 279–281. doi: 10.1111/j.1749-6632.2008.03707.x

Judge, J. O., Davis, R. B. III, and Ounpuu, S. (1996). Step length reductions in advanced age: the role of ankle and hip kinetics. *J. Gerontol. A Biol. Sci. Med. Sci.* 51, M303–M312.

Kerrigan, D. C., Todd, M. K., Della Croce, U., Lipsitz, L. A., and Collins, J. J. (1998). Biomechanicalgait alterations independent of speed in the healthy elderly: evidence forspecific limiting impairments. *Arch. Phys. Med. Rehabil.* 79, 317–322. doi: 10.1016/s0003-9993(98)90013-2

Lovden, M., Schaefer, S., Pohlmeyer, A. E., and Lindenberger, U. (2008). Walking variability and working-memory load in aging: a dual-process account relating cognitive control to motor control performance. *J. Gerontol. B Psychol. Sci. Soc. Sci.* 63, 121–128.

Menz, H. B., Lord, S. R., and Fitzpatrick, R. C. (2003). Age-related differences in walkingstability. *Age Ageing* 32, 137–142.

Mezzarobba, S., Grassi, M., Pellegrini, L., Catalan, M., Kruger, B., Furlanis, G., et al. (2018). Action observation plus sonification. a novel therapeutic protocol for parkinson's patient with freezing of Gait. *Front. Neurol.* 8:723. doi: 10.3389/fneur.2017.00723

Montero-Odasso, M., Schapira, M., Soriano, E. R., Varela, M., Kaplan, R., Camera, L. A., et al. (2005). Gait velocity as a single predictor of adverse events in healthy seniors aged 75 years and older. *J. Gerontol. A Biol. Sci. Med. Sci.* 60, 1304–1309. doi: 10.1093/gerona/60.10.1304

Murgia, M., Pili, R., Corona, F., Sors, F., Agostini, T. A., Bernardis, P., et al. (2018). The use of footstep sounds as rhythmic auditory stimulation for gait rehabilitation in parkinson's disease: a randomized controlled trial. *Front. Neurol.* 9:348. doi: 10.3389/fneur.2018.00348

Pau, M., Corona, F., Pili, R., Casula, C., Sors, F., Agostini, T., et al. (2016). Effects of physical rehabilitation integrated with rhythmic auditory stimulation on spatio-temporal and kinematic parameters of gait in parkinson's disease. *Front. Neurol.* 7:126. doi: 10.3389/fneur.2016.00126

Streiner, D. L. (2015). Best (but oft-forgotten) practices: the multiple problems of multiplicity-whether and how to correct for many statistical tests. *Am. J. Clin. Nutr.* 102, 721–728. doi: 10.3945/ajcn.115.113548

Studenski, S., Perera, S., Patel, K., Rosano, C., Faulkner, K., Inzitari, M., et al. (2011). Gait speed and survival in older adults. *JAMA* 305, 50–58. doi: 10.1001/jama.2010.1923

Thaut, M. H., McIntosh, G. C., Rice, R. R., Miller, R. A., Rathbun, J., and Brault, J. M. (1996). Rhythmic auditory stimulation in gait training for Parkinson's disease patients. *Mov. Disord.* 11, 193–200. doi: 10.1002/mds.870110213

Tian, Q., Chastan, N., Bair, W. N., Resnick, S. M., Ferrucci, L., and Studenski, S. A. (2017). The brain map of gait variability in aging, cognitive impairment and dementia-A systematic review. *Neurosci. Biobehav. Rev.* 74, 149–162. doi: 10.1016/j.neubiorev.2017.01.020

Verhoeff, L. L., Horlings, C. G., Janssen, L. J., Bridenbaugh, S. A., and Allum, J. H. (2009). Effects of biofeedback on trunk sway during dual tasking in the healthy young and elderly. *Gait Posture* 30, 76–81. doi: 10.1016/j.gaitpost.2009.03.002

Wall, I. I. I. C. (2010). Application of vibrotactile feedback of body motion to improve rehabilitation in individuals with imbalance. *J. Neurol. Phys. Ther.* 34, 98–104. doi: 10.1097/NPT.0b013e3181dde6f0

Whittle, M. W. (1999). Generation and attenuation of transient impulsive forces beneath the foot: a review. *Gait Posture* 10, 264–275. doi: 10.1016/s0966-6362(99)00041-7

Woollacott, M., and Shumway-Cook, A. (2002). Attention and the control of posture and gait: a review of an emerging area of research. *Gait Posture* 16, 1–14. doi: 10.1016/s0966-6362(01)00156-4

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Experiences of Upper Limb Somatosensory Retraining in Persons With Stroke: An Interpretative Phenomenological Analysis

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Purpose: The aim of this study was to explore experiences of upper limb somatosensory discrimination retraining in persons with stroke.

Methods: A qualitative methodology was used within the context of a randomized control trial of somatosensory retraining: the CoNNECT trial. Participants in the CoNNECT trial completed a treatment program, known as SENSe therapy, to retrain upper limb somatosensory discrimination and recognition skills, and use of these skills in personally valued activities. Eight participants were interviewed on their experience of this therapy. Data were analyzed using Interpretative Phenomenological Analysis (IPA).

Results: Five themes represented participants' experiences of upper limb somatosensory retraining after stroke: (1) loss of sensation and desire to reclaim normality; (2) harnessing positivity in the therapeutic relationship and specialized therapy; (3) facing cognitive and emotional challenges; (4) distinct awareness of gains and differences in bodily sensations; and (5) improved functioning: control and choice in daily performance. Persons with stroke experienced somatosensory retraining as a valuable treatment that provided them with sensory and functional gains.

Conclusion: Upper limb somatosensory retraining is a treatment that persons with stroke perceived as challenging and rewarding. People who have experienced stroke believed that somatosensory retraining therapy assisted them to improve their sensation, functional arm use, as well as daily performance and participation in life.

Keywords: stroke, somatosensation, therapy, rehabilitation, interpretative phenomenological analysis

INTRODUCTION

Stroke happens unexpectedly with rapid adverse effects on brain function (Sacco et al., 2013). Global estimates reveal 62 million people survive stroke, with numbers continuing to increase (Strong et al., 2007; Mukherjee and Patil, 2011). Stroke causes various impairments leading to disability (Sturm et al., 2002; Hartman-Maeir et al., 2007; Strong et al., 2007; Mendis, 2012). In particular, somatosensory impairment occurs commonly after stroke; approximately 50% of people cannot detect or interpret bodily sensations in the upper limb, such as touch or body position (Carey and Matyas, 2011; Kessner et al., 2016). Somatosensory loss is associated with reduced motor ability and poor functional outcomes after stroke (Blennerhassett et al., 2007; Tyson et al., 2008; Meyer et al., 2014, 2016).

Two recent qualitative studies provide insight into the experience of upper limb somatosensory loss in people who have experienced stroke (Connell et al., 2014; Doyle et al., 2014). In these studies, participants report that somatosensory loss impacts negatively on their performance, roles, and participation in life situations (Connell et al., 2014; Doyle et al., 2014). Some cannot express what it feels likes to have reduced or absent sensation in the upper limb post-stroke and instead describe sensory loss in relation to movement difficulties (Connell et al., 2014). In general, somatosensory impairment is reported to be an unpleasant physical and emotional experience, and people live with uncertainty regarding whether to use their sensory affected arm in daily life (Connell et al., 2014; Doyle et al., 2014). People remain hopeful that their sensation will return after stroke, yet they receive minimal rehabilitation to treat sensory impairment (Connell et al., 2014; Doyle et al., 2014). If rehabilitation occurs, treatment generally involves strategies to compensate for sensory loss (i.e., use of vision or use of the 'unaffected' arm). Never-the-less, people who have experienced stroke value treatment that improves somatosensation (i.e., remediates deficits) (Doyle et al., 2014), such as somatosensory discrimination retraining.

Quantitative evidence shows somatosensory discrimination retraining can help people improve their sensation after stroke (Carey, 1993; Carey et al., 1993, 2011a; Yekutiel and Guttman, 1993; Byl et al., 2003, 2008; Carey and Matyas, 2005; Turville et al., 2019). For example, an active remedial approach to sensory discrimination retraining commonly involves learning-based tasks that focus on sensory discrimination and recognition skills (Yekutiel, 2000; Carey et al., 2011a). Principles of retraining originate from theories of perceptual learning and brain recovery; treatment harnesses peoples' potential for neuroplasticity and learning after stroke (Carey, 1993, 2012b; Yekutiel, 2000). As a consequence, sensory retraining may be a demanding and intense treatment. Previous qualitative studies have focused on the experience of somatosensory impairment, yet no study has specifically investigated experiences of somatosensory discrimination retraining in persons with stroke as a method for upper limb somatosensory recovery.

We therefore aimed to investigate experiences of people with stroke participating in a program of somatosensory discrimination retraining that is based on principles of neural plasticity and learning and designed to help the person with stroke regain a sense of touch. Our focus was on better understanding the facilitators, challenges, and self-perceived changes following upper limb somatosensory retraining post-stroke. Specifically, we wanted to understand: (a) How do persons with stroke perceive and describe their experience of somatosensory discrimination retraining?; (b) What motivates persons with stroke to participate in somatosensory discrimination training?; (c) What variables do persons with stroke perceive as facilitating or limiting their ability to learn and/or perform during somatosensory discrimination retraining?; and (d) What changes do persons with stroke experience following upper limb somatosensory retraining?

MATERIALS AND METHODS

Setting and Study Design

This study recruited persons with stroke with somatosensory impairment who had participated in a randomized control trial of upper limb sensory retraining - the CoNNECT trial (Connecting New Networks for Everyday Contact through Touch) (Carey et al., 2011b). The CoNNECT trial is registered with the Australian New Zealand Clinical Trials Registry (ACTRN12613001136796). The current study was approved as an amendment to the existing ethics approval for the CoNNECT trial, and was obtained from Austin Health and La Trobe University Human Ethics Committees. As part of CoNNECT, participants retrained upper limb sensory discrimination and recognition skills in tactile, proprioception, and object recognition modalities using specially designed training tasks and perceptual learning protocols (Carey, 2012a). Participants also applied sensory retraining principles in relation to two self-selected tasks they considered important in their daily life but had difficulty with due to sensory impairment, e.g., using a wallet or using a fork when eating. This sensory discrimination retraining program is known as SENSe (Carey et al., 2011a).

SENSe therapy is based on seven key principles that are operationalised as follows: (1) selecting specially designed tasks that involve graded somatosensory discrimination of tactile, proprioceptive and haptic object recognition attributes, such as texture surfaces that vary in degree of roughness, friction or pattern, flexion/extension positions of the wrist in space, and object pairs that vary specifically in shape, size, texture, temperature, weight, hardness and function; (2) using goal-directed attention to explore the sensory task with vision occluded and making a perceptual discrimination choice, e.g., about whether the stimulus feels the same or different, or the relative position (angle) of the upper limb joint; (3) receiving feedback from the therapist about the accuracy of sensory discrimination choice (outcome) and method of exploring the sensation (performance); (4) using vision and the experience of feeling the sensory stimulus with the 'unaffected' limb in order to calibrate sensation in the affected limb; (5) knowing what to expect to feel (i.e., deliberate use of anticipation) in subsequent sensory discrimination trials; (6) repeating discrimination trials, with task difficulty progressively increased over time; and (7) using a matrix of varied stimuli and training conditions, i.e., learning the above principles within a variety of tactile, proprioception, tactual object recognition and functional tasks, so skills can be transferred to new tasks and situations performed outside of formal training sessions. Further information about this treatment program is detailed in the Carey et al. (2011a) randomized control trial publication and in the SENSe training manual and DVD for therapists (Carey, 2012b). A YouTube video of how the training principles are operationalised is also available online[1].

Methodology

A qualitative methodology guided this study; more specifically, Interpretative Phenomenological Analysis (IPA) (Smith et al., 2009) was used to understand, in detail, each participant's unique view of somatosensory retraining after stroke. Phenomenology is concerned with how people perceive their lived experiences (Merleau-Ponty, 1962) (i.e., phenomenology of perception). As such, IPA seemed particularly relevant for this study to investigate the perceptive process and changes people experience with treatment that addresses an abstract bodily impairment, such as upper limb somatosensory loss. Further, interpretative analysis would enable a depth in understanding the process of somatosensory retraining and potential changes in sensory impairment (Smith et al., 2009). IPA has previously been used in the field of neurology and to understand patient's treatment experiences (Smith, 2011).

Participants and Recruitment

We purposively selected a sample of 14 persons with stroke to contact for potential participation in the current study, out of a current sample of 36 from the CoNNECT trial who had all experienced upper limb somatosensory retraining as part of their involvement in the CoNNECT trial. IPA research typically involves detailed investigation of a small sample (Smith et al., 2009). We therefore planned to sample 6–8 persons with stroke. We elected to identify and contact 14 persons with the expectation that approximately half might be available and willing to be involved. In order to maximize the representativeness of the sample and minimize bias we chose to stratify this sample (Patton, 2002) according to their treating therapist and age. These features were selected for stratification because we wanted to (a) sample the experience of treatment delivery across therapists and ensure the interviewer had not previously treated the participant, and (b) sample a range of ages of participants from the CoNNECT sample that comprised a majority of participants under the age of 65 years. In regard to age, we stratified the sample according to (a) those aged over 65 years and (b) those aged less than 65 years. We sent letters to the stratified subset of 14 possible people inviting them to participate in the study. A total of eight participants replied to this invitation and participated between August 2016 and January 2017.

Procedure

Participants were engaged in semi-structured interviews to obtain qualitative data. This method is often used in IPA research because it enables rich, detailed data on people's experiences (Smith et al., 2009). Our interview guide was developed using recommendations from Smith et al. (2009) and is presented as **Supplementary Material**. Interview questions were open-ended to facilitate a detailed understanding of experience. Other types of questions were also used to clarify participants' experiences, such as: follow-up, probing, or specifying questions (Steinar, 1996; Smith et al., 2009). Interviews were audio-recorded with permission from participants. Interviews and consent took approximately 50 min and occurred either at participants' homes or at the research clinic. The interviewers were research occupational therapists with no prior relationship with the participant, yet had experience delivering SENSe sensory retraining. Two researchers (MT and JW) completed interviews and reflections were recorded immediately after each interview to begin the interpretative process.

Data Analysis

The primary author (MT) conducted the primary data analysis, and to ensure trustworthiness in the analysis process, a second researcher (JW) assisted in thematic analysis of four interviews (i.e., 4/8 interviews). Reflectivity statements were employed as a process of reflexivity, and audit trials as a process of recording decision making during the analysis process, to maintain rigor (Krefting, 1991; Roulston, 2010). The iterative analysis process occurred using the following steps, suggested by Smith et al. (2009):

- Audio recording were listened to and transcribed verbatim into written form.
- Participant transcripts were read with initial noting of linguistic, descriptive, and conceptual comments.
- Initial notes were reviewed and conceptualized as themes, which involved deciding on phrases that reflected the psychological essence of that piece of the transcript.
- Themes were categorized into subthemes and then these subthemes were categorized into superordinate themes (i.e., five main themes of this study). Interview extracts that reflected themes were compiled for each participant. Written post-interview reflections from interviewers (MT and JW) were also consulted at this point to ensure completeness of individual participant themes.
- Data was analyzed according to similarities and differences in themes amongst participants. Superordinate and subthemes were identified as group themes if they occurred in interviews of six to eight participants (i.e., were representative of at least 75% of the sample), and as individual themes if they occurred in interviews from less than five participants (Smith et al., 2009).
- Individual themes were categorized in relation to superordinate group themes and the write-up of results maintained a diverse and detailed idiographic focus (Smith et al., 2009).
- Extracts were included in the results section if they represented group themes or individual variability and depth in experience (Smith et al., 2009; Smith, 2011).

RESULTS

Findings relate to the experience of eight participants; three females and five males with a mean age of 45 years (SD = 11). On average, participants had completed somatosensory

[1] https://www.youtube.com/watch?v=G9V3I30pn68&feature=youtu.be

discrimination retraining 2.5 years prior to participating in this interview study (*SD* = 1.6 years; Range = 5.5 months to 4.6 years). Additional characteristics of these participants are presented in **Table 1**. Five superordinate themes represent participants' experience of upper limb somatosensory discrimination retraining. These themes are schematically represented in **Figure 1** and are presented sequentially in the following section.

Loss of Sensation in Arm and Desire to Reclaim Normality

Somatosensory impairment evoked an extreme sense of loss for participants, as Carlos states: "I don't feeling nothing, nothing at all [...] no sensation at all" (Carlos). Participants had lost a vital sensory connection to their body, with some describing complete detachment from their upper limb: "It pretty much was not in my consciousness [...] it was pretty much dead on arrival [...] there was nothing" (James). The affected arm vanished from people's known bodily reality. Participants also endured pain (hypersensitivity) in their altered bodily experience. Veronica explains:

> I had virtually no touch sensation at all and in the meantime I had and still have got incredible pain through my affected side [...] It is very difficult for people to understand the experience that you are having when you can move your hand but you can't feel, and a big part of the kind of grieving fight is the fight for validation effectively, and when absolutely everything bilateral that you are trying to do is taking enormous effort and causing huge amounts of cognitive fatigue and no-one around you will accept that it is real, you are kind of fighting on both fronts (Veronica).

Upper limb sensory loss may amplify other hidden stroke symptoms, such as fatigue, and impacts negatively on daily task performance, roles, and connection with others. Maria says: "Oh, it was horrible, actually, because I couldn't really do daily stuff [...] I couldn't hold anything, things were just dropping, yeah so I had nothing, there was nothing there" (Maria). For Veronica, sensory loss affected her central role as a mother – protector of her young:

> Initially, I couldn't walk to the playground at the end of my street with my two children holding their hand because I couldn't feel at all if I was holding their hands because they were little and they were runners. They were too little to have near roads if I wasn't sure of holding their hands (Veronica).

To provide for his family, Kevin states "I don't want to be a burden to my family. After the stroke, I need to move on straight away – I'm the head of the family" (Kevin). Overall, participants were confronted with sensory loss and keen to reclaim normality in their body and functioning. Michael reveals the wish to get back to normality as a motivator when asked why he wanted to participate in sensory retraining:

> Ah, because, ah, why not give it a go, like, I've got nothing to lose [...] and if you got no touch, geez [...] yeah basically I wanted to get my life back on track and return back to normal (Michael).

Participants had lost so much and, therefore, perceived only gain in participating in upper limb sensory retraining. In addition, participants were grieving after stroke and possibly coped through participating in research and therapy-orientated action, as Julie explains:

> I think you just want to get as good as you think you're going to and that is hard. I mean I was [...] too young. I know other people have things when they are very early but you know it changed my life totally. But this I think was one of the best things I had done. I tried a few different things but this I found was really good (Julie).

Harnessing Positivity in the Therapeutic Relationship and Specialized Therapy

Participants recalled the discrimination tasks and functional retraining they completed as part of this program, with some participants describing the breadth and interest of activities. For example, Simon says:

> Um, I think it was multifaceted really, which made it um particularly interesting. We didn't do exceptionally repetitive tasks necessarily, although there was some repeating of tasks in the sense of assessing differences from yesterday to today for example. It had multiple areas of focus from grid training, to texture training, to object training, um to functional everyday activities like writing, maneuvering objects with my affected limb. So it was really fantastic, it was very holistic approach to functional retraining (Simon).

Discrimination tasks were performed using the learning and neuroscience principles of this program, and participants had declarative and procedural knowledge of treatment principles. Despite this, participants spoke most about the therapeutic milieu in which these principles were enacted. Participants trusted the therapist knew and would teach them sensory retraining principles. For some participants, such as Veronica, education and trust were essential in preparing to participate in sensory retraining.

> I couldn't see the direct cause and effect of how they were going to help me, they seemed a bit abstract and I knew I was going to have to put in a lot effort to make gains and so I was sitting there asking umm polite doubting questions [...] Yeah, what does this do and how does it work, and it was like 'okay now I get it and cool off we go' (Veronica).

With trust forming, participants used the therapeutic relationship to further understand and cope with learning involved in retraining upper limb sensation. "Look, we all done it. The help of the therapists because by myself, forget it." (Carlos). Various aspects of the therapeutic relationship were uniquely valued in the learning context of sensory retraining, such as:

- Collaborative effort: "We both worked so hard, so, so, so hard. Like we really both gave it our all" (Veronica).
- Goal-focused: "This is a goal and we will do it. She is very caring [...] Yeah, like she is a lovely lady and um yeah and um she's um helping me every step of the way" (Michael).
- Shared knowledge: "Not only, was doing the activities as important but also from my point of view was understanding, and the therapist was really good at explaining why we were doing certain things [...] and that was fantastic" (Simon).

TABLE 1 | Participant characteristics.

Name	Affected Arm	Time post-stroke (wks)	Initial tactile impairment	Initial proprioception impairment	Initial object recognition impairment	Initial motor ability	Self-selected tasks involved in retraining
Michael	Right	82	17.92	23.05	2	38	Using key and stabilizing food
Maria	Left	44	53.54	15.05	41	n/a	Doing up jewelry and hair
Veronica	Left	63	−0.15	34.70	12	62	Typing and brushing hair
Simon	Right	21	8.12	7.60	20	55	Typing and handwriting
James	Right	85	53.03	16.00	19	33	Typing and handwriting
Kevin	Right	16	22.57	11.90	26	45	Using buttons and remote controller
Carlos	Right	29	22.05	18.65	8	31	Using knife and using hammer
Julie	Right	40	15.34	9.95	38	45	Handling money and stirring

Pseudonyms are used for participant's names. All participants were right hand dominant. Time post stroke refers to time between stroke and completion of somatosensory retraining program. Initial tactile somatosensory impairment was based on quantitative measurement using the Tactile Discrimination Test (Carey et al., 1997), with an area under the curve score of less than 60.25 indicating impairment in tactile discriminative sensibility. Initial proprioception somatosensory impairment was measured using the Wrist Position Sense Test, with a score above 10.37 degrees indicating impairment in wrist position sense (Carey et al., 1996). Initial object recognition somatosensory impairment was assessed using the functional Tactile Object Recognition Test, with a score below 32 indicating impairment in functional tactile object recognition ability (Carey et al., 2006). Initial motor ability was measured using the upper extremity component of the Fugl Meyer Scale, which has a maximum score of 66 (Fugl-Meyer et al., 1974). n/a means not available. Sensory retraining principles were also practiced in relation to two meaningful tasks chosen by participants – these are indicated in the table for each participant. Consistent with eligibility criteria for the CoNNECT study, participants in this sample did not have: central nervous system dysfunction other than stroke; peripheral neuropathy; nor unilateral spatial neglect.

- Problem solving resources for retraining: "Asking her where she got that from and she would say 'oh yeah I walk around thinking oh yeah that would be good' and you just don't think about that" (Julie).
- Encouragement and motivation: "So yeah we did a lot [...] really encouraging and would always make me feel welcome and would tell me how I was going [...] and I think pretty much she kept me going" (Maria).
- Emotional support: "Positive, positive. There was always an element where I was really asked how I was feeling in the training and that was fantastic [...] They were very diligent with that, always conscious to how I felt with different activities" (Simon).

Participants appreciated the one-on-one therapeutic relationship developed during sensory retraining. They felt positive about retraining within a therapeutic relationship that focused on quality practice, scientific information, goal achievement, and personal support.

Facing Cognitive and Emotional Challenges

Retraining involved demanding and intense work. Participants' cognitive and coping resources were challenged during treatment; "By the end of it I was like 'phew' so exhausted" (James). Participants struggled to sustain their concentration

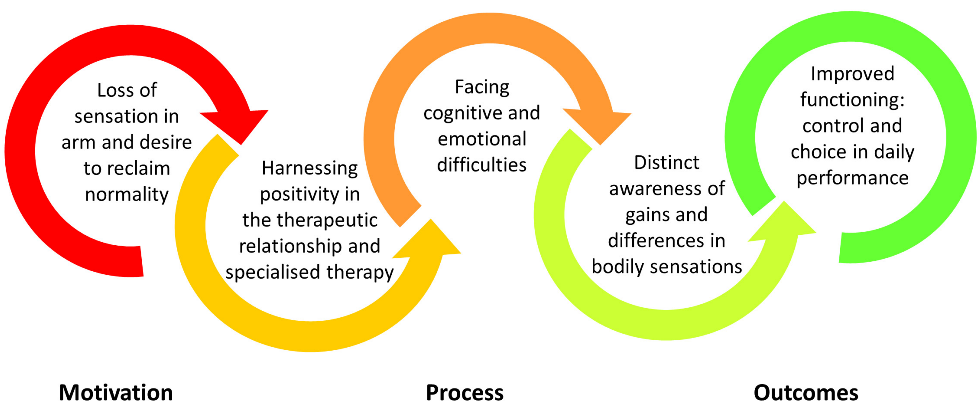

FIGURE 1 | Schematic representation of the main themes that represented participants' experience of upper limb somatosensory retraining post-stroke.

on sensory tasks, yet they believed this challenge was necessary if they were to change how their brain understands bodily sensory information.

> It was from a completely different type of thinking and processing than I had ever been used to [...] It was always a positive thing, it was challenging but I wouldn't have changed it, I knew it was working then. [...] I used to be exhausted afterward, my brain was just fried [...] it was full on [...] I think, the way I understood it was that you are just rewiring your brain to connect things again and from your brain to the nerves in your arm so they work properly again (Maria).

Participants were committed to putting in effort to attend to sensory discrimination tasks. Some participants were in awe of their brain and sensation during this process.

> When I first started, with the first, as we went on each session I get very tired, very, very tired and then I would not be very good and I would know I was getting enough [...] It's amazing how much the brain says everything. I was just amazed how much [...] I don't think I realized how much the change had occurred and it is ongoing. That something is gone but then something else is on (Julie).

Participants spoke of an understanding of neuroplasticity prior to retraining; however, as Simon outlines the difference between knowing about brain plasticity at an intellectual level versus lived experience. "Until you're in that position and going through it personally, um, I don't think you can really appreciate the complexity of it" (Simon). Participants were engaged in a dynamic and complex learning process during sensory retraining, with two participants likening retraining to effortful child development. "Just rewiring everything, like starting again, like a child how they start to learn things that was how I was doing that. [...] yeah were as they (children) soak it in, I had to work at it" (Maria). "Because I believe like a little kid to have to do everything again" (Carlos).

Participants coped with the demands of sensory retraining while processing a range of emotions, such as sadness, anxiety, and frustration. Such negative emotional responses seemed to originate from grief following sensory impairment and stroke, and expectations of recovery, learning, and/or performance. For example, while in a perceived regressed stage of development, Carlos describes emotions of sadness during retraining: "Yes, because when the people ask me if I feeling or what I have in my hand, or this, oh and it makes me so upset because I can't feeling" (Carlos). Carlos initially felt anxious and uncertain about the possibility of sensory recovery with discrimination retraining, and he coped with expressing skeptic thoughts and possible avoidance behavior.

> I'm going there [sensory retraining] and I sure nothing going to happen. I just think to myself what am I doing here you know [...] It look a little bit stupid what I'm doing there [...] The therapists explained things very well just the way I feeling cos I never had a stroke before, thank god for that anyways. I don't know the way things work you know (Carlos).

Kevin also faced his own challenges with grief and sadness; he coped with acceptance self-talk: "Yes, I am not upsetting myself because I need to accept that I have a problem on myself, I'm a stroke survivor. I need to learn things again from 0 to 100" (Kevin). Other participants reported frustration as a common emotion experienced during retraining. Simon wanted fast results and says:

> That was my own frustration in that I wanted to achieve the results quicker than my body and brain would allow [...] It didn't deter me, certainly some frustration around it [...] It was a constant challenge for me personally (Simon).

In contrast, Julie narrows her frustration to the perceived right or wrong nature of discrimination tasks:

> Oh it was really hard [...] I think cos I couldn't feel. Then we used to have a guess [...] You know you hate being, not that you are suffering, but I like to be right [...] When we would do the grids I would think 'argh oh not now' that's because I don't like it getting the better of me (Julie).

Overall, some negative emotions were felt during sensory retraining when experiencing: the effort involved in learning-based brain plasticity and perceptual discrimination tasks, the losses associated with life changes after stroke, and the desire to recover quickly. Some participants also experienced physical and communication challenges during sensory retraining, such as: persistent pain (2/8), increased muscle tone in upper limb affecting object manipulation and proprioception (2/8), and intermittent difficulties with receptive and expressive communication (2/8).

Distinct Awareness of Gains and Differences in Bodily Sensations

Participants held a positive view of sensory retraining as a treatment to remediate upper limb sensory deficits; all felt their sensation improved with retraining. Sensory gains appeared striking and participants struggled to convey the extent of improvements within the constraints of language. "When I started I had no clue they were different and by the end I was picking everything up [. . .] Um, so, so, so the changes that I experienced in terms of my sensing were pretty remarkable" (James). Michael uses an analogy to explain the change in his sensation:

> Yeah, 100%. Like, yeah, it just like when I didn't have the retraining to when I done it, it's like chalk and cheese, just, chalk and cheese [...] It done wonders for me, like, um, in sensation. [...] It's not 100% but I've really got gains of it and I think it will never be 100%. Yeah, like, um from when I started the program to when I finished I've made a huge gains (Michael).

Participants described sensory improvements with reference to sensation still not being normal, like before the stroke. Veronica and Simon inform:

> No question whatsoever, I have, um, immeasurable greater access to touch sensation and proprioception information than what I had when I started the therapy. The difference that it made for me is indescribable. Um, it is like for a blind person their eyes move but they don't see, it is that, your hand moves but it doesn't see. And the difference in what you can do when you can feel

> something as opposed to not feel something just is indescribably different in life [...] I still have imperfect touch (Veronica).

> Phenomenally so [...] I think what it allowed me to do was relearn how to feel as best as I could on my affected side, especially my arm [...] The training has helped that to improve, is it back to pre-level, not completely (Simon).

Participants expressed intimate knowledge about sensory gains and losses after retraining. Participants appraised sensory improvements in relation to their life-long understanding of bodily sensations. At an individual level, Michael indicates that the process of retraining revealed the extent of his sensory loss post-stroke, which further defined the context from which he perceived sensory gains. "Like you don't know how much you've lost until you've done the sensation course and it's like 'wow, have I lost that much?' [...] Yeah it puts it in your brain how much you can't do" (Michael).

Sensory improvements motivated ongoing effort in retraining. In the following extract, we hear how improvements dissolved Carlo's initial ambivalence about retraining:

> When I start see the difference I'm so happy going there. I feeling happy, feeling happy every time I going there, I don't know why [...] when I start feeling something it doesn't matter the time [...] The therapist ask me what I have in my hand, you know, and because the feeling is not much and I tell exactly what I have in my hand and, oh, I feeling so good, you know (Carlos).

Sensory improvements were felt not only during the course of therapy but also after formal treatment. "Sensation, no I think I'm still going. It is only very small but it is still improving for me" (Julie). Some participants believed that sensation no longer required as much conscious attention after retraining. "But it sort of gets stuck in your brain, like how it feels, you don't even like realize that" (Michael). Some participants additionally believed that ongoing sensory gains took time and required dedicated practice of somatosensory retraining principles in daily life.

> That was really the key, to understand the principles behind it and transfer that into practice and that certainly helped me to achieve some positivity [...] It has become part of my routine, especially things like transferring what I feel on my good side and critically thinking about that and trying to understand what feels it like on my good side and then transferring that to my affected side and trying to feel the same ridges on a piece of clothing, or top, or whatever [...] But if I do continue, then there is no reason why it can't improve albeit slowly over time (Simon).

Simon and Carlos believed that increased arm use was also the catalyst for further sensory gains. "I think it (sensation) is better now. Um, but that is just based on my everyday activities because I even catch myself out because I'm actually incorporating my right hand more now" (Simon). "Yeah because I have never stopped, like I use my hand. That is why I'm feeling more things in my hand" (Carlos).

Improved Functioning: Control and Choice in Daily Performance

Sensory improvements related to functional improvements; retraining helped participants to use their arm more in daily tasks. Participants improved their performance of meaningful daily activities, such as: eating, grooming, dressing, cooking, exercise, driving, work, and gardening. "I always use my right (affected) hand. In our daily life, sensory retraining does a lot of things for me [...] I can do all the things at work, at home, the driving" (Kevin). "It helped me like getting dressed, cos like you have to use both hands to pull up your pants and just day to day stuff like driving, just feeling the steering wheel, like cutting up food" (Michael). This time, Carlos uses an analogy in his attempt to explain the extent of difference he experienced in his function after sensory retraining:

> Much easier, everything is different, unbelievable. It's like a glass of water and a glass of wine, but its true [...] always I play with my hand [...] and now I go for walk and if I see a coin I pick it up (laughter) (Carlos).

Following sensory retraining, participants perceived their arm was more useful in completing daily activities, with the return of spontaneity and playfulness in arm use. Participants owned renewed control and confidence in their arm and this allowed them to choose (i.e., problem solve) how daily tasks could be performed.

> I think there is a bit of spontaneity to my right hand but at the same time I can quickly recall the spontaneity of my brain saying 'just get that tissue with your left hand' and so I have to pull it back at that stage and 'hang on, I can do it with my right hand.' So it is a little bit of both [...] then particularly during participating in the study and this time post I'm more reticent to say 'no; no I can do it.' It's the challenge that I set myself (Simon).

Encouraging self-talk promoted ongoing arm use after retraining. Other strategies for arm use and task performance involved extra time to focus and reassurance that the 'unaffected' hand can assist if necessary.

> When I do things, especially with my affected right hand, I always remember not to rush. Do it slowly, slowly until you do it [...] when I'm focusing using my right hand I can do it well. [...] Always if my right hand is not working very well I have another hand to help (Kevin).

Like Kevin, most participants stated they needed extra time to focus during task performance because sensation was still vulnerable to other competing stimuli and demands (e.g., noise, fatigue). As Simon reflects: "Through the training [...] there is no other external stimulus distracting you so it is different outside of the therapy room" (Simon). Participants indicated that sometimes it was not possible to arrange extra time for task practice and performance using the affected arm because of external pressures; however, they believed this strategy of extra time in daily routines was worth prioritizing and helpful when implemented. Extra time for task practice and performance assisted ongoing challenges with specific fine motor tasks. Participants also found it helpful to occasionally share the task load between hands or pass the task to another person for the sake of efficiency.

> To be honest I don't actually really recognize that I'm using my hand now [...] On my jacket with a zip, I use this hand to hold it down while this pulls up, or vice-versa. But I will say 'hold on a sec, while I' [...] In the bathroom I brush my teeth with right hand for half the time, then I carry on with my left hand [...] When I use a knife I can cut through a lot of things but sometimes I'll go, like if I'm having a steak or something I will go I'll do one now can you cut the rest (to wife) [...] the glasses are quite big so I use this (unaffected) hand. I'm just scared I think.' (James).

Some participants limited use of their hand if they perceived damage may occur or if they had an alternative efficient resource available, such as typing (technology) instead of handwriting. Simon informs in relation to work:

> Given that nowadays we don't have to write too much anyways, [...] so I'll type notes on an iPad and I think with technologies today there is no reason why that should be a limiting factor for anyone [...] I think that being back at work was therapeutic, absolutely. (Simon).

As Simon indicates, this participant group connected strongly with their working identity; return to work was an important motivator for sensory arm use. Half of the participants specifically reported that sensory retraining assisted them to return to work:

> Particularly at work I've improved since the beginning of program [...] you know when I started I was just doing little basic pieces of work, right now I'm doing bigger jobs. I'm actually a [job title] (James).

> It gave me skills for everything I need in my job, my daily work [...] I felt so proud and so grateful [...] I don't know what I would be like without it and I don't want to think about that (Maria).

Sensory retraining positively influenced participant's performance and participation in daily life. In the final section, emotional healing through doing is explained by Veronica – carer of her young:

> The improvement is out of sight, and what that means in everyday life is also out of sight [...] The things I needed to do just weren't that exhausting [...] I was able to do many, many, many things that my children were saying "mummy, can you?" "Mummy, I've threaded the beads, now can you tie the knot for me?" [...] being able to look after myself, my kids, get on with life, make meals, hang out washing stuff, for me giving me back that meditative connection with handcrafts in emotional recovery was an amazing gift. So, the blockages for people that it can unblock are not obvious. (Veronica).

DISCUSSION

The purpose of the current study was to gain an understanding of how people who have experienced stroke and impaired sensation perceive their experience of upper limb somatosensory retraining, including: the motivators to participate in this therapy; the factors that facilitate or hinder their ability to learn and/or perform during retraining; and the perceived changes that occur as a result of this treatment. Five main themes emerged from participants' experience of upper limb somatosensory retraining: (1) loss of sensation in arm and desire to reclaim normality; (2) harnessing positivity in the therapeutic relationship and specialized therapy; (3) facing cognitive and emotional challenges; (4) distinct awareness of gains and differences in bodily sensations; and (5) improved functioning: control and choice in daily performance. These themes are discussed with reference to clinical literature and the philosophy of phenomenology (study of the essence of perception) (Merleau-Ponty, 1962).

Persons with stroke perceived and described intense differences in upper limb somatosensation after stroke. We, therefore, found our results contrasted the Connell et al. (2014) IPA study that discovered people had limited awareness and/or difficulties describing stroke-related sensory impairment. Participants in the current study were seeking and had engaged in treatment for sensory impairment and were a younger sample of participants (i.e., less than 65 years of age); hence this sample may reflect a different subset of people with stroke compared to those interviewed in the Connell et al. (2014) study who were aged 65–75 years, with one participant aged 45 years. Some participants reported increased awareness of their sensory impairment during training. Most participants described upper limb impairment as distressing; a common thread across other studies (Barker and Brauer, 2005; Connell et al., 2014; Doyle et al., 2014). The invisible nature of upper limb somatosensory loss appeared to add to the grief and distress for some participants in our study. Severity of upper limb sensory loss varied amongst participants; despite this, all felt distinct somatosensory loss that impacted on their connection to self, others, and the environment.

From a phenomenological perspective, some participants may have initially lacked a sense of ownership of their sensory-affected arm. A sense of ownership relates to "a sense that it is I who am experiencing the movement or thought" (Gallagher, 2005, 173); this fundamental component of self can be affected when afferent connection in the body is impaired (Gallagher, 2012a,b). In addition, participant's sense of agency was disrupted after stroke-related sensory loss. Sense of agency refers to the "sense of being the initiator or source of a movement, action, or thought" (Gallagher, 2005, 173); this process occurs pre-reflectively (i.e., akin to automatically), or reflectively as attributions of agency when we consciously think about what we are doing (Gallagher and Zahavi, 2007; Gallagher, 2012a). Participants felt and thought their arm was ineffective, untrustworthy, and even a liability. Participant's embodied self may have felt threatened, hence remediation therapy (i.e., sensory retraining) was viewed as a desirable and worthy treatment pursuit.

The therapeutic relationship developed during sensory retraining enabled participants to progress positively through sensory retraining; engagement aided success. Findings confirm the value of the therapeutic relationship and client-centered practice as a process of partnership (Law et al., 1995; Polatajko et al., 2015). Our view of engagement fits with recent conceptualisations of this process being co-constructed in the client-therapist relationship (Bright et al., 2015, 2017). Within the therapeutic relationship, either person can influence the other depending on their perception of engagement, skills, attitudes, and behaviors (Bright et al., 2017). While this study did not focus on therapists' perceptions, findings revealed participants perceived the therapist as having knowledge and skills in sensory retraining, alongside support and care for them as a person. Mutual respect and encouragement aid satisfaction in stroke rehabilitation (Mangset et al., 2008; Peoples et al., 2011); in addition, the therapeutic dyad in sensory retraining requires shared control, knowledge, and responsibility (Yekutiel, 2000). In the current study, participants seemed to value a safe and supportive therapeutic space to begin using an arm that feels different and unpleasant. Development of a strong, trusting therapeutic relationship appears to assist persons with stroke to engage in sensory retraining and use their arm. In addition, valued features of the therapeutic relationship in this specialized therapy may have assisted participants to cope with challenges encountered during the somatosensory retraining process. The experience of processing and filtering relevant somatosensory information along with positive affirmation may have assisted participants in this therapeutic process after stroke.

Upper limb somatosensory retraining involves cognitive and emotional challenges. Participants viewed cognitive effort (i.e., sustained concentration) and resultant fatigue as part of the neuroplasticity process to retrain sensation. Similarly, Signal et al. (2016) found that persons with stroke considered fatigue as a natural part of high intensity exercise. While most of us are familiar with exercise, specific education on learning-based neuroplasticity seems to be required after stroke, and this information on brain recovery was perceived as important to participants during retraining. Participants also experienced retraining in relation to their life narrative and coping styles. At times, participants responded to the demands of retraining with thoughts related to self-expectations and loss after stroke. Such thoughts led to negative emotions of anxiety, frustration, or sadness that presented intermittently during treatment sessions. In stroke care, clinicians must attend to a persons' physical, psychosocial, and relational health (Kitson et al., 2013); hence in retraining, persons with stroke appear to require time and support in the therapeutic relationship to regulate emotions. Therapists are witness to people's effort and gains made during retraining, and active listening skills from therapists may be essential in this learning-based process. Overall the therapeutic milieu may interact to mediate the effect of emotional or cognitive challenges, and this can enable persons with stroke to progress positively through and meet the challenges of an intensive somatosensory discrimination retraining program.

Results indicated that somatosensory and functional changes occurred with upper limb sensory retraining. Participants described clear improvements in their ability to interpret bodily sensations, and all had a sense of ownership of their arm. In clinical trials, sensory improvements were found using quantitative measurement before and after somatosensory retraining (Yekutiel and Guttman, 1993; Byl et al., 2003, 2008; Carey et al., 2011a). Retraining was not fully curative of sensory deficits, yet facilitated sensory improvements to the degree that people felt more connection with and use in their arm. Participants interviewed reported using their arm more in daily activities, which is essential for ongoing brain and arm recovery (Barker et al., 2007). Participants felt positive changes in their performance and participation of daily activities, such as returning to work. Return to work indicates success in rehabilitation (Alaszewski et al., 2007; Treger et al., 2007), and generally, persons with stroke view good upper limb recovery as return of sensation and movement, functional arm use, and potential for ongoing improvements (Barker and Brauer, 2005). From this perspective, we consider that participants experienced a good recovery with upper limb sensory retraining. Participants felt positive emotions (i.e., happiness, gratitude, and pride) about sensory and functional changes, which also confirms that retraining aided their pursuit of recovery after stroke. All participants recommended retraining to other people with stroke and potential somatosensory loss.

Findings suggest participant's sense of agency also changed as a result of sensory retraining. Our pre-reflective sense of agency involves a fundamental feeling of embodiment and perceptual awareness that our actions have influence in the world (Gallagher, 2005, 2012a,b). With the return of sensation, participants naturally felt more in their upper limb and spontaneously used their arm more to perform actions. Reflective attributions of agency (Gallagher and Zahavi, 2007; Gallagher, 2012a) was also enhanced as participants controlled and choose how they would use their arm to perform daily activities. Participants' used various strategies to achieve task practice and performance, such as: self-talk, allowing extra time, or sharing task load with the other hand and/or another person. Self-talk encouraged arm use and/or prompted slower task performance and practice. Other researchers also reveal the significance of self-talk for ongoing upper limb rehabilitation (Sabini et al., 2013). Participants' arm use strategies were context specific; our actions are continually grounded in time and situation (Gallagher, 2012b). In sum, participants attempted to do more with increased success after upper limb somatosensory retraining and this appears to have contributed to a renewed sense of agency.

Results relate to persons with stroke who participated in a clinical trial of sensory retraining. It is possible this study involved highly motivated people who related well to health professionals and were cooperative (Maclean et al., 2000). Most participants had some degree of motor ability post-stroke, and most experienced upper limb somatosensory impairment in their right dominant hand (n = 6/8), which may have influenced the importance they placed on sensory loss as a problem, and thus retraining as a potential solution. All were between 31 and 61 years of age (M = 45), thus results may be more applicable to the growing cohort of younger persons with stroke (Wolf et al., 2009). Despite aiming to include older participants (aged 65 years or older) via a stratified sampling method (Patton, 2002), the majority of participants (80%) from the CoNNECT trial were aged 60 years and under at the time this study was conducted. In regard to the data analysis procedure, trustworthiness was promoted with a second researcher (JW) analyzing 4 of 8 interview transcripts. It is recognized, however, that this process did not occur for all interviews completed in this study and is thus a limitation.

The experience of sensory retraining involved an active remedial (learning based) approach to somatosensory discrimination training. The retraining approach, known as SENSe, has been well characterized (Carey et al., 2011a; Carey, 2012a,b) and was delivered in the context of a randomized controlled trial (Carey et al., 2011a). Future research into the client experience of sensory retraining should occur within a typical clinical environment, including investigation of therapists' perception of the process of therapeutic engagement that persons with stroke value during sensory retraining. Two therapists conducted sensory retraining with participants and there may be particular characteristics of these therapists that influenced findings.

CONCLUSION

In conclusion, somatosensory loss exists as a bodily impairment after stroke, which is visibly concealed, often distressing, and intensely personal. People desire restoration of their embodied self and therefore aspire to complete upper limb sensory retraining. Retraining demands cognitive and emotional energy and to maintain a positive outlook, people value a therapeutic relationship that involves a shared vision of effort and change. People change with somatosensory retraining; they know joy and pride in their sensory and functional gains. Sensation still feels less than perfect after retraining, yet people can connect with and use their arm in ways that provide control, confidence, and choice in daily performance and participation.

In regard to the implications for rehabilitation, people experience meaningful somatosensory and functional gains with a perceptual learning, neuroscience based approach to upper limb sensory discrimination retraining after stroke. People may report a desire to improve their sensation and reclaim normality following stroke, and thus should be offered the opportunity in rehabilitation to remediate somatosensory deficits (i.e., somatosensory discrimination retraining). People manage the demands of somatosensory retraining within a therapeutic relationship that contains trust and support. Therapists need to listen to and validate the person's experience of somatosensory impairment. From this beginning, the therapist and person with stroke can partner in somatosensory retraining to create change and reflect on gains.

AUTHOR'S NOTE

LC is the original developer of the sensory retraining program investigated in this study. For this reason, MT and JW were involved in data collection and analysis.

DATA AVAILABILITY

All datasets generated for this study are included in the manuscript and/or the **Supplementary Files**.

ETHICS STATEMENT

All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by and conducted in accordance with recommendations of the Austin Health and La Trobe University Human Ethics Committees.

AUTHOR CONTRIBUTIONS

MT was involved in the study design, ethics application, recruitment, data collection, data analysis, and manuscript drafting and editing. JW completed the data collection, partial data analysis, and manuscript review. JB reviewed manuscript drafts. LC was involved in the study design, data interpretation at the level of a manuscript review, and manuscript revision.

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REFERENCES

Alaszewski, A., Alaszewski, H., Potter, J., and Penhale, B. (2007). Working after a stroke: survivors' experiences and perceptions of barriers to and facilitators of the return to paid employment. *Disabil. Rehabil.* 29, 1858–1869. doi: 10.1080/09638280601143356

Barker, R., and Brauer, S. (2005). Upper limb recovery after stroke: the stroke survivors' perspective. *Disabil. Rehabil.* 27, 1213–1223. doi: 10.1080/09638280500075717

Barker, R. N., Gill, T. J., and Brauer, S. G. (2007). Factors contributing to upper limb recovery after stroke: a survey of stroke survivors in Queensland Australia. *Disabil. Rehabil.* 29, 981–989. doi: 10.1080/09638280500243570

Blennerhassett, J. M., Matyas, T. A., and Carey, L. M. (2007). Impaired discrimination of surface friction contributes to pinch grip deficit after stroke. *Neurorehabil. Neural Repair* 21, 263–272. doi: 10.1177/1545968306295560

Bright, F. A., Kayes, N. M., Cummins, C., Worrall, L. M., and McPherson, K. M. (2017). Co-constructing engagement in stroke rehabilitation: a qualitative study exploring how practitioner engagement can influence patient engagement. *Clin. Rehabil.* 31, 1396–1405. doi: 10.1177/0269215517694678

Bright, F. A., Kayes, N. M., Worrall, L., and McPherson, K. M. (2015). A conceptual review of engagement in healthcare and rehabilitation. *Disabil. Rehabil.* 37, 643–654. doi: 10.3109/09638288.2014.933899

Byl, N., Pitsch, E. A., and Abrams, G. M. (2008). Functional outcomes can vary by dose: learning-based sensorimotor training for patients stable poststroke. *Neurorehabil. Neural Repair* 22, 494–504. doi: 10.1177/1545968308317431

Byl, N., Roderick, J., Mohamed, O., Hanny, M., Kotler, J., Smith, A., et al. (2003). Effectiveness of sensory and motor rehabilitation of the upper limb following the principles of neuroplasticity: patients stable poststroke. *Neurorehabil. Neural Repair* 17, 176–191. doi: 10.1177/0888439003257137

Carey, L. M. (1993). *Tactile and Proprioceptive Discrimination Loss After Stroke: Training Effects and Quantitative Measurement*. Ph.D. dissertation, La Trobe University: Melbourne, VIC.

Carey, L. M. (2012a). *SENSe: Helping Stroke Survivors Regain a Sense of Touch: a Manual and DVD For Therapists*. Melbourne, VIC: Florey Neuroscience Institutes.

Carey, L. M. (2012b). "Touch and body sensations," in *Stroke Rehabilitation: Insights from Neuroscience and Imaging*, ed. L. M. Carey (New York, NY: Oxford University Press), 157–172. doi: 10.1093/med/9780199797882.003.0012

Carey, L. M., Macdonell, R., and Matyas, T. A. (2011a). SENSe: study of the effectiveness of neurorehabilitation on sensation: a randomized controlled trial. *Neurorehabil. Neural Repair* 25, 304–313. doi: 10.1177/1545968310397705

Carey, L. M., Seitz, R., Levi, C., and Tournier, J. (2011b). *Effective Sensory Rehabilitation After Stroke: Targeting Viable Brain Networks*. Available from: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=364147&isReview=true (accessed March 30, 2019).

Carey, L. M., and Matyas, T. A. (2005). Training of somatosensory discrimination after stroke: facilitation of stimulus generalization. *Am. J. Phys. Med. Rehabil.* 84, 428–442. doi: 10.1097/01.PHM.0000159971.12096.7F

Carey, L. M., and Matyas, T. A. (2011). Frequency of discriminative sensory loss in the hand after stroke in a rehabilitation setting. *J. Rehabil. Med.* 43, 257–263. doi: 10.2340/16501977-0662

Carey, L. M., Matyas, T. A., and Oke, L. E. (1993). Sensory loss in stroke patients: effective training of tactile and proprioceptive discrimination. *Arch. Phys. Med. Rehabil.* 74, 602–611. doi: 10.1016/0003-9993(93)90158-7

Carey, L. M., Nankervis, J., LeBlanc, S., and Harvey, L. (2006). "The new functional Tactual Object Recognition Test (fTORT) for stroke clients: normative standards and discriminative validity," in *Paper Presented at the 14th International Congress of the World Federation of Occupational Therapists*, (Sydney).

Carey, L. M., Oke, L. E., and Matyas, T. A. (1996). Impaired limb position sense after stroke: a quantitative test for clinical use. *Arch. Phys. Med. Rehabil.* 77, 1271–1278. doi: 10.1016/S0003-9993(96)90192-6

Carey, L. M., Oke, L. E., and Matyas, T. A. (1997). Impaired touch discrimination after stroke: a quantiative test. *Neurorehabil. Neural Repair* 11, 219–232. doi: 10.1177/154596839701100404

Connell, L. A., McMahon, N. E., and Adams, N. (2014). Stroke survivors' experiences of somatosensory impairment after stroke: an interpretative phenomenological analysis. *Physiother* 100, 150–155. doi: 10.1177/0269215508090674

Doyle, S., Bennett, S., and Dudgeon, B. (2014). Upper limb post-stroke sensory impairments: the survivor's experience. *Disabil. Rehabil.* 36, 993–1000. doi: 10.3109/09638288.2013.825649

Fugl-Meyer, A. R., Jääskö, L., Leyman, I., Olsson, S., and Steglind, S. (1974). The post-stroke hemiplegic patient, 1: a method for evaluation of physical performance. *Scand J. Rehabil. Med.* 7, 13–31.

Gallagher, S. (2005). *How The body Shapes the Mind*. Oxford: Oxford University Press.

Gallagher, S. (2012a). Multiple aspects in the sense of agency. *New Ideas Psychol.* 30, 15–31. doi: 10.1016/j.newideapsych.2010.03.003

Gallagher, S. (2012b). *Phenomenology*. London: Palgrave Macmillan.

Gallagher, S., and Zahavi, D. (2007). *The Phenomenological Mind: an Introduction to Philosophy of Mind and Cognitive Science*. Hoboken: Taylor and Francis.

Hartman-Maeir, A., Soroker, N., Ring, H., Avni, N., and Katz, N. (2007). Activities, participation and satisfaction one-year post stroke. *Disabil. Rehabil.* 29, 559–566. doi: 10.1080/09638280600924996

Kessner, S. S., Bingel, U., and Thomalla, G. (2016). Somatosensory deficits after stroke: a scoping review. *Topics Stroke Rehabil.* 23, 136–146. doi: 10.1080/10749357.2015.1116822

Kitson, A. L., Dow, C., Calabrese, J. D., Locock, L., and Athlin, ÅM. (2013). Stroke survivors' experiences of the fundamentals of care: a qualitative analysis. *Int. J. Nurs. Stud.* 50, 392–403. doi: 10.1016/j.ijnurstu.2012.09.017

Krefting, L. (1991). Rigor in qualitative research: the assessment of trustworthiness. *Am. J. Occup. Ther.* 45, 214–222. doi: 10.5014/ajot.45.3.214

Law, M., Baptiste, S., and Mills, J. (1995). Client-centred practice: what does it mean and does it make a difference? *Can J. Occ. Ther.* 62, 250–257. doi: 10.1177/000841749506200504

Maclean, N., Pound, P., Wolfe, C., and Rudd, A. (2000). Qualitative analysis of stroke patients' motivation for rehabilitation. *BMJ.* 321, 1051–1054. doi: 10.1136/bmj.321.7268.1051

Mangset, M., Dahl, T. E., Førde, R., and Wyller, T. B. (2008). 'We're just sick people, nothing else': factors contributing to elderly stroke patients' satisfaction with rehabilitation. *Clin Rehabil.* 22, 825–835. doi: 10.1177/0269215508091872

Mendis, S. (2012). Stroke disability and rehabilitation of stroke: World Health Organization perspective. *Int. J. Stroke.* 8, 3–4. doi: 10.1111/j.1747-4949.2012.00969.x

Merleau-Ponty, M. (1962). *Phenomenology of Perception*. New York, NY: The Humanities Press.

Meyer, S., De Bruyn, N., Krumlinde-Sundholm, L., Peeters, A., Feys, H., Thijs, V., et al. (2016). Associations between sensorimotor impairments in the upper limb at 1 week and 6 months after stroke. *J. Neurol. Physical. Ther.* 40, 186–195. doi: 10.1097/NPT.0000000000000138

Meyer, S., Karttunen, A. H., Thijs, V., Feys, H., and Verheyden, G. (2014). How do somatosensory deficits in the arm and hand relate to upper limb impairment, activity, and participation problems after stroke? *Syst. Rev. Phys. Ther.* 94, 1220–1231. doi: 10.2522/ptj.20130271

Mukherjee, D., and Patil, C. G. (2011). Epidemiology and the global burden of stroke. *World Neurosurg.* 76, S85–S90. doi: 10.1016/j.wneu.2011.07.023

Patton, M. (2002). *Qualitative Research and Evaulation Methods. 3rd ed. Thousand Oaks*. California: Sage Publications.

Peoples, H., Satink, T., and Steultjens, E. (2011). Stroke survivors' experiences of rehabilitation: a systematic review of qualitative studies. *Scand. J. Occup. Ther.* 18, 163–171. doi: 10.3109/11038128.2010.509887

Polatajko, H. J., Davis, J. A., and McEwen, S. E. (2015). "Thereaputic use of self: a catalyst in the client-therapist alliance for change," in *Occupational Therapy: Performance, Participation, and Well-Being*, eds C. Christiansen, C. Baum, and J. Bass (Thorofare, N.J: Slack), 81–92.

Roulston, K. (2010). *Reflective Interviewing: a Guide to Theory and Practice. Thousand Oaks*. California: Sage Publications.

Sabini, R. C., Dijkers, M. P., and Raghavan, P. (2013). Stroke survivors talk while doing: development of a therapeutic framework for continued rehabilitation of hand function post stroke. *J. Hand Ther.* 26, 124–131. doi: 10.1016/j.jht.2012.08.002

Sacco, R. L., Kasner, S. E., Broderick, J. P., Caplan, L. R., Culebras, A., Elkind, M. S., et al. (2013). An updated definition of stroke for the 21st century a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 44, 2064–2089. doi: 10.1161/STR.0b013e318296aeca

Signal, N., McPherson, K., Lewis, G., Kayes, N., Saywell, N., Mudge, S., et al. (2016). What influences acceptability and engagement with a high intensity exercise programme for people with stroke? A qualitative descriptive study. *NeuroRehabilitation* 39, 507–517. doi: 10.3233/NRE-161382

Smith, J. A. (2011). Evaluating the contribution of interpretative phenomenological analysis. *Health Psych. Rev.* 5, 9–27. doi: 10.1080/17437199.2010.510659

Smith, J. A., Flowers, P., and Larkin, M. (2009). *Interpretative Phenomenological Analysis*. London: Sage.

Steinar, K. (1996). *Interviews: an Introduction to Qualitative Research Interviewing. Thousand Oaks*. California: Sage Publications.

Strong, K., Mathers, C., and Bonita, R. (2007). Preventing stroke: saving lives around the world. *Lancet Neurol.* 6, 182–187. doi: 10.1016/S1474-4422(07)70031-5

Sturm, J. W., Dewey, H. M., Donnan, G. A., Macdonell, R. A. L., McNeil, J. J., and Thrift, A. G. (2002). Handicap after stroke: how does it relate to disability, perception of recovery, and stroke subtype? The North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke.* 33, 762–768. doi: 10.1161/hs0302.103815

Treger, I., Shames, J., Giaquinto, S., and Ring, H. (2007). Return to work in stroke patients. *Disabil. Rehabil.* 29, 1397–1403. doi: 10.1080/09638280701314923

Turville, M. L., Cahill, L. S., Matyas, T. A., Blennerhassett, J. M., and Carey, L. M. (2019). The effectiveness of somatosensory retraining for improving sensory function in the arm following stroke: a systematic review. *Clin. Rehabil.* 33, 834–846. doi: 10.1177/0269215519829795

Tyson, S. F., Hanley, M., Chillala, J., Selley, A. B., and Tallis, R. C. (2008). Sensory loss in hospital-admitted people with stroke: characteristics, associated factors, and relationship with function. *Neurorehabil. Neural Repair* 22, 166–172. doi: 10.1177/1545968307305523

Wolf, T. J., Baum, C., and Connor, L. T. (2009). Changing face of stroke: implications for occupational therapy practice. *Am. J. Occup. Ther.* 63, 621–625. doi: 10.5014/ajot.63.5.621

Yekutiel, M. (2000). *Sensory Re-Education of the Hand After Stroke*. London: Whurr.

Yekutiel, M., and Guttman, E. (1993). A controlled trial of the retraining of the sensory function of the hand in stroke patients. *J. Neurol. Neurosurg. Psychiatry.* 56, 241–244. doi: 10.1136/jnnp.56.3.241

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ORIGINAL RESEARCH
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Skillful Cycling Training Induces Cortical Plasticity in the Lower Extremity Motor Cortex Area in Healthy Persons

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Cycling exercise is commonly used in rehabilitation to improve lower extremity (LE) motor function and gait performance after stroke. Motor learning is important for regaining motor skills, suggesting that training of motor skills influences cortical plasticity. However, the effects of motor skill learning in dynamic alternating movements of both legs on cortical plasticity remain unclear. Here, we examined the effects of skillful cycling training on cortical plasticity of the LE motor area in healthy adults. Eleven healthy volunteers participated in the following three sessions on different days: skillful cycling training, constant-speed cycling training, and rest condition. Skillful cycling training required the navigation of a marker up and down curves by controlling the rotation speed of the pedals. Participants were instructed to fit the marker to the target curves as accurately as possible. Amplitudes of motor evoked potentials (MEPs) and short-interval intracortical inhibition (SICI) evoked using transcranial magnetic stimulation (TMS) were assessed at baseline, after every 10 min of the task (a total of 30 min), and 30 min after the third and final trial. A decrease in tracking errors was representative of the formation of motor learning following skillful cycling training. Compared to baseline, SICI was significantly decreased after skillful cycling training in the tibialis anterior (TA) muscle. The task-induced alterations of SICI were more prominent and lasted longer with skillful cycling training than with the other conditions. The changes in SICI were negatively correlated with a change in tracking error ratio at 20 min the task. MEP amplitudes were not significantly altered with any condition. In conclusion, skillful cycling training induced long-lasting plastic changes of intracortical inhibition, which corresponded to the learning process in the LE motor cortex. These findings suggest that skillful cycling training would be an effective LE rehabilitation method after stroke.

Keywords: short-interval intracortical inhibition, lower extremity, motor learning, cortical plasticity, cycling, rehabilitation

INTRODUCTION

Motor impairments following stroke remain one of the leading causes of long-term disability in daily life (Miller et al., 2010; Lee and Cho, 2017). There is substantial evidence that rehabilitative training such as constraint-induced movement therapy promotes cortical plasticity (Mark et al., 2006), and that plastic changes in the motor cortex, as measured by transcranial magnetic stimulation (TMS) and functional neuroimaging, are related to functional recovery of the upper extremity in stroke patients (Choo et al., 2015; Beaulieu and Milot, 2018). Cortical plasticity following rehabilitative training plays an important role in recovery of motor function (Nudo, 1997).

Cycling exercise has been proposed as an effective approach to improve lower extremity (LE) motor function and gait performance in patients with stroke (Brown and Kautz, 1998; Fujiwara et al., 2003; Brown et al., 2005; Ferrante et al., 2011). Fujiwara et al. (2003) reported that phasic muscle activity is induced in the affected LE during cycling training. They also found that muscle activity in the quadriceps femoris and tibialis anterior (TA) was significantly increased after cycling training in chronic stroke patients. Furthermore, Ferrante et al. (2011) have reported that a 2 week regimen of cycling training improved gait speed and asymmetry in patients with chronic stroke. Neuroimaging studies have shown that motor related cortical areas are activated during cycling exercise (Christensen et al., 2000; Pyndt and Nielsen, 2003; Mehta et al., 2009; Promjunyakul et al., 2015). Neurophysiological studies have reported the changes of H-reflex, reciprocal inhibition and short-interval intracortical inhibition (SICI) after cycling exercise in healthy persons (Mazzocchio et al., 2006; Yamaguchi et al., 2012, 2013) and patients with stroke (Tanuma et al., 2017). These studies suggest that cycling exercise may induce neural plasticity which contributes to functional recovery in the LE. However, the relationship between neural mechanisms that enhance cortical plasticity of the LE and motor learning of bipedal performance is unclear.

Motor learning is important for regaining motor skills including gait, and motor skill training may influence cortical plasticity after brain injury (Nudo, 1997). Pharmacological and neurophysiological studies have suggested the involvement of inhibitory interneuronal circuits reflected by altered intracortical γ-aminobutyric acid (GABA)-ergic transmission (Matsumura et al., 1991, 1992; Bütefisch et al., 2000; Lech et al., 2001). In fact, pretreatment with a GABA receptor agonist resulted in a significant reduction in the effects of motor training (Tegenthoff et al., 1999; Bütefisch et al., 2000; Ziemann et al., 2001; Floyer-Lea et al., 2006), showing the functional relevance of GABA-based systems in motor training. GABAergic inhibitory systems can be examined with the use of paired-pulse TMS (Kujirai et al., 1993; Ziemann et al., 1996). Indeed, Perez et al. (2004) reported that skillful motor training with tracking tasks controlled by plantar dorsiflexion of unilateral ankle joints induced a reduction in SICI in motor learning assessed using the paired-pulse TMS method.

Motor learning of coordinated alternating movements of both legs, such as in cycling, is important to efficiently reacquire gait performance following stroke. A functional MRI study by Marchal-Crespo et al. (2017) revealed that gait-like motor learning depends on the interplay between subcortical, cerebellar, and fronto-parietal brain regions including the primary motor cortex during robotic bilateral training. However, no studies to date have investigated alterations in intracortical inhibition with the learning of dynamic bilateral alternating exercises. We hypothesized that progress in motor learning would induce on-going cortical plastic changes with the implementation of skillful training to an exercise that involved alternating movements of both legs (Mazzocchio et al., 2006). In this study, we examined the effects of a cycling motor task which incorporates skillful tracking via the adjustment of rotational speed on cortical plasticity using paired-pulse TMS.

MATERIALS AND METHODS

Participants

Eleven healthy volunteers participated in this study (eight males; mean age ± standard deviation, 25.4 ± 2.5). Sample size was determined based on previous studies investigating the effects of cycling exercise or ankle exercise on intracortical inhibition (Perez et al., 2004; Yamaguchi et al., 2012). Exclusion criteria were a history of neurological diseases, orthopedic problems in the LE, severe cardiac disorders or receiving any medications which affect the central nervous system. All participants provided written informed consent prior to participation in the study. The experimental procedures were approved by the Ethics Committee of the Tokyo Bay Rehabilitation Hospital and conformed to the requirements of the Declaration of Helsinki.

Experimental Paradigm

The present study employed a randomized crossover design. All participants performed the following sessions on different days: (1) skillful cycling training, (2) constant-speed cycling training, and (3) rest condition (see **Figure 1**). The task order was counterbalanced among participants. To prevent carry-over effects from previous interventions, washout intervals of 1 week or more were implemented between sessions in all participants.

Tasks

Participants were comfortably seated on a servo-dynamically controlled recumbent ergometer (StrengthErgo240, Mitsubishi Electric Co., Japan). Their feet were firmly strapped to the pedals and a seat belt and adjustable backrest with a tilt angle of 80° was used to stabilize their trunk. The ergometer used was able to achieve a highly precise load control (coefficient of variation, 5%) over a wide range of cycling resistances (0–240 Nm). The ergometer seat and crank heights were set at 51 and 17 cm, respectively. The distance from the seat edge to the crank axis and the height of the pedal axis were adjusted so that the knee extension angle was −10° during maximal extension. An isotonic mode was utilized with load sets at 5 Nm (Fujiwara et al., 2003). The load was determined according to previous studies at a setting which could be achieved even by stroke patients with leg motor paralysis (Fujiwara et al., 2003; Tanuma et al., 2017).

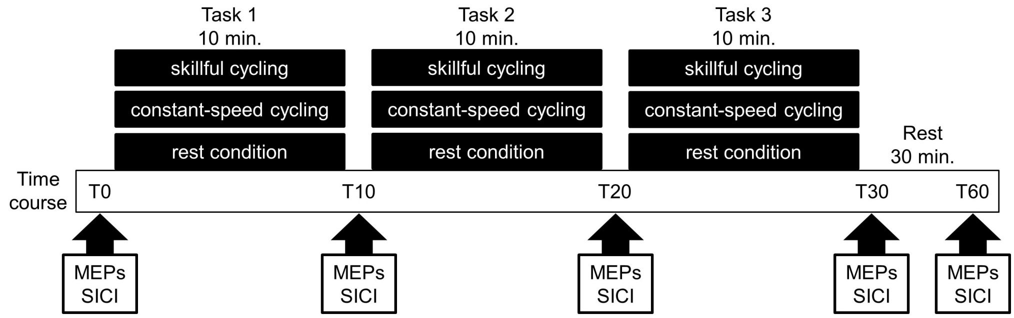

FIGURE 1 | Experimental protocol. Eleven volunteers participated in the following three sessions on different days: (1) skillful cycling training, (2) constant-speed cycling training, and (3) rest condition. During each condition, the motor evoked potentials (MEPs) and short-interval intracortical inhibition (SICI) were measured at baseline (T0), 10 min (T10), 20 min (T20), 30 min (T30), and 60 min (T60) after the start of the experiment.

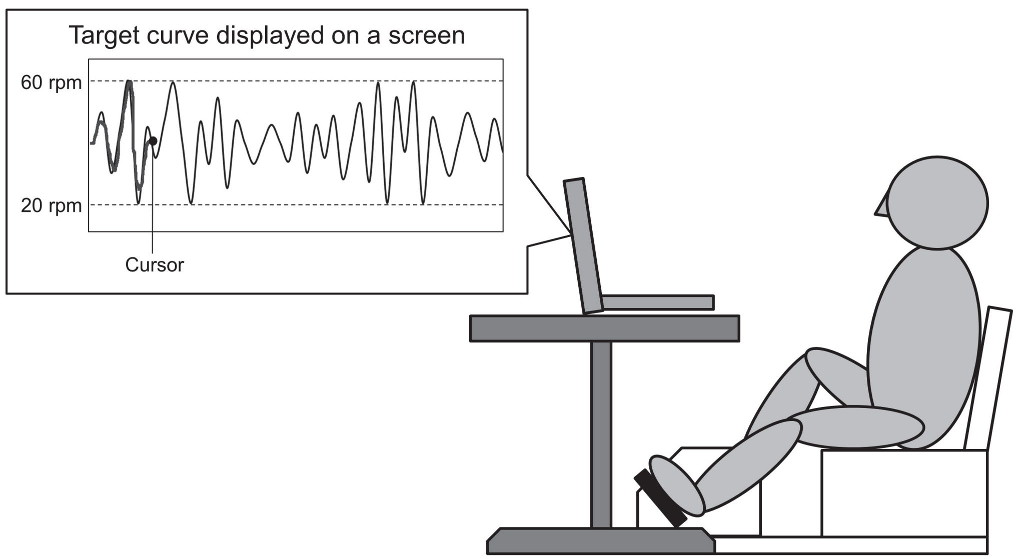

FIGURE 2 | Experimental setting. A schematic diagram of the task is shown. The participants controlled the movement of a cursor on the screen by changing the pedaling speed. Pedaling movements made the cursor move upward. The participants were required to adjust the speed at which the pedals revolved to match the cursor to the target curve displayed on a screen.

Skillful Cycling Training

Participants performed skillful cycling training, whereby they controlled the movement of a cursor on a computer screen by adjusting the pedaling speed in order to track a marker to target curves (see **Figure 2**). Pedaling movements caused the cursor to move upward. Participants were instructed to match the cursor (a dot) to the target curves on the screen as accurately as possible by changing the pedaling speed. Participants received real time feedback on the screen which represented the difference between the cursor and the target curves. The displayed waveform was set to a minimum value of 20 revolutions per minutes (rpm), maximum value of 60 rpm, and average pedaling speed of 40 rpm. During skillful cycling, participants were instructed to perform 10 min of cycling for each of three trials (termed Task 1, Task 2, and Task 3). Motor performance was evaluated based on the area of error between the target-tracking waveform and the position of the dot. The area of error was presented as arbitrary units. A custom-written computer program (LabVIEW software, ver. 7.1; National Instruments Corp., Austin, TX, United States) was used to design the tracking task and connect the ergometer to the computer.

Constant-Speed Cycling Training

The ergometer settings were identical to during skillful cycling training. To control the amount of exercise, a trial required a constant pedaling speed of 40 rpm for 10 min. Using a similar program to the one used during skillful cycling training, participants maintained the appropriate number of rotations while observing a tracking line set at 40 rpm.

Rest Condition

As a control, a 10-min rest condition was carried out whereby participants sat on the ergometer in the same manner as during other conditions, but did not engage in cycling.

Electromyogram (EMG) Recording

Prior to electrode attachment, the area of skin over the recording area of the target muscle was cleansed with alcohol. Throughout the experiments, skin resistance was kept below 5 kΩ. Surface electrodes were placed on the skin overlying the left TA in a bipolar montage (inter-electrode distance of 20 mm). A Neuropack^{TR} electromyography machine (Nihon Kohden Co., Tokyo, Japan) was used to record and analyze the EMG data. A band pass filter was applied between 30 Hz and 2 kHz. Signals were recorded at a sampling rate of 5 kHz and stored on the computer for subsequent analysis using LabVIEW software.

Transcranial Magnetic Stimulation

Participants seated on an ergometer with a backrest in a relaxed position with 80° hip flexion, 80° knee flexion, 10° ankle plantar flexion, and their feet on the floor. TMS was performed using a magnetic stimulator (Magstim200, Magstim, Dyfed, United Kingdom) capable of delivering a magnetic field of 2.2 T with 100 μs pulse duration through a double cone coil. Each cone had a diameter of 110 mm. The stimulating coil was located 0–2 cm posterior to the vertex and was placed over the site that was optimal for eliciting responses in the left TA and oriented so that the current in the brain flowed in a posterior to anterior direction through this site (Madhavan et al., 2010; Kesar et al., 2018; Škarabot et al., 2019). Since the direction of current flow can affect the motor evoked potential (MEP) responses (Terao et al., 1994, 2000) and the distance from the coil to the cortex affects the MEP amplitude (Stokes et al., 2005), we positioned the double-cone coil to closely conform with the scalp.

The rationale for choosing TA as the target muscle was mainly for the technical reasons that TMS over M1 can induce reliable MEPs from TA (Petersen et al., 2003; Groppa et al., 2012; Kesar et al., 2018). The threshold was determined the TA was at rest, and during voluntary contractions. The threshold was defined as the minimum stimulus intensity that evoked responses of approximately 100 μV with a similar shape and latency in 5 out of 10 successive stimuli. Each participant was requested to relax during measurement of the resting motor threshold (rMT) during which EMG silence was monitored. To determine the active motor threshold (aMT), participants held a muscle contraction at an intensity of 5–10% of their maximum with the help of visual feedback from the EMG.

The intensity of single-pulse TMS was set at 120% of the rMT to measure MEPs as an indicator of corticospinal excitability. A total of 10 MEPs were recorded in the rest condition. Peak-to-peak amplitudes were averaged for each time point. Ten measurements of the peak-to-peak MEP amplitude were averaged, and the mean value and standard error among subjects were calculated.

In the present study, we sought to evaluate cortical plasticity by measuring changes in SICI after the cycling training (Perez et al., 2004; Yamaguchi et al., 2012; Sidhu et al., 2013). In order to induce SICI, we applied sub-threshold conditioning paired-pulse stimulation (Kujirai et al., 1993). Two magnetic stimuli were supplied via the same stimulating coil to the right primary motor cortex. We used 80% of the aMT for the conditioning stimulus and 120% of the rMT for the test stimulus. Throughout the experiment, the intensity of test pulse was adjusted to induce MEPs of equivalent amplitude to prior to the intervention in the relaxed TA. The inter-stimulus interval in the current experiment was set at 2 ms, and 20 frames each were recorded of the paired-pulse and single stimulation conditions for each trial (Yamaguchi et al., 2012). Stimuli were applied every 5 s in pseudorandom order by a laboratory computer programed by LabVIEW software. Amplitude of SICI during the paired-pulse protocol was calculated as the average conditioned MEP amplitude expressed as a percentage of the average unconditioned MEP amplitude (Massé-Alarie et al., 2016). SICI values of 1 therefore represents no inhibition. Evaluation of corticospinal excitability and SICI was performed before cycling (Time 0, T0), immediately after each trial (T10, T20, T30), and 30 min after the third trial (T60).

Statistical Analyses

We compared the total number of pedal rotations during skillful and constant-speed cycling using two-factor repeated-measures analysis of variance (ANOVA) to analyze the effects of "trial" (Task 1, Task 2, Task 3) and "condition" (skillful cycling training, constant-speed cycling training). Additionally, to compare the degree of arousal between conditions, we compared heart rate data recorded after the skillful and constant-speed cycling using a paired t-test.

To confirm the occurrence of motor learning following skillful cycling training, a one-factor repeated-measures ANOVA was performed to analyze the change in area of error between the three trials.

To analyze MEP amplitude and SICI, two-factor repeated measures ANOVA was used to analyze the effects of cycling "time" (T0, T10, T20, T30, T60) and "condition" (skillful cycling training, constant-speed cycling training, rest condition) and any interaction. One-way ANOVA was performed to compare MEP amplitude and SICI between each condition using T0 as a baseline. When analyzing SICI, in order to confirm that the test MEP was not different between trials and conditions, we performed two-factor repeated measures ANOVA using the statistical model described above. A paired t-test with Bonferroni's correction for multiple comparisons was used for *post hoc* analysis if a given ANOVA showed a significant interaction. Retrospective power calculations were performed for paired t-tests, with an effect size represented by Cohen's d.

To investigate the relationship between plastic changes in SICI and motor learning, we calculated the tracking error ratio and SICI ratio and correlations between them were assessed using Pearson's correlation analysis, after checking for normal distribution of the data with the Shapiro–Wilk test. The tracking error ratio values were calculated by dividing values of Task 2 and Task 3 by the value of Task 1. The SICI ratio was calculated as the SICI values of T20 and T30 divided by the value of T10 in order to minimize the exercise-induced changes in SICI values at each time point. All statistical analyses were conducted using IBM SPSS statistics 21 for Windows (SPSS Inc., Chicago, IL, United States). Statistical significance was set at a value of $P < 0.05$ for all tests.

RESULTS

Total Number of Pedal Revolutions and Analysis of Physical Conditions

The average number of rotations of the pedals during the skillful and constant-speed cycling conditions was 444.9 ± 4.0 and 448.4 ± 4.4, respectively (mean ± standard error). Two-factor repeated measures ANOVA did not reveal a significant interaction ($F_{2,20}$ = 2.613, P = 0.098) nor any significant main effect (trial: $F_{2,20}$ = 0.421, P = 0.662; condition: $F_{1,10}$ = 0.351, P = 0.567). No participants complained of fatigue after cycling for each condition. There were no significant differences in heart rate after training between the skillful and constant-speed cycling conditions [mean heart rate ± standard deviation for skillful cycling = 75.0 ± 8.0; constant = 72.5 ± 6.2, $t(10)$ = 1.63, P = 0.135]. These results indicate that there was no difference in the amount of exercise or arousal between the two conditions or between trials.

Performance Test

Figure 3 shows the individual and mean data for the area of error as an indicator of motor learning across the three trials of skillful cycling training. One-factor repeated-measures ANOVA revealed a significant main effect ($F_{2,20}$ = 18.829, P < 0.001). *Post hoc* test revealed that the area of error for the value of Task 2 and Task 3 was significantly smaller than the value of Task 1 (vs. Task 2, P = 0.010; vs. Task 3, P = 0.003). Additionally, the area of error of Task 3 was smaller than that of Task 2 (P = 0.002). The variance of the individual performance was large at baseline, but gradually decreased with the skillful cycling training (**Figure 3**).

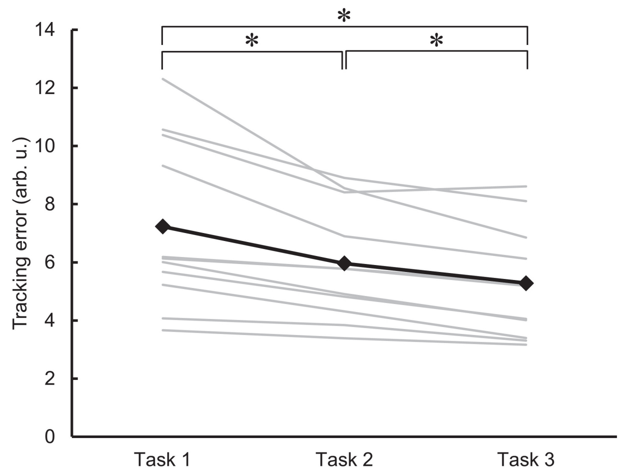

FIGURE 3 | Changes in motor performance. The errors in task performance during the skillful cycling session in Task 1, 2, and 3 are expressed as the area of error in arbitrary units (arb. u.). The gray lines represent individual participants. The black line and markers represent the mean data of all participants. One-factor repeated-measures ANOVA, N = 11, *P < 0.05.

MEP Amplitudes

There was no significant main effect in the baseline of MEP amplitudes between the three conditions ($F_{2,20}$ = 0.150, P = 0.862). Two-factor repeated measures ANOVA did not reveal a significant interaction ($F_{8,80}$ = 1.383, P = 0.217) or any significant main effect (time: $F_{4,40}$ = 1.723, P = 0.164; condition: $F_{2,20}$ = 0.042, P = 0.959) (see **Figure 4**). These results indicated that a consistent trend for corticospinal excitability was not confirmed for any conditions including skillful cycling training.

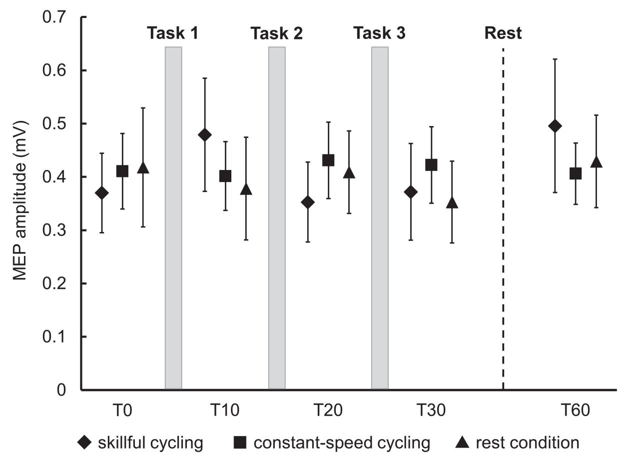

FIGURE 4 | Changes in MEP amplitudes. Each marker represents the mean MEP amplitudes in the tibialis anterior of all participants. Error bars represent standard error.

SICI

Figure 5 shows the temporal changes and the comparison of SICI in TA between each condition. There was no significant main effect in the baseline of SICI between the three conditions ($F_{2,20}$ = 1.083, P = 0.358). A significant interaction was observed between each the time and condition ($F_{8,80}$ = 8.793, P < 0.001). There were significant main effects of time ($F_{4,40}$ = 15.005, P < 0.001) and condition ($F_{2,20}$ = 8.318, P = 0.002). *Post hoc* testing of the temporal change results revealed that SICI was decreased at all time points relative to T0 in skillful cycling training (vs. T10: Cohen's d = 1.311, power = 0.832; vs. T20: Cohen's d = 1.282, power = 0.816; vs. T30: Cohen's d = 2.002, power = 0.994; vs. T60: Cohen's d = 1.489, power = 0.913). There was a significant difference between T10 and T30 (Cohen's d = 0.942, power = 0.557). In constant-speed cycling training, SICI was significantly decreased at T10 (Cohen's d = 0.609, power = 0.275) and T20 (Cohen's d = 0.807, power = 0.437) compared to T60. Comparisons between conditions revealed that SICI was significantly decreased in skillful cycling training compared to that in the rest condition at T10 or later (T10: Cohen's d = 1.410, power = 0.882; T20: Cohen's d = 1.328, power = 0.842; T30: Cohen's d = 2.257, power = 0.999; T60: Cohen's d = 1.955, power = 0.992). Furthermore, at T30 and T60, SICI for skillful cycling training was significantly decreased compared to that for constant-speed cycling training (T30: Cohen's d = 1.236, power = 0.788; T60: Cohen's d = 1.000, power = 0.607) (see **Figure 5**). These results suggest that cycling training induced sustained plastic changes in the primary motor cortex, and that these changes were more profound in the skillful cycling than the constant-speed cycling training.

Correlations Between Tracking Error and SICI

There was a significant negative correlation between the tracking error ratio and the SICI ratio measured after Task 2 ($r = -0.614$, $P = 0.044$). However, there was no correlation after Task 3 ($r = -0.134$, $P = 0.695$).

DISCUSSION

In the present study, we demonstrated for the first time that skillful cycling training enables motor skill learning for dynamic alternating movements of both legs, which induces long-lasting plastic changes of intracortical inhibition in the LE area of the motor cortex. These findings indicate that skillful cycling training would be more effective than conventional cycling as a neurorehabilitation method.

We adopted a tracking task to adjust the revolution speed of the pedals as a novel skill task for participants. Even when the number of pedal rotations was controlled, there was a significant difference in SICI changes between skillful and constant-speed cycling. Yamaguchi et al. (2012) reported that 7 min of constant-speed cycling reduced SICI in both TA and soleus (SOL) immediately after cycling. Another study reported that 32 min of motor skill training using a tracking task adjusting unilateral ankle joint dorsiflexion or plantar flexion movement induced a reduction in SICI; these effects persisted for 15 min after training (Perez et al., 2004). In our study, 30 min of intermittent skillful cycling induced a reduction in SICI for at least 30 min after training, but these changes were not observed after constant-speed cycling training. These results support the reproducibility of previous results, and suggest that skillful cycling training, which required learning of dynamic alternating movements of both legs, can more effectively induce cortical plastic changes than an equivalent amount of constant-speed cycling. Given the short-term plastic changes in SICI following constant-speed cycling training and lack of changes following passive cycling exercise (Yamaguchi et al., 2012), motor control and skill learning elements may be necessary to induce long-lasting plastic change in SICI in addition to sensorimotor integration. These findings suggest that skillful cycling training may be an effective rehabilitation method for gait disorders. This is supported by previous reports demonstrating that skillful training which require frequent changes in sensory input, led to greater effects than constant training or rest on acquisition of locomotor-related skills (Lam and Pearson, 2002; Mazzocchio et al., 2006).

Alternatively, as GABA is closely involved in control of arousal and sleep (e.g., Saper and Fuller, 2017), it can be argued that the decrease in SICI observed in the present study may reflect non-learning effects such as an increase in arousal after exercise. However, there were no significant differences in heart rate after the training between skillful and constant cycling conditions. This suggests no difference in arousal between the conditions. Therefore, a difference in arousal between the conditions cannot explain the reduction of SICI with the skillful cycling training.

We measured the SICI up to 30 min after the end of pedaling. However, the SICI change in the skillful condition did not return to the baseline at the last measurement of the experiment. Perez et al. (2004) have reported that the reduction of SICI

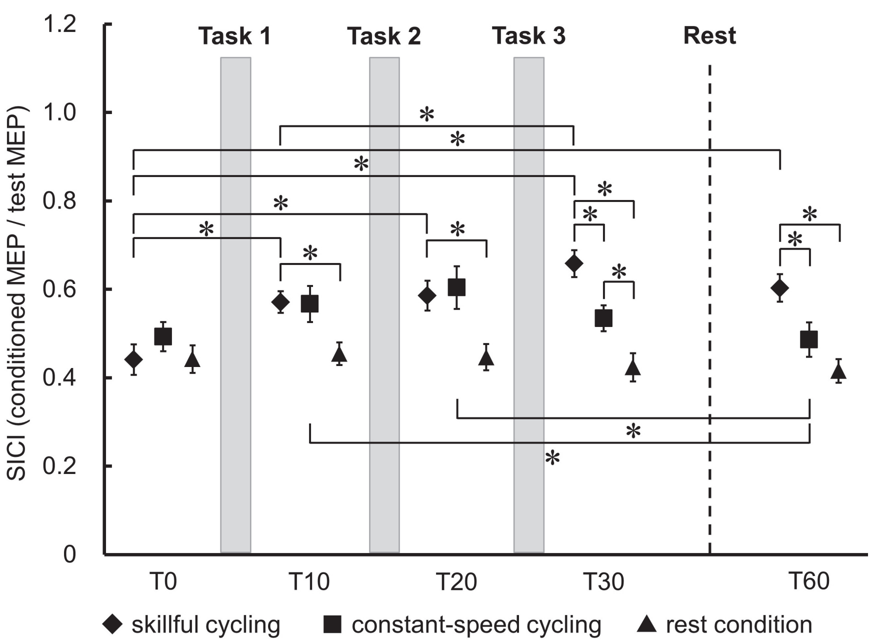

FIGURE 5 | Temporal changes in SICI between each condition. Each marker represents the mean short-interval intracortical inhibition (SICI) in the tibialis anterior. Error bars represent standard error. Two-factor repeated measures ANOVA, $N = 11$, $^*P < 0.05$.

was diminished 15–32 min after skillful leg movement training. Taken together, we speculate that the change in SICI could occur immediately after training but may disappear within a few hours after training.

Several studies have reported that modulation of SICI contributes to motor skill acquisition (Pascual-Leone et al., 1995; Liepert et al., 1998; Classen et al., 1999; Perez et al., 2004). Zimerman et al. (2012) reported that a significant correlation was observed between performance improvement during sequential skillful training and changes in SICI when transcranial direct current stimulation was applied to stroke patients. These phenomena were described as rewiring processes in M1 during acquisition of a novel motor skill, which are most likely based on unmasking of pre-existing connections within the cortex, allowing rapid changes in sensorimotor representations by reducing the activity of existing inhibitory connections (Mengia et al., 1998; Zimerman et al., 2012). The modulation of SICI may also reflect functional input from the cerebellum to M1 during learning (Daskalakis et al., 2004). These findings may support our observation of a significant correlation between the learning acquisition process and changes in SICI. However, the correlation was only present immediately after 20 min of skillful cycling exercise. Coxon et al. (2014) proposed that motor learning may be associated with disinhibition through reduction of SICI with paired-pulse TMS after repetitive pinch force training, particularly in the early acquisition stage (Coxon et al., 2014). The temporal relationship between the learning acquisition process and changes in SICI remains unclear. Thus, the present study provides novel findings on motor learning and cortical plasticity in the LE.

In the present study, no significant increases of MEP amplitude were observed with any cycling conditions. As well as the present study, several previous studies have reported no significant changes in MEP amplitude after LE motor training (Perez et al., 2004; Mazzocchio et al., 2006). Why was no significant increase in MEP amplitude observed? One possibility is that the increase in cortical excitability may be masked by a decrease of excitability at spinal levels when MEP is used as an outcome. Mazzocchio et al. (2006) reported that cycling training induced a decrease in H-reflex amplitude without any significant changes in MEP. Tanuma et al. (2017) reported that the Hmax/Mmax ratio (maximum group I reflex response/maximum direct muscle motor response) was significantly decreased after cycling training. These studies show that the decrease of the spinal excitability occurs after cycling training. Thus, as MEPs are considered to evaluate the total amount of cortical and spinal excitability, the decrease of the spinal excitability may mask the increase of the cortical excitability even if it exists.

While, we did not measure EMG activity during cycling in the present study, previous studies have examined EMG activity in the knee and ankle joints during cycling (Baum and Li, 2003; Fujiwara et al., 2003; da Silva et al., 2016; Roy et al., 2018; Ando et al., 2019). For example, Roy et al. (2018) measured EMG activities from the rectus femoris (RF), biceps femoris, TA, and gastrocnemius muscles during cycling and found that the EMG of the TA (1.5 V) during cycling was similar to that of the RF (1.7 V). What is the role of the TA during cycling? Momeni et al. (2014) have discussed the different roles of the RF and the TA during cycling. They state that the primary function of the RF during cycling is to generate energy in the extension phase, while the energy generated in the limb is transferred to the crank by the TA in the flexion phase (Momeni et al., 2014). Therefore, the change in the cortical plasticity after the skillful cycling training that we observed might be associated with the acquisition of the more sophisticated movement of the TA for these functions.

Cycling has been proposed as an effective approach to improve LE motor function and gait performance in patients with stroke (Brown and Kautz, 1998; Fujiwara et al., 2003; Brown et al., 2005; Ferrante et al., 2011; Promjunyakul et al., 2015; Tanuma et al., 2017). Here, we demonstrated that skillful cycling training could efficiently induce changes in intracortical inhibition in M1. Plastic changes in the cerebral cortex play an important role in regaining motor skills (Zimerman et al., 2012). Therefore, skillful cycling training alone may be useful for stroke patients. Alternatively, several studies reported that cycling training combined with functional electrical stimulation (FES) can improve walking and balancing abilities compared to cycling training without FES in stroke patients (Ambrosini et al., 2011; Bauer et al., 2015; Iyanaga et al., 2019). From these findings, further effects could be expected by applying a method for adjusting afferent sensory input via FES to skillful cycling training.

Several limitations of this study should be noted. First, the sample size of the current study was relatively small, although similar to prior studies targeting LE muscles (Perez et al., 2004; Yamaguchi et al., 2012). Hence, some marginal results, e.g., close to the cutoff for the correlation between the tracking error ratio and SICI ratio (P = 0.044), should be interpreted with caution. In the future, we will investigate based on power analysis with enhanced detection power. Second, present results showed no differences in the total number of pedal revolutions and that physical conditions were not different. However, we did not measure EMG activities to investigate the exercise load differences between skillful cycling and constant-speed cycling training, which could have affected the results. Further study is needed to clarify the effects of exercise load on cortical plasticity. Another limitation is that the present study included only healthy adults. The relationship between decreased SICI in spastic patients and improved performance requires further investigation. To verify the effectiveness of this method, studies on stroke patients are required.

CONCLUSION

Our study revealed that skillful cycling training which involves a learning task for both legs induced a significant reduction in SICI in the LE motor cortex area compared with conventional cycling. The effects lasted for at least 30 min after training. The current findings provide insight into our understanding of the relationship between cortical plasticity and motor learning in leg performance which could be applied to improve gait function in patients with stroke. In the future, the efficacy of skillful cycling training should be examined in stroke patients as a means to improve gait disorder.

DATA AVAILABILITY

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Human Subject Research: The studies involving human participants were reviewed and approved by the Ethics Committee of the Tokyo Bay Rehabilitation Hospital. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SaT and TY conceived and supervised the study. TT, SaT, and TY designed the experiments and wrote the manuscript. TT, KM, and KK carried out the experiments. ShT constructed the computer program. TT and KM analyzed the data. All authors approved the final version of the submitted manuscript.

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REFERENCES

Ambrosini, E., Ferrante, S., Pedrocchi, A., Ferrigno, G., and Molteni, F. (2011). Cycling induced by electrical stimulation improves motor recovery in postacute hemiparetic patients: a randomized controlled trial. *Stroke* 42, 1068–1073. doi: 10.1161/STROKEAHA.110.599068

Ando, R., Kondo, S., Katayama, K., Ishida, K., and Akima, H. (2019). Neuromuscular activation of the knee and hip extensor muscles during high-intensity interval and moderate-intensity constant cycling. *J. Electromyogr. Kinesiol.* 44, 64–69. doi: 10.1016/j.jelekin.2018.11.012

Bauer, P., Krewer, C., Golaszewski, S., Koenig, E., and Müller, F. (2015). Functional electrical stimulation-assisted active cycling–therapeutic effects in patients with hemiparesis from 7 days to 6 months after stroke: a randomized controlled pilot study. *Arch. Phys. Med. Rehabil.* 96, 188–196. doi: 10.1016/j.apmr.2014.09.033

Baum, B. S., and Li, L. (2003). Lower extremity muscle activities during cycling are influenced by load and frequency. *J. Electromyogr. Kinesiol.* 13, 181–190. doi: 10.1016/s1050-6411(02)00110-4

Beaulieu, L.-D., and Milot, M.-H. (2018). Changes in transcranial magnetic stimulation outcome measures in response to upper-limb physical training in stroke: a systematic review of randomized controlled trials. *Ann. Phys. Rehabil. Med.* 61, 224–234. doi: 10.1016/j.rehab.2017.04.003

Brown, D. A., and Kautz, S. A. (1998). Increased workload enhances force output during pedaling exercise in persons with poststroke hemiplegia. *Stroke* 29, 598–606. doi: 10.1161/01.STR.29.3.598

Brown, D. A., Nagpal, S., and Chi, S. (2005). Limb-loaded cycling program for locomotor intervention following stroke. *Phys. Ther.* 85, 159–168.

Bütefisch, C. M., Davis, B. C., Wise, S. P., Sawaki, L., Kopylev, L., Classen, J., et al. (2000). Mechanisms of use-dependent plasticity in the human motor cortex. *Proc. Natl. Acad. Sci. U.S.A.* 97, 3661–3665. doi: 10.1073/pnas.050350297

Choo, P. L., Gallagher, H. L., Morris, J., Pomeroy, V. M., and van Wijck, F. (2015). Correlations between arm motor behavior and brain function following bilateral arm training after stroke: a systematic review. *Brain Behav.* 5, 1–25. doi: 10.1002/brb3.411

Christensen, L. O., Johannsen, P., Sinkjaer, T., Petersen, N., Pyndt, H. S., and Nielsen, J. B. (2000). Cerebral activation during bicycle movements in man. *Exp. Brain Res.* 135, 66–72. doi: 10.1007/s002210000493

Classen, J., Liepert, J., Hallett, M., and Cohen, L. (1999). Plasticity of movement representation in the human motor cortex. *Electroencephalogr. Clin. Neurophysiol. Suppl.* 51, 162–173.

Coxon, J. P., Peat, N. M., and Byblow, W. D. (2014). Primary motor cortex disinhibition during motor skill learning. *J. Neurophysiol.* 112, 156–164. doi: 10.1152/jn.00893.2013

da Silva, J. C. L., Tarassova, O., Ekblom, M. M., Andersson, E., Rönquist, G., and Arndt, A. (2016). Quadriceps and hamstring muscle activity during cycling as measured with intramuscular electromyography. *Eur. J. Appl. Physiol.* 116, 1807–1817. doi: 10.1007/s00421-016-3428-3425

Daskalakis, Z. J., Paradiso, G. O., Christensen, B. K., Fitzgerald, P. B., Gunraj, C., and Chen, R. (2004). Exploring the connectivity between the cerebellum and motor cortex in humans. *J. Physiol.* 557, 689–700. doi: 10.1113/jphysiol.2003.059808

Ferrante, S., Ambrosini, E., Ravelli, P., Guanziroli, E., Molteni, F., Ferrigno, G., et al. (2011). A biofeedback cycling training to improve locomotion: a case series study based on gait pattern classification of 153 chronic stroke patients. *J. Neuroeng. Rehabil.* 8:47. doi: 10.1186/1743-0003-8-47

Floyer-Lea, A., Wylezinska, M., Kincses, T., and Matthews, P. M. (2006). Rapid modulation of GABA concentration in human sensorimotor cortex during motor learning. *J. Neurophysiol.* 95, 1639–1644. doi: 10.1152/jn.00346.2005

Fujiwara, T., Liu, M., and Chino, N. (2003). Effect of pedaling exercise on the hemiplegic lower limb. *Am. J. Phys. Med. Rehabil.* 82, 357–363. doi: 10.1097/01.PHM.0000064722.01940.E4

Groppa, S., Oliviero, A., Eisen, A., Quartarone, A., Cohen, L. G., Mall, V., et al. (2012). A practical guide to diagnostic transcranial magnetic stimulation: report of an IFCN committee. *Clin. Neurophysiol.* 123, 858–882. doi: 10.1016/j.clinph.2012.01.010

Iyanaga, T., Abe, H., Oka, T., Miura, T., Iwasaki, R., Takase, M., et al. (2019). Recumbent cycling with integrated volitional control electrical stimulation improves gait speed during the recovery stage in stroke patients. *J. Exerc. Rehabil.* 15, 95–102. doi: 10.12965/jer.1836500.250

Kesar, T. M., Stinear, J. W., and Wolf, S. L. (2018). The use of transcranial magnetic stimulation to evaluate cortical excitability of lower limb musculature: challenges and opportunities. *Restor. Neurol. Neurosci.* 36, 333–348. doi: 10.3233/RNN-170801

Kujirai, T., Caramia, M. D., Rothwell, J. C., Day, B. L., Thompson, P. D., Ferbert, A., et al. (1993). Corticocortical inhibition in human motor cortex. *J. Physiol.* 471, 501–519. doi: 10.1113/jphysiol.1993.sp019912

Lam, T., and Pearson, K. G. (2002). The role of proprioceptive feedback in the regulation and adaptation of locomotor activity. *Adv. Exp. Med. Biol.* 508, 343–355. doi: 10.1007/978-1-4615-0713-0_40

Lech, M., Skibinska, A., and Kossut, M. (2001). Delayed upregulation of GABA(A) alpha1 receptor subunit mRNA in somatosensory cortex of mice following learning-dependent plasticity of cortical representations. *Brain Res. Mol. Brain Res.* 96, 82–86. doi: 10.1016/s0169-328x(01)00271-6

Lee, K., and Cho, E. (2017). Activities of daily living and rehabilitation needs for older adults with a stroke: a comparison of home care and nursing home care. *Japan J. Nurs. Sci.* 14, 103–111. doi: 10.1111/jjns.12139

Liepert, J., Classen, J., Cohen, L. G., and Hallett, M. (1998). Task-dependent changes of intracortical inhibition. *Exp. Brain Res.* 118, 421–426. doi: 10.1007/s002210050296

Madhavan, S., Rogers, L. M., and Stinear, J. W. (2010). A paradox: after stroke, the non-lesioned lower limb motor cortex may be maladaptive. *Eur. J. Neurosci.* 32, 1032–1039. doi: 10.1111/j.1460-9568.2010.07364.x

Marchal-Crespo, L., Michels, L., Jaeger, L., López-Olóriz, J., and Riener, R. (2017). Effect of error augmentation on brain activation and motor learning of a complex locomotor task. *Front. Neurosci.* 11:526. doi: 10.3389/fnins.2017.00526

Mark, V. W., Taub, E., and Morris, D. M. (2006). Neuroplasticity and constraint-induced movement therapy. *Eura. Medicophys.* 42, 269–284. doi: 10.1002/14651858.CD005654

Massé-Alarie, H., Elgueta Cancino, E., Schneider, C., and Hodges, P. (2016). Paired-pulse TMS and fine-wire recordings reveal short-interval intracortical inhibition and facilitation of deep multifidus muscle fascicles. *PLoS One* 11:e0159391. doi: 10.1371/journal.pone.0159391

Matsumura, M., Sawaguchi, T., and Kubota, K. (1992). GABAergic inhibition of neuronal activity in the primate motor and premotor cortex during voluntary movement. *J. Neurophysiol.* 68, 692–702. doi: 10.1152/jn.1992.68.3.692

Matsumura, M., Sawaguchi, T., Oishi, T., Ueki, K., and Kubota, K. (1991). Behavioral deficits induced by local injection of bicuculline and muscimol into the primate motor and premotor cortex. *J. Neurophysiol.* 65, 1542–1553. doi: 10.1152/jn.1991.65.6.1542

Mazzocchio, R., Kitago, T., Liuzzi, G., Wolpaw, J. R., and Cohen, L. G. (2006). Plastic changes in the human H-reflex pathway at rest following skillful cycling training. *Clin. Neurophysiol.* 117, 1682–1691. doi: 10.1016/j.clinph.2006.04.019

Mehta, J. P., Verber, M. D., Wieser, J. A., Schmit, B. D., and Schindler-Ivens, S. M. (2009). A novel technique for examining human brain activity associated with pedaling using fMRI. *J. Neurosci. Methods* 179, 230–239. doi: 10.1016/j.jneumeth.2009.01.029

Mengia, S. R.-P., Daniel, F., Grzegorz, H., and John, P. D. (1998). Strengthening of horizontal cortical connections following skill learning. *Nat. Neurosci.* 1, 230–234. doi: 10.1038/678

Miller, E. L., Murray, L., Richards, L., Zorowitz, R. D., Bakas, T., Clark, P., et al. (2010). Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient: a scientific statement from the American Heart Association. *Stroke* 41, 2402–2448. doi: 10.1161/STR.0b013e3181e7512b

Momeni, K., Faghri, P. D., and Evans, M. (2014). Lower-extremity joint kinematics and muscle activations during semi-reclined cycling at different workloads in healthy individuals. *J. Neuroeng. Rehabil.* 11:146. doi: 10.1186/1743-0003-11-146

Nudo, R. J. (1997). Remodeling of cortical motor representations after stroke: implications for recovery from brain damage. *Mol. Psychiatry* 2, 188–191. doi: 10.1038/sj.mp.4000188

Pascual-Leone, A., Nguyet, D., Cohen, L. G., Brasil-Neto, J. P., Cammarota, A., and Hallett, M. (1995). Modulation of muscle responses evoked by transcranial magnetic stimulation during the acquisition of new fine motor skills. *J. Neurophysiol.* 74, 1037–1045. doi: 10.1152/jn.1995.74.3.1037

Perez, M. A., Lungholt, B. K. S., Nyborg, K., and Nielsen, J. B. (2004). Motor skill training induces changes in the excitability of the leg cortical area in healthy humans. *Exp. Brain Res.* 159, 197–205. doi: 10.1007/s00221-004-1947-1945

Petersen, N. T., Pyndt, H. S., and Nielsen, J. B. (2003). Investigating human motor control by transcranial magnetic stimulation. *Exp. Brain Res.* 152, 1–16. doi: 10.1007/s00221-003-1537-y

Promjunyakul, N., Schmit, B. D., and Schindler-Ivens, S. M. (2015). A novel fMRI paradigm suggests that pedaling-related brain activation is altered after stroke. *Front. Hum. Neurosci.* 9:324. doi: 10.3389/fnhum.2015.00324

Pyndt, H. S., and Nielsen, J. B. (2003). Modulation of transmission in the corticospinal and group Ia afferent pathways to soleus motoneurons during bicycling. *J. Neurophysiol.* 89, 304–314. doi: 10.1152/jn.00386.2002

Roy, S., Alves-Pinto, A., and Lampe, R. (2018). Characteristics of Lower leg muscle activity in patients with cerebral palsy during cycling on an ergometer. *Biomed Res. Int.* 2018:6460981. doi: 10.1155/2018/6460981

Saper, C. B., and Fuller, P. M. (2017). Wake-sleep circuitry: an overview. *Curr. Opin. Neurobiol.* 44, 186–192. doi: 10.1016/j.conb.2017.03.021

Sidhu, S. K., Cresswell, A. G., and Carroll, T. J. (2013). Short-interval intracortical inhibition in knee extensors during locomotor cycling. *Acta Physiol.* 207, 194–201. doi: 10.1111/apha.12004

Škarabot, J., Ansdell, P., Brownstein, C. G., Hicks, K. M., Howatson, G., Goodall, S., et al. (2019). Corticospinal excitability of tibialis anterior and soleus differs during passive ankle movement. *Exp. Brain Res.* 237, 2239–2254. doi: 10.1007/s00221-019-05590-5593

Stokes, M. G., Chambers, C. D., Gould, I. C., Henderson, T. R., Janko, N. E., Allen, N. B., et al. (2005). Simple metric for scaling motor threshold based on scalp-cortex distance: application to studies using transcranial magnetic stimulation. *J. Neurophysiol.* 94, 4520–4527. doi: 10.1152/jn.00067.2005

Tanuma, A., Fujiwara, T., Yamaguchi, T., Ro, T., Arano, H., Uehara, S., et al. (2017). After-effects of pedaling exercise on spinal excitability and spinal reciprocal inhibition in patients with chronic stroke. *Int. J. Neurosci.* 127, 73–79. doi: 10.3109/00207454.2016.1144055

Tegenthoff, M., Witscher, K., Schwenkreis, P., and Liepert, J. (1999). Pharmacological modulation of training-induced plastic changes in human motor cortex. *Electroencephalogr. Clin. Neurophysiol. Suppl.* 51, 188–196.

Terao, Y., Ugawa, Y., Hanajima, R., Machii, K., Furubayashi, T., Mochizuki, H., et al. (2000). Predominant activation of I1-waves from the leg motor area by transcranial magnetic stimulation. *Brain Res.* 859, 137–146. doi: 10.1016/s0006-8993(00)01975-1972

Terao, Y., Ugawa, Y., Sakai, K., Uesaka, Y., Kohara, N., and Kanazawa, I. (1994). Transcranial stimulation of the leg area of the motor cortex in humans. *Acta Neurol. Scand.* 89, 378–383. doi: 10.1111/j.1600-0404.1994.tb02650.x

Yamaguchi, T., Fujiwara, T., Liu, W., and Liu, M. (2012). Effects of pedaling exercise on the intracortical inhibition of cortical leg area. *Exp. Brain Res.* 218, 401–406. doi: 10.1007/s00221-012-3026-3027

Yamaguchi, T., Fujiwara, T., Saito, K., Tanabe, S., Muraoka, Y., Otaka, Y., et al. (2013). The effect of active pedaling combined with electrical stimulation on spinal reciprocal inhibition. *J. Electromyogr. Kinesiol.* 23, 190–194. doi: 10.1016/j.jelekin.2012.08.007

Ziemann, U., Muellbacher, W., Hallett, M., and Cohen, L. G. (2001). Modulation of practice-dependent plasticity in human motor cortex. *Brain* 124, 1171–1181. doi: 10.1093/brain/124.6.1171

Ziemann, U., Rothwell, J. C., and Ridding, M. C. (1996). Interaction between intracortical inhibition and facilitation in human motor cortex. *J. Physiol.* 496(Pt 3), 873–881. doi: 10.1113/jphysiol.1996.sp021734

Zimerman, M., Heise, K. F., Hoppe, J., Cohen, L. G., Gerloff, C., and Hummel, F. C. (2012). Modulation of training by single-session transcranial direct current stimulation to the intact motor cortex enhances motor skill acquisition of the paretic hand. *Stroke* 43, 2185–2191. doi: 10.1161/STROKEAHA.111.645382

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An MRI-Compatible Foot-Sole Stimulation System Enabling Characterization of the Brain Response to Walking-Related Tactile Stimuli

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Foot-sole somatosensory impairment is a main contributor to balance decline and falls in aging and disease. The cortical networks involved in walking-related foot sole somatosensation, however, remain poorly understood. We thus created and tested a novel MRI-compatible device to enable study of the cortical response to pressure stimuli applied to the foot sole that mimic those stimuli experienced when walking. The device consists of a dual-drive stimulator equipped with two pneumatic cylinders, which are separately programed to apply pressure waveforms to the entire foot sole. In a sample of nine healthy younger adults, the pressure curve applied to the foot sole closely correlated with that experienced during over ground walking ($r = 0.811 \pm 0.043$, $P < 0.01$). MRI compatibility testing indicated that the device has no or negligible impact on MR image quality. Gradient-recalled echo-planar images of nine healthy young adults using a block-designed 3.5-min walking-related stimulation revealed significant activation within the supplementary motor area, supramarginal gyrus, paracingulate gyri, insula, precentral gyrus, middle temporal gyrus, and hippocampus (uncorrected $P < 0.001$, $k \geq 10$). Together, these results indicate that this stimulation system is MRI-compatible and capable of mimicking walking-related pressure waveforms on foot sole. It may thus be used as a research tool to identify cortical targets for interventions (e.g., non-invasive brain stimulation) aimed at enhancing this important source of input to the locomotor control system.

Keywords: somatosensory, foot-sole stimulator, walking, fMRI, pneumatic, MRI-compatible

INTRODUCTION

The decline in foot-sole somatosensation is highly prevalent in older adults and is a primary contributor to diminished gait and increased risk of falling (Richardson and Hurvitz, 1995; Roll et al., 2002; Hijmans et al., 2007; Kars et al., 2009; Manor et al., 2010). There are widely distributed skin receptors on the plantar surface of the foot sole, such as Merkel nerve endings, sensitive to the force, and distribution of contact pressures (Kennedy and Inglis, 2002; Halata et al., 2003). When walking, the foot soles are the only part of the body in direct contact with the ground, the skin receptors in the foot sole perceive the ground reaction forces during the stance phase of the gait cycle, and provide afferent input to the central nervous system in the regulation of walking. This input is not only involved in sub-cortical reflex loops, but is also delivered to cortical networks of the brain where it is integrated with other sensory inputs and used to form volitional movements during walking (Deliagina et al., 2008). However, the characteristics of the brain cortical networks pertaining to the regulation of this walking-related foot-sole somatosensation are not well understood.

Functional magnetic resonance imaging (fMRI) enables non-invasively measuring the neural activity in response to a given stimulus by quantifying the intensity of blood oxygenation level-dependent (BOLD) signal (Kwong et al., 1992; Glover, 2011). It requires people to remain motionless, however, and thus is not applicable to measure the characteristics of the brain during walking. Recently, several types of MRI-compatible mechatronic devices have been developed to stimulate foot during the fMRI scan. Gallasch et al. (2006) proposed a stationary moving magnet actuator to contact and vibrate the sole of foot with 20–100 Hz oscillations and 20 N maximum contact force to study cerebral responses evoked from mechanoreceptors. Hao et al. (2013) created and validated a pneumatic tactile stimulator applying programmable single-point pressure stimuli to a small area on the plantar surface of the foot. Such devices have proven to effectively activate several cortical regions, as measured by the change of intensity of BOLD signal. However, these previous studies focused on low-force and high-frequency stimuli, and stimulated only small surface of the foot sole, which therefore cannot enable the recreation of the pressure-waveform change on foot soles as experienced when walking over the ground.

In this study, we created a novel MRI-compatible foot-sole stimulation system, which is capable of applying controlled dynamic pressure waveform-type stimuli to the foot soles that mimic those experienced when walking, when the person lies motionless in the scanner. We completed two separate tests to (1) determine the similarity between real foot sole pressures experienced when walking and those simulated by the stimulation system, and (2) establish the effects of using this stimulation system on the quality of MR images. We then (3) completed a pilot study to explore the activation of the cortical networks in healthy younger adults, by assessing by the fMRI BOLD signal, when applying this stimulation system to the foot soles.

MATERIALS AND METHODS

Foot-Sole Stimulation System Design

We designed a foot-sole pressure stimulation system (**Figure 1**) to enable the simulation of the pressure waveforms as experienced by the foot sole during the stance phase of the gait cycle. The stance phase typically progresses from the heel (i.e., heel strike), to the ball of the foot (i.e., foot flat) and then the toe (i.e., toe-off) (Tiberio, 1987).

This system included an air-compressor (GL0205, Greeloy, Shanghai, China) as the source of pressure, an execution unit, and a control unit (**Figure 2**). The execution unit (**Figure 2**, upper panel) consisted of two air cylinders (CG1BN32-40-XC6, SMC, Tokyo, Japan), a rigid plastic movable plate and a support platform. The two air cylinders were installed on the fixed support plate and respectively attached to a translatable and rotatable joint inside the movable plate so that they can actuate the plate asynchronously. The plastic movable plate pressed against the foot sole directly. To secure the plastic movable plate during the stimulating action, a rigid aluminum rod between the two cylinders was attached to a rotatable joint inside the movable plate through the fixed support plate. The entire execution unit was attached to a non-ferromagnetic (i.e., plastic and nylon materials) support platform, which is secured to the scanner table to limit the translation of applied pressures to the body and head. The control unit (**Figure 2**, lower panel) comprised two five-port solenoid valves (SY5120-5LZD-C6, SMC Corporation, Tokyo, Japan), a proportional valve (ITV2030-312L, SMC Corporation, Spain), a microcontroller (MSP430F168, Texas Instruments, Dallas, TX, United States), and a custom-developed user interface. A proportional valve was linked to the air compressor and the pressure of output airflow is controlled by the direct voltage (V_{DC}) produced by digital to analog converter (DAC) of the microcontroller. The relationship between V_{DC} input to the proportional valve and the pressure of output airflow was linear, enabling precise control of the magnitude of applied pressure. The proportional valve transfers output airflow to the two five-port solenoid valves through a tee coupling, and these two valves control two air cylinders separately to produce one-degree-of-freedom (DOF) oscillations by shaping the airflow following the control signal wave sequences. The signal wave sequences were pre-programed and produced by the GPIOs (General-Purpose Input/Output) of the microcontroller. The custom-developed user interface is based on Matlab (The MathWorks, Inc., Natick, MA, United States) and able to communicate with the microcontroller through UART (i.e., universal asynchronous receiver-transmitter). The V_{DC} and frequency of control signal wave sequences produced

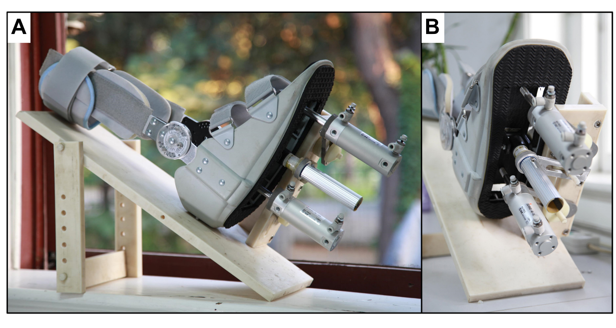

FIGURE 1 | (A) The dual-drive foot-sole stimulator. **(B)** The executive unit of the stimulator.

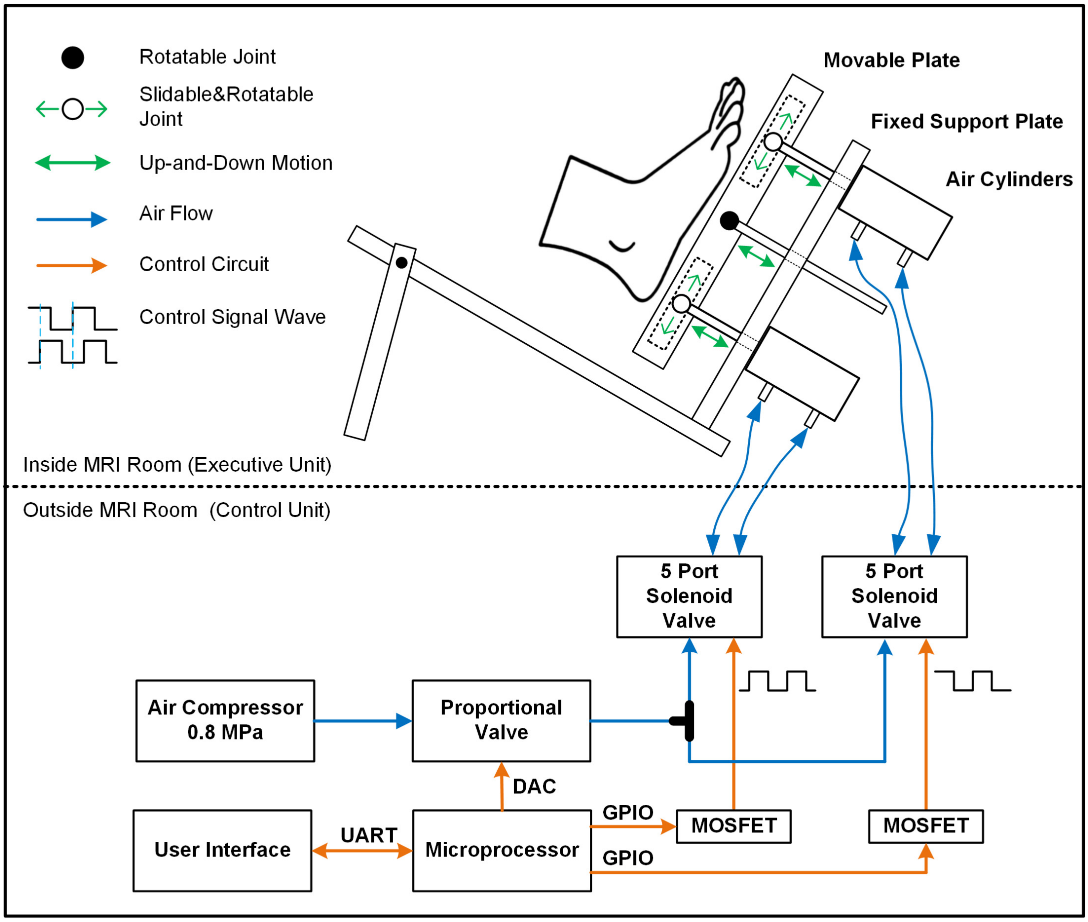

FIGURE 2 | The diagram of the entire foot-sole pressure stimulation system. The control unit regulated the pressure by controlling the proportional valve and five-port solenoid valves following the pre-designed control signal waves (orange line). Airflow (blue line) generated from air compressor went through the designed routine to provide force to air cylinders. The pressure is applied to the foot sole by a rigid plastic movable plate board, which was actuated by two non-ferromagnetic aluminum air cylinders on the support platform. The middle item between two air cylinders was a support device to secure the stableness of the movable plate during the simulation.

by microcontroller can be configured in real-time easily by user. By doing so, the microcontroller can regulate the magnitude, frequency, and sequence of pressure applied to the foot sole following the configuration.

According to the configuration, the cylinder can then reverse its movement direction within 100 ms, enabling a maximal oscillatory frequency of 10 Hz. The output force of this stimulator ranged from 5 to 500 N approximately, and the speed of the movable plate's movement is between 40 and 1000 mm/s. When using this stimulator within the MRI setting, the air compressor and control unit were located outside the scanner room and concatenated with the two air cylinders inside the scanner room via four 5 m-long and 6 mm-diameter high-pressure polyurethane tubes.

As shown in **Figure 1**, we also modified and installed a medical ankle joint support brace on the support platform, which is used to secure the shin and make the foot sole face the movable plate passively. The angle of knee and hip joint is adjustable based upon the comfort of each participant. We chose to fix the ankle joint at 90° of dorsiflexion to minimize head movements during stimulation following the previous study (Hao et al., 2013).

Study Protocol

Experiment 1: Simulation of Walking-Related Foot-Sole Stimuli Using the Foot-Sole Stimulator

We first examined the capacity of our stimulation system to apply pressures to the foot sole that mimic those experienced when walking, by comparing the pressures generated by the stimulation system to actual pressures experienced during walking.

Participants

Nine healthy young participants aged 20–29 years with right-foot dominance were recruited and provided written informed consent as approved by the local ethical committee. Exclusion criteria included any acute illness, self-reported history of cardiovascular, metabolic, or neurological disease, musculoskeletal disorders, major foot deformity or history of surgery or major injury to the lower extremities.

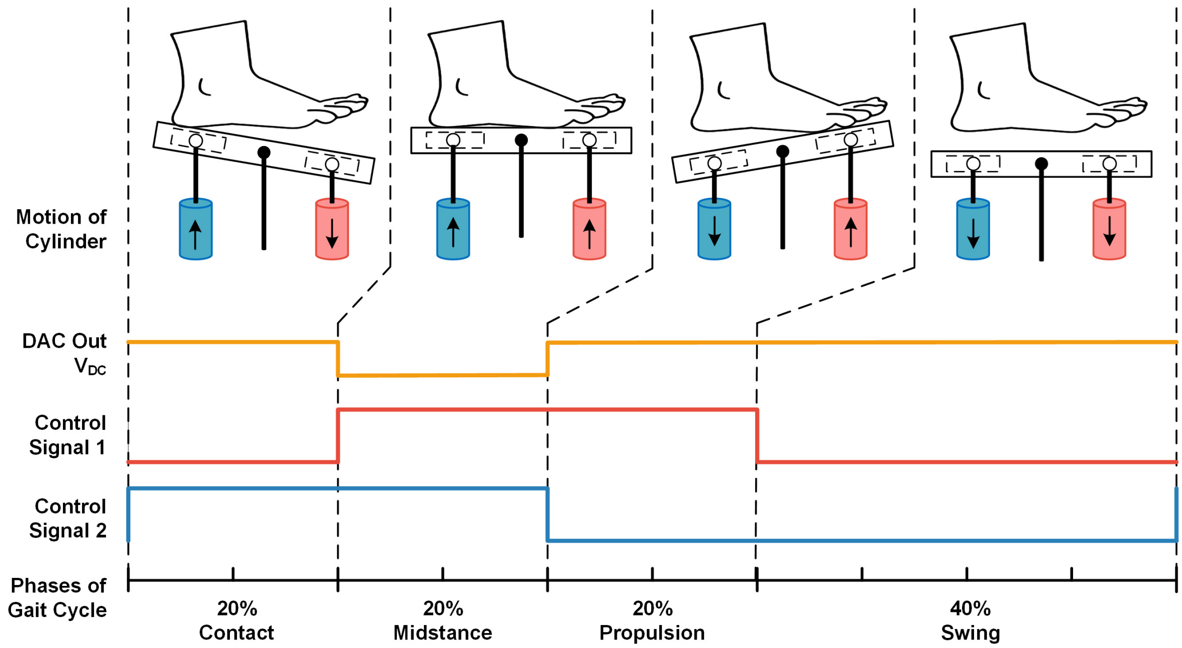

FIGURE 3 | The example of pre-designed signals from two cylinders to mimic pressures in one complete gait cycle. The V_{DC} signal produced by DAC (orange line) regulates the output pressure force of the cylinder. The control signal 1 (red line) controls the up-and-down motion of the red cylinder, and the control signal two (blue line) controls the blue cylinder's motion (i.e., Logical high corresponds to up-motion, logical low corresponds to down-motion). There were four states in one period of the control signal waves (i.e., LH, HH, HL, and LL), corresponding to the four phases of one stimulating gait cycle: contact, midstance, propulsion, and swing.

Test procedure

Each participant completed four trials within each of the following tests: walking test and stimulating test. We used an instrumented foot pressure insole (F-scan 3000E, Tekscan, United States) to measure the pressure on the foot soles in the two tests.

In the walking test, the insole was inserted into the participant shoes to record pressure waveforms during four trials of straight walking at preferred speed. Participants performed at least four complete gait cycles within each trial.

In stimulating test, we programed the force of pressure in midstance phase to equal the bodyweight of each participant. The frequency of applied pressure stimuli was configured following the frequency of the walking pattern. The force control signal V_{DC} and two motion control signal waves were shown in **Figure 3**. Lower V_{DC} signal was programed in the midstance phase compared to other gait phases, since the force in the contact and propulsion phases of gait is oftentimes greater than the force in stance phase (i.e., body weight) during walking. To match the gait phases of general walking, the time ratios of the four stimulating phases over the entire gait cycle were set as: contact-20%, midstance-20%, propulsion-20%, and swing-40% (Perry et al., 1992). We used dual adhesive tape to fix the pressure sensor of insoles on the movable plate surface to record the pressure applied on the right foot sole by the stimulator. When participants were lying supine (similar to their posture in MRI scanner), the foot sole was stimulated at least four times in each trial. All participants were told to relax their lower limbs during the test.

Experiment 2: MRI Compatibility Test

To verify the influence of the stimulator to the MRI scanner stability, following the fMRI Quality Assurance protocol (Friedman and Glover, 2006) and the previous study (Hao et al., 2013), we then measured the signal-to-noise ratio (SNR), signal-to-fluctuation noise ratio (SFNR) and magnetic field map in MRI scan by imaging a water phantom in each of the following conditions. (1) Power-on: foot-sole stimulator was working in only 100 cm (closer than the distance when the participants in scanning) away from the phantom center in MR scanner room. (2) Power-off: the stimulator was 100 cm away from the phantom center in the MR scanner room but not working. (3) Absent from MRI: foot-sole stimulator was out of the MR scanner room.

MRI scan

The MR imaging was performed on a 3T scanner (Discovery MR750, GE Healthcare, Milwaukee, WI, United States) using an eight-channel head coil. The Acquisition parameters were shown in **Table 1**.

Data analysis

All images in each condition were processed using SPM8 (the Wellcome Trust Centre for Neuroimaging, London, United Kingdom) (Tzourio-Mazoyer et al., 2002) and custom programing with MATLAB. In addition to a visual inspection of artifacts, we quantified the image quality using three types of parameters: SNR, SFNR, and magnetic field map. A 21 × 21 voxel region-of-interest (ROI) placed in the center of the image was created. The SNR parameters were

TABLE 1 | List of acquisition parameters in MRI compatibility test.

Parameter	Functional	Field map
Sequence type	Gradient-recalled echo-planar imaging	2D fast spoiled gradient echo
Scan plane	Axial	Axial
Repetition time (TR)	2000 ms	488 ms
Echo time (TE)	30 ms	2.5 ms/5.8 ms
Field of view	23 cm × 23 cm	23 cm × 23 cm
Flip angle	90°	60°
Matrix size	64 × 64	256 × 256
Number of slices	28 interleaved axial slices	15
Slice thickness	4 mm with 1 mm spacing	3 mm with 1 mm spacing
Number of volumes	200	1

measured following the methods delivered by the National Electrical Manufacturers Association (Friedman and Glover, 2006; National Electrical Manufacturers Association [NEMA], 2008); The SFNR of functional images was calculated following the fMRI Quality Assurance protocol (Friedman and Glover, 2006). The magnetic field maps were estimated based on EPI, and the local resonance frequency shift of each voxel was calculated to check the field non-uniformities and the subtle magnetic field perturbations potentially arising from the presence of the stimulator (Reber et al., 1998; Windischberger et al., 2004; Hao et al., 2013).

Experiment 3: Brain Activation Test

Participants

Nine healthy young participants (6 males, 3 females, 23 ± 3 years, 61 ± 10 kg, and 171 ± 10 cm) were included in this test. All of them signed written informed consent approved by the local ethical committee. Inclusion criteria were right-foot dominance; the ability to perceive 10 g of pressure at five weight-bearing sites on the right foot sole as determined with a 5.07-gauge Semmes–Weinstein monofilament; and the preferred walking speed faster than 1.0 m/s. Exclusion criteria included any known neurological or musculoskeletal disorders, previous surgery on the back or lower extremities and contraindication for MRI.

fMRI scan

A gradient-recalled echo-planar imaging (GRE-EPI) sequence was utilized in the same 3T MRI machine. Acquisition parameters were: TR = 2000 ms, TE = 30 ms, flip angle = 90°, matrix = 64 × 64, thickness/spacing = 4 mm/1 mm, field of view (FOV) = 24 × 24 cm, and 33 interleaved axial slices. The maximum stimulation pressure was set equal to 10% of the body mass of each participant, as determined by a dynamometer (NK-500, AIPU, Anhui, China). All participants were barefooted and instructed to relax their lower limbs. A block-designed 3.5-min stimulation protocol consisting of alternating blocks of 30 s-Rest (i.e., no stimulation) and 30 s-Stim (**Figure 4**) was applied to the right foot sole during fMRI scan. During 30 s-Stim, the stimulator applied 1 Hz square wave with 50-percent duty cycle and 90° phase difference to the two actuators, thus could alternately press the participants' front sole and heel, mimicking the typical ground reaction force experienced when walking.

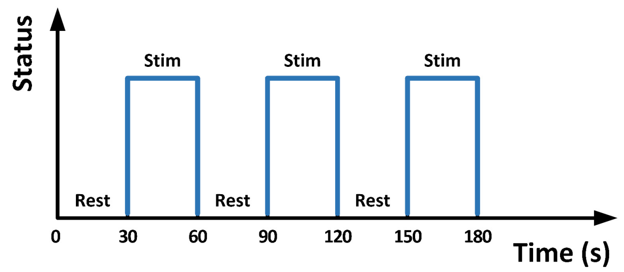

FIGURE 4 | The 30 s Stim-Rest block designed stimulation.

Data analysis

SPM8 was applied to calculate functional activation maps. To correct for potential head movement between scans, images were realigned with the first scan image and compensated delays associated with acquisition time differences via time correction. Six-parameter head motion curves were obtained. A 2 × 2 × 2 mm^3 Montreal Neurological Institute template was applied to normalize all images. Activation patterns for each individual were detected by general linear modeling. With the full width/half maximum parameter set to 8 mm and temporally filtered using a cutoff of 128 s, functional images were spatially smoothed using a Gaussian filter. Head motion was monitored by head motion parameters in SPM8. The head motion was significantly higher in the *Z*-axis (i.e., the direction of applied pressure) compared to the other directions, but was still less than 1 mm.

Statistical Analysis

All the statistics were performed by using IBM SPSS Statistics (IBM, Inc., United States) and custom MATLAB programing (The MathWorks, Inc., Natick, MA, United States).

Experiment 1

We obtained four walking pressure curves and four stimulating pressure curves from each of the participants. Focusing on the similarities in one gait cycle, we split a one-gait-cycle pressure curve from each of the eight pressure curves by using the Footscan Insole Software (Version2.39, Tekscan, United States) for the following analysis. To determine the correlation (i.e., similarity) between the pressure of walking and stimulating, we calculated 16 Spearman's correlation coefficients between the four one-gait-cycle walking pressure curves and four one-gait-cycle stimulating pressure curves. Significant level was set at $P < 0.01$. To assess the difference between the magnitude of pressure in walking and stimulating, we calculated the percent difference (PD) of pressures in three exertion phases: contact, midstance, and propulsion. The PD was defined as (MSP–MWP)/MWP, in which the MSP was mean of stimulating pressure and the MWP was mean of walking pressure. For comparison of pressure maps, we obtained five pressure maps (i.e., in contact phase, midstance phase, propulsion phase, swing phase, and complete gait cycle) from pressure records of walking and stimulating, respectively. The trajectory points of gravity center during each phase were also calculated.

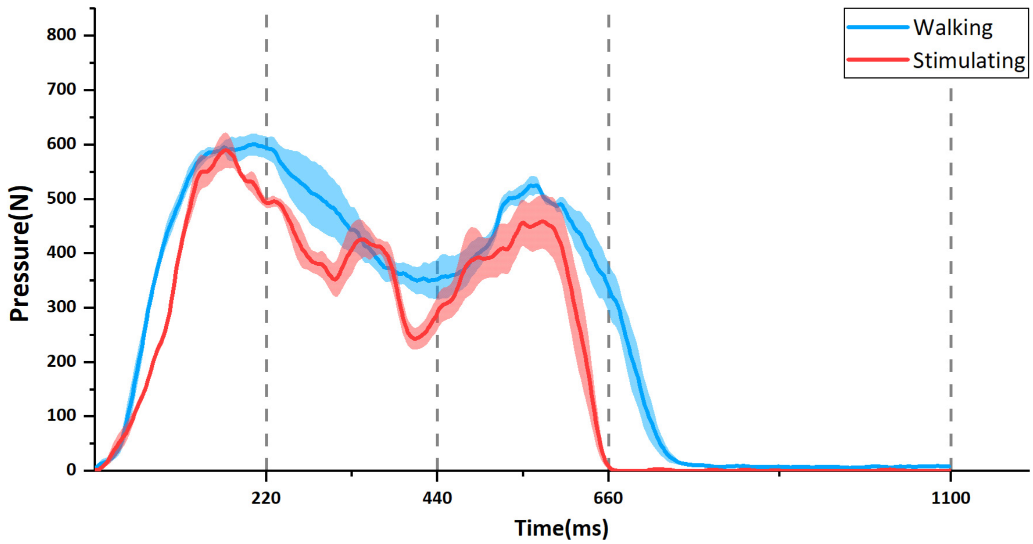

FIGURE 5 | The example of temporal change in foot-sole pressure in one participant. The blue line is the change during walking and the red is when stimulated by the stimulator. Each curve is the mean value with standard errors (shadow) from four separate pressure curves. Corresponding to the four states of control signal waves shown in **Figure 3**, the time axis is divided into four phases: Contact (0–220 ms), Midstance (220–440 ms), Propulsion (440–660 ms), and Swing (660–1100 ms).

Experiment 2

To test the effect of the device on the image quality, we performed a one-way analysis of variance (ANOVA). Model effects were the testing conditions (i.e., device power-on, power-off, and absent from MRI, and the dependent variables were the image quality parameters (i.e., SNR, SFNR, and magnetic field map).

Experiment 3

We applied one-sample *t*-tests to generate a group result on the t-map of each individual (uncorrected $P < 0.05$, at least 10 contiguous voxels).

RESULTS

The Pressure Applied by Stimulator Was Correlated to That Experienced During Walking

Figure 5 showed one example of participant's gait-cycle pressure curve. The two curves are the mean value with standard error bars of four pieces of real walking pressure curve (blue line) and stimulating pressure curve (red line), respectively. Both of them had similar trend and fluctuation. Particularly, the pressure peaks in the heel contact phase and propulsion phase occurred in both two curves. All other participants' pressure curves are available in the **Supplementary Materials** (**Supplementary Figure S1**).

The participant's pressure maps with trajectory points of gravity center (red circles) during walking and stimulating were shown in **Figure 6**. In contact phase, the plantar pressure distribution in stimulating first appeared on the heel (**Figure 6b1**) and spread to the anterior foot sole during mid-stance phase (**Figure 6b2**), then focused on the ball of foot in propulsion phase (**Figure 6b3**) and disappeared in the swing phase (**Figure 6b4**), similar to the pattern of pressure distribution changes during

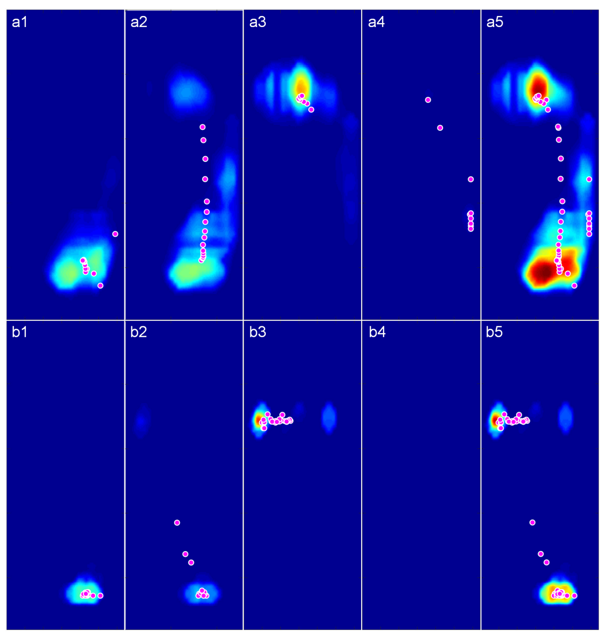

FIGURE 6 | The pressure maps with trajectory points of gravity center (Magenta circles with white edge) during walking and stimulating. **(a1–a4)** Pressure maps in contact, midstance, propulsion, and swing phase of a complete walking gait cycle. **(b1–b4)** Pressure maps in the four phases of a complete stimulating gait cycle. **(a5)** Pressure map of the whole walking gait cycle. **(b5)** Pressure map of the whole stimulating gait cycle.

TABLE 2 | Mean and standard deviation of 16 (4 walking trials with 4 stimulating trials) Spearman's correlation coefficients of each participant.

Participant	1	2	3	4	5	6	7	8	9	Average
Mean	0.800	0.746	0.829	0.711	0.899	0.725	0.899	0.805	0.887	0.811
SD	0.084	0.067	0.049	0.041	0.018	0.029	0.023	0.034	0.046	0.043

SD, standard deviation. The detailed results were shown in ***Supplementary Table S1****.*

walking (**Figures 6a1–a4**). The higher-pressure values in both contact and propulsion phases were consistent with the two pressure peaks shown in the pressure curves (**Figure 5**). During the whole gait cycle, the gravity center transferred from heel to ball of foot both in walking and stimulating, the difference is that the trajectory points tended to a straight line in stimulating (**Figure 6b5**, red circles), while in walking, the trajectory points protruded to the right lateral (**Figure 6a5**, red circles). Other eight participants' pressure maps were shown in the **Supplementary Materials** (**Supplementary Figures S2–S9**).

The results of Spearman's correlation coefficient analyses showed the programed pressure was significantly correlated with the actual pressure as experienced during walking ($r = 0.811 \pm 0.043$, $P < 0.01$, **Table 2**). The results of mean pressure difference ratio of all nine participants showed that the stimulating pressures were lower than the walking pressures ($-16.76 \pm 6.33\%$ in contact phase, $-16.64 \pm 8.00\%$ in midstance phase, $-17.80 \pm 5.57\%$ in propulsion phase, **Table 3**).

Compatibility of the Foot-Sole Pressure Simulator With 3T MRI

Images of the phantom demonstrated that the foot sole stimulator had no impact on the quality of MR images. Specifically, visual inspection revealed no observable differences between conditions (device power-on, power-off, and absent from MRI). Within the tested ROI of images, no significant differences were observed among the SNR parameters ($P = 0.82$, $F = 0.198$, Fcrit = 3.03) and the SFNR parameters ($P = 0.43$, $F = 0.845$, Fcrit = 3.00) of functional images (**Table 4**). The results of field mapping test were shown in **Figure 7**, the field non-uniformities under the three testing conditions were all less than ±50 Hz, and there was no observable differences in visual inspection among the conditions.

TABLE 3 | Percent difference (PD) of mean stimulating pressure compared to mean walking pressure in contact, midstance and propulsion phase of each participant.

Participants	PD in contact/%	PD in midstance/%	PD in propulsion/%
1	−22.87	22.14	−36.24
2	−22.56	−12.17	2.51
3	−38.95	11.07	−25.87
4	−10.37	−27.88	−12.14
5	1.01	−56.17	−9.88
6	−45.83	−38.57	8.13
7	3.26	−7.72	−23.78
8	−14.49	−15.83	−20.60
9	−20.80	−24.67	−42.36
Mean	−16.76	−16.64	−17.80
Standard error	6.33	8.00	5.57

PD, percent difference = (mean stimulating pressure − mean walking pressure)/mean walking pressure.

Cortical Response to Foot-Sole Pressure Simulator

The fMRI results showed that, compared to the rest condition, the intensity of BOLD signal (i.e., excitability) of supplementary motor area in left medial frontal gyrus, supramarginal gyrus of right inferior parietal lobule, median cingulate and paracingulate gyri, left insula, precentral gyrus, middle temporal gyrus, and hippocampus of left parahippocampal gyrus were significantly increased (uncorrected $P < 0.001$, $k \geq 10$) (**Figure 8**). Besides, we did not visually detect arresting motion artifacts or deviant statistical parameters during data processing.

DISCUSSION

We designed a novel foot sole stimulation system to enable the study of the cortical response to walking-related foot sole pressure stimuli. In this study, we demonstrated that: (1) the pressure waveforms applied to the foot soles provided by this dual-drive stimulation system closely mimicked those experienced during over-ground walking; (2) the use of this stimulation system has no interference with the quality of MR image; and (3) the walking-related foot sole stimuli activates a distributed functional network that includes multiple motor and somatosensory cortical regions.

The foot-sole pressure stimulation system we developed mimics the temporal change of pressure as experienced during over-ground walking. The map of pressure applied by the stimulator matched with that of actual walking, demonstrating that the stimulator is able to spatially simulate the pressure distribution on plantar to a certain extent. Compared to those previous MRI-compatible stimulators (Gallasch et al., 2006; Hollnagel et al., 2011; Hao et al., 2013; Hartwig et al., 2017)

TABLE 4 | MRI compatibility test on phantom center ROI.

Stimulator condition	SNR (Mean ± SD)	SFNR (Mean ± SD)
Power-on	29.43 ± 3.25	631 ± 51
Power-off	29.69 ± 3.63	627 ± 52
Absent from scanner	29.71 ± 3.52	630 ± 45

SNR, signal-to-noise ratio; SD, standard deviation; SFNR, signal-to-fluctuation noise ratio.

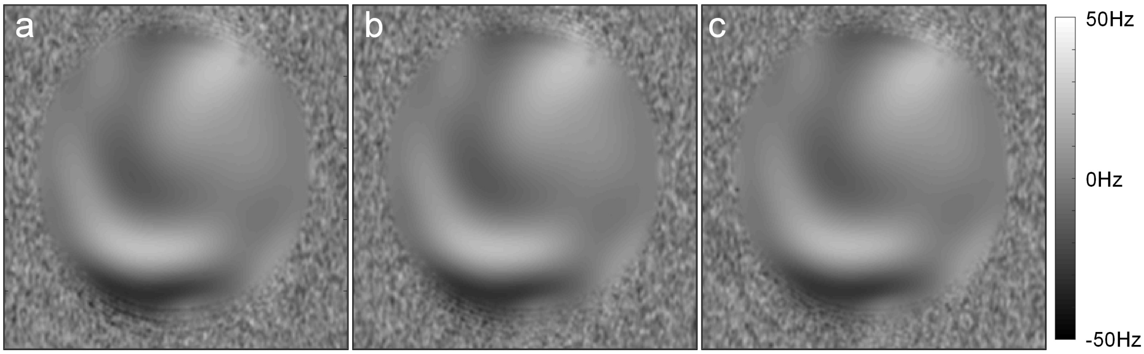

FIGURE 7 | The field maps tested in the three conditions: **(a)** Power-on, **(b)** Power-off, **(c)** absent from MRI.

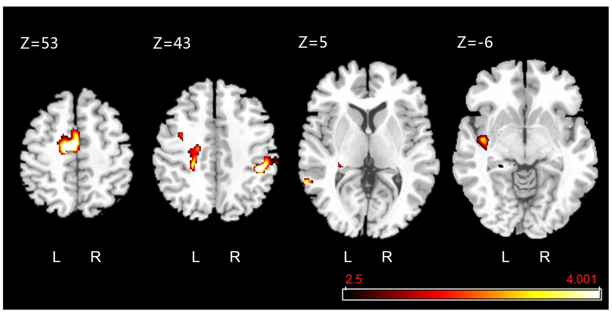

FIGURE 8 | Active clusters overlaid on a standard T1 template obtained during foot-sole pressure simulation compared to rest. Walking-related pressure stimuli applied to the right foot sole simulation was associated with increased BOLD signal intensity within the pre-motor and supplementary motor cortex (SMA.L, $Z = 53$), precentral gyrus (PreCG.L, $Z = 43$), median cingulate and paracingulate gyri (DCG.L, $Z = 43$), supramarginal gyrus (SMG.R, $Z = 43$), middle temporal gyrus (MTG.L, $Z = 5$), hippocampus (HIP.L, $Z = 5$), and insula (INS.L, $Z = -6$) (uncorrected $P < 0.001$, $k \geq 10$).

applying solely vibrotactile stimuli, here this stimulator delivers the pressures on the whole foot sole surface by using two separately controlled pneumatic cylinders to drive a large plate. Moreover, the pressure magnitude and stimulation frequency can be controlled separately to match stance-phase pressures of healthy participants with very small motion artifact to the MRI scan. Future studies are worthwhile to explore if this stimulator can simulate the walking pressure patterns in those with impaired mobility, such as those suffering from Parkinson's disease.

Activation of multiple brain cortical regions, including the pre-motor and supplementary motor cortex (SMA.L) of the left medial frontal gyrus and precentral gyrus [i.e., primary motor cortex (MI)], left insula (INS.L), median cingulate and paracingulate gyri (DCG.L), supramarginal gyrus, middle temporal gyrus, and hippocampus, was observed in response to the walking-related pressure stimuli applied by this stimulator. Several studies (Seitz and Roland, 1992; Gallasch et al., 2006) observed the activation in SMA.L and MI in response to high-frequency vibratory stimuli and low-frequency, large-force pressure stimulation (Hao et al., 2013). The results of our study confirmed those results and provided evidence that these regions are pertaining to the regulation of pressures on the foot soles as experienced during walking over the ground. The activation within INS.L and DCG.L is consistent with previous studies applying the vibratory stimulation to foot soles (Golaszewski et al., 2002; Gallasch et al., 2006), revealing the insula and cingulate cortex play important role in somatosensory processing (Vogt et al., 1992); (Schneider et al., 1993). Future studies are needed to explore the underlying neurophysiology inside the activation of supramarginal gyrus, middle temporal gyrus, and hippocampus in response to the walking-related foot sole stimulation, which can be taken into account when designing the strategies to target the cortical regions for the restoration/improvement in foot-sole somatosensation.

It should be noted that the characteristics of each stride (e.g., length or time) are different between each other within one walking trial and between each walking trial. In this study, the pressure waveforms applied by the stimulator simulates the averaged tempo-spatial characteristics of strides across trials. Future studies are thus needed to introduce the cycle-to-cycle variation of pressures, enabling a more appropriate replication of walking-related pressure stimuli. The observed lower magnitude of stimulating pressure, compared to real ground-pressure during walking, maybe because the maximum output force of the air cylinder is limited and the fixation to foot was not stable enough to resist the exerted pressure. The center of gravity track tended to a straight-line during stimulation. The potential reason is that the pressure was limited in one degree of freedom, but during real walking, the ankle can also be flipped inward or outward to adjust the bearing area of foot sole. We investigated the brain's response in a cohort of relatively small sample size by applying pressures of 10% of body mass. Future studies of larger sample size are thus needed to confirm the results of this pilot study and explore the effects of pressures with different intensity on excitability of brain regions. This study explored the brain's response to the entire gait cycle. It will thus be worthwhile to explore such response to different gait phase separately in future studies, enabling a sophisticated understanding of cortical regulation in the walking. Meanwhile, regarding to the optimization of the stimulator, future studies can: (1) add a DOF perpendicular to the existing DOF to mimic the twist of ankle; (2) equip each air cylinder with a separate proportional valve to enable more smoother control for pressure output; and (3) mount multi-point pressure sensor on the movable plate and fed back the real-time pressure distribution to the controller, forming closed control loop for more accurate stimuli.

CONCLUSION

This novel foot-sole stimulation system is feasible to mimic the pressure on foot soles as those experienced during walking on the ground and is compatible to be used during the MRI scan. The walking-related foot sole pressure stimuli applied by this system activated a distributed cortical network within the brain. Therefore, it can serve as a valuable tool stimulating personalized pressures to explore the characteristics of functional brain networks relating to the perception and modulation of foot-sole somatosensation during walking.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the Institutional Review Board of Academy for Advanced Interdisciplinary Studies at Peking University and the Institutional Review Board of Department of Radiology, Peking University First Hospital with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the Academy for Advanced Interdisciplinary Studies at Peking University and Department of Radiology at Peking University First Hospital.

AUTHOR CONTRIBUTIONS

TZ performed the pressure compare test, MRI compatibility test, and data analysis. KZ designed the stimulator and made the prototype. JnZ helped with experiment design, statistical analysis, and manuscript revising. YC provided indispensable guidance on the mechanical design and electrical control of the stimulation system. YL conducted the brain activation test and assisted fMRI data processing. XW provided the MRI scanner and gave valuable instruction for MRI data collection. BM, JeZ, and JF conceptualized the study and supervised the research. All authors contributed to the writing of the manuscript and have approved the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnins.2019.01075/full#supplementary-material

REFERENCES

Deliagina, T. G., Beloozerova, I. N., Zelenin, P. V., and Orlovsky, G. N. (2008). Spinal and supraspinal postural networks. *Brain Res. Rev.* 57, 212–221. doi: 10.1016/j.brainresrev.2007.06.017

Friedman, L., and Glover, G. H. (2006). Report on a multicenter fMRI quality assurance protocol. *J. Magn. Reson. Imaging* 23, 827–839. doi: 10.1002/jmri.20583

Gallasch, E., Golaszewski, S. M., Fend, M., Siedentopf, C. M., Koppelstaetter, F., Eisner, W., et al. (2006). Contact force- and amplitude-controllable vibrating probe for somatosensory mapping of plantar afferences with fMRI. *J. Magn. Reson. Imaging* 24, 1177–1182. doi: 10.1002/jmri.20742

Glover, G. H. (2011). Overview of functional magnetic resonance imaging. *Neurosurg. Clin. N. Am.* 22, 133–139. doi: 10.1016/j.nec.2010.11.001

Golaszewski, S. M., Siedentopf, C. M., Baldauf, E., Koppelstaetter, F., Eisner, W., Unterrainer, J., et al. (2002). Functional magnetic resonance imaging of the human sensorimotor cortex using a novel vibrotactile stimulator ⋆. *Neuroimage* 17, 421–430. doi: 10.1006/nimg.2002.1195

Halata, Z., Grim, M., and Bauman, K. I. (2003). Friedrich sigmund merkel and his "merkel cell", morphology, development, and physiology: review and new results. *Anat. Rec. A Discov. Mol. Cell Evol. Biol.* 271, 225–239. doi: 10.1002/ar.a.10029

Hao, Y., Manor, B., Liu, J., Zhang, K., Chai, Y., Lipsitz, L., et al. (2013). Novel MRI-compatible tactile stimulator for cortical mapping of foot sole pressure stimuli with fMRI. *Magn. Reson. Med.* 69, 1194–1199. doi: 10.1002/mrm.24330

Hartwig, V., Carbonaro, N., Tognetti, A., and Vanello, N. (2017). Systematic review of fMRI compatible devices: design and testing criteria. *Ann. Biomed. Eng.* 45, 1819–1835. doi: 10.1007/s10439-017-1853-1

Hijmans, J. M., Geertzen, J. H., Dijkstra, P. U., and Postema, K. (2007). A systematic review of the effects of shoes and other ankle or foot appliances on balance in older people and people with peripheral nervous system disorders. *Gait Posture* 25, 316–323. doi: 10.1016/j.gaitpost.2006.03.010

Hollnagel, C., Brugger, M., Vallery, H., Wolf, P., Dietz, V., Kollias, S., et al. (2011). Brain activity during stepping: a novel MRI-compatible device. *J. Neurosci. Methods* 201, 124–130. doi: 10.1016/j.jneumeth.2011.07.022

Kars, H. J. J., Hijmans, J. M., Geertzen, J. H. B., and Zijlstra, W. (2009). The effect of reduced somatosensation on standing balance: a systematic review. *J. Diabetes Sci. Technol.* 3, 931–943. doi: 10.1177/193229680900300441

Kennedy, P. M., and Inglis, J. T. (2002). Distribution and behaviour of glabrous cutaneous receptors in the human foot sole. *J. Physiol.* 538, 995–1002. doi: 10.1113/jphysiol.2001.013087

Kwong, K. K., Belliveau, J. W., Chesler, D. A., Goldberg, I. E., Weisskoff, R. M., Poncelet, B. P., et al. (1992). Dynamic magnetic resonance imaging of human brain activity during primary sensory stimulation. *Proc. Natl. Acad. Sci. U.S.A.* 89, 5675–5679. doi: 10.1073/pnas.89.12.5675

Manor, B., Costa, M. D., Hu, K., Newton, E., Starobinets, O., Kang, H. G., et al. (2010). Physiological complexity and system adaptability: evidence from postural control dynamics of older adults. *J. Appl. Physiol.* 109, 1786–1791. doi: 10.1152/japplphysiol.00390.2010

National Electrical Manufacturers Association [NEMA] (2008). *Determination of Signal-To-Noise Ratio (SNR) in Diagnostic Magnetic Resonance Imaging. NEMA*

Standards Publications MS 1-2008. Rosslyn: National Electrical Manufacturers Association.

Perry, J., k, S., and Davids, J. R. (1992). Gait analysis: normal and pathological function. *J. Pediatr. Orthop.* 12:815. doi: 10.1097/01241398-199211000-00023

Reber, P. J., Wong, E. C., Buxton, R. B., and Frank, L. R. (1998). Correction of off resonance-related distortion in echo-planar imaging using EPI-based field maps. *Magn. Reson. Med.* 39, 328–330. doi: 10.1002/mrm.1910390223

Richardson, J. K., and Hurvitz, E. A. (1995). Peripheral neuropathy: a true risk factor for falls. *J. Gerontol.* 50, M211–M215. doi: 10.1093/gerona/50A.4.M211

Roll, R., Kavounoudias, A., and Roll, J.-P. (2002). Cutaneous afferents from human plantar sole contribute to body posture awareness. *Neuroreport* 13, 1957–1961. doi: 10.1097/00001756-200210280-00025

Schneider, R. J., Friedman, D. P., and Mishkin, M. (1993). A modality-specific somatosensory area within the insula of the rhesus monkey. *Brain Res.* 621, 116–120. doi: 10.1016/0006-8993(93)90305-7

Seitz, R. J., and Roland, P. E. (1992). Vibratory stimulation increases and decreases the regional cerebral blood flow and oxidative metabolism: a positron emission tomography (PET) study. *Acta Neurol. Scand.* 86, 60–67. doi: 10.1111/j.1600-0404.1992.tb08055.x

Tiberio, D. (1987). The effect of excessive subtalar joint pronation on patellofemoral mechanics: a theoretical model. *J. Orthop. Sports Phys. Ther.* 9, 160–165. doi: 10.2519/jospt.1987.9.4.160

Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., et al. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *Neuroimage* 15, 273–289. doi: 10.1006/nimg.2001.0978

Vogt, B. A., Finch, D. M., and Olson, C. R. (1992). Functional heterogeneity in cingulate cortex: the anterior executive and posterior evaluative regions. *Cereb. Cortex* 2, 435–443. doi: 10.1093/cercor/2.6.435-a

Windischberger, C., Robinson, S., Rauscher, A., Barth, M., and Moser, E. (2004). Robust field map generation using a triple-echo acquisition. *J. Magn. Reson. Imaging* 20, 730–734. doi: 10.1002/jmri.20158

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Robot-Assisted Stair Climbing Training on Postural Control and Sensory Integration Processes in Chronic Post-stroke Patients: A Randomized Controlled Clinical Trial

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Background: Postural control disturbances are one of the important causes of disability in stroke patients affecting balance and mobility. The impairment of sensory input integration from visual, somatosensory and vestibular systems contributes to postural control disorders in post-stroke patients. Robot-assisted gait training may be considered a valuable tool in improving gait and postural control abnormalities.

Objective: The primary aim of the study was to compare the effects of robot-assisted stair climbing training against sensory integration balance training on static and dynamic balance in chronic stroke patients. The secondary aims were to compare the training effects on sensory integration processes and mobility.

Methods: This single-blind, randomized, controlled trial involved 32 chronic stroke outpatients with postural instability. The experimental group (EG, $n = 16$) received robot-assisted stair climbing training. The control group ($n = 16$) received sensory integration balance training. Training protocols lasted for 5 weeks (50 min/session, two sessions/week). Before, after, and at 1-month follow-up, a blinded rater evaluated patients using a comprehensive test battery. Primary outcome: Berg Balance Scale (BBS). Secondary outcomes:10-meter walking test, 6-min walking test, Dynamic gait index (DGI), stair climbing test (SCT) up and down, the Time Up and Go, and length of sway and sway area of the Center of Pressure (CoP) assessed using the stabilometric assessment.

Results: There was a non-significant main effect of group on primary and secondary outcomes. A significant Time × Group interaction was measured on 6-min walking test ($p = 0.013$) and on posturographic outcomes ($p = 0.005$). *Post hoc* within-group analysis showed only in the EG a significant reduction of sway area and the CoP length on compliant surface in the eyes-closed and dome conditions.

Conclusion: Postural control disorders in patients with chronic stroke may be ameliorated by robot-assisted stair climbing training and sensory integration balance training. The robot-assisted stair climbing training contributed to improving sensorimotor integration processes on compliant surfaces. Clinical trial registration (NCT03566901).

Keywords: sensory feedback, proprioception, postural balance, motor skill disorders, sensory function

INTRODUCTION

Postural control disturbances are one of the leading causes of disability in stroke patients, leading to problems with transferring, maintaining body position, mobility, and walking (Bruni et al., 2018). Therefore, the recovery of postural control is one of the main goals of post-stroke patients. Various and mixed components (i.e., weakness, joint limitation, alteration of tone, loss of movement coordination and sensory organization components) can affect postural control. Indeed, the challenge is to determine the relative weight placed on each of these factors and their interaction to plan specific rehabilitation programs (Bonan et al., 2004).

The two functional goals of postural control are postural orientation and equilibrium. The former involves the active alignment of the trunk and head to gravity, the base of support, visual surround and an internal reference. The latter involves the coordination of movement strategies to stabilize the center of body mass during self-initiated and externally triggered stability perturbations. Postural control during static and dynamic conditions requires a complex interaction between musculoskeletal and neural systems (Horak, 2006). Musculoskeletal components include biomechanical constraints such as the joint range of motion, muscle properties and limits of stability (Horak, 2006). Neural components include sensory and perceptual processes, motor processes involved in organizing muscles into neuromuscular synergies, and higher-level processes essential to plan and execute actions requiring postural control (Shumway-Cook and Woollacott, 2012). A disorder in any of these systems may affect postural control during static (in quite stance) and dynamic (gait) tasks and increase the risk of falling (Horak, 2006).

Literature emphasized the role of impairments of sensory input integration from visual, somatosensory and vestibular systems in leading to postural control disorders in post-stroke patients (Bonan et al., 2004; Smania et al., 2008). Healthy persons rely on somatosensory (70%), vision (10%) and vestibular (20%) information when standing on a firm base of support in a well-lit environment (Peterka, 2002). Conversely, in quite stance on an unstable surface, they increase sensory weighting to vestibular and vision information as they decrease their dependence on surface somatosensory inputs for postural orientation (Peterka, 2002). Bonan et al. (2004) investigate whether post-stroke postural control disturbances may be caused by the inability to select the pertinent somatosensory, vestibular or visual information. Forty patients with hemiplegia after a single hemisphere chronic stroke (at least 12 months) performed computerized dynamic posturography to assess the patient's ability to use sensory inputs separately and to suppress inaccurate inputs in case of sensory conflict. Six sensory conditions were assessed by an equilibrium score, as a measure of body stability. Results show that patients with hemiplegia seem to rely mostly on visual input. In conditions of altered somatosensory information, with visual deprivation or visuo-vestibular conflict, the patient's performance was significantly lower than healthy subjects. The mechanism of this excessive visual reliance remains unclear. However, higher-level inability to select the appropriate sensory input rather than to elementary sensory impairment has been advocated as a potential mechanism of action (Bonan et al., 2004).

Sensory strategies and sensory reweighting processes are essential to generate effective movement strategies (ankle, hip, and stepping strategies) which can be resolved through feed-back or feed-forward postural adjustments. The cerebral cortex shapes these postural responses both directly via corticospinal loops and indirectly via the brainstem centers (Jacobs and Horak, 2007). Moreover, the cerebellar- and basal ganglia-cortical loop is responsible for adapting postural responses according to prior experience and for optimizing postural responses, respectively (Jacobs and Horak, 2007).

Rehabilitation is the cornerstone in the management of postural control disorders in post-stroke patients (Pollock et al., 2014). To date, no one physical rehabilitation approach can be considered more effective than any other approach (Pollock et al., 2014). Specific treatments should be chosen according to the individual requirements and the evidence available for that specific treatment. Moreover, it appears to be most beneficial a mixture of different treatment for an individual patient (Pollock et al., 2014). Considering that, rehabilitation involving repetitive, high intensity, task-specific exercises is the pathway for restoring motor function after stroke (Mehrholz et al., 2013; Lo et al., 2017) robotic assistive devices for gait training have been progressively being used in neurorehabilitation to Sung et al. (2017). In the current literature, three primary evidence have been reported.

Firstly, a recent literature review highlights that robot-assisted gait training is advantageous as add-on therapy in stroke rehabilitation, as it adds special therapeutic effects that could not be afforded by conventional therapy alone (Morone et al., 2017; Sung et al., 2017). Specifically, robot-assisted gait training was beneficial for improving motor recovery, gait function, and postural control in post-stroke patients (Morone et al., 2017; Sung et al., 2017). Stroke patients who received physiotherapy treatment in combination with robotic devices were more likely to reach better outcomes compared to patients who received conventional training alone (Bruni et al., 2018).

Second, the systematic review by Swinnen et al. (2014) supported the use of robot-assisted gait therapy to improve postural control in subacute and chronic stroke patients. A wide variability among studies was reported about the robotic-device system and the therapy doses (3–5 times per week, 3–10 weeks, 12–25 sessions). However, significant improvements (Cohen's $d = 0.01$ to 3.01) in postural control scores measured with the Berg Balance Scale (BBS), the Tinetti test, postural sway tests, and the Timed Up and Go (TUG) test were found after robot-assisted gait training. Interestingly, in five studies an end-effector device (gait trainer) was used (Peurala et al., 2005; Tong et al., 2006; Dias et al., 2007; Ng et al., 2008; Conesa et al., 2012). In two study, the exoskeleton was used (Hidler et al., 2009; Westlake and Patten, 2009). In one study, a single joint wearable knee orthosis was used (Wong et al., 2012). Because the limited number of studies available and methodological differences among them, more specific randomized controlled trial in specific populations are necessary to draw stronger conclusions (Swinnen et al., 2014).

Finally, technological and scientific development has led to the implementation of robotic devices specifically designed to overcome the motor limitation in different tasks. With this perspective, the robot-assisted end-effector-based stair climbing (RASC) is a promising approach to facilitate task-specific activity and cardiovascular stress (Hesse et al., 2010, 2012; Tomelleri et al., 2011; Stoller et al., 2014, 2016; Mazzoleni et al., 2017).

To date, no studies have been performed on the effects of RASC training in improving postural control and sensory integration processes in chronic post-stroke patients.

The primary aim of the study was to compare the effects of robot-assisted stair climbing training against sensory integration balance training on static and dynamic balance in chronic stroke patients. The secondary aims were to compare the training effects on sensory integration processes and mobility. The hypothesis was that the task-specific and repetitive robot-assisted stairs climbing training might act as sensory integration balance training, improving postural control because sensorimotor integration processes are essential for balance and walking.

MATERIALS AND METHODS

Trial Design

A single-blind randomized clinical trial (robot-assisted stair climbing training – RASCT) and control group (sensory integration balance training – SIBT). The study was conducted based on the Declaration of Helsinki. The guidelines for Good Clinical Practice, and the Consolidated Standards of Reporting Trials (CONSORT), were followed. The local Ethics Committee "Nucleo ricerca clinica–Research and Biostatistic Support Unit" (1442CESC) approved the study, which was registered at clinical trial (NCT03566901).

Participants

Consecutive chronic post-stroke outpatients referring to the Neurorehabilitation Unit (AOUI Verona) were assessed for eligibility from October 2017 to November 2018. Inclusion criteria were: age $\geq$ 18 years, first-ever ischemic or hemorrhagic stroke as documented by a magnetic resonance imaging or a computerized tomography scan; more than or equal to 6 months post stroke; ability to stand for at least 1 min without arm support; positive Pull test; Mini-Mental State Evaluation (MMSE) score $\geq$ 24/30; ability to walk independently for at least 10 m without walking aids; VAS score $<$ 7/10 at lower limbs. Exclusion criteria were: severe visual, cognitive or cardiovascular dysfunction; deep venous thrombosis; lower limb spasticity $<$2 on the Modified Ashworth Scale; Botulinum toxin injection in the lower limb in the 3 months before the enrollment and during the study; other concomitant neurological or orthopedic diseases interfering with balance and ambulation. Patients gave their written, informed consent after being informed about the experimental nature of the study. They were not allowed to undergo any rehabilitation intervention during the month before the recruitment.

Interventions

Patients underwent 10 individual rehabilitation sessions as outpatients (2 days/week, 5 weeks) at the Neurorehabilitation Unit (AOUI Verona). Each rehabilitation sessions lasted 50 min.

Experimental Group

Patients underwent Robot-Assisted Stair-Climbing Training (RASCT) with the G-EO system device (Reha Technology, Olten, Switzerland) (**Figure 1**). This end-effector robotic device can reproduce the gait pattern and realistically simulates the ability to carry out stairs up and down. The patients stood with feet secured to two foot-plates whose kinetics and kinematics parameters of the movement were adjustable. The foot-plates have three degrees of freedom each, allowing to control the step length and height and the foot-plates angles. The maximum step length corresponds to 550 mm, and the maximum achievable step height is 400 mm. The maximum angle of rotation is $\pm$ 90°. This angle controlled the plantar- and dorsiflexion of the ankles during the steps. The maximum foot-plates speed is 2.3 km/h. A physiotherapist set the pace and step length according to the patient's impairment and the improvements achieved. Patients were secured by a harness fixed to an electric patient lift system. This system helped patients to be sustained during the walking or stair climbing task. Moreover, the G-EO system provides real-time feedback on the patient's movements (Hesse et al., 2012).

FIGURE 1 | The G-EO system used in the Robot-Assisted Stair-Climbing Training (Written informed consent was obtained from the individual pictured, for the publication of this image).

Treatments were performed in three different modalities: (Bruni et al., 2018) passive mode (Bonan et al., 2004) active assistive mode and (Horak, 2006) active mode. Time to get in and out was 5 min. The net RASCT lasted 45 min/session. Patients were instructed to "help" the foot-plates gait-like movements during the training. The initial step-length, cadence and gait speed was individually set according to the spatiotemporal gait parameters measured by the GAITRite system (CIR Systems, Havertown, PA, United States) (minimum cadence: 30 step/min; gait speed range: 0.8–1.4 km/h; step height range: 12–18 cm; step cadence minimum: 14 step/min). The range of the body-weight support was between 50 and 0% to allow the patient to walk more symmetrically with higher velocities. It resulted in the facilitation of lower limb muscles and a more efficient gait (Hussein et al., 2008). Each training session consisted of robot-assisted gait training (15 min), robot-assisted stairs up (10 min) and down (10 min), passive lower limb joint mobilization and stretching exercises (10 min). The exercises (i.e., type of exercise, number of repetitions) and any adverse events that occurred during the study were recorded by the physiotherapist on the patient's chart.

The Sensory Integration Balance Training

The SIBT consisted of exercises aimed at improving the ability to integrate and reweight visual, proprioceptive and vestibular sensory input to maintain postural control. Each training session consisted of overground gait training (15 min), stairs up (10 min), and down (10 min), passive lower limb joint mobilization and stretching exercises (10 min). The net SIBT lasted 45 min/session. Exercises were repeated on a firm surface (floor) and compliant surfaces (i.e., mats of different section and resistance) (Smania et al., 2008; Gandolfi et al., 2014, 2015).

Outcomes

At enrollment, clinical and demographic data were collected. A blinded examiner assessed primary and secondary outcomes before (T0), after treatment (T1) and 1 month after treatment (T2).

The primary outcome measure was the BBS. It is a validated 14-items measure for the assessment of static and dynamic balance in stroke patients. ICF domain: activity, maximum score: 54 (higher = better performance) (Cattaneo et al., 2006).

Secondary outcome measures were validated clinical scales to evaluate the training effects of electromechanical and robotic devices in post-stroke patients (Geroin et al., 2013). The Ten Meters Walking Test (10MWT) assessed the gait speed by measuring the time needed to walk 10 m and have been widely used in stroke patients. ICF domain: activity. A cut-off of 0.84 m/s has been reported to identify community ambulators (Bowden et al., 2008). The 6 min Walking Test (6MWT) assessed the distance walked over 6 min as a measure of endurance and aerobic capacity of the patient. It is commonly used in many neurologic conditions including stroke. ICF domain: activity. Normative data reported a score >400 m (Wevers et al., 2011). The Dynamic Gait Index (DGI) measured the patient's ability to walk modifying balance according to external demands. Scores are based on a four-point scale, and tasks include steady-state walking, changing speed, turning head, overcoming obstacles and pivoting while walking and climbing stairs. ICF domain: activity, maximum score: 24 (higher = better performance) (Jonsdottir and Cattaneo, 2007). The TUG was used to measure of walking ability, balance, and fall risk in older adults. In the starting position patients sat on a chair and were asked to stand up, walk for 3 m at a self-selected speed, turn, walk back and sat on the same chair. The time between the starting position and the end of the task was recorded. ICF domain: activity. A minimal detectable change of 2.9 s was measured in patients with chronic stroke (Flansbjer et al., 2005). The Stair Climbing Test (SCT) assessed the ability to climb stair by measuring the time needed for the ascend and descend of stairs (nine steps). Step height was set at 20 cm. It has previously been used in the trial including subjects with cerebrovascular disease. ICF domains: activity (Harries et al., 2015).

The instrumental evaluation consisted of the stabilometric assessment using a force monoaxial platform (Stability System ST 310 Plus, Technobody). Patients were evaluated in the standing position without upper limb support. Feet position was standardized using a V-shaped frame, and patients were tested standing barefoot with arms alongside the body. According to the Sensory Organization Test protocol (Shumway-Cook and Horak, 1986), patients were assessed in six conditions, each lasting 30 s: (Bruni et al., 2018) stable surface with eyes open, (Bonan et al., 2004) eyes closed, and (Horak, 2006) dome condition; (Shumway-Cook and Woollacott, 2012) compliant surface with eyes open, (Smania et al., 2008) compliant surface with eyes closed, and (Peterka, 2002) compliant surface in dome condition (Shumway-Cook and Horak, 1986; Scoppa et al., 2013). In the dome condition, patients wore a visual-conflict dome positioned on patients' head. An "*x*" sign was placed in the internal face of the dome aligned with the straight-ahead gaze of the patients. The dome moved in phase with patients' head producing inaccurate visual orientation input (Shumway-Cook and Horak, 1986). This six-conditions test was used to examine the ability of the patients to maintain balance when sensory inputs were disrupted (Shumway-Cook and Horak, 1986). Data acquisition began after 10 s of patient's familiarization with the task to limit non-stationary data, and the acquisition was stopped before patients were told to end the task (Da-Silva et al., 2016). The platform measures the position of the Center of Pressure (CoP) while subjects are standing on it with a sampling rate of 20 Hz. The coordinates of the Cop were used to calculate the length of the planar migration of the CoP over the platform (perimeter) [mm] and the sway area [mm^2] in each condition. The sway area was computed as the area of the ellipse containing the 95% of CoP data points. Ellipse's axes were calculated using principal component analysis (Oliveira et al., 1996). A platform integrated software computed Posturometric parameters.

Sample Size

A sample size of 30 patients were necessary assuming α = 0.05 (probability of type 1 error) and a 95% power to detect a mean difference of 4.66 (DS 5.2) on the primary outcome measure (BBS) (Hiengkaew et al., 2012).

Assuming a 10% drop-out rate, 32 patients were necessary to perform the study.

Randomization

An automated randomization system[1] was used to assign eligible patients to either the EG or the CG using. Group allocation was kept concealed. Only the principal investigator could access to the randomization list.

[1]http://www.randomization.com

Blinding

Primary and secondary outcomes were assessed by the same examiner blinded to the patient's group allocation.

Statistical Analysis

An intention-to-treat analysis (Last Observation Carry Forward – LOCF-method) was used to handle missing data. Descriptive statistics included means and standard deviation. The X^2 test was performed for categorical variables. Data distribution was checked to detect outliers (**Figure 2**). One patient in the EG

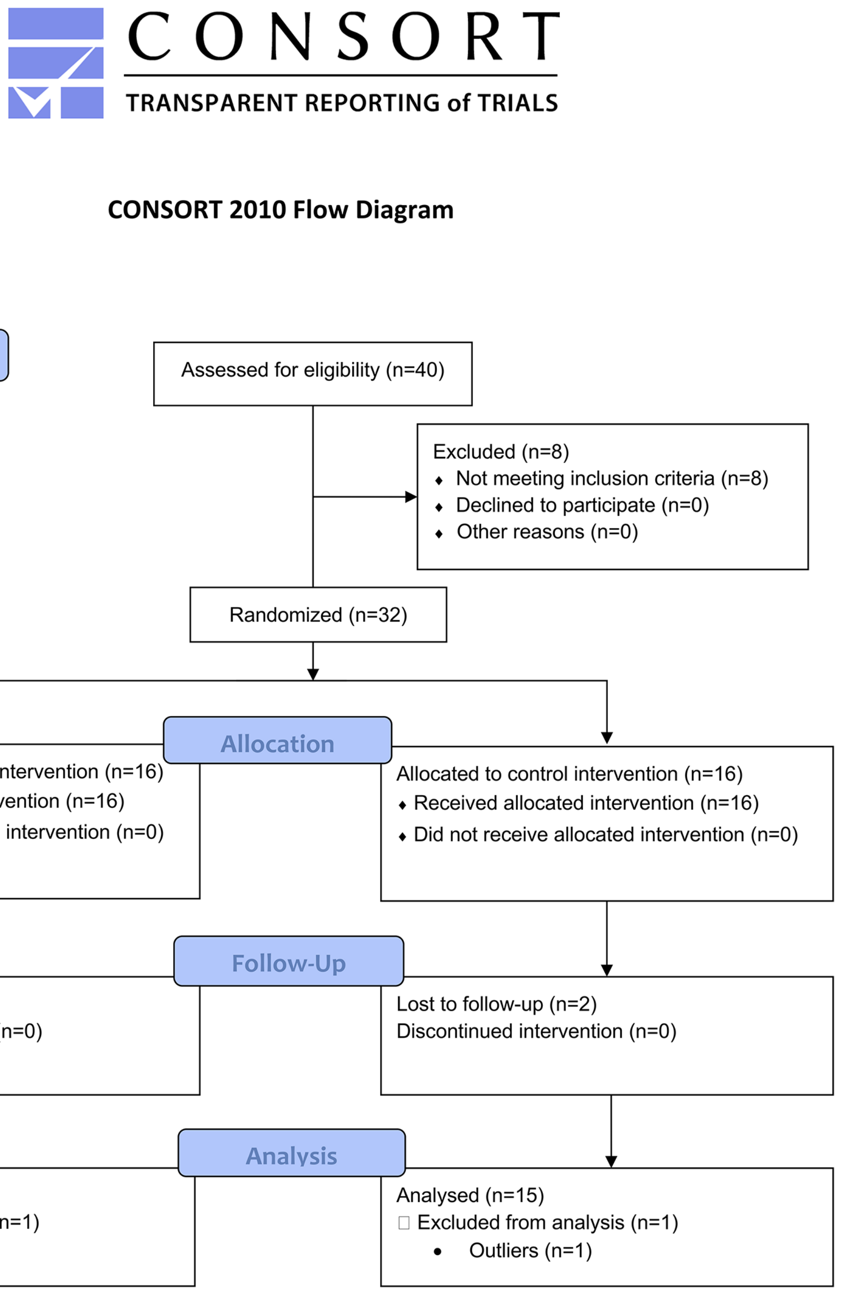

FIGURE 2 | CONSORT flowchart.

and one patient in the CG differed significantly from the other observations (outliers) in all outcome measures and then they were excluded from the analysis. Data distribution was assessed with Shapiro–Wilk Test indicating a normal distribution. A two-way mixed ANOVA was used to analyze clinical outcome with Time as within-group independent variable, Group as between-group factor and the Time × Group factor to measure any interaction. Similarly, a two-way mixed ANOVA was used to evaluate the effects on the stabilometric assessment considering Group (×2) and Time (×3) factors and the six conditions for the analysis of stabilometric outcomes. Two-tailed Student's *t*–test for unpaired data was used for between-group comparisons. The level of significance was set at $p < 0.05$. Bonferroni's correction was applied for multiple comparisons. Statistical analysis was performed with SPSS 22.0 (IBM SPSS Statistics, Version 22.0, 2013, Armonk, NY, United States).

RESULTS

A total of 40 patients were assessed for eligibility: 8 were excluded because they did not meet inclusion criteria. Thirty-two patients were randomly assigned to either the EG (n = 16) or the CG (n = 16). Two patients in the EG and two in the CG were lost to follow-up (drop-out). Two patients were excluded from the analysis because they presented extreme values and, therefore, were considered outliers. No adverse events or safety concerns was reported during the conduction of the study.

Between-group analysis showed no significant differences in demographics and clinical data (**Table 1**) in primary and secondary outcome measures at baseline (T0).

There was a non-significant main effect of group on primary and secondary outcomes (**Table 2**). A significant Time × Group interaction was measured on 6MWT (p = 0.013). Therefore, groups were analyzed separately. Overall significant changes over time were found in both groups (EG: $p < 0.001$; CG: p = 0.04). *Post hoc* analysis measured significant improvements in EG at T1 ($p < 0.001$) and T2 ($p < 0.001$). In CG significant changes were measured only at T2 (p = 0.008). An overall within-group

TABLE 1 | Demographic and clinical characteristics of patients.

	Experimental Group (n = 16)	Control Group (n = 16)	Group comparison
	Mean (SD)	Means (SD)	*p*-Value
Age (years)	63.87 (11.44)	64.37 (10.56)	n.s.[a]
Sex M/F	10/6	13/3	n.s.[b]
BMI	26.49 (2.42)	26.19 (4.11)	n.s.[a]
Time from event (months)	54.81 (36.28)	53.06 (41.73)	n.s.[a]
Type of event I/E	13/3	13/3	n.s.[b]
Affection side L/R	6/10	4/12	n.s.[b]
European Stroke Scale (0–100)	72.12 (11.72)	72.56 (14.47)	n.s.[b]
Barthel Index (0–100)	90.93 (11.13)	90.62 (11.38)	n.s.[b]

SD, standard deviation; M, male; F, female; BMI, body mass index; I, ischemic; E, hemorrhagic; L, left; R, right; [a], Mann-Whitney test; [b], chi square test.

TABLE 2 | Descriptive and inferential statistics for clinical outcome measures.

	Group	Descriptive statistics						Repeated measure ANOVA			Between-group comparison T0 IC 95%				Between-group comparison T1 IC 95%				Between-group comparison T2 IC 95%			
		T0		T1		T2		Time *P*-value	Time* Group *P*-value	Group *P*-value	*P*-value	Diff media	LB	UP	*P*-value	Diff media	LB	UP	*P*-value	Diff media	LB	UP
		Mean	SD	Mean	SD	Mean	SD															
BBS	EG	45.33	7.04	48.80	6.46	49.27	5.99	< 0.001*	0.7	0.76	0.67	1.07	−4.04	6.18	0.81	0.53	−3.94	5.01	0.85	0.40	−3.79	4.59
	CG	44.27	6.62	48.27	5.47	48.87	5.17															
10 MWT	EG	12.76	5.53	11.08	5.09	10.72	4.82	< 0.001*	0.71	0.77	0.65	−0.95	−5.26	3.35	0.95	−0.13	−4.22	3.96	0.72	−0.71	−4.66	3.24
	CG	13.72	5.97	11.21	5.82	11.43	5.71															
6 MWT	EG	203.4	80.1	237.9	95.3	234.3	90.1	< 0.001*	0.013*	0.49	0.75	10.73	−56.85	78.31	0.32	36.70	−37.42	110.82	0.49	24.47	−47.89	96.82
	CG	192.7	99.6	201.2	102.8	209.9	103.0															
DGI	EG	16.67	3.13	18.47	4.16	18.93	4.10	< 0.001*	0.49	0.56	0.24	1.53	−1.09	4.16	0.76	0.47	−2.66	3.59	0.8	0.40	−2.76	3.56
	CG	15.13	3.85	18.00	4.21	18.53	4.34															
TUG	EG	22.81	8.65	19.17	8.14	18.59	8.44	< 0.001*	0.41	0.94	0.73	−1.08	−7.50	5.33	0.89	0.37	−5.22	5.96	0.97	0.12	−5.91	6.15
	CG	23.89	8.50	18.80	6.74	18.47	7.67															
SCT Up	EG	13.10	4.53	10.72	4.01	10.72	3.87	< 0.001*	0.51	0.83	0.99	−0.02	−3.50	3.46	0.85	−0.31	−3.73	3.11	0.68	−0.70	−4.17	2.76
	CG	13.12	4.78	11.03	5.08	11.42	5.29															
SCT Down	EG	13.50	4.55	10.98	4.37	10.73	4.34	< 0.001*	0.37	0.43	0.52	−1.23	−5.10	2.63	0.53	−1.21	−5.07	2.65	0.33	−2.11	−6.48	2.25
	CG	14.74	5.72	12.19	5.84	12.85	7.01															

*SD, standard deviation; EG, experimental group; CG, control group; T0, pre-treatment; T1, post-treatment; T2, 1-month follow-up; BBS, berg balance scale; 10MWT, 10-meter walking test; 6MWT, 6-minute walking test; DGI, dynamic gait index; stocktickerTUG, timed-up-and-go TEST; CI: confidence interval; LB: lower bound; UB: upper bound; *, statistically significant; °, better performance.*

improvement was found in 6MWT ($p < 0.001$), DGI ($p < 0.001$), 10 mWT ($p < 0.001$), TUG ($p < 0.001$) and SCT both in ascending ($p < 0.001$) and descending condition ($p < 0.001$).

The posturographic analysis showed a significant time × group interaction ($p = 0.005$). Therefore, groups were analyzed separately. Overall significant changes over time were measured in EG in CoP Perimeter in condition 2 ($p = 0{,}015$), 5 ($p = 0{,}02$), and 6 ($p = 0{,}013$). In contrast, no significant changes were measured in the CG. *Post hoc* within-group analysis showed a significant improvement at T1 in condition 5 ($p = 0{,}024$) and T2 in condition 6 ($p = 0{,}008$). Concerning the CoP Area, significant improvements were measured in EG in condition 4 ($p = 0{,}014$), 5 ($p = 0{,}05$), and 6 ($p = 0{,}027$). Significant differences were found at T2 in all conditions (4: $p = 0{,}012$; 5: $p = 0{,}02$; and 6: $p = 0{,}012$) but not at T1 (**Figure 3** and **Table 3**).

DISCUSSION

The main finding of this RCT is twofold. Firstly, RASCT and SIBT produced comparable effects either to postural control or mobility in chronic post-stroke patients. Second, only the group that received the robot-assisted stair-climbing training reported significant improvements in the distance walked over 6 min and significant reduction of sway area and the CoP length on compliant surface in the eyes-closed and dome conditions.

Robot-assisted gait intervention offers the advantage of high-intensity and task-specific training that can be delivered, decreasing the physiotherapist physical burden (Morone et al., 2017; Sung et al., 2017). Over the last 20 years, the robot-assisted application in neurorehabilitation has inspired clinicians and researchers in further investigating the training effects on the multifaceted aspects involved in functional recovery after neurological disorders (Morone et al., 2017). A wide range of motor control dysfunctions might contribute to gait impairments in people with stroke. However, postural control disorders account for most of the gait-related disability such as problems with transferring, maintaining body position, mobility, and walking (Bruni et al., 2018). The development of evidence-based rehabilitation protocols is therefore of particular importance.

A pilot RCT study in 22 patients with Multiple Sclerosis (Expanded Disability Status Scale: 1.5–6.5) showed evidence that a robot-assisted gait training (Gait Trainer, Reha-stim, Berlin – Germany) might improve postural stability and the level of balance confidence perceived while performing Activities of Daily Lining (ADLs) as much as a sensory integration balance training (Gandolfi et al., 2014). For the first time, it has been suggested the various types of potential training effects of the end-effectors system in restoring gait function in people with a demyelinating disease. The hypothesis was that the robot-assisted approach would act as a form of "destabilization training" in the context of a "task-specific balance training" by the end-effector system. Destabilization training includes tasks that induced unexpected external or internal destabilizations of the center-of-body mass (CoP), while patients are asked to keep the standing posture. Our findings cannot be fully discussed with those by Gandolfi et al., 2014 due to differences about patients and the type of the robot-assisted device. However, our results confirm these literature findings in patients with chronic stroke.

The two interventions showed comparable effects on static and dynamic activities of varying difficulty, on the ability to modify balance while walking in the presence of external demands and on mobility as assessed by the clinical scales. Note that, neither the experimental nor the control group achieved the minimum clinical significance change of five points post-treatment in the primary outcome measure (Donoghue et al., 2009). The BBS is psychometrically robust (Tyson and Connell, 2009a) and very sensitive to exercise intervention in neurological population (Pedroso et al., 2012). However, we did not measure clinically significant changes. Therefore, we could not exclude accustoming effects during the training or ceiling effects. Similarly, both interventions improved walking speed

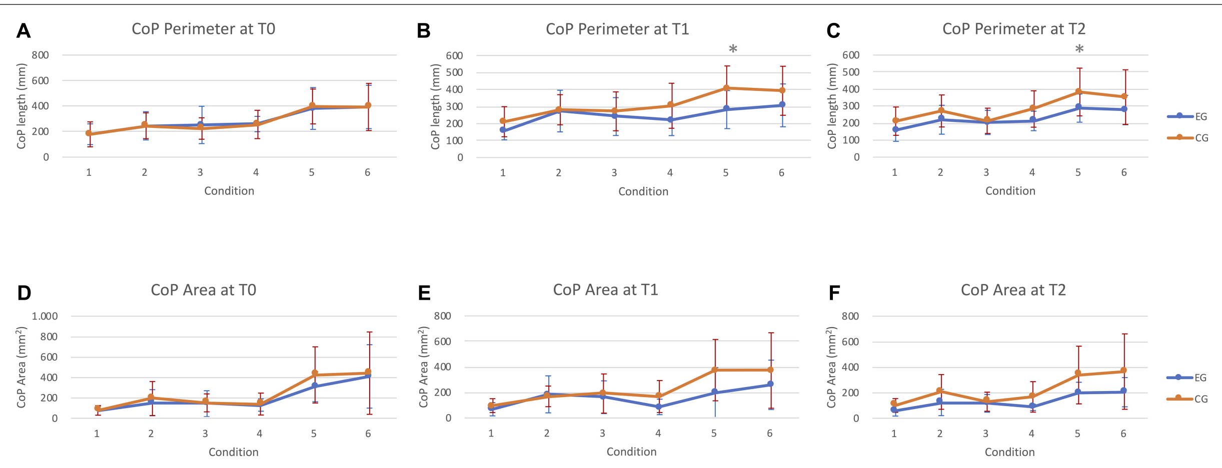

FIGURE 3 | Instrumental assessment of postural control. **(A–C)** means ± standard deviation of CoP perimeter. Abscissa indicates the six conditions. Ordinate indicates the CoP perimeter (mm). **(D–F)** means ± standard deviation of sway area. Abscissa indicates the six conditions. Ordinate indicates the sway area (mm^2). Asterisks indicates significant differences in between-group comparison.

TABLE 3 | Descriptive and intra-group comparison of treatment effects.

Outcome	Group	T0		T1		T2		Repeated measures ANOVA	*Post Hoc* analysis - Mean within-group differences							
									IC 95% T0-T1				IC 95% T0–T2			
		Mean	SD	Mean	SD	Mean	SD	Time *p*-value	*P*-value	Mean diff	LB	UP	*P*-value	Mean diff	LB	UP
Perimeter CoP																
Condition 1	EG	179.53	81.51	157.47	52.77	159.87	66.52	0.11	0.064	22.07	−1.50	45.63	0.111	19.67	−5.11	44.44
	CG	178.50	97.74	202.86	88.46	203.57	83.21	0.14	0.122	−24.36	−56.21	7.50	0.132	−25.07	−58.80	8.66
Condition 2	EG	245.47	110.74	272.80	122.33	215.67	84.93	0.015*	0.042	−27.33	−53.51	−1.15	0.121	29.8	−8.94	68.54
	CG	245.93	101.21	277.36	88.57	267.00	94.14	0.29	0.182	−31.43	−79.63	16.77	0.399	−21.07	−73.24	31.09
Condition 3	EG	252.20	146.18	242.27	111.37	202.80	71.12	0.23	0.767	9.93	−60.63	80.50	0.155	49.40	−21.17	119.97
	CG	224.29	84.04	278.14	114.42	215.57	74.55	0.06	0.098	−53.86	−119.02	11.31	0.619	8.71	−28.26	45.69
Condition 4	EG	259.33	59.87	218.40	90.33	211.20	57.31	0.09	0.016*	40.93	8.73	73.13	0.019*	48.13	9.05	87.22
	CG	256.07	111.09	306.79	132.30	283.71	106.98	0.16	0.024*	−50.71	−93.66	−7.77	0.242	−27.64	−76.41	21.12
Condition 5	EG	381.27	164.00	281.07	111.81	287.67	82.81	0.02*	0.024*	100.20	14.92	185.48	0.030	93.60	10.71	176.49
	CG	397.00	136.64	416.14	130.23	388.71	140.33	0.72	0.517	−19.14	−81.19	42.91	0.846	8.29	−82.13	98.70
Condition 6	EG	393.53	169.95	306.13	125.92	273.93	86.41	0.013*	0.056	87.40	−2.67	177.47	0.008*	119.60	37.04	202.16
	CG	393.00	184.78	404.71	144.07	362.14	160.45	0.56	0.812	−11.71	−115.94	92.51	0.427	30.86	−50.39	112.10
Area CoP																
Condition 1	EG	74.40	45.04	69.60	51.57	59.07	41.14	0.36	0.687	4.80	−20.26	29.86	0.091	15.33	−2.76	33.43
	CG	77.00	46.97	83.57	54.32	87.21	53.85	0.64	0.619	−6.57	−34.40	21.26	0.498	−10.21	−41.88	21.45
Condition 2	EG	152.07	127.69	186.87	144.97	121.07	103.00	0.08	0.187	−34.80	−88.64	19.04	0.289	31.00	−29.35	91.35
	CG	193.36	166.52	154.07	81.00	193.57	136.06	0.38	0.329	39.29	−44.38	122.96	0.995	−0.21	−68.65	68.22
Condition 3	EG	142.67	126.94	164.87	128.13	115.67	69.31	0.17	0.394	−22.20	−76.36	31.96	0.327	27.00	−30.02	84.02
	CG	150.64	88.02	185.50	153.51	119.21	74.79	0.13	0.281	−34.86	−101.87	32.15	0.069	31.43	−2.88	65.74
Condition 4	EG	129.53	60.58	86.53	60.69	85.33	24.52	0.014*	0.026	43.00	5.81	80.19	0.012*	44.20	11.02	77.38
	CG	139.00	107.42	153.07	125.49	152.29	119.39	0.78	0.529	−14.07	−61.07	32.93	0.585	−13.29	−64.49	37.92
Condition 5	EG	308.73	147.56	198.47	194.77	195.60	84.82	0.05*	0.053	110.27	−1.57	222.11	0.021*	113.13	19.03	207.24
	CG	424.36	275.20	361.00	240.39	322.36	225.86	0.35	0.399	63.36	−93.67	220.39	0.183	102.00	−54.52	258.52
Condition 6	EG	409.93	310.44	261.80	193.63	202.60	114.56	0.027*	0.096	148.13	−29.90	326.17	0.012*	207.33	51.76	362.91
	CG	441.93	403.59	378.36	295.79	371.64	295.61	0.56	0.554	63.57	−162.40	289.54	0.196	70.29	−41.22	181.79

*EG, experimental group; CG, control group; CoP, center of pression; T0, pre-treatment; T1, post-treatment; T2, 1-month follow-up; 1, open eyes - stable surface condition; 2, closed eyes - stable surface condition; 3, dome - stable surface condition; 4, open eyes - compliant surface condition; 5, closed eyes – compliant surface condition; 6, dome – compliant surface condition; *, statistically significant.*

over a short duration, as evaluated by the 10-meter walking test. In the framework proposed by Horak (2006) both pieces of training might have exerted their effects improving movement and sensory strategies (sensory integration and reweighting), orientation in space and control of dynamic (Horak, 2006) acting as task-specific balance training (Gandolfi et al., 2014). The robot-assisted training in addition may have improved proprioception, and the integration of proprioceptive and vestibular sensory input, in standing on compliant surface (condition n. 4-5-6) (Gandolfi et al., 2014). A possible explanation is that the robotic approach might have reinforced the neural circuits that contribute to face postural adjustments. The G-EO system is an end-effector system (Hesse et al., 2012). In this context, a reduced number of constraints interact with the patients allowing freedom, especially for ankle and hip movements, on a mobile base of support. The gait-like footplates movement might shape ankle strategies required to maintain balance for small amounts of sway when standing on a firm surface (Horak and Kuo, 2000). The lack of constraints, especially for the pelvic movement, might account for hip strategies improvements, in which the body exerts torque at the hips to quickly move the body CoM, is used to stand on narrow or compliant surfaces that do not allow adequate ankle torque (Horak and Kuo, 2000). The fact that the physiotherapist set the step and gait parameters (i.e., step length and pace) according to the patient's improvements emphasized the progression of the task demand. Moreover, the passive training mode might have been improved Compensatory Postural Adjustments (CPAs – Feedback mechanisms) by providing high-intensity and repetitive external destabilization. Note that, the stair climbing protocol might have further strengthened these effects enhancing the amplitude of the external perturbation on different planes (climbing up and down). Stair climbing up and down can be seen as a repeated sequence of balance challenges that rarely can be applied in patients with stroke because of the danger of the task. Negotiating stairs is a typical community ambulation requirement and the final goal of the rehabilitation plan, as the hallmark of complete recovery of mobility in the environment. Challenges of stair climbing, and level walking in the same rehabilitation session under different (active, passive and robot-assisted) training modalities allow to train specifically reactive, anticipatory and voluntary movement strategies (Emken and Reinkensmeyer, 2005; Horak, 2006; Lam et al., 2006; Gandolfi et al., 2014). Stair climbing is demanding from a neuromuscular (Nadeau et al., 2003) and metabolically point of view (Modai et al., 2015). Interestingly, only the robot-assisted group showed a clinically significant improvement in the distance walked over 6 min reaching the MCID value after treatment (34.53 m), as a proof of aerobic capacity/endurance improvements. According to the literature, stair climbing training can improve post-stroke aerobic capacity (Nadeau et al., 2003; Modai et al., 2015). In the context of conventional rehabilitation training, it is not possible to train postural reaction passively as well as intensive and repetitive stair climbing training.

An important issue that required discussion was the chronic stages of the illness. Literature has highlighted that in the chronic stage of stroke, the brain is relatively likely to support endogenous recovery. However, modifications in brain structures and function are still possible after specific interventions (Cramer, 2018). For patients with severe lower limb impairment, robotic training produces better outcomes than conventional training (Lo et al., 2017). Thus, results might be affected by the fact that enrollees had mild motor deficits, as measured at the enrollment. To date, no normative data on time to climb up and down stairs are available in the literature.

The strengths of the present study are the low drop-out rate confirming the feasibility of training in patients with chronic stroke. The comprehensive assessment of postural control using validated and psychometrically robust measures, and instrumental assessment are further strengths of this study (Tyson and Connell, 2009a,b). However, the use of clinical balance outcome measures specific to explore the underlying sensorimotor mechanisms contributing to the balance training effects (i.e., Mini Best Test) should have explored more specifically the training effects (Mancini and Horak, 2010). The study limitations are the lack of a real control group without any intervention, the use of functional balance assessment (i.e., BBS) instead of a system approach (i.e., Mini Best Test) and the lack of patient with more severe neurological impairment. Future studies should evaluate the training effects on participation and quality of life.

To conclude, RASCT is a feasible and valid approach to improve postural control and mobility in patients with chronic stroke. Robotics held promise and ensured to enrich rehabilitation when combined with sensory integration balance training. The advantages of combined training might be beneficial to overcome their limits. The present study is an effort to provide a reference for robot-assisted balance training protocols. Issues such as optimal dosage according to the degree of neurological disability need still to be addressed.

DATA AVAILABILITY STATEMENT

The datasets for this manuscript are not publicly available because CRRNC property. Requests to access the datasets should be directed to MG, marialuisa.gandolfi@univr.it.

ETHICS STATEMENT

The study was conducted according to the tenets of the Declaration of Helsinki, the guidelines for Good Clinical Practice, and the Consolidated Standards of Reporting Trials (CONSORT), approved by the local Ethics Committee (1442CESC). Clinical trial registration NCT03566901.

AUTHOR CONTRIBUTIONS

MG and ED have made substantial contributions to conception and design. EB and AP participated in the enrollment phase. NM and CG carried out the clinical assessment and instrumental assessments. MB and ED carried out the rehabilitation treatments. MG and NV participated in the statistical analysis and drafted the manuscript. MZ revised the statistical analysis. NS and AW participated in the manuscript revision process and gave the final approval of the version.

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REFERENCES

Bonan, I. V., Colle, F. M., Guichard, J. P., Vicaut, E., Eisenfisz, M., Ba Huy, P., et al. (2004). Reliance on visual information after stroke. part I: balance on dynamic posturography. *Arch. Phys. Med. Rehabil.* 85, 268–273. doi: 10.1016/j.apmr.2003.06.017

Bowden, M. G., Balasubramanian, C. K., Behrman, A. L., and Kautz, S. A. (2008). Validation of a speed-based classification system using quantitative measures of walking performance poststroke. *Neurorehabil. Neural. Repair.* 22, 672–675. doi: 10.1177/1545968308318837

Bruni, M. F., Melegari, C., De Cola, M. C., Bramanti, A., Bramanti, P., and Calabrò, R. S. (2018). What does best evidence tell us about robotic gait rehabilitation in stroke patients: a systematic review and meta-analysis. *J. Clin. Neurosci.* 48, 11–17. doi: 10.1016/j.jocn.2017.10.048

Cattaneo, D., Regola, A., and Meotti, M. (2006). Validity of six balance disorders scales in persons with multiple sclerosis. *Disabil. Rehabil.* 30, 789–795. doi: 10.1080/09638280500404289

Conesa, L., Costa, Ú, Morales, E., Edwards, D. J., Cortes, M., León, D., et al. (2012). An observational report of intensive robotic and manual gait training in sub-acute stroke. *J. Neuroeng. Rehabil.* 9:13. doi: 10.1186/1743-0003-9-13

Cramer, S. C. (2018). Treatments to promote neural repair after stroke. *J. Stroke* 20, 57–70. doi: 10.5853/jos.2017.02796

Da-Silva, P. J. G., Cagy, M., and Infantosi, A. F. C. (2016). Developing a dynamic virtual stimulation protocol to induce linear egomotion during orthostatic posture control test. *Res. Biomed. Eng.* 32, 273–282. doi: 10.1590/2446-4740.01616

Dias, D., Laíns, J., Pereira, A., Nunes, R., Caldas, J., Amaral, C., et al. (2007). Can we improve gait skills in chronic hemiplegics? A randomised control trial with gait trainer. *Eura. Medicophys.* 43, 499–504.

Donoghue, D., Physiotherapy Research and Older People group, and Stokes, E. K. (2009). How much change is true change? The minimum detectable change of the berg balance scale in elderly people. *J. Rehabil. Med.* 41, 343–346. doi: 10.2340/16501977-0337

Emken, J. L., and Reinkensmeyer, D. J. (2005). Robot-enhanced motor learning: accelerating internal model formation during locomotion by transient dynamic amplification. *IEEE Trans. Neural. Syst. Rehabil. Eng.* 13, 33–39. doi: 10.1109/tnsre.2004.843173

Flansbjer, U. B., Holmbäck, A. M., Downham, D., Patten, C., and Lexell, J. (2005). Reliability of gait performance tests in men and women with hemiparesis after stroke. *J. Rehabil. Med.* 37, 75–82. doi: 10.1080/16501970410017215

Gandolfi, M., Geroin, C., Picelli, A., Munari, D., Waldner, A., Tamburin, S., et al. (2014). Robot-assisted vs. sensory integration training in treating gait and balance dysfunctions in patients with multiple sclerosis: a randomized controlled trial. *Front. Hum. Neurosci.* 8:318. doi: 10.3389/fnhum.2014.00318

Gandolfi, M., Munari, D., Geroin, C., Gajofatto, A., Benedetti, M. D., Midiri, A., et al. (2015). Sensory integration balance training in patients with multiple sclerosis: a randomized, controlled trial. *Mult. Scler.* 21, 1453–1462. doi: 10.1177/1352458514562438

Geroin, C., Mazzoleni, S., Smania, N., Gandolfi, M., Bonaiuti, D., Gasperini, G., et al. (2013). Systematic review of outcome measures of walking training using electromechanical and robotic devices in patients with stroke. *J. Rehabil. Med.* 45, 987–996. doi: 10.2340/16501977-1234

Harries, N., Loeppky, J. A., Shaheen, S., Al-Jarrah, M., Molteni, F., Hutzler, Y., et al. (2015). A stair-climbing test for measuring mechanical efficiency of ambulation in adults with chronic stroke. *Disabil. Rehabil.* 37, 1004–1008. doi: 10.3109/09638288.2014.948131

Hesse, S., Tomelleri, C., Bardeleben, A., Werner, C., and Waldner, A. (2012). Robot-assisted practice of gait and stair climbing in non-ambulatory stroke patients. *JRRD* 4, 613–622.

Hesse, S., Waldner, A., and Tomelleri, C. (2010). Innovative gait robot for the repetitive practice of floor walking and stair climbing up and down in stroke patients. *J. Neuroeng. Rehabil.* 28:30. doi: 10.1186/1743-0003-7-30

Hidler, J., Nichols, D., Pelliccio, M., Brady, K., Campbell, D. D., Kahn, J. H., et al. (2009). Multicenter randomized clinical trial evaluating the effectiveness of the lokomat in subacute stroke. *Neurorehabil. Neural. Repair.* 23, 5–13. doi: 10.1177/1545968308326632

Hiengkaew, V., Jitaree, K., and Chaiyawat, P. (2012). Minimal detectable changes of the berg balance scale, fugl-meyer assessment scale, timed "up & go" test, gait speeds, and 2-minute walk test in individuals with chronic stroke with different degrees of ankle plantarflexor tone. *Arch. Phys. Med. Rehabil.* 93, 1201–1208. doi: 10.1016/j.apmr.2012.01.014

Horak, F. B. (2006). Postural orientation and equilibrium: what do we need to know about neural control of balance to prevent falls? *Age Ageing.* 35(Suppl. 2), ii7–ii11. doi: 10.1093/ageing/afl077

Horak, F. B., and Kuo, A. (2000). "Postural Adaptation for Altered Environments, Tasks and Intentions," in *Biomechanics and Neuronal Control of Posture and Movement*, eds J. M. Winters, and P. E. Crago (New York, NY: Springer), 267–281. doi: 10.1007/978-1-4612-2104-3_19

Hussein, S., Schmidt, H., Volkmar, M., Werner, C., Helmich, I., Piorko, F., et al. (2008). Muscle coordination in healthy subjects during floor walking and stair climbing in robot assisted gait training. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2008, 1961–1964. doi: 10.1109/IEMBS.2008.4649572

Jacobs, J. V., and Horak, F. B. (2007). Cortical control of postural responses. *J. Neural. Transm.* 114, 1339–1348. doi: 10.1007/s00702-007-0657-0

Jonsdottir, J., and Cattaneo, D. (2007). Reliability and validity of the dynamic gait index in persons with chronic stroke. *Arch. Phys. Med. Rehabil.* 88, 1410–1415. doi: 10.1016/j.apmr.2007.08.109

Lam, T., Anderschitz, M., and Dietz, V. (2006). Contribution of feedback and feedforward strategies to locomotor adaptations. *J. Neurophysiol.* 95, 766–773. doi: 10.1152/jn.00473.2005

Lo, K., Stephenson, M., and Lockwood, C. (2017). Effectiveness of robotic assisted rehabilitation for mobility and functional ability in adult stroke patients: a systematic review. *JBI Database System. Rev. Implement. Rep.* 15, 3049–3091. doi: 10.11124/JBISRIR-2017-003456

Mancini, M., and Horak, F. B. (2010). The relevance of clinical balance assessment tools to differentiate balance deficits. *Eur. J. Phys. Rehabil. Med.* 46, 239–248.

Mazzoleni, S., Focacci, A., Franceschini, M., Waldner, A., Spagnuolo, C., Battini, E., et al. (2017). Robot-assisted end-effector-based gait training in chronic stroke patients: a multicentric uncontrolled observational retrospective clinical study. *Neurorehabilitation* 40, 483–492. doi: 10.3233/NRE-161435

Mehrholz, J., Elsner, B., Werner, C., Kugler, J., and Pohl, M. (2013). Electromechanical-assisted training for walking after stroke. *Cochrane Database Syst. Rev.* 5:CD006185. doi: 10.1002/14651858

Modai, G., Sharon, B., Bar-Haim, S., and Hutzler, Y. (2015). Stair climbing test post-stroke: feasibility, convergent validity and metabolic, cardiac, and respiratory responses. *Top. Stroke Rehabil.* 22, 281–288. doi: 10.1179/1074935714Z.0000000021

Morone, G., Paolucci, S., Cherubini, A., De Angelis, D., Venturiero, V., Coiro, P., et al. (2017). Robot-assisted gait training for stroke patients: current state of the art and perspectives of robotics. *Neuropsychiatr. Dis. Treat.* 13, 1303–1311. doi: 10.2147/NDT.S114102

Nadeau, S., McFadyen, B. J., and Malouin, F. (2003). Frontal and sagittal plane analyses of the stair climbing task in healthy adults aged over 40 years: what are the challenges compared to level walking? *Clin. Biomech.* 18, 950–959. doi: 10.1016/s0268-0033(03)00179-7

Ng, M. F., Tong, R. K., and Li, L. S. (2008). A pilot study of randomized clinical controlled trial of gait training in subacute stroke patients with partial body-weight support electromechanical gait trainer and functional electrical stimulation: six-month follow-up. *Stroke* 39, 154–160. doi: 10.1161/strokeaha.107.495705

Oliveira, L. F., Simpson, D. M., and Nadal, J. (1996). Calculation of area of Stabilometric signals using principal component analysis. *Physiol. Meas.* 17, 305–312. doi: 10.1088/0967-3334/17/4/008

Pedroso, R. V., Coelho, F. G., Santos-Galduróz, R. F., Costa, J. L., Gobbi, S., and Stella, F. (2012). Balance, executive functions and falls in elderly with Alzheimer's disease (AD): a longitudinal study. *Arch. Gerontol. Geriatr.* 54, 348–351. doi: 10.1016/j.archger.2011.05.029

Peterka, R. J. (2002). Sensorimotor integration in human postural control. *J. Neurophysiol.* 88, 1097–1118. doi: 10.1152/jn.2002.88.3.1097

Peurala, S. H., Tarkka, I. M., Pitkänen, K., and Sivenius, J. (2005). The effectiveness of body weight-supported gait training and floor walking in patients with chronic stroke. *Arch. Phys. Med. Rehabil.* 86, 1557–1564. doi: 10.1016/j.apmr.2005.02.005

Pollock, A., Baer, G., Campbell, P., Choo, P. L., Forster, A., Morris, J., et al. (2014). Physical rehabilitation approaches for the recovery of function and mobility following stroke. *Cochrane Database Syst. Rev* 22:CD001920. doi: 10.1002/14651858.CD001920.pub3

Scoppa, F., Capra, R., Gallamini, M., and Shiffer, R. (2013). Clinical stabilometry standardization: basic definitions–acquisition interval–sampling frequency. *Gait Posture* 37, 290–292. doi: 10.1016/j.gaitpost.2012.07.009

Shumway-Cook, A., and Horak, F. B. (1986). Assessing the influence of sensory interaction of balance. Suggestion from the field. *Phys. Ther.* 66, 1548–1550. doi: 10.1093/ptj/66.10.1548

Shumway-Cook, A., and Woollacott, M. H. (2012). *Motor Control Translating Research into Clinical Practice*, 4th Ed. Philadelphia PA: Wolters Kluver Lippincott.

Smania, N., Picelli, A., Gandolfi, M., Fiaschi, A., and Tinazzi, M. (2008). Rehabilitation of sensorimotor integration deficits in balance impairment of patients with stroke hemiparesis: a before/after pilot study. *Neurol. Sci.* 29, 313–319. doi: 10.1007/s10072-008-0988-980

Stoller, O., Schindelholz, M., Bichsel, L., and Hunt, K. J. (2014). Cardiopulmonary responses to robotic end-effector-based walking and stair climbing. *Med. Eng. Phys.* 36, 425–431. doi: 10.1016/j.medengphy.2013.12.016

Stoller, O., Schindelholz, M., and Hunt, K. J. (2016). Robot-assisted end-effector-based stair climbing for cardiopulmonary exercise testing: feasibility, reliability, and repeatability. *PLoS One* 11:e0148932. doi: 10.1371/journal.pone.0148932

Sung, J., You, H., and Kim, H. Y. (2017). A review of robot-assisted gait training in stroke patients. *Brain Neurorehabil.* 10:e9. doi: 10.12786/bn.2017.10.e9

Swinnen, E., Beckwée, D., Meeusen, R., Baeyens, J. P., and Kerckhofs, E. (2014). Does robot-assisted gait rehabilitation improve balance in stroke patients? A systematic review. *Top. Stroke Rehabil.* 21, 87–100. doi: 10.1310/tsr2102-87

Tomelleri, C., Waldner, A., Werner, C., and Hesse, S. (2011). Adaptive locomotor training on an end-effector gait robot: evaluation of the ground reaction forces in different training conditions. *IEEE Int. Conf. Rehabil. Robot.* 2011, 5975492. doi: 10.1109/ICORR.2011.5975492

Tong, R. K., Ng, M. F., and Li, L. S. (2006). Effectiveness of gait training using an electromechanical gait trainer, with and without functional electric stimulation, in subacute stroke: a randomized controlled trial. *Arch. Phys. Med. Rehabil.* 87, 1298–1304. doi: 10.1016/j.apmr.2006.06.016

Tyson, S. F., and Connell, L. A. (2009a). How to measure balance in clinical practice. a systematic review of the psychometrics and clinical utility of measures of balance activity for neurological conditions. *Clin. Rehabil.* 23, 824–840. doi: 10.1177/0269215509335018

Tyson, S. F., and Connell, L. A. (2009b). The psychometric properties and clinical utility of measures of walking and mobility in neurological conditions: a systematic review. *Clin. Rehabil.* 23, 1018–1033. doi: 10.1177/0269215509339004

Westlake, K. P., and Patten, C. (2009). Pilot study of lokomat versus manual-assisted treadmill training for locomotor recovery post-stroke. *J. Neuroeng. Rehabil.* 6:18. doi: 10.1186/1743-0003-6-18

Wevers, L. E., Kwakkel, G., and van de Port, I. G. (2011). Is outdoor use of the six-minute walk test with a global positioning system in stroke patients' own neighbourhoods reproducible and valid? *J. Rehabil. Med.* 43, 1027–1031. doi: 10.2340/16501977-0881

Wong, C. K., Bishop, L., and Stein, J. (2012). A wearable robotic knee orthosis for gait training: a case-series of hemiparetic stroke survivors. *Prosthet. Orthot. Int.* 36, 113–120. doi: 10.1177/0309364611428235

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Brief Sensory Training Narrows the Temporal Binding Window and Enhances Long-Term Multimodal Speech Perception

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Our ability to integrate multiple sensory-based representations of our surrounding supplies us with a more holistic view of our world. There are many complex algorithms our nervous system uses to construct a coherent perception. An indicator to solve this 'binding problem' are the temporal characteristics with the specificity that environmental information has different propagation speeds (e.g., sound and electromagnetic waves) and sensory processing time and thus the temporal relationship of a stimulus pair derived from the same event must be flexibly adjusted by our brain. This tolerance can be conceptualized in the form of the cross-modal temporal binding window (TBW). Several studies showed the plasticity of the TBW and its importance concerning audio-visual illusions, synesthesia, as well as psychiatric disturbances. Using three audio-visual paradigms, we investigated the importance of length (short vs. long) as well as modality (uni- vs. multimodal) of a perceptual training aiming at reducing the TBW in a healthy population. We also investigated the influence of the TBW on speech intelligibility, where participants had to integrate auditory and visual speech information from a videotaped speaker. We showed that simple sensory trainings can change the TBW and are capable of optimizing speech perception at a very naturalistic level. While the training-length had no different effect on the malleability of the TBW, the multisensory trainings induced a significantly stronger narrowing of the TBW than their unisensory counterparts. Furthermore, a narrowing of the TBW was associated with a better performance in speech perception, meaning that participants showed a greater capacity for integrating informations from different sensory modalities in situations with one modality impaired. All effects persisted at least seven days. Our findings show the significance of multisensory temporal processing regarding ecologically valid measures and have important clinical implications for interventions that may be used to alleviate debilitating conditions (e.g., autism, schizophrenia), in which multisensory temporal function is shown to be impaired.

Keywords: multisensory integration, speech perception, word recognition, simultaneity judgment, temporal binding, double flash illusion

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INTRODUCTION

As Sumby and Pollack (1954) showed more than half a century ago, especially in situations with low signal-to-noise ratios, we utilize visual factors, such as the speakers' lips and facial movements, to maximize our speech intelligibility. This use of concurrent sensory information from different modalities is plausible on the level of perception and agrees with our everyday experience. On single-cell level Meredith and Stein (1985) were able to show that response from some neurons to stimuli from one specific sensory modality can be influenced by inputs from other modalities. This subpopulation of nerve cells is found in different brain regions that are involved in different functions, but they share substantial similarities (Stein and Wallace, 1996). These *multisensory* neurons have the ability to integrate information about multiple representations of our surrounding and thus supply us with a more holistic picture of what we call 'reality'. To this regard, it is not arbitrary which stimuli our nervous system will bind together to be different representations of the same 'object'. There are many different mechanisms our nervous system can use to determine which and in what manner stimuli are processed and integrated to a coherent perception of our world. One indicator for example is the spatial location of the stimuli, meaning that two stimuli are more likely to be attributed to the same source of origin, the more spatially proximate they are (Meredith and Stein, 1986). Analogously, the temporal characteristics are of important value with the specificity that environmental information has different propagation speeds (e.g., sound and electromagnetic waves) and sensory processing time and thus the temporal relationship of a stimulus pair derived from the same event must be adjusted by our multisensory system (Meredith et al., 1987). This tolerance for temporal co-occurrence of stimuli from different sensory modalities can be conceptualized in the form of the *multimodal temporal binding window (TBW)*. The average TBWs for typically developing adults range from 160 ms for simple audio-visual stimuli (flash/beep) to 250 ms for more complex stimuli like speech (Wallace and Stevenson, 2014).

A widened TBW was demonstrated to occur in autism (Mongillo et al., 2008; Russo et al., 2010; Donohue et al., 2012; de Boer-Schellekens et al., 2013; Woynaroski et al., 2013; Zmigrod et al., 2013; Stevenson et al., 2014a,b,c), developmental dyslexia (Bastien-Toniazzo et al., 2010; for a critical discussion about the specific disease mechanism see Hairston et al., 2005; Francisco et al., 2017) and schizophrenia (De Gelder et al., 2003, 2005; Foucher et al., 2007; Ross et al., 2007b; De Jong et al., 2009; Pearl et al., 2009; Hass et al., 2017; Zvyagintsev et al., 2017). Zmigrod and Zmigrod (2016) showed additionally that a narrower TBW was associated with a better performance in verbal and non-verbal problem-solving tasks in a healthy population.

Studies have shown the short- and longer-term malleability of the TBW. The former is mostly referred to as *recalibration* and can be induced by an exposure to asynchronous stimuli for a certain time, which results in a 'lag adaptation' in the sensory processing system (e.g., Fujisaki et al., 2004; Vroomen et al., 2004; Navarra et al., 2005; Hanson et al., 2008). To their own surprise Powers et al. (2009) induced a narrowing of the multimodal TBW. The changes persisted over a period of seven days. The authors used a perceptual learning paradigm in which participants were given feedback during a two-alternative forced choice audiovisual simultaneity judgement task (SJT) and could exclude the possibility of changes in cognitive biases as the underlying mechanism. Another study showed similar results using an unisensory training (Stevenson et al., 2013). In both studies, most of the effect was seen after one training session, raising the question whether there is the need for multiple iterations of the procedure. Using another paradigm as a criterion Fujisaki et al. (2004) demonstrated that the recalibration of the TBW altered the temporal tuning in an audio-visual illusion. Furthermore (2016) investigated the effects of a multisensory training on a sound-induced flash illusion (SIFI) and found a correlation between the degree of TBW narrowing and increases in sensitivity (d-prime), but no improvements in response bias. On the other hand (2012) as well as (2014) found a reduction of susceptibility to an audio-visual illusion with improvements in multisensory temporal processes. Surig et al. (2018) varied the task difference of a two-alternative forced-choice SJT (either at each participant's individual threshold or randomly chosen) and discovered faster improvements in the 'adaptive' condition regarding the processing speed of auditory inputs as well as the size of the ventriloquist effect. De Niear et al. (2016) altered the task difficulty of a SJT and observed that enhancements in temporal acuity could be optimized by employing audio-visual stimuli for which it is difficult to judge temporal synchrony. In another study, De Niear et al. (2018) showed that perceptual training was capable of enhancing temporal acuity for simple stimuli ('flashes' and 'beeps') as well as for more complex speech stimuli (the phoneme 'ba'). However, they failed to observe a generalization across levels of stimulus complexity.

The investigations carried out so far showed the plasticity of the TBW and its importance concerning audio-visual illusions, problem-solving tasks, dyslexia, as well as severe psychiatric disturbances with an early onset, like autism and schizophrenia (for an overview see Wallace and Stevenson, 2014). Thus, using specific training paradigms to influence the width of TBW could be interesting to reduce multisensory deficits of the previous mentioned populations.

In the current study we address different issues related to both the malleability of the TBW and the generalization effects of the trained sensory modality and also of the potential effects on speech perception. Based on the aforementioned investigations, we hypothesized that a long- and short-term training, regardless of their modality, should have no different effects on the narrowing of the TBW. An exploratory hypothesis was formulated concerning the role of the modality (uni- vs. multimodal training). Last, we assumed that a narrowing of the TBW should have a positive effect on speech intelligibility - more precisely in situations with low signal-to-noise ratios, where you would expect people to benefit from seeing the speakers' lips and facial movements.

MATERIALS AND METHODS

All procedures had been approved by the local Ethics Committee of the Hannover Medical School and have been performed in accordance with the ethical standards laid down in the Declaration of Helsinki. The participants gave written informed consent and participated for a small monetary compensation.

Participants

A total of 40 subjects (age $M = 22.60$ years, $SD = 3.50$, range = 20–37; females = 23) participated in the study. Five additional control subjects (age $M = 30.00$ years, $SD = 6.29$, range = 21–38; females = 2) were involved in a short experiment to control for possible effects resulting from repeated presentation of speech stimuli. Participants were mostly undergraduate and graduate students of biology and biochemistry as well as psychologists. Only subjects with normal or corrected to normal vision and normal hearing were included. No participant had a history of neurological or psychiatric diseases. In all cases German was the native language.

We randomized the subjects in four groups equal in size ($n = 10$). To control for possible differences regarding intelligence (especially the crystallized intelligence), a multiple-choice vocabulary intelligence test 'Mehrfachwahl-Wortschatz-Intelligenztest – MWT-B' (Lehrl, 2005) was used. The MWT-B consists of 37 items arranged by difficulty. Every item consists of one word as defined by the German dictionary as well as four fictitious words. Participants have to indicate the 'real' word by underlining it. The test took about 5 min to complete.

Stimuli and Design

The study included analysis of four experimental groups in 2 × 2 design with factors training-length (short vs. long) and training-modality (unisensory vs. multisensory). For the training we used only visual (unimodal) and audiovisual (multisensory) modifications of the SJT. The training length varied between only one training unit and three units on three consecutive days. To assess the training effects, we used three well-established audio-visual paradigms, namely the SJT, the Double Flash Illusion Task (DFIT) and the Word Recognition Task (WRT). We collected the data before the first training (T0, first day), after the training (T1, first respective third day) and seven days after (T2). Between each measurement/training, participants had the chance to rest for maximum 5 min. During experiments, the investigator observed the behavior of the subject via video stream, beyond that there was no interaction between subjects and the examiner. Participants were advised to make a decision as fast as possible and otherwise to guess the right decision. The paradigms as well as the timeline of the experimental procedure are depicted in **Figures 1**, **2** and described in more detail beyond.

SJT

To assess the audio-visual temporal processing, we used a task in which participants judge whether a visual and an auditory stimulus were presented synchronous or asynchronous by pressing appropriate button on a response device. Visual stimuli consist of a white ring (6 deg. of visual angle) on a black background presented for one refresh cycle (8.3 ms) in the center of the visual field. The auditory stimulus was an 1850 HZ tone presented for 8 ms at stimulus onset asynchronies (SOAs) in relation to the visual stimulus onset ranging from 0 to 250 ms at 25 ms intervals constituting one synchronous and ten asynchronous SOA conditions. We used only visual-leading conditions. A total of 165 trials in pseudorandom order made up the task resulting in 15 trials per SOA condition. Between the stimuli presentations a white fixation cross (2 deg. of visual angle) on a black background was presented in the middle of the visual field for 1000 ms. The whole paradigm duration was 189 s plus the variable time for the subjects' response. Subjects indicated perceiving the stimuli as synchronous or asynchronous by pressing either the button of the left or the right response device.

DFIT

The cross-modal double flash illusion, also called the SIFI, occurs, when two short auditory stimuli (inducers) are presented in quick succession accompanied by a single visual flash (target) and these auditory stimuli are perceptually grouped by being attributed to the same source of origin (Roseboom et al., 2013). In this case, the illusionary perception of an additional visual flash (fission illusion) manifests itself (Shams et al., 2000, 2002). During the whole experiment a white fixation cross (2 deg. of visual angle) on a black background was presented in the middle of the visual field. To induce the illusion, a white flash (4 deg. of visual angle) on a black background was presented in the peripheral visual field (4 deg. beyond the center of the fixation cross) accompanied by two sound beeps (1850 Hz, 8 ms in duration) with SOAs ranging from 25 to 250 ms at 25 ms intervals. We decided to present the flashes in the peripheral visual field because is known that this results in the strongest induction of the fission illusion (Shams et al., 2002). A total of 170 trials in pseudorandom order made up the task resulting in 15 trials per SOA condition with an additional 20 trials consisting of two control conditions with presentation of 'one flash, one beep' as well as 'two flashes, no beep'. Subjects indicated perceiving one or two flashes by pressing either the button of the left or the right response device. The whole paradigm duration was 216 s plus the variable time for the subjects' response.

WRT

We used the same WRT as Sinke et al. (2014). This task contains german high frequency disyllabic lemmas derived from the CELEX-Database (Baayen et al., 1995) with a Mannheim frequency 1.000.000 (MannMln). The MannMln frequency indicates the down scaled occurrence of the selected word per one million words taken from the Mannheim 6.0-million-word corpus. The videotaped stimuli were spoken by a male native speaker of german with linguistic experience. Each stimulus had a duration of 2-s showing the frontal view of the speaker's face. For the auditory-alone condition, the video stream was replaced with a frozen image of the speaker's face. The audio-visual condition comprised stimuli with synchronous auditory and visual speech information. In addition, the audio stream of both conditions was mixed with white noise of either 0 or 12 dB

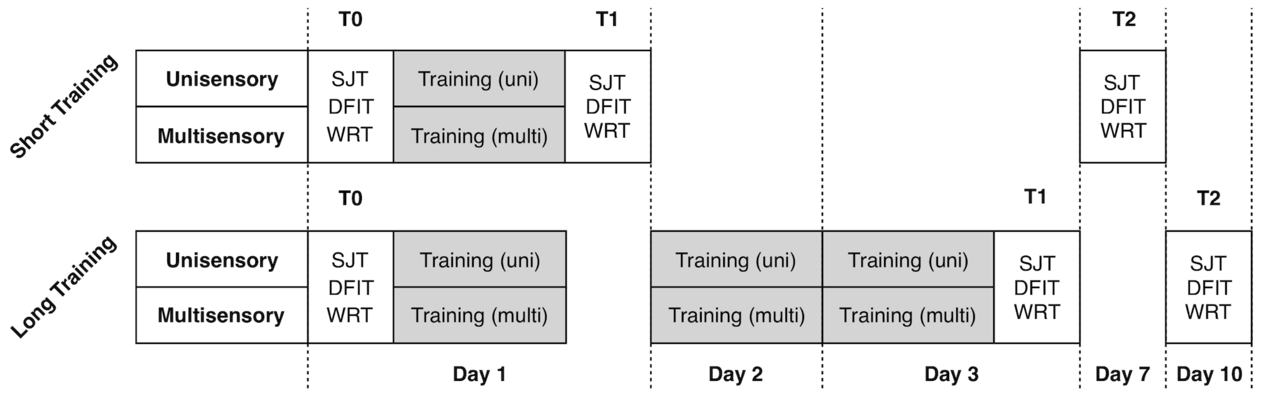

FIGURE 1 | Timeline of the experimental procedure. 40 participants were randomly assigned to the four experimental training conditions.

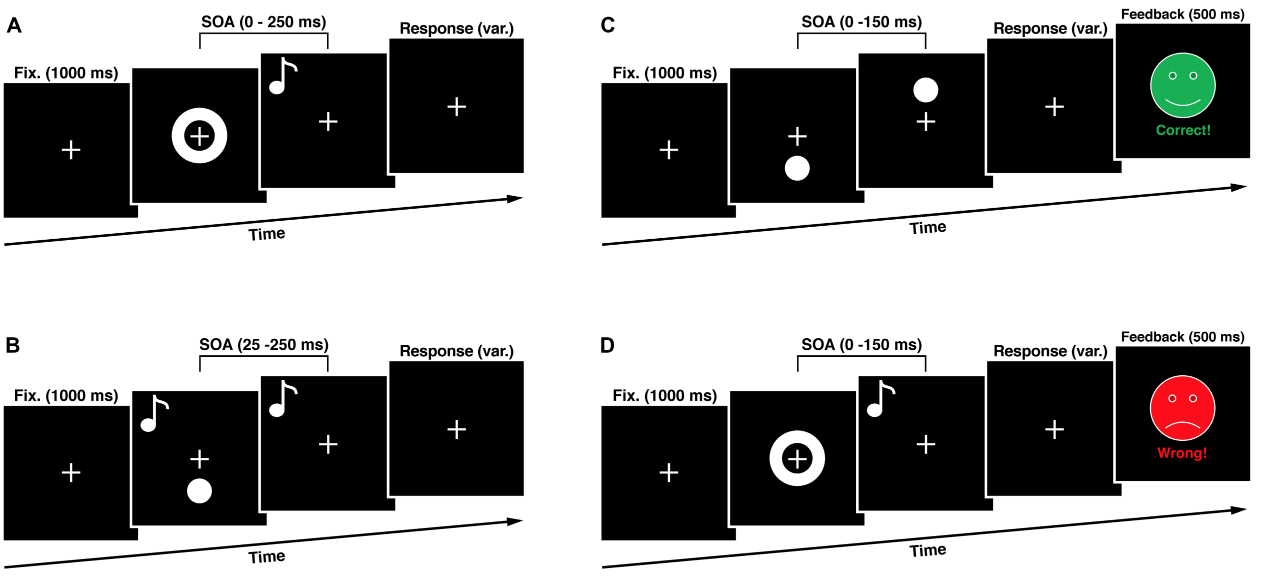

FIGURE 2 | Experimental Sequences. **(A)** In the simultaneity judgment task (SJT) participants had to judge whether an audio-visual stimulus pair was presented synchronous or asynchronous. **(B)** In the double flash illusion task (DFIT) participants indicated perceiving one or two visual flashes. **(C)** The unisensory training consisted of a visual simultaneity judgment task with feedback. **(D)** The multisensory training consisted of an audio-visual simultaneity judgment task with feedback. SOA, stimulus onset asynchrony.

resulting in a total of four conditions (0 dB audio, 12 dB audio, 0 dB audio-visual and 12 dB audio-visual). Twenty words were used for each of the four WRT-conditions resulting in a total of 80 stimuli. All stimuli were presented in a pseudorandom order. The experimental procedure was designed according to Ross et al. (2007a). After the presentation of each stimulus the subjects were asked to report which word they understood. If a word was not clearly understood, they were instructed to guess the word. Otherwise they should report 'I did not understand anything'. The answer was recorded by the experimenter. Any answer different from the presented stimulus was counted as false, meaning only whole-word recognitions was counted as correct. When the answer was given, the experimenter triggered the next trial which began with a fixation cross 1 s of duration followed by the next stimulus.

Multisensory Training

The multisensory training task was designed according to Powers et al. (2009) and differed in one key aspect from the SJT used in our study, as it contained a feedback. The subject was presented with either the phrase "Correct!" paired with a happy green face, or "Incorrect" paired with a sad red face corresponding to the correctness of their choice. These faces (8 deg. of visual angle) were presented in the center of the visual field for 500 ms after the response of the subject. For the training only SOAs between 0 and 150 ms, in 25 ms intervals, were used. In addition, the veridical simultaneous condition (SOA 0 ms) had a 6:1 ratio to any of the other six non-simultaneous conditions creating an equal likelihood of simultaneous/non-simultaneous conditions and thus minimizing concerns about response bias. There were 120 trials presented pseudorandomly in the training phase (60 times SOA 0 ms condition and 10 times each other SOA condition). We only used visual-leading conditions for two reasons. On the one hand, we tried to keep the cognitive load of our subjects as low as possible to ensure enough concentration for the whole experiment. Therefore we decided to use a small amount of trials to shorten the experimental tasks duration. On the other hand, there is growing evidence that visual- and auditory-leading stimulus compositions are based on different multisensory sampling mechanisms. The auditory-leading condition presents itself as non-malleable and the effects of the visual-leading condition seem to be non-transferable to it (Cecere et al., 2016), which was also demonstrated by Powers et al. (2009) and Stevenson et al. (2013). A plausible explanation for this asymmetry is the fact that, because of the substantial higher transmission speeds of electromagnetic waves, auditory-leading conditions never occur in nature and thus never had to be flexibly specified by the nervous system.

Unisensory Training

Our unisensory training was designed with the same timing structure as the multisensory training in this study but contained only visual stimuli (visual flashes), which had to be judged regarding their synchronicity. Visual stimuli (4 deg. of visual angle) were presented 4 deg. of visual angel underneath and above the fixation mark. There were 120 trials presented pseudorandomly in the training phase (60 times SOA 0 ms condition and 10 times each other SOA condition).

Considering the findings of Powers et al. (2009) as well as Stevenson et al. (2013), who demonstrated the necessity of feedback for inducing long-lasting changes in the TBW, we decided to use feedback for our subjects regarding the synchronicity of the stimuli within the SJT training units. Both, the unisensory and multisensory training had duration of approximately four to 5 min depending on the response times of the participants.

All stimuli were presented binaural via loudspeakers placed beside of a high refresh rate monitor (Sony Multiscan G520, 120 Hz) placed in a quiet room approximately 60 cm in front of the subjects. All auditory stimuli were presented at individual subjective level of good audibility. Presentation software (Neurobehavioral Systems, Inc., Albany, CA, United States, version 14.9) was used to control all experiments and collect data.

Data Analysis

The effects of the four training conditions on the SJT, the DFIT and the WRT were examined using several univariate repeated measures analyses of variance (ANOVAs) followed by *post hoc* t-tests with correction for multiple comparisons (Bonferroni). To investigate possible repetition-effects of the WRT, we used the non-parametric Friedman-Test. If parametric tests were used, they met the assumptions. In cases, were the assumption of sphericity was not met (i.e., significant Mauchly Test), depending on the magnitude of ε, we used either the Greenhouse-Geisser ($\varepsilon < 0.75$) or the Huynh-Feldt ($\varepsilon > 0.75$) correction according to (Girden, 1992). The SJT was used to estimate a TBW. This window was defined to represent the x-value of the intersection between the equation $y = 0.75$ (75% frequency of simultaneity judgment) and a sigmoidal function (Eq. I) generated by Matlab R2017b (MathWorks, Natick, MA, United States) to fit the empirical data (see also Powers et al., 2009; Hillock-Dunn and Wallace, 2012).

$$sig(x) = \frac{1}{1 + e^{\frac{x+\alpha}{\beta}}} \tag{1}$$

RESULTS

Baseline

To rule out the possibility of effects driven by mechanisms (e.g., floor or ceiling effects or insufficient randomization) other than implied by our hypotheses, we tested whether the randomization procedure created comparable groups regarding all dependent measures. Several one-way ANOVAs were computed showing no significant differences at the first point of measurement for all of the 11 SJT-, 10 DFIT- und 4 WRT-Conditions (for full statistics, we refer to our **Supplementary Material**). On average, there were no significant differences regarding age ($F_{(3,\ 36)} = 0.375$, $p = 0.771$, $\eta^2{}_p = 0.03$), gender ($\chi^2 = 4.289$, $p = 0.232$, $\eta^2{}_p = 0.04$) as well as performance in the MWT-B ($F_{(3,\ 36)} = 1.845$, $p = 0.156$, $\eta^2{}_p = 0.13$) across the four experimental groups. There was no attrition bias and no non-compliant participant behavior ensuring treatment integrity throughout the whole experiment. Furthermore, there was no data missing.

Simultaneity Judgment Task

Using the above-mentioned equation, we derived TBW's for each participant although we did not use them for the assessment of a potential training effect due to a strongly varying quality of goodness of fit (adjusted R-square ranging from 0.1 to 0.9). Instead, we used SOA's to track increases in performance in the SJT and report TBW's online at group-level, where they showed to have a high goodness of fit (adjusted R-square ranging from 0.92 to 0.98).

To measure the effect of the training on the performance in the SJT, we conducted an univariate repeated measures analysis of variance with point of measurement and SOA as within-subjects factors and training-modality and training-length as between-subjects factors.

As expected, SOA had a significant main effect on SJT-performance ($F_{(1.939,\ 69.804)} = 115.625$, $p < 0.001$, $\eta^2{}_p = 0.76$) meaning that subjects had higher accuracies in simultaneity judgments as SOA increased. Also point of measurement had a significant main effect ($F_{(1.763,\ 63.456)} = 52.684$, $p < 0.001$, $\eta^2{}_p = 0.59$), with accuracies improving after training. Furthermore, training-modality revealed a main effect ($F_{(1,\ 36)} = 10.731$, $p = 0.002$, $\eta^2{}_p = 0.23$), with higher accuracies in simultaneity judgments in the multisensory trainings. Training-length, however, remained insignificant ($F_{(1,\ 36)} = 1.333$, $p = 0.256$, $\eta^2{}_p = 0.04$), thus all following calculations were collapsed across the factor training-length. Looking at the first-order-interaction effects, point of measurement and training-modality showed a significant effect ($F_{(1.763,\ 63.456)} = 14.666$, $p < 0.001$, $\eta^2{}_p = 0.29$) with higher accuracies in the multisensory trainings after the training. Also there was a significant effect between SOA and training-modality ($F_{(1.939,\ 69.804)}$ = 4.250, p = 0.019, η^2_p = 0.11) with higher accuracies in the multisensory trainings with increasing SOA's. Also there was a significant effect between point of measurement and SOA ($F_{(11.028,\ 369.992)}$ = 7.135, $p < 0.001$, η^2_p = 0.17) with higher accuracies after the training with increasing SOA's.

Taking point of measurement, SOA and training-modality into consideration, a significant second-order interaction ($F_{(11.028,\ 369.992)}$ = 2.263, p = 0.002, η^2_p = 0.07) indicated performance benefits in simultaneity judgments after the multisensory trainings at higher SOA's. A closer examination revealed that the multisensory training contributed consistently to a better performance between pre-training (T0) and post-training (T1) as well as T0 and follow up (T2) across all SOAs > 25 ms, but not between T1 and T2 denoting a stable effect over the course of seven days. The improvements contributed to a decrease of the TBW's in the multisensory group from 151.2 ms (T0) to 65.5 ms (T1), respectively 66.1 ms (T2) compared to only a slight reduction from 162.3 ms (T0) to 130.2 ms (T1) and 118.0 ms (T2) in the unisensory group (**Figure 3**).

On the other hand, the unisensory training revealed only one significant effect between T1 and T2 at SOA = 25 ms. To analyze the possible generalization effect from the unisensory to multisensory modality, we examined the data from the trainings itself. First, we compared the accuracy of judgments between the three training sessions regarding training-modality. Therefore, only the both long trainings with more than one training session were included (N = 20). For simplicity, we collapsed all SOA-conditions creating an indicator for the overall-performance. A univariate repeated measures analysis of variance with point of measurement as a within-subjects factor and training-modality as a between-subjects factor revealed a main effect of point of measurement ($F_{(1.166,\ 20.995)}$ = 13.408, $p < 0.001$, η^2_p = 0.43) and training-modality ($F_{(1,\ 18)}$ = 10.988, p = 0.004, η^2_p = 0.38) as well as a significant interaction effect of both factors ($F_{(1.166,\ 20.995)}$ = 5.550, p = 0.024, η^2_p = 0.24). A closer look showed that between-training-improvements took place between the first and second ($T_{(19)}$ = 3.167, p = 0.005, d = 71) as well as between the first and third ($T_{(19)}$ = 3.644, p = 0.002, d = 0.81), but not between the second and third training session ($T_{(19)}$ = −0.130, p = 0.898, d = 0.03). Furthermore, these improvements were only noticeable after the multisensory training. We cross-checked these results by comparing the overall-performance between the first vs. the second half of the training at T0. Therefore, all subjects could be included. A univariate repeated measures analysis of variance with the first and second half of the training data at T0 as a within-subjects factor as well as training-modality and training-length as between-subjects factors revealed more accurate judgments in the second half of the training ($F_{(1,\ 36)}$ = 72.552, $p < 0.001$, η^2_p = 0.67) as well as a higher performance in the multisensory trainings ($F_{(1,\ 36)}$ = 9.951, p = 0.003, η^2_p = 0.22). Training-length ($F_{(1,\ 36)}$ = 0.142, p = 0.708, $\eta^2_p < 0.01$) as well as the interaction of training-modality and training-length failed to reach significance ($F_{(1,\ 36)}$ = 0.946, p = 0.337, η^2_p = 0.03). While the interaction of the first and second half of the training and training-length ($F_{(1,\ 36)}$ = 0.130, p = 0.720, $\eta^2_p < 0.01$) as well as the second-order interaction of all three factors remained insignificant ($F_{(1,\ 36)}$ = 0.321, p = 0.575, η^2_p = 0.01), the interaction of the first and second half of the training and training-modality showed a significant effect ($F_{(1,\ 36)}$ = 44.259, $p < 0.001$, η^2_p = 0.55), meaning, there were within-session-improvements only in the multisensory training.

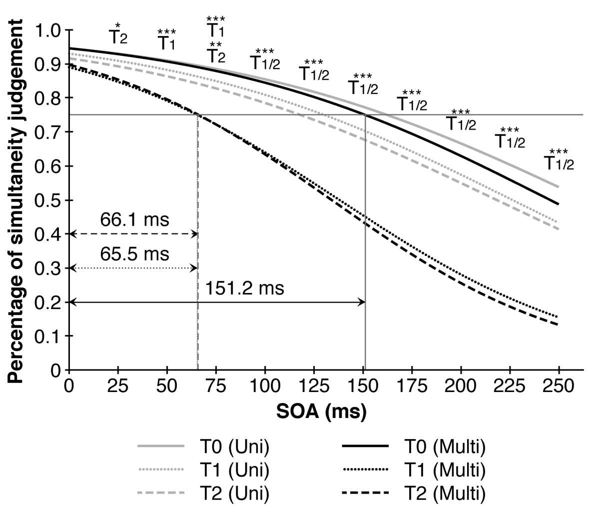

FIGURE 3 | Multisensory trainings narrows audio-visual temporal binding window in comparison to unisensory training. Depicted are significant differences in multisensory trainings between different points of measurement in reference to the 1th point of measurement (T0) resulting in a substantial decrease in the temporal binding window from 151.2 ms (T0) to 65.5 ms (T1) resp. 66.1 ms (T2). Black lines represent multisensory trainings, gray lines represent unisensory trainings. SOA = Stimulus onset asynchrony. *$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

Double Flash Illusion Task

An univariate repeated measures analysis of variance with point of measurement and SOA as within-subjects factors and training-modality and training-length as between-subjects factors revealed a main effect of SOA ($F_{(1.713,\ 66.666)}$ = 51.394, $p < 0.001$, η^2_p = 0.59), an first-order interaction effect of SOA and point of measurement ($F_{(6.929,\ 249.126)}$ = 3.551, p = 0.001, η^2_p = 0.09) as well as a second-order interaction of SOA, training-length and training-modality ($F_{(1.713,\ 61.666)}$ = 3.691, p = 0.037, η^2_p = 0.09). The main effect of SOA points to a less frequent occurrence of the double-flash illusion as SOA increases, which was expected. The significant interaction of SOA and point of measurement revealed a total of four significant *post hoc* tests, but without any consistent pattern whatsoever: there was a significant decrease of illusions between T0 and T2 at SOA = 25 ($T_{(39)}$ = 2.828, p = 0.025, d = 0.45), between T0 and T1 at SOA = 75 ms ($T_{(39)}$ = 2.566, p = 0.029, d = 0.41), between T0 and T1 at SOA = 125 ms ($T_{(39)}$ = 2.802, p = 0.022, d = 0.44) as well as a significant increase in illusion between T1 and T2 also at SOA = 125 ms ($T_{(39)}$ = −3.189, p = 0.009, d = 0.50). Similarly, this was the case for the three-way interaction with only one significant *post hoc* test ($T_{(18)}$ = −1.524, p = 0.046, d = 0.72). The results of the DFIT unraveled by training-modality are depicted in **Figure 4**.

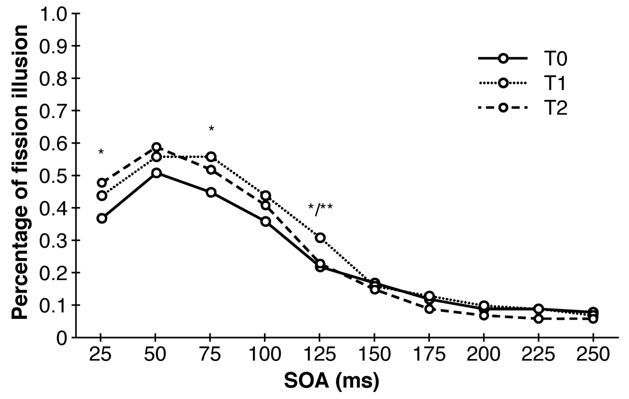

FIGURE 4 | Sensory trainings have no consistent effects on the occurrence of the double-flash illusion. Depicted are significant differences between different points of measurements collapsed across training-modality and training-length. SOA, stimulus onset asynchrony. $^{*}p < 0.05$. $^{**}p < 0.01$.

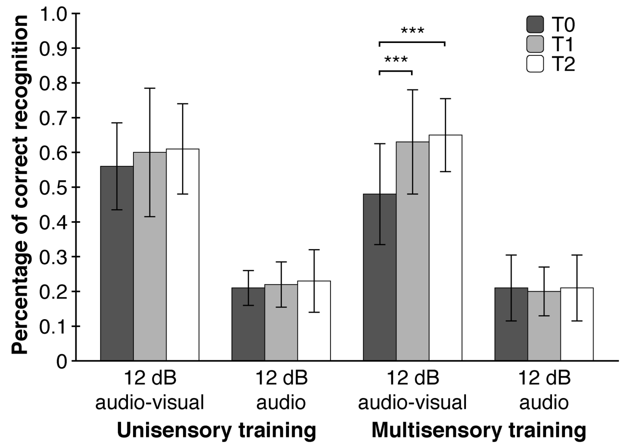

FIGURE 5 | Multisensory trainings contribute to an increased performance in word recognition in situations with a low signal-to-noise ratio (12 dB audio-visual). Depicted are two of the four WRT conditions of interest. Error Bars indicate SDs. $^{***}p < 0.001$.

Word Recognition Task

To measure the effect of the training on the performance in the WRT, we conducted an univariate repeated measures analysis of variance with point of measurement and WRT-condition as within-subjects factors and training-modality and training-length as between-subjects factors.

As hypothesized, point of measurement had a significant main effect on WRT-performance ($F_{(1.897,\ 68.295)} = 12.453$, $p < 0.001$, $\eta^2_p = 0.26$) meaning that subjects had higher accuracies in word recognition after the training. As expected, subjects differed in WRT-performance between the four WRT-conditions ($F_{(1.328,\ 47.814)} = 459.216$, $p < 0.001$, $\eta^2_p = 0.93$). A significant interaction effect of point of measurement and WRT-Condition ($F_{(3.617,\ 130.215)} = 7.118$, $p = 0.002$, $\eta^2_p = 0.17$) showed that the effect of the training was apparent only in the ’12 db audio-visual’ – condition with significant improvements between T0 and T1 ($T_{(39)} = -3.968$, $p < 0.001$, $d = 0.63$) as well as T0 and T2 ($T_{(39)} = -4.773$, $p < 0.001$, $d = 0.75$), but not between T1 and T2 ($T_{(39)} = -0.834$, $p = 0.409$, $d = 0.13$). A second-order interaction effect between point of measurement, WRT-condition and training-modality ($F_{(3.617,\ 130.215)} = 3.560$, $p = 0.034$, $\eta^2_p = 0.09$), implicating a moderating role of training-modality, showed significant improvements in word recognition between T0 and T1 ($T_{(19)} = -4.199$, $p < 0.001$, $d = 0.94$) as well as T0 and T2 ($T_{(19)} = -5.403$, $p < 0.001$, $d = 1.21$), but not between T1 and T2 ($T_{(19)} = -0.873$, $p = 0.394$, $d = 0.20$). These improvements took place only in the ’12 db audio-visual’ – condition and only after the multisensory trainings. Furthermore, we tested whether each of the four WRT-conditions differed with respect to training-length and training-modality. We assumed a higher WRT-performance only in the ’12 dB - audio-visual’ - condition due to the just mentioned significant training effect and a lack of baseline-differences at T0. To our surprise, the four WRT-conditions did not show differences regarding training-length and training-modality at T1 and T2. A closer examination of the WRT-data showed, though not significant, a substantial lower baseline-level ($\eta^2_p = 0.11$) in the ’12 dB audio-visual’ – condition in the multisensory group compared to the unisensory group at T0 (**Figure 5**).

To rule out the possibility that differences in performance are based solely on the repetition of the WRT, five additional participants accomplished the WRT three times without any training. A Friedman-Test for dependent measures revealed no significant differences in the ’12 dB audio-visual condition’ across the three points of measurement ($\chi^2_{(2)} = 0.471$, $p = 0.790$, $W = 0.05$). Additionally, we compared the first and second half of the ‘12 dB audio-visual’ data at T0. Should there be a repetition effect, which manifests itself in a higher WRT-performance at post-training, than this should also be the case when comparing the first and second half within the pre-training data. An univariate repeated measures analysis of variance with the first and second half of the ‘12 dB audio-visual’ WRT-data from pre-training as a within-subjects factor and training-modality and training-length as between-subjects factors failed to reach significance for the main effect of WRT ($F_{(1,\ 36)} = 0.000$, $p > 0.999$, $\eta^2_p = 0.000$) as well as all interaction effects (see **Supplementary Material**).

DISCUSSION

In the current study, we demonstrated that a short multisensory training can change the cross-modal TBW and is capable of enhancing speech perception at a very naturalistic level over the course of at least 7 days. Based on previous research results we hypothesized, trainings longer in duration should have no additional effect on TBW. Indeed, both long trainings showed no performance advantages over the short trainings, which is represented by insignificant main and interaction effects with the factor length. This finding stands in line with Powers et al. (2009), who observed significant effects after a single day of training with no incremental performance benefit with repetition. While our multisensory trainings induced a strong narrowing of the TBW, the unisensory trainings failed to do so. This contradicts the results of Stevenson et al. (2013) although we had a higher statistical power due to a higher number of subjects completing the training ($n = 14$ vs. $n = 20$ in our study). One major difference between both studies concerns the use of different paradigms: In our study, participants had to judge the synchronicity of two stimuli. Stevenson et al. used a temporal order judgment task (TOJT), where participants were instructed to indicate which of the two presented visual stimuli appeared first. Like Schneider and Bavelier (2003) pointed out, the TOJT and SJT are prone to different response biases. In our training, subjects may anticipate stimuli to be more likely synchronous just because of the instruction to judge the synchronicity. In the TOJT, participants may believe that stimuli never appear simultaneous because the temporal order has to be judged. Another difference concerns the selection of SOAs: The range of SOAs in the study of Stevenson et al. was smaller (−37,5 to 37,5 ms compared to 0 to 250 ms in our study), which might have led to a stronger training effect, because most of our SOA's could have been out of range for contributing to a training effect in a visual SJT. Another difference concerns the number of trials: In our study, a total number 120 trials were presented compared to 780 trials in the study of Stevenson et al. (2013), which might have led to a much weaker training effect in our study. Despite the same number of trials, this obviously was not the case for the multisensory training, which might point to a facilitation effect due to bimodal information processing.

The main finding of our study was the generalization effect of the multisensory training on speech perception. We assumed that a narrowing of the TBW should have a positive effect on speech intelligibility in situations with a low signal-to-noise ratio, where informations from an additional modality enhances comprehensibility and therefore an optimized multimodal processing is advantageous. Indeed, a narrowing of the TBW after multisensory trainings was associated with a 33.9% increase in WRT-performance in the '12 dB audio-visual' – condition compared to an 8.1% increase in WRT-performance after unisensory trainings (collapsed across the second and third point of measurement). Interestingly, WRT-performance in the '12 dB audio-visual' – condition did not differ between uni- and multi-sensory trainings at T1 and T2. A closer examination of the WRT-data showed, though not significant, a substantial lower baseline-level ($\eta^2_p = 0.11$) in the '12 dB audio-visual' – condition in the multisensory group compared to the unisensory group at T0. This non-significant lower baseline combined with an also non-significant difference in WRT-performance in the '12 dB audio-visual' – condition at T1 and T2 between the different training-modalities could 'enable' a statistically significant training-effect to emerge. The lower baseline limits the interpretability of the training effect, although the difference in correct word recognition between the unisensory (55.5% correct recognitions) and multisensory group (47,5% correct recognitions) at T0 seems to be too small for a floor effect of such a size to arise. The fact that the significant training effect in the multisensory group is associated with an improvement in SJT supports its validity.

Despite the narrowing of the TBW, we failed to observe an effect on the DFIT, which is in line with the investigation of Powers et al. (2016) but contradicts the results of Stevenson et al. (2012) as well as Setti et al. (2014). An explanation for the effect of a narrowed TBW on speech perception and its absence on the DFIT concerns possible differences in signal processing mechanism underlying the WRT and DFIT. In the WRT, the presentation of visual stimuli (lip movements) influences the processing of auditory information (speech). In the DFIT (especially in the fission illusion) sound stimuli impacts visual perception.

Our findings have imported clinical implications regarding severe psychiatric conditions like autism and schizophrenia, where a widened TBW was demonstrated to occur (for example Stevenson et al., 2014c; Hass et al., 2017). Because even healthy subjects benefit from our training regarding speech intelligibility, one can assume that subjects with a chronically widened TBW would do so even more. Patients with schizophrenia show a variety of deficits in the processing of multisensory information, such as a smaller facilitation effect of lip reading on auditory speech information (De Gelder et al., 2003; Ross et al., 2007b). This 'perceptual incoherence' may give rise to incoherent self-experiences including depersonalization, ambivalence, diminished sense of agency and 'loosening of associations' between thoughts (Postmes et al., 2014). Our short multisensory training could be used to address this perceptual incoherence in people with schizophrenia by reducing the TBW. On the other hand, subjects with autism spectrum disorder (ASD) also show audio-visual integration deficits (Feldman et al., 2018). Worse performance in this population is more pronounced in younger subjects and is correlated with autism symptom severity. But deficits in audio-visual speech perception seem to disappear in early adolescence (Foxe et al., 2015). Thus, multisensory integration problems may be directly related to disturbed or prolonged maturation of the sensory system in ASD (Brandwein et al., 2015; Beker et al., 2018). In these cases, multisensory training as used in our study and applied to young subjects with ASD may influence in positive manner performance of audio-visual integration and contribute to reduction of symptom severity in this population. Another open question concerns the generalizability of our findings to younger as well as older populations, where multisensory deficits are occurring.

Our study had several important restrictions, limiting its conclusiveness. The SOA's used in our unisensory training could have been out of range for a substantial training effect to arise, thus underestimating the impact of the unisensory training. Taking the results of De Niear et al. (2016) into account, our training procedures could have been optimized by employing an adaptive algorithm that automatically selects SOA's based on every participant's unique threshold. This approach could have led to smaller SOA's in our unisensory training and therefore ultimately to a significant effect. Another important limitation relates to the SIFI. We only assessed the fission illusion neglecting the possible effect of the TBW on the fusion illusion, which should be considered more differentiated. Another important issue is related to a not optimal goodness of fit deriving the TBW's on an individual level from our SJT. Our findings would have a stronger explanatory power, if we had observed a significant correlation between the degree of TBW-narrowing and improvement in the WRT.

Future research should try to replicate the generalization effect of simple audio-visual trainings on speech perception with individually adopted SOA's, or at least using significant reduced SOA distances. This appears to be relevant because both variables could be related in a non-linear fashion. This notion is supported by an investigation of Sinke et al. (2014), where the authors observed a reduced speech perception in subjects with synesthesia, which are known to have a narrower TBW then the general population. This would imply the existence of an 'optimal' TBW with deviations in both ways leading to detrimental effects regarding speech intelligibility, constituting an inverted U-shape.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Hannover Medical School. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MZ performed the measurements, participated in the statistical analysis and interpretation of the data, and drafted the manuscript. CF and HS participated in the coordination of the study and performed the measurement. CS participated in the coordination of the study, study design, and statistical analysis. AM and SB participated in the interpretation of the data. TM participated in the study design and interpretation of the data. GS conceived the study, participated in the study design and coordination, and statistical analysis and interpretation of the data, and drafted the manuscript. All authors read and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

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REFERENCES

Baayen, R. H., Piepenbrock, R., and Gulikers, L. (1995). *The CELEX lexical database [CD-ROM]*. Philadelphia: University of Pennsylvania.

Bastien-Toniazzo, M., Stroumza, A., and Cavé, C. (2010). Audio-visual perception and integration in developmental dyslexia: an exploratory study using the mcgurk effect. *Curr. Psychol. Lett. Behav. Brain Cogn.* 25, 1–15.

Beker, S., Foxe, J. J., and Molholm, S. (2018). Ripe for solution: delayed development of multisensory processing in autism and its remediation. *Neurosci. Biobehav. Rev.* 84, 182–192. doi: 10.1016/j.neubiorev.2017.11.008

Brandwein, A. B., Foxe, J. J., Butler, J. S., Frey, H. P., Bates, J. C., Shulman, L. H., et al. (2015). Neurophysiological indices of atypical auditory processing and multisensory integration are associated with symptom severity in autism. *J. Autism Dev. Disord.* 45, 230–244. doi: 10.1007/s10803-014-2212-9

Cecere, R., Gross, J., and Thut, G. (2016). Behavioural evidence for separate mechanisms of audiovisual temporal binding as a function of leading sensory modality. *Eur. J. Neurosci.* 43, 1561–1568. doi: 10.1111/ejn.13242

de Boer-Schellekens, L., Eussen, M., and Vroomen, J. (2013). Diminished sensitivity of audiovisual temporal order in autism spectrum disorder. *Front. Integr. Neurosci.* 7:8. doi: 10.3389/fnint.2013.00008

De Gelder, B., Vroomen, J., Annen, L., Masthof, E., and Hodiamont, P. (2003). Audio-visual integration in schizophrenia. *Schizophr. Res.* 59, 211–218. doi: 10.1016/s0920-9964(01)00344-9

De Gelder, B., Vroomen, J., de Jong, S. J., Masthoff, E. D., Trompenaars, F. J., and Hodiamont, P. (2005). Multisensory integration of emotional faces and voices in schizophrenics. *Schizophr. Res.* 72, 195–203. doi: 10.1016/j.schres.2004.02.013

De Jong, J. J., Hodiamont, P. P., Van den Stock, J., and de Gelder, B. (2009). Audiovisual emotion recognition in schizophrenia: reduced integration of facial and vocal affect. *Schizophr. Res.* 107, 286–293. doi: 10.1016/j.schres.2008.10.001

De Niear, M. A., Gupta, P. B., Baum, S. H., and Wallace, M. T. (2018). Perceptual training enhances temporal acuity for multisensory speech. *Neurobiol. Learn. Mem.* 147, 9–17. doi: 10.1016/j.nlm.2017.10.016

De Niear, M. A., Koo, B., and Wallace, M. T. (2016). Multisensory perceptual learning is dependent upon task difficulty. *Exp. Brain Res.* 234, 3269–3277. doi: 10.1007/s00221-016-4724-3

Donohue, S. E., Darling, E. F., and Mitroff, S. R. (2012). Links between multisensory processing and autism. *Exp. Brain Res.* 222, 377–387. doi: 10.1007/s00221-012-3223-4

Feldman, J. I., Dunham, K., Cassidy, M., Wallace, M. T., Liu, Y., and Woynaroski, T. G. (2018). Audiovisual multisensory integration in individuals with autism spectrum disorder: a systematic review and meta-analysis. *Neurosci. Biobehav. Rev.* 95, 220–234. doi: 10.1016/j.neubiorev.2018.09.020

Foucher, J. R., Lacambre, M., Pham, B. T., Giersch, A., and Elliott, M. A. (2007). Low time resolution in schizophrenia Lengthened windows of simultaneity for visual, auditory and bimodal stimuli. *Schizophr. Res.* 97, 118–127. doi: 10.1016/j.schres.2007.08.013

Foxe, J. J., Molholm, S., Del Bene, V. A., Frey, H. P., Russo, N. N., Blanco, D., et al. (2015). Severe multisensory speech integration deficits in high-functioning school-aged children with Autism Spectrum Disorder (ASD) and their resolution during early adolescence. *Cereb. Cortex* 25, 298–312. doi: 10.1093/cercor/bht213

Francisco, A. A., Jesse, A., Groen, M. A., and McQueen, J. M. (2017). A general audiovisual temporal processing deficit in adult readers with dyslexia. *J. Speech Lang. Hear. Res.* 60, 144–158. doi: 10.1044/2016_JSLHR-H-15-0375

Fujisaki, W., Shimojo, S., Kashino, M., and Nishida, S. (2004). Recalibration of audiovisual simultaneity. *Nat. Neurosci.* 7, 773–778. doi: 10.1038/nn1268

Girden, E. R. (1992). *ANOVA: Repeated Measures*. Newbury Park, CA: Sage Publication.

Hairston, W. D., Burdette, J. H., Flowers, D. L., Wood, F. B., and Wallace, M. T. (2005). Altered temporal profile of visual-auditory multisensory interactions in dyslexia. *Exp. Brain Res.* 166, 474–480. doi: 10.1007/s00221-005-2387-6

Hanson, J. V., Heron, J., and Whitaker, D. (2008). Recalibration of perceived time across sensory modalities. *Exp. Brain Res.* 185, 347–352. doi: 10.1007/s00221-008-1282-3

Hass, K., Sinke, C., Reese, T., Roy, M., Wiswede, D., Dillo, W., et al. (2017). Enlarged temporal integration window in schizophrenia indicated by the double-flash illusion. *Cogn. Neuropsychiatry* 22, 145–158. doi: 10.1080/13546805.2017.1287693

Hillock-Dunn, A., and Wallace, M. T. (2012). Developmental changes in the multisensory temporal binding window persist into adolescence. *Dev. Sci.* 15, 688–696. doi: 10.1111/j.1467-7687.2012.01171.x

Lehrl, S. (2005). *Mehrfachwahl-Wortschatz-Intelligenztest MWT-B*, 5 Edn. Balingen: Spitta.

Meredith, M. A., Nemitz, J. W., and Stein, B. E. (1987). Determinants of multisensory integration in superior colliculus neurons. I. Temporal factors. *J. Neurosci.* 7, 3215–3229. doi: 10.1523/jneurosci.07-10-03215.1987

Meredith, M. A., and Stein, B. E. (1985). Descending efferents from the superior colliculus relay integrated multisensory information. *Science* 227, 657–659. doi: 10.1126/science.3969558

Meredith, M. A., and Stein, B. E. (1986). Spatial factors determine the activity of multisensory neurons in cat superior colliculus. *Brain Res.* 365, 350–354. doi: 10.1016/0006-8993(86)91648-3

Mongillo, E. A., Irwin, J. R., Whalen, D. H., Klaiman, C., Carter, A. S., and Schultz, R. T. (2008). Audiovisual processing in children with and without autism spectrum disorders. *J. Autism Dev. Disord.* 38, 1349–1358. doi: 10.1007/s10803-007-0521-y

Navarra, J., Vatakis, A., Zampini, M., Soto-Faraco, S., Humphreys, W., and Spence, C. (2005). Exposure to asynchronous audiovisual speech extends the temporal window for audiovisual integration. *Brain Res. Cogn. Brain Res.* 25, 499–507. doi: 10.1016/j.cogbrainres.2005.07.009

Pearl, D., Yodashkin-Porat, D., Katz, N., Valevski, A., Aizenberg, D., Sigler, M., et al. (2009). Differences in audiovisual integration, as measured by McGurk phenomenon, among adult and adolescent patients with schizophrenia and age-matched healthy control groups. *Compr. Psychiatry* 50, 186–192. doi: 10.1016/j.comppsych.2008.06.004

Postmes, L., Sno, H. N., Goedhart, S., van der Stel, J., Heering, H. D., and de Haan, L. (2014). Schizophrenia as a self-disorder due to perceptual incoherence. *Schizophr. Res.* 152, 41–50. doi: 10.1016/j.schres.2013.07.027

Powers, A. R. III, Hillock, A. R., and Wallace, M. T. (2009). Perceptual training narrows the temporal window of multisensory binding. *J. Neurosci.* 29, 12265–12274. doi: 10.1523/JNEUROSCI.3501-09.2009

Powers, A. R. III, Hillock-Dunn, A., and Wallace, M. T. (2016). Generalization of multisensory perceptual learning. *Sci. Rep.* 6:23374. doi: 10.1038/srep23374

Roseboom, W., Kawabe, T., and Nishida, S. (2013). The cross-modal double flash illusion depends on featural similarity between cross-modal inducers. *Sci. Rep.* 3:3437. doi: 10.1038/srep03437

Ross, L. A., Saint-Amour, D., Leavitt, V. M., Javitt, D. C., and Foxe, J. J. (2007a). Do you see what I am saying? Exploring visual enhancement of speech comprehension in noisy environments. *Cereb. Cortex* 17, 1147–1153. doi: 10.1093/cercor/bhl024

Ross, L. A., Saint-Amour, D., Leavitt, V. M., Molholm, S., Javitt, D. C., and Foxe, J. J. (2007b). Impaired multisensory processing in schizophrenia: deficits in the visual enhancement of speech comprehension under noisy environmental conditions. *Schizophr. Res.* 97, 173–183. doi: 10.1016/j.schres.2007.08.008

Russo, N., Foxe, J. J., Brandwein, A. B., Altschuler, T., Gomes, H., and Molholm, S. (2010). Multisensory processing in children with autism: high-density electrical mapping of auditory-somatosensory integration. *Autism Res.* 3, 253–267. doi: 10.1002/aur.152

Schneider, K. A., and Bavelier, D. (2003). Components of visual prior entry. *Cogn. Psychol.* 47, 333–366. doi: 10.1016/s0010-0285(03)00035-5

Setti, A., Stapleton, J., Leahy, D., Walsh, C., Kenny, R. A., and Newell, F. N. (2014). Improving the efficiency of multisensory integration in older adults: audio-visual temporal discrimination training reduces susceptibility to the sound-induced flash illusion. *Neuropsychologia* 61, 259–268. doi: 10.1016/j.neuropsychologia.2014.06.027

Shams, L., Kamitani, Y., and Shimojo, S. (2000). Illusions. What you see is what you hear. *Nature* 408:788. doi: 10.1038/35048669

Shams, L., Kamitani, Y., and Shimojo, S. (2002). Visual illusion induced by sound. *Brain Res. Cogn. Brain Res.* 14, 147–152. doi: 10.1016/s0926-6410(02)00069-1

Sinke, C., Neufeld, J., Zedler, M., Emrich, H. M., Bleich, S., Munte, T. F., et al. (2014). Reduced audiovisual integration in synesthesia–evidence from bimodal speech perception. *J. Neuropsychol.* 8, 94–106. doi: 10.1111/jnp.12006

Stein, B. E., and Wallace, M. T. (1996). Comparisons of cross-modality integration in midbrain and cortex. *Prog. Brain Res.* 112, 289–299. doi: 10.1016/s0079-6123(08)63336-1

Stevenson, R. A., Segers, M., Ferber, S., Barense, M. D., and Wallace, M. T. (2014a). The impact of multisensory integration deficits on speech perception in children with autism spectrum disorders. *Front. Psychol.* 5:379. doi: 10.3389/fpsyg.2014.00379

Stevenson, R. A., Siemann, J. K., Schneider, B. C., Eberly, H. E., Woynaroski, T. G., Camarata, S. M., et al. (2014b). Multisensory temporal integration in autism spectrum disorders. *J. Neurosci.* 34, 691–697. doi: 10.1523/JNEUROSCI.3615-13.2014

Stevenson, R. A., Siemann, J. K., Woynaroski, T. G., Schneider, B. C., Eberly, H. E., Camarata, S. M., et al. (2014c). Brief report: arrested development of audiovisual speech perception in autism spectrum disorders. *J. Autism Dev. Disord.* 44, 1470–1477. doi: 10.1007/s10803-013-1992-7

Stevenson, R. A., Wilson, M. M., Powers, A. R., and Wallace, M. T. (2013). The effects of visual training on multisensory temporal processing. *Exp. Brain Res.* 225, 479–489. doi: 10.1007/s00221-012-3387-y

Stevenson, R. A., Zemtsov, R. K., and Wallace, M. T. (2012). Individual differences in the multisensory temporal binding window predict susceptibility to audiovisual illusions. *J. Exp. Psychol. Hum. Percept. Perform.* 38, 1517–1529. doi: 10.1037/a0027339

Sumby, W. H., and Pollack, I. (1954). Visual contribution to speech intelligibility in noise. *J. Acoust. Soc. Am.* 26, 212–215. doi: 10.1121/1.1907309

Surig, R., Bottari, D., and Roder, B. (2018). Transfer of audio-visual temporal training to temporal and spatial audio-visual tasks. *Multisens. Res.* 31, 556–578. doi: 10.1163/22134808-00002611

Vroomen, J., Keetels, M., de Gelder, B., and Bertelson, P. (2004). Recalibration of temporal order perception by exposure to audio-visual asynchrony. *Brain Res. Cogn. Brain Res.* 22, 32–35. doi: 10.1016/j.cogbrainres.2004.07.003

Wallace, M. T., and Stevenson, R. A. (2014). The construct of the multisensory temporal binding window and its dysregulation in developmental disabilities. *Neuropsychologia* 64, 105–123. doi: 10.1016/j.neuropsychologia.2014.08.005

Woynaroski, T. G., Kwakye, L. D., Foss-Feig, J. H., Stevenson, R. A., Stone, W. L., and Wallace, M. T. (2013). Multisensory speech perception in children with autism spectrum disorders. *J. Autism Dev. Disord.* 43, 2891–2902. doi: 10.1007/s10803-013-1836-5

Zmigrod, L., and Zmigrod, S. (2016). On the temporal precision of thought: individual differences in the multisensory temporal binding window predict performance on verbal and nonverbal problem solving tasks. *Multisens. Res.* 29, 679–701. doi: 10.1163/22134808-00002532

Zmigrod, S., de Sonneville, L. M., Colzato, L. S., Swaab, H., and Hommel, B. (2013). Cognitive control of feature bindings: evidence from children with autistic spectrum disorder. *Psychol. Res.* 77, 147–154. doi: 10.1007/s00426-011-0399-3

Zvyagintsev, M., Parisi, C., and Mathiak, K. (2017). Temporal processing deficit leads to impaired multisensory binding in schizophrenia. *Cogn. Neuropsychiatry* 22, 361–372. doi: 10.1080/13546805.2017.1331160

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Audio-Motor Training Enhances Auditory and Proprioceptive Functions in the Blind Adult

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Several reports indicate that spatial perception in blind individuals can be impaired as the lack of visual experience severely affects the development of multisensory spatial correspondences. Despite the growing interest in the development of technological devices to support blind people in their daily lives, very few studies have assessed the benefit of interventions that help to refine sensorimotor perception. In the present study, we directly investigated the impact of a short audio-motor training on auditory and proprioceptive spatial perception in blind individuals. Our findings indicate that auditory and proprioceptive spatial capabilities can be enhanced through interventions designed to foster sensorimotor perception in the form of audio-motor correspondences, demonstrating the importance of the early introduction of sensorimotor training in therapeutic intervention for blind individuals.

Keywords: blindness, training, plasticity, audition, proprioception

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INTRODUCTION

Recent evidence suggests that some spatial capabilities in blind individuals may be delayed or compromised (Pasqualotto and Proulx, 2012; Gori et al., 2013; Voss et al., 2015; Cuturi et al., 2016). This has been associated with the reduced accessibility to multisensory experiences caused by the lack of vision during the first years of life when plasticity is maximal and the critical period for the development of spatial representation can develop (Putzar et al., 2007; Cappagli et al., 2017b). Impairments of spatial representation is not limited to tactile and auditory perception (Röder et al., 2004; Gori et al., 2013; Finocchietti et al., 2015a; Vercillo et al., 2016), but it also extends to proprioception (Rossetti et al., 1996; Gaunet and Rossetti, 2006; Fiehler et al., 2009; Cappagli et al., 2017a). Given the risk of developing spatial deficits due to the lack of vision, specific training to improve spatial skills would be fundamental for individuals with a visual disability.

Despite their potential usefulness for rehabilitation purposes, the benefit of interventions based on sensorimotor contingencies, such as audio-motor correspondence, has been barely studied in the blind population. Conversely, the use of auditory information coupled with visual or motor feedback has been mainly studied in robotic therapy systems to motivate or guide patients in the execution of performance tasks (Maulucci and Eckhouse, 2001; Robertson et al., 2009), generally reporting positive outcomes (Sigrist et al., 2013). Several works have demonstrated that the use of audition to complement or substitute visual information provides users with additional feedback of their own movements (Bevilacqua et al., 2016; Cappagli et al., 2019). For instance, it has been shown that when coupled with visual feedback, continuous task-related audio information can improve motor performance and facilitate the learning of a novel visuomotor perturbation, indicating that auditory augmentation of visual feedback can enhance upper limb sensorimotor learning (Rosati et al., 2012). Auditory feedback can also substitute visual feedback for specific tasks, e.g., it can convey information to estimate the curvature of a virtual shape when visual feedback is temporarily removed (Boyer et al., 2015), suggesting that specific stimulus features can be translated from one modality to another. These results demonstrate that interventions based on meaningful multisensory correspondences can augment sensorimotor learning.

To date, research investigating the effect of auditory information to improve spatial perception in the case of blindness mainly focused on the evaluation of sensory substitution devices which tend to substitute vision with audition without specifically providing sensorimotor correspondences (Amedi et al., 2007; Auvray and Myin, 2009; Chebat et al., 2011; Striem-Amit et al., 2012). Only few studies assessed the effects of pure audio-motor training on spatial cognition in the blind, reporting positive outcomes in the case of training with an external auditory sound source that provides sonorous feedback of body movements (Aggius-Vella et al., 2017; Cappagli et al., 2017b, 2019; Finocchietti et al., 2017). In all these studies, the auditory feedback was actively generated by the individual through his own body movements thus spatial information emerged from the coupling of sensorimotor contingencies. For this reason, the training was less demanding compared to the training required for sensory substitution devices, since it only required individuals to naturally associate auditory and motor information coming from their body without learning codification rules requested by an external substitution device. These studies demonstrated that an audio-motor training has a positive effect on auditory and proprioceptive spatial perception in blind children, but they did not tested if the same effect is visible for blind adults, which has been shown to be impaired from an early age for proprioceptive functions (Rossetti et al., 1996; Gaunet and Rossetti, 2006; Cappagli et al., 2017a). We recently showed that sighted people improve their proprioceptive spatial abilities after an audio-motor training (Cuppone et al., 2018), highlighting substantial differences between training modalities and feedback types, but no studies to date have explored if blind individuals show similar enhancement in their proprioceptive functions.

For this reason, in the present study, we assessed the impact of an audio-motor training on spatial capabilities in visually impaired individuals, to test whether experiencing an auditory feedback of body movements can refine spatial mapping across multiple domains, namely auditory and proprioceptive domains. With this aim, we compared auditory and proprioceptive localization accuracy before and after a short sensorimotor training in which passive movements of the dominant arm of participants were enriched with a continuous or discrete audio feedback that creates a spatial audio-motor association. To assess the presence of generalization effects, we examined whether auditory and proprioceptive functions were improved also on the untrained side of the body, namely the non-dominant arm.

MATERIALS AND METHODS

Participants

The study involved 16 participants with no known neuromuscular disorders and naïve to the task. The participants were divided into two groups: a sighted training group (n = 7; age: 32 ± 4) and a blind training group (n = 9; age: 41 ± 15) who performed the same training. A t-test confirmed that the two groups did not differ in terms of chronological age [$t(14) = -1.54$, $p > 0.05$]. Blind participants have been considered as *early blind* since the loss of vision occurred within the third year of age despite the fact that diagnosis was known at birth. The clinical details of the early blind participants are reported in **Table 1**. The research conformed to the ethical standards laid down in the 1964 Declaration of Helsinki and was approved by the local ethics committee (ASL3 Ligure). Each participant signed an informed consent form conforming to these guidelines.

Procedure

The protocol consisted of one pre-test and one post-test session (*Assessment phase*) where two different aspects of spatial cognition were investigated (auditory and proprioceptive localization) and one training session (*Training phase*) performed between the pre-test and post-test sessions. The first assessment task is related to the auditory domain and investigated participants' ability to localize sounds in space (*Reaching of auditory cue task*) while the second assessment task is related to the proprioceptive domain and investigated the participants' ability to reproduce a position in space (*Joint position matching task*). The tasks included in the *Assessment phase* have been already presented in Cuppone et al. (2018). During both tasks, all participants were blindfolded and each participant performed the assessment tests both with the dominant and non-dominant arms. During the *Training phase*, the trained arm was always the dominant one. This allowed us to assess whether the training effect generalizes to the untrained (non-dominant) arm.

Assessment Phase

The setup shown in **Figure 1** utilized a set of 16 loudspeakers embedded in an array covered by tactile sensors (1 cm · 1 cm)

TABLE 1 | Clinical details of the group of visually impaired participants.

Subject	Age range	Residual vision	Pathology
1	55–60	*	Uveitis
2	20–25	^	Leber's congenital amaurosis
3	25–30	^	Retinopathy of Prematurity
4	20–25	^	Congenital cataract
5	55–60	^	Congenital glaucoma
6	25–30	^	Retinopathy of Prematurity
7	60–65	^	Atrophy of the eyeball
8	40–45	^	Congenital glaucoma
9	50–55	*	Retinitis pigmentosa

*The table shows for each subject the information related to age, residual vision and pathology. ^No residual vision, *residual vision (light and shadow).*

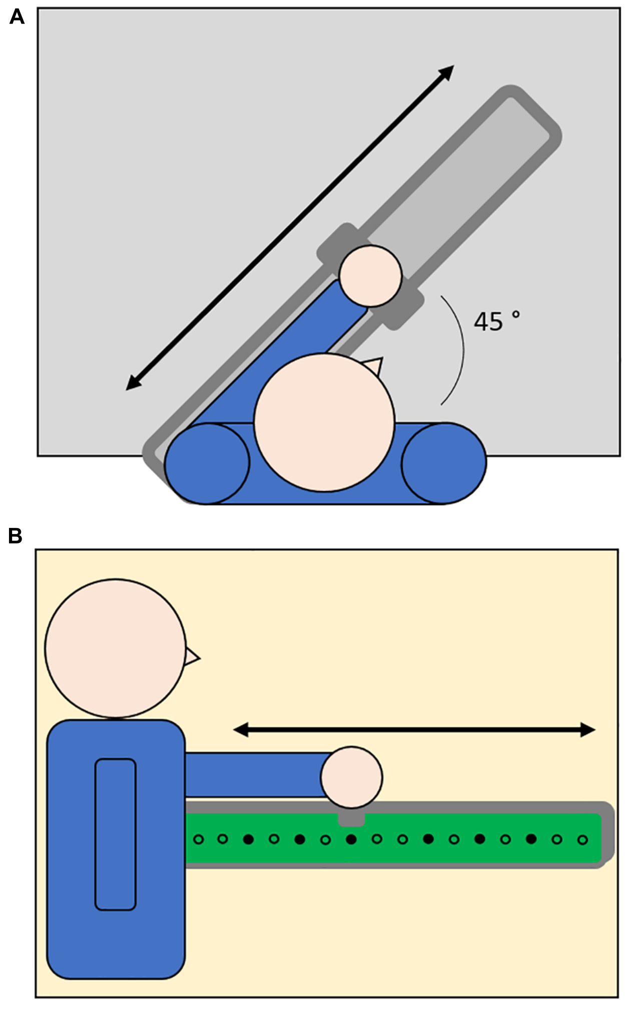

FIGURE 1 | Top-view **(A)** and side-view **(B)** of setup configuration. Participants were seated at a table and their dominant or non-dominant arm was positioned on a metallic rail (light gray, 1A) placed above an array of audio speakers (dots, 1B) mounted on a tactile surface that can register the position of the contact (green surface, 1B). To perform the task, participants were asked to hold a handle to slide over the metallic rail and indicate the position of auditory (Reaching of Auditory Cue Task) or proprioceptive (Joint Position Matching Task) targets (filled dots).

that can register the position of the contact and provide accurate information about spatial errors. The setup was fixed on the desk in front of the participants along a line inclined with an angle of 45° with respect to the frontal axis of the human body (**Figure 1A**). The center of the setup was kept 20 cm far from the center of the body in order to allow participants to easily reach farther positions. The participants held a handle to slide on a metallic rail positioned on the setup. The system was controlled by a workstation and the software environment was implemented in Matlab. The serial communication between the workstation and the loudspeakers was bidirectional and it allowed the selected loudspeaker to execute the sonorous stimulus and register the position of the activated sensor.

Reaching of Auditory Cue Task

In order to test spatial perception in the auditory domain, we asked participants to reach a sonorous stimulus produced in turn by one out of the six target speakers (**Figure 1B**). The sonorous stimulus was a pink noise with a duration of 1 s. After the end of the stimulus, the participant moved the arm in order to place the handle over the sound source position and the experimenter confirmed his response by touching the corresponding position over the tactile surface. The six target positions were equally distributed in order to test auditory spatial perception on the entire workspace (target loudspeakers: 3, 5, 7, 10, 12, 14 with loudspeaker number one being the closest to the participants in each configuration). Each target was presented in randomized order for five times, for a total of 30 trials.

Joint Position Matching Task

In order to test spatial perception in the proprioceptive domain, we asked participants to perform an ipsilateral joint position matching task (Goble, 2010). After guiding the participants' arm from the starting position corresponding to loudspeaker number 1 to the target proprioceptive position and then back to the starting position, the experimenter asked participants to replicate the movement in order to indicate the proprioceptive position experienced. Then the experimenter confirmed the participant's response by touching the corresponding position over the tactile surface. The six target positions were the same as the auditory task. Each target was presented in randomized order for five times, for a total of 30 trials.

Training Phase

Between the pre-test and post-test assessment phases, participants performed an audio-motor training that coupled the proprioceptive feedback and the auditory feedback from the body thanks to the use of a device that produces a sound whenever moved. The device is called Audio Bracelet for Blind Interaction (Finocchietti et al., 2015b) and it is a system developed to train spatial abilities in visually impaired people thanks to its potential to associate motor and auditory signals from the body (Finocchietti et al., 2015a; Cappagli et al., 2017b, 2019).

The training lasted 10 min in total, divided into four blocks of 2.5 min each. Between each training block, participants rested for 5 min. During the training, participants wore on the dominant arm the wearable audio device while their wrist was passively moved by the experimenter on the rail over the setup in two ways: (a) continuous back-and-forth movement along the setup; (b) discrete back-and-forth movements where the participants' arm was positioned for 1 s over each of the sixteen loudspeakers embedded in the setup. The main aim of the training was to couple the proprioceptive feedback deriving from arm displacement with the auditory feedback deriving from the auditory source positioned on their wrist. The differentiation between continuous and discrete movements helped participants to respectively explore the setup and understand where each target position was placed by combining auditory and proprioceptive information. The ABBI was programmed in remote control, therefore, the audio command was triggered by the experimenter using a mobile phone. The wearable device produced a continuous pink noise sound.

Analysis

In order to evaluate the accuracy and the precision of participants in both the *Reaching of Auditory Cue* and the *Joint Position Matching* tasks, we computed the distance error in millimeters between each target and indicated position and then averaged across all target positions, extracting two variables: Matching Error (ME) and the Variability (SD).

Matching Error represents a measure of accuracy or its inverse, bias. It is defined as the Euclidean distance between the target and the final arm position.

$$ME = \sum_{i=1}^{N} (x_{EE} - x_{TG})^2 \quad (1)$$

where N is the number of Target repetitions (5), x_{EE} is the participants' final position and x_{TG} is the Target position. This variable is then averaged across targets.

The Variability (SD) is a measure of precision and it is evaluated as the standard deviation of the error positions.

$$SD = \sqrt{\frac{1}{N-1} \sum_{i=1}^{N} (d_i - \underline{\mathrm{d}})^2} \quad (2)$$

where d is the error distance $x_{EE} - x_{TG}$, and N is the number of target repetitions. SD is evaluated for each target and then averaged.

For both variables, we performed the incremental difference pre-post training (Δ), as follows:

$$\Delta = 100 \frac{var_{pre} - var_{post}}{var_{pre}} \quad (3)$$

where var_{pre} represents the performance at the pre-training assessment session and var_{post} represents the performance at the post-training assessment session.

RESULTS

Proprioceptive and Auditory Spatial Representations

In order to investigate whether sighted and blind individuals differ in their auditory and proprioceptive spatial representations, we compared the performance of sighted and blind participants at the pre-training session in auditory and proprioceptive domains separately both for ME and variability variables. Specifically, we performed four two-way ANOVAs with group (sighted, blind) and side (dominant, non-dominant) as main factors separately for auditory domain and proprioceptive domain and for ME and variability (SD). In case of significant effect ($p < 0.05$), we applied the *post hoc t*-test with Bonferroni correction. **Figure 2A** depicts auditory and proprioceptive spatial accuracy in terms of ME of sighted and blind participants at the pre-training session for the dominant and non-dominant arms for all six target locations, while **Figure 2B** depicts the auditory and proprioceptive spatial performance of sighted and blind participants independently of the arm considered (dominant, non-dominant) and across all target locations. The statistical analysis of spatial accuracy (ME) confirms what shown in **Figure 2**, which is that for the auditory domain a significant difference in terms of auditory accuracy exists between sighted and blind participants ($F = 10.33$, $p = 0.003$) while neither main effect of side ($F = 0.03$, $p > 0.05$) nor interaction between group and side ($F = 0.62$, $p > 0.05$) exist, suggesting that overall sighted individuals are less accurate than blind individuals for audio spatial localization [$t(14) = 2.7$, $p = 0.015$, **Figure 2B**, top panel]. Opposite results are shown for the proprioceptive domain, for which a significant difference in terms of proprioceptive accuracy exists between sighted and blind participants ($F = 8.87$, $p = 0.005$) while neither main SIDE effect ($F = 0.25$, $p > 0.05$) nor interaction between group and side ($F = 0.2$, $p > 0.05$) exist, suggesting overall that blind individuals are less accurate than sighted individuals for proprioceptive spatial localization [$t(14) = -2.51$, $p = 0.024$, **Figure 2B**, bottom panel].

Figure 3A depicts the difference between the performance of sighted and blind individuals at the pre-training session for auditory and proprioceptive spatial precision (SD) for all target locations, while **Figure 3B** shows the same comparison between sighted and blind participants across targets locations. The statistical analysis of SD revealed that in the auditory domain, no main effects of group (sighted vs. blind, $F = 0.52$, $p > 0.05$), side (dominant vs. non-dominant, $F = 1.84$, $p > 0.05$) or interaction (group × side, $F = 0.31$, $p > 0.05$) exist, suggesting overall that sighted individuals are as precise as blind individuals for audio spatial localization independently of the side of the body used to localize sounds (**Figures 3A,B**, top panel). Instead variability analysis in the proprioceptive domain reveals that both a significant difference between groups ($F = 4.69$, $p = 0.039$) and a significant interaction between group and side ($F = 5.26$, $p = 0.029$) exist while no main effect of side is present ($F = 1.19$, $p > 0.05$), suggesting that blind participants are less precise in the non-dominant compared to the dominant arm [$t(8) = -3.5$, $p = 0.008$, **Figures 3A,B**, bottom panel].

Training Effect on Proprioceptive and Auditory Spatial Representations

In order to evaluate the effect of the audio-motor training on auditory and proprioceptive spatial representation, we performed two main analyses, respectively related to the ME and ΔME variables (see Analysis). Specifically, for ME we performed four three-way ANOVAs with group (sighted, blind), side (dominant, non-dominant) and time (pre, post) as main factors separately for auditory domain and proprioceptive domain and for ME and variability (SD). In case of significant effect ($p < 0.05$), we applied the *post hoc t*-test with Bonferroni correction. For ΔME we performed a two-way ANOVA with group (sighted, blind) and side (dominant, non-dominant) as main factors and the consequent *post hoc t*-test with Bonferroni correction in case of significant result.

Training results for ME and ΔME are shown in **Figure 4**. **Figure 4A** shows the mean ME of the pre-training and

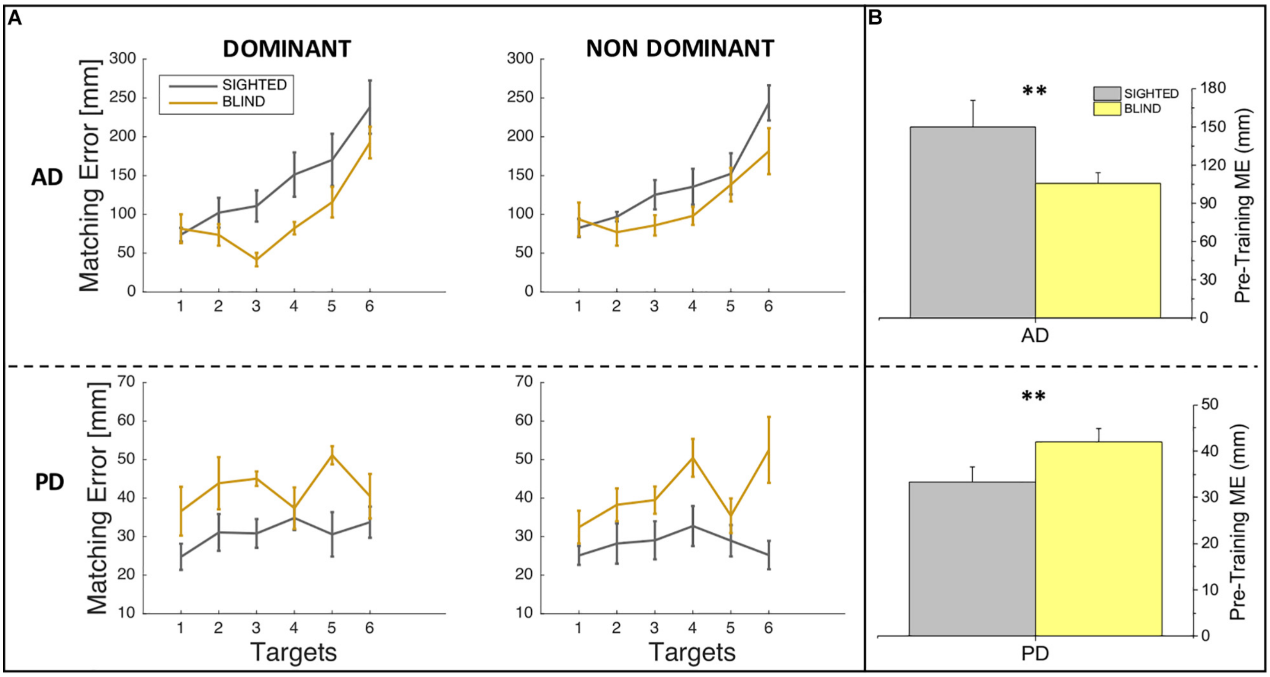

FIGURE 2 | Auditory and proprioceptive performance at the pre-training session. **(A)** The panel represents the auditory (top) and proprioceptive (bottom) matching errors (in mm) for the dominant (left) and non-dominant (right) arms. Results are shown for each target location and indicate that for the auditory but not for the proprioceptive domain, matching error increases therefore performance decreases with increasing target location distance. **(B)** The panel represents the auditory (top) and proprioceptive (bottom) matching errors (in mm) independently of the arm trained (dominant, non-dominant). Results indicate that blind participants outperformed sighted participants in the auditory domain, while sighted participants outperformed blind participants in the proprioceptive domain. **Indicates *p*-values < 0.01.

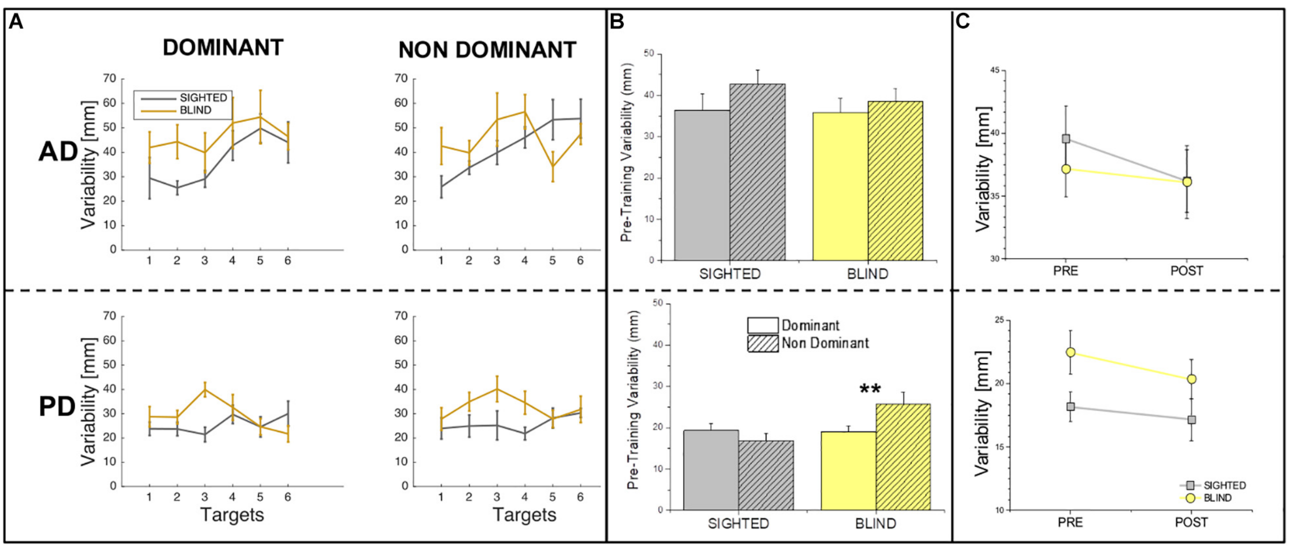

FIGURE 3 | Variability in the auditory and proprioceptive domains. **(A)** The panel represents the auditory (top) and proprioceptive (bottom) variability (in mm) for the dominant (left) and non-dominant (right) arms. Results are shown for each target location and indicate that for both the auditory and proprioceptive domain, variability is target location independent for both groups. **(B)** The panel represents the auditory (top) and proprioceptive (bottom) variability (in mm) at the pre-training session for the dominant (plain bars) and non-dominant (pattern bars) arms. Results indicate that for each group, there is not difference in terms of variability between the dominant and non-dominant sides across domains with the only exception for blind participant in the Proprioceptive domain, who present a higher variability on the non-dominant hand. **(C)** The panel represents the comparison of variability (mm) in the pre-training and post-training sessions across sides (dominant and non-dominant pulled together) in the auditory (top) and proprioceptive (bottom). Results indicate that for both auditory and proprioceptive domains, variability does not change from the pre-training to the post-training session neither for the sighted nor for the blind participants. **Indicates *p*-values < 0.01.

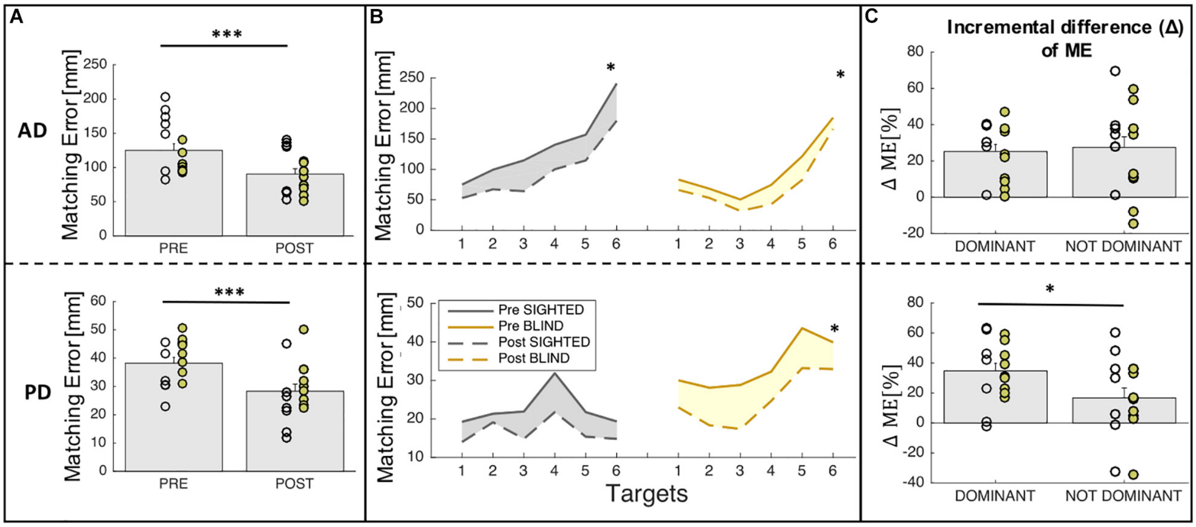

FIGURE 4 | Auditory and proprioceptive performance after the training session. **(A)** The panel shows the mean (bars) and individual (circles) values of ME before and after training; yellow represent blind individuals while gray represent sighted individuals. Results indicate that matching error decreases after the training both for auditory and proprioceptive domain. **(B)** The panel represents the auditory (top) and proprioceptive (bottom) matching errors (in mm) independently on the body side (dominant and non-dominant). Results are shown for each target location in each domain. **(C)** The panel represents the auditory (top) and proprioceptive (bottom) Δ matching errors (ΔME in %) for the trained (dominant) and the not trained (non-dominant) sides in both groups (sighted, blind). Results indicate that for the proprioceptive domain, participants improve their spatial performance more in the dominant side on which they performed the training. ***Indicates p-values < 0.001 and * indicates p-values < 0.05.

post-training phases for both groups (sighted and blind) across sides (dominant, non-dominant). **Figure 4B** depicts the auditory and proprioceptive spatial performance of sighted and blind participants at the pre-training (continuous line) and post-training (dashed line) sessions for all six target locations independently of side. **Figure 4C** depicts the ΔME expressed as incremental difference between the pre-training and post-training sessions for both groups (sighted and blind) for the dominant (trained) and the non-dominant (untrained) sides.

For what concerns the analysis related to spatial accuracy (ME), we found that for the auditory domain, there is a significant main effect of group (sighted vs. blind, $F = 12.45$, $p = 0.0008$) and time (pre vs. post, $F = 14.27$, $p = 0.0004$) but neither main effect of side (dominant vs. non-dominant, $F = 0.1$, $p > 0.05$) nor interactions among factors (group × time, $F = 1.29$, $p > 0.05$; group × side, $F = 1.02$, $p > 0.05$; time × side, $F = 0.09$, $p > 0.05$). Indeed **Figure 4A** (top panel) represents the main effect of time, for which participants (sighted and blind pooled together) decreased significantly their ME after training [$t(15) = 6.7$, $p < 0.0001$]. Moreover, as can be seen in **Figure 4B** (top panel), the ME decrease is homogeneous for all the target locations considered for both groups and when merging performance accuracy in the dominant and non-dominant arms both sighted [$t(6) = 5.3$, $p = 0.002$] and blind individuals [$t(8) = 5.9$, $p = 0.0003$] improved their performance. Similarly, for the proprioceptive domain, there is a significant main effect of group (sighted vs. blind, $F = 11.61$, $p = 0.001$) and time (pre vs. post, $F = 17.16$, $p = 0.0001$) but neither main effect of side (dominant vs. non-dominant, $F = 0.48$, $p > 0.05$) nor interactions among factors (group × time, $F = 0.08$, $p > 0.05$; group x side, $F = 1.1$, $p > 0.05$; time × side, $F = 1.93$, $p > 0.05$). **Figure 4A** (bottom panel) represents the main effect of time, for which participants (sighted and blind pooled together) decreased significantly their ME after training [$t(15) = 5.76$, $p < 0.0001$]. Moreover, as can be seen in **Figure 4B** (bottom panel), the ME decrease is homogeneous for all the target locations considered for both groups but when merging performance accuracy in the dominant and non-dominant arms, only blind individuals showed relevant enhancements in proprioceptive function after the training [$t(8) = 4.9$, $p < 0.01$] while sighted individuals showed a weaker improvement [$t(6) = 3.08$, $p = 0.02$ not significant with the Bonferroni correction >0.05].

For what concerns the analysis related to the incremental difference (Δ) of ME, which is the change of accuracy between pre and post training scaled by the initial error, we performed a two-way ANOVA with group (sighted, blind) and side (dominant, non-dominant) as main factors. The statistical analysis reported a significant side effect for the proprioceptive domain ($p = 0.05$) while neither main effect of group nor interaction between factors has been found. **Figure 4C** represents the main effect of side, for which the improvement after the training is equivalent for the dominant or trained side and the non-dominant or untrained side for the auditory domain ($p > 0.05$) but it is much higher for the dominant compared to the non-dominant side in the proprioceptive domain (dominant: 34.72% ± 5.12%; non-dominant: 16.74% ± 6.58%; $t(15) = 2.7$, $p = 0.016$).

For what concerns SD, the statistical analysis revealed that no effect of time on SD is present neither for the auditory domain ($F = 0.7$, $p > 0.05$) nor for the proprioceptive domain ($F = 1.09$,

$p > 0.05$). Results for SD are depicted in **Figure 3C** by reporting the difference between the pre and post-training sessions for auditory and proprioceptive SD.

DISCUSSION

Despite the pivotal role of multisensory contingencies in the development of spatial perception, to date very few studies have investigated the effect of training based on audio-motor contingency on spatial competence in blind individuals. With this study, we demonstrated that training based on audio-motor contingencies enhances spatial perception of blind individuals in the auditory and proprioceptive domains, confirming the importance of sensory-motor experiences during therapeutic intervention.

This study highlights two main results. The first evidence is that after the audio-motor training, ME decreases in the trained (dominant) side for both sighted and blind individuals, while generalization effects much evident for the auditory domain in both groups. This result is in line with previous findings showing that auditory spatial perception in the blind can be enhanced with a proper training based on multisensory feedback (Aggius-Vella et al., 2017; Finocchietti et al., 2017; Cappagli et al., 2019) and that similarly both auditory and proprioceptive spatial capabilities can be improved in the sighted (Cuppone et al., 2018). The fact that a generalization effect to the untrained side of the body is more evident within the auditory domain for both sighted and blind participants can be due to the different nature of the auditory and proprioceptive modalities. Indeed, while audition is allocentric, proprioception is intrinsically egocentric therefore gains in spatial accuracy might not transfer as easily as within the auditory modality from a body part to another. The second result is that blind participants outperformed sighted participants in the auditory domain, while sighted participants outperformed blind participants in the proprioceptive domain in terms of spatial accuracy at the pre-training session. This result is in line with previous findings showing that proprioception can be altered in the blind (Rossetti et al., 1996; Gaunet and Rossetti, 2006; Cappagli et al., 2017a) but some aspects of auditory perception can be enhanced (Gori et al., 2013). Moreover, some evidence demonstrate that blindfolding procedures can alter perceptual capabilities in the sighted (Tabry et al., 2013). Finally, the fact that spatial accuracy decreases as target positions increases in both sighted and blind individuals suggests that similar perceptual mechanisms are in the act when auditory stimuli are processed, independently of overall performance accuracy.

The main aim of this study was to assess whether a training based on multisensory (audio-motor) feedback can improve spatial perception, more specifically can calibrate altered proprioceptive function. Participants were trained to couple the proprioceptive feedback deriving from arm displacement with the auditory feedback provided by the external source positioned on their wrist. On the contrary, most of the studies conducted so far have investigated the effect of more artificial training based on the use of sensory substitution devices. These approaches typically require to learn how to transform visual properties of a stimulus into auditory or tactile information. Specifically, for the blind, visual-to-auditory sensory substitution devices artificially translate visual properties of a stimulus into auditory information by means of specifically developed devices that mimic the physiological functions of the visual modality (Auvray and Myin, 2009; Velázquez, 2010). For example, in some cases, the information about the contrast between light and dark in a visual image is conveyed with sounds of different frequencies (Amedi et al., 2007). Sensory substitution devices can improve object localization (Renier et al., 2005) and form recognition (Arno et al., 1999; Cronly-Dillon et al., 1999; Cronly–Dillon et al., 2000; Pollok et al., 2005) by translating visual properties of surrounding objects via changes in auditory parameters such as pitch and amplitude. Nonetheless, it is worth noting that the perceptual outcome of such devices might result artificial in the sense that the auditory output provided by the system is not directly connected with the spatial information but strictly depends on the codification rules applied by the coupling system, which are typically internalized by users through extensive training. Moreover, we recently outlined that not all the technological devices developed so far can be used by blind individuals in their everyday life, principally due to the long and extensive training they require. For this reason, our aim was to test whether a simpler device that provides audio-motor contingencies can enhance auditory and proprioceptive functions in the blind adult.

In conclusion, we demonstrated that spatial perception can improve in blind individuals thanks to training based on audio-motor contingencies, confirming the importance of multisensory experiences to acquire spatial competence. Overall the findings of the present study confirmed the importance of visual experience in the construction and calibration of non-visual spatial maps and stressed the importance of early therapeutic intervention to support the acquisition of fundamental spatial competencies from infancy.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The research conformed to the ethical standards laid down in the 1964 Declaration of Helsinki and was approved by the local ethics committee (ASL3 Ligure). Each participant signed a consent form conforming to these guidelines.

AUTHOR CONTRIBUTIONS

AC, GC, and MG developed the design of the study. AC collected most of the data. GC helped in the final part of data collection. AC and GC analyzed the data and wrote the manuscript. MG reviewed the manuscript and provided feedback for discussion of results.

REFERENCES

Aggius-Vella, E., Campus, C., Finocchietti, S., and Gori, M. (2017). Audio motor training at the foot level improves space representation. *Front. Integ. Neurosci.* 11:36. doi: 10.3389/fnint.2017.00036

Amedi, A., Stern, W. M., Camprodon, J. A., Bermpohl, F., Merabet, L., Rotman, S., et al. (2007). Shape conveyed by visual-to-auditory sensory substitution activates the lateral occipital complex. *Nat. Neurosci.* 10:687. doi: 10.1038/nn1912

Arno, P., Capelle, C., Wanet-Defalque, M.-C., Catalan-Ahumada, M., and Veraart, C. (1999). Auditory coding of visual patterns for the blind. *Perception* 28, 1013–1029. doi: 10.1068/p281013

Auvray, M., and Myin, E. (2009). Perception with compensatory devices: from sensory substitution to sensorimotor extension. *Cogn. Sci.* 33, 1036–1058. doi: 10.1111/j.1551-6709.2009.01040.x

Bevilacqua, F., Boyer, E. O., Françoise, J., Houix, O., Susini, P., Roby-Brami, A., et al. (2016). Sensori-motor learning with movement sonification: perspectives from recent interdisciplinary studies. *Front. Neurosci.* 10:385. doi: 10.3389/fnins.2016.00385

Boyer, E. O., Vandervoorde, L., Bevilacqua, F., and Hanneton, S. (2015). "Touching sounds: perception of the curvature of auditory virtual surfaces," in *Paper Presented at the Virtual Reality (VR)*, (Arles: IEEE).

Cappagli, G., Cocchi, E., and Gori, M. (2017a). Auditory and proprioceptive spatial impairments in blind children and adults. *Dev. Sci.* 20:e12374. doi: 10.1111/desc.12374

Cappagli, G., Finocchietti, S., Baud-Bovy, G., Cocchi, E., and Gori, M. (2017b). Multisensory rehabilitation training improves spatial perception in totally but not partially visually deprived children. *Front. Integ. Neurosci.* 11:29. doi: 10.3389/fnint.2017.00029

Cappagli, G., Finocchietti, S., Cocchi, E., Giammari, G., Zumiani, R., Cuppone, A. V., et al. (2019). Audio motor training improves mobility and spatial cognition in visually impaired children. *Sci. Rep.* 9:3303. doi: 10.1038/s41598-019-39981-x

Chebat, D.-R., Schneider, F. C., Kupers, R., and Ptito, M. (2011). Navigation with a sensory substitution device in congenitally blind individuals. *Neuroreport* 22, 342–347. doi: 10.1097/WNR.0b013e3283462def

Cronly-Dillon, J., Persaud, K., and Gregory, R. (1999). The perception of visual images encoded in musical form: a study in cross-modality information transfer. *Proc. R. Soc. Lond. B Biol. Sci.* 266, 2427–2433. doi: 10.1098/rspb.1999.0942

Cronly–Dillon, J., Persaud, K., and Blore, R. (2000). Blind subjects construct conscious mental images of visual scenes encoded in musical form. *Proc. R. Soc. Lond. B Biol. Sci.* 267, 2231–2238. doi: 10.1098/rspb.2000.1273

Cuppone, A. V., Cappagli, G., and Gori, M. (2018). Audio feedback associated with body movement enhances audio and somatosensory spatial representation. *Front. Integ. Neurosci.* 12:37. doi: 10.3389/fnint.2018.00037

Cuturi, L. F., Aggius-Vella, E., Campus, C., Parmiggiani, A., and Gori, M. (2016). From science to technology: orientation and mobility in blind children and adults. *Neurosci. Biobehav. Rev.* 71, 240–251. doi: 10.1016/j.neubiorev.2016.08.019

Fiehler, K., Reuschel, J., and Rösler, F. (2009). Early non-visual experience influences proprioceptive-spatial discrimination acuity in adulthood. *Neuropsychologia* 47, 897–906. doi: 10.1016/j.neuropsychologia.2008.12.023

Finocchietti, S., Cappagli, G., and Gori, M. (2015a). Encoding audio motion: spatial impairment in early blind individuals. *Front. Psychol.* 6:1357. doi: 10.3389/fpsyg.2015.01357

Finocchietti, S., Cappagli, G., Porquis, L. B., Baud-Bovy, G., Cocchi, E., and Monica, G. (2015b). Evaluation of the audio bracelet for blind interaction for improving mobility and spatial cognition in early blind children - a pilot study. *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2015, 7998–8001. doi: 10.1109/EMBC.2015.7320248

Finocchietti, S., Cappagli, G., and Gori, M. (2017). Auditory spatial recalibration in congenital blind individuals. *Front. Neurosci.* 11:76. doi: 10.3389/fnins.2017.00076

Gaunet, F., and Rossetti, Y. (2006). Effects of visual deprivation on space representation: immediate and delayed pointing toward memorised proprioceptive targets. *Perception* 35, 107–124. doi: 10.1068/p5333

Goble, D. J. (2010). Proprioceptive acuity assessment via joint position matching: from basic science to general practice. *Phys. Ther.* 90, 1176–1184. doi: 10.2522/ptj.20090399

Gori, M., Sandini, G., Martinoli, C., and Burr, D. C. (2013). Impairment of auditory spatial localization in congenitally blind human subjects. *Brain* 137, 288–293. doi: 10.1093/brain/awt311

Maulucci, R. A., and Eckhouse, R. H. (2001). Retraining reaching in chronic stroke with real-time auditory feedback. *NeuroRehabilitation* 16, 171–182.

Pasqualotto, A., and Proulx, M. J. (2012). The role of visual experience for the neural basis of spatial cognition. *Neurosci. Biobehav. Rev.* 36, 1179–1187. doi: 10.1016/j.neubiorev.2012.01.008

Pollok, B., Schnitzler, I., Stoerig, P., Mierdorf, T., and Schnitzler, A. (2005). Image-to-sound conversion: experience-induced plasticity in auditory cortex of blindfolded adults. *Exp. Brain Res.* 167, 287–291. doi: 10.1007/s00221-005-0060-8

Putzar, L., Goerendt, I., Lange, K., Rösler, F., and Röder, B. (2007). Early visual deprivation impairs multisensory interactions in humans. *Nat. Neurosci.* 10:1243. doi: 10.1038/nn1978

Renier, L., Collignon, O., Poirier, C., Tranduy, D., Vanlierde, A., Bol, A., et al. (2005). Cross-modal activation of visual cortex during depth perception using auditory substitution of vision. *Neuroimage* 26, 573–580. doi: 10.1016/j.neuroimage.2005.01.047

Robertson, J. V., Hoellinger, T., Lindberg, P., Bensmail, D., Hanneton, S., and Roby-Brami, A. (2009). Effect of auditory feedback differs according to side of hemiparesis: a comparative pilot study. *J. Neuroeng. Rehab.* 6:45. doi: 10.1186/1743-0003-6-45

Röder, B., Rösler, F., and Spence, C. (2004). Early vision impairs tactile perception in the blind. *Curr. Biol.* 14, 121–124. doi: 10.1016/s0960-9822(03)00984-9

Rosati, G., Oscari, F., Spagnol, S., Avanzini, F., and Masiero, S. (2012). Effect of task-related continuous auditory feedback during learning of tracking motion exercises. *J. Neuroeng. Rehabil.* 9:79. doi: 10.1186/1743-0003-9-79

Rossetti, Y., Gaunet, F., and Thinus-Blanc, C. (1996). Early visual experience affects memorization and spatial representation of proprioceptive targets. *NeuroReport* 7, 1219–1223. doi: 10.1097/00001756-199604260-00025

Sigrist, R., Rauter, G., Riener, R., and Wolf, P. (2013). Augmented visual, auditory, haptic, and multimodal feedback in motor learning: a review. *Psychon. Bull. Rev.* 20, 21–53. doi: 10.3758/s13423-012-0333-8

Striem-Amit, E., Cohen, L., Dehaene, S., and Amedi, A. (2012). Reading with sounds: sensory substitution selectively activates the visual word form area in the blind. *Neuron* 76, 640–652. doi: 10.1016/j.neuron.2012.08.026

Tabry, V., Zatorre, R. J., and Voss, P. (2013). The influence of vision on sound localization abilities in both the horizontal and vertical planes. *Front. Psychol.* 4:932. doi: 10.3389/fpsyg.2013.00932

Velázquez, R. (2010). "Wearable assistive devices for the blind," in *Wearable and Autonomous Biomedical Devices and Systems for Smart Environment*, Vol. 75, eds A. Lay-Ekuakille, and S. C. Mukhopadhyay, (Berlin: Springer), 331–349. doi: 10.1007/978-3-642-15687-8_17

Vercillo, T., Burr, D., and Gori, M. (2016). Early visual deprivation severely compromises the auditory sense of space in congenitally blind children. *Dev. Psychol.* 52:847. doi: 10.1037/dev0000103

Voss, P., Tabry, V., and Zatorre, R. J. (2015). Trade-off in the sound localization abilities of early blind individuals between the horizontal and vertical planes. *J. Neurosci.* 35, 6051–6056. doi: 10.1523/JNEUROSCI.4544-14.2015

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Individuals With Hemiparetic Stroke Accurately Match Torques They Generate About Each Elbow Joint

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Background: Successful execution of a task as simple as drinking from a cup and as complicated as cutting food with a fork and knife requires accurate perception of the torques that one generates in each arm. Prior studies have shown that individuals with hemiparetic stroke inaccurately judge their self-generated torques during bimanual tasks; yet, it remains unclear whether these individuals inaccurately judge their self-generated torques during unimanual tasks.

Objective: The goal of this work was to determine whether stroke affected how accurately individuals with stroke perceive their self-generated torques during a single-arm task.

Methods: Fifteen individuals with hemiparetic stroke and fifteen individuals without neurological impairments partook in this study. Participants generated a target torque about their testing elbow while receiving visual feedback, relaxed, and then matched the target torque about the same elbow without receiving feedback. This task was performed for two target torques (5 Nm, 25% of maximum voluntary torque), two movement directions (flexion, extension), and two arms (left, right).

Results: Clinical assessments indicate that eleven participants with stroke had kinaesthetic deficits and two had altered pressure sense; their motor impairments spanned from mild to severe. These participants matched torques at each elbow, for each target torque and movement direction, with a similar accuracy and precision to controls, regardless of the arm tested ($p > 0.050$).

Conclusions: These results indicate that an individual with sensorimotor deficits post-hemiparetic stroke may accurately judge the torques that they generate within each arm. Therefore, while survivors of a hemiparetic stroke may have deficits in accurately judging the torques they generate during bimanual tasks, such deficits do not appear to occur during unimanual tasks.

Keywords: perception, torque, stroke, evaluation methodology, mechatronics

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1. INTRODUCTION

Activities of daily living, including pulling open a drawer and cutting a fruit, require not only the correct generation, but also the accurate interpretation of movements (Cole and Sedgwick, 1992; Cole, 1995). Intact sensorimotor control is required for an individual to seamlessly carry out such actions. After a hemiparetic stroke, changes to force production and motor task execution of the paretic limb have been well-studied and documented (e.g., Hermsdörfer et al., 2003; Stinear et al., 2007; Lodha et al., 2010; Chang et al., 2013; Kang and Cauraugh, 2015). Changes in the paretic limb include weakness (Twitchell, 1951; Brunnström, 1970), hyperactive stretch reflexes (McPherson et al., 2018a,b), and loss of independent joint control (Dewald et al., 1995; Dewald and Beer, 2001; Sukal et al., 2007). Evidence also suggests that the non-paretic limb is affected after a stroke (Corkin et al., 1973; Carey and Matyas, 2011; Sainburg et al., 2016). However, the impact of a hemiparetic stroke on an individual's ability to perceive their self-generated forces in each limb has not been as extensively characterized.

Literature suggests that the perception of force is formed based on the processing of the descending motor commands and/or ascending sensory information (Proske and Allen, 2019). Previous research, using between-arms protocols, suggests that individuals with hemiparetic stroke perceive a reference torque about their elbow based mainly on the effort required to produce the torque (Bertrand et al., 2004; Mercier et al., 2004; Lodha et al., 2012; Yen and Li, 2015; van der Helm et al., 2017). Our earlier work revealed errors in matching torques between arms to the extent that an individual with hemiparetic stroke perceived their self-generated torque at their paretic arm as being seven times greater than at their non-paretic arm (Gurari et al., 2019). The deficit observed in a between-arms task could arise due to deficits within the paretic arm itself. Yet, previous studies have not addressed whether these individuals can accurately identify the torques that they generate during a single-arm task. This gap exists in our understanding of how a hemiparetic stroke impacts an individual's perception of torques they generate at their paretic limb. Therefore, we aimed to evaluate whether individuals with hemiparetic stroke can accurately match torques about their elbow within one arm.

Given the possibility that stroke impacts the non-paretic limb (Corkin et al., 1973; Carey and Matyas, 2011; Sainburg et al., 2016), we assessed the accuracy in matching self-generated torques about the elbow in both the paretic and non-paretic arms of individuals with hemiparetic stroke. We also compared their performance with that of similarly-aged individuals without neurological impairments, i.e., controls, who provided the baseline performance. Given the controversial impact of hand dominance on an individual's judgement of their self-generated torques (Weerakkody et al., 2003; Wang and Sainburg, 2004; Park et al., 2008; Sleimen-Malkoun et al., 2011; Wang et al., 2011; Adamo et al., 2012; Gueugnon et al., 2014; Scotland et al., 2014; van der Helm et al., 2017), we tested both the dominant and non-dominant arms of controls. Therefore, our goal was to characterize the impact of paresis from stroke, as well as hand dominance, on an individual's accuracy in judging their self-generated torques during a single-arm task. While studies support the notion that judging the torques that one generates during a between-arms task may be inaccurate, we hypothesize that this inaccurate judgement will not be apparent during a single-arm task. We hypothesize that individuals with sensorimotor deficits post-hemiparetic stroke will match torques within the same arm with a similar accuracy as controls.

2. METHODS

The methods presented here were designed to resemble the methods used in our assessment of torque perception during a between-arms task so that we could interpret our results in light of those findings (van der Helm et al., 2017; Gurari et al., 2019). As such, we refer the reader to these previous publications for further information relevant to the design of this study.

2.1. Participants

The Northwestern University Institutional Review Board authorized human subject testing (STU00208205), and participants included in this study provided written informed consent. Inclusion criteria for all participants were the ability to understand and successfully execute the task and no serious pain or injury to the arm or peripheral nerves that could interfere with task execution and perception. Individuals with diabetes were excluded to avoid the possibility of participants having diabetic sensory neuropathies. For controls, they were required to be right-hand dominant and a similar age as the participants with hemiparetic stroke.

A licensed physical therapist (i.e., Dr. Justin M. Drogos) screened all participants with stroke to confirm their eligibility and to assess their motor and perceptual impairments via the upper-extremity Fugl-Meyer Motor Assessment (UE FMA) (Fügl-Meyer et al., 1975) and revised Nottingham Sensory Assessment (rNSA) (Lincoln et al., 1998; Stolk-Hornsveld et al., 2006), respectively. Additional inclusion criteria for participants with stroke were a single unilateral lesion of the brain located above the brainstem and not in the cerebellum; brain injury occurring >6 months prior to testing; no use of antispastic agents, e.g., Baclofen, in the past 6 months; and no neurological comorbidities.

2.2. Experimental Setup

The experimental setup, as shown in **Figure 1**, was comprised of a custom mechatronic system, monitor, speakers, and Biodex chair (System 3 Pro^{TM}; Shirley, NY, USA). The mechatronic system included an isometric measurement device, which quantified the torques that the participant generated about their elbow joint using a six-degree-of-freedom force/torque sensor (JR3, Model: 45E15A 1000N; Woodland, CA, USA). The monitor provided the participant real-time visual feedback about the magnitude of their torques generated, and the speakers played aloud recorded audio cues instructing the participant which actions to execute. The Biodex chair restricted movements of the participant at their torso and waist. The software updated at 4 kHz, and trial-related data were stored at 1 kHz.

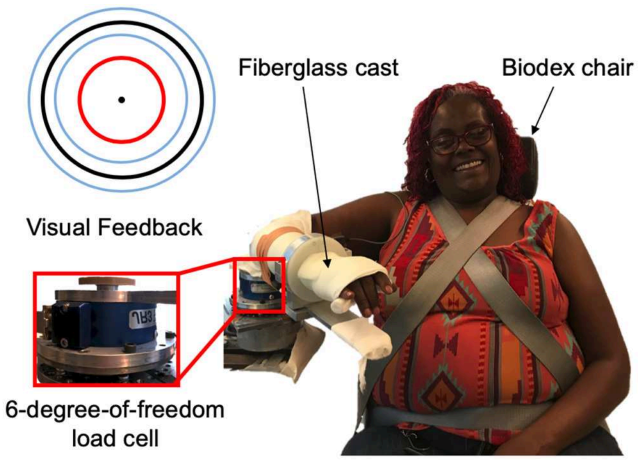

FIGURE 1 | Experimental setup. (Right) An example individual interacting with the experimental setup. (Top, left) Visual feedback displayed on a monitor relayed information about the participant's applied torques about their elbow at the testing arm (red circle), target torque (black circle), and allowable range of applied torques (blue inner and outer circles). (Bottom, left) A multi-axis load cell captured the torques that the participant applied about their testing elbow.

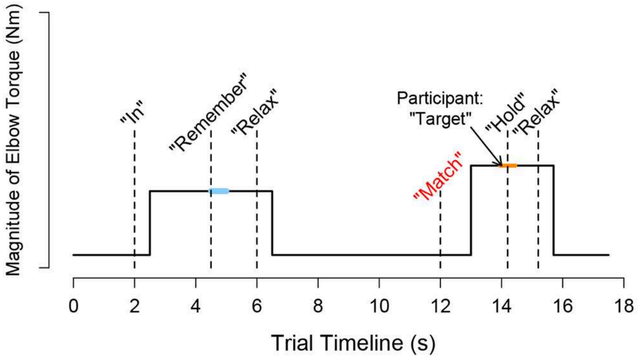

FIGURE 2 | Schematic trial timeline for a torque matching task in flexion. During a trial, *i*, the participant followed automated audio and visual cues to generate a target torque with an arm and then to subjectively match the target torque using the same arm without visual feedback. The participant's self-generated torque at the target ($\tau_{target,i}$) was calculated as the average measured torque following 0.5 s after the audio cue "remember" played, as indicated by the light blue thick horizontal line. The participant's self-generated torque when indicating that the torque matched ($\tau_{indicator,i}$) was calculated as the average measured torque from 0.25 s before and after the "hold" sound played, as indicated by the orange thick horizontal line.

2.3. Experimental Protocol

The participant was requested to not exercise the day before and of testing to avoid muscle fatigue. At the beginning of the testing session, the participant sat with their torso and waist strapped to the Biodex chair. The participant's first testing arm was affixed to an isometric measurement device at 85° shoulder abduction, 40° shoulder flexion, and 90° elbow flexion.

Data collection began with quantifying the maximum voluntary torque (MVT) that the participant could generate about their elbow joint in flexion and extension. Next, we confirmed that motor impairments did not affect the ability of the participant to successfully match torques by verifying that the participant could generate and hold for 4 s 20 and 40% of their MVT in flexion and extension. Following, the participant completed the torque-matching trials. A target torque of 5 Nm was chosen as the fixed torque, and a target torque of 25% MVT was chosen as the percentage torque to address the strength differences in each arm of every participant. The four testing conditions were comprised of two directions (flexion, extension) at two target torques (fixed, percentage). For each of four testing conditions, the participant first became familiarized with the task by completing two practice trials. Then, the participant completed eight testing trials, which were used in the data analyses. Presentation order of the testing conditions was randomized across participants using a Latin square design.

These testing procedures were repeated for the opposite arm. The order of the arm first tested was randomized across participants.

2.4. Trial Timeline

A visual depiction of the events occurring throughout a trial is provided in **Figure 2**. A trial began with the target torque visually depicted as a stationary blue circle on the monitor, which was situated in front of the participant. The acceptable range of torques that the participant could generate, i.e., a minimum of 80% and a maximum of 120% of the target torque, was visually depicted as the inner and outer light blue circles, respectively. To initiate the trial, an automated audio cue stated aloud "in" or "out" to the participant to indicate whether the direction of the target torque was in flexion or extension, respectively. The torque that the participant generated was visually conveyed by a red circle [**Figure 1** (top, left)], whose diameter changed corresponding to the magnitude of the torque that the participant produced. The target torque was reached when the red circle, representing the magnitude of the participant's applied torque, was within the allowable range of applied torques (outlined by the inner and outer light blue circles) for 2 s. The audio cue, "remember," then played to encourage the participant to remember and maintain the target torque for one additional second. Following, the participant was prompted by the automated audio cue to "relax." After 6 s, "match" played to prompt the participant to generate a torque without receiving visual feedback on their self-generated torque. The participant verbally informed the experimenter "target" when the previously held target torque was perceived as matched. The audio cue, "hold," played to instruct the participant to hold this indicator torque for 1 s. Following, "relax" played to signal the ending of the trial. The participant did not receive feedback about their torque-matching ability. The participant then briefly activated their antagonist muscles and relaxed for 20 s before starting the next trial to encourage quiescent muscle activity (McPherson et al., 2008).

3. ANALYSIS

3.1. Strength Asymmetry Index

We used a strength asymmetry index for each direction (i.e., flexion, extension) to quantify the asymmetry in participant strength between arms. The strength asymmetry index was calculated in participants with stroke as the ratio of the MVT of the paretic arm divided by the MVT of the non-paretic arm, and in controls as the ratio of the MVT of the non-dominant arm divided by the MVT of the dominant arm. A strength asymmetry index of 1.0 indicates equal strength between arms. A strength asymmetry index <1.0 indicates that the paretic arm is weaker than the non-paretic arm for participants with stroke and the non-dominant arm is weaker than the dominant arm for controls. A strength asymmetry index >1.0 indicates that the paretic arm is stronger than the non-paretic arm for participants with stroke and the non-dominant arm is stronger than the dominant arm for controls.

3.2. Data Extraction

Data segments extracted and analyzed for each trial, i, are visually depicted in **Figure 2**. The measured target torque, $\tau_{\text{target},i}$, was defined as the mean of 0.5 s of torque data when the participant held the target torque, and the measured indicator torque, $\tau_{\text{indicator},i}$, as the mean of 0.5 s of torque data when the participant indicated that the torques were matched. The error in matching the target torque, $\tau_{\text{error},i}$, was defined for each trial as the difference between the magnitude of the measured target torque and measured indicator torque, i.e., $|\tau_{\text{indicator},i}| - |\tau_{\text{target},i}|$. A positive and negative error indicated that the target torque was overshot and undershot, respectively. Three outcome measures were obtained for each testing condition (i.e., 2 target torques × 2 directions) of each arm of every participant. Constant error, or the mean error across the eight testing trials, indicated whether the participant generated too much or too little torque when matching the target torque. Absolute error, or the mean absolute error across the eight testing trials, indicated whether the participant accurately matched the target torque, regardless of whether too much or too little torque was generated. Variable error, or the standard deviation of the error across the eight testing trials, indicated whether the participant matched consistently using the same torque or was highly variable.

3.3. Statistical Testing

Analyses were run for each direction (i.e., flexion, extension), separately, to determine whether strength, i.e., MVT, depended on the arm tested. Additionally, analyses were run for each testing condition (i.e., 2 target torques × 2 directions), separately, to determine whether the three outcome measures (i.e., CE, AE, VE) depended on the arm tested. We used a linear-mixed effects model (Laird and Ware, 1982; Pinheiro and Bates, 2000) to run this analysis, where arm (i.e., dominant and non-dominant in controls; non-paretic and paretic in participants with stroke) was defined as a fixed effect and participant as a random effect. We ran an analysis of variance to identify significant differences and accounted for the multiple outcome measures using a Holm correction (Holm, 1979).

4. RESULTS

4.1. Participants

Relevant information about each participant is provided in **Table 1**. Ten male and five female controls were tested. All participants were right-hand dominant (Oldfield, 1971) and had a mean ± standard deviation age of 57 ± 10 (range: 28–67).

Thirteen male and two female participants with hemiparetic stroke were tested. Twelve were right-hand dominant (Oldfield, 1971), and nine had a right-arm paresis. Participants with stroke had a mean ± standard deviation age of 57 ± 11 (range: 29–83) and were 11 ± 8 years since their stroke (range: 1–31).

Sensorimotor deficits of participants with stroke, as determined by the UE FMA and rNSA, are reported in **Table 1**. Participants with stroke had an UE FMA score that spanned 17–57 ($\mu \pm \sigma$: 33 ± 15), representing motor impairments ranging from mild to severe. Based on their rNSA elbow kinaesthetic sensation score, eleven of the fifteen participants with stroke had deficits in identifying the location of their paretic limb in space. Based on their rNSA elbow pressure sensation score, out of the fifteen participants with stroke, only two participants had altered pressure sensation in their paretic arm.

4.2. Sensorimotor Control

4.2.1. Strength

The strength among participants in flexion and extension is summarized in **Table 1**. Participants with stroke generated less MVT in their paretic arm than their non-paretic arm (flexion: $p<0.001$; extension: $p < 0.001$), the non-dominant arm of controls (flexion: $p = 0.004$; extension: $p = 0.003$), and the dominant arm of controls (flexion: $p = 0.001$; extension: $p = 0.004$). Comparing the non-paretic arm of participants with stroke with either arm of controls, our analyses did not reveal significant differences in the MVT generated in either flexion (non-dominant: $p = 0.838$; dominant: $p = 0.515$) or extension (non-dominant: $p = 0.942$; dominant: $p = 0.830$). For controls, the MVT generated by their dominant and non-dominant arms did not significantly differ in either flexion ($p = 0.427$) or extension ($p = 0.839$).

In **Figure 3** (top, left) and **Figure 4** (top, left), we identify the percentage of MVT at which participants were tested during the fixed task when the target torque was 5 Nm. When matching in flexion, the 5 Nm target torque corresponded to a mean ± standard deviation of 8.8 ± 3.4 and 9.2 ± 3.4% of the MVT of the dominant and non-dominant arm in controls, and 10.0 ± 5.6 and 17.1 ± 9.5% of the non-paretic and paretic arm in participants with stroke. When matching in extension, the 5 Nm target torque corresponded to 12.7 ± 4.6 and 13.4 ± 6.0% of the MVT of the dominant and non-dominant arm in controls, and 13.4 ± 7.8 and 24.0 ± 12.2% of the non-paretic and paretic arm in participants with stroke.

In **Figure 3** (top, right) and **Figure 4** (top, right), we indicate the magnitude of torque at which participants were tested when the target torque was 25% of their testing arm's MVT. 25% MVT in flexion corresponded to a mean ± standard deviation of 16.0 ± 5.4 and 15.2 ± 5.2 Nm at the dominant and non-dominant arm of

TABLE 1 | Participant information.

Participant	Age (years)/ Gender	UE FMA score	rNSA elbow kinaesthetic sensation score (Max of 3)	rNSA elbow pressure sensation score (Max of 2)	Year(s) since stroke	Lesion location(s) (L: Left/R: Right)	$\tau_{MVT:flex}$ Par/Non-Dom arm (Nm)	$\tau_{MVT:flex}$ Non-Par/Dom arm (Nm)	$\tau_{MVT:ext}$ Par/Non-Dom arm (Nm)	$\tau_{MVT:ext}$ Non-Par/Dom arm (Nm)
Stroke 1	53/M	17	2	2	31	NA	48	88	29	56
Stroke 2	49/M	31	2	2	15	R: Th, IC	48	77	25	48
Stroke 3	63/M	24	2	2	12	R: Th, IC, BG	39	84	11	62
Stroke 4	72/M	40	2	2	8	R: IC, Th, I	20	45	24	36
Stroke 5	48/M	18	2	1	11	R: Th, IC, BG	14	76	23	66
Stroke 6	66/F	25	2	2	11	L: BG, IC	16	19	15	12
Stroke 7	44/M	43	2	2	5	L: IC,BG,Th,F,P	57	70	34	47
Stroke 8	72/M	12	2	2	24	L: I, IC, Th, BG	23	76	16	69
Stroke 9	55/M	58	3	2	11	L: T-P	35	46	28	29
Stroke 10	29/F	20	3	2	1	L: F	17	26	13	17
Stroke 11	62/M	32	3	2	8	NA	47	65	40	51
Stroke 12	83/M	50	2	2	3	L: IC, I, P	52	63	37	46
Stroke 13	59/M	19	2	0	10	R: F, P	30	53	11	50
Stroke 14	62/M	45	3	2	5	R: IC	48	58	34	52
Stroke 15	60/M	57	2	2	8	L: IC, BG	50	72	35	51
Control 1	62/M	–	–	–	–	–	90	97	69	71
Control 2	44/M	–	–	–	–	–	73	79	52	52
Control 3	60/M	–	–	–	–	–	62	66	35	42
Control 4	63/M	–	–	–	–	–	90	94	42	66
Control 5	64/F	–	–	–	–	–	46	42	32	31
Control 6	62/M	–	–	–	–	–	78	80	75	65
Control 7	55/M	–	–	–	–	–	62	75	50	51
Control 8	61/M	–	–	–	–	–	82	99	59	58
Control 9	28/M	–	–	–	–	–	74	61	54	42
Control 10	67/M	–	–	–	–	–	33	34	23	27
Control 11	60/F	–	–	–	–	–	35	37	22	24
Control 12	61/F	–	–	–	–	–	37	36	23	26
Control 13	50/F	–	–	–	–	–	39	42	27	28
Control 14	64/F	–	–	–	–	–	44	39	28	31
Control 15	61/M	–	–	–	–	–	62	65	56	55

This table summarizes relevant clinical and experimental information about each participant. M, male; F, female; UE FMA, upper-extremity Fugl-Meyer Motor Assessment; rNSA, revised Nottingham Sensory Assessment; Max, maximum; $\tau_{MVT:flex}$, maximum voluntary torque in elbow flexion; $\tau_{MVT:ext}$, maximum voluntary torque in elbow extension; Dom, dominant; Non-Dom, non-dominant; Par, paretic; Non-Par, non-paretic; NA, not available; -, data not relevant to the participant; Th, thalamus; IC, internal capsule; BG, basal ganglia; F, frontal; P, parietal; O, occipital; T, temporal; T-P, tempo-parietal; I, insula.

controls, and 14.8 ± 4.9 and 9.4 ± 4.4 Nm at the non-paretic and paretic arm of participants with stroke. 25% MVT in extension corresponded to a range of 11.0 ± 3.6 and 11.2 ± 4.7 Nm at the dominant and non-dominant arm of controls, and 11.3 ± 4.0 and 6.5 ± 3.0 Nm at the non-paretic and paretic arm of participants with stroke.

4.2.2. Strength Asymmetry Between Arms

The strength asymmetry index for controls ranged from 0.83 to 1.21 ($\mu \pm \sigma$: 0.98 ± 0.10) and 0.64 to 1.29 ($\mu \pm \sigma$: 0.96 ± 0.15) in flexion and extension, respectively. For participants with stroke, the strength asymmetry index in flexion ranged from 0.18 to 0.84 ($\mu \pm \sigma$: 0.62 ± 0.20) and in extension ranged from 0.18 to 1.25 ($\mu \pm \sigma$: 0.62 ± 0.29).

4.3. Matching of Torques

4.3.1. Flexion

The accuracy and precision of participants when matching each target torque are reported in **Table 2** and **Figure 3**. Among the three outcome measures quantifying torque-matching errors, no differences between the dominant and non-dominant arm of the controls and non-paretic and paretic arm of the participants with stroke were found when matching a torque in flexion of 5Nm (CE: $p = 0.307$;

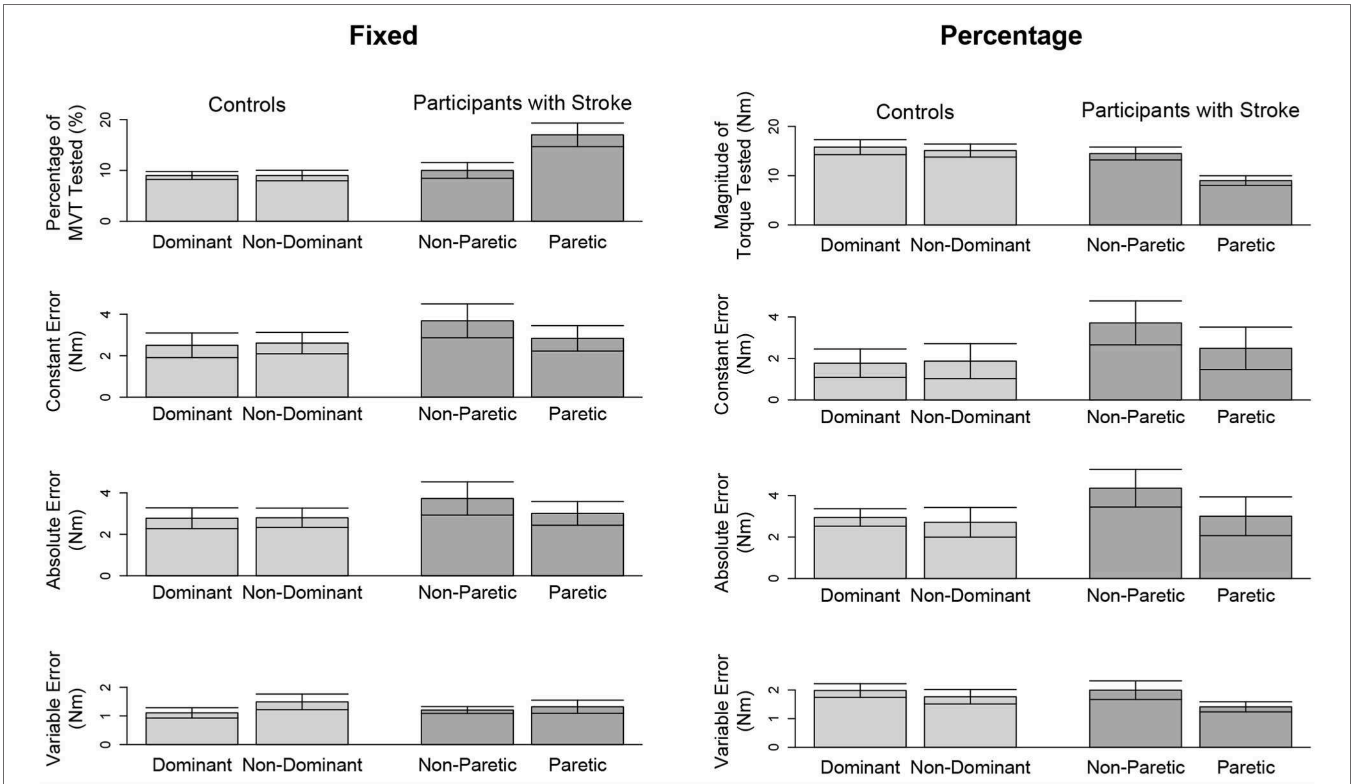

FIGURE 3 | Outcome measures when matching in flexion. Mean and standard error of participants' tested target torques, constant errors, absolute errors, and variable errors when matching in flexion a target torque of **(left)** 5 Nm and **(right)** 25% of their testing arm's MVT.

AE: $p = 0.422$; VE: $p = 0.383$) or 25% MVT (CE: $p = 0.410$; AE: $p = 0.271$; VE: $p = 0.160$). Additionally, we acknowledge that the lesioned hemisphere and arm dominance of the participants with stroke were heterogeneous. Our analyses, however, did not reveal differences in torque-matching errors depending on arm dominance or lesioned hemisphere ($p > 0.050$).

4.3.2. Extension

Due to a lack of steady control, Stroke 6 was unable to hold their self-generated torques in extension within 80 and 120% of the target torque for 2 s when using their paretic arm. Therefore, this participant's data were not included in the following analyses. The accuracy and precision of the remaining 14 participants when matching each target torque are reported in **Table 3** and **Figure 4**. Among the three outcome measures quantifying the torque-matching errors, no differences between the dominant and non-dominant arm of the controls and non-paretic and paretic arm of the participants with stroke were found when matching a torque in extension of 5Nm (CE: $p = 0.533$; AE: $p = 0.297$; VE: $p = 0.531$) or 25% MVT (CE: $p = 0.367$; AE: $p = 0.892$; VE: $p = 0.522$). Our analyses did not find any significant differences in torque-matching errors depending on the lesioned hemisphere and arm dominance of the participants with stroke ($p > 0.050$).

5. DISCUSSION

This work investigated whether individuals with hemiparetic stroke could accurately identify the torques that they generated about each elbow joint, independently. The main finding is that our tested participants with stroke could judge sub-maximal isometric torques that they generated within each limb with a similar accuracy and precision as our tested participants without neurological impairments.

5.1. Controls

We included the results of controls to quantify baseline performance when referencing a sub-maximal torque about each elbow. Findings based on the controls indicate that the accuracy and precision in matching sub-maximal torques about a single elbow were not impacted by the arm tested (i.e., dominant, non-dominant), regardless of the direction (i.e., flexion, extension) and magnitude (i.e., 5 Nm, 25% MVT) of the torque. Several previous studies have suggested a potential effect of arm dominance on the utilization of proprioceptive feedback (Scotland et al., 2014), especially for position control (Goble and Brown, 2007; Goble et al., 2009). However, in terms of accuracy and precision in matching a torque, we did not observe an effect of arm dominance. A possible reason for not observing a significant effect is the relatively

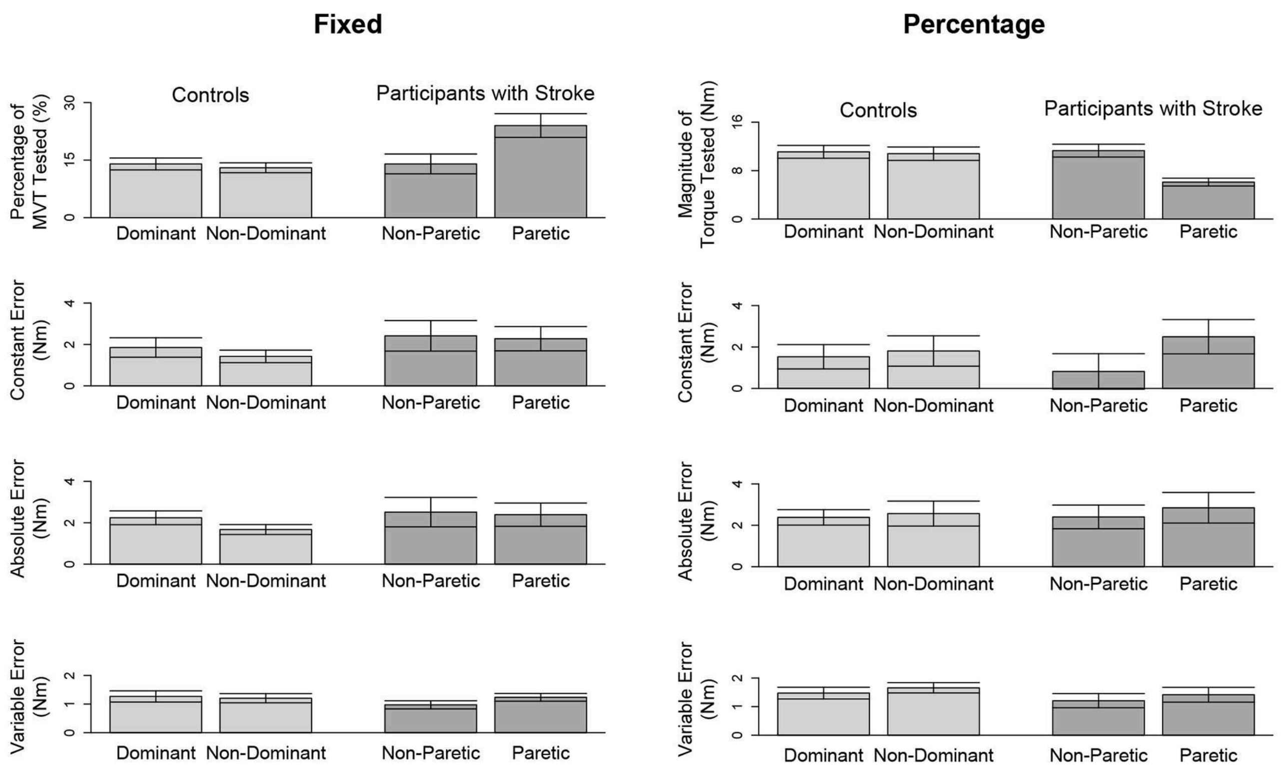

FIGURE 4 | Outcome measures when matching in extension. Mean and standard error of participants' tested target torques, constant errors, absolute errors, and variable errors when matching in extension a target torque of **(left)** 5 Nm and **(right)** 25% of their testing arm's MVT.

TABLE 2 | Statistical results when matching in flexion.

Target Torque	Group	Arm	μ_{torque} (Nm)	CE (Nm)	AE (Nm)	VE (Nm)
5 Nm	Controls	Dominant	5.1 ± 0.3 (4.5, 5.5)	2.5 ± 2.3 (−1.6, 6.8)	2.8 ± 1.9 (0.5, 6.8)	1.1 ± 0.7 (0.4, 3.0)
		Non-dominant	5.1 ± 0.2 (4.7, 5.4)	2.6 ± 2.0 (−0.9, 7.5)	2.8 ± 1.8 (0.7, 7.5)	1.5 ± 1.1 (0.5, 4.5)
	Participants with stroke	Non-paretic	5.0 ± 0.2 (4.6, 5.3)	3.7 ± 3.1 (−0.2, 11.2)	3.7 ± 3.1 (0.4, 11.2)	1.2 ± 0.5 (0.4, 2.3)
		Paretic	4.8 ± 0.3 (4.4, 5.6)	2.8 ± 2.3 (0.1, 5.9)	3.0 ± 2.2 (0.4, 5.9)	1.3 ± 0.9 (0.4, 3.9)
25%MVT	Controls	Dominant	16.1 ± 5.6 (8.7, 23.8)	1.8 ± 2.6 (−3.6, 6.3)	2.9 ± 1.6 (0.6, 6.3)	2.0 ± 0.9 (0.8, 3.7)
		Non-dominant	14.9 ± 5.2 (8.2, 24.7)	1.9 ± 3.3 (−1.3, 11.0)	2.7 ± 2.8 (0.6, 11.0)	1.8 ± 1.0 (0.7, 4.0)
	Participants with stroke	Non-paretic	14.5 ± 4.8 (4.7, 19.9)	3.7 ± 4.1 (−1.7, 10.7)	4.4 ± 3.5 (0.5, 10.9)	2.0 ± 1.3 (0.3, 5.4)
		Paretic	9.0 ± 4.5 (3.3, 18.8)	2.5 ± 4.0 (−0.9, 13.5)	3.0 ± 3.6 (0.5, 13.5)	1.4 ± 0.7 (0.3, 2.3)

Mean ± standard deviation and range (minimum, maximum) are reported for the measured target torque and every outcome measure. μ_{torque}, mean magnitude of measured target torque; CE, constant error; AE, absolute error; VE, variable error.

TABLE 3 | Statistical results when matching in extension.

Target Torque	Group	Arm	μ_{torque} (Nm)	CE (Nm)	AE (Nm)	VE (Nm)
5 Nm	Controls	Dominant	5.0 ± 0.3 (4.5, 5.5)	1.9 ± 1.8 (−1.4, 5.2)	2.2 ± 1.3 (0.4, 5.2)	1.3 ± 0.8 (0.5, 3.2)
		Non-dominant	4.9 ± 0.2 (4.5, 5.4)	1.4 ± 1.2 (−0.7, 3.2)	1.7 ± 1.0 (0.4, 3.2)	1.2 ± 0.6 (0.5, 2.3)
	Participants with stroke	Non-paretic	4.9 ± 0.2 (4.5, 5.4)	2.4 ± 2.7 (−0.3, 8.0)	2.5 ± 2.6 (0.3, 8.1)	1.0 ± 0.5 (0.4, 2.4)
		Paretic	4.8 ± 0.3 (4.4, 5.5)	2.3 ± 2.2 (0.2, 7.9)	2.4 ± 2.1 (0.5, 7.9)	1.2 ± 0.5 (0.6, 2.4)
25%MVT	Controls	Dominant	10.9 ± 3.7 (6.0, 17.5)	1.5 ± 2.3 (−1.9, 5.5)	2.4 ± 1.5 (0.3, 5.5)	1.5 ± 0.8 (0.3, 3.3)
		Non-dominant	10.9 ± 4.5 (5.4, 17.8)	1.8 ± 2.8 (−1.6, 8.6)	2.6 ± 2.3 (0.4, 8.6)	1.7 ± 0.7 (0.5, 2.8)
	Participants with stroke	Non-paretic	11.3 ± 3.8 (3.9, 17.5)	0.8 ± 3.0 (−3.3, 6.9)	2.4 ± 2.0 (−0.2, 6.9)	1.2 ± 0.9 (0.2, 2.9)
		Paretic	6.1 ± 3.3 (2.4, 13.6)	2.5 ± 2.9 (−1.4, 8.5)	2.8 ± 2.6 (0.5, 8.5)	1.4 ± 0.9 (0.4, 3.4)

Mean ± standard deviation and range (minimum, maximum) are reported for the measured target torque and every outcome measure. μ_{torque}, mean magnitude of measured target torque; CE, constant error; AE, absolute error; VE, variable error.

small sample size of the controls. Even so, the magnitude of torque-matching errors (i.e., absolute error) between the dominant and non-dominant arm in controls did not differ more than 0.5 Nm, regardless of the torque magnitude and direction. Therefore, while collecting data from additional controls might lead to a significant difference in torque-matching errors, the current data indicate that the effect size, or difference, would be quite small.

5.2. Participants With Stroke

To begin, we highlight that the tested participants with stroke had motor impairments, according to their UE FMA scores and paretic limb weakness, that ranged from mild to severe. Even so, we confirmed that their ability to match torques was not influenced by their motor impairments. This was achieved by verifying prior to testing that the participant could generate and maintain a target torque for at least 4 s.

We compared the torque-matching ability of the participants post-stroke with that of the controls to identify potential deficits in judging torques within a single arm. Previous studies suggest that errors in matching torques between arms are associated with the relative weakness of the paretic arm (Bertrand et al., 2004; Mercier et al., 2004; Yen and Li, 2015). In our study, participants with stroke had varying degrees of hemiparesis, represented by the strength asymmetry index ranging from 0.18 to 1.25. Nonetheless, our participants with hemiparetic stroke, when matching torques within a single arm, had magnitudes of errors considerably less than those in our group's previous studies in which individuals with stroke were requested to match torques between arms (e.g., van der Helm et al., 2017; Gurari et al., 2019). For comparison, in this study, when matching a fixed torque of 5 Nm within a single arm, torque-matching errors reached upwards of 7.9 Nm at the paretic arm of our participants with stroke and 6.8 Nm at the dominant arm of controls. Previous testing on matching a fixed torque of 5 Nm between-arms revealed errors that reached upwards of 18.5 Nm in a similar group of participants with stroke and 7.6 Nm in controls (Gurari et al., 2019). Therefore, even though our participants with stroke were hemiparetic, and consequently, might exhibit deficits in matching torques between-arms, our findings indicate they could judge their self-generated torques within each arm similarly to controls.

The perception of forces in individuals without neurological impairments is generally thought to have both a peripheral origin from mechanoreceptors (Jones and Piateski, 2006; Luu et al., 2011), such as the Golgi tendon organ (Roland and Ladegaard-Pedersen, 1977; Jami, 1992), and a central origin from signals related to motor commands (McCloskey et al., 1974; Jones and Hunter, 1983; Scotland et al., 2014). However, the exact neural mechanism underlying the perception of forces has yet to be elucidated and remains an area of debate (Proske and Allen, 2019). Results of our study suggest that individuals with hemiparetic stroke were able to reproduce a rotational force, i.e., torque, about their elbow using the same arm, with a comparable accuracy and precision as individuals without neurological impairments. It is possible that they utilized centrally generated signals, such as an efference copy, when matching using the same arm, even if the signal was erroneous. It is also possible that participants with stroke relied on afferent feedback, albeit potentially erroneous, arising from the mechanoreceptors to match an elbow torque in the same arm. As such, our study does not provide insight about potential neural mechanisms used when judging torques in individuals post-stroke. Nevertheless, this study aids in our current understanding of force perception post-stroke by demonstrating that information used to match sub-maximal torques within a single arm is reliable enough to allow an accurate and precise reproduction of previously generated torques in individuals with hemiparetic stroke.

5.3. Limitations

Our experimental design required individuals to control a steady torque for 3 s to successfully execute a torque-matching trial. For individuals with stroke, due to weakness or lack of control of their self-generated torques, it could be difficult to maintain a constant torque for 3 s. We had to exclude four individuals with stroke during screening. Hence, findings from this study are unable to address torque-matching ability within a single arm of individuals with hemiparetic stroke who present such motor impairments.

Additionally, daily activities may involve a generation of torques lasting longer than 3 s, and maintaining a torque for a longer duration could result in increased variability of the torque production for individuals with stroke (Lodha et al., 2013; Kang and Cauraugh, 2015). An increase in torque production variability can negatively affect how precisely a torque is perceived (Gurari et al., 2017). As such, a limitation of this work is that it does not assess how accurately and precisely individuals post-hemiparetic stroke can identify torques that are maintained for >3 s. However, fatigue would pose an experimental challenge, particularly for participants with stroke, if participants are required to hold target torques for a longer duration.

Moreover, our recruitment did not yield participants with stroke who were clinically assessed with severe sensory impairments. Therefore, it is not clear whether findings from this study can be extended to populations who are identified as having more severe sensory deficits.

6. CONCLUSIONS AND FUTURE DIRECTIONS

Current evidence suggests that, when matching a sub-maximal torque about the elbow within a single arm, individuals with hemiparetic stroke can achieve a similar accuracy and precision as individuals with neurological impairments. This result highlights that, even though individuals with hemiparetic stroke might have deficits in matching torques between-arms as indicated by previous studies (Bertrand et al., 2004; Yen and Li, 2015; Gurari et al., 2019), they may reliably reproduce previously generated torques within a single arm. Future work plans to expand this line of research to address how accurately individuals with hemiparetic stroke perceive their self-generated torques during multi-degree-of-freedom isometric tasks. Participants in this study were asked to generate a one-degree-of-freedom isometric torque, i.e., a torque about their elbow joint, which has limited applications in the real world. Most activities of daily living involve the simultaneous generation of torques at numerous joints. Furthermore, the literature highlights the challenges that individuals with hemiparetic stroke face in controlling independent joint movements (Dewald et al., 1995; Dewald and Beer, 2001; Sukal et al., 2007). Therefore, future work can address the effect of multi-joint isometric tasks on the accuracy of individuals with hemiparetic stroke in judging their self-generated torques.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Northwestern University Institutional Review Board. The patients/participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

AUTHOR CONTRIBUTIONS

NG, NC, JMD, and JPAD: study design and manuscript editing. NG, NC, and JMD: data acquisition. NG and NC: data analysis, data interpretation, and manuscript preparation.

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REFERENCES

Adamo, D. E., Scotland, S., and Martin, B. J. (2012). Asymmetry in grasp force matching and sense of effort. *Exp. Brain Res.* 217, 273–285. doi: 10.1007/s00221-011-2991-6

Bertrand, A. M., Mercier, C., Shun, P. L. W., Bourbonnais, D., and Desrosiers, J. (2004). Effects of weakness on symmetrical bilateral grip force exertion in subjects with hemiparesis. *J. Neurophysiol.* 91, 1579–1585. doi: 10.1152/jn.00597.2003

Brunnström, S. (1970). *Movement Therapy in Hemiplegia: A Neurophysiological Approach*. New York, NY: Harper & Row.

Carey, L. M., and Matyas, T. A. (2011). Frequency of discriminative sensory loss in the hand after stroke in a rehabilitation setting. *J. Rehabil. Med.* 43, 257–263. doi: 10.2340/16501977-0662

Chang, S. H., Durand-Sanchez, A., Ditommaso, C., and Li, S. (2013). Interlimb interactions during bilateral voluntary elbow flexion tasks in chronic hemiparetic stroke. *Physiol. Rep.* 1, 1–9. doi: 10.1002/phy2.10

Cole, J. (1995). *Pride and a Daily Marathon*. Cambridge: The MIT Press.

Cole, J. D., and Sedgwick, E. M. (1992). The perceptions of force and of movement in a man without large myelinated sensory afferents below the neck. *J. Physiol.* 449, 503–515.

Corkin, S., Milner, B., and Taylor, L. (1973). Bilateral sensory loss after unilateral cerebral lesion in man. *Trans. Am. Neurol. Assoc.* 98, 118–22.

Dewald, J. P. A., and Beer, R. F. (2001). Abnormal joint torque patterns in the paretic upper limb of subjects with hemiparesis. *Muscle Nerve* 24, 273–283. doi: 10.1002/1097-4598(200102)24:2<273::AID-MUS130>3.0.CO;2-Z

Dewald, J. P. A., Pope, P. S., Given, J. D., Buchanan, T. S., and Rymer, W. Z. (1995). Abnormal muscle coactivation patterns during isometric torque generation at the elbow and shoulder in hemiparetic subjects. *Brain* 118, 495–510.

Fügl-Meyer, A. R., Jääskö, L., Leyman, I., Olsson, S., and Steglind, S. (1975). The post-stroke hemiplegic patient. 1. A method for evaluation of physical performance. *Scand. J. Rehabil. Med.* 7, 13–31.

Goble, D. J., and Brown, S. H. (2007). Task-dependent asymmetries in the utilization of proprioceptive feedback for goal-directed movement. *Exp. Brain Res.* 180, 693–704. doi: 10.1007/s00221-007-0890-7

Goble, D. J., Noble, B. C., and Brown, S. H. (2009). Proprioceptive target matching asymmetries in left-handed individuals. *Exp. Brain Res.* 197, 403–408. doi: 10.1007/s00221-009-1922-2

Gueugnon, M., Torre, K., Mottet, D., and Bonnetblanc, F. (2014). Asymmetries of bilateral isometric force matching with movement intention and unilateral fatigue. *Exp. Brain Res.* 232, 1699–1706. doi: 10.1007/s00221-014-3862-8

Gurari, N., Okamura, A., and Kuchenbecker, K. (2017). Perception of force and stiffness in the presence of low-frequency haptic noise. *PLoS ONE* 12:e178605. doi: 10.1371/journal.pone.0178605

Gurari, N., van der Helm, N. A., Drogos, J. M., and Dewald, J. P. A. (2019). Accuracy of individuals post-hemiparetic stroke in matching torques between arms depends on the arm referenced. *Front. Neurol.* 10:921. doi: 10.3389/fneur.2019.00921

Hermsdörfer, J., Hagl, E., Nowak, D. A., and Marquardt, C. (2003). Grip force control during object manipulation in cerebral stroke. *Clin. Neurophysiol.* 114, 915–929. doi: 10.1016/S1388-2457(03)00042-7

Holm, S. (1979). A simple sequentially rejective multiple test procedure. *Scand. J. Stat.* 6, 65–70.

Jami, L. (1992). Golgi tendon organs in mammalian skeletal muscle: functional properties and central actions. *Physiol. Rev.* 72, 623–666.

Jones, L. A., and Hunter, I. W. (1983). Effect of fatigue on force sensation. *Exp. Neurol.* 81, 640–650.

Jones, L. A., and Piateski, E. (2006). Contribution of tactile feedback from the hand to the perception of force. *Exp. Brain Res.* 168, 298–302. doi: 10.1007/s00221-005-0259-8

Kang, N., and Cauraugh, J. H. (2015). Force control in chronic stroke. *Neurosci. Biobehav. Rev.* 52, 38–48. doi: 10.1016/j.neubiorev.2015.02.005

Laird, N. M., and Ware, J. H. (1982). Random-effects models for longitudinal data. *Biometrics* 38, 963–974.

Lincoln, N. B., Jackson, J. M., and Adams, S. A. (1998). Reliability and revision of the Nottingham Sensory Assessment for stroke patients. *Physiotherapy* 84, 358–365.

Lodha, N., Misra, G., Coombes, S. A., Christou, E. A., and Cauraugh, J. H. (2013). Increased force variability in chronic stroke: contributions of force modulation below 1 Hz. *PLoS ONE* 8:e83468. doi: 10.1371/journal.pone.0083468

Lodha, N., Naik, S. K., Coombes, S. A., and Cauraugh, J. H. (2010). Force control and degree of motor impairments in chronic stroke. *Clin. Neurophysiol.* 121, 1952–1961. doi: 10.1016/j.clinph.2010.04.005

Lodha, N., Patten, C., Coombes, S. A., and Cauraugh, J. H. (2012). Bimanual force control strategies in chronic stroke: finger extension versus power grip. *Neuropsychologia* 50, 2536–2545. doi: 10.1016/j.neuropsychologia.2012.06.025

Luu, B. L., Day, B. L., Cole, J. D., and Fitzpatrick, R. C. (2011). The fusimotor and reafferent origin of the sense of force and weight. *J. Physiol.* 589, 3135–3147. doi: 10.1113/jphysiol.2011.208447

McCloskey, D. I., Ebeling, P., and Goodwin, G. M. (1974). Estimation of weights and tensions and apparent involvement of a "sense of effort". *Exp. Neurol.* 42, 220–232.

McPherson, J. G., Ellis, M. D., Harden, R. N., Carmona, C., Drogos, J. M., Heckman, C. J., et al. (2018a). Neuromodulatory inputs to motoneurons contribute to the loss of independent joint control in chronic moderate to severe hemiparetic stroke. *Front. Neurol.* 9:470. doi: 10.3389/fneur.2018.00470

McPherson, J. G., Ellis, M. D., Heckman, C. J., and Dewald, J. P. A. (2008). Evidence for increased activation of persistent inward currents in individuals with chronic hemiparetic stroke. *J. Neurophysiol.* 100, 3236–3243. doi: 10.1152/jn.90563.2008

McPherson, J. G., McPherson, L. M., Thompson, C. K., Ellis, M. D., Heckman, C. J., and Dewald, J. P. A. (2018b). Altered neuromodulatory drive may contribute to exaggerated tonic vibration reflexes in chronic hemiparetic stroke. *Front. Hum. Neurosci.* 12:131. doi: 10.3389/fnhum.2018.00131

Mercier, C., Bertrand, A. M., and Bourbonnais, D. (2004). Differences in the magnitude and direction of forces during a submaximal matching in hemiparetic subjects. *Exp. Brain Res.* 157, 32–42. doi: 10.1007/s00221-003-1813-x

Oldfield, R. C. (1971). The assessment and analysis of handedness: the Edinburgh Inventory. *Neuropsychologia* 9, 97–113.

Park, W.-H., Leonard, C. T., and Li, S. (2008). Finger force perception during ipsilateral and contralateral force matching tasks. *Exp. Brain Res.* 189, 301–310. doi: 10.1007/s00221-008-1424-7

Pinheiro, J. C., and Bates, D. M. (2000). *Mixed-Effects Models in S and S-Plus*. New York, NY: Springer.

Proske, U., and Allen, T. (2019). The neural basis of the senses of effort, force and heaviness. *Exp. Brain Res.* 237, 589–599. doi: 10.1007/s00221-018-5460-7

Roland, P. E., and Ladegaard-Pedersen, H. (1977). A quantitative analysis of sensations of tensions and of kinaesthesia in man. *Brain* 100, 671–692.

Sainburg, R. L., Maenza, C., Winstein, C., and Good, D. (2016). "Motor lateralization provides a foundation for predicting and treating non-paretic arm motor deficits in stroke," in *Progress in Motor Control*, Vol. 957, eds J. Laczko, and M. L. Latash (Cham: Springer International Publishing), 257–272.

Scotland, S., Adamo, D. E., and Martin, B. J. (2014). Sense of effort revisited: relative contributions of sensory feedback and efferent copy. *Neurosci. Lett.* 561, 208–212. doi: 10.1016/j.neulet.2013.12.041

Sleimen-Malkoun, R., Temprado, J.-J., Thefenne, L., and Berton, E. (2011). Bimanual training in stroke: how do coupling and symmetry-breaking matter? *BioMed. Central Neurol.* 11:11. doi: 10.1186/1471-2377-11-11

Stinear, C. M., Barber, P. A., Smale, P. R., Coxon, J. P., Fleming, M. K., and Byblow, W. D. (2007). Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain* 130, 170–180. doi: 10.1093/brain/awl333

Stolk-Hornsveld, F., Crow, J. L., Hendriks, E. P., van der Baan, R., and Harmeling-van der Wel, B. C. (2006). The Erasmus MC modifications to the (revised) Nottingham Sensory Assessment: a reliable somatosensory assessment measure for patients with intracranial disorders. *Clin. Rehabil.* 20, 160–172. doi: 10.1191/0269215506cr932oa

Sukal, T. M., Ellis, M. D., and Dewald, J. P. A. (2007). Shoulder abduction-induced reductions in reaching work area following hemiparetic stroke: neuroscientific implications. *Exp. Brain Res.* 183, 215–223. doi: 10.1007/s00221-007-1029-6

Twitchell, T. E. (1951). The restoration of motor function following hemiplegia in man. *Brain* 74, 443–480.

van der Helm, N. A., Gurari, N., Drogos, J. M., and Dewald, J. P. (2017). "Task directionality impacts the ability of individuals with chronic hemiparetic stroke to match torques between arms: preliminary findings," in *2017 IEEE International Conference on Rehabilitation Robotics* (London), 714–719.

Wang, J., Przybyla, A., Wuebbenhorst, K., Haaland, K. Y., and Sainburg, R. L. (2011). Aging reduces asymmetries in interlimb transfer of visuomotor adaptation. *Exp. Brain Res.* 210, 283–290. doi: 10.1007/s00221-011-2631-1

Wang, J., and Sainburg, R. L. (2004). Interlimb transfer of novel inertial dynamics is asymmetrical. *J. Neurophysiol.* 92, 349–360. doi: 10.1152/jn.00960.2003

Weerakkody, N., Percival, P., Morgan, D. L., Gregory, J. E., and Proske, U. (2003). Matching different levels of isometric torque in elbow flexor muscles after eccentric exercise. *Exp. Brain Res.* 149, 141–150. doi: 10.1007/s00221-002-1341-0

Yen, J. T., and Li, S. (2015). Altered force perception in stroke survivors with spastic hemiplegia. *J. Rehabil. Med.* 47, 917–923. doi: 10.2340/16501977-2019

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Cerebellar Repetitive Transcranial Magnetic Stimulation and Noisy Galvanic Vestibular Stimulation Change Vestibulospinal Function

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Background: The cerebellum strongly contributes to vestibulospinal function, and the modulation of vestibulospinal function is important for rehabilitation. As transcranial magnetic stimulation (TMS) and electrical stimulation may induce functional changes in neural systems, we investigated whether cerebellar repetitive TMS (crTMS) and noisy galvanic vestibular stimulation (nGVS) could modulate vestibulospinal response excitability. We also sought to determine whether crTMS could influence the effect of nGVS.

Methods: Fifty-nine healthy adults were recruited; 28 were randomly allocated to a real-crTMS group and 31 to a sham-crTMS group. The crTMS was conducted using 900 pulses at 1 Hz, while the participants were in a static position. After the crTMS, each participant was allocated to either a real-nGVS group or sham-nGVS group, and nGVS was delivered (15 min., 1 mA; 0.1–640 Hz) while patients were in a static position. The H-reflex ratio (with/without bilateral bipolar square wave pulse GVS), which reflects vestibulospinal excitability, was measured at pre-crTMS, post-crTMS, and post-nGVS.

Results: We found that crTMS alone and nGVS alone have no effect on H-reflex ratio but that the effect of nGVS was obtained after crTMS.

Conclusion: crTMS and nGVS appear to act as neuromodulators of vestibulospinal function.

Keywords: cerebellum, transcranial magnetic stimulation, H-reflex, vestibular, galvanic vestibular stimulation

INTRODUCTION

The vestibular system and cerebellum allow for postural control and adaptation to several physical environments in human daily life. The investigation of the function of vestibular, cerebellum, and functional connectivity of both is important for the improvement of rehabilitation protocols. Studies using electrical stimulation and magnetic stimulation have revealed these functions.

Electrical stimulation to deep cerebellar nuclei induces excitatory and inhibitory postsynaptic potentials in vestibular neurons through polysynaptic pathways (Ito et al., 1970), and lesions in the cerebellum disturb long-term adaptive changes in vestibular reflexes in animal models (Miles and Eighmy, 1980; Ito, 1998). These findings provide evidence for the functional connectivity between the cerebellum and vestibular complex (Jang et al., 2018). This connectivity is established through avenues such as the fastigial nucleus and interposed and dentate nuclei (Delfini et al., 2000). Such connectivity also refers to cerebellar involvement in the modulation of the excitability of vestibular reflexes (Straka et al., 2016).

Transcranial magnetic stimulation (TMS) non-invasively induces action potentials in cortical neurons and inhibits contralateral corticospinal excitability when applied over the cerebellar hemisphere (Ugawa et al., 1995; Daskalakis et al., 2004; Grimaldi et al., 2014; Matsugi and Okada, 2017, 2020). Repetitive TMS (rTMS) applied over a cerebellar hemisphere changes cerebellar brain inhibition (CBI) (Popa et al., 2010), indicating that cerebellar TMS (crTMS) can stimulate certain cerebellar tissues and that crTMS can modulate the excitability of cerebellar outputs. TMS applied over the inion improves eye-head coordination (Nagel and Zangemeister, 2003); as this effect requires vestibule-ocular function, the aforementioned finding indicates that TMS applied over the medial cerebellum affects vestibule-ocular function. Furthermore, as the vestibular nuclei comprise the common center for both vestibulo-ocular and vestibulospinal function (Straka et al., 2016), cerebellar TMS may affect vestibulospinal function. Therefore, in this study, we used the rTMS over inion to stimulate the central cerebellum, investigating whether cerebellar stimulation affect the vestibulospinal function (first aim of this study).

To test vestibulospinal function, galvanic vestibular stimulation (GVS) can be used (Fitzpatrick and Day, 2004). The firing rate of primary vestibular afferents can be decreased by the anodal square-wave pulse GVS (sqGVS) and increased by the cathodal sqGVS (Kim and Curthoys, 2004). Direct recording demonstrates that this stimulation induces action potentials in the vestibulospinal tract of the spinal cord and motor responses in target muscles with short latency (Muto et al., 1995). Furthermore, sqGVS can induce body sway in standing individuals (Fitzpatrick et al., 1994; Day et al., 2002). Changes in the activities of muscles that maintain postural control can be measured by electromyography (EMG) and the Hoffman reflex (H-reflex) (Iles and Pisini, 1992; Britton et al., 1993; Ali et al., 2003; Matsugi et al., 2017; Matsugi, 2019), which reflect the excitability of the spinal motoneuron pool (Knikou, 2008). Applied to an individual in a static position unaffected by natural body sway, change in the range of joints, or background EMG activity, sqGVS modulates the excitability of the H-reflex in the soleus muscle (Kennedy and Inglis, 2001; Ghanim et al., 2009; Lowrey and Bent, 2009; Okada et al., 2018). These observations indicate that the H-reflex-modulation induced by sqGVS reflects changes in the excitability of the vestibulospinal response. Therefore, in this study, we used this method to test vestibulospinal function.

Galvanic vestibular stimulation is often used not only to test vestibulospinal function but also to improve it. To improve balance mediated via facilitation of vestibulospinal function, the square-wave pulse GVS has not been used and random noise GVS (nGVS) is often used recently. The nGVS reportedly improves body balance in adults irrespective of age as well as in patients with vestibular disorder (Wuehr et al., 2017; Fujimoto et al., 2018). The stochastic resonance of noise addition to non-linear systems inducing the change in plasticity of information processing in neural systems may change the threshold or excitability of the motor response by vestibular input (McDonnell and Ward, 2011). However, it is unclear whether nGVS induces changes in vestibulospinal response excitability. Therefore, we investigated whether nGVS modulates the vestibulospinal function, as estimated by the H-reflex-modulation induced by sqGVS (second aim of this study).

Furthermore, the cerebellum is involved in the plasticity of vestibular reflex excitability, because crTMS modulates the effect of intervention for increased vestibulo-ocular movement for dynamic gaze (Matsugi et al., 2019). Deep cerebellar nuclei and Purkinje fibers in the cerebellar gray matter project to the vestibular nucleus. Stimulation of the cerebellar surface induces postsynaptic inhibitory or excitatory postsynaptic potentials in vestibular nuclei (Ito et al., 1970). Low-frequency repetitive stimulation of cortical neurons induces the long-term depression of synaptic excitability (Huerta and Volpe, 2009). Therefore, we hypothesized that crTMS affects the vestibular modulation via interventions such as nGVS in addition to that of exercise. Therefore, as the third aim of this study, we investigated whether rTMS applied over the cerebellum influenced the effect of nGVS on vestibulospinal excitability.

In summary, in this study, we investigated whether crTMS alone and nGVS alone modulate vestibulospinal function estimated by the H-reflex modulation induced by sqGVS. Further, we investigated whether crTMS modulates the effect of nGVS on the H-reflex-modulation induced by sqGVS.

MATERIALS AND METHODS

Participants

Fifty-nine healthy adults (mean age, 23.8 ± 4.5 years; 40 men) participated in this study. None of the participants had histories of epilepsy or other neurological diseases. The Ethics Committee of Shijonawate Gakuen University approved the experimental procedures (approval code: 29-4), and this study was conducted according to the principles and guidelines of the Declaration of Helsinki; written informed consent was obtained from all participants.

General Procedure

This study was conducted with a sham-controlled, double-blind design. The crTMS and nGVS conditions were blinded for participants and assessors when the assessments of vestibulospinal response were performed. **Figure 1** presents the general procedures. All participants were allocated to either the sham-crTMS (n = 31) or real-crTMS groups (n = 28). After

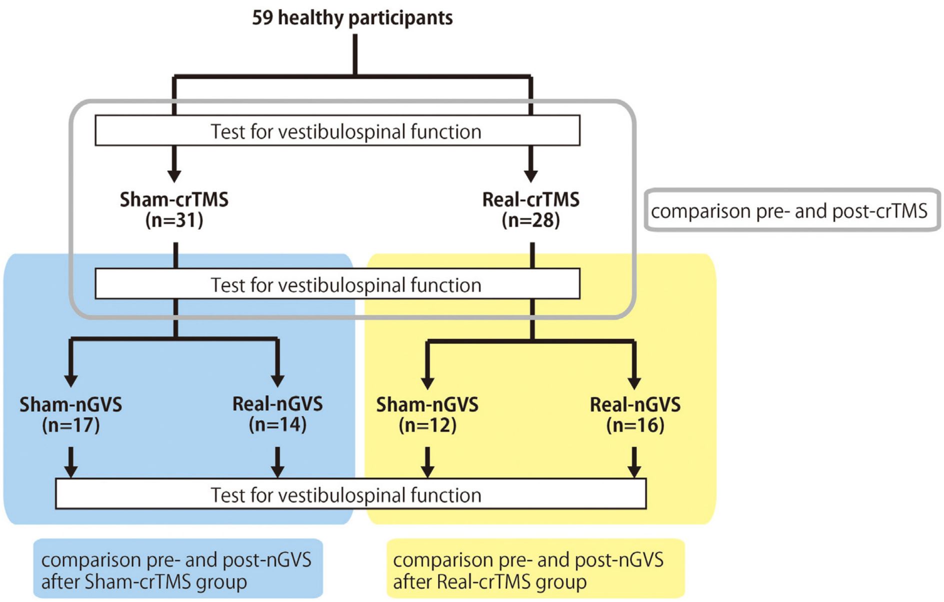

FIGURE 1 | Experimental procedure and analysis. Fifty-nine healthy participants were allocated to either the sham-cerebellar repetitive TMS (crTMS) or real-crTMS groups. After crTMS, the participants were further allocated to either sham-noisy galvanic vestibular stimulation (nGVS) or real-nGVS groups. Tests for vestibulospinal function, including the H-reflex with/without conditioning square-wave pulse GVS, were conducted pre-crTMS, post-crTMS, and post-nGVS. In Analysis 1, the test parameters were compared between pre- and post-crTMS to elucidate the effect of crTMS on vestibulospinal function. In Analysis 2, the test parameters were compared between pre- and post-nGVS (post-sham-crTMS) to assess the effect of nGVS on vestibulospinal function. In Analysis 3, the test parameters were compared between pre- and post-nGVS (post-real-crTMS) to gauge the influence of crTMS on the effect of nGVS on vestibulospinal function. crTMS, repetitive transcranial magnetic stimulation; nGVS, noisy galvanic vestibular stimulation.

sham- or real-crTMS was completed, the participants in both groups were further subdivided into sham-nGVS and real-nGVS groups (after sham-crTMS: n = 17 and n = 14, respectively; after real-crTMS: n = 12 and n = 16, respectively), and then nGVS were conducted. Hence, all participants were randomly assigned to one of four groups, and three assessments of vestibulospinal function were conducted before (1st) and after crTMS (2nd) and after nGVS (3rd). If the participant experienced the sensation of the nGVS or could not endure the sqGVS in the test stimulation, the examination was ceased immediately.

Before the examination, we confirmed that the sqGVS did not produce sensations of pain or phosphine behind the eyes but did prompt body sway to the anodal side in participants standing with their eyes closed, feet together, and head facing forward (Fitzpatrick and Day, 2004) to test whether they were responders or non-responders to square-wave pulse GVS. In this timing, if the participant cannot endure square-wave pulses at 3 mA using all tests for vestibulospinal function, the participant did not participate in subsequent experiments. No participant responded to sqGVS at 3 mA, but four participants were excluded owing to the existence of unbearable pain (see "Results" section). We asked participants to report any sensation in response to nGVS; participants reporting sensation were excluded from analysis.

During the tests for vestibulospinal function (1st, 2nd, and 3rd), crTMS (sham or real) and nGVS (sham or real), participants lay down in the prone position while relaxing on the bed. The experiments were performed in the following order: (1) test for vestibulospinal function (1st test), (2) sham- or real-crTMS, (3) test for vestibulospinal function (2nd test), (4) sham- or real-nGVS, and (5) test for vestibulospinal function (3rd test).

Conditioning Stimulation

Cerebellar Repetitive TMS (crTMS)

The participants were instructed to lie down on a bed in the prone position. Because previous studies have shown that the figure-of-eight coil could stimulate the cerebellum (Haarmeier and Kammer, 2010; Popa et al., 2010; Tremblay et al., 2016), a magnetic stimulator (MagPro compact, MagVenture, Denmark) was used to deliver TMS to the cerebellum with a butterfly coil (MC-B70, MagVenture, Denmark) (Matsugi et al., 2019). The center of the coil's junction was set at a distance 1 cm below the inion to stimulate the central region of the cerebellum (Zangemeister and Nagel, 2001; Nagel and Zangemeister, 2003; Jayasekeran et al., 2011; Hardwick et al., 2014; van Dun et al., 2017); prior research has demonstrated that stimulation from this position can modulate vestibular and ocular motor functions (Zangemeister and Nagel, 2001; Nagel and Zangemeister, 2003; Jenkinson and Miall, 2010). As previous studies have observed that an upward current applied to the cerebellum can effectively stimulate this region (Ugawa et al., 1995; Hiraoka et al., 2010; Matsugi et al., 2013), the coil was oriented such that the current therein was directed downward to deliver the upward current to the brain (van Dun et al., 2017). TMS intensity was set to 50% of the maximum stimulator output: the same setting as those employed by previous studies investigating cerebellar and vestibular functions (Zangemeister and Nagel,

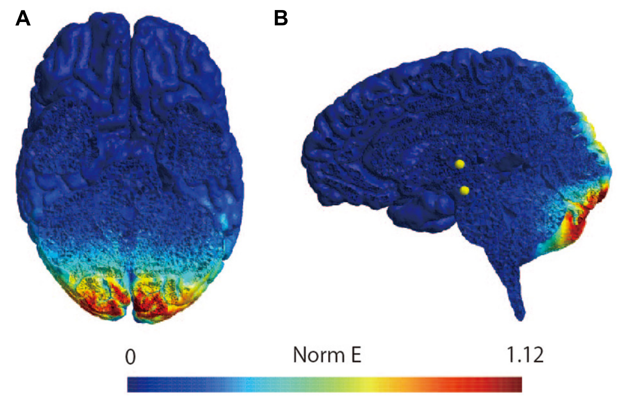

FIGURE 2 | Simulation of the electrical field induced by cerebellar TMS. Simulation of the electrical field induced by TMS with butterfly coil using SimNIBS in horizontal slice **(A)** and sagittal slice **(B)**. The scale represents the magnitude of the electric field (Volts/meter) induced by TMS over the site at 1 cm under the inion.

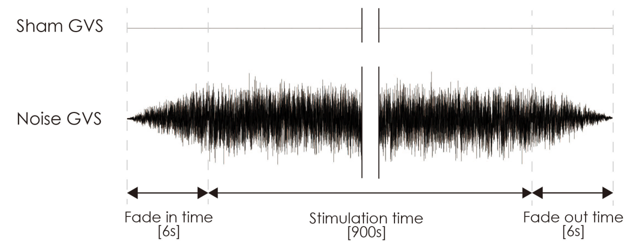

FIGURE 3 | Typical waveform of nGVS and sham-nGVS. nGVS, noisy galvanic vestibular stimulation.

2001; Nagel and Zangemeister, 2003; Haarmeier and Kammer, 2010; Jenkinson and Miall, 2010; van Dun et al., 2017; Matsugi et al., 2019). Because a 1-Hz crTMS reduces motor function and motor adaptation (Miall and Christensen, 2004; Jenkinson and Miall, 2010) the inter-stimulus interval was set at 1 s, and 900 pulses were applied (Fierro et al., 2007; Popa et al., 2010; Matsugi et al., 2019). In the stimulation condition, electrical field stimulation of the brain structures was performed with SimNIBS software (version 2.1.1) using default head models, biological tissue conductivity values included in the software, and the aforementioned parameters of the TMS using a butterfly coil (shown in **Figure 2**) (Thielscher et al., 2015). The coil was held at a 90° angle from the scalp over the inion when delivering sham-TMS (Hiraoka et al., 2010; Matsugi et al., 2013, 2014, 2019).

Noisy Galvanic Vestibular Stimulation (nGVS)

Noisy galvanic vestibular stimulation was performed as previously reported (Inukai et al., 2018). nGVS was delivered via Ag/AgCl surface electrodes (Blue Sensor EKG Snap Electrode, overall dimensions: 48 mm × 57 mm, Ambu, Baltorpbakken, Denmark) affixed to the right and left mastoid processes. A DC-STIMULATOR PLUS (Eldith, NeuroConn GmbH, Ilmenau, Germany) was used to deliver random noise galvanic stimulation to the primary vestibular nerve. For nGVS in the stimulation mode, "noise" was used, a random level of current was generated for every sample (sample rate, 1280 samples/s) (Moliadze et al., 2012; Inukai et al., 2018), and the intensity was set at 1 mA. Statistically, the random numbers were normally distributed over time, the probability density followed a Gaussian bell curve, and all coefficients featured a similar size in the frequency spectrum of this mode. A waveform was applied with 99% of the values between −0.5 and +0.5 mA, and only 1% of the current level was within ±0.51 mA. The stimulation time was set to 900 s, and the current was ramped up and down from 6 s before the stimulation to 6 s after its completion (**Figure 3**). Even if a slight sensation was felt, the participant was excluded from the experiment on account of the condition no longer being blind. For sham stimulation, direct current stimulation was applied at an intensity of 0 mA (sham-nGVS). If the participant sensed the stimulation of the real- or sham-nGVS, the participant was disqualified from further testing.

Test for Vestibulospinal Function

To estimate the excitability of the vestibulospinal response, the H-reflex during short duration square-wave pulse GVS was measured (Kennedy and Inglis, 2001, 2002; Ghanim et al., 2009; Lowrey and Bent, 2009; Matsugi et al., 2017) before and after crTMS and after nGVS (see **Figure 1**). The H-reflex indicates the excitability of the spinal motoneuron pool (Knikou, 2008). Short duration square-wave pulse GVS can alter the firing rate of primary vestibular neurons in a polarity-dependent manner (Goldberg et al., 1984), indicating that electrostimulation of the mastoid processes provides constant stimulation to vestibular neurons. Therefore, the modulation of the H-reflex by short duration square-wave pulse GVS reflects the excitability of the vestibulospinal response.

The participant lay down on a bed in the prone position with his or her eyes closed, right and left ankle joints fixed at 90 degrees, and with braces to prevent unwanted movement of ankle joints. A bipolar binaural square-wave pulse GVS was delivered via Ag/AgCl surface electrodes affixed to the mastoid processes (Britton et al., 1993; Fitzpatrick et al., 1994; Welgampola and Colebatch, 2001; Ghanim et al., 2009; Lowrey and Bent, 2009; Matsugi et al., 2017) (right, cathode; left, anode; **Figure 4**). The GVS consisted of a 200-ms square-wave pulse that was delivered using an electrical isolator (SS-104J, Nihon Kohden, Japan) driven by a stimulator (SEN-3301, Nihon Kohden, Japan); the intensity was set at 3 mA (Fitzpatrick and Day, 2004; Okada et al., 2018).

Electromyography signals used to measure the H-reflex were recorded as previously described (Matsugi et al., 2017). Two Ag/AgCl surface-recording electrodes were placed 2 cm apart on the right soleus muscle. The EMG signals were amplified using an amplifier (MEG-1200, Nihon Kohden, Japan) with a pass-band filter of 15 Hz to 3 kHz. The EMG signals were converted to digital signals at a sampling rate of 10 kHz using an A/D converter (PowerLab 800S, AD Instruments; AD Instruments, Colorado Springs, CO, United States). The digital signals were then stored on a personal computer.

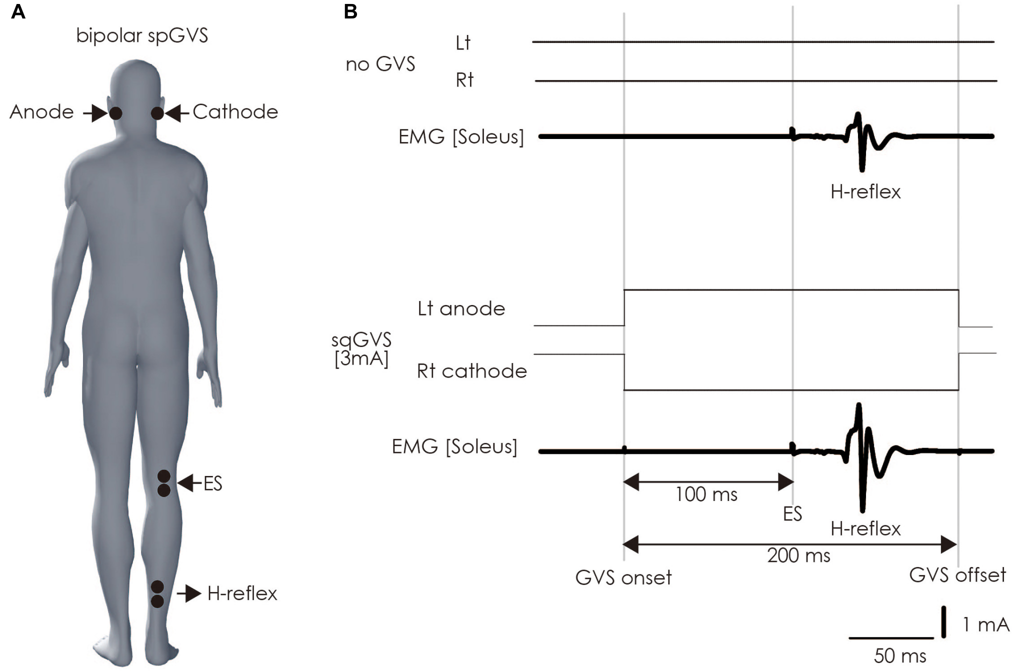

FIGURE 4 | Method of assessing vestibulospinal function. **(A)** Electrode positioning. The electrode for the GVS was placed on bilateral mastoid processes. The electrodes were placed on the right soleus muscle to stimulate the tibial nerve to induce H-reflex therein and perform electromyography. **(B)** The sqGVS and typical H-reflex waveforms. The ES to induce the H-reflex was delivered 100 ms before sqGVS onset. GVS, galvanic vestibular stimulation; sqGVS, square-wave pulse galvanic vestibular stimulation; EMG, electromyography; ES, electrical stimulation.

We delivered electrical stimulation (ES) to the right tibial nerve to evoke the H-reflex in the right soleus muscle 100 ms after the onset of the short duration square-wave pulse GVS (Kennedy and Inglis, 2001; Ghanim et al., 2009; Matsugi et al., 2017) (**Figure 4**). The H-reflex is reportedly facilitated by cathodal GVS in the inter-stimulus interval (Ghanim et al., 2009). The maximal M-wave (M-max) was measured at the beginning of all of the experimental trials, and the test for the right soleus H-reflex amplitude was periodically adjusted to a level 15–25% of the M-max during the experiment to adjust for the ascending limb of the H-reflex recruitment curve (Crone et al., 1990; Matsugi et al., 2017). Ten H-reflexes were elicited and recorded in the non-GVS condition (as control). In the right cathodal sqGVS condition, the two trials were performed in a random order, and the interval between tests was set to >7 s.

Before the test, we confirmed that the sqGVS did not produce sensations of pain or phosphine behind the eyes but did prompt body sway to the anodal side in participants standing with their eyes closed, feet together, and head facing forward (Fitzpatrick and Day, 2004). Furthermore, the GVS response test was conducted more than four times to ensure the participants were habituated to the sqGVS before test trials; although the first GVS responses were larger than the fifth, there was no subsequent change after the fifth trial (Balter et al., 2004).

Analysis

H-reflex amplitude and M-wave amplitude in individual wave form was measured, and H-reflex as a percent of M-max amplitude was calculated in all trials and examinations based on the formula: H-reflex amplitude/M-max amplitude × 100. M-wave a percent of M-max amplitude was similarly calculated: M-wave amplitude/M-max amplitude × 100. To estimate the excitability of vestibulospinal function, the H-reflex ratio was calculated as the conditioned H-reflex amplitude/unconditioned H-reflex amplitude (Matsugi et al., 2017; Matsugi and Okada, 2020).

To test the baseline stimulation is equal, the paired sample test was conducted. If test of normality (Shapiro–Wilk test) revealed that normality of data, *t*-test was used. If in not normality of data, Wilcoxon test was used.

To test the effect of intervention of crTMS or nGVS (Sham and Real) and time (Pre- and Post-stimulation) on the H-reflex ratio, two-way analysis of variance (TW-ANOVA) was used if equality of variances was confirmed by Levene's test. When a main effect was observed on these parameters, *post hoc* comparison (*t*-test) was conducted. When an interaction effect was observed on the means of H-reflex ratios, the *post hoc* comparison (*t*-test) was conducted to detect significant differences between groups.

In Analysis 1, to estimate the effect of crTMS on excitability of the vestibulospinal response, the H-reflex ratios obtained from pre-crTMS and post-crTMS in the real- and sham-crTMS conditions were analyzed (**Figure 1**). In Analysis 2, to gauge the effect of nGVS on the excitability of the vestibulospinal response, the H-reflex ratios obtained from the four pre- and post-nGVS trials performed after the sham-crTMS were analyzed

TABLE 1 | Paired Samples *T*-Test (unconditioned M-wave).

		Test of normality (Shapiro-Wilk)								95% CI for effect size	
		W	p	Test	Statistic	df	p	VS-MPR*	Effect Size	Lower	Upper
Analysis 1	Sham	0.942	0.091	**Student**	**1.939**	**30**	**0.062**	**2.135**	**0.348**	**−0.017**	**0.708**
				Wilcoxon	322		0.152	1.286	0.298	−0.095	0.611
	Real	0.708	<0.001	Student	−1.259	27	0.219	1.107	−0.238	−0.612	0.14
				Wilcoxon	**177**		**0.782**	**1**	**−0.128**	**−0.503**	**0.287**
Analysis 2	Sham	0.931	0.228	**Student**	**−1.552**	**16**	**0.14**	**1.335**	**−0.376**	**−0.864**	**0.122**
				Wilcoxon	56		0.353	1.001	−0.268	−0.673	0.26
	Real	0.836	0.014	Student	0.458	13	0.655	1	0.122	−0.406	0.646
				Wilcoxon	**62**		**0.583**	**1**	**0.181**	**−0.39**	**0.651**
Analysis 3	Sham	0.7	<0.001	Student	−1.215	11	0.25	1.062	−0.351	−0.927	0.241
				Wilcoxon	**30**		**0.519**	**1**	**−0.231**	**−0.704**	**0.385**
	Real	0.818	0.005	Student	1.045	15	0.313	1.012	0.261	−0.242	0.756
				Wilcoxon	**84**		**0.433**	**1**	**0.235**	**−0.307**	**0.662**

**Vovk-Sellke Maximum p-ratio: based on the p -value, the maximum possible odds in favor of H_1 over H_0 equals 1/[−e p log(p)] for p ≤ 0.37 (Sellke et al., 2001). For the Student t-test, effect size is given by Cohen's d; for the Wilcoxon test, effect size is given by the matched rank biserial correlation. Significant results suggest a deviation from normality inTest of Normality (Shapiro-Wilk). Bolded values/terms indicate accepted results.*

TABLE 2 | Paired samples *T*-Test (unconditioned H-reflex).

		Test of normality (Shapiro-Wilk)								95% CI for effect size	
		W	p	Test	Statistic	df	p	VS-MPR*	Effect Size	Lower	Upper
Analysis 1	Sham	0.975	0.652	**Student**	**−1.547**	**30**	**0.132**	**1.374**	**−0.278**	**−0.634**	**0.083**
				Wilcoxon	150		0.056	2.278	−0.395	−0.676	−0.015
	Real	0.958	0.318	**Student**	**−0.408**	**27**	**0.687**	**1**	**−0.077**	**−0.447**	**0.295**
				Wilcoxon	194		0.849	1	−0.044	−0.437	0.362
Analysis 2	Sham	0.969	0.8	**Student**	**−0.011**	**16**	**0.992**	**1**	**−0.003**	**−0.478**	**0.473**
				Wilcoxon	80		0.89	1	0.046	−0.459	0.528
	Real	0.563	<0.001	Student	1.226	13	0.242	1.071	0.328	−0.217	0.86
				Wilcoxon	**74**		**0.194**	**1.157**	**0.41**	**−0.158**	**0.774**
Analysis 3	Sham	0.92	0.285	**Student**	**1.34**	**11**	**0.207**	**1.128**	**0.387**	**−0.209**	**0.967**
				Wilcoxon	51		0.38	1	0.308	−0.312	0.744
	Real	0.941	0.36	**Student**	**0.054**	**15**	**0.958**	**1**	**0.013**	**−0.477**	**0.503**
				Wilcoxon	66		0.94	1	−0.029	−0.528	0.484

**Vovk-Sellke Maximum p-ratio: based on the p -value, the maximum possible odds in favor of H_1 over H_0 equals 1/[−e p log(p)] for p ≤ 0.37 (Sellke et al., 2001). For the Student t-test, effect size is given by Cohen's d; for the Wilcoxon test, effect size is given by the matched rank biserial correlation. Significant results suggest a deviation from normality inTest of Normality (Shapiro-Wilk). Bolded values/terms indicate accepted results.*

(**Figure 1**). In analysis 3, to estimate the effect of cerebellar crTMS on the effect of nGVS, the H-reflex ratios obtained from the pre- and post-nGVS trials performed after the real-crTMS were analyzed (**Figure 1**).

The alpha level was set at 0.05 in all statistical analyses. Statistical analyses were conducted with using R software (version 3.1.2; the R Foundation for Statistical Computing, Vienna, Austria).

Post hoc power analysis was conducted to estimate the power (1 – beta error probability) for conducting Wilcoxon signed rank sum tests to compare the smallest groups (sham-nGVS in post-real-crTMS, $n = 12$) with software G*power 3.1 (Version 3.1.9.4) provided by Faul et al. (2007).

RESULTS

None of the participants experienced any harmful side effects attributable to any of the examinations. As four participants were unable to endure the sqGVS before the examination, the examinations were terminated for these participants. Fifty-nine participants responded to the sqGVS while standing by engaging in a body sway to the anodal side (Fitzpatrick and Day, 2004), and no participant reported to sensation to nGVS.

Tables 1, **2** show the results of Shapiro–Wilk test, and paired sample test in M-wave and unconditioned H-reflex amplitude (**Figures 5**, **6**). These results indicate the there was no significant difference between stimulation conditioned.

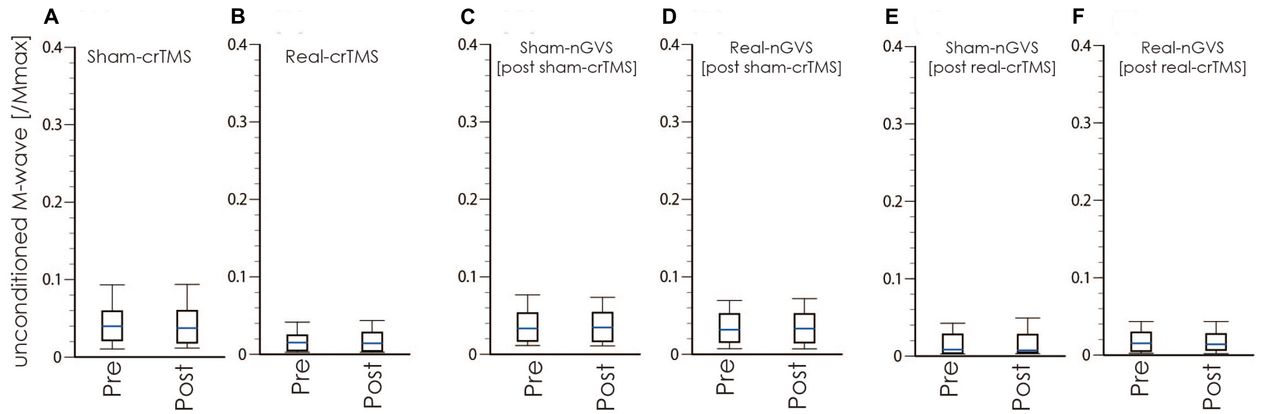

FIGURE 5 | Boxplots of the M-wave amplitude in crTMS **(A,B)**, post-sham-crTMS **(C,D)**, and post-real-crTMS **(E,F)**. The middle horizontal lines indicate the median; the top and bottom lines of the box indicate the third and first quartiles, respectively; and the top and bottom vertical lines indicate the 90th and 10th percentiles, respectively. nGVS, noisy galvanic vestibular stimulation; crTMS, cerebellar repetitive transcranial magnetic stimulation.

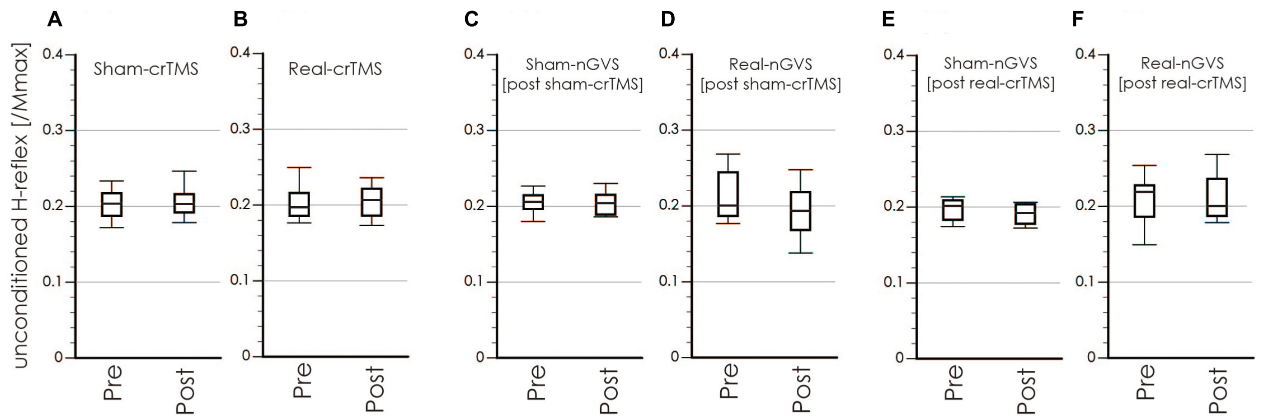

FIGURE 6 | Boxplots of the unconditioned H-reflex amplitude in crTMS **(A,B)**, post-sham-crTMS **(C,D)**, and post-real-crTMS **(E,F)**. The middle horizontal lines indicate the median; the top and bottom lines of the box indicate the third and first quartiles, respectively; and the top and bottom vertical lines indicate the 90th and 10th percentiles, respectively. nGVS, noisy galvanic vestibular stimulation; crTMS, cerebellar repetitive transcranial magnetic stimulation.

Table 3 shows result of Levene's test, and this test revealed that all parameters had equal variances for TW-ANOVA. These results indicate that there were equality of data and we can accept the result of parametric TW-ANOVA. **Table 4** shows the For the H-reflex ratio in analyses 1 and 2, there was no significant effect of intervention and time, but in analysis 3, there was a significant main effect of intervention and no significant effect of time on the H-reflex ratio (**Figure 7**).

TABLE 3 | Test for equality of variances (Levene's) for two-way ANOVA.

	F	df1	df2	*p*	VS-MPR*
Analysis 1	2	3	114	0.118	1.459
Analysis 2	1.428	3	58	0.244	1.069
Analysis 3	0.967	3	52	0.415	1

**Vovk-Sellke maximum p-ratio: based on the p-value, the maximum possible odds in favor of H_1 over H_0 equals $1/[-e\ p\ \log(p)]$ for $p \leq 0.37$ (Sellke et al., 2001).*

The *post hoc* power analysis revealed that the effect degree was 3, as calculated using the mean and standard deviation difference in this group were 0.06 and 0.02, respectively. Further, the input parameters were set as alpha error = 0.05 and sample size = 12, resulting in a power (1 − beta error probability) of 1.

DISCUSSION

The present study aimed to investigate whether crTMS and nGVS modulate the excitability of vestibulospinal function. An indicator of vestibulospinal response excitability, the H-reflex ratio was not significantly changed by real- or sham-crTMS (first analysis) or by real- or sham-nGVS (second analysis). On the other hand, our third analysis revealed a significant main effect of nGVS on the H-reflex ratio after real-crTMS. These findings indicate that crTMS alone and nGVS alone cannot affect excitability of the vestibulospinal

TABLE 4 | ANOVA.

	Cases	Sum of squares	df	Mean square	F	p	VS-MPR*	η^2
Analysis 1	CS	0.049	1	0.049	1.127	0.291	1.024	0.01
	Time	0.091	1	0.091	2.111	0.149	1.297	0.018
	CS * Time	4.388e-4	1	4.388e-4	0.01	0.92	1	0
	Residual	4.911	114	0.043				
Analysis 2	CS	0.14	1	0.14	3.093	0.084	1.769	0.048
	Time	5.538e-5	1	5.538e-5	0.001	0.972	1	0
	CS * Time	0.134	1	0.134	2.953	0.091	1.686	0.046
	Residual	2.634	58	0.045				
Analysis 3	CS	0.046	1	0.046	1.85	0.18	1.193	0.031
	Time	0.136	1	0.136	5.489	**0.023**	4.241	0.092
	CS * Time	2.745e-4	1	2.745e-4	0.011	0.917	1	0
	Residual	1.29	52	0.025				

*Type III Sum of Squares. CS, conditioning stimulation, *Vovk-Sellke Maximum p-ratio: based on the p -value, the maximum possible odds in favor of H_1 over H_0 equals 1/[−e p log(p)] for p = 0.37 (Sellke et al., 2001). Bolded value indicates significant.*

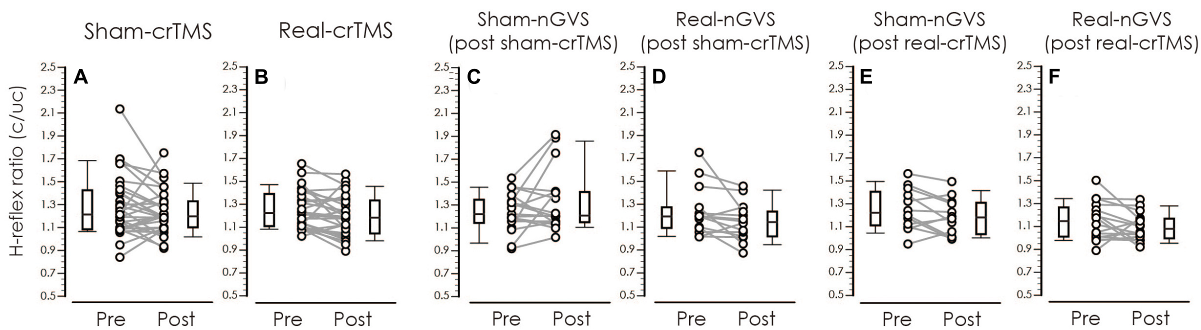

FIGURE 7 | Boxplots of the H-reflex ratio (conditioned/unconditioned H-reflex amplitude) in crTMS **(A,B)**, post-sham-crTMS **(C,D)**, and post-real-crTMS **(E,F)**. The middle horizontal lines indicate the median; the top and bottom lines of the box indicate the third and first quartiles, respectively; and the top and bottom vertical lines indicate the 90th and 10th percentiles, respectively. The circles indicate the values of individual participants, and the gray lines connect the pre- and post-circles. There were significant reductions of the H-reflex ratio of post-real-crTMS **(B)** and of real-nGVS in post-sham-crTMS **(D)**. nGVS, noisy galvanic vestibular stimulation; crTMS, cerebellar repetitive transcranial magnetic stimulation.

response in participants in the static prone position; however, the nGVS effect could be observed after crTMS. These new findings suggest that crTMS facilitates the effect of nGVS on vestibulospinal function.

Our first analysis revealed that real- and sham-crTMS had no significant effect on the H-reflex ratio, indicating that crTMS does not directly affect excitability of the vestibulospinal response. A previous study showed that low-frequency crTMS reduces CBI, but does not change the excitability of contralateral M1 (Popa et al., 2010), indicating that the low-frequency crTMS disinhibits the excitability of the cerebellar output, but that the stimulation cannot directly affect excitability of remote brain sites. Therefore, in this study, the excitability of vestibular nuclei in the brainstem could not have been directly changed by crTMS alone.

Our secondary analysis showed that the H-reflex ratio was not changed by nGVS after sham-crTMS. This finding suggests the effect of nGVS alone, because sham-crTMS should not affect the cerebellar and vestibular function. Therefore, this result indicates that the application of nGVS alone cannot affect excitability of the vestibulospinal response of a healthy population in the static prone position. Moreover, nGVS modulates the threshold of the motor response through vestibular input and improves body balance in standing humans (Fujimoto et al., 2016, 2018; Wuehr et al., 2017; Inukai et al., 2018). The stochastic resonance and noise addition to non-linear systems inducing the change in plasticity of information processing in neural systems may account for these findings (McDonnell and Ward, 2011). On the other hand, the effect was obtained only in participants with large body sway during upright standing and no effect in participant with small body sway in young adult populations (Inukai et al., 2018). Therefore, in the present study, the effect of nGVS on vestibulospinal function in participants in a static prone position may be small compared to that of participants in an unstable position. As a result, we may have failed to discover an effect of nGVS alone on excitability of the vestibulospinal response in participants in a static prone position.

Our third analysis showed a significant main effect of nGVS on excitability of the vestibulospinal response after real-crTMS. The following mechanisms may account for the facilitation of the nGVS effect after crTMS. The modulation of vestibular reflex is affected by the cerebellum (Jang and Kim, 2019). The cerebellum contributes to adaptive changes in the vestibulo-ocular reflex, as shown by the observation that cerebellar lesions disturb long-term adaptive changes in the vestibular reflex (Miles and Eighmy, 1980; Ito, 1998). In a previous study, low-frequency crTMS applied as a pre-conditioning stimulation could not immediately change the vestibulo-ocular movement, but affected the trainability of vestibulo-ocular movement for dynamic gazing (Matsugi et al., 2019). Therefore, in the present study, using the same stimulation paradigm, the change of cerebellar activity induced by crTMS may affect the susceptibility of vestibulospinal response excitability in response to nGVS.

Balance function was not measured in this study, because body movement may affect H-reflex excitability (Knikou, 2008). Therefore, the effect of crTMS and/or nGVS on balance function in positions such as the standing position should be further investigated. As to the question of whether TMS, applied using a butterfly coil, can induce an electrical field on the cerebellar structure, our simulation using SimNIBS suggests that the electrical field, induced during TMS using the butterfly coil, was localized to the cerebellum. Furthermore, Popa reported that crTMS, performed using a figure-eight coil at an angle of 180° to the coil surface, could modulate the excitability of cerebellar output measured by CBI (Popa et al., 2010). Considered alongside our results, these findings suggest that crTMS applied with a butterfly coil could stimulate the cerebellum. Nevertheless, it is difficult to fully guarantee that deep cerebellar tissue has been stimulated. Recently it was reported that deep brain TMS using H-coil can stimulate the deep brain areas (Roth et al., 2014; Zibman et al., 2019). Therefore, we should conduct future study using H-coil for more certainly stimulating the deep cerebellar tissue in this study design to make sure that our result is due to cerebellar stimulation. Another consideration was the small sample size in the sham-nGVS in post-real-crTMS group. However, our *post hoc* power analysis revealed a power value of 1, which is larger than the 0.8 value of the reference study (Faul et al., 2007); accordingly, this analytic power is sufficient to conduct Wilcoxon signed rank sum tests, even in the smallest group.

CONCLUSION

Low-frequency crTMS alone and nGVS alone were insufficient to modulate excitability of the vestibulospinal response in a young population in the static prone position. In contrast, an effect of nGVS on vestibular function was obtained after crTMS. These findings suggest that the cerebellum modulates vestibulospinal function. Further clinical studies are required to investigate the effect of crTMS and nGVS in patients with vestibulospinal dysfunction.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by ethics committee of Shijonawate Gakuen University. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

AM, YO, and NY initially designed this study. Experimental equipment for magnetic stimulation was provided by KH and YS, while AM, NY, and SN provided other equipment. The experiments were conducted by AM, SD, RH, and NM (SD and RH were blinded assessors). Data analyses were conducted by AM, and NM. AM conducted a simulation of the distribution of E-fields induced by TMS. AM initially wrote the manuscript. All authors revised the manuscript.

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REFERENCES

Ali, A., Rowen, K., and Iles, J. (2003). Vestibular actions on back and lower limb muscles during postural tasks in man. *J. Physiol.* 546, 615–624.

Balter, S. G., Stokroos, R. J., Eterman, R. M., Paredis, S. A., Orbons, J., and Kingma, H. (2004). Habituation to galvanic vestibular stimulation. *Acta Otolaryngol.* 124, 941–945.

Britton, T., Day, B., Brown, P., Rothwell, J., Thompson, P., and Marsden, C. (1993). Postural electromyographic responses in the arm and leg following galvanic vestibular stimulation in man. *Exp. Brain Res.* 94, 143–151.

Crone, C., Hultborn, H., Mazières, L., Morin, C., Nielsen, J., and Pierrot-Deseilligny, E. (1990). Sensitivity of monosynaptic test reflexes to facilitation and inhibition as a function of the test reflex size: a study in man and the cat. *Exp. Brain Res.* 81, 35–45.

Daskalakis, Z. J., Paradiso, G. O., Christensen, B. K., Fitzgerald, P. B., Gunraj, C., and Chen, R. (2004). Exploring the connectivity between the cerebellum and motor cortex in humans. *J. Physiol.* 557, 689–700.

Day, B., Guerraz, M., and Cole, J. (2002). Sensory interactions for human balance control revealed by galvanic vestibular stimulation. *Adv. Exp. Med. Biol.* 508, 129–137.

Delfini, C., Diagne, M., Angaut, P., Buisseret, P., and Buisseret-Delmas, C. (2000). Dentatovestibular projections in the rat. *Exp. Brain Res.* 135, 285–292.

Faul, F., Erdfelder, E., Lang, A. G., and Buchner, A. (2007). G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behav. Res. Methods* 39, 175–191.

Fierro, B., Giglia, G., Palermo, A., Pecoraro, C., Scalia, S., and Brighina, F. (2007). Modulatory effects of 1 Hz rTMS over the cerebellum on motor cortex excitability. *Exp. Brain Res.* 176, 440–447.

Fitzpatrick, R., Burke, D., and Gandevia, S. C. (1994). Task-dependent reflex responses and movement illusions evoked by galvanic vestibular stimulation in standing humans. *J. Physiol.* 478(Pt 2), 363–372.

Fitzpatrick, R., and Day, B. (2004). Probing the human vestibular system with galvanic stimulation. *J. Appl. Physiol.* 96, 2301–2316.

Fujimoto, C., Egami, N., Kawahara, T., Uemura, Y., Yamamoto, Y., Yamasoba, T., et al. (2018). Noisy galvanic vestibular stimulation sustainably improves posture in bilateral vestibulopathy. *Front. Neurol.* 9:900. doi: 10.3389/fneur.2018.00900

Fujimoto, C., Yamamoto, Y., Kamogashira, T., Kinoshita, M., Egami, N., Uemura, Y., et al. (2016). Noisy galvanic vestibular stimulation induces a sustained improvement in body balance in elderly adults. *Sci. Rep.* 6:37575. doi: 10.1038/srep37575

Ghanim, Z., Lamy, J., Lackmy, A., Achache, V., Roche, N., Pénicaud, A., et al. (2009). Effects of galvanic mastoid stimulation in seated human subjects. *J. Appl. Physiol.* 106, 893–903. doi: 10.1152/japplphysiol.90594.2008

Goldberg, J., Smith, C., and Fernández, C. (1984). Relation between discharge regularity and responses to externally applied galvanic currents in vestibular nerve afferents of the squirrel monkey. *J. Neurophysiol.* 51, 1236–1256.

Grimaldi, G., Argyropoulos, G. P., Boehringer, A., Celnik, P., Edwards, M. J., Ferrucci, R., et al. (2014). Non-invasive cerebellar stimulation–a consensus paper. *Cerebellum* 13, 121–138. doi: 10.1007/s12311-013-0514-7

Haarmeier, T., and Kammer, T. (2010). Effect of TMS on oculomotor behavior but not perceptual stability during smooth pursuit eye movements. *Cereb. Cortex* 20, 2234–2243. doi: 10.1093/cercor/bhp285

Hardwick, R. M., Lesage, E., and Miall, R. C. (2014). Cerebellar transcranial magnetic stimulation: the role of coil geometry and tissue depth. *Brain Stimul.* 7, 643–649. doi: 10.1016/j.brs.2014.04.009

Hiraoka, K., Horino, K., Yagura, A., and Matsugi, A. (2010). Cerebellar TMS evokes a long latency motor response in the hand during a visually guided manual tracking task. *Cerebellum* 9, 454–460. doi: 10.1007/s12311-010-0187-4

Huerta, P. T., and Volpe, B. T. (2009). Transcranial magnetic stimulation, synaptic plasticity and network oscillations. *J. Neuroeng. Rehabil.* 6:7. doi: 10.1186/1743-0003-6-7

Iles, J., and Pisini, J. (1992). Vestibular-evoked postural reactions in man and modulation of transmission in spinal reflex pathways. *J. Physiol.* 455, 407–424.

Inukai, Y., Otsuru, N., Masaki, M., Saito, K., Miyaguchi, S., Kojima, S., et al. (2018). Effect of noisy galvanic vestibular stimulation on center of pressure sway of static standing posture. *Brain Stimul.* 11, 85–93. doi: 10.1016/j.brs.2017.10.007

Ito, M. (1998). Cerebellar learning in the vestibulo-ocular reflex. *Trends Cogn. Sci.* 2, 313–321.

Ito, M., Udo, M., Mano, N., and Kawai, N. (1970). Synaptic action of the fastigiobulbar impulses upon neurones in the medullary reticular formation and vestibular nuclei. *Exp. Brain Res.* 11, 29–47.

Jang, D. C., and Kim, S. J. (2019). Plasticity leading to cerebellum-dependent learning: two different regions, two different types. *Pflugers Arch.* 471, 927–934. doi: 10.1007/s00424-019-02282-3

Jang, S. H., Lee, M. Y., Yeo, S. S., and Kwon, H. G. (2018). Structural neural connectivity of the vestibular nuclei in the human brain: a diffusion tensor imaging study. *Neural Regen. Res.* 13, 727–730. doi: 10.4103/1673-5374.230304

Jayasekeran, V., Rothwell, J., and Hamdy, S. (2011). Non-invasive magnetic stimulation of the human cerebellum facilitates cortico-bulbar projections in the swallowing motor system. *Neurogastroenterol. Motil.* 23, 831–e341. doi: 10.1111/j.1365-2982.2011.01747.x

Jenkinson, N., and Miall, R. C. (2010). Disruption of saccadic adaptation with repetitive transcranial magnetic stimulation of the posterior cerebellum in humans. *Cerebellum* 9, 548–555. doi: 10.1007/s12311-010-0193-6

Kennedy, P. M., and Inglis, J. T. (2001). Modulation of the soleus H-reflex in prone human subjects using galvanic vestibular stimulation. *Clin. Neurophysiol.* 112, 2159–2163.

Kennedy, P. M., and Inglis, J. T. (2002). Interaction effects of galvanic vestibular stimulation and head position on the soleus H reflex in humans. *Clin. Neurophysiol.* 113, 1709–1714.

Kim, J., and Curthoys, I. S. (2004). Responses of primary vestibular neurons to galvanic vestibular stimulation (GVS) in the anaesthetised guinea pig. *Brain Res. Bull.* 64, 265–271.

Knikou, M. (2008). The H-reflex as a probe: pathways and pitfalls. *J. Neurosci. Methods* 171, 1–12. doi: 10.1016/j.jneumeth.2008.02.012

Lowrey, C. R., and Bent, L. R. (2009). Modulation of the soleus H-reflex following galvanic vestibular stimulation and cutaneous stimulation in prone human subjects. *Muscle Nerve* 40, 213–220. doi: 10.1002/mus.21275

Matsugi, A. (2019). Reader response: cerebello-spinal tDCS in ataxia: a randomized, double-blind, sham-controlled, crossover trial. *Neurology* 92:1121.

Matsugi, A., Douchi, S., Suzuki, K., Oku, K., Mori, N., Tanaka, H., et al. (2020). Cerebellar transcranial magnetic stimulation reduces the silent period on hand muscle electromyography during force control. *Brain Sci.* 10:63. doi: 10.3390/brainsci10020063

Matsugi, A., Iwata, Y., Mori, N., Horino, H., and Hiraoka, K. (2013). Long latency electromyographic response induced by transcranial magnetic stimulation over the cerebellum preferentially appears during continuous visually guided manual tracking task. *Cerebellum* 12, 147–154. doi: 10.1007/s12311-012-0402-6

Matsugi, A., Mori, N., Uehara, S., Kamata, N., Oku, K., Mukai, K., et al. (2014). Task dependency of the long-latency facilitatory effect on the soleus H-reflex by cerebellar transcranial magnetic stimulation. *Neuroreport* 25, 1375–1380. doi: 10.1097/WNR.0000000000000275

Matsugi, A., and Okada, Y. (2017). Cerebellar transcranial static magnetic field stimulation transiently reduces cerebellar brain inhibition. *Funct. Neurol.* 32, 77–82.

Matsugi, A., and Okada, Y. (2020). Cerebellar transcranial direct current stimulation modulates the effect of cerebellar transcranial magnetic stimulation on the excitability of spinal reflex. *Neurosci. Res.* 150, 37–43. doi: 10.1016/j.neures.2019.01.012

Matsugi, A., Ueta, Y., Oku, K., Okuno, K., Tamaru, Y., Nomura, S., et al. (2017). Effect of gaze-stabilization exercises on vestibular function during postural control. *Neuroreport* 28, 439–443. doi: 10.1097/WNR.0000000000000776

Matsugi, A., Yoshida, N., Nishishita, S., Okada, Y., Mori, N., Oku, K., et al. (2019). Cerebellum-mediated trainability of eye and head movements for dynamic gazing. *PLoS One* 14:e0224458. doi: 10.1371/journal.pone.0224458

McDonnell, M. D., and Ward, L. M. (2011). The benefits of noise in neural systems: bridging theory and experiment. *Nat. Rev. Neurosci.* 12, 415–426. doi: 10.1038/nrn3061

Miall, R. C., and Christensen, L. O. (2004). The effect of rTMS over the cerebellum in normal human volunteers on peg-board movement performance. *Neurosci. Lett.* 371, 185–189.

Miles, F. A., and Eighmy, B. B. (1980). Long-term adaptive changes in primate vestibuloocular reflex. I. Behavioral observations. *J. Neurophysiol.* 43, 1406–1425.

Moliadze, V., Atalay, D., Antal, A., and Paulus, W. (2012). Close to threshold transcranial electrical stimulation preferentially activates inhibitory networks before switching to excitation with higher intensities. *Brain Stimul.* 5, 505–511. doi: 10.1016/j.brs.2011.11.004

Muto, N., Shinomiya, K., Komori, H., Mochida, K., and Furuya, K. (1995). Spinal cord monitoring of the ventral funiculus function. Analysis of spinal field potentials after galvanic vestibular stimulation. *Spine* 20, 2429–2434.

Nagel, M., and Zangemeister, W. H. (2003). The effect of transcranial magnetic stimulation over the cerebellum on the synkinesis of coordinated eye and head movements. *J. Neurol. Sci.* 213, 35–45.

Okada, Y., Shiozaki, T., Nakamura, J., Azumi, Y., Inazato, M., Ono, M., et al. (2018). Influence of the intensity of galvanic vestibular stimulation and cutaneous stimulation on the soleus H-reflex in healthy individuals. *Neuroreport* 29, 1135–1139. doi: 10.1097/WNR.0000000000001086

Popa, T., Russo, M., and Meunier, S. (2010). Long-lasting inhibition of cerebellar output. *Brain Stimul.* 3, 161–169. doi: 10.1016/j.brs.2009.10.001

Roth, Y., Levkovitz, Y., Pell, G. S., Ankry, M., and Zangen, A. (2014). Safety and characterization of a novel multi-channel TMS stimulator. *Brain Stimul.* 7, 194–205. doi: 10.1016/j.brs.2013.09.004

Sellke, T., Bayarri, M. J., and Berger, J. O. (2001). Calibration of ρ values for testing precise null hypotheses. *Am. Stat.* 55:10. doi: 10.1198/000313001300339950

Straka, H., Zwergal, A., and Cullen, K. E. (2016). Vestibular animal models: contributions to understanding physiology and disease. *J. Neurol.* 263(Suppl. 1), S10–S23. doi: 10.1007/s00415-015-7909-y

Thielscher, A., Antunes, A., and Saturnino, G. B. (2015). Field modeling for transcranial magnetic stimulation: A useful tool to understand the physiological effects of TMS? *Conf. Proc. IEEE Eng. Med. Biol. Soc.* 2015, 222–225. doi: 10.1109/EMBC.2015.7318340

Tremblay, S., Austin, D., Hannah, R., and Rothwell, J. C. (2016). Non-invasive brain stimulation as a tool to study cerebellar-M1 interactions in humans. *Cerebellum Ataxias* 3:19.

Ugawa, Y., Uesaka, Y., Terao, Y., Hanajima, R., and Kanazawa, I. (1995). Magnetic stimulation over the cerebellum in humans. *Ann. Neurol.* 37, 703–713.

van Dun, K., Bodranghien, F., Manto, M., and Marien, P. (2017). Targeting the cerebellum by noninvasive neurostimulation: a review. *Cerebellum* 16, 695–741. doi: 10.1007/s12311-016-0840-7

Welgampola, M. S., and Colebatch, J. G. (2001). Vestibulospinal reflexes: quantitative effects of sensory feedback and postural task. *Exp. Brain Res.* 139, 345–353.

Wuehr, M., Decker, J., and Schniepp, R. (2017). Noisy galvanic vestibular stimulation: an emerging treatment option for bilateral vestibulopathy. *J. Neurol.* 264, 81–86. doi: 10.1007/s00415-017-8481-4

Zangemeister, W. H., and Nagel, M. (2001). Transcranial magnetic stimulation over the cerebellum delays predictive head movements in the coordination of gaze. *Acta Otolaryngol. Suppl.* 545, 140–144.

Zibman, S., Pell, G. S., Barnea-Ygael, N., Roth, Y., and Zangen, A. (2019). Application of transcranial magnetic stimulation for major depression: coil design and neuroanatomical variability considerations. *Eur. Neuropsychopharmacol.* doi: 10.1016/j.euroneuro.2019.06.009 [Epub ahead of print].

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The Functional Tactile Object Recognition Test: A Unidimensional Measure With Excellent Internal Consistency for Haptic Sensing of Real Objects After Stroke

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Introduction: Our hands, with their exquisite sensors, work in concert with our sensing brain to extract sensory attributes of objects as we engage in daily activities. One in two people with stroke experience impaired body sensation, with negative impact on hand use and return to previous valued activities. Valid, quantitative tools are critical to measure somatosensory impairment after stroke. The functional Tactile Object Recognition Test (fTORT) is a quantitative measure of tactile (haptic) object recognition designed to test one's ability to recognize everyday objects across seven sensory attributes using 14 object sets. However, to date, knowledge of the nature of object recognition errors is limited, and the internal consistency of performance across item scores and dimensionality of the measure have not been established.

Objectives: To describe the original development and construction of the test, characterize the distribution and nature of performance errors after stroke, and to evaluate the internal consistency of item scores and dimensionality of the fTORT.

Method: Data from existing cohorts of stroke survivors (n = 115) who were assessed on the fTORT quantitative measure of sensory performance were extracted and pooled. Item and scale analyses were conducted on the raw item data. The distribution and type of errors were characterized.

Results: The 14 item sets of the fTORT form a well-behaved unidimensional scale and demonstrate excellent internal consistency (Cronbach alpha of 0.93). Deletion of any item failed to improve the Cronbach score. Most items displayed a bimodal score distribution, with function and attribute errors (score 0) or correct response (score 3) being most common. A smaller proportion of one- or two-attribute errors occurred. The total score range differentiated performance over a wide range of object recognition impairment.

Conclusion: Unidimensional scale and similar factor loadings across all items support simple addition of the 14 item scores on the fTORT. Therapists can use the fTORT to quantify impaired tactile object recognition in people with stroke based on the current set of items. New insights on the nature of haptic object recognition impairment after stroke are revealed.

Keywords: somatosensation, haptic, object recognition, perception, touch, stroke, assess, sensation

INTRODUCTION

Our hands, with their exquisite sensors, work in concert with our sensing brain to extract sensory attributes of objects to interact with those objects as we engage in our daily activities. This ability is critical to tactually recognize objects (e.g., a cup from a jar), locate objects (e.g., locate a button from the background of the clothing on which it is fastened), appreciate the tactile features of objects (e.g., the shape and warmth of a child's hand), and to connect with the people and objects that we interact with in the immediate (reachable) space around us.

The capacity underlying these tasks is commonly referred to as tactile (or haptic) object recognition. Tactile (haptic) object recognition is the ability to identify common objects through the use of touch without the aid of vision. Haptic object recognition relies on all the somatosensory inputs used by the tactile system and skin sensors in combination with information from position and movement sensors in joints and muscles and force receptors in tendons (Lederman and Klatzky, 1990, 2009). It involves extraction of various object attributes and the integration of that information to recognize what the object is. The sensory object attributes extracted include texture, shape, size, weight, temperature, hardness, and function/motion of objects (Lederman and Klatzky, 1987, 1990). Haptic perception typically involves active manual exploration. When people use their haptic system, they typically focus on their experiences of the external world and objects and their properties, such as roughness, shape, and weight (Lederman and Klatzky, 2009).

One in four adults are likely to suffer a stroke, based on the estimated global lifetime risk of stroke (Feigin et al., 2018). One in two stroke survivors experience impairment in the ability to receive and interpret body sensations such as touch, limb position sense, and to recognize objects through touch (Carey, 1995; Connell et al., 2008; Tyson et al., 2008; Carey and Matyas, 2011; Kessner et al., 2016). It is like the hand is blind (Turville et al., 2019). The person has difficulty holding and using simple objects such as a fork, and frequently learns not to use his/her hand. The impairment negatively impacts the person's ability to interact with the world around them (Connell et al., 2014; Turville et al., 2019), hand function (Blennerhassett et al., 2007, 2008), goal-directed use of the arm (Jeannerod, 1997; Turville et al., 2017), and return to previous life activities (Carey et al., 2016b, 2018). It is associated with poorer functional outcome (Reding and Potes, 1988; Carey et al., 2016b), yet it is a "neglected" area of stroke rehabilitation (Kalra, 2010). Valid, quantitative measurement is critical to diagnose somatosensory impairment and assess change over time (Carey, 1995).

Assessment of the ability to recognize common objects through the sense of touch is important after stroke. It has face validity for the person with stroke and allows direct translation of capacity to the context of everyday tasks. Some measures have been developed to assess recognition of a subset of object features such as shape and size, often using a two-dimensional layout (Rosen and Lundborg, 1998) or arbitrary shapes (Kalisch et al., 2012). However, in the real world, we typically need to interact with three-dimensional (3D) common objects that have multiple sensory object features. Further, we know that real 3D common objects can be recognized very efficiently in non-neurologically impaired adults (Lederman and Klatzky, 1987). Haptic recognition of everyday objects is quite fast and highly accurate with 96% correctly named: 68% in less than 3 s and 94% within 5 s (Klatzky et al., 1985). Further, in using common objects, it may be important to not only recognize sensory features but also recognize the type of object, such as a drinking vessel (typically characterized by a cluster of object features).

Our overall objective was to develop a quantitative and psychometrically sound tool to measure the capacity of haptic object recognition using 3D common objects. Our approach involved two sub-aims:

1. To construct a quantitative measure of the ability to recognize everyday objects through touch, the functional Tactile Object Recognition Test (Part 1).
2. To evaluate the internal consistency of item scores and dimensionality of the functional Tactile Object Recognition Test, an evidence-based assessment to measure somatosensory impairment in the hand after stroke (Part 2).

PART 1: DEVELOPMENT AND CONSTRUCTION OF THE FUNCTIONAL TACTILE OBJECT RECOGNITION TEST (fTORT)

The functional Tactile Object Recognition Test (fTORT) was developed to quantitatively measure tactile (haptic) object recognition in adult persons who experience stroke (Carey et al., 2006). The test has been designed to include common objects to maximize face validity and because humans are accurate and efficient at recognizing real 3D common objects by touch (Klatzky et al., 1985). The measure is designed to capture the interface between tactile exploration and sensing and to systematically sample haptic object recognition across a range of somatosensory attributes. This is the first full description of the development and construction of the fTORT by the originator of the tool.

Selection of Test Items

In developing the assessment tool, it was first important to select objects that could be used to sample different attributes of somatosensation in the context of everyday objects. Seven sensory attributes of objects have been identified by Lederman and Klatzky (1987, 1990, 1993) based on the optimal exploratory procedures used to extract those sensory attributes. Lederman and Klatzky (1987) first systematically characterized the association between attributes of objects, such as shape and texture, and the movements (exploratory procedures) used to recognize those features. They used cluster analysis of the exploratory movements to classify the associated object attribute (Lederman and Klatzky, 1990). They then investigated the most optimal movements used to recognize 100 real 3D common objects across different functional categories important for knowledge-driven exploration (Lederman and Klatzky, 1990). The seven object attributes (e.g., shape) and the corresponding optimal exploratory procedure used to extract the attribute (e.g., contour following) are as follows: exact shape – contour following; volume/global shape – enclosure; texture – lateral motion; hardness – pressure; weight – unsupported holding; temperature – static contact; part motion or motion of a part – characteristic movement specific to the object (e.g., flick of a light switch) (Lederman and Klatzky, 1987, 1990).

Objects used for the current assessment were selected to represent the seven sensory object attributes, and corresponding optimal exploratory procedure used to recognize that attribute, as defined by Lederman and Klatzky (1987), and were selected from the set of 100 common objects described by them (Lederman and Klatzky, 1990). To capture a range of objects commonly encountered, the objects included were selected across the different object categories investigated, including household, personal, office, leisure, and food, and spanned large, medium, and small objects that were capable of being readily manipulated. Objects were selected to sample each of the seven sensory attributes twice. Thus, the test comprises 14 object sets. Object sets were also constructed to permit discrimination of the distinctive somatosensory attribute associated with that object set, by varying the specific sensory attribute (e.g., weight, shape) between object pairs. For example, in selecting objects to test temperature, a review of the 100 common objects revealed that objects such as metal doorknob (function category: door opener), wooden bowl (function category: container), and plastic paperclip (function category: paper fastener) were most optimally recognized via the sensory attribute of temperature, based on the matched exploratory procedure of static contact. In constructing the object sets for the fTORT, we selected doorknobs and bowls for object sets, with objects included having different surface temperatures, e.g., wooden and metal doorknob. Somatosensory attributes tested and the corresponding object sets are listed in **Table 1**.

Object Sets and Response Poster

Object sets were constructed where two objects differed in the sensory attribute of interest (e.g., weight) whereas the third object in the set was a distractor object, i.e., that varied in the object attribute of interest but also in another attribute (e.g., weight and shape). Object sets had a common function, e.g., food jar, drinking vessel, and security device. These categories of function were based on the work of Lederman and Klatzky (1990).

Each object set, 14 in total, was displayed visually on a photo response poster (see **Figure 1**). A response poster was used to restrict the number of possible responses and to facilitate ease of response for participants. Visual display of objects was selected given the face validity of this approach and the alignment of visual and tactile modalities when recognizing object properties, e.g., the shape of an object can be seen, and that visual image aligns with the tactile shape when explored haptically using contour following or enclosure (Lacey and Sathian, 2014). Use of a visual response poster that was in full view during object exploration

TABLE 1 | Somatosensory attribute sampled and corresponding test objects and object function category.

Sensory attribute tested	Test object	Matched pair	Object function category
Weight	Full milk bottle	Half-full milk bottle	Drink container
Weight	Empty jar	Full jar	Food jar
Temperature	Metal doorknob	Wooden doorknob	Door opener
Temperature	Stainless steel bowl	Plastic bowl	Container – bowl
Hardness	Hardcover book	Soft cover book	Reading material
Hardness	Firm plastic cup	Crushable plastic cup	Drinking vessel
Function/motion	Zipper	Buttons	Clothing fastener
Function/motion	Click switch	Turn switch	Wall attachment
Shape (exact)	Spoon	Fork	Eating utensil
Shape (exact)	Cylindrical pasta	Spiral-shaped pasta	Food
Size (volume)	Small faced watch	Large-faced watch	Timepiece
Size (volume)	House key	Filling cabinet key	Security device
Texture	Plastic card	Paper card	Office supplies
Texture	Wooden clothes peg	Plastic clothes peg	Clothes hanging device

FIGURE 1 | Functional Tactile Object Recognition Test response poster displaying object sets. Sensory attribute tested within object sets, e.g., weight, is labeled for each set in the figure. Figure adapted from Turville et al. (2018). Reproduced with permission. The final publication is available at IOS Press through http://dx.doi.org/10.3233/NRE-182439.

also minimized memory-related demands. Each object (test item) may be described according to two main features:

1. Type of object and the object function category (object set) it belongs to, e.g., cup – drinking vessel; key – security device.
2. Sensory attribute it tests, e.g., weight – full jar/empty jar; hardness – crushable plastic cup/firm plastic cup.

For example, in the object set of bottles that have the same function (drink container), objects 1 and 3 are a matching pair that vary by weight only (i.e., one is a full milk bottle and the other a half-full milk bottle), whereas object 2, the distractor object, varies by weight (empty) but also by shape of the bottle (i.e., a Coke bottle) (see **Figure 1**).

Test Scale and Scoring

Test scores were constructed to achieve a ranking in the type and amount of response error while sampling the seven object attributes. Response error for each object set permitted sampling whether the person could recognize the type of object through touch (i.e., object category of function, such as drinking vessel), the presence of the distinctive object attribute being tested (i.e., was it recognized relative to similar object types with distractor attributes, e.g., crushability of cup?), and the accuracy of attribute recognition (i.e., was the amount of distinctive sensory object attribute correctly identified, e.g., hardness of cup being firm or crushable?). Scoring according to these levels of recognition was operationalized according to the criterion descriptors outlined in **Table 2**. Each of the seven object attributes to be tested were sampled twice (i.e., use of two different object sets for a specific object attribute such as weight) and scored.

Item responses were scored according to descriptors in **Table 2**. This permitted quantification of the amount of error (using ordinal scale) within object sets. However, it is unclear whether these item error scores can be summed to give an overall error score for the fTORT. We therefore sought to examine empirically whether the item scores form a unidimensional scale permitting addition of item scores into a single total score.

PART 2: EVALUATION OF THE INTERNAL CONSISTENCY OF ITEM SCORES AND DIMENSIONALITY OF THE fTORT

The fTORT has been constructed, as detailed earlier, as a research and clinical tool to quantitatively measure tactile (haptic) object recognition using real 3D common objects. It has been used in clinical research settings to measure somatosensory impairment within several studies. Preliminary findings indicate that the tool has good discriminative validity to detect impairment in people with stroke relative to age-matched healthy controls (Carey et al.,

TABLE 2 | Item response scoring according to the object and sensory attribute descriptors, with example.

Item Score	Response	Object match/error descriptor	Detailed description	**Example:** Test object is the half-full milk bottle (response given)
3	Correct object	Exact match	Object matched to correct category of function and correct amount of sensory attribute	Half-full milk bottle
2	Object pair	Error in distinctive sensory object attribute	Error in recognition/discrimination of amount of distinctive sensory attribute being tested. Object category correct	Full milk bottle (error in weight of bottle)
1	Object distractor	Error in two or more sensory object attributes	Error in recognition of the attribute being tested (weight) and at least one other attribute as evident in distractor object. Object category correct	Empty coke bottle (error in weight and shape of bottle)
0	Incorrect	Error of object type/function and sensory object attribute	A gross error of object type/function and sensory attribute. This error is more severe than being incorrect in even two sensory attributes	For example, food jar or reading material (different type of object category)

2006). The purpose of the current empirical study was to establish the internal consistency of performance across item scores, and the dimensionality of the measurement scale, e.g., whether haptic object recognition as tested using the fTORT can be represented on a single scale or not.

MATERIALS AND METHODS

Sample: Participants, Study Cohorts, and Study Design

Baseline data from existing cohorts of stroke survivors who were assessed on the fTORT were extracted and pooled. This included data from 115 stroke survivors who were enrolled in the following studies: SENSe (*S*tudy of the *E*ffectiveness of *N*eurorehabilitation on *Se*nsation; *n* = 52) (Carey et al., 2011), CoNNECT (*Co*nnecting *N*ew *N*etworks for *E*veryday *C*ontact through *T*ouch; *n* = 45) (Carey, 2013; Goodin et al., 2018), and IN_Touch (*I*maging *N*europlasticity of *Touch*; *n* = 18) (Bannister et al., 2015; Carey et al., 2016a). There were no overlapping participants across studies.

Data were extracted and pooled across these existing cohorts of stroke survivors who had similar characteristics and inclusion/exclusion criteria. Stroke participants were medically stable, and able to give informed consent and comprehend simple instructions. Exclusion criteria included evidence of unilateral spatial neglect based on standard neuropsychological testing, previous history of other central nervous system dysfunction, or peripheral neuropathy. Additional selection criteria for the CoNNECT and IN_Touch studies included participants being right-handed dominant, no brainstem infarct, first episode infarct, and being suitable for MRI. All participants gave voluntary informed consent and procedures were approved by Human Ethics committees of participating hospitals and La Trobe University, Australia.

All participants were assessed at baseline on the fTORT. Timing of the baseline assessment post-stroke varied across the studies, from a median of 4 weeks to 53 weeks post-stroke. The fTORT was administered to assess tactile object recognition both for the hand contralateral to the side of lesion ("affected" hand) and ipsilateral to the lesion (commonly referred to as the "unaffected" hand). Data included in the current study relate to scores for the "affected" hand contralateral to the side of lesion only.

Measure: fTORT

The fTORT is designed to test recognition of objects through the sense of touch. Test equipment includes 14 actual test objects to be felt and 14 matched pair objects (**Table 1**); response poster displaying 14 object sets, i.e., 42 objects in total (**Figure 1**); five display objects – for size calibration (metal bowl, desert spoon, full jar, paper business card, and house key); trial object (Coke bottle); curtain to occlude vision; mat to minimize any sound if object is dropped; ear muffs to minimize identification of object via sound made when exploring the object; stop watch; waist height table; two chairs; and assessment form and pen.

Set-Up

The therapist sits opposite or to the side of the person being tested, depending on which arm is being tested (i.e., if the right arm is to be tested, sit on the right side of the person). A screen is placed in front of or to the side of the person to occlude vision of the test object. The poster of the test and distractor objects is placed on the table at a comfortable viewing distance. Objects used for size calibration are positioned along the top of the poster, in the same orientation as the object in the poster. The person's hand to be tested is placed through the screen with their palm facing up and their arm resting on the table. Posture variations are allowed if required due to positioning restrictions or motor impairment, e.g., unable to achieve supination position due to tonal changes. A padded mat is placed under the test arm to minimize noise if the object is dropped. The person is instructed to put on the ear muffs to minimize any auditory clues from the test items. A stopwatch, test form, and pen are nearby for testing. During testing, the actual test objects are kept out of the person's view.

Testing Procedure

During each trial, one object from each object set (14 in total) is presented to the person using standard test instructions. The test items are listed on the assessment form (**Figure 2**). The test item (object) is placed in the person's hand to be tested or the

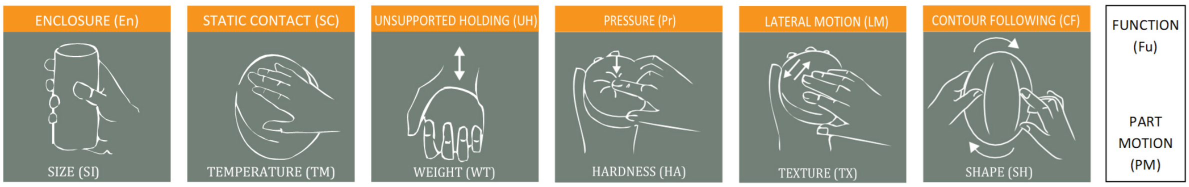
functional Tactile Object Recognition Test (fTORT)
Scoring Sheet - Full 14-Item Version
(Carey, 2020)

Time Start: ___________________ Time End: ________________

Hand Tested: Left / Right (circle) **Affected Hand:** Left / Right (circle)

Test Item #	**Test object**	**MDA**	**Response** (object no. or name)	**Score*** (3,2,1,0)	**Time taken** (msec)	**Exploratory procedures used ^** (see images below) Guided movement required: Yes / No; Comment ______							
Trial (2)	Coke Bottle					En	SC	UH	Pr	LM	CF	Fu	PM
39	Plastic clothes peg	TX				En	SC	UH	Pr	LM	CF	Fu	PM
34	House key	SI				En	SC	UH	Pr	LM	CF	Fu	PM
9	Paperback book	HA				En	SC	UH	Pr	LM	CF	Fu	PM
3	Half full milk bottle	WT				En	SC	UH	Pr	LM	CF	Fu	PM
33	Paper card	TX				En	SC	UH	Pr	LM	CF	Fu	PM
15	Button	MO				En	SC	UH	Pr	LM	CF	Fu	PM
40	Cylinder shaped pasta	SH				En	SC	UH	Pr	LM	CF	Fu	PM
29	Crush plastic cup	HA				En	SC	UH	Pr	LM	CF	Fu	PM
27	Empty jar	WT				En	SC	UH	Pr	LM	CF	Fu	PM
23	Small faced watch	SI				En	SC	UH	Pr	LM	CF	Fu	PM
12	Plastic bowl	TM				En	SC	UH	Pr	LM	CF	Fu	PM
16	Click switch	MO				En	SC	UH	Pr	LM	CF	Fu	PM
20	Spoon	SH				En	SC	UH	Pr	LM	CF	Fu	PM
6	Wooden doorknob	TM				En	SC	UH	Pr	LM	CF	Fu	PM

***Score: 3- Correct match/exact item; 2- Item pair; 1- Item distracter; 0- Incorrect**



^ Exploratory procedures based on Lederman and Klatzky (1987). Images adapted from www.psy.cmu/faculty/klatzky/lab/pictures/index.html (retrieved March 26,2012)

FIGURE 2 | Assessment form for the functional Tactile Object Recognition Test (fTORT). MDA, most diagnostic attribute, i.e., the sensory attribute that distinguishes the test object from the object pair for each of the object sets; TX, texture; SI, size; HA, hardness; WT, weight; MO, motion; SH, shape; TM, temperature.

person's hand is placed on the object, behind the curtain, in a standard manner. Only one hand, the tested hand, is allowed to be used to explore the object. The person is told that it is important to select the object that most closely matches what he/she feels from the response poster (comprising 42 everyday objects or 14 item sets), that not all objects will be used, and the same object may be presented on more than one occasion. The participant may need to be encouraged to look at all the object photographs before choosing their final answer. The person is instructed that as soon as he/she recognizes which object it is from the 14 object sets shown in the poster, they should put the object down and indicate the matching object by either pointing to the object or saying the identifying number of that object, for example, "27" (empty jar). They are instructed not to feel the object any more once they have given their response. The time to identification is recorded in milliseconds. The exploratory procedures (EPs) used by the person are also recorded. The assessor circles the EPs observed. The EP that is most optimal for the object pair is highlighted on the assessor sheet. People with stroke may need assistance to adequately explore the object. In this instance, the assessor helps the person explore the object using the most optimal exploratory procedure, as highlighted for that object set, in a standard manner. Thus the "standard" manner is matched to the object set and the guidance required (either moving the participant's hand or moving the object) is provided in a way that simulates the optimal exploratory procedure for that object set. For example, if the set relates to weight, then the assessor would assist the person to achieve the unsupported holding exploratory procedure. Level of assistance required is recorded on the assessment form. Four different test protocol versions were available for testing.

Data Analysis

Test scores were extracted and pooled. Four protocol versions were employed that varied in the order in which item sets were presented and/or which object in the matched pair was presented. After appropriate alignment of the item scores across the four protocol versions, a complete sample of test scores for 115 participants, each with 14 item scores, was available for analysis. Item and scale analyses were conducted on the raw item data. Distributions of item and total scores were determined and displayed graphically. Internal consistency of item scores was quantified using Cronbach alpha. Dimensionality analysis was conducted using principal component analysis.

RESULTS

Background Characteristics of the Sample

Background data on age, sex, side of lesion, and time post-stroke for participants are presented in **Table 3**.

TABLE 3 | Demographic and clinical characteristics of pooled stroke sample.

Demographics	Pooled sample (*n* = 115)	SENSe cohort (*n* = 52)	CoNNECT cohort (*n* = 45)	IN_Touch cohort (*n* = 18)
Age, *years, M (SD)*	58 (14)	61 (13)	53 (14)	60 (15)
Gender, *n (%)*				
Men	81 (70)	38 (73)	32 (71)	11 (61)
Women	34 (30)	14 (27)	13 (29)	7 (39)
Lesion type, *n* (%)				
Cortical	49 (43)	15 (29)	26 (58)	8 (44)
Subcortical	42 (36)	17 (33)	15 (33)	10 (56)
Both	16 (14)	12 (23)	4 (9)	0 (0)
Unknown	8 (7)	8 (15)	0 (0)	0 (0)
Stroke type, *n* (%)				
Ischemic	84 (73)	34 (65)	32 (71)	18 (100)
Hemorrhagic	31 (27)	18 (35)	13 (29)	0 (0)
Hemisphere affected, *n* (%)				
Right	48 (42)	31 (60)	21 (47)	12 (67)
Left	65 (56)	21 (40)	22 (49)	6 (33)
Both	2 (2)	0 (0)	2 (4)	0 (0)
Handedness, *n* (%)				
Right	110 (96)	47 (90)	45 (100)	18 (100)
Left	5 (4)	5 (10)	0 (0)	0 (0)
Affected side, *n* (%)				
Dominant	64 (56)	30 (58)	22 (49)	12 (67)
Non-dominant	51 (44)	22 (42)	23 (51)	6 (33)
Time post-stroke, *weeks, median (IQR)*	40 (15–78)	45 (21–129)	53 (30–81)	4 (3–6)
Level and frequency of physical assistance provided[a], *n (%)*	*for n = 97*			
Fully guided	37 (38)	24 (46)	13 (29)	N/A
Partial guided	17 (17)	3 (6)	14 (31)	N/A
No guidance	16 (16)	4 (8)	12 (27)	N/A
Uncertain	27 (28)	21 (40)	6 (13)	N/A
Motor activity log[b], *Average score/item,*				
Median (IQR)	2.1 (0.6–3.5)	1.3 (0.2–2.4)	2.6 (1.6–3.6)	2.8 (0.9–4.7)
Range	0–4.94	0–4.93	0–4.42	0–4.94

SENSe, Study of the Effectiveness of Neurorehabilitation on Sensation; CoNNECT, Connecting New Networks for Everyday Contact Through Touch; IN_Touch, Imaging Neuroplasticity of Touch; M, mean; SD, standard deviation; IQR, interquartile range; N/A, not available. [a]Level of physical assistance from blinded assessors during testing using the functional Tactile Object Recognition Test. Presence and type of guidance was summarized from assessor comments by authors (YM-Y and LC). If assessors did not specify presence or level of guidance, the data for those participants were categorized as "Uncertain." [b]Motor activity log (MAL) – average score per item (total/number of valid items) to measure perceived "Amount of Use" of the arm in daily activities. Please note: SENSe and IN_Touch used the 30-item version and CoNNECT used the 14-item version of the MAL.

Distributions of Item Scores and Relationship to Total Scores

Distributions of Item Scores

The distributions of scores for each item set of the fTORT are presented in **Figure 3** for the sample of 115 participants (scaled in percentages out of the 115 cases). Most items, with only one exception (item 9), displayed a bimodal score distribution, with pronounced modes at scores of 0 and 3, i.e., errors of object function and sensory attribute (score 0), or exact match including sensory attribute (score 3). Only a minority of cases demonstrated errors solely in sensory attributes (i.e., scores of 1 or 2). For all items, except for item 9 (Wooden/Plastic Clothes Peg), markedly more participants committed object function and attribute errors (scoring 0) than either single or double sensory attribute errors (scores of 1 or 2). Two sensory attribute errors had a frequency from zero (item 8) to 11.3% (item 2) per item set. Single sensory attribute errors tended to be more frequent than two-attribute errors and ranged from a low of 3.5% (item 10) to a high of 25.2% for item 9. Item 9 was also the only item where a score of 2 was more common than a score of 3 and only by a small margin. The lowest mean score for a particular item set (possible range 0–3) was 1.2 for item 9 whereas the highest was 1.9 for item 12. Similar distributions of item scores are evident and item SDs are homogeneous, ranging from 1.27 to 1.44. All 14 item sets demonstrated that people can both correctly recognize or fail to recognize the test item; thus, none were either too easy or too difficult.

Relationship Between Frequency of Item Scores and Total Scores

The cumulative bar plot (**Figure 4**) illustrates the proportion of items scoring 0, 1, 2, or 3 at each total score (sum over

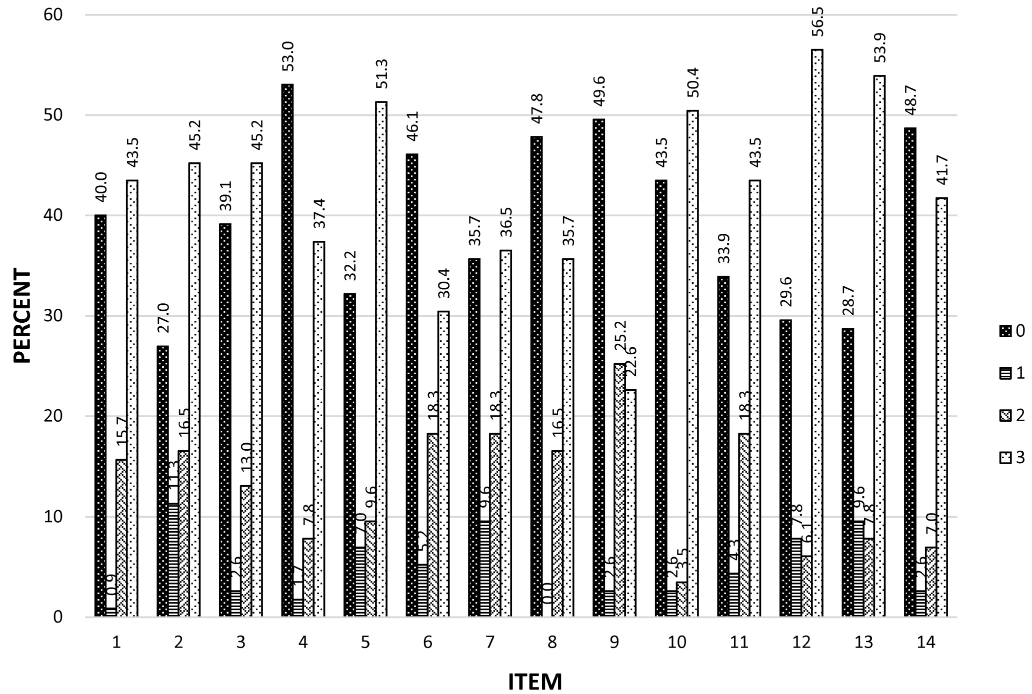


FIGURE 3 | Distributions of fTORT item scores. Distribution of 0, 1, 2, and 3 scores for each of the 14 test items. Values above each bar are the percent of cases showing each score out of the total 115 independent scores available for each item. The sensory attribute tested and corresponding test object pair for each test item set are as follows: item 1 = shape (spoon/fork); item 2 = temperature (metal/wooden doorknob); item 3 = temperature (stainless steel/plastic bowl); item 4 = texture (paper/plastic card); item 5 = function/motion (zipper/buttons); item 6 = size (small-faced/large-faced watch); item 7 = weight (full/empty jar); item 8 = size (house key/filing cabinet key); item 9 = texture (wooden/plastic clothes peg); item 10 = hardness (hardcover book/soft cover book); item 11 = weight (full/half-full milk bottle); item 12 = hardness (firm/crushable plastic cup); item 13 = function/motion (click switch/turn switch); item 14 = shape (cylindrical pasta/spiral shaped pasta).

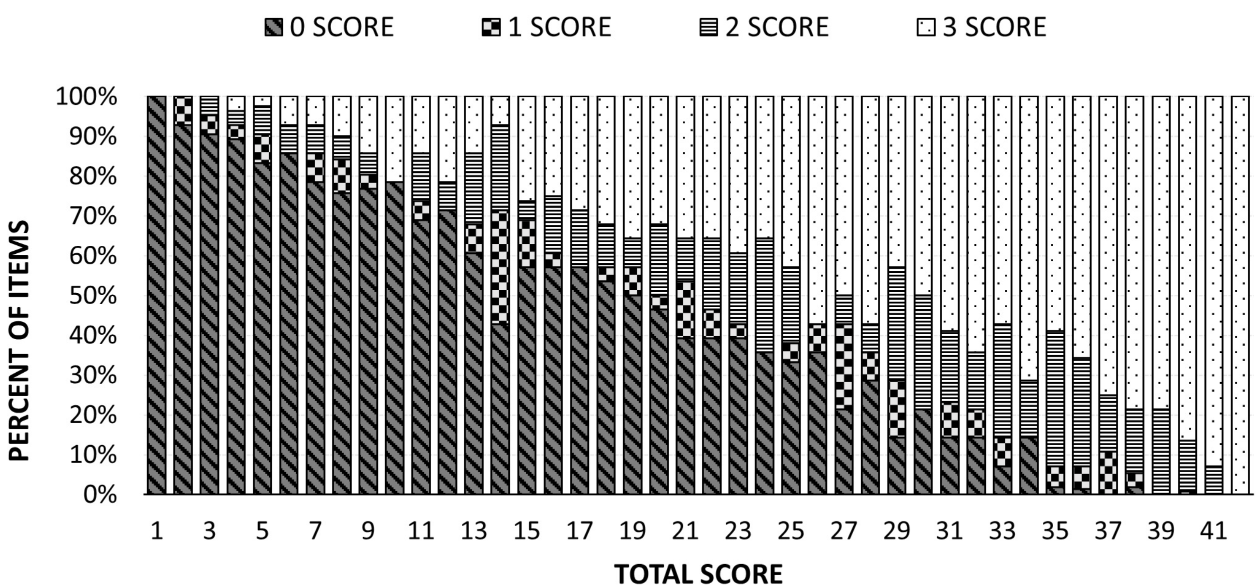


FIGURE 4 | Cumulative bar plot showing pooled frequency of 0, 1, 2, and 3 item scores as a function of total score.

14 items), obtained by pooling over cases with the same total score. As expected, the proportion of 0 scores diminished when total scores increased, whereas the proportion of 3 (completely correct) scores climbed at similar rates, a complementary inverse pattern. The proportion of errors restricted to specific sensory attributes, represented by scores of 1 and 2, were typically

lower than object function and attribute errors (scores of 0) for most total score values. Specific somatosensory attribute errors consistently exceeded object function and attribute errors only for scores above 29.

Probability of Zero Scores

Given the very high proportion of zero scores, we investigated if this was greater than mathematically necessary. Scores as low as 14 can occur without a single item being a zero score, 13 with only item being a zero score, 12 if two items are allowed to be zero, etc. However, the probability of occurrence of zero score items observed in individuals at the same total score climbs steadily for scores below 35 (**Figure 5**), radically departing from the mathematically required probability, which is zero until 14 and only then climbs linearly. The difference between the observed probability of zero scoring items and that required to obtain each total score was statistically significant according to a Kolmogorov–Smirnov test ($p < 0.001$).

Distribution of Total Scores, Internal Consistency of Items, and Dimensionality Analysis

Distribution of Total Scores

Total scores were widely dispersed and displayed a relatively uniform distribution (**Figure 6**), ranging from the lowest to the highest possible scores, with an apparent slight increase in frequency at scores of 40 and 41. The total score distribution did not show a ceiling or floor effect.

Internal Consistency

Inter-item correlations ranged from 0.37 to 0.66. Cronbach's alpha for the 14-item scale was 0.93, indicating very good internal consistency. Examination of item-total statistics (**Table 4**) showed that no improvement in internal consistency could be gained by deleting any of the 14 items. Variations in both scale mean and variance were comparable regardless of which item was deleted. Thus, coefficient alpha, item mean and item variance statistics do not offer a case for deletion of any of the 14 items.

Dimensionality

Discovery of a high level of internal consistency suggested that a unidimensional scale is likely, but that is not a direct demonstration of such structure. Given the non-normal (bimodal) distribution of item scores and the low resolution of a four-point item scale, a principal components analysis was undertaken, one of the methods least impacted by distribution issues. The correlation matrix indicated all inter-item correlations were above 0.37 and ranged to 0.66, suggesting a promising matrix for factor extraction. Principal component analysis discovered that all item communalities were acceptable, ranging from 0.39 to 0.61. Component extraction revealed that only the first had an eigenvalue exceeding the Kaiser criterion of 1. This component accounted for 53% of the variance (**Figure 7**). For subsequent components, eigenvalues dropped sharply to below 1 and formed a clear elbow in the scree plot (the Cattell indicator) indicative of a one-component solution, i.e., a unidimensional scale. Item loadings on this first component were all of good magnitude, in a relatively narrow range from 0.62 to 0.78.

DISCUSSION

The fTORT as constructed works well to form a simple, internally consistent, and unidimensional scale, which is encouraging given the effort taken to select the items. The test was designed to assess

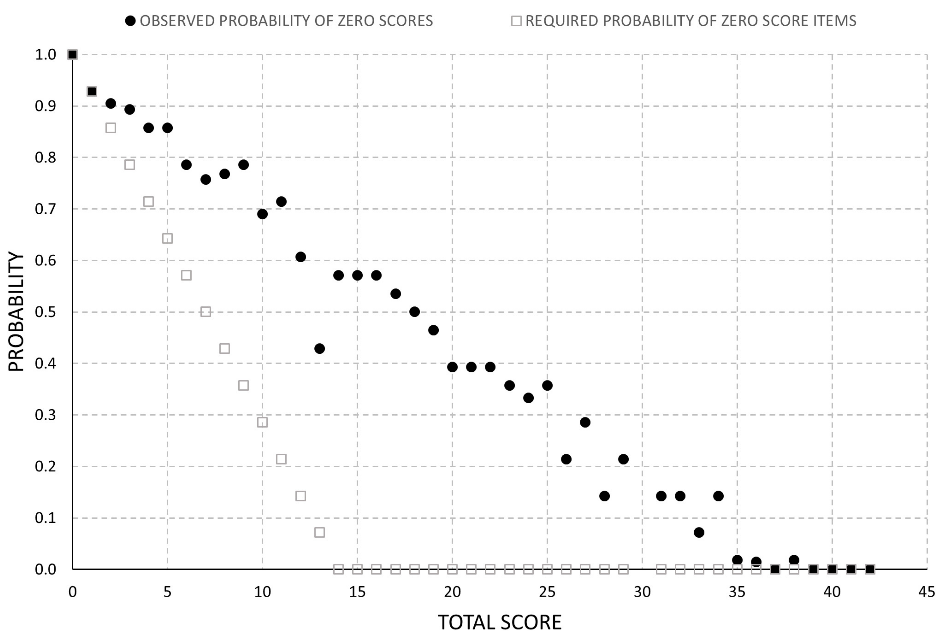


FIGURE 5 | Observed probability of zero scores relative to the minimum probability required to achieve a given total score.

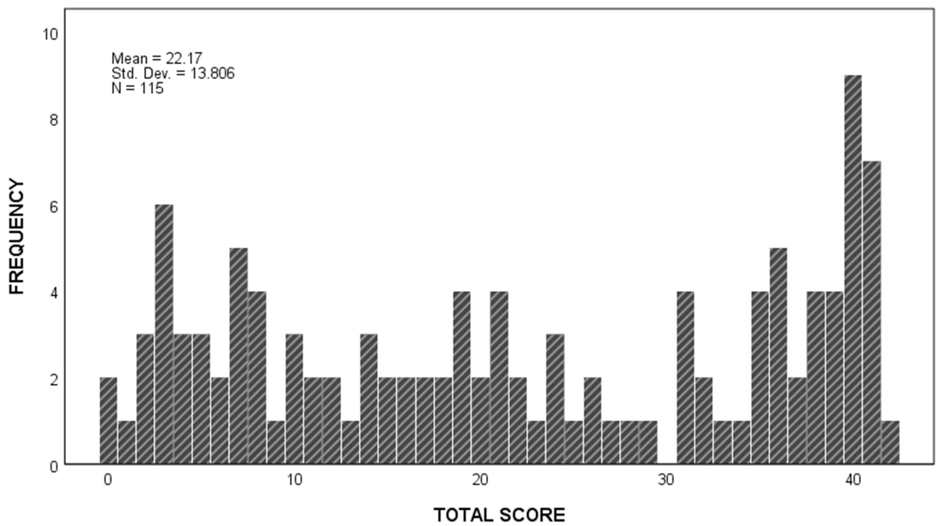


FIGURE 6 | Frequency distribution of total fTORT scores.

TABLE 4 | Item-total statistics and loadings on first principal component.

Item set	Scale mean if item deleted	Scale variance if item deleted	Corrected item-total correlation	Squared multiple correlation	Cronbach's alpha if item deleted	Loadings on first component
Item 1	20.54	164.058	0.694	0.547	0.925	0.743
Item 2	20.37	167.901	0.640	0.522	0.926	0.695
Item 3	20.52	163.743	0.701	0.571	0.924	0.751
Item 4	20.87	162.921	0.705	0.552	0.924	0.756
Item 5	20.37	167.023	0.619	0.408	0.927	0.673
Item 6	20.83	163.894	0.733	0.597	0.923	0.781
Item 7	20.61	164.521	0.728	0.589	0.924	0.776
Item 8	20.77	163.339	0.714	0.601	0.924	0.764
Item 9	20.96	165.656	0.712	0.598	0.924	0.762
Item 10	20.56	164.267	0.646	0.462	0.926	0.701
Item 11	20.45	164.899	0.701	0.577	0.924	0.752
Item 12	20.27	166.725	0.631	0.510	0.927	0.686
Item 13	20.30	169.193	0.566	0.372	0.929	0.622
Item 14	20.75	165.173	0.632	0.460	0.927	0.685

Total scale (14 items) statistics: mean = 22.17; variance = 190.6; Cronbach alpha = 0.930.

recognition of 3D common objects, including amount of specific sensory attribute within an object set (e.g., size of keys). An important feature of the test is use of exploratory procedures; a characteristic of knowledge-driven haptic exploration (Lederman and Klatzky, 1987, 1990). Scale analyses indicate the original 14 item sets devised for object recognition testing form a well-behaved unidimensional scale, with very good internal consistency. The Cronbach alpha was 0.93 and deletion of any item set failed to improve the very good Cronbach alpha. A simple, unweighted addition of the 14 item scores, which is also simple to implement, is supported based on a single component solution with similar loadings across the items. Of interest is the observation that *impaired* performance is dominated by severe error of object recognition (i.e., score of zero), rather than accumulation of simpler one- or two-attribute somatosensory errors. Importantly, we did not observe a skewed distribution within item sets where an item showed *only* 0 scores (i.e., suggesting that item might be too difficult) or *only* 3 scores (i.e., suggesting that item might be too easy). Further, the total score range appears to differentiate individuals over a wide range of object recognition impairment.

The 14 item sets comprising the fTORT were constructed to promote good content and face validity for object recognition, with minimal reliance on language (via use of poster). For stroke and clinician stakeholders, the face validity of the fTORT as a test of the ability to recognize common objects through the sense of touch is argued on the basis that everyday objects are used as test items, that these objects are readily sourced and commonly used, and that real 3D common objects should be used as humans are accurate and efficient in recognizing

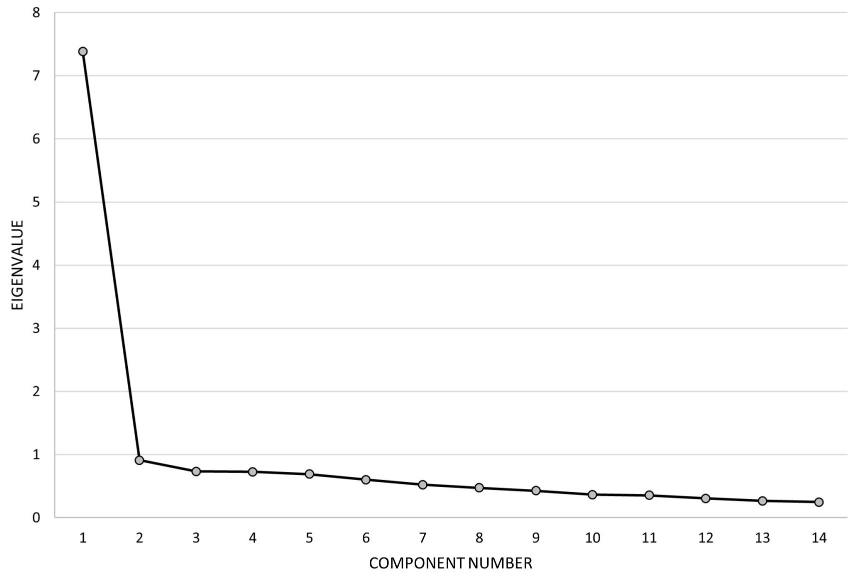


FIGURE 7 | Scree plot summarizing eigenvalues obtained from the principal component analysis. A clear one-component solution is supported by the rapid drop in eigenvalues after the first component.

such objects (Klatzky et al., 1985). The content validity of the test items as representing everyday objects that have key somatosensory features is defended on the basis that all items have been systematically selected from a larger pool of the population of everyday objects (n = 100) that have been categorized in relation to the key somatosensory features aligned with haptic exploration of them, as established in the extensive, empirical work of Lederman and Klatzky (1987, 1990, 1993). The test includes item sets that sample each of the known seven somatosensory attributes (Lederman and Klatzky, 1987, 1990, 1993), supporting the content validity of the fTORT as representing all aspects of the construct of haptic object recognition. Further, the test procedure aligns with recognition of those distinctive somatosensory features, i.e., through object pair response choices. Use of visual representation of object features in the response poster, together with opportunity for visual calibration of actual objects above the poster, is defended based on the alignment of visual and tactile object features (Lacey and Sathian, 2014). Finally, the test is designed to minimize impact of confounds such as memory and language.

The Nature of Haptic Object Recognition Errors

Participants were most often observed to correctly identify the object or not. This pattern was obtained on all item sets with a possible mild deviation only for item 9 where there was some lack of clarity about the upper mode (i.e., exact match and one-attribute sensory error scores were of similar frequency) (**Figure 3**). The dominance of correct response or complete failure over presence of somatosensory attribute errors was strongest in participants with lower total scores, e.g., 29 or less (62% of cases). Only cases with relatively good total scores (30 or better) showed errors mostly in one or two somatosensory attributes, while correctly identifying the object type.

The work by Lederman and Klatzky (1987, 1990, 2009) identified the somatosensory attributes, and corresponding exploratory procedures, that permit most optimal recognition of common 3D objects by persons without neurological impairment. This information was used both in the selection of a representative range of common objects that are recognized most optimally according to the seven somatosensory attributes, as well as to test the ability to correctly discriminate the amount of the distinctive sensory attribute of similar objects within an object set (i.e., via object pair). It was expected that this higher level of discrimination, in addition to the recognition of object function, would be observed in participants with relatively mild overall impairment. This hypothesis is consistent with the observation that the errors in individuals with mild total score reductions (i.e., scores of 30–39) were predominantly due to somatosensory attribute errors rather than complete failure to recognize the type of object. It suggests that those with relatively few errors may be able to recognize the object function category but miss accurate discrimination of the distinctive somatosensory features of the object or may not be able to distinguish those attributes from other sensory attribute(s) in related objects. The fifth percentile criterion of abnormality in older healthy individuals is 37 out of possible score of 42 (Carey et al., 2006), i.e., within the range where errors are predominantly due to inaccuracy of sensory attribute recognition.

These findings of baseline performance suggest that scoring could be simplified to some degree, i.e., error in both function and sensory attribute versus complete success. However, there is likely value is separating deficits of (1) object function and attribute, (2) one or more sensory attribute errors, and (3) complete correct recognition, based on functional significance for individuals and focus for somatosensory retraining. The ability to detect improvement in specific somatosensory attributes recognized may also permit more sensitive monitoring of change in haptic object recognition over time and in relation to sensory retraining outcomes. A dichotomous score would prevent this insight. Our findings suggest the need for further investigation of test scores over time and their interpretation, given the potential impact on clinical application.

New Insights Into the Nature of Somatosensory Impairment After Stroke

Our findings suggest new insights into the "sensing brain" and nature of somatosensory impairment after stroke. The observed strong bimodal pattern of scores across all items could reflect an expression of two subsystems. Lederman and Klatzky (1987) describe two haptic subsystems: a "sensory" subsystem that is directed to perception of specific sensory features of spatial layout and structure, and a "motor" subsystem linked with exploratory procedures that enhances the sensory subsystem to efficiently extract and recognize the desired knowledge about objects (e.g., shape) and recognize what the object is (e.g., fork). Lederman and Klatzky highlight that the sensory subsystem may be less than optimal at perceiving specific spatial layout and structure measures when tested in isolation. In comparison, purposive use of exploratory procedures that are optimized to extract knowledge about distinctive object attributes in an interdependent way leads to a very efficient recognition of 3D common objects (Lederman and Klatzky, 1987). The fTORT was designed to assess 3D haptic object recognition using both subsystems, as is typically required in daily activities. The current bimodal distribution of scores could reflect the contribution from these subsystems, when both are working interdependently, or neither are working. For example, a completely correct response on the fTORT may suggest that the subsystems are working successfully together to recognize the desired knowledge about an object (e.g., shape) and what the object is, *as well as* quantity of that distinctive sensory attribute.

The very high proportion of severe errors (score of 0) suggest that stroke survivors have difficulty recognizing object function *and* sensory attributes. The frequency of these severe errors rose steadily with the increase in impairment score and at an earlier point in the impairment scale than expected mathematically. The steady rise in errors observed could be attributed to breakdown of multiple contributing factors and/or to the poor integration of critical capacities. It is also possible that the integrated whole is greater than the sum of its parts, consistent with Lederman and Klatzky's findings that our haptic system is most efficient when it is enhanced by the motor system and optimal exploratory procedures (Lederman and Klatzky, 1987). A reflection from a stroke survivor captures this interdependence: "…it is like for a blind person their eyes move but they don't see, it is that, your hand moves but it doesn't see. And the difference in what you can do when you can feel something as opposed to not feel something just is indescribably different in life" (Turville et al., 2019). Our finding and previous evidence highlights the potential importance of the interdependence of sensory and motor subsystems in optimal object recognition, including the use of exploratory procedures to search for desired knowledge about objects.

Exploratory procedures provide a window into haptic object recognition (Lederman and Klatzky, 1987). They are purposive, knowledge-driven, and may be necessary, sufficient, and/or optimal in the recognition of specific somatosensory attributes. A clinical observation when using the fTORT is that often the stroke survivor does not use the most optimal exploratory movement, even when they have the movement capability. Rather, they frequently employ a global enclosure movement or a non-specific squeezing movement. *Post hoc* review of exploratory procedures recorded in the current study for each of the seven sensory attributes (based on 75% of the sample, as EPs were unclear or unknown for 25%) revealed that the use of the correct EP matched for the sensory attribute in the item set was relatively low, ranging from 31% for part motion/function item sets to 65% for size item sets, mean 50.57% across item sets. In comparison for those who were recorded as having full active movement, when a score of 3 was obtained (i.e., 62% of occasions), the optimal EP was used in 81% of instances, with additional EPs also recorded. For those who required full (n = 38) or partial (n = 18) guided movement of EPs from the assessor during testing (total n = 56), 56% reported a score of zero, whereas 28% achieved a score of 3 (indicating a score of 3 is still possible with guided exploratory procedures).

Dimensionality of the fTORT, Distribution of Performance Errors, and Internal Consistency of Test Items

The fTORT was designed to assess recognition of 3D common objects (involving clusters of features relating to object function) and to discriminate/recognize the amount of a specific sensory attribute within an object set (e.g., different sizes of keys). The total score involves simple addition of the 14 item scores, based on evidence of a unidimensional scale with similar loadings across test items. The principal component result (**Figure 7**) provides clear evidence of a one-component solution, i.e., a unidimensional scale, with all item loadings of good magnitude and in a relatively narrow range from 0.62 to 0.78. The high loading across all 14 items suggests commonality and meaning. The items are common in that they sample recognition of 3D common objects through the sense of touch (vision occluded), and are closely aligned with the objects and construct of haptic object recognition empirically tested and validated by Lederman and Klatzky (1987, 1990, 1993). Although objects were also selected to differ in sensory attributes optimal for recognition, all objects were everyday objects, requiring attentive exploration, and appearing to need a combination of haptic tactile and proprioceptive input to be correctly sensed and recognized. The spread of items across the seven diagnostic attributes of sensation support previous evidence that each of these attributes contributes to haptic object recognition and may suggest a dependence on multisensory input and interpretation. The spread of error scores across the stroke sample also suggests that the impairment after brain injury is sufficiently distributed, such that patterns of error across specific sensory attributes did not emerge to create a multicomponent structure.

The spread of total scores across the full range of possible scores, from normal performance to most severe impairment, suggests that the 14-item measure worked well, at least for the current sample. The wide spread of scores, shown in **Figure 6**, is not unexpected given the high variability in stroke severity and lesion location, and the complex processing that is thought to occur in haptic object recognition. The spread suggests presence of a range in severity of impairment, consistent with existing literature (Carey, 1995; Connell et al., 2008; Tyson et al., 2008; Carey and Matyas, 2011; Kessner et al., 2016). The slight increase in frequency at scores of 40 and 41 is indicative of unimpaired performance relative to age-matched healthy controls (Carey et al., 2006). The pooled cohort represents stroke survivors who were screened clinically for presence of somatosensory impairment, are able to follow at least two-stage commands, are able to participate in rehabilitation, and do not have neglect. There were more men than women and the mean age is lower than the general population of stroke survivors (Feigin et al., 2003), although the burden of stroke in people younger than 65 years has increased over the last few decades (Katan and Luft, 2018). Nevertheless, the sample was relatively heterogeneous, including those with cortical and/or subcortical lesions, right or left hemisphere lesions, and ischemic or hemorrhagic stroke. It included people who had either the dominant (56%) or non-dominant (44%) hand affected, and were at varying times post-stroke, ranging from 3 to 129 weeks post-stroke. Thus, they may be considered relatively representative of the population of stroke survivors who present for rehabilitation (Carey and Matyas, 2011).

Object sets included were carefully selected to sample the full range of object sensory attributes (Lederman and Klatzky, 1987) and a wide range of 3D objects commonly encountered and previously categorized according to object function and corresponding optimal EP (Lederman and Klatzky, 1990). Despite this range, item means and SDs did not differ markedly, suggesting a limited range of item difficulty and discriminability potential. This finding suggests that there is no difficulty hierarchy evident across items. Further, the items that contributed low scores varied for people with the same total score, and higher total scores were obtained from high scoring items across a variety of items. The representativeness of sampled individuals and test objects increases confidence that errors across an increasing number of item sets indicates more severe impairment. The wide spread of scores also suggests the potential for future determination of levels of impairment severity across the scale. Presence of errors in object function and sensory attribute (score of 0) is suggestive of an impairment, even for relatively mild total impairment scores. In addition to the total impairment score, therapists can gain insight into the nature of impairment – i.e., errors that include recognition of object function and errors relating to specific sensory attributes (or modalities) for the individual tested.

Knowledge-Driven Haptic Exploration and the fTORT

The fTORT provides an assessment of tactile object recognition that aligns with how the haptic object recognition system works in recognizing common everyday objects. It requires recognition of object function and discrimination of specific somatosensory attributes, potentially requiring both sensory and motor haptic subsystems (Lederman and Klatzky, 1987). Extraction of object features and sensory attributes is prompted by the object sets visually displayed on the poster, and hence is set up for knowledge-driven exploration. The test aims to capture the interdependence of sensory object attributes and the exploratory procedures used to extract them. It uses real 3D objects and sensory attributes that are typically recognized using the matched optimal exploratory procedure.

An important part of testing is the observation of exploratory procedures actually used. Exploratory procedures are recorded by the therapist, with the most optimal exploratory procedure identified on the testing form to prompt observation and recording. Although these observations are not used in scoring, they provide information on how the person explores the object and this can be used in therapy. In cases where movement is limited, the therapist uses standardized guided movement of the most optimal exploratory procedure, matched for a given object set to make sure an adequate stimulus is presented. Although time taken to recognize objects haptically is important for everyday function, the response time may be impacted by impairment in motor control after stroke. Time was recorded to monitor the expected efficiency of haptic object recognition, as observed in adults without stroke or movement deficits. It may be of value when testing those with only mild deficits. We recommend recording the time taken, but did not limit the time nor penalize for longer time taken in the fTORT, especially as in some instances guided movement was required.

Testing Procedures and Implications

The fTORT was designed to assess rapid recognition of objects through the sense of touch. During testing, participants were instructed that they would be timed, but were given a relatively unrestricted time to explore the object and its distinctive somatosensory attribute (prompted by the response poster). Participants were encouraged to give a response within 60 s, although some participants took more than 30 or 60 s to discriminate the object and distinctive somatosensory attribute. In other tests, a time of greater than 30 s may be interpreted as an error (Carey, 1995). In the fTORT, response was timed but scoring was based on response errors. The additional time allowed may have permitted some to achieve the maximum correct score of 3 only after extensive and deliberate searching and recognition.

The fTORT requires the person to attend to object features during exploration (active or guided) and then to nominate their response using the response poster. Importantly, the object poster is in full view throughout object exploration (minimizing memory confounds) and the participant is reminded that they are to point to or name the object (or object number) that most closely matches the object that they are feeling out of view. A possible explanation for the high proportion of severe error scores could be a lack of understanding of test instruction and/or impaired attention and cognition. However, this is an unlikely explanation as participants were screened for cognition, some items were correctly matched during testing, and most participants showed scores within the normal range, or at least significantly better, for the "unaffected" hand. The standard protocol permits reminders of test protocol by the assessor if required.

Implications for Assessing Haptic Object Recognition and Clinical Practice

Our findings have implication not only in relation to better understanding the nature of haptic object recognition errors observed in people who experience somatosensory impairment after stroke but also the type of measurement tools used to assess this capacity. To date, quantitative measures have tended to focus on a single attribute alone, such as shape (Rosen and Lundborg, 1998; Kalisch et al., 2012), rather than discrimination and integration of multiple attributes in the context of 3D real objects. In comparison, clinical testing has involved recognition of non-standard everyday objects without knowing whether the range of somatosensory object attributes are being adequately sampled nor whether a person can discriminate differences in distinctive somatosensory attributes (Carey, 1995). It is argued that the fTORT represents one step forward in capturing haptic object recognition of real 3D objects after stroke, with quantification of the extent and nature of object recognition errors. The fTORT assessment has also been adapted and tested for use with children with cerebral palsy (Taylor et al., 2018). The adapted test demonstrated preliminary construct validity and was positively associated with an upper limb activity measure (Taylor et al., 2018).

Future Directions

Future studies should establish age-matched normative standards and the discriminative validity of the test with larger samples, beyond the early preliminary data reported to date (Carey et al., 2006), as well as retest and inter-assessor reliability. In addition, empirical investigation of the criterion validity of the fTORT as a measure that relates to and/or predicts recognition and functional use of such objects in real-world contexts by stroke survivors would be of benefit to support clinical use. It would help to establish concurrent validity for outcomes measured at the same time and/or predictive validity for future outcomes. One potential limitation of use of the test across different cultures and over time relates to the familiarity of the common objects included as items in the test. For example, a fork is likely to be less familiar in Asian populations, whereas a clothes peg may not be so commonly used in the future. The potential exists to adapt some objects to different cultures.

The fTORT includes 14 item sets to assess haptic object recognition, sampling the seven attributes of sensation twice. Sampling each attribute twice was the minimal testing burden possible to investigate if multiple sampling of an attribute is needed, given likely complexity of information processing demanded by real-world objects. Our findings support initial selection of 14 items on the basis that each object attribute is only tested twice, correlations for attribute pairs are not overly high (ranging from 0.37 to 0.64), and longer tests are theoretically more reliable than shorter tests, unless items are highly correlated. However, the ultimate decision on length of a test is a compromise between opposing test design objectives: brevity that saves time and minimizes fatigue versus higher reliability. At this stage of development and testing, inclusion of two item sets for each attribute permitted initial investigation of whether a specific attribute (e.g., shape) is consistently impaired and could inform selection of item sets for future investigations. However, redundancy among items was not assessed in detail within this work. Future investigations may reveal the feasibility of shorter test duration and the best item combination, which would be of value to support the clinical utility of the tool.

Further investigation of the relationship between item scores and exploratory procedures employed would be of value to help unravel the nature of the disruption to knowledge-driven haptic recognition after stroke. Investigation of type and severity of response error over time may also be of value to better understand features of haptic object recognition that may change over time and/or be impacted by sensory rehabilitation. The impact of factors such as side of lesion and brain networks affected by the stroke (including somatosensory, motor, and multimodal processing hubs) may also help to better understand the nature of the impairment and the role of connected regions and networks that could contribute to recovery and rehabilitation. Evidence of how the somatosensory and motor systems can work together within a knowledge-driven framework suggests important pathways for development of interventions that directly use this knowledge. The SENSe (*S*tudy of the *E*ffectiveness of *N*eurorehabilitation on *Se*nsation) approach (Carey et al., 2011) is one such therapy that helps stroke survivors regain a sense of touch and better recognize the function and sensory attributes of real objects through a perceptual learning approach coupled with principles of neuroscience, specific training modules (Carey, 2012), and carefully designed and graded therapeutic equipment. The success of this approach has been demonstrated in a randomized controlled intervention study (Carey et al., 2011). In line with this special issue on the sensing brain, the potential value of combining training of sensation and movement (Gopaul et al., 2019) in an integrated manner for goal-oriented action is also highlighted.

CONCLUSION

In conclusion, the fTORT functions well as a unidimensional scale, supporting simple addition of the 14 item scores on the fTORT. The excellent internal consistency of items supports assessment of haptic object recognition using the item sets selected. Therapists can use the fTORT to quantify impaired tactile object recognition in people with stroke. New insights into the nature of somatosensory impairment after stroke are revealed.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on reasonable request to the corresponding author.

ETHICS STATEMENT

All participants gave voluntary informed consent and procedures were approved by Human Ethics committees of participating hospitals and La Trobe University, Australia.

AUTHOR CONTRIBUTIONS

LC wrote the article, developed the measurement tool, conceived and conducted the studies, designed the pooled data study, obtained ethics, and contributed to data analysis and interpretation of results. YM-Y extracted and pooled data from existing studies, assisted with data collection, and contributed to data analysis and article drafting and editing for important intellectual content. TM contributed to the conception of the study, led and conducted the data analysis, contributed to drafting and editing of the article for important intellectual content, and had a major input to interpretation of results. All authors contributed to the article and approved the submitted version.

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REFERENCES

Bannister, L. C., Crewther, S. G., Gavrilescu, M., and Carey, L. M. (2015). Improvement in touch sensation after stroke is associated with resting functional connectivity changes. *Front. Neurol.* 6:165. doi: 10.3389/fneur.2015.00165

Blennerhassett, J. M., Carey, L. M., and Matyas, T. A. (2008). Impaired discrimination of sensory information about slip between object and skin is associated with handgrip limitation poststroke. *Brain Impair.* 9, 114–121. doi: 10.1375/brim.9.2.114

Blennerhassett, J. M., Matyas, T. A., and Carey, L. M. (2007). Impaired discrimination of surface friction contributes to pinch grip deficit after stroke. *Neurorehabil. Neural Repair* 21, 263–272. doi: 10.1177/1545968306295560

Carey, L. (2012). *Sense: Helping Stroke Survivors Regain a Sense of Touch: a Manual and DVD for Therapists*. Melbourne: Florey Institute of Neuroscience and Mental Health.

Carey, L. M. (1995). Somatosensory loss after stroke. *Crit. Rev. Phys. Rehabil. Med.* 7, 51–91. doi: 10.1615/critrevphysrehabilmed.v7.i1.40

Carey, L. M. (2013). *Effective Sensory Rehabilitation After Stroke: Targeting Viable Brain Networks*. Australian and New Zealand Clinical Trials Registry. ACTRN12613001136796.

Carey, L. M., Abbott, D. F., Lamp, G., Puce, A., Seitz, R. J., Donnan, G. A., et al. (2016a). Same intervention-different reorganisation: the impact of lesion location on training-facilitated somatosensory recovery after stroke. *Neurorehabil. Neural Repair* 30, 988–1000. doi: 10.1177/1545968316653836

Carey, L. M., Lamp, G., and Turville, M. (2016b). The state of the science of somatosensory function and its impact on daily life in adults and older adults, and following stroke: a scoping review. *OTJR Occup. Particip. Health* 36(2 Suppl.), 27S–41S.

Carey, L. M., Matyas, T., and Baum, C. (2018). Effects of somatosensory impairment on participation after stroke. *Am. J. Occup. Ther.* 72, 1–10.

Carey, L. M., and Matyas, T. A. (2011). Frequency of discriminative sensory loss in the hand after stroke. *J. Rehabil. Med.* 43, 257–263. doi: 10.2340/16501977-0662

Carey, L. M., Nankervis, J., LeBlanc, S., and Harvey, L. (2006). "A new functional tactual object recognition test (fTORT) for stroke clients: Normative standards and discriminative validity," in *Proceedings of the 14th International Congress of the World Federation of Occupational Therapists*, Sydney. Australia 23–28 July.

Carey, L. M., Macdonnell, R., and Matyas, T. (2011). SENSe: study of the effectiveness of neurorehabilitation on sensation. A randomized controlled trial. *Neurorehabil. Neural Repair* 25, 304–313. doi: 10.1177/1545968310397705

Connell, L. A., Lincoln, N. B., and Radford, K. A. (2008). Somatosensory impairment after stroke: frequency of different deficits and their recovery. *Clin. Rehabil.* 22, 758–767. doi: 10.1177/0269215508090674

Connell, L. A., McMahon, N. E., and Adams, N. (2014). Stroke survivors' experiences of somatosensory impairment after stroke: an interpretative phenomenological analysis. *Physiotherapy* 100, 150–156. doi: 10.1016/j.physio.2013.09.003

Feigin, V. L., Lawes, C. M., Bennett, D. A., and Anderson, C. S. (2003). Stroke epidemiology: a review of population-based studies of incidence, prevalence, and case-fatality in the late 20th century. *Lancet Neurol.* 2, 43–53. doi: 10.1016/s1474-4422(03)00266-7

Feigin, V. L., Naguyen, G., Cercy, K., Johnson, C. O., Alam, T., and Parmer, P. G. (2018). The GBD 2016 lifetime risk of stroke collaborators. Global, regional, and country-specific lifetime risks of stroke, 1990 and 2016. *N. Engl. J. Med.* 379, 2429–2437. doi: 10.1056/nejmoa1804492

Goodin, P., Lamp, G., Vidyasagar, R., McArdle, D., Seitz, R. J., Carey, L. M., et al. (2018). Altered functional connectivity differs in stroke survivors with impaired touch sensation following left and right hemisphere lesions. *Neuroimage Clin.* 18, 342–355. doi: 10.1016/j.nicl.2018.02.012

Gopaul, U., van Vliet, P., Callister, R., Nilsson, M., and Carey, L. (2019). COMbined Physical and somatoSEnsory training after stroke: development and description of a novel intervention to improve upper limb function. *Physiother. Res. Intern.* 24:e1748. doi: 10.1002/pri.1748

Jeannerod, M. (1997). "Neural mechanisms underlying representations for action," in *Handbook of Neuropsychology*, eds F. Boller and J. Grafman (Amsterdam: Elsevier Science), 167–183. doi: 10.1016/j.neuron.2015.09.040

Kalisch, T., Kattenstroth, J. C., Kowalewski, R., Tegenthoff, M., and Dinse, H. R. (2012). Cognitive and tactile factors affecting human haptic performance in later life. *PLoS One* 7:e30420. doi:10.1371/journal.pone.0030420

Kalra, L. (2010). Stroke rehabilitation 2009: old chestnuts and new insights. *Stroke* 41, e88–e90.

Katan, M., and Luft, A. (2018). Global burden of stroke. *Semin. Neurol.* 38, 208–211.

Kessner, S. S., Bingel, U., and Thomalla, G. (2016). Somatosensory deficits after a stroke: a scoping review. *Top. Stroke Rehabil.* 23, 136–146. doi: 10.1080/10749357.2015.1116822

Klatzky, R. L., Lederman, S. J., and Metzger, V. A. (1985). Identifying objects by touch: an "expert system". *Percept. Psychophys.* 37, 299–302. doi: 10.3758/bf03211351

Lacey, S., and Sathian, K. (2014). Visuo-haptic multisensory object recognition, categorization, and representation. *Front. Psychol.* 5:730. doi: 10.3389/fpsyg.2014.00730

Lederman, S. J., and Klatzky, R. L. (1987). Hand movements: a window into haptic object recognition. *Cogn. Psychol.* 19, 342–368. doi: 10.1016/0010-0285(87)90008-9

Lederman, S. J., and Klatzky, R. L. (1990). Haptic classification of common objects: knowledge-driven exploration. *Cogn. Psychol.* 22, 421–459. doi: 10.1016/0010-0285(90)90009-s

Lederman, S. J., and Klatzky, R. L. (1993). Extracting object properties through haptic exploration. *Acta Psychol.* 84, 29–40. doi: 10.1016/0001-6918(93)90070-8

Lederman, S. J., and Klatzky, R. L. (2009). Haptic perception: a tutorial. *Attent. Percept. Psychophys.* 71, 1439–1459. doi: 10.3758/app.71.7.1439

Reding, M. J., and Potes, E. (1988). Rehabilitation outcome following initial unilateral hemispheric stroke: life table analysis approach. *Stroke* 19, 1354–1358. doi: 10.1161/01.str.19.11.1354

Rosen, B., and Lundborg, G. (1998). A new tactile gnosis instrument in sensibility testing. *J. Hand Ther.* 11, 251–257. doi: 10.1016/s0894-1130(98)80020-3

Taylor, S., Girdler, S., Parsons, R., McLean, B., Falkmer, T., Carey, L., et al. (2018). Construct validity and responsiveness of the functional tactile object recognition test for children with cerebral palsy. *Austr. Occup. Ther. J.* 65, 420–430. doi: 10.1111/1440-1630.12508

Turville, M., Carey, L. M., Matyas, T. A., and Blennerhassett, J. (2017). Change in functional arm use is associated with somatosensory skills after sensory retraining poststroke. *Am. J. Occup. Ther.* 71:7103190070. doi: 10.5014/ajot.2017.024950

Turville, M. L., Matyas, T. A., Blennerhassett, J. M., and Carey, L. M. (2018). Initial severity of somatosensory impairment influences response to upper limb sensory retraining post-stroke. *NeuroRehabilitation*, 43, 413–423. doi: 10.3233/NRE-182439

Turville, M. L., Walker, J., Blennerhassett, J. M., and Carey, L. M. (2019). Experiences of upper limb somatosensory retraining in persons with stroke: an interpretative phenomenological analysis. *Front. Neurosci.* 13:756. doi: 10.3389/fnins.2019.00756

Tyson, S. F., Hanley, M., Chillala, J., Selley, A. B., and Tallis, R. C. (2008). Sensory loss in hospital-admitted people with stroke: characteristics, associated factors, and relationship with function. *Neurorehabil. Neural Repair* 22, 166–172. doi: 10.1177/1545968307305523

Conflict of Interest: LC is the originator of and led the development of the functional Tactile Object Recognition Test. The test is now available for purchase as part of an evidence-based assessment and training unit from a not-for-profit organization (The Florey Institute of Neuroscience and Mental Health).

The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.