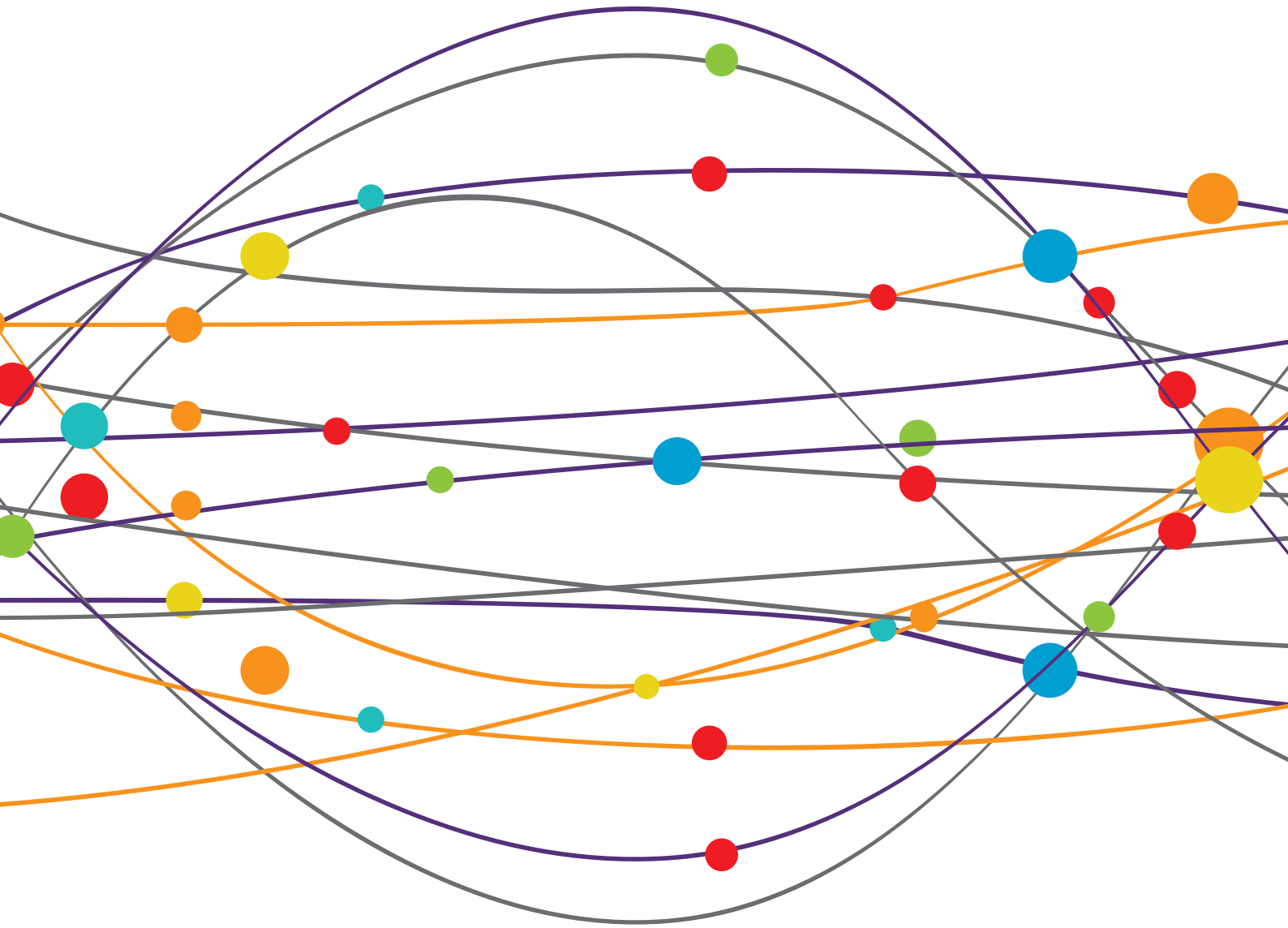
PROMOTING MANUAL DEXTERITY RECOVERY AFTER STROKE

EDITED BY: Martin Lotze and Påvel G. Lindberg
PUBLISHED IN: Frontiers in Neurology



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frontiers

ISSN 1664-8714
ISBN 978-2-88963-173-5
DOI 10.3389/978-2-88963-173-5

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PROMOTING MANUAL DEXTERITY RECOVERY AFTER STROKE

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Citation: Lotze, M., Lindberg, P. G., eds. (2019). Promoting Manual Dexterity Recovery After Stroke. Lausanne: Frontiers Media. doi: 10.3389/978-2-88963-173-5

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frontiers in Neurology

EDITORIAL
published: 30 July 2019
doi: 10.3389/fneur.2019.00815

Editorial: Promoting Manual Dexterity Recovery After Stroke

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Keywords: stroke, neurorehabiliation, recovery, dexterity, prediction

Editorial on the Research Topic

Promoting Manual Dexterity Recovery After Stroke

Manual dexterity is often affected following stroke and is a major issue for autonomy in daily living. How best to improve recovery of manual dexterity remains a key clinical and scientific challenge. Although impressive insights in brain plasticity have been demonstrated in the last decade, aging and degree of lesion to the corticospinal tract, along with other factors, severely restrict functional restoration. Individual factors limiting brain plasticity requires further study. Biomarkers of motor recovery and mechanisms of therapy-mediated gains are also issues of research interest.

There have been a number of evidence based therapy approaches which are candidates for further longitudinal studies on motor recovery associated neurophysiological parameters which can then be used as biomarkers/monitoring parameters for therapy control and outcome prediction. For instance, impairment-oriented training, had shown considerable effect sizes for upper limb motor gain following stroke and many neurophysiological parameters have already been identified using a number of different techniques. The contribution of Platz and Lotze in this issue provides an overview on that field and more specifically recent studies on the Arm Ability Training (AAT) approach. AAT incorporates tasks allowing training of various aspects of upper limb sensorimotor control, including selective wrist and finger movements, arm reach and dexterity tasks (manipulation of both large and small objects), and tasks requiring coordination (steadiness and precision). Studies suggest that AAT is superior to conventional therapy, that it can induce sensorimotor learning and that it is coupled with brain plasticity, particularly with recruitment of ipsilesional premotor cortex activation.

When collecting biomarkers, possibly important for prediction of sensorimotor outcome, specific testing of motor impairment is one of the first candidates. Kim et al. reported on a fast version of the Bilateral Arm Reaching Test (BART) for measurement of spontaneous arm use after stroke. This version of BART leads to enhanced reliance on the less-affected arm in stroke patients and the test had good test-retest reliability and correlation with Actual Amount of Use Test (cross-validation). In addition, more comprehensive testing might improve documentation of hand motor impairments for instance including kinematic and kinetic measures such as presented in the review of Collins et al. in this issue. This synthesis showed that stroke was associated with increased movement times, lower velocity, greater trunk displacement, more curved reach-to-path-ratio and reduced movement smoothness. Such measures may serve as targets when developing tailored interventions. Parry et al. emphasize the importance of impaired grasping control and altered grasping configuration after stroke. Interestingly, prehension strategies compound difficulties with grip force scaling and inhibit the synchrony of grasp onset and object release.

With respect to neurophysiology, Zhou et al. investigated the role of electroencephalography (EEG) for the investigation of gains achieved by visuospatial training. Here frontoparietal coherence predicted training-related gains in visuomotor tracking change, measured as change in

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Edited and reviewed by:
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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *25 June 2019*
Accepted: *15 July 2019*
Published: *30 July 2019*

Citation:
Lotze M and Lindberg PG (2019) Editorial: Promoting Manual Dexterity Recovery After Stroke. Front. Neurol. 10:815. doi: 10.3389/fneur.2019.00815

Success Rate score, highlighting potential importance of sensorimotor connectivity. Cortico (EEG)-Muscular (EMG) coherence measures also enables quantification of motor recovery as shown by Krauth et al. During successful therapy EEG–EMG coherence increased over time, as wrist mobility recovered clinically. Coherence also involved a larger and more bilaterally distributed activation of cortical areas in stroke patients. With respect to Transcranial Magnetic Stimulation, Yarossi et al. focus on the measurement of corticospinal intergrity using TMS. However, here they used motor evoked potential (MEP)-mapping strategies to investigate the responsive areas for eliciting MEPs longitudinally during a motor training in the subacute stage after stroke. They found changes on MEP maps along with changes in motor tests only for responders to motor training both over the lesioned and the non-lesioned hemisphere. They conclude that the association of recovery to bilateral changes in motor topography may depend on integrity of the ipsilesional cortical spinal tract. Rosso and Lamy performed a systematic review of studies correlating upper limb function to resting motor threshold, a TMS measure of functional integrity of corticospinal tract. The findings showed that a low motor threshold correlates with good motor function, both early and in chronic phase post-stroke. Authors concluded that further studies are required on how such TMS measures interact with other factors such as time post-stroke and degree of structural corticospinal damage. Less investigated than MEPs, short intracortical inhibition (SICI) during a motor task is decreased after stroke in the ipsilesional hemisphere and correlated with motor impairment as described here by Ding et al. They concluded, that disinhibition is associated with greater motor impairment and worse dexterity in chronic hemiparetic individuals. This study also highlights benefit of TMS measures when collected during both rest and active states. Finally, neuroimaging measures of structural integrity of corticospinal tract were also found to predict AAT therapy gains in the study by Lotze et al.

Currently, novel interventions are being tested including non-invasive brain stimulation techniques and movement technologies allowing enhanced motivation, intensity of training and enhanced sensory feedback. Interestingly, secondary somatosensory cortex activation is observed especially over the right hemisphere independent on the hand stimulated as reviewed here applying an Activation Likelihood Estimate (ALE) meta-analysis by Lamp et al. This finding suggests a lateralized pattern of somatosensory activation in right secondary somatosensory region. Furthermore, it has also methodological implications for brain mapping studies on the somatosensory system when using a flipping strategy of left or right hemispheric lesions for the purpose to describe functional representation only in an ipsi- and contralesional space.

With this Research Topic we intended to provide latest insight on varied aspects of upper limb and motor and dexterity recovery following stroke. We ended in a range of contributions which have been addressing especially longitudinal observations on stroke survivors, an especially important way to go in the future to understand the neurophysiological basis of motor recovery post-stroke.

AUTHOR CONTRIBUTIONS

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

Conflict of Interest Statement: The 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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 26 March 2019
doi: 10.3389/fneur.2019.00258

The Association Between Reorganization of Bilateral M1 Topography and Function in Response to Early Intensive Hand Focused Upper Limb Rehabilitation Following Stroke Is Dependent on Ipsilesional Corticospinal Tract Integrity

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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: 11 August 2018
Accepted: 26 February 2019
Published: 26 March 2019

Citation:
Yarossi M, Patel J, Qiu Q, Massood S, Fluet G, Merians A, Adamovich S and Tunik E (2019) The Association Between Reorganization of Bilateral M1 Topography and Function in Response to Early Intensive Hand Focused Upper Limb Rehabilitation Following Stroke Is Dependent on Ipsilesional Corticospinal Tract Integrity. Front. Neurol. 10:258. doi: 10.3389/fneur.2019.00258

Transcranial magnetic stimulation (TMS) induced motor evoked potentials (MEPs) are an established proxy of corticospinal excitability. As a binary measure, the presence (MEP+) or absence (MEP-) of ipsilesional hemisphere MEPs early following stroke is a robust indicator of long-term recovery, however this measure does not provide information about spatial cortical reorganization. MEPs have been systematically acquired over the sensorimotor cortex to "map" motor topography. In this investigation we compared the degree to which functional improvements resulting from early (<3 months post-stroke) intensive hand focused upper limb rehabilitation correlate with changes in motor topography between MEP+ and MEP- individuals. Following informed consent, 17 individuals (4 Female, 60.3 ± 9.4 years, 24.6 ± 24.01 days post first time stroke) received 8 one hour-sessions of training with virtual reality (VR)/Robotic simulations. Clinical tests [Box and Blocks Test (BBT), Wolf Motor Function Test (WMFT), Upper Extremity Fugl-Meyer (UEFMA)], kinematic and kinetic assessments [finger Active Range of Motion (finger AROM), Maximum Pinch Force (MPF)], and bilateral TMS mapping of 5 hand muscles were performed prior to (PRE), directly following (POST), and 1 month following (1M) training. Participants were divided into two groups (MEP+, MEP-) based on whether an MEP was present in the affected first dorsal interosseous (FDI) at any time point. MEP+ individuals improved significantly more than MEP- individuals from PRE to 1M on the WMFT, BBT, and finger AROM scores. Ipsilesional hemisphere FDI

area increased significantly with time in the MEP+ group. FDI area of the contralesional hemisphere was not significantly different across time points or groups. In the MEP+ group, significant correlations were observed between PRE-1M changes in ipsilesional FDI area and WMFT, BBT, and finger AROM, and contralesional FDI area and UEFMA and MPF. In the MEP- group, no significant correlations were found between changes in contralesional FDI area and functional outcomes. We report preliminary evidence in a small sample that patterns of recovery and the association of recovery to bilateral changes in motor topography may depend on integrity of the ipsilesional cortical spinal tract as assessed by the presence of TMS evoked MEPs.

Keywords: stroke, upper limb, subacute, virtual reality, robotics, transcranial magnetic stimulation

INTRODUCTION

Stroke is a leading cause of adult long-term disability in the United States and the financial burden of related care is among the fastest-growing expenses for Medicare (1). Proportionally more stroke survivors are left with upper extremity impairment and disability than that of the lower extremity (2). At 6 months post-stroke, about 30–60% of affected individuals do not regain functional use and only 5–20% achieve full return of arm function (3, 4). Recovery of hand function is notably impervious to intervention in part due to the complexity of motor control required for dexterous function. At six months post-stroke ∼65% of affected persons continue to have hand deficits that profoundly affect their ability to perform their usual activities and affect their independence (2, 5); and only 5% of those with initial severe paresis will have full recovery (6). Importantly, impaired hand function is often the most disabling deficit for many post lesion (7).

Numerous investigations have provided evidence indicating rehabilitation interventions must be initiated early after stroke to maximize recovery (8, 9). Although the optimal time period is not clear, the first month post-stroke is a crucial time for plasticity (8). Yet the vast majority of studies on emerging therapeutic interventions have focused on individuals in the chronic phase after stroke with limited work looking at interventions during acute and sub-acute phases (10–12). In fact, as reported in a 2013 review, only 6% of all stroke motor rehabilitation clinical trials have enrolled all patients within the first 30 days after a stroke (9). In light of recent evidence for the greater effectiveness of early rehabilitation, this staggering statistic highlights the need for investigation of intensive hand focused upper limb rehabilitation initiated early after stroke.

Perhaps most important are investigations comparing changes in impairments, function and neurophysiology early following stroke to identify the biomarkers of recovery. Transcranial Magnetic Stimulation (TMS) induced motor evoked potentials (MEPs) are an established proxy of corticospinal excitability (13). Numerous previous investigations have found that the presence (MEP+) or absence (MEP-) of MEPs early after stroke is a robust indicator of long-term recovery (14, 15). More recently, Stinear (16) suggested that people without MEPs (MEP-) at 2 weeks post-stroke have "limited or no predicted potential for upper extremity recovery" at 12 weeks after stroke.

Though numerous studies have indicated that the presence or absence of MEPs may be a strong predictor of recovery, change in the distribution of activation indicating reorganization of motor topography may provide additional insight into patterns of recovery. MEPs can be acquired over the sensorimotor cortex such that the two-dimensional position of the coil over the scalp can be used to generate a multivariate excitability map akin to those classically acquired with invasive stimulation, albeit with lower resolution. Use of TMS mapping to track ipsilesional motor reorganization over the first months to 1 year following stroke has generally indicated that increased excitable area in the ipsilesional hemisphere was associated with recovery of the impaired hand (17–19), though other studies found no change in ipsilesional excitable area over the same period (20, 21). Association of better outcomes with expansion of ipsilesional cortex activation is in line with numerous findings in human and animal models [see (22, 23) for a review]. Two investigations using TMS mapping during this early time period found increased excitable area in the contralesional hemisphere was associated with poorer outcomes (17, 24). This finding is in contrast with a number of studies which did not find changes in contralesional hemisphere excitable area or associations between changes in contralesional hemisphere topography and recovery of function in the subacute period (18–20). The association between contralesional topographic reorganization and functional recovery is complex, with numerous conflicting findings in both human and animal models, indicating beneficial or maladaptive influence on function [see (22, 23) for a review]. Although, these studies provide some indication of the general pattern of recovery; it is equally important to investigate the changes in functional-structural associations during focused intervention.

Interventional studies in the chronic phase post-stroke have used TMS based mapping of the ipsilesional hemisphere to quantify the spatial patterns of recovery of the corticospinal system in MEP+ patients (25, 26); all noting an increase in the peak MEP and area of MEPs representing the hand in the ipsilesional sensorimotor cortex. To date, there have been few studies that have investigated the association of functional outcomes and TMS measures of cortical topography with

intensive upper limb intervention in the early stages following stroke (27–30). Findings from Ro et al. (30), Boake et al. (28) and Sawaki et al. (29) [in which patients were enrolled either in the first 14 days (28, 30), or at 3 to 9 months (29)] indicate that increased area of excitation in the ipsilesional hemisphere is associated with increased functional improvement in individuals receiving Constraint Induced Movement Therapy (CIMT) compared to controls receiving usual care. Contrary to this finding, Platz et al. (27) did not find any change in the number of active sites in their two treatment groups (Bobath and BASIS training), though reduction in map area was shown in the usual care group (27). Ludemann-Posdubecka and Nowak (31) offer a comprehensive review of observation and interventional studies assessing TMS mapping of cortical hand motor representation as a marker for recovery of function after stroke. Overall, most studies have compared changes in motor topography to a limited set of clinical measures of function or impairment and no study to date has compared contralesional changes between those individuals who do and do not have ipsilesional MEPs.

In this investigation, we examined the relationship between changes in function/motor recovery and cortical motor topography in a group of patients undergoing early (<3 months) and intensive hand focused upper limb rehabilitation using the NJIT-RAVR, an integrated VR/Robotic platform that was shown to be effective at reducing impairments in a chronic stroke population (32–34). With the exception of one small study from our group, no study has yet examined this relationship post VR/Robotic training (35). Data was collected in preparation for a now ongoing randomized controlled trial (RCT) to study the effects of timing and dosing of VR/Robotic intervention, and results for the intervention group are presented to show feasibility for use of TMS to measure neurophysiological correlates of recovery. Because specific hand therapy, by and large, is a small percentage of therapy received in the subacute period in US rehabilitation practice, selection of subjects from the intervention group only ensured that each individual did indeed receive therapy and that the dosage, in actual movement repetitions, was roughly equal among our sample. Specifically, we tested the degree to which clinical, kinematic, and kinetic measures of functional improvement correlated with changes in bilateral motor cortical topography (assessed by TMS mapping) in individuals with and without preserved ipsilesional corticospinal integrity (also assessed with TMS). We hypothesized that functional improvements would be greater in MEP+ individuals and that an increase in ipsilesional cortical territory would correlate to markers of functional improvement. In a secondary analysis we compared functional and topographical changes in the contralesional hemisphere between individuals who were positive for the presence of MEPs in the ipsilesional hemisphere (MEP+) and those who were not (MEP–). We predicted greater expansion of contralesional cortical territory in MEP- individuals, and that the degree of expansion would be associated with worse outcomes in this cohort of subjects. An important and novel tertiary exploratory analysis of MEP "converters," individuals who were MEP- at baseline and later converted to MEP+, was also carried out to understand how reinstatement of MEPs is related to functional recovery.

MATERIALS AND METHODS

Subjects

Subjects were recruited from the in-patient rehabilitation department of a suburban hospital. After initial screening by the department's physician, a physical therapist screened subjects based on the following criteria: *Inclusion:* (1) within 3 months post-stroke, (2) between the ages of 30 and 80, (3) for the severely impaired group: categorized as Stage 1 on the Hand Impairment Inventory of the Chedoke-McMaster Stroke Assessment (36), for the moderately impaired group: have partial active shoulder flexion, or abduction, elbow extension and wrist extension against gravity, and trace extension at the fingers (detected visually) that can be reproduced several times in a minute. *Exclusion:* (1) severe spasticity [Modified Ashworth score of 3 or higher (37)], (2) cognitive deficits rendering them unable to follow three step commands or attend to a task for at least 10 min (3) hemispatial neglect rendering them unable to interact with an entire 24 inch computer monitor—positioned at midline, (4) proprioceptive loss that rendered a potential subject unable to interact with a virtual environment without looking at their hand (5) unstable blood pressure and oxygen saturation responses to activity. A separate screening and consent process for the motor mapping evaluation using TMS was conducted. Exclusion criteria for TMS included metallic or electronic implants in the head, pregnancy, and history of epilepsy.

Training Protocol and Schedule of Outcomes Assessment

All subjects participated in 8 sessions over a 2-week period. In each session, subjects trained for 1 h using the NJIT-RAVR system interfaced with virtual reality simulations. Additionally, all subjects participated in their on-going in/out-patient physical, occupational and speech therapy. Clinical, kinematic/kinetic, and TMS evaluations were performed on the day prior to beginning training (PRE), the day following the last day of training (POST), and 1 month thereafter (1M).

Description of the VR/Robotic System

The NJIT-RAVR system is comprised of an arm training robot (Haptic Master [Moog NCS, The Netherlands]) combined with a 3 degree of freedom gimbal, and an integrated system for the hand that consists of an instrumented measurement glove (CyberGlove [Immersion, USA]), a cable actuated hand exoskeleton that facilitates finger extension for those persons with more severe impairment (CyberGrasp [Immersion, USA], and a 3-dimensional magnetic tracking system that tracks hand and arm position (TrackSTAR™ [(Ascension Technology, USA])—the NJIT Track–Glove System. The system utilizes an ATI Nano17™ force sensor (ATI Industrial Automation, USA) for pinch force measurement. The Haptic Master was individually programmed to provide assistance to lower functioning subjects with progressive adaptations that lessened the help provided as subjects improved over time. Please refer to Adamovich

FIGURE 1 | NJIT-RAVR system.

et al. (38) and Fluet et al. (39) for detailed information on this system (**Figure 1**).

Description of Simulations and Targeted Hand Training

The VR environment was developed with Virtools 4.0 software package (Dassault Systemes, France) and a VRPack Plug-in that communicates with an open source Virtual Reality Peripheral Network (VRPN) interface. The NJIT-RAVR robotic system that interfaces with our suite of impairment and activity based virtual reality simulations was used to train the hand and arm separately. Individuals with moderate initial impairment were provided training comprising three hand and three proximal arm simulations ∼10 min on each of the six simulations during each session. The hand simulations consisted of the Virtual Piano, Monkey Business, and Space Pong games, and the arm simulations were the Cups, Hammer, and Space Ship games (32, 33). Individuals with severe deficits were provided with a modified training protocol consisting of two types of priming (virtual mirror feedback and contralaterally controlled hand opening) to prime the motor cortex and reinforce motor networks in the lesioned hemisphere (40) prior to training their affected hand with a force modulation task (41).

Clinical Outcome Measures

Three clinical tests measuring functional and impairment based deficits were performed by a physical therapist: (1) Wolf Motor Function Test (WMFT), a time-based series of tasks to evaluate upper extremity function (42), (2) the upper extremity portion of the Fugl-Meyer Assessment of Sensorimotor Recovery After Stroke (UEFMA), a task performance exam that assesses motor impairment after stroke (43, 44), and (3) the Blocks and Box test (BBT), a unilateral assessment of gross manual dexterity (45).

Kinematic and Kinetic Measures

Finger angles were collected using a CyberGlove™ (Immersion, USA). Finger range of motion (finger AROM) was measured as the difference between all of the joint angles with the fingers in a maximal actively flexed position and the joint angles of all of the fingers in a maximal actively extended position. Larger differences indicated better active finger range of motion. Pinch force was measured with an ATI Nano17™ force sensor (ATI Industrial Automation, USA) as the maximum voluntary pinch force (MPF) a subject can exert on a force sensor held between their paretic thumb and index finger, given two trials. Higher numbers indicate stronger pinch grip.

TMS Mapping Procedure

Subjects were seated with their arm, hand, and fingers comfortably secured in a brace to limit motion. Surface electromyographic activity (EMG, Delsys Trigno, 2 kHz) was recorded from 5 muscles of the limb contralateral to stimulation side (first dorsal interosseus [FDI], abductor pollis brevis [APB], abductor minimi [ADM], flexor digitorum superficialis [FDS], and the extensor digitorum communis [EDC]. To assure spatial TMS precision, each subject's head was coregistered to a canonical high-resolution anatomical MRI for frameless neuronavigation (Brainsight–Rogue Research, Canada). All TMS measures were taken at rest and background EMG was monitored to ensure that muscles remained relaxed. The TMS coil (Magstim, 70 mm double coil) was held tangential to the scalp, with the handle posterior 45° off the sagittal plane (46). Motor evoked potentials (MEPs) were sampled until the loci with the largest MEP was located (14, 47). This method has been shown to have high intra and inter experimenter reliability (47), has been cross-validated with fMRI, and is robust in identifying the loci of greatest activation for a given muscle (48). Resting motor threshold (RMT) was determined at this location as the minimum intensity required to elicit MEPs >50 uV in the FDI muscle on 50% of 6 consecutive trials (49). The choice of intensity, 110% FDI RMT, represented a compromise between the different excitability thresholds of the selected muscles, as has been done previously in other studies investigating multi-muscle topography using TMS (17, 50). The hotspot and threshold were determined at each mapping session. All mapping was performed with the subject at rest and stimulation intensity set to 110% of the determined RMT (51). A 7 × 7 cm area surrounding the motor hotspot was marked using the neuronavigation software to provide consistent map boundaries. TMS pulses (150) were delivered at a 4 s interstimulus interval within the bounds with special attention paid to regions surrounding the hotspot territory. Real time feedback of multi-muscle MEPs and neuronavigated coil position was used to maximize the map information obtained by increasing the density of points in excitable and border regions while giving less attention in far-away non-responsive areas (52). Mapping procedures were conducted for both the ipsilesional and contralesional hemispheres (**Figure 3**). For each stimulation point the motor evoked potential (MEP) was calculated as the peak-to-peak amplitude of the EMG signal 20–50 ms after the TMS pulse.

TMS Mapping Analysis

A threshold of 50 uV was used to identify MEPs from background EMG (51). To allow comparisons across maps and sessions, MEP amplitudes and stimulation points were interpolated to

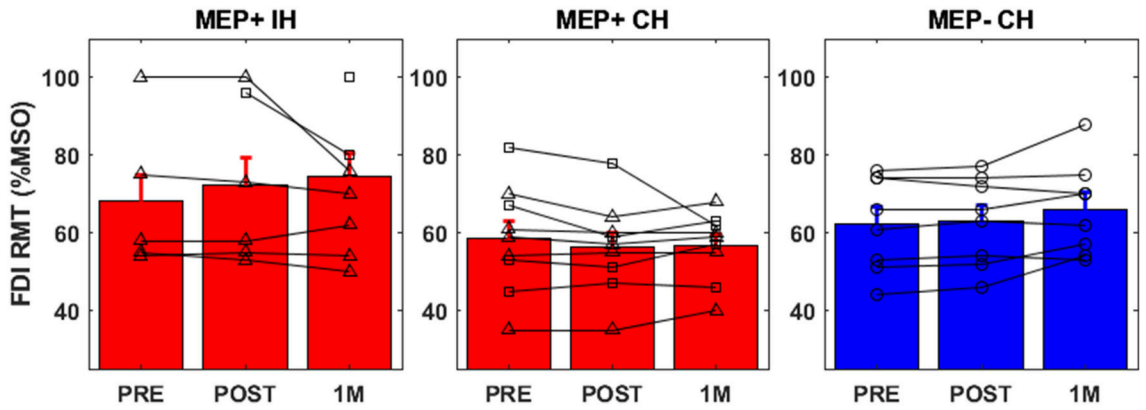

FIGURE 2 | FDI resting motor threshold for all groups [Ipsilesional Hemisphere (IH), Contralesional Hemisphere (CH)]. Individuals who were MEP+ at baseline are denoted with triangle markers, individuals who converted to MEP+ at POST or 1M are denoted with square markers, and MEP- individuals are denoted by circular markers.

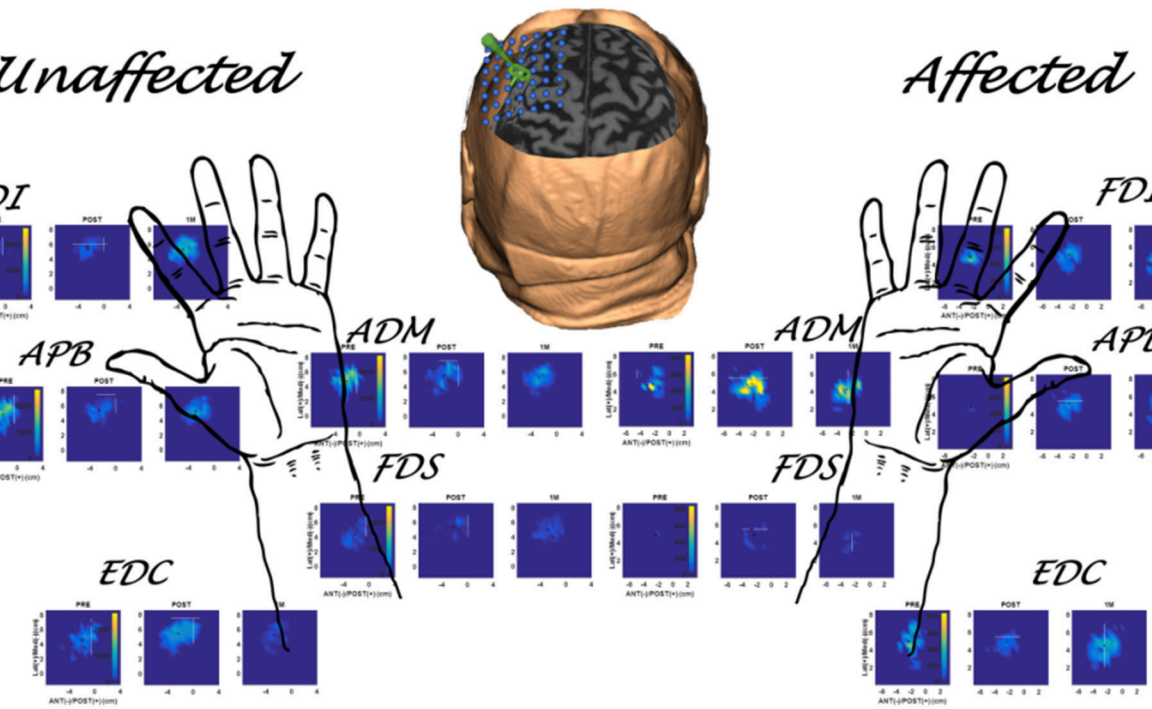

FIGURE 3 | Multiple muscle mapping data for the unaffected hand (contralesional hemisphere) and affected hand (ipsilesional hemisphere) of a representative subject (S1 in **Table 1**) in the MEP+ group. PRE, POST, and 1M maps are presented for each muscle.

a 7 × 7 cm mesh of 0.375 mm resolution, centered around the M1 hotspot, using cubic surface interpolation (54, 55). Extent of the representation producing corticospinal output (MEPs) for individual muscle, or map area, was calculated using double trapezoidal integration of the interpolated map (35). Map area has been used extensively to describe sensorimotor cortex reorganization after stroke [for a review see Cortes et al. (56)]. Furthermore, a recent systematic review of the use of TMS as an outcome measure for rehabilitative interventions found that map area was the most likely measure to correlate to changes in clinical outcomes (57).

Statistical Analysis

Ipsilesional hemisphere maps were analyzed with a one-way repeated measures ANOVA, with a within factor of Time (PRE, POST, 1M). Significant findings were further analyzed using *post-hoc* paired comparisons with Bonferroni correction for multiple comparisons. Contralesional hemisphere maps, resting motor

TABLE 1 | Participant characteristics.

Subject	Group	Age	Sex	Days post stroke	UEFMA/Severity* At PRE	Lesion location
S1	MEP+	62	F	39	25/Mod	R parietal
S2	MEP+	62	M	92	27/Mod	R MCA
S3	MEP+	45	M	12	32/Mod	L Putamen
S4	MEP+	62	F	6	47/Mod	L MCA
S5	MEP+	76	M	7	33/Mod	R frontal, parietal, temporal
S6	MEP+	70	M	10	37/Mod	R MCA
S7	MEP+	60	M	7	11/Severe	R periventricular white matter
S8	MEP+	53	M	13	21/Mod	L temporal, parietal
S9	MEP+	65	F	5	3/Severe	R pons
Mean (SD)		61.7 (9.0)		21.2 (28.5)	26.2 (14.3)	
S10	MEP–	76	M	54	46/Mod	L pons
S11	MEP–	63	M	68	41/Mod	R pons
S12	MEP–	64	M	29	44/Mod	R - unknown
S13	MEP–	43	F	7	31/Mod	L MCA/ACA
S14	MEP–	66	M	10	3/Severe	R basal ganglia
S15	MEP–	53	M	7	4/Severe	L MCA
S16	MEP–	55	M	9	2/Severe	R PLIC
S17	MEP–	51	M	44	6/Severe	R basal ganglia
Mean (SD)		58.9 (10.4)		28.50 (24.2)	22.1 (20.2)	

**Based on Woodbury et al. (53). Woodbury classification was calculated post-hoc and was not used for stratification into moderate and severe groups.*

threshold, kinematic, and clinical outcomes were each analyzed with a two-way mixed factorial ANOVA, with a within factor of Time (PRE, POST, 1M) and a between factor of ipsilesional MEP presence (MEP+, MEP–). Significant interactions were analyzed with independent samples *t*-test to test for differences at PRE, and to test for differences in PRE-POST, POST-1M, and PRE-1M change scores. To test the relationship between M1 changes and function, PRE-1M changes in FDI area were correlated to PRE-1M changes in clinical, kinematic, and kinetic measurements. Alpha level was set at 0.05.

RESULTS

Seventeen individuals (4 Female, 60.3 ± 9.4 years, 24.64 ± 24.01 days post CVA) with first time stroke participated in the intervention. Participant characteristics are listed in **Table 1**. All training was well-tolerated without adverse events or fatigue that had a negative impact on their rehabilitative program in or out of the intervention.

Participants were divided into two groups (MEP+, MEP–) based on whether TMS to the ipsilesional hemisphere produced an MEP in the affected FDI muscle at rest. Participants stratified into the MEP+ group included all individuals for whom a response could be elicited from the FDI at any time point (PRE, POST or 1M). Of these individuals 5/9 participants were MEP+ at baseline, and 4/9 "converted" to MEP+ at either POST or 1M. Participants in the MEP- group were those individuals for whom a response could not be elicited from the FDI at all time points (PRE, POST, and 1M). Analysis was performed for the ipsilesional hemisphere in the MEP+ group only (the MEP- group did not have ipsilesional MEP responses to analyze), and the contralesional hemisphere in both MEP+ and MEP− groups. There was no statistical difference in the days post-stroke between MEP+ (21.22 ± 28.51) and MEP– (28.5 ± 24.19) participants [$t_{(15)} = -0.56$, $p = 0.582$]. There was also no statistical difference in the baseline UEFMA scores between MEP+ (26.22 ± 14.3) and MEP– (22.13 ± 20.2) participants [$t_{(15)} = 0.50$, $p = 0.62$] (**Table 1**).

Corticospinal Integrity, Impairment, and Function

Mixed factorial ANOVAs with factors Time (PRE, POST, 1M) and Group (MEP+, MEP–) were used to test for main effects and interactions in clinical, kinematic, and kinetic outcomes. A main effect of Time was significant for all measured outcomes indicating that impairment level decreased over time. Group main effect was significant for finger AROM only [$F_{(1,15)} = 9.94$, $p = 0.028$]. Time X Group interactions were significant for the WMFT, BBT, and finger AROM evaluations. Significant interactions were followed with independent samples comparisons between groups to test for differences at PRE and differences in the amount of change from PRE to POST, and PRE to 1M. *Post-hoc* independent comparisons revealed no significant differences between groups at PRE for any outcome, indicating baseline function was similar between groups. There were significant between Group differences in the amount of change from PRE to POST in the WMFT [$t_{(11.02)} = -2.22$, $p = 0.048$], BBT [$t_{(12.12)} = 2.25$, $p = 0.044$], and finger AROM [$t_{(11.66)} = 2.29$, $p = 0.04$], and from PRE and 1M in the WMFT [$t_{(15)} = -3.44$, $p = 0.004$], BBT [$t_{(15)} = 2.66$, $p = 0.018$], and finger AROM [$t_{(10.13)} = 3.19$, $p = 0.01$] indicating that MEP+ participants improved more than the MEP- participants for both time periods (**Tables 2a,b**).

TABLE 2a | Mixed factorial ANOVA outcomes for MEP+ and MEP- groups compared across time on clinical, kinematic, and kinetic measures.

Test	Time	Group	TIME X Group
Log WMFT	$F_{(2,30)} = 28.98$ $p < 0.001$	$F_{(1,15)} = 0.18$ $p = 0.676$	$F_{(2,30)} = 7.73$ $p = 0.002$
BBT	$F_{(1.30,19.47)} = 23.94$ $p < 0.001$*	$F_{(1,15)} = 1.72$ $p = 0.210$	$F_{(1.30,19.47)} = 6.14$ $p = 0.017$*
UEFMA	$F_{(2,30)} = 51.42$ $p < 0.001$	$F_{(1,15)} = 1.42$ $p = 0.252$	$F_{(2,30)} = 2.06$ $p = 0.146$
Finger AROM	$F_{(2,30)} = 7.26$ $p = 0.003$	$F_{(1,15)} = 9.94$ $p = 0.028$	$F_{(2,30)} = 5.12$ $p = 0.012$
Max Pinch Force	$F_{(2,30)} = 14.14$ $p < 0.001$	$F_{(1,15)} = 0.15$ $p = 0.701$	$F_{(2,30)} = 0.19$ $p = 0.822$

**Greenhouse Geisser corrected.*

TABLE 2b | *Post hoc* outcomes on clinical, kinematic, and kinetic measures for PRE – POST and PRE – 1M change scores between groups.

Test	Pre – post	Pre – 1 month
Log WMFT	$t_{(11.02)} = -2.22$ $p = 0.048$*	$t_{(15)} = -3.44$ $p = 0.004$
BBT	$t_{(12.12)} = 2.25$ $p = 0.044$*	$t_{(15)} = 2.66$ $p = 0.018$
UEFMA	$t_{(15)} = 1.67$ $p = 0.116$	$t_{(15)} = 1.76$ $p = 0.099$
Finger AROM	$t_{(11.66)} = 2.29$ $p = 0.04$*	$t_{(10.13)} = 3.19$ $p = 0.01$*
Max Pinch Force	$t_{(15)} = 0.02$ $p = 0.981$	$t_{(15)} = 0.56$ $p = 0.586$

**Levene's test for equality of variances significant.*

The MEP+ group included both individuals who were MEP+ at baseline ($n = 5$) and individuals who became MEP+ at a later time point ($n = 4$). To date, few studies have addressed these "converters" and no study has specifically compared recovery between those who are MEP+ at baseline and those who convert to MEP+ at a later time. We performed a subanalysis looking at the differences in clinical and functional recovery measures between those who were MEP+ at baseline and those who were baseline-negative but converted to MEP+ over time. Mixed ANOVAs found no statistical differences or interaction effects between these two groups over time and provided justification for combining the two subgroups into one cohort: WMFT: [$F_{(2,14)} = 0.949$, $p = 0.411$]; Finger AROM: [$F_{(1.202,8.417)} = 0.083$, $p = 0.824$]; BBT: [$F_{(1.22,8.51)} = 2.77$, $p = 0.13$]; UEFMA: [$F_{(2,14)} = 1.8942$, $p = 0.195$]; MPF: [$F_{(2,14)} = 1.055; 0.374$]. However, comparisons after stratification into subgroups should be interpreted with caution due to limited sample size.

Ipsilesional and Contralesional Resting Motor Threshold

Individual resting motor thresholds for the ipsilesional (MEP+ only) and contralesional hemispheres at each time point are reported in **Figure 2**. Contralesional resting motor thresholds were generally consistent across sessions and accordingly a 2 × 3 ANOVA with factors of Group (MEP+/MEP-) and TIME (PRE, POST, 1M) produced no significant main effects or interactions. Ipsilesional resting motor thresholds of MEP+ individuals were higher than those found in the contralesional hemisphere for 7/9 subjects including all subjects that converted to MEP+ status at either POST or 1M. At 1M, when data were available for all participants, an independent samples *t*-test confirmed significantly higher iplsilesional than contralesional resting motor threshold [$t_{(16)} = -2.714$, $p = 0.015$]. Also at 1M, there was a significant difference in resting motor threshold between those individuals who we MEP+ at PRE and those individuals who converted to MEP+ at a later time [$t_{(7)} = 3.697$, $p = 0.008$]. Absence of MEPs at 100% of stimulator output prevented the correlation of ipsilesional motor threshold to measures of impairment and function. There were no statistically significant correlations between contralesional resting motor threshold and any measure of impairment or function in either MEP+ or MEP- individuals.

Ipsilesional and Contralesional Motor Topography

In the ipsilesional hemisphere of the MEP+ group, excitable territory for upper limb muscles increased steadily in the period from PRE to 1M, with greater changes appearing in the intrinsic (FDI, APB, ADM) than extrinsic finger muscles [FDI (7.67 ± 10.4), APB (6.61 ± 5.6), ADM (10.9 ± 12.4), FDS (0.11 ± 1.1), EDC (4.67 ± 8.9)]. In the contralesional hemisphere of the MEP+ group, the excitable territory for all five muscles showed an increase from PRE to POST and decrease from POST to 1M (non-significant change at both time frames). Changes in the contralesional hemisphere of the MEP- group were more variable and were characterized by minimal change across measurement times at the group level (**Figure 4**).

Repeated measures ANOVAs testing ipsilesional hemisphere map area changes for each muscle of the MEP+ group revealed a significant effect of Time for the FDI [$F_{(2,16)} = 7.84$, $p = 0.004$], APB [$F_{(2,16)} = 12.57$, $p = 0.001$], and ADM [$F_{(2,16)} = 6.41$, $p = 0.009$]. Pairwise *post-hoc* comparisons indicated a significant increase in map area between PRE and 1M for the FDI [$t_{(8)} = -3.37$, $p = 0.016$], APB [$t_{(8)} = -3.63$, $p = 0.007$], and ADM [$t_{(8)} = -3.05$, $p = 0.016$], and between POST and 1M for the FDI [$t_{(8)} = -2.37$, $p = 0.022$] and APB [$t_{(8)} = -3.81$, $p = 0.005$]. EDC and FDS map area changes were not significant. Mixed factorial ANOVAs to test for changes in map areas in the contralesional hemisphere with factors Time (PRE, POST, 1M) and Group (MEP+, MEP–) indicated no significant main effects of Time or Group and no Time X Group interaction for all muscles tested.

PRE to 1M changes in FDI area were correlated to changes in clinical, kinematic, and kinetic outcomes over the same period (**Figure 5**). In the ipsilesional hemisphere of the MEP+ group, significant correlations were observed between changes in FDI area and changes in the WMFT ($r = -0.75$, $p = 0.017$), BBT score ($r = 0.865$, $p = 0.002$), and finger AROM ($r = 0.809$, $p = 0.008$. Contralesional hemisphere FDI area change in the

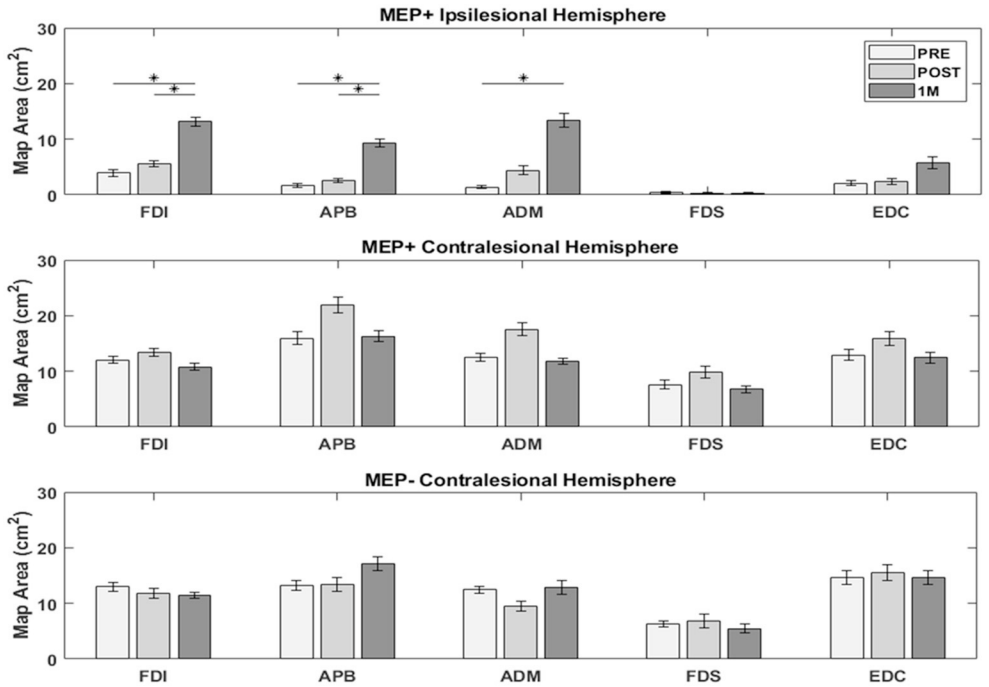

FIGURE 4 | Excitable cortical area for each muscle. Intrinsic muscle map area in the ipsilesional hemisphere of MEP+ participants increased significantly over the measured time period. Changes were less notable, or absent in the contralesional hemisphere for both groups. (*) indicates significant differences between time points ($p < 0.05$).

MEP+ group was significantly correlated to the change in UEFMA ($r = -0.84$, $p = 0.004$) and MPF ($r = 0.806$, $p = 0.008$). No significant correlations were found between contralesional hemisphere cortical changes and clinical, kinetic, or kinematic outcomes for the MEP- group.

DISCUSSION

Recovery of neural function post-stroke is a complex process that involves initial reversal of diaschisis and activation of cell repair followed by changes in axonal sprouting in existing neuronal pathways, and synaptogenesis with concomitant modification in the cortical excitability and somatotopic remapping (58). Critically, these recovery processes involve both hemispheres and are heightened in the first 3 months after stroke (59). In this study, 2 weeks of intensive VR/Robotic based hand focused/upper limb therapy was initiated in the first 3 months post-stroke with the aim of capitalizing on the natural recovery processes. TMS mapping was used to evaluate macro-level changes in ipsi- and contralesional reorganization of M1 topography for five hand muscles. FDI muscle map changes were compared to clinical, kinematic, and kinetic outcomes to determine any correlation between TMS map changes and upper limb motor recovery. In light of recent evidence that the presence or absence of MEPs in the ipsilesional hemisphere measured shortly after stroke is an important neurophysiological biomarker of recovery and outcomes (60), patterns of motor recovery in the paretic upper limb and contralesional TMS map changes were compared between individuals who had MEPs (MEP+) and those who did not have MEPs (MEP-) in the ipsilesional hemisphere.

Corticospinal Integrity, Impairment, and Function

Clinical and functional measures were not significantly different between MEP+ and MEP- groups at baseline, and as in Stinear et al. (61) there was a wide range of improvement for any given baseline measure of an individual patient (61). Individuals who were MEP+ showed significantly greater improvement on the WMFT, BBT, and in finger AROM from PRE−1M compared to MEP- individuals. This finding is in agreement with recent investigations from Stinear and Byblow that show individuals who have MEPs early after stroke experience proportional recovery of ∼70% of impairment, whereas individuals who are MEP- do not have a stereotypical pattern of recovery (62–64). Interestingly, differences were not significant for the UEFMA and maximum pinch force despite a general pattern of improvement similar to the other three measures.

Understanding the recovery patterns of individuals who are MEP- at baseline but convert to MEP+ at a later time point is a poignant topic and a key aim of our current RCT (https://clinicaltrials.gov, NCT03569059). Several studies (17, 18, 24) have included these individuals but did not report specific analyses or descriptions of converters. Instead,

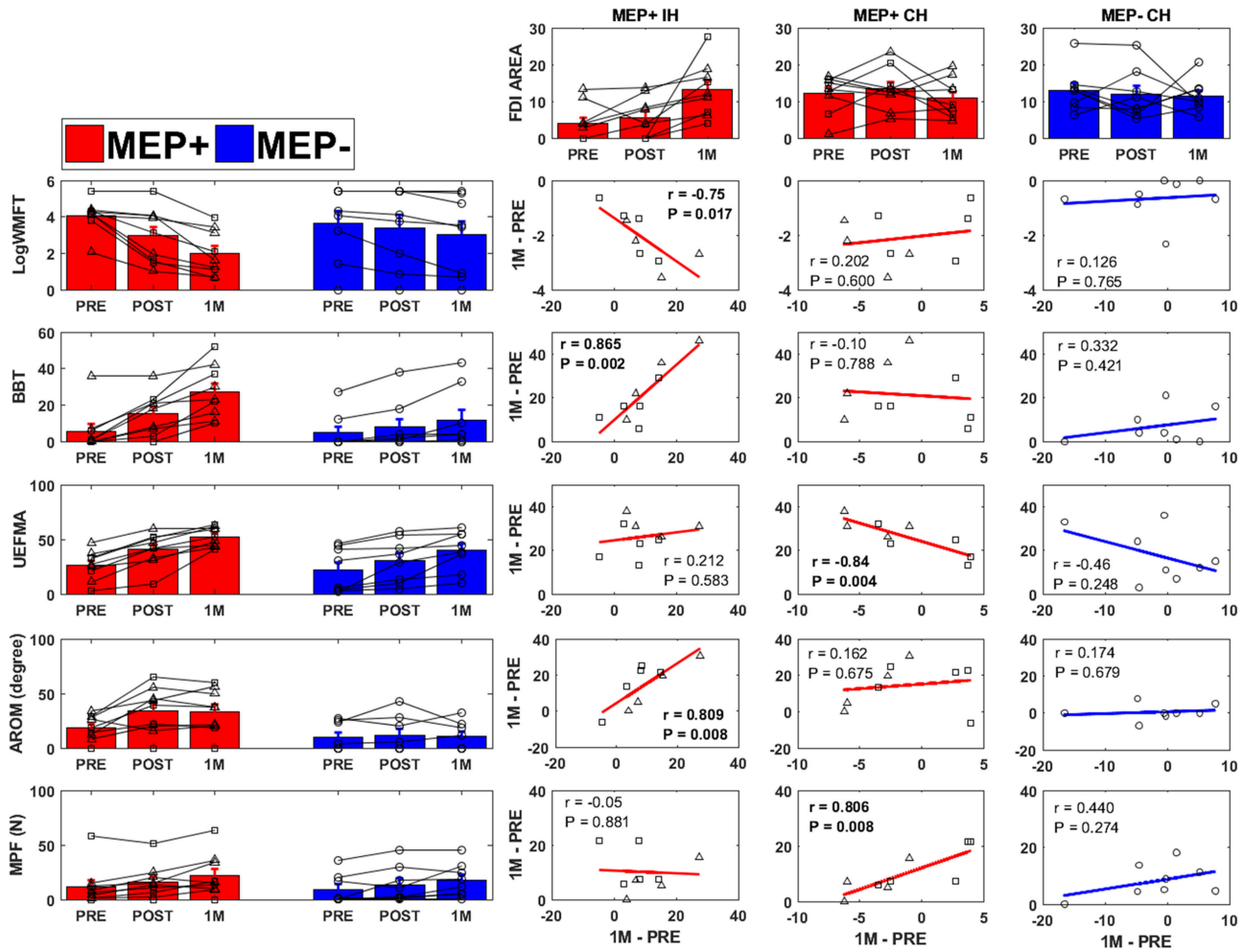

FIGURE 5 | Clinical, kinematic, and FDI area changes for all groups [Ipsilesional Hemisphere (IH), Contralesional Hemisphere (CH)]. Individuals who were MEP+ at baseline are denoted with triangle markers, individuals who converted to MEP+ at POST or 1M are denoted with square markers, and MEP− individuals are denoted by circular markers. PRE to 1 Month change in FDI area (top row) was correlated to the change in WMFT (2nd row), BBT (3rd row), UEFMA (4th row), finger AROM (5th row), and MPF (6th row). Significant correlations are indicated in bold.

these individuals were grouped as MEP- for comparison of associations of contralesional hemisphere map changes and functional recovery between MEP+ and MEP- individuals. In those studies that provide at least some description of this cohort, conversion to MEP+ at a later time point has not always been found to indicate more favorable clinical improvement (21, 65, 66). However, conflicting reports exist and in two studies, individuals who gained MEP+ status at a later time point showed consistent clinical improvement (19, 20). In the data presented here, lack of significant differences between individuals who were MEP+ at baseline and those who became MEP+ at POST or 1M appear to be in agreement with these studies. Furthermore, the relationship between cortical expansion and changes in clinical and functional measures of recovery in the period of PRE-1M suggests these individuals may share more in common with individuals who are MEP+ at baseline (see **Figure 5**).

Resting Motor Threshold

Resting motor threshold reflects efficiency of TMS to excite corticospinal neurons which is dependent on the excitability of individual neurons and their local density (67). Consistency of contralesional resting motor threshold across time and higher resting motor threshold in the ipsilesional hemisphere, in comparison to the contralesional hemisphere, are in line with previous investigations in stroke. High reliability of the resting motor threshold as well as ease of collection has made it the most-used TMS outcome measures in intervention studies post-stroke, however, a recent review found that the post-intervention change in resting motor threshold was significant in only 2 of the 11 investigations reviewed (57). We did not find significant differences in contralesional resting motor thresholds between individuals who were MEP+ and those who were MEP- as might be expected given previous evidence of reduced interhemispheric inhibition from the ipsilesional to contralesional hemisphere

and/or greater contralesional compensations for lost function of ipsilesional hemisphere with greater ipsilesional damage (68). This may be due to the small sample size in the current study. Alternatively, it could be that the VR/Robotic intervention prevented contralesional compensation; however, without a usual care control group this interpretation remains speculative. Ipsilesional resting motor threshold among individuals who recovered MEPs at time points after PRE were higher than those recorded in individuals who were MEP+ at the initial assessment. This finding is in agreement with the findings of Delvaux et al. (21), and suggests that these individuals may have different recovery patterns from those individuals who are consistently MEP- and individuals who are MEP+ soon after stroke with resting motor threshold values in the range of the contralesional hemisphere.

Reorganization of Motor Topography

Motor map area has been suggested to reflect a combination of corticospinal excitability and somatotopy of the targeted muscles' M1 representation (69). In absence of consistent large changes in resting motor thresholds, changes in map area were more likely associated with changes in motor somatotopy (29).

The ipsilesional hemisphere in the MEP+ group was marked by significant expansion of map area across testing sessions for the intrinsic hand muscles (FDI, APB, ADM) only. The VR/Robotic intervention that we used incorporated similar doses of training for both fine motor and gross motor tasks of the hand-arm, and therefore, it is unlikely that differences in map area changes between intrinsic and extrinsic hand muscles are due to a training-specific effect. Patterns of reorganization may inherently differ between the intrinsic hand muscles–which are known to have larger and more excitable representations when compared to the extrinsic hand muscles in healthy individuals. However, this result should be interpreted with caution as differences may have resulted from choosing the stimulation intensity for mapping based on the FDI RMT, which is likely lower than that of the EDC or FDS. Unfortunately, it would not have been feasible to collect multiple maps, each one relative to each muscle's activation threshold, so the decision was made to base the mapping on the most commonly reported muscle, the FDI.

Expansion of FDI and APB territories in the ipsilesional hemisphere of the MEP+ group were significant between the POST and 1M time points, but not between the PRE and POST time points. This result is surprising given evidence that spontaneous recovery related cortical plasticity decreases after the first month following stroke (8). It is possible that the 2 weeks intervention using virtual reality and robotics was able to change the pattern of neurophysiological recovery *post intervention*; however without a control comparison this remains speculative at this time. Our ongoing RCT, once completed, is designed to address this possibility.

The PRE-1M changes in ipsilesional FDI area were significantly correlated with clinical markers of recovery (WMFT, BBT, and finger AROM) over the same period (**Figure 5**). Current evidence indicates that unilateral ipsilesional M1 excitation is important for the recovery of dexterous movement post stroke [see (70) and references within]. Scores on the WMFT, BBT, and finger AROM are likely to improve with more coordinated control of the index finger, which is representative of a motor task requiring use of corticospinal projections from the contralateral primary motor cortex (71). Strong correlation of these measures to map expansion may indicate that map expansion is a marker of intracortical reorganization of muscle representations which has been shown to correlate to recovery in animal models (72, 73).

In contrast to the ipsilesional hemisphere of the MEP+ group, area changes in the contralesional hemisphere of the same group were smaller and more variable. A pattern of increased excitable area from PRE-POST followed by a return to PRE levels at 1M, as was reported by Chieffo et al. (17), was observed but not significant. Increased contralesional area was significantly correlated with poorer performance on the UEFMA, a finding that appears to correspond with the findings of Chieffo et al. (17). In contrast, increased pinch force was associated with greater expansion of the contralesional area. Evidence for bilateral activation in the production of high forces with one hand is well-established in studies of healthy individuals (74). It is possible that individuals who showed significant increases in force production were better able to access bilateral networks, but this may have had a negative effect on control of movement and therefore the inverse relationship between clinical tests of impairment (UEFMA) and force production.

Changes in cortical topography in the contralesional hemisphere of MEP- individuals were nominal and did not correlate to any of the five measures of motor recovery. This provides preliminary evidence that the functional recovery processes related to contralesional hemisphere reorganization in individuals without MEPs may be fundamentally different than in individuals who show intact ipsilesional corticospinal integrity. It is possible that intact signaling from the ipsilesional hemisphere may be necessary to reorganize contralesional pathways, and when signaling from the ipsilesional hemisphere is absent, these individuals become more reliant on subcortical pathways for movement at the cost of fine motor control (75). Further research is necessary to understand the complex role of the contralesional hemisphere in recovery of hand function following stroke.

CONCLUSIONS

Individuals engaged in VR/Robotic based training in the acute to early subacute period (<3 months) (76) following stroke showed significant recovery of upper limb function. We report preliminary evidence in a small sample that patterns of recovery and the association of recovery to bilateral changes in motor topography may depend on integrity of the ipsilesional cortical spinal tract as assessed by the presence of TMS evoked MEPs. Functional recovery was greater in individuals who were MEP+, and was significantly correlated to ipsilesional and contralesional changes in excitable cortical territory for an intrinsic hand muscle. Specific correlations were indicative that ipsilesional map expansion may be associated with increased manual dexterity, while contralesional change may be associated with

strength. A subanalysis comparing those who were MEP+ at PRE and those who "converted" to MEP+ at POST or 1M found no differences in clinical or functional outcomes between the two groups. However, higher resting motor threshold at 1M in converters may indicate some fundamental difference from early MEP+ individuals. Individuals who were MEP- showed smaller and more variable patterns of recovery and no correlation between function outcomes and changes in contralesional map topography indicating the possible use of non-cortical compensatory pathways. Findings of the study were limited by small sample size and lack of a comparative control group. Given these limitations, interpretation was limited to the association between map changes and clinical and functional outcomes, and the prognostic value of early post-stroke mapping was not discussed. Furthermore, no recommendations were made endorsing early VR/Robotic therapy over usual care. Future investigations should test whether rehabilitation using VR/Robotic therapy in the early period post-stroke can influence recovery and to what extent TMS mapping can be used to predict who may benefit most from intervention.

ETHICS STATEMENT

All subjects provided written and verbal informed consents approved by Institutional Review Boards of the New Jersey Institute of Technology, Rutgers University, and St. Joseph's Hospital-Wayne prior to participating.

AUTHOR CONTRIBUTIONS

Medical advisement was provided by SM. QQ designed the virtual reality video games used in the interventions. AM, ET, GF, and SA designed the training protocol. MY and ET designed the TMS assessment. Data was collected by JP, MY, QQ, and GF. Data analysis was performed by MY and JP. Manuscript writing was performed by MY and JP equally, and revised by SA, AM, ET, QQ, and GF.

FUNDING

This work was supported by National Institute of Health grants R01NS085122 (ET), K01HD059983 (ET), R01HD58301 (SA), and F31NS092268 (MY), and NIDILRR grant 90RE5021 (SA).

ACKNOWLEDGMENTS

The authors thank the clerical, nursing, and rehabilitation staff of the Acute Rehabilitation Department at St. Joseph's Hospital, Wayne, NJ for their assistance with medical advisement, subject recruitment, scheduling.

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Conflict of Interest Statement: The 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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 19 March 2019
doi: 10.3389/fneur.2019.00240

Effects of Hand Configuration on the Grasping, Holding, and Placement of an Instrumented Object in Patients With Hemiparesis

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Objective: Limitations with manual dexterity are an important problem for patients suffering from hemiparesis post stroke. Sensorimotor deficits, compensatory strategies and the use of alternative grasping configurations may influence the efficiency of prehensile motor behavior. The aim of the present study is to examine how different grasp configurations affect patient ability to regulate both grip forces and object orientation when lifting, holding and placing an object.

Methods: Twelve stroke patients with mild to moderate hemiparesis were recruited. Each was required to lift, hold and replace an instrumented object. Four different grasp configurations were tested on both the hemiparetic and less affected arms. Load cells from each of the 6 faces of the instrumented object and an integrated inertial measurement unit were used to extract data regarding the timing of unloading/loading phases, regulation of grip forces, and object orientation throughout the task.

Results: Grip forces were greatest when using a palmar-digital grasp and lowest when using a top grasp. The time delay between peak acceleration and maximum grip force was also greatest for palmar-digital grasp and lowest for the top grasp. Use of the hemiparetic arm was associated with increased duration of the unloading phase and greater difficulty with maintaining the vertical orientation of the object at the transitions to object lifting and object placement. The occurrence of touch and push errors at the onset of grasp varied according to both grasp configuration and use of the hemiparetic arm.

Conclusion: Stroke patients exhibit impairments in the scale and temporal precision of grip force adjustments and reduced ability to maintain object orientation with various grasp configurations using the hemiparetic arm. Nonetheless, the timing and magnitude of grip force adjustments may be facilitated using a top grasp configuration. Conversely, whole hand prehension strategies compound difficulties with grip force scaling and inhibit the synchrony of grasp onset and object release.

Keywords: hand function, grasp, stroke, assessment, instrumented objects for rehabilitation

OPEN ACCESS

Edited by:
Martin Lotze,
University of Greifswald, Germany

Reviewed by:
Margit Alt Murphy,
University of Gothenburg, Sweden
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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *10 September 2018*
Accepted: *22 February 2019*
Published: *19 March 2019*

Citation:
Parry R, Macias Soria S, Pradat-Diehl P, Marchand-Pauvert V, Jarrassé N and Roby-Brami A (2019) Effects of Hand Configuration on the Grasping, Holding, and Placement of an Instrumented Object in Patients With Hemiparesis. Front. Neurol. 10:240. doi: 10.3389/fneur.2019.00240

INTRODUCTION

Cerebrovascular accidents (stroke) are a frequent cause of disability (1) and the recovery of upper-limb function in particular, is a key determinant of independence in activities of daily living (2). Broadly speaking, the physical impairment experienced by patients is characterized by loss of strength, abnormal movement patterns (pathological synergies), and changes in muscle tone to the side of the body contralateral to the stroke (3, 4). This presentation is commonly referred to as hemiparesis and its severity tends to reflect the extent of the lesion to the corticospinal tract (5). Subtle changes in movement kinematics and hand function on the ipsilesional upper-limb have also been documented and may be the consequence of direct impairment of ipsilateral motor pathways (6, 7), as well as reorganization of the non-lesioned hemisphere to support recovery of motor-function in the hemiparetic limb (8–10). Above all though, patients living with stroke find that limitations with manual dexterity of the hemiparetic arm have the most significant effect upon their ability to carry out activities involving hand use in daily life (11).

These impairments in patient hand function manifest in multiple different aspects of motor performance. This may include reduced strength (3), loss of individuated finger control (12), and abnormal force control at the level of the fingers (13). Increased muscle tone and spasticity though the flexors of the wrist and hand may further compound these difficulties and inhibit the ability to open the hand in preparation for grasping (14). Atypical reaching and grasping patterns are often seen to emerge both as a consequence of and as a response to the motor dysfunction (15, 16).

Unfortunately, rehabilitation of upper limb impairments proves to be challenging. Whilst numerous therapeutic modalities (e.g., bilateral training, constraint-induced therapy, electrical stimulation, task-oriented, high intensity programs) have been evaluated in clinical trials, none have demonstrated consistent effects upon hand function (17–19). Indeed, previous research papers have described therapy outcomes in upper limb rehabilitation post stroke as "unacceptably poor" (20). Ideally, the design of neurorehabilitation programs should be grounded upon an understanding of basic mechanisms involved in neural plasticity and motor learning (21, 22). Part of this process implies coming to terms with the factors which characterize the disorganization in voluntary motor output (21). However, the majority of clinical tools currently used for evaluating hand function distinguish motor performance according to ordinal rating scales or task completion time (e.g., Frenchay Arm Test, Jebson-Taylor Hand Function Test) (23, 24). These kinds of assessments lack sensitivity and may prove insufficient for detecting the presence of mild motor deficits or subtle, yet clinically important changes in hand coordination (25, 26). Evidence based frameworks for hand rehabilitation have specifically called for the integration of new technology to support patient assessment and treatment planning (27). Despite this, the transposition of technology for upper limb rehabilitation from the research domain into clinical practice has been limited (28, 29). In the assessment of manual dexterity, the underlying challenge involves analyzing sensorimotor function of the hand with respect to its interaction with objects in the environment (30).

Successfully managing grasping and object handling tasks requires skilled control of prehensile finger forces. In healthy adults, grip forces are regulated to be marginally greater than the minimum required to prevent the object from slipping (31). This safety margin is calibrated according to the shape, surface friction and weight distribution of the object (32, 33). As the hand moves through space (lifting, transporting, object placement), grip force is continually modulated, proportional to the load forces associated with the mass and acceleration of that object (34). This temporal coupling between grip and load forces is considered a hallmark of anticipatory sensorimotor control (35). Disruption to motor planning, volitional motor control or somatosensory feedback may lead to a breakdown in the timing and magnitude of grip force adjustments.

Numerous studies have examined grip force regulation in neurological pathologies including cerebellar dysfunction (36), peripheral sensory neuropathy (37, 38), Parkinson's disease (36, 37, 39, 40) as well as congenital and acquired brain lesions (13, 36, 41–45). For patients suffering from hemiparesis post stroke, difficulty with coordinating the grasping and lifting action are frequently associated with temporal discrepancies between grip forces and load forces (46). The cerebral hemisphere implicated in the CVA (13, 47) and the extent of the resulting sensory deficits (48, 49) have also been observed to influence anticipatory grip force scaling. This body of work highlights the potential interest of using instrumented objects for the diagnosis and evaluation of the impairments associated with hemiparesis (45, 46, 48, 50–53).

As it stands, these objective studies of hand function post stroke have focused primarily upon either the lifting or the vertical movement components in object handling. To a certain extent, this limitation has been related to technical restrictions. Other than a handful of studies by Hermsdorfer et al. (8, 49), research in this field has predominantly used manipulanda designed for the study of precision grip, where strain gauge force transducers are attached to a separate base unit [e.g., (23–25, 29, 33, 35, 37)]. These devices cannot be freely handled by subjects, much less a person with an upper-limb movement disorder. Indeed, patients with hemiparesis often experience specific impairments with precision grip (53) and regularly use alternative grasping strategies such as whole hand grasping (15, 16, 54). Previous researchers have hypothesized that these alternative grasp strategies may impact grip force scaling (55) and compromise patient ability to manage hand-object-environment relationships during object manipulation (56).

In a recent study with healthy adult subjects, (57) we demonstrated how an instrumented object with multiple load cells and an integrated inertial measurement unit (58) may be used to examine relationships between different grasp configurations, grip force regulation and object orientation. The purpose of the present investigation was to extend this work to the study of patients with hemiparesis post stroke. The first objective was to compare how four alternative grasp configurations commonly used in daily tasks affect grip force regulation in this population. The second objective was to

explore the timing and coordination of the whole task sequence (grasping, lifting, holding, placement and object release). The third and final objective was to evaluate the stability of the hand-held object's orientation across the different phases of the task.

MATERIALS AND METHODS

Participants

Twelve adult patients (6 males, 6 females) with a diagnosis of a unique stroke and a mean age of 58 years (range 48–70 years) participated in this study. Of these patients, 8 suffered from hemiparesis on their dominant right hand side; 4 right handed patients and 1 ambidextrous patient suffered from left sided hemiparesis [hand preference verified using the Edinburgh Handedness Inventory, see (59)]. Each patient was in a subacute or chronic phase of recovery and was assessed between 1 and 13 months following the neurological event. The ability to grasp and hold an object was a requirement for inclusion to this study. Patients with additional neurological or orthopedic conditions, important cognitive deficits or aphasia were not eligible for this study. A summary of clinical characteristics of the patient group is provided in **Table 1**. This study was approved by the local ethics committee at University Paris Descartes and all subjects provided written consent prior to commencement of the evaluation.

Clinical Measures of Upper-Limb Function

Prior to completing the experimental phase of this study, an upper-limb motor-function assessment was carried out. The Fugl-Meyer upper-limb evaluation (FME) and Frenchay Arm Test (FAT) was conducted for each patient and, in addition to this, 8 of the 12 patients completed the Jebsen Taylor Hand Function test (JTT). The FME evaluation provides an overall score of upper limb function (max of 126), which may then be broken down into its sensory function component (max of 60) motor function component (max of 66) (60). The FAT assesses patient ability to carry out five different actions providing a score on a scale of 1 to 5 (61). The JTT provides an overall score in seconds, representing the time taken to complete a series of functional task with each arm. Finally, hand strength for both arms was measured using a grip-strength dynamometer (DGS).

Experimental Apparatus

An instrumented object (iBox) with 6 integrated load cells and an inertial measurement unit (IMU) was used for the purposes of this study (see **Figure 1A**). This device measures 108 × 70 × 40mm and has a mass of 0.370 kg. It enables recording of acceleration, rotational velocity, orientation of the unit as well as the forces applied normally to each of its six faces. The force of the load cell on the bottom face was calibrated so that the weight of the device, equivalent to 3.63 N, was subtracted (i.e., the reference force signal was zero when the object lay on the table and decreased to −3.63 N when the object was lifted from the supporting surface). All data was sampled at a frequency of 100 Hz and transmitted wirelessly to a local computer via Bluetooth. Overall acceleration was measured as a combination of gravity and kinematic acceleration (39). Object orientation was calculated from IMU data and expressed as the alpha angle, indicating the deviation of the longitudinal axis of the iBox from the vertical axis. Further technical details regarding the iBox are provided in (58).

Installation

Subjects were seated at a horizontal table throughout the experiment. In the starting posture, both hands were positioned at each corner of the proximal edge of the table. The iBox was placed vertically before the patient. It was positioned in the parasagittal plane, 20 cm in front of the hand used for the pinch, precision and top grasps. For the palmar digital grasp, the iBox was placed in front of the opposite hand so as to ensure a comfortable grasp (15, 57). In all cases the iBox was rotated 30° around the vertical axis, in the direction of the patient's midline. This reference orientation was calibrated at the beginning of the experiment and repeated prior to each trial. The experimental setup is illustrated in **Figure 1B**.

Grasp Configurations Used

The experimental procedure involved grasping and holding the iBox using 4 different hand configurations. Each of these grasps, described below is illustrated in **Figure 2**.

Precision grip: opposition between the pads of the thumb and index (**Figure 2A**).
Top Grasp: opposition using a pinch grip, the object is approached and grasped from above (**Figure 2B**).
Pinch grasp: opposition between the pads of the thumb and palmar aspect of the four fingers (**Figure 2C**).
Palmar-digital grasp: opposition of fingers and palm, with the thumb in abduction as for a power grip (**Figure 2D**).

This combination of grasps was selected to represent common hand configurations which may support functionally different tasks in daily activities. For example, pinch grasps are a versatile hand configuration that can support an object whilst enabling transition to in-hand manipulation if necessary, while precision grasps are important for handling smaller objects. By contrast, a palmar digital grasp serves to fix an object in the hand while the arm is in motion (i.e., scrubbing a surface with a sponge) whereas the top grasp configuration may assist with tasks such as repositioning objects on a table's surface [see (62) for greater detail on the frequency of grasp configuration in household tasks].

Experimental Procedure

Each patient was given a brief period of time to handle the iBox with both hands prior to beginning the experimental tasks in order to become familiar with the weight and surface characteristics of the object. During the experimental task, patients were asked to lift and hold the iBox approximately 10 cm above the table. For the pinch, precision and palmar-digital hand configurations, patients were instructed to hold the iBox for between 2 and 5 s before replacing it in an approximately similar position. For the top grasp configuration, patients were asked to place the iBox in the frontal plane, 10 cm distal to the initial position (deposit area indicated in **Figure 1**) (57). A demonstration was provided prior to commencement of each

TABLE 1 | Results from the functional upper limb evaluations for stroke patients.

Patient ID	Hemiparetic arm	Time since stroke	Dynamometer grip strength (reference from less-affected side)	Fugl-Meyer upper limb evaluation (sensory/motor subscores)	Jebsen Taylor hand function test (reference from less-affected side)	Frenchay arm test
P1	Right (d)	5 months	361.6 N (353.1 N)	124 (58/66)	79 s (80 s)	5
P2	Right (d)	13 months	156.8 N (473.3 N)	95 (39/56)	303 s (95 s)	3
P3	Right (d)	11 months	215.6 N (363.6 N)	105 (56/49)	89 s (84 s)	5
P4	Right (d)	2 months	38.2 N (197.0 N)	84 (42/42)	337 s (110 s)	5
P5	Right (d)	18 months	245.9 N (382.8 N)	105 (56/49)	261 s (163 s)	5
P6	Left (n)	1 months	107.8 N (367.2 N)	109 (53/56)	308 s (52 s)	4
P7	Left (n)	2 months	52.9 N (235.9 N)	78 (41/37)	362 s (45 s)	3
P8	Right (d)	19 months	146.0 N (189.4 N)	124 (59/65)	61 s (65 s)	5
P9	Left (n)	5 months	26.5 N (156.8 N)	104 (38/66)	NA	3
P10	Left (a)	13 months	266.6 N (275.4 N)	120 (60/60)	NA	5
P11	Right (d)	2 months	332.2 N (381.2 N)	125 (65/60)	NA	5
P12	Right (d)	14 months	16.7 N (124.5 N)	96 (48/48)	NA	5
***n* = 12**	**8 right/4 left**	**9 months**	**163.7 N (291.7 N)**	**106 (51/55)**	**225 s (87 s)**	**5**

For the hemiparetic arm, (d), (n), (a) signify if this is the dominant, non-dominant or ambidextrous hand. Grip strength scores are provided in newton with values for the less affected side in brackets. Fugl-Meyer provides the total score on the upper limb evaluation with sensory and motor subscores indicated in brackets. The Jebsen Taylor provides a score in seconds, being the total time required to complete a series of manual handling tasks; the score in brackets provides the reference time for the less affected arm.

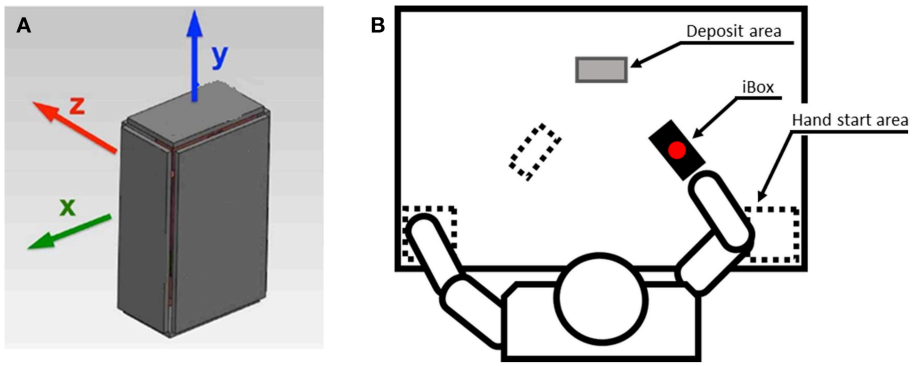

FIGURE 1 | Illustration of the iBox device and the experimental setup. **(A)** The iBox instrumented object. **(B)** Setup for the experimental procedure. Initial positions of the iBox and hand start area are indicated by the dotted lines. The gray shaded rectangle indicates the deposit area for the top grasp task.

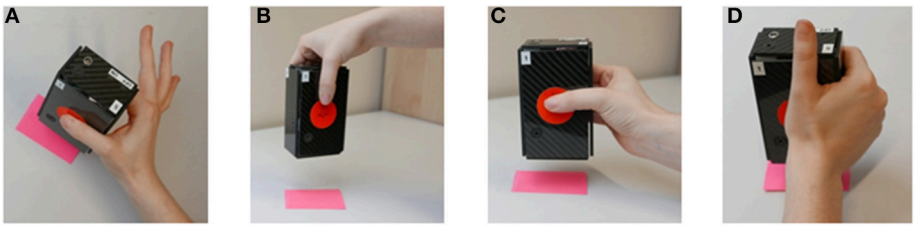

FIGURE 2 | Grasp configurations used during the iBox protocol. **(A)** Precision grip. **(B)** Top grasp. **(C)** Pinch grip. **(D)** Palmar-digital grasp. Image adapted from Martin-Brevet et al. (57).

task. Patients were asked to perform each grasp and place task 3 times to the best of their ability. The ensemble of grasping and holding tasks were performed first with the less affected arm and then with the hemiparetic arm. The experimenter verified the patient's initial posture and repositioned the iBox between movements as required.

Visual inspection of all force, acceleration and orientation signals was carried out immediately following data acquisition. Events where signals were compromised or patients were unable to complete the set task were excluded. All patients were able to perform the palmar and top grasp tasks with both limbs. Using the hemiparetic arm, one patient (patient 9) was unable to

perform the pinch grasp task and four patients (patients 3,6,7,9) were unable to complete the precision grip task.

Data Processing and Analysis

Transitions between grasping, lifting, and placement phases were identified in an automated manner with reference to load cell data (57) (**Figure 3** indicates the different phase transitions with vertical lines). *Grasp onset* (*tg*) was defined as the moment when the mean of the forces applied to the two lateral load cells exceeded 0.15 N. O*nset of lifting* (*tl*), when the base load cell value was inferior to the −3.4 N threshold. *Placement time* (*tp*) was the moment when the base load cell then returned to the threshold value of −3.4 N. *Object release time* (*tr*) was defined as the moment when the mean of the forces applied to the two lateral load cells were inferior to 0.15 N. The *hold onset* (*ho*) and *hold end* (*he*) events were chosen subjectively to delimit a plateau of relative stability during holding and tagged manually from data in each trial using a graphic interface. From these events, five separate phases were identified: (1) *unloading* of the bottom face between *tg* and *tl*[1], (2) *lifting* between *tl* and *ho*, (3) *holding* between *ho* and *he*, (4) *descent* between *he* and *tp*, and (5) *release* between *tp* and *te*.

Further to this, the occurrence of *push* and *touch* errors (57) were identified. Touches were identified where extraneous forces were applied to the object prior to grasp onset or following object release. A touch was defined as an event where the sum of forces on the exposed (front, back, top, and lateral) load cells exceeded 0.7 N before *tg* or after *tr* for any given trial. The first face of the object touched was identified and noted. A push was detected as increased force (>0.4 N) on the base load cell during the unloading or release phases. Examples of touch and push events are illustrated in the load cell signals provided in **Figure 3C2**.

Based upon the time-tagged data sequences, the following series of variables were extracted for analysis:

- Duration and rate of grip force change for unloading and release phases
- Grip force at *tg*, *tl*, *tp*, *te* (mean of the front and back load cells)
- Maximal grip force and peak acceleration during the lifting phase
- Time difference between maximal grip force and peak acceleration during the lifting phase
- Grip force during holding (median and standard deviation of the *front and back load cells* during the whole period)
- iBox orientation at times *tg*, *tl*, *td*, *te* (alpha angle)
- iBox orientation during holding (alpha angle median and standard deviation)
- Frequency of touch events before grasping and after object release and of push events during the unloading and release phases

All data analysis was performed using customized Matlab scripts.

[1]Probably due to the design of the iBox, we could not distinguish a first phase of increasing grasping force without change in vertical force (see inset of **Figure 3**). The unloading period in this work corresponds to the sum of pre-loading and loading periods commonly identified in previous studies where the vertical force sensor is fitted between the handle of the manipulandum and its main mass.

Statistical Analysis

Data for continuous variables were examined using Shapiro-Wilk tests. As the ensemble of these variables was found to have non-normal distributions, Kruskall-Wallis non-parametric analysis of variance was used for statistical comparisons. Both side (hemiparetic arm/less-affected arm) and grasp configuration (pinch/precision/palmar digital/top) factors were included. Where indicated, *post-hoc* analysis was conducted using Dunn's method. The frequency of touch and push errors was analyzed using Chi-Squared tests. The Bonferroni method was used for correction of *p*-values when comparing across grasp configurations. The threshold for statistical significance was set at $p = 0.05$.

In order to evaluate relationships between clinical characteristics and task performance, test results from the DGS, FME, JTT, and FAT were transformed into z-scores prior to testing with Spearman correlation coefficients against the hemiparetic upper-limb variables assessed using the iBox. Values >0.7 or <-0.7 were considered to represent strong correlation between clinical motor-function tests and iBox variables. In order to control for multiple correlation analysis, a resampling method with 10,000 randomized permutations of each iBox variable was used. Percentile values (2.5 and 97.5%) from the distribution of the resulting coefficient matrix served as a symmetric two-sided 95% confidence interval (63). Correlations of clinical motor tests and iBox variables outside of this confidence interval were considered as statistically significant. All statistical analyses were conducted using Matlab and the JASP software package (https://jasp-stats.org).

RESULTS

Clinical Measures of Upper-Limb Function

Average grip-strength for the affected arm was 163.7 N (s.d. 120.5 N; range 16.7–361.6 N) compared to 292.0 N (s.d. 109.8 N; range 124.46–473.3 N) for the less affected arm. The patient group was assessed as having mild to moderate upper-limb impairment using the FME motor assessment (median = 56; range 37–66) with variable levels of sensory deficits (range 38–60 on the sensory function subscore). The median score on the Frenchay Arm Test was 5 (range 3–5), indicating that patients were able to carry out basic functional tasks with their affected upper-limb. The median time for completion of the JTT with the hemiparetic arm was 282 s (range 61–362 s), vastly superior to that of average times for similarly aged individuals (average 30 s, (64, 65). Clinical measures of upper-limb function are displayed in **Table 1**.

Time Courses for iBox Data Signals

Time courses of force, acceleration and object orientation signals were generally consistent across the different grasp patterns used. Changes in grip forces reflected the phase progression in the grasping, lifting, holding and placement of the iBox, although the regularity and magnitude of these signals were less consistent. **Figure 3** provides typical examples of these signals for two patients with contrasting functional abilities (patient 1 had a FME motor score of 66 compared to 37 for patient 7). Broadly

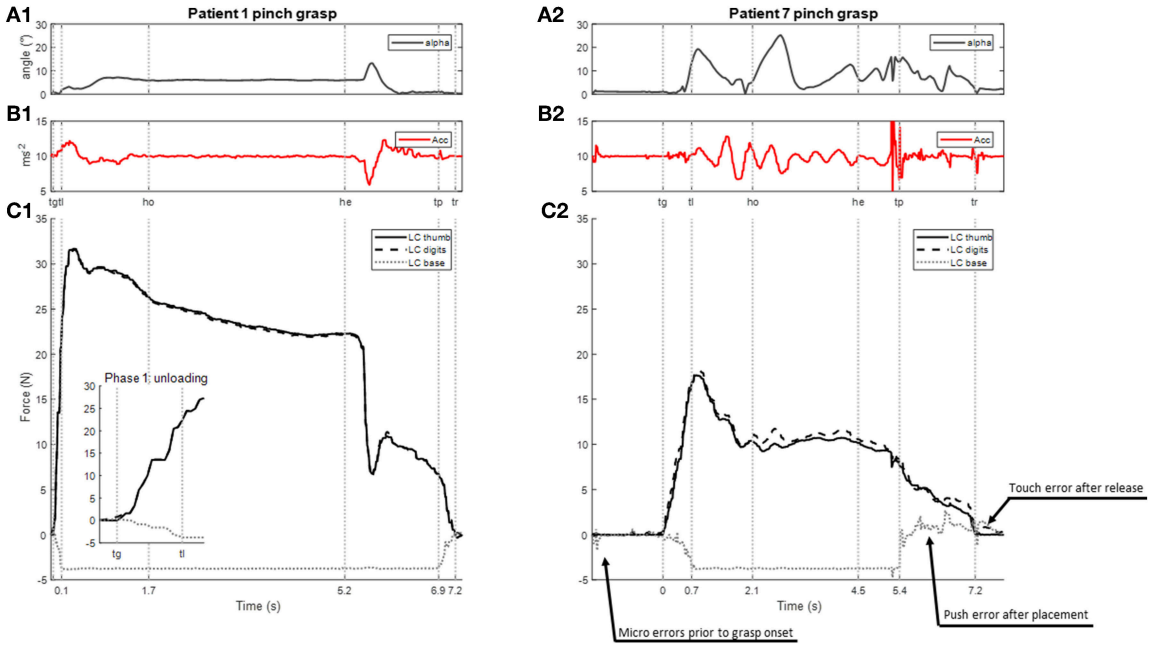

FIGURE 3 | Examples of recording of a lifting task carried out with the hemiparetic arm using the pinch grip in two patients with contrasting functional abilities (P1, FME 66 and P7 FME 37; see **Table 1** for details). From top to bottom: **(A1,2)** angle measuring the deviation of the iBox from the vertical **(B1,2)** vertical acceleration of the iBox **(C1,2)** force signals: grasping force is indicated with plain (thumb) and dashed lines (digits), the unloading of the bottom face of the object is indicated with (dotted lines); inset in **(C1)** shows a larger scale. Vertical lines indicate the times of transitions between phases *tg* = onset of grip; *tl* = onset of lifting; *ho* = hold onset; *he* = hold end; *tp* = placement time; *tr* = release time. Time = 0 s at *tg*. In **(C2)**, arrows indicate touch and push errors upon establishing and releasing grasp.

speaking, those patients who experienced a better recovery had regular acceleration and orientation profiles. For these patients, maximal grip force occurred during lifting and a smooth decrease of force was observed before placement while the holding phase was characterized by relative stability of grip forces. Patients with more severe motor deficits demonstrated greater variability in the acceleration and object orientation profiles (see examples in **Figures 3A1,2,B1,2**). In the following section, the main results of this experiment are presented according to the five phases (unloading, lifting, holding, descent, release) which characterize the task.

Unloading Phase

Grip force at *tg* was found to vary with grasp configuration (Kruskal Wallis, $p = 0.011$) and *post-hoc* testing showed that force in the palmar-digital grasp was greater than in the precision ($p = 0.009$) and top grasps ($p = 0.018$).

The subsequent unloading phase was characterized by a progressive increase in grasp forces and a corresponding decreased load on the base of the instrumented object until *tl* when it reached −3.63 N (see examples in **Figures 3C1,2**). At *tl*, grip force was found to vary with grasp configuration (Kruskall-Wallis $p = 0.038$, **Figure 4A**). Grip forces were significantly lower when using the top grasp (average of 12.85 N) than when using a palmar-digital grasp (average of 19.03 N; $p = 0.013$). The overall duration of the unloading phase was greater when using the hemiparetic arm (0.85 s on average) than the less-affected arm (0.49 s on average) (Kruskal Wallis, $p = 0.002$; **Figure 5A**) and grip force rate was accordingly diminished on the hemiparetic side (Kruskal Wallis, $p = 0.003$; **Figure 5B**).

The mean orientation of the iBox at *tl* was 5.4° on the hemiparetic arm, significantly greater than that of the 1.8° for the less affected arm (Kruskall-Wallis $p = 0.001$; **Figure 6A**).

The occurrence of touch and push errors varied with both the grasp configuration and the arm used (Chi-Squared $p < 0.001$; per **Figure 7**). Touch errors were most frequent when using the palmar (48% of trials) and pinch grasps (23% of trials). This type of error was also twice as frequent in the hemiparetic arm (35% of trials) than in the less-affected arm (17% of trials). When using the hemiparetic arm, these errors were associated predominantly with sub-threshold touches on the load cell corresponding to finger contact (18%) than for the load cell corresponding to the thumb (8%). On the unaffected arm, this trend was reversed with many more errors attributed to sub-threshold contact from the thumb (10%) than for the fingers (2%). Push errors occurred more systematically than touch errors. They occurred most frequently with the top grasp (91% of trials) and pinch grasps (68% of trials). Again, these errors were more common for the hemiparetic arm (75% of trials) than for the less-affected arm (64% of trials).

Lifting Phase

During the lifting phase, grip forces were generally observed to continue to increase in accordance with the vertical acceleration

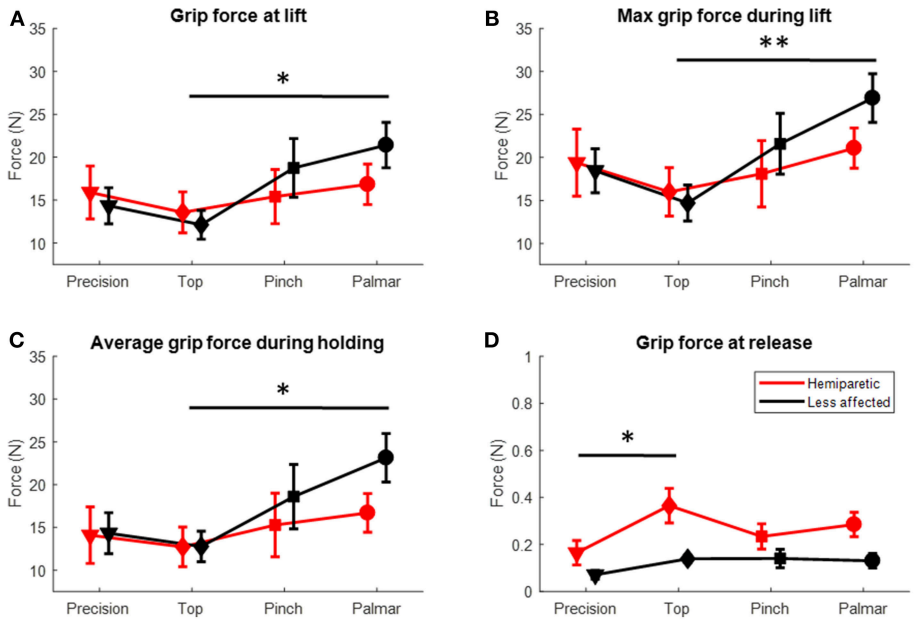

FIGURE 4 | Grip forces for the hemiparetic (red symbols) and less affected arms (black symbols) for the different grasp configurations (in abscissa). **(A)** Grip force at the time of lifting (tl). **(B)** Maximum grip force during the lifting phase **(C)** Average force during the holding phase **(D)** Grip force at the time of release.*Dunn's *post-hoc* $p < 0.05$; **Dunn's *post-hoc* $p < 0.01$.

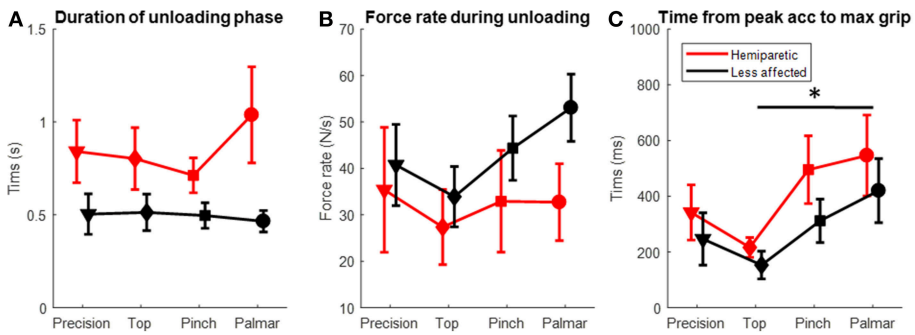

FIGURE 5 | Temporal data for unloading and lifting phases in the hemiparetic (red symbols) and less affected arms (black symbols) using different grasp configurations (in abscissa). **(A)** Duration of the unloading phase. **(B)** Time difference between maximal grip force and peak acceleration during the lifting phase. **(C)** Rate of grip force change during the unloading phase. *Dunn's *post-hoc* $p < 0.05$.

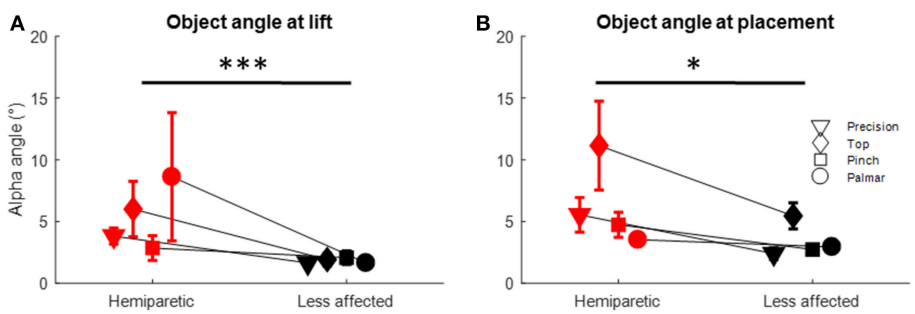

FIGURE 6 | Object orientation for the hemiparetic (red symbols) and less affected arms (black symbols) at: **(A)** Time of lift and, **(B)** Time of placement. *Dunn's *post-hoc* $p < 0.05$; ***Dunn's *post-hoc* $p < 0.001$.

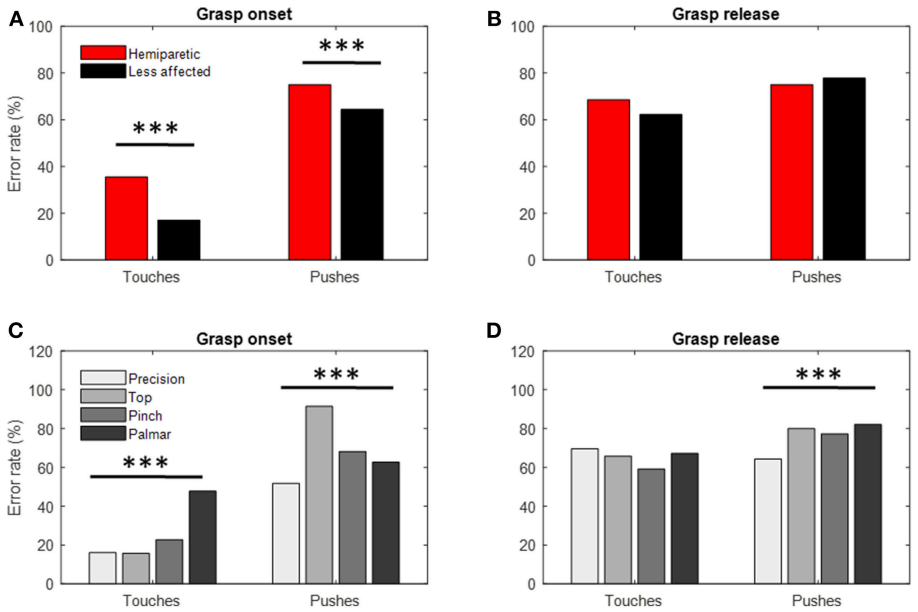

FIGURE 7 | Frequency of touch and push errors. **(A)** Frequency of touch and push errors made at grasp onset by the hemiparetic (red) and less affected (black) arms. **(B)** Same data distributed according to the different types of grasps used. **(C)** Frequency of touch and push errors made at grasp release by the hemiparetic (red) and less affected (black) arms. **(D)** Same data distributed according to the different types of grasps used. ***Chi-squared test $p < 0.001$.

of the iBox (examples in **Figures 3B1–C1, B2–C2**). Several patients (1, 10–12) were found to have particularly high maximal grip forces in the lifting phase, to the point where the load cells were saturated (limit of 40 N) on several trials. While no differences were observed for peak acceleration, the maximal grip force through the lifting phase varied with the grasp used (Kruskall-Wallis $p = 0.009$, **Figure 4B**) and *post-hoc* testing showed that the maximal grip forces were significantly greater for the palmar-digital than for the top grasp ($p = 0.003$).

Time difference between maximal grip force and peak acceleration varied with grasp configuration (Kruskall-Wallis $p = 0.02$) and the arm used (Kruskall-Wallis $p = 0.03$; see **Figures 5C**, **8B**). For example, the average lag time was 185 ms when using a top grasp, significantly lower than that of 486 ms when using the palmar-digital grasp ($p = 0.02$).

Holding Phase

Grip forces during the holding phase were observed to be particularly variable from one individual to another (s.d. 9.70 N; range 3.92–40 N). In the examples provided in **Figure 3**, the grip force during holding for patient 1 (panel C1) is more than twice as great as the grip force for patient 7 (panel C2) for the same grasp and place task using the pinch grip. Three patients (10–12) were again observed to saturate load cells during this phase. **Figure 8A** provides a comparison of average grip force during holding when using the pinch grasp. Overall, grip force during holding was found to vary in relation to grasp configuration (Kruskall-Wallis $p = 0.027$; see **Figure 4C**). On average, grip force when holding with the top grasp was 12.75 N, significantly lower than holding with a palmar-digital grasp at 19.77 N ($p = 0.022$).

Descent and Placement

In the descent phase, average object orientation and standard deviation were observed to vary with grasp configuration (Kruskall-Wallis $p < 0.001$; $p = 0.007$), *post-hoc* testing confirmed that these variables were greater for top grasp than for pinch ($p = 0.011$; $p = 0.037$), precision ($p = 0.001$; $p = 0.047$) and palmar-digital grasps ($p = 0.003$; $p = 0.004$).

Upon placement of the iBox, certain patients appeared to control downward acceleration smoothly, whereas others exhibited important variations in acceleration around the time of placement, *tp*, suggesting vibrations due to the impact of the object on the table (see examples in **Figures 3B1,2**). Despite this, no significant differences in grip force at *tp* were found.

The deviation of the object from the vertical was greater when using the hemiparetic arm (alpha angle at *tp* of 6.38°) than for the less affected side (alpha angle at *tp* of 3.45°) (Kruskall Wallis $p = 0.012$; see **Figure 6B**). Grasp configuration was also found to influence object orientation at *tp* (Kruskal-Wallis $p = 0.003$). When using top grasp, alpha angle was 8.18° on average, significantly greater than for the precision ($p = 0.008$), pinch ($p = 0.06$) and palmar-digital grasps ($p = 0.007$).

Release

During the release phase, the force on the bottom face of the object increased while the grip forces decreased. Those patients with better functional ability appeared to perform this transition relatively smoothly (progressive increase of force on bottom face of iBox and progressive decrease in grip forces, see **Figure 3C1**).

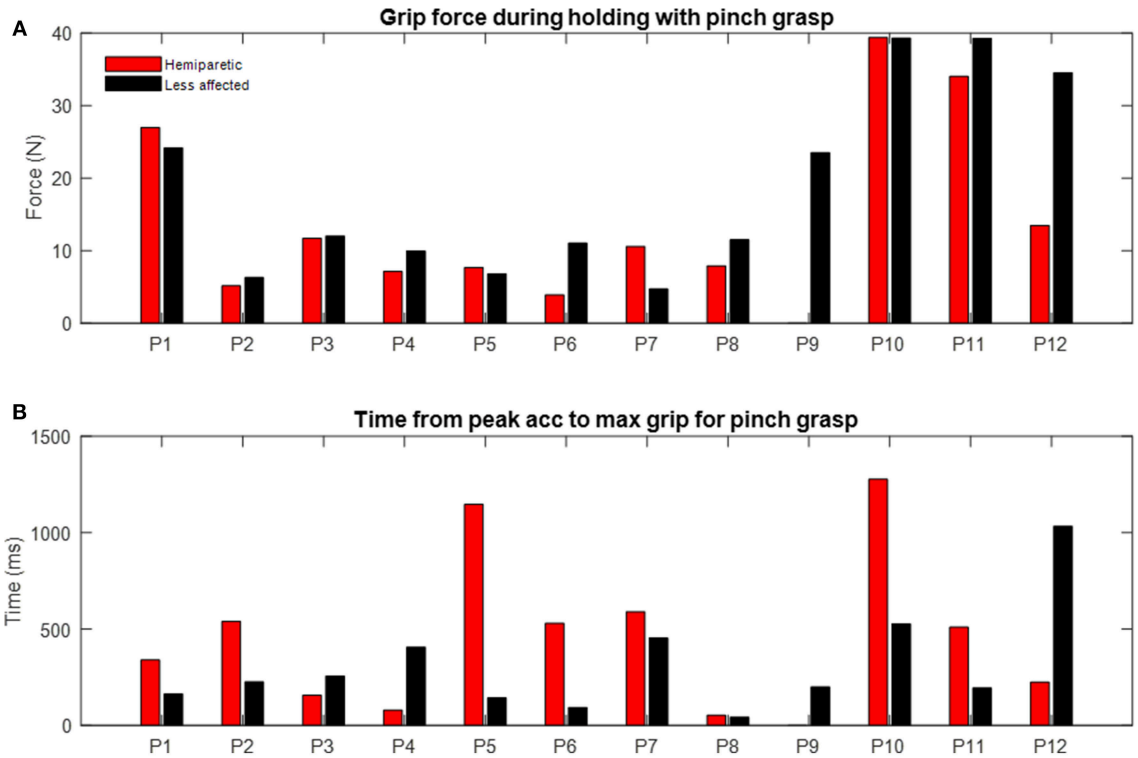

FIGURE 8 | Examples of individual differences during pinch grasp with hemiparetic (red) and less affected arms (black). **(A)** Grip force during holding. Each bar represents median grip force recorded for each patient. **(B)** Time delay from peak acceleration to maximum grip force. Each bar represents mean of time delay over three trials.

The release phase was comparatively more irregular in patients with poorer functional ability and occasionally associated with an impact of the object on the surface of the table in addition to extraneous touch and push errors (see **Figure 3C2**).

Grip force at *tr* was greater on the hemiparetic side (average of 0.27 N) than on the less-affected side (0.12 N) (Kruskal-Wallis $p = 0.01$; **Figure 4D**). At the same time, grip force at *tr* was also observed to vary according to grasp configuration (Kruskal-Wallis $p = 0.032$) and *post-hoc* testing showed that these forces were significantly higher in top grasp than in precision grasp ($p = 0.017$).

The occurrence of push errors was found to vary with grasp configuration (Chi-Squared $p < 0.001$), the palmar-digital grasp being associated with the greatest frequency (82% of trials, see **Figure 7D**).

Correlation of Clinical Measures for Upper-Limb Function With iBox Variables

A summary of statistically significant correlations of dynamometer grip-strength (DGS), Fugl Meyer evaluation (FME) and Frenchay Arm Tests (FAT) scores with iBox variables for each grasp configuration is provided in **Figure 9**. Each line represents a significant Spearman correlation (black) or negative correlation (red) between a clinical variable (FAT, FMA, and DGS, on the left) and a biomechanical behavioral variable (grouped according force, timing and orientation variables). A table providing all significant correlation data is provided in **Tables S1–S6**.

For the precision grip, FME was correlated with the temporal parameters of the task (positive correlation with the rate of force change during lifting and placement, inverse correlation with the duration of unloading and placement phases,) and inversely correlated with the angle of the object during holding and at *tp*. Further to this, the FME sensory function subscore was also positively correlated with grip force at several stages of the task (*tl*, *tp*, maximal grip force, average grip force during holding), while the FME motor subscore was positively correlated with peak acceleration and negatively correlated with the angle of the object during holding (refer to **Tables S2, S3**, respectively). DGS was correlated with the grip force during holding and at *tp*.

In the case of top grasp, FAT was inversely correlated with touch frequency at grip onset, grip force at *tg*, object angle at *tl* and variability of object angle during holding. It was positively correlated with the rate of force during unloading. The FME motor subscore was negatively correlated with the duration of the unloading and loading phases. The JTT was correlated with temporal parameters during the unloading phase, object angle at *tg* and grip force at *tl* (see **Table S5**).

For the pinch grip, FAT was inversely correlated with the object angle at *tl* and FME was inversely correlated with the duration of the loading phase and the grip force at *tr*. Both the sensory and motor subscores of the FME were found to

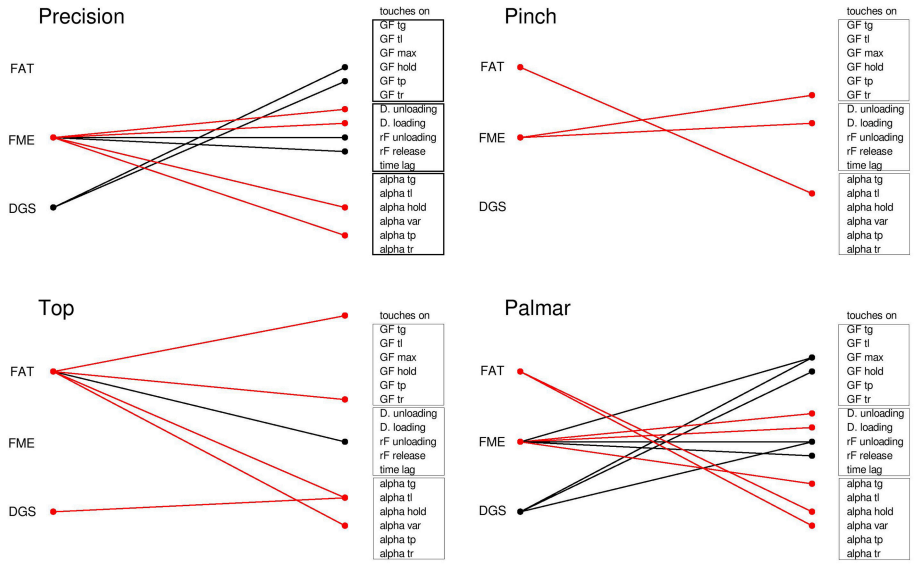

FIGURE 9 | Correlation between clinical data and behavioral variables for the different grasp types. Lines represent significant Spearman correlations (positive in black, negative in red) between clinical measures and iBox variables. FAT, Frenchay arm test; FME, Fugl Meyer Evaluation; DGS, dynamometer grip strength; Touches on, frequency of touches before *tg*; GF, grip force at different time points; D, phase duration; Time lag, time difference between maximal grip force and peak acceleration during lifting; Alpha, deviation of the iBox from the vertical at the different time points; Alpha var, variability of alpha angle during holding.

be correlated with temporal parameters and force parameters during object release (positive correlation with rate of force change during release, negative correlation with release phase duration and grip force at *tr*). The JTT was correlated with several temporal parameters (positive correlation with release phase duration and lag time from maximal grip force to peak acceleration, negative correlation with rate of force change during unloading and release) as well as being positively correlated with object angle at *tp*.

For the palmar-digital grasp, FAT was inversely correlated with the object angle and object angle variability during holding. FME was correlated with the maximum grip force, the rate of force change during the unloading and loading phases, and inversely correlated with the duration of the unloading and loading phases as well as object angle at *tg*. The FME sensory subscore was negatively correlated with object angle at *tl* and average object angle during the holding phase, while the FME motor subscore was associated with temporal parameters (negative correlation with duration of unloading and loading phases, negative correlation with rate of force change during loading and unloading phases). JTT score was positively correlated with object angle during the holding phase. DGS was correlated with the rate of grip force change during loading, maximum grip force and average grip force during the holding phase.

DISCUSSION

This study investigated the hand function of stroke patients. Using an instrumented object, several aspects of dexterity were examined: grip force regulation, timing and coordination of the action sequence (grasping, lifting, holding, placement, and release) and stability of the hand-held object. Motor performance was compared across four different grasp configurations commonly used in daily life activities for both the hemiparetic and less affected arms. The results of this study confirmed the hypothesis that grasp configuration has a significant effect upon grip force scaling for patients suffering from hemiparesis (55). The ability to manage object orientation was reduced in the hemiparetic arm when compared to the less affected arm while grasp configuration had comparably less effect.

Grip Force Regulation During Lifting and Holding

The results of this study are generally consistent with previous research in demonstrating that patients with hemiparesis were globally capable of regulating grip forces with respect to load force variations (8, 22–25, 27, 47). Specific impairments manifested as irregularities in the magnitude and timing of grip force modulation through the grasping, lifting, holding and release of the instrumented object.

Broadly speaking, excessive grip force has been a notable feature of quantitative research on object manipulation in patients with neurological disorders (52). Hermsdorfer et al. reported particularly important grip force increases for holding, transportation and cyclical vertical movements when using a pinch grip for the hemiparetic arm of stroke patients when compared to the less affected arm. This type of "grip force overshoot" (52) has been interpreted as an increase in the safety margin between the applied force and the minimum force necessary to prevent the object from slipping

(49). Large security margins used by stroke patients have previously been associated with the level of somatosensory impairment (37, 48). Nonetheless, Wenzelburger et al. also observed moderate increases in grip force during holding in patients with purely motor capsular stroke (45). In the present study, we observed limited correlation between grip force magnitude with either the FME sensory or motor subscores obtained on the hemiparetic upper limb. Furthermore, consistent with the observation of Nowak et al. (8), a number of patients in the present study also presented with excessive grip forces in their less affected arm (e.g., **Figure 8A**, patients 1,10,11,12;). Perhaps most striking though was the important variability between patients, with grip force during holding in the range of 4 N−40 N. These vast differences in grip forces underscore the fact that stroke patients are a heterogeneous population and that a clinical presentation of hemiparesis alone is not sufficient for one to presume the magnitude, nor the laterality of changes in grip force scaling. Increased grip force magnitude may reflect compensatory mechanisms in order to compensate for deficits with sensory feedback mechanisms (37, 48) or motor deficits involving poor rate of force development (49). Generalized weakness however may be difficult to discern during lifting and holding as grip forces may be comparable to the grip-load force safety margin.

Issues with the timing of grip force modulation were most notable during the unloading and lifting phases of the task sequence. The increased duration of the grasp time prior to the object being raised from a flat surface is consistent with results from prior studies (10, 13, 49, 66) and reflects the diminished rate of change in grip force during this phase (45, 46, 67). The temporal discrepancy between peak acceleration and maximum grip force observed for the hemiparetic arm in this study is typical of a breakdown in the nervous system's ability to regulate the coupling of grip forces with load forces. McDonnell et al. (46) previously documented a disruption to the coupling between grip and load forces in stroke patients during lifting with a precision grip. The present study expands upon these results, demonstrating that this effect is consistent across the pinch, palmar-digital and top grasps. At the same time, it should be noted that experiments by Hermsdorfer et al. did not observe similar temporal delays when examining cyclical vertical movements (48, 49). This suggests that deficits with temporal coupling for the hemiparetic arm depends upon the type of activity and supports the postulate that motor control for rhythmic motion is relatively distinct from discrete movements (68). Mechanisms for predictive control may be sufficient to regulate grip force load force coupling in regular, continuous alternating movement (48) whereas discrete actions such as lifting would require highly efficient integration of sensory feedback and corresponding muscular adjustments (69). Another (non-exclusive) interpretation is that the lifting and holding task performed by stroke patients with severe impairment is composed of multiple segmented actions and/or may be corrupted by irregularities in proximal control of the arm such that that maximum grip force and acceleration do not coincide.

Orientation and Stability of the Hand-Held Object

The current body of literature on hand-object orientation in manual dexterity tasks is limited. In the previous study using the iBox with healthy young adults performing the same tasks, Martin-Brevet et al. reported that the object was close to vertical (angle $<0.5°$) at the times of lifting and placement and marginally more variable during holding ($<3°$). The values obtained in the present study are considerably higher, particularly during holding. Moreover, significant differences between the hemiparetic and less affected sides were observed (per **Figure 6**). Whilst not directly measuring object orientation, García Álvarez et al. (53) previously rated object stability for stroke patients when grasping daily objects. They found that object stability was correlated with upper-limb strength (Medical Research Council Scale) and spasticity (Modified Ashworth Scale). Here, quantitative data on iBox orientation resulted in multiple correlations with the Frenchay Arm Test (FAT), although the limited range of scores means caution should be taken with interpretation. Nonetheless, these combined observations suggest that global upper-limb strength is a key factor in regulating the vertical object orientation during lifting, holding and placement tasks.

Timing and Coordination Errors at Grasp Initiation and Release

The specific design of the instrumented object used in this study allowed us to identify micro errors upon grasp initiation and object release. The rate of these touch and push errors was greater for both the hemiparetic and the less affected side than the rates observed in healthy young adults (57). The increased frequency of push errors during lifting here is generally consistent with the observations of McDonnel et al. (46). Similarly, Duque et al. (44) observed a greater duration between the first touch by the thumb or index and the onset of grasp forces for children with cerebral palsy when compared to age-matched controls. These kinds of touch errors may be seen as evidence of an impairment in the transition between reach and grasp. We would suggest that the apparent lack of synchrony between thumb and finger movement as they close upon or withdraw from an object may be associated with the hand and palmar arch pre-shaping deficits previously documented by Sangole et al. (70).

Effect of Grasp Configuration

The effects of hand configuration upon grasp regulation during lifting, holding and object placement represents the central finding of the present study. As hypothesized, the use of the different grasps (precision, top, pinch, palmar-digital) had important effects upon the magnitude and timing of grip force adjustments, object orientation as well as the frequency of errors. Most notably, grip forces were greatest when using the palmar-digital grasp. This observation is consistent with prior results in healthy adult subjects (57). Whilst coupling between grip forces and load forces was apparent across all the grasp combinations, the time delay between maximum grip and peak acceleration was greater in the palmar-digital grasp

than the top grasp. In an experimental paradigm involving cyclic vertical movements, Flanagan and Tresilian similarly observed temporal delays in the coordination between grip forces and load forces when using a palmar-digital grasp (34). They suggested that these differences may reflect diminished tactile information in certain parts of the hand. A lower density of glabrous skin receptors through the palm than in the thumb and fingers may limit the precision of fine tuning abilities (32). The increased grip force observed in palmar-digital grasp would thus represent an increased safety margin to account for this limitation. In the present study, we found that the frequency of touch errors was greatest when initiating a palmar-digital grasp and that this grasp configuration was associated with variable object orientation at *tl*. Importantly, stroke patients with more important impairments tend to use palmar-digital grasp configurations more consistently than less impaired stroke patients or healthy adults (53). Therefore, whilst this behavior may assist stroke patients to compensate for reduced dexterity or muscle strength (53), the results presented here indicate that this preferential use of the palmar-digital grasping strategies may impact upon task execution in terms of grip force economy, temporal precision of grip force adjustments, and stability of the hand-held object.

In contrast to this, the top grasp configuration was associated with lower grip forces and comparably lower temporal discrepancies between peak acceleration and maximal grip force. The increased levels of wrist flexion when using the top grasp configuration may contribute to these differences. In healthy subjects, maximum grip-strength varies according to wrist position (71–73) and influences grip force regulation (74). Of course, when in an extended position, extrinsic flexors of the wrist and fingers are stretched, and conversely, a flexed position brings about passive finger extension (tenodesis effect). Increased flexor tone is common following a stroke, hence this effect may be exaggerated (75). Additionally, it has been proposed that the modification of afferent input associated with the changes in muscle length across the wrist could affect cortical and spinal excitability (74). Allowing a stroke patient to use a top grasp may thus limit these passive increases in muscle tension and further inhibit (excessive) neurological drive. Regardless of the precise mechanisms involved, the increased temporal precision of grip force adjustments when using a top grasp may be informative in clinical practice. It would suggest that use of top grasp hand configurations may be an adaptive strategy to assist stroke patients with tasks specifically requiring responsive grip force adjustments.

Effects of Side

Differences in grasp regulation between the hemiparetic and less affected arms were observed most notably in the frequency of errors at grasp onset, the duration of the unloading phase and object angle at lifting and placement. Interestingly, the frequency of touch errors on grasping with the hemiparetic side was associated with sub-threshold finger contact, whereas in the less affected arm, touches they were more frequently associated with sub-threshold thumb contact. This appears consistent with previously described kinematic patterns where patients move their hand around an object in the approach phase, a strategy which may serve to compensate for weakness in the wrist extensors and/or finger flexors (54, 76). In other terms, this could be thought of as "leading with the fingers" in preparing for object handling with the hemiparetic arm as opposed to "leading with the thumb" when preparing for object handling with the less affected arm. Release phase transitions were also characterized by asynchrony between the thumb and fingers on the hemiparetic side. Certain studies have suggested that this type of issue is linked to a distinct impairment of the grasp release mechanisms (77, 78). At the same time, such an error could also conceivably be hindered by limitations with proximal control as the patient attempts to withdraw their hand. Future studies should seek to combine kinematic analysis of upper-limb movement with measures from instrumented objects in order to understand patterns of coordination across the arm, hand and object as an ensemble. Finally, as evoked above (section Orientation and Stability of the Hand-Held Object), it is likely that upper-limb strength is important for maintaining vertical object orientation. The specific increases in the variability of object orientation at *tl* and *tp* seen in the hemiparetic arm (per **Figure 6**) further suggest that patients have the greatest difficulty maintaining object stability in the transition of the object to and from the working surface.

LIMITATIONS OF THE STUDY

The principal limitation in the design of this study is the lack of control group. Whilst one of our previous studies involved a similar protocol, data was obtained only for young adults. In the absence of an age matched control group we have limited our analysis to differences in grasp regulation between the hemiparetic and less affected arms of patients following a stroke. Secondly, whilst the iBox affords certain advantages (ease of manipulation, multiple integrated sensors), it measures exlusively those forces normal to the surface of each face—it is unable to estimate tangential forces or torque. The choice for linear load cells was motivated by the possibility of an affordable object which could be used in the clinic or at home (58).

Finally, the design of this study allows for considerable variation in surface contact. The coefficient of friction between a hand and an object varies according to the properties of a subject's skin (79) and the texture of the object (31). Increasing surface contact increases the coefficient of friction (80), a factor which was not controlled for in this experiment from one grasp configuration to the next. Consequently, the analysis of force exchanges with the iBox has certain limits for comparison across the grasping strategies. It is interesting to note however, that the subjects employed greater grasp forces when using the palmar-digital grasp despite having a greater coefficient of friction. This underscores that grip force regulation is contingent upon numerous biomechanical and neurological variables. In the present study, we consider the measurable behaviors as representative of the strategies associated with each grasp configuration.

CONCLUSION AND PERSPECTIVES

To surmise, the magnitude and temporal precision of grip force adjustments varied according to the different grasp configurations employed by hemiparetic patients. More specifically, grip forces were consistently greatest when patients used a palmar-digital grasp and lowest when using a top grasp. Similarly, the time delay between peak acceleration and maximum grip during lifting were highest in palmar-digital grasp and lowest top grasp. Use of the hemiparetic arm resulted in greater variability in the vertical orientation of the object, in particular upon lifting the object from and placing the object upon the working surface. Both grasp configuration and use of the hemiparetic arm were found to contribute to the occurrence of touch and push errors when establishing grasp or releasing the object. Our interpretation of this is that structural aspects of hand configuration contribute considerably to the grip force scaling while the effects of hemiparesis on upper-limb coordination more globally bring about deficits with object control and orientation at transitions in task sequence such as grasp onset, lifting, object placement and release.

These observations may assist in understanding the functional implications of compensatory grasp strategies in patients with hemiparesis and assist with facilitating adaptive prehension patterns in the context of rehabilitation. That is to say, whilst patients suffering from stroke may have exhibit preferences for taking objects with palmar-digital grasp configurations (53), this strategy may have negative effects upon grip force economy and temporal precision of grip force adjustments. The use of top grasp may thus be indicated in order to facilitate more responsive control in day to day object handling for this population.

AUTHOR CONTRIBUTIONS

RP, SM, and PP-D were responsible for patient recruitment. Data collection and patient evaluations were carried out by RP and SM. The iBox device and software was designed and adapted by NJ. Data analysis was performed by RP, NJ, and AR-B while VM-P participated in the discussions. The manuscript was drafted by RP and AR-B. All authors participated in the revision of the manuscript.

FUNDING

This work was made possible by funding from the Sorbonne University and the Labex SMART project (ANR-11-LABX-65), Investissements d'Avenir programme (ANR-11-DEX-0004-02).

ACKNOWLEDGMENTS

We would like to extend a special thank you to Sara Panera, Ariane Bozon-Verduraz and Marie-Laure Descamps of the physiotherapy department of the Salpêtrière Hospital, as well as to Claire Kemlin, Eric Moulton and Charlotte Rosso of the Institut du Cerveau et de la Moelle Epiniere for their assistance in the recruitment of patients for this study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00240/full#supplementary-material

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Conflict of Interest Statement: The 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.

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ORIGINAL RESEARCH
published: 20 February 2019
doi: 10.3389/fneur.2019.00126

Cortico-Muscular Coherence Is Reduced Acutely Post-stroke and Increases Bilaterally During Motor Recovery: A Pilot Study

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Motor recovery following stroke is believed to necessitate alteration in functional connectivity between cortex and muscle. Cortico-muscular coherence has been proposed as a potential biomarker for post-stroke motor deficits, enabling a quantification of recovery, as well as potentially indicating the regions of cortex involved in recovery of function. We recorded simultaneous EEG and EMG during wrist extension from healthy participants and patients following ischaemic stroke, evaluating function at three time points post-stroke. EEG–EMG coherence increased over time, as wrist mobility recovered clinically, and by the final evaluation, coherence was higher in the patient group than in the healthy controls. Moreover, the cortical distribution differed between the groups, with coherence involving larger and more bilaterally scattered areas of cortex in the patients than in the healthy participants. The findings suggest that EEG–EMG coherence has the potential to serve as a biomarker for motor recovery and to provide information about the cortical regions that should be targeted in rehabilitation therapies based on real-time EEG.

Keywords: cortico-muscular coherence, EEG, EMG, stroke, rehabilitation, wrist

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Edited by:
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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *10 September 2018*
Accepted: *30 January 2019*
Published: *20 February 2019*

Citation:
Krauth R, Schwertner J, Vogt S, Lindquist S, Sailer M, Sickert A, Lamprecht J, Perdikis S, Corbet T, Millán JdR, Hinrichs H, Heinze H-J and Sweeney-Reed CM (2019) Cortico-Muscular Coherence Is Reduced Acutely Post-stroke and Increases Bilaterally During Motor Recovery: A Pilot Study. Front. Neurol. 10:126. doi: 10.3389/fneur.2019.00126

INTRODUCTION

Stroke is one of the leading causes of disability, ranking third in the world as a contributor to disability-adjusted life years (DALYs) (1). Over the 20 years from 1990 to 2010, stroke incidence and absolute numbers of stroke survivors have increased dramatically, with the number of survivors in the age group over 75 years showing a drastic rise (2). Better understanding of the mechanisms involved in motor recovery has the potential to lead to improved approaches

to rehabilitation. Evidence suggests that the functional recovery achieved after stroke involves different cortical areas taking over the function of those that are damaged, including ipsilateral motor cortex. For instance, increased cerebral blood flow in sensorimotor cortex and both parietal lobes has been observed on positron emission tomography (3, 4). Functional magnetic resonance imaging has also revealed greater activation in patients post-stroke both in the same motor regions as healthy participants and also in the ipsilateral hemisphere (5). Enhanced understanding of how different brain areas are involved in motor recovery after stroke should lead to improved targeting of these regions in rehabilitation programmes.

Motor deficits are widely thought to result from a loss of functional connectivity between motor cortex and musculature. The aim of rehabilitation is to restore this function, either by re-establishing this connectivity or supporting the development of alternative brain–muscle connectivity. Cortico-muscular coherence (CMC) between brain electrical activity (electroencephalogram: EEG) and electrical activity recorded from muscle (electromyogram: EMG) has been proposed as a potential biomarker reflecting the regain of muscular control by cortex (6). Brain-computer interfaces (BCI) and transcranial electrical stimulation (TES) are receiving growing attention as rehabilitation approaches in which motor recovery is promoted by neurofeedback based on recordings of or direct manipulation of brain electrical activity (7–14). These therapies are based on an ability to identify cortical regions engaged in movement noninvasively and to monitor their activity associated with movement or movement attempts in real time.

A robust association has been observed between oscillatory rhythms in the motor cortex and movement (15–19). EEG–EMG coherence provides a measure of functional connectivity and could reflect the extent to which a particular motor cortical area is able to generate limb movement. Firstly, coherence was observed between local field potentials recorded from motor cortex and EMG signals in macaques that was modulated by movement (20). Second, EEG–EMG coherence has been found to increase with motor learning in healthy individuals (21, 22). Third, a reduction in EEG–EMG coherence has been observed following stroke (6, 23), and a recent case study suggested that quantifying EEG–EMG coherence could provide a measure of recovery of motor function post-stroke (24). EEG–EMG coherence thus represents a potential biomarker for monitoring regain of function during rehabilitation. Here we expand these findings to a larger patient group, evaluating CMC over the course of motor recovery and also comparing CMC at the final evaluation with that in healthy participants. We present here a preliminary study investigating the clinical progression and parallel CMC changes through the subacute and chronic phases in a group of 4 patients who had suffered an acute, left-hemispheric ischaemic stroke and compare their recovery with CMC in 7 healthy volunteers. We also present a case of right-hemispheric ischaemic stroke. On the basis of the current findings, we provide an estimate of the number of patients that would need to be recruited for a study in which stroke rehabilitation over the first months post-stroke is compared between treatment groups.

METHODS

Participants and Design

We recorded simultaneous EEG and EMG data from 7 right-handed healthy volunteers, and from 4 left-sided stroke patients (see **Table 1** for handedness) and one right-sided, right-handed stroke patient during the acute and subacute recovery phase following stroke. All participants were seated in front of a screen, with their forearms comfortably rested on a table in front of them, and visual cues were presented via Presentation (Neurobehavioral Systems, USA). Both groups received the instruction to extend their wrist when an arrow pointed upwards and to remain still and relaxed when the arrow pointed downwards. The healthy participants and the right-sided stroke patient were instructed to perform continuous, self-paced movements during movement trials. Each movement trial was followed by a rest trial. 16 rest condition trials and 16 movement condition trials of the right hand were recorded, with one trial lasting 20 s. The left-sided stroke patients were asked to extend or attempt to extend the right wrist once on presentation of an arrow pointing upwards and to rest when the arrow pointed downwards. The arrows were accompanied by a bar moving upwards for movement and downwards for rest. For the patients the up arrow was green and the down arrow was red, but otherwise, for both groups, the visual stimuli for movement and rest were identical except for the direction of the arrow. The movement of the bar downwards during rest was to ensure that visual cortical activation did not differ between movement and rest conditions. Right hand movement and movement attempts were evaluated for all participants except for the right-sided stroke patient, in whom left hand movement and movement attempts were also studied. This study was carried out in accordance with the recommendations of the Local Ethics Committee of the Otto-von-Guericke University, Magdeburg. Approval was granted for data collection and analysis from patients and from healthy participants for separate studies evaluating motor function using EEG and EMG. All patients and healthy participants gave written informed consent in accordance with the Declaration of Helsinki. The stroke patients were enrolled in a multi-center BCI-based rehabilitation study, and the healthy participants were enrolled as a part of a separate, preceding study, intended to inform the BCI study. The patients presented here are a subset of the patients recruited so far at the University Clinic, Magdeburg, and include all those with a left-sided subcortical stroke. The initial plan was to employ repeated movements in the BCI study, to maximize the classification rate of movement attempts in the early phase of rehabilitation, in which movement may be minimal or absent, on the basis of successful classification of imagined movement with this approach (25, 26). One patient (right-sided stroke patient: male, 56 years old, ischaemic, subcortical stroke to right centrum ovale, right-handed with Edinburgh Handedness Inventory Score of 68) performed this paradigm during piloting of the rehabilitation study. The decision was subsequently taken to employ single movement attempts, because this method is more natural (27), and thus potentially offers a more physiological approach to re-establishing functional connectivity between cortex and muscle.

The paradigm was then altered for the subsequent patients, including the 4 left-sided subcortical stroke patients presented here. In order to provide continuous visual feedback to the patient regarding the success of the movement attempt, a moving bar was chosen. The downward movement was used for rest, so that visual stimulation would be similar for both conditions. A color difference was deemed unlikely to yield detectable EEG differences and was used to make it easier for patients to know the current condition. We additionally present CMC during movements of the affected and the unaffected hand the pilot data from the single patient as these data provide a bridge between the paradigms employed.

Scalp EEG recordings were made using an EEG cap from Brain Products. EEG electrodes were placed according to the 10-10 system montage (**Figure 1**). Data were recorded against an FCz reference. 4 of the 64 electrodes (FP1, FP2, AF7, AF8) were used for bipolar EMG recording from wrist extensor muscles (2 electrodes for each hand). Electrodes were placed approximately 5 cm apart over the wrist extensor musculature as determined by palpation on wrist extension. Data were digitized with a sampling rate of 500 Hz.

Impedance in the healthy participant group in the data analyzed (motor cortex electrodes: FC5, FC3, FC1, FC2, FC4, FC6, C5, C3, C1, Cz, C2, C4, C6, CP5, CP3, CP1, CPz, CP2, CP4, CP6) was below 5 kΩ. In the patient group, the impedance levels were higher due to caution taken to avoid excessive skin abrasion in hospital in-patients. This approach was considered to be of additional importance in an EEG-based BCI study, in which daily electrode application was required for the therapy sessions and was deemed essential to minimize the study dropout rate, which is known to be high in acute stroke patients. The impedance in the patient group was mainly kept below 10 kΩ and did not exceed 50 kΩ (except at FC1 in Patient 1, Session 1: 77 kΩ–no significant CMC was identified at this site in Session 1 but also not in Session 2, when the impedance at FC1 was 1 kΩ). A recent event-related potential (ERP) study comparing ERPs from high- with low-impedance recordings, reported a reduced signal-to-noise ratio (SNR) when recording commenced with an impedance >30 kΩ (28). In the current study, impedance exceeded 30 kΩ for Patient 1 at 5 electrode sites (FC1, FC2, FC6, C5, CP5) in Session 1 and at no electrode sites in Session 2, for Patient 2 at 2 electrode sites (CP3, CP5) in Session 1 and at 2 electrode sites in Session 2 (C2, CP6), for Patient 3 at no electrode sites in either Session, and for Patient 4, at 3 electrode sites (C1, CPz, CP6) in Session 1 and at 3 electrode sites (FC2, C1, CP2) in Session 2. When the patients returned to the clinic for Session 3, the impedances did not exceed 20 kΩ. Impedance did not exceed 30 kΩ at any electrode site for the right-sided stroke patient. Given the amplifier's input impedance of 10 MΩ, it should be noted that impedance does not result in a reduction in recorded signal amplitude (29, 30), and a lower SNR in ERP calculation simply resulted in a requirement for more trials to yield significant findings (28). We do not expect our examination of the temporal relationship between EEG and EMG signals to be affected by impedance, given that signals were successfully recorded.

The patient inclusion criteria were an infarction diagnosed on structural magnetic resonance imaging (MRI) lasting more than 24 h, resulting in a score of 0–2/5 on the Medical Research Council power scale for wrist movement. Exclusion criteria were aphasia or cognitive impairment to an extent that prevented ability to understand and perform the task, medication with L-dopa, and severe pain, fatigue, or depression. All patients received individualized rehabilitation therapy in the Neurorehabilitation Centre, Magdeburg. Patients underwent a clinical assessment and EEG–EMG recordings at Session 1: several days after stroke (11.75 ± 5.40 days), Session 2: 7 weeks ± 1.87 days after stroke, and a longer-term follow-up at Session 3: 11.3 ± 3.04 months post-stroke. The main outcome measure was the motor function section of the upper extremity evaluation of the Fugl-Meyer Assessment (FMA-UE) (24) with a maximum score of 66 points. We also evaluated the wrist section of the FMA separately. It involves 5 items, where movement was scored from 0 to 2, 0 being no movement and 2 being full movement, resulting in a maximum of 10 points. FMA scores were compared across sessions using the Friedman test.

Pre-processing

For all analyses, Matlab, version 2015b (The Math Works, USA) was used. The data recordings were imported using EEGLAB (31). First, data epochs were extracted during right hand movement and rest. Using the Current Source Density toolbox (32), a Laplacian Filter was applied to each dataset to improve spatial resolution of the signals. The Laplacian filter was constructed using a current source density transformation (32) The radially flowing current, passing from the cortex beneath the electrode into the skull and scalp, was estimated for each electrode location, using a spatially weighted sum of the potential gradients directed at this location from all other electrode sites. The scalp Laplacian used was derived from the negative second spatial derivative of the interpolated scalp surface potentials, resulting in reference-free, spatially-enhanced potentials. This step was followed by applying a 1–200 Hz bandpass filter and a 49–51 Hz notch filter to eliminate line noise. EMG recordings were re-referenced to provide a bipolar recording for each side. As McClelland et al. showed that rectification was an unnecessary step in EMG pre-processing (33), unrectified EMG data were used for our analysis.

Data recorded from healthy participants during 16 movement epochs and 16 randomly selected rest epochs were concatenated, respectively, to provide a time series for each condition. Recordings were taken from second 3 to 18.36 (15.36 s), in order to include only data during which there was actual movement during all the movement episodes, resulting in one time series comprising 16 times 15.36 s (=245.76 s) for each condition. These data were then windowed into 2.048 s epochs. Data containing artifacts, determined by visual inspection and using EEGLAB's automated artifact rejection with default settings (threshold voltage: 1,000 μV, probability threshold: 5 standard deviations), were excluded from subsequent analysis. The artifact inspection was performed by RK and JS, under the supervision of CS, who is experienced in EEG artifact inspection. Blinding to data sets was not deemed necessary, because CMC could not be estimated in raw EEG and EMG data. Independent component analysis (ICA) was performed to identify and remove eye-blink

TABLE 1 | Clinical data from patients.

Patient	EHI	Lesion location	Session 1		Session 2		Session 3	
			Time post-stroke	FMA: wrist, FMA/66	Time post-stroke	FMA: wrist, FMA/66	Time post-stroke	FMA: wrist, FMA/66
1	−20	Subcortical: left medial internal capsule, and re-infarction directly behind, in dorsolateral internal capsule.	8 days	0, 10	7 weeks, 1 day	5, 38	11 months	10, 65
2	0	Subcortical: left Internal capsule.	6 days	0, 8	7 weeks	0, 11	12 months	10, 58
3	100	Subcortical: small lacunar infarct in posterior part of left internal capsule.	13 days	0, 16	7 weeks, 2 days	9, 61	6.5 months	10, 62
4	−78	Cortical: left central motor area. Cortical, occipital left. Unclear whether new or old. Subcortical: old, bilateral small lacunar infarction in white matter.	20 days	0, 20	6 weeks, 4 days	2, 47	15 months	7, 53

EHI, Edinburgh Handedness Inventory. Mean age 58.3 years (range 52–64 years).

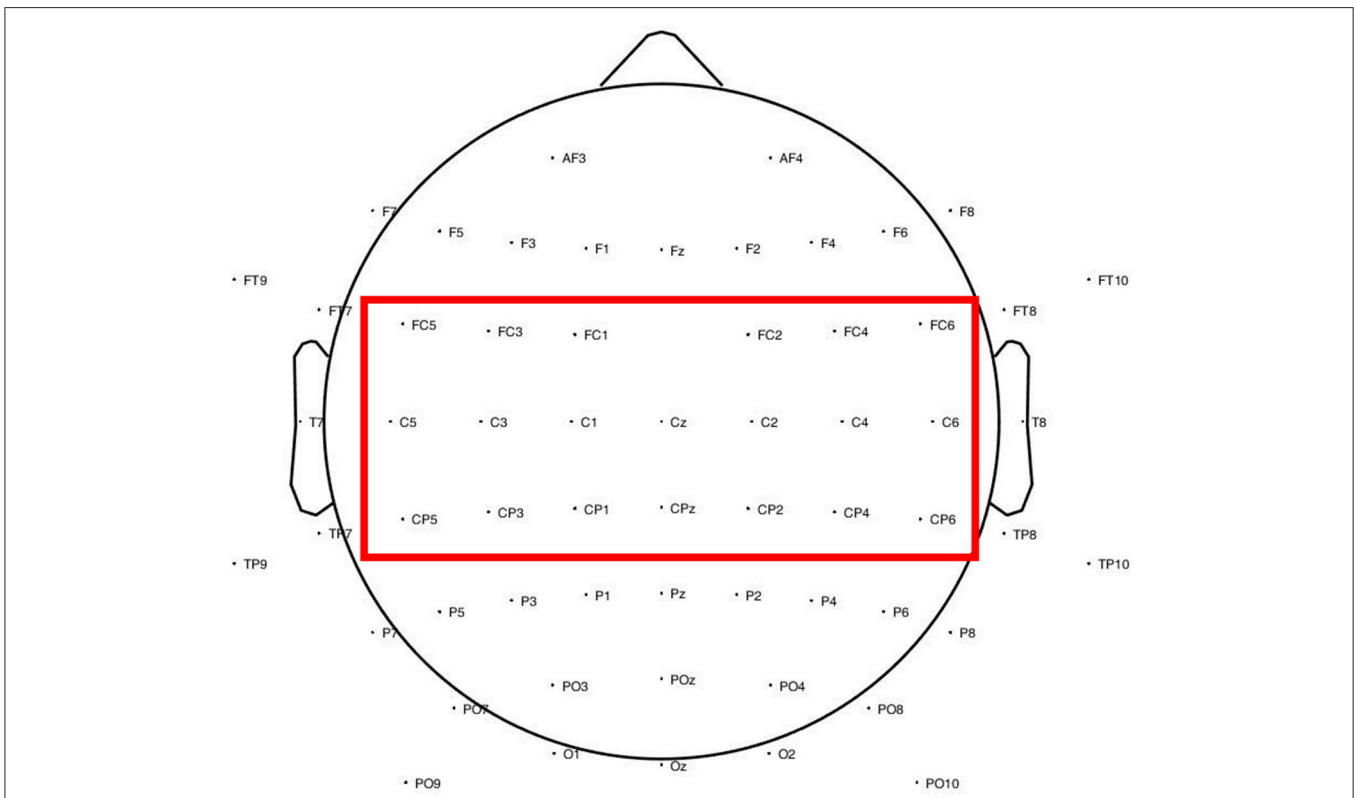

FIGURE 1 | Electrode locations according to the 10-10 system. The electrode locations over motor cortex are indicated by the red box.

artifact components. Rejection criteria for ICA components were unipolar frontal representations on component topographic channel plots (topoplots), additionally to identification of eye blink-related activations on visual inspection. After artifact rejection, movement data were aligned in 2.048 s windows according to movement onsets. The Teager-Kaiser energy operator (TKEO) (34, 35) was calculated according to the following formula:

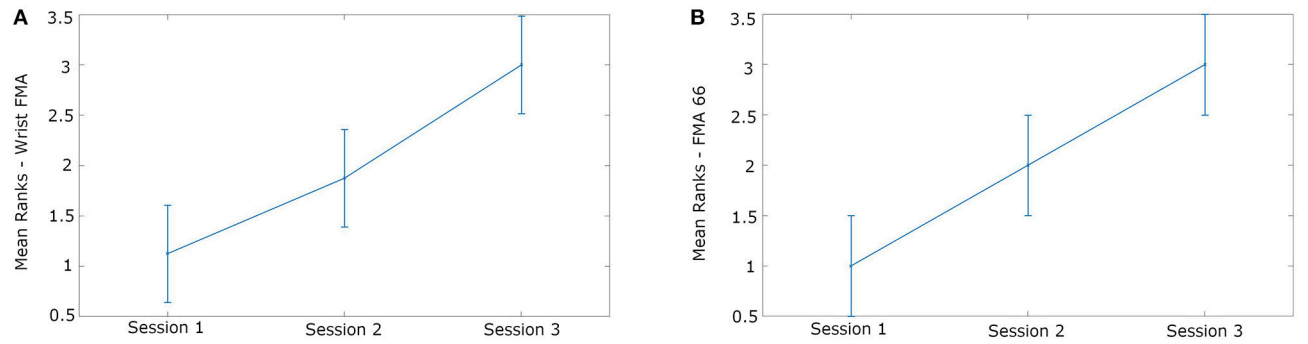

FIGURE 2 | Improvement in upper limb mobility in the patient group, as indexed by **(A)** the wrist-FMA, and **(B)** the motor function section of the FMA-UE score, was observed over the Sessions.

$$TKEO\,(n) = x^2\,(n) - x\,(n+1)\,x(n-1) \tag{1}$$

for the movement data and rest data of the corresponding EMG channel, depending on the hand that was moved. x is the EMG voltage in the frame number n. If the energy operator in movement data exceeded 10 standard deviations of the energy operator of the rest data for at least 100 consecutive bins (0.2 s), a movement onset was defined. Data from −512 to 512 bins surrounding onsets were extracted, resulting in 2.048 s time windows.

As movement for the left-hemispheric stroke patients was not self-paced but cued, their recordings were not aligned to movement onsets but to cue signals. 2 s windows, starting from 1 s after cue presentation, were used for analysis. Artifact removal was conducted in the same manner as described for the healthy participant data.

Coherence

For coherence analysis, the movement epochs were concatenated to a single time series. Coherence spectra for every combination of scalp electrode with EMG electrode of the moved hand were calculated using the multitaper method implemented in the Neurospec toolbox for Matlab (Neurospec, Version 2.0, 2008, see (36) for a theoretical framework). Non-overlapping windows consisting of 1,024 frames (2.048 s) were used to estimate and average frequency domain auto-spectra of the EEG and EMG signals in the time series. The spectra were calculated at a frequency resolution of 0.49 Hz per bin. Coherence was calculated as shown in Equation 1, expressed as the magnitude squared correlation coefficient between two signals:

$$\left|R^2_{x\ EMG}\right| = \frac{\left|S_{x\ EMG}\,(f)\right|^2}{S_{xx}\,(f)\,S_{EMG\ EMG}\,(f)} \tag{2}$$

where $|S_{xEMG}(f)|$, the estimated cross-spectrum between scalp electrode x and the EMG electrode at frequency f, is analogous to the covariance. $S_{xx}(f)$ and $S_{EMGEMG}(f)$, the estimated auto-spectra at frequency f, are analogous to the variance of each signal (36). However, artifact rejection resulted in different numbers of trials for healthy participants and patients, which can affect the strength of coherence. In order to eliminate the effect of trial length on coherence, we performed bootstrapping in a similar fashion to Carlowitz-Ghori et al. (37), using 5,000 repetitions. After determining the smallest number of trials available (n = 41), coherence spectra were assessed as the mean of 5,000 bootstrap spectra calculated from n randomly selected trials for each patient and healthy participant. One Hundred permutations were performed, calculating coherence for stacked 2 s sequences with randomly selected starting points. Coherence involving a particular EEG electrode at a frequency was deemed significant if the bootstrapping estimate exceeded 95% of the values of the permutations in that channel and frequency.

In the following calculations, significant coherence values in the beta band (12–30 Hz) over motor cortex electrodes (FC5, FC3, FC1, FC2, FC4, FC6, C5, C3, C1, Cz, C2, C4, C6, CP5, CP3, CP1, CPz, CP2, CP4, CP6), as shown in **Figure 1**, were included. The number of significant bins, reflecting the spatial extent and the frequency range involved in CMC, was determined by counting the number of EEG electrode sites over the motor cortex at which coherence was deemed significant from bootstrapping and permutation in the steps described above, for each of the 37 frequency bins in the beta band. We examined the level of coherence: peak coherence values over the motor electrodes during right hand movement were extracted for further statistical analysis. We also investigated the ratio of coherence between the affected and unaffected hemispheres of the patients and compared the findings to those of the healthy participants.

Laterality indices were calculated according to Equation 3:

$$LI = \frac{Q_{Left\ hemisphere} - Q_{Right\ hemisphere}}{Q_{Left\ hemisphere} + Q_{Right\ hemisphere}} \tag{3}$$

where Q is the maximum coherence in the corresponding hemisphere. Laterality indices could range from −1 to 1, with positive values indicating a lateralization to the left (lesioned) hemisphere and vice versa. Friedman Tests for repeated measures were conducted to compare patient data across three Sessions. Significant results from Friedman tests were further analyzed with *post-hoc* Wilcoxon rank sum tests.

In order to compare session 3 patient data to data from healthy participants a one-sided ANOVA was performed with the factor *Group* (healthy participant/stroke patient), following Levene's tests where parameters were first tested for significant differences in variance between patient and healthy participant data. If there was no significant difference in variance ($p > 0.05$), an ANOVA was performed.

Correlation was calculated between clinical outcome measure (FMA-UE and FMA wrist) and the peak beta CMC, for each patient at each of the three assessment times.

On the basis of the change in EEG–EMG coherence over the course of the study, a power estimation was performed, in order to indicate the number of patients that would need to be recruited in a rehabilitation study, such as that comparing use of a BCI with a sham treatment group, in order to achieve 80 % power to detect a difference between groups with a significance threshold of $p = 0.05$.

RESULTS

Clinical Evaluation

All patients showed an increase in FMA score over the course of the study, with the mean FMA-UE and the mean FMA wrist subsection improving (**Table 1**). The FMA-UE change over sessions was significant [Friedman's ANOVA: $\chi^2(2) = 8.0$, $p = 0.018$], with *post hoc* testing showing a significant increase from 13.5 at Session 1 (directly post-stroke: mean of 11.8 days later) to 59.5 at Session 3 (mean of 11.1 months later) (Wilcoxon test: $p = 0.029$). The mean score in the section of the FMA relating to wrist movement also specifically improved from 0 to 9.75. The improvement in wrist-FMA scores across sessions was significant [Friedman's ANOVA: $\chi^2(2) = 7.6$, $p = 0.022$] (**Figure 2**). *Post-hoc* analysis showed a significant increase from Session 1 to Session 3 (Wilcoxon test: $p = 0.029$), while wrist-FMA did not show significant improvements between Sessions 1 and 2 ($p = 0.14$), and Sessions 2 and 3 ($p = 0.057$).

CMC

In the healthy participants, beta EEG–EMG coherence was observed in the contralateral hemisphere during movement (**Figure 3**). Coherence was deemed significant if the bootstrapping estimate exceeded 95% of the values of the permutations in a specific channel and frequency.

The EEG–EMG coherence in the beta frequency band in the stroke patients changed over time, both increasing in degree and changing in topographic distribution (**Figure 4**). The beta peak coherence increased over the course of the three evaluation sessions [Friedman's ANOVA: $\chi^2(2) = 7.6$, $p = 0.022$] (**Figure 5A**). *Post-hoc* Wilcoxon's rank sum tests revealed that the beta peak coherence in Session 3 was significantly higher than in Session 1 ($p = 0.029$) and Session 2 ($p = 0.029$). The increase from Session 1 to Session 2, however, was not significant ($p = 0.229$). The number of bins across individual beta frequencies (37 frequencies over 12–30 Hz) and motor electrodes (20 electrodes) also increased over the period of observation [Friedman's ANOVA: $\chi^2(2) = 6.53$, $p = 0.038$] (**Figure 5B**). The increase in the number of significant bins in Session 1 and Session 2 was not significant ($p = 0.49$) while the rises from Session 2 to Session 3 ($p = 0.029$) and Session 1 to Session 3 ($p = 0.029$) were significant. The laterality of coherence in patients did not show a significant shift across sessions, however [Friedman's ANOVA: $\chi^2(2) = 0.93$, $p = 0.63$]. The degree of laterality of the maximum beta EEG–EMG coherence did not differ between patients at session 3 and healthy participants [one-way ANOVA: $F(1, 9) = 0.04$, $p = 0.84$] (**Figure 5C**). The peak coherence over motor cortex was higher in patients at the final evaluation session than in the healthy participants [one-way ANOVA: $F(1, 9) = 10.22$, $p = 0.011$] (**Figure 5D**).

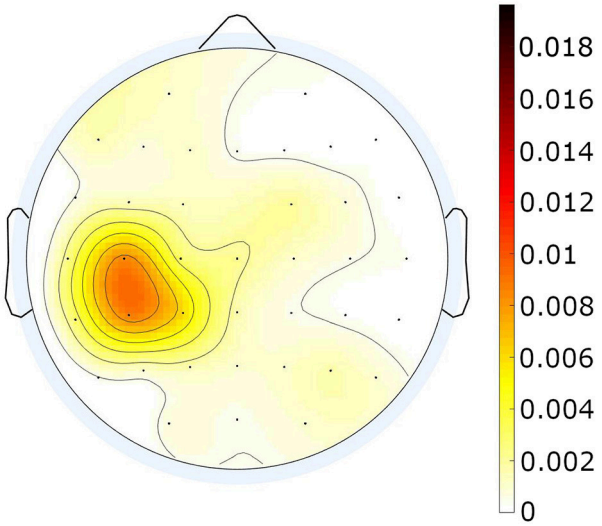

FIGURE 3 | Mean beta EEG–EMG coherence across 7 healthy participants. The values shown resulted from averaging the individual mean coherence patterns in the beta band across all 37 frequency bins across the 7 healthy participants. CMC values determined to be non-significant with the methods described were set to zero. Color scale: CMC.

The mean increase in beta CMC in our patient group was 0.092 (STD: 0.047) from initial evaluation to the third evaluation. On the basis of the current preliminary study, the number of patients that would need to be enrolled in future studies comparing a group participating in a new rehabilitation programme to a control group receiving standard rehabilitation therapy, using a change in peak beta coherence as a marker of improvement, and assuming an improvement equal to the observed standard deviation in the control group, was calculated. To achieve 80% power, with a significance threshold of $p = 0.05$, $N = 34$ patients (17 per group) would be required.

A correlation was observed between the mean beta peak coherence and FMA-UE ($r = 0.84$; $p = 0.0006$) and also specifically wrist FMA ($r = 0.79$; $p = 0.0021$) (**Figure 6**). Note that correlation was calculated over values from four patients, each with three evaluation times.

We note that patient 2 had no wrist movement and moreover no detectable movement-related change in the EMG during

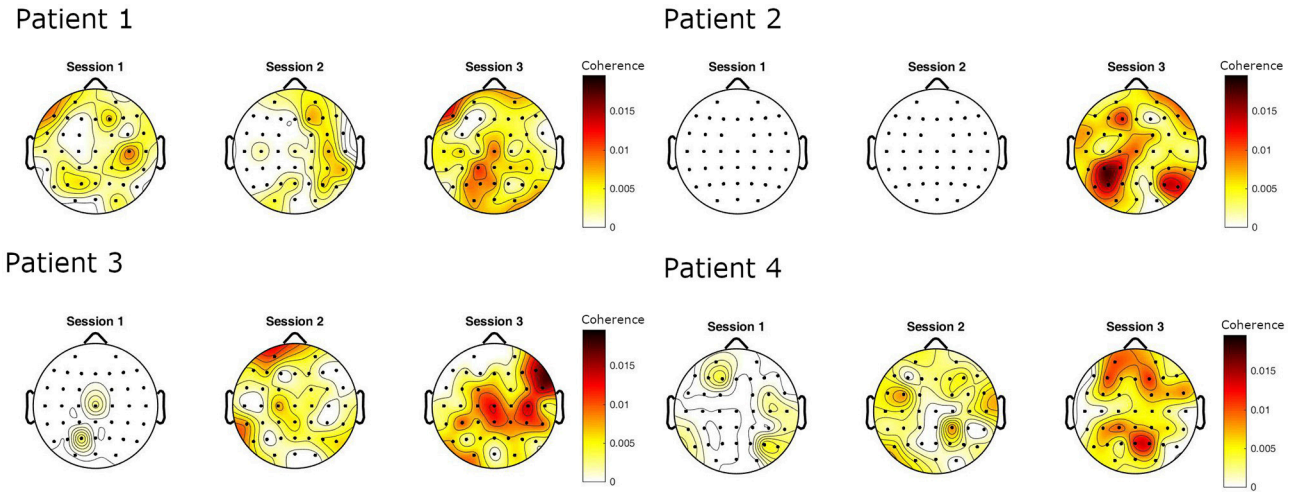

FIGURE 4 | EEG–EMG coherence in the beta frequency range in four patients following stroke, evaluated at three sessions during motor recovery. Color scale: CMC.

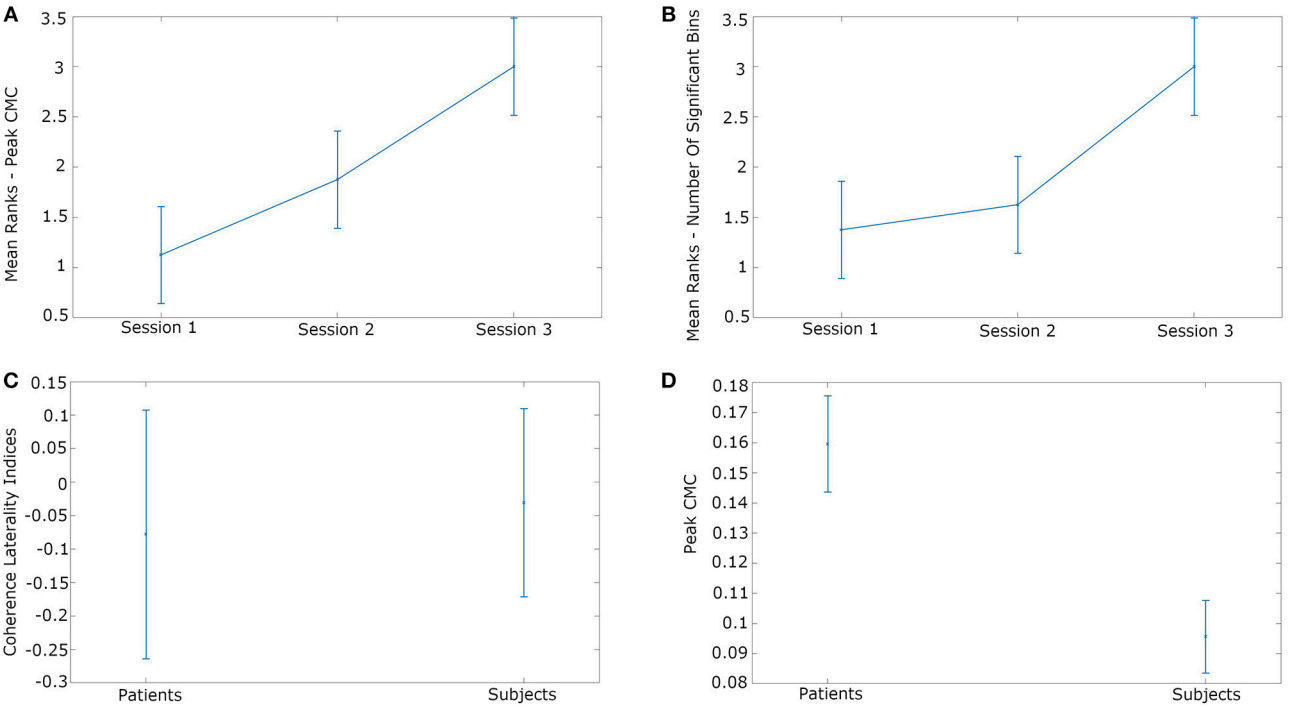

FIGURE 5 | Changes in beta EEG–EMG coherence over time post-stroke. **(A)** Mean ranks of coherence peak in the beta frequency range. **(B)** Mean ranks of number of bins across electrodes and beta frequencies. **(C)** Coherence laterality index ($p = 0.84$). **(D)** Comparison between peak level of beta EEG–EMG coherence between patients on final evaluation and healthy participants ($p = 0.011$).

movement attempts. The plots are thresholded for significant CMC, and no CMC was significant for this patient at these times.

CMC in the alpha (8–12 Hz) and gamma (30–40 Hz) frequency ranges was also increased contralaterally during movement in the healthy participant group but to a lesser extent than the beta CMC (**Supplementary Figure 1**).

The data recorded during a single recording session from the single right-sided stroke patient (wrist FMA: 4/10; FMA-UE: 32/66) show stronger left-sided and more locally focused beta CMC during right hand movements than right-sided during left hand movements (**Supplementary Figure 2**).

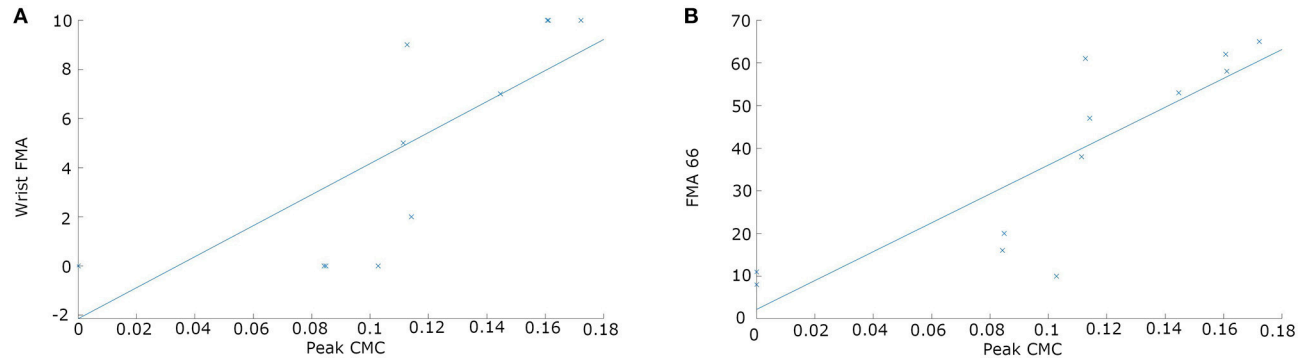

FIGURE 6 | Scatterplots of peak CMC against FMA values **(A)** Correlation between peak CMC and FMA-wrist ($r = 0.79$; $p = 0.0021$). **(B)** Correlation between peak CMC and motor function section of FMA-UE ($r = 0.84$; $p = 0.0006$). Note that each panel contains 12 data points, with three evaluation times for each of four patients. In panel A, two points overlap completely at a CMC peak of 0 with a wrist FMA of 0, and two points are partially overlapping at CMC peaks of 0.085 and 0.016. In panel B, two data points are plotted at a CMC peak of 0.

DISCUSSION

We identified EEG–EMG coherence in the beta frequency range focused over motor cortex on the contralateral side to hand movement in healthy participants and monitored the development of this marker during the course of motor recovery in patients who had suffered an ischaemic stroke. CMC was initially minimal in the acute recovery phase, then gradually increased over time to reach a greater level than that seen in healthy participants. Moreover, its distribution differed from that found in healthy participants, with CMC observed in both the contralesional (ipsilateral) and the lesioned hemisphere and incorporating both a greater number of frequency bands within the beta range and a larger area of cortex, including posterior cortical areas. These changes in CMC were accompanied by significant motor recovery as evaluated using the wrist subsection of the FMA and the FMA-UE motor function section, with a correlation observed between these FMA scores and the CMC. Our findings suggest that EEG–EMG coherence in the beta frequency range has the potential to be used as a biomarker during stroke recovery. Furthermore, the findings suggest rehabilitation therapies that are steered by EEG activity, such as BCIs and TES, should target broad areas of cortex, with regular updating of the parameters used over the course of the recovery period, as CMC correlated with cortico-spinal communication and was shown to change in its spatial distribution over the course of stroke rehabilitation

Our results are in line with the findings of Rossiter et al. (38). They reported increased CMC in the ipsilateral (contralesional) hemisphere in eight of 25 stroke patients, based on a study examining EEG–EMG coherence in stroke patients. The study involved a large cohort of patients, enabling evaluation of the impact of diverse factors, including subcortical and cortical stroke, as well as different time intervals post-stroke. Some patients had ipsilateral CMC, while others had a peak in CMC in the lesioned (contralateral) hemisphere. These patients did not differ in age, time interval post-stroke, or degree of impairment. Of those with ipsilateral CMC, two had subcortical and six had cortical infarcts. In the current study, we report increasing bilateral CMC in all four of our patients, all of whom had subcortical infarctions and one of whom also had a motor cortical infarction. Evaluation was performed at similar times post-stroke for all patients, and all patients had a similar degree of recovery by the third evaluation. It is likely that the variability in the findings of Rossiter et al. results from their widely ranging cohort, including stroke affecting either hemisphere in both left- and right-handed participants. While handedness was also mixed in our cohort, all patients had a stroke affecting their right side (left brain hemisphere).

Changes in CMC over the course of stroke recovery have also been examined by Carlowitz-Ghori et al. (37). They investigated CMC during movement of the affected and unaffected hands in the acute and chronic stages of stroke in 11 patients. They found a significant decrease in coherence during movement of the affected hand in the acute phase compared to the unaffected hand. In the chronic period, this difference in coherence diminished and peak coherence lessened significantly for the unaffected hand in comparison to the acute period. Contrary to our findings, they did not observe an increase in peak coherence over the time course for the affected hand. However, this could be attributed to the fact that the patients they included had Medical Research Council scores of at least 3, while three of our four patients had no movement at all (reflected by wrist-FMA scores of 0) prior to therapy.

No significant differences in laterality indices were identified in the current study, which is consistent with the findings of a previous study comparing 11 chronic stroke patients (mean years after stroke: 6.5) with nine age-matched participants (39). While Graziadio et al. evaluated absolute laterality, we specifically took account of the side to which lateralization occurred. Contrary to our findings, they did not report significant differences in peak coherence values for healthy participants and patients but rather a dependency between recovery and the degree of symmetry. While our data do not allow evaluation of such a dependency, because all four of our patients achieved similar recovery levels and showed a similar degree of bilaterality of CMC, our findings

in this aspect are nonetheless consistent with theirs in terms of CMC showing a bilateral distribution post-stroke.

Our patients showed a more widespread, bilateral activation pattern after motor recovery, with more involvement of the contralesional hemisphere. In contrast, in a study involving chronic stroke patients, only the hemisphere contralateral to the affected hand showed CMC during wrist extension (6). It is plausible that in the more acute phase after stroke, cortical areas neighboring the lesion temporarily take over motor function to compensate for the loss of cortical influence, which may again shift back to a spatial pattern more similar to healthy participants over the course of rehabilitation. We also note that the CMC in our patients was posterior relative to that in the healthy participant group, consistent with findings of increased cortical activity previously reported following stroke (3, 4). A plethora of neuroimmune mediators and biological factors that could index stroke recovery are currently under investigation (40). The engagement of widespread areas of cortex in post-stroke motor recovery may be related to the widespread release of biomolecules following stroke.

The longer time periods after stroke in the aforementioned studies may suggest that the changes we observed are associated with earlier compensatory mechanisms of the central nervous system, while laterality may shift from a high index to the contralesional side in earlier phases of recovery to a more bilateral pattern, as suggested by Bellardinelli et al. (41). They studied eight right-handed patients with stroke affecting the left side. They presented a bi-hemispheric coherence pattern in chronic stroke patients, with increasing amplitude associated with improved clinical performance, as measured with Upper Extremity-FMA after novel BCI-assisted therapy.

The current study has a number of limitations. The direct comparison between data from healthy participants and patients must be interpreted with caution, because the details of the movement paradigms during EEG-EMG recordings differed in the two cohorts compared. While healthy participants performed repetitive, self-paced movements, patients' movements more closely resembled an isometric contraction due to the difficulty of the task in the early post-stroke period, in which mobility restriction was marked. CMC in the beta band is predominantly described as being associated with submaximal, isometric contractions (37, 38), although it has also been observed in recovering stroke patients involving dynamic muscle contraction (41). The data shown from the single patient who performed the repeated movement paradigm indicate greater contralateral and more lateralized beta CMC during movements of the unaffected wrist than the wrist affected by the stroke. Although coherence in the healthy participant group appeared predominantly in the beta frequency band (alpha and gamma coherence were less marked), the difference in beta peak coherence could also be attributed to the different types of movement instead of solely to cortical plasticity following stroke. The significant CMC–FMA-UE and CMC–FMA-wrist correlations should be interpreted with caution given the low sample number of 4 patients and three measurement points.

Furthermore, the FMA-UE and the wrist section of FMA may not differentiate sensitively enough between the individual levels of rehabilitation in wrist dexterity, as movements are only scored with 0, 1 or 2 points. Although the FMA has proven to be a reliable and efficient assessment of motor function, with high intra- and inter-rater reliability (42, 43), it may not be sensitive enough to the changes in motor performance we are seeking. A ceiling effect for FMA scores regarding the hand has been criticized due to missing out on more complex finger movements (42). Further studies in rehabilitation of motor capacities focusing on rehabilitation of manual dexterity may require a more differentiated scoring system with more discrete levels.

It should also be noted that recordings were performed once in the healthy participant group and three times in the patient group. While we cannot exclude potential alterations in CMC in the healthy participants with repetition of the paradigm, the simplicity of the task makes a practice effect unlikely.

The estimated patient numbers for a future rehabilitation study using peak beta CMC as a biomarker should be considered with caution. The patients involved in this preliminary study received individualized in-patient rehabilitation programmes in the first weeks post-stroke, which likely contributed to their functional improvement and associated CMC. On the other hand, in the absence of an active rehabilitation programme, functional improvement is expected in around half of patients (12).

The current study presents preliminary work, which has the potential to contribute to understanding the mechanisms underlying the plasticity of the link between motor cortex and affected muscles during stroke recovery. Further studies involving greater participant numbers are required to provide plausible answers regarding the role of re-establishing beta-band CMC in the recovery of motor function in the hand.

AUTHOR CONTRIBUTIONS

CS-R: study conception and design. RK, JS, and CS-R: clinical and electrophysiological data acquisition. SV and SL: clinical data acquisition. SL, MS, AS, and JL: patient rehabilitation. RK, JS, and CS-R: data analysis and interpretation. SL: data interpretation. RK and CS-R: drafting of manuscript. JS, SV, SL, MS, AS, JL, SP, TC, JdRM, HH, and H-JH: critically revised the manuscript. All authors contributed to planning of patient data collection and read and approved the final manuscript.

FUNDING

The study was internally funded by the Dept. of Neurology, Otto-von-Guericke University, Magdeburg and the Neurorehabilitation Centre, Magdeburg. SP, TC, and JdRM acknowledge support from the Wyss Center for Bio and Neuroengineering in Geneva.

ACKNOWLEDGMENTS

The authors would like to thank Anne-Katrin Baum, Manuela Reichwald, Angelika Klemme, and Laura Hermann for support in data acquisition and are grateful to the patients and healthy volunteers who kindly agreed to participate in the study.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2019.00126/full#supplementary-material

Supplementary Figure 1 | Topography of CMC during right hand movement in healthy participants. **(A)** CMC in the alpha (8–12 Hz) frequency band. **(B)** CMC in the gamma (30–40 Hz) frequency band were also increased contralaterally during movement in the healthy participant group but to a lesser extent than the beta CMC. Color scale: CMC.

Supplementary Figure 2 | Topography of beta-range CMC from the single right-sided stroke patient. The data recorded show stronger left-sided and more locally focused beta CMC. **(A)** Beta CMC was lower over the affected right hemisphere during left hand movements than **(B)** over the left hemisphere during right-handed movements. Color scale: CMC.

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Conflict of Interest Statement: The 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.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 10 January 2019
doi: 10.3389/fneur.2018.01129

Activation of Bilateral Secondary Somatosensory Cortex With Right Hand Touch Stimulation: A Meta-Analysis of Functional Neuroimaging Studies

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Background: Brain regions involved in processing somatosensory information have been well documented through lesion, post-mortem, animal, and more recently, structural and functional neuroimaging studies. Functional neuroimaging studies characterize brain activation related to somatosensory processing; yet a meta-analysis synthesis of these findings is currently lacking and in-depth knowledge of the regions involved in somatosensory-related tasks may also be confounded by motor influences.

Objectives: Our Activation Likelihood Estimate (ALE) meta-analysis sought to quantify brain regions that are involved in the tactile processing of the right (RH) and left hands (LH) separately, with the exclusion of motor related activity.

Methods: The majority of studies ($n = 41$) measured activation associated with RH tactile stimulation. RH activation studies were grouped into those which conducted whole-brain analyses ($n = 29$) and those which examined specific regions of interest (ROI; $n = 12$). Few studies examined LH activation, though all were whole-brain studies ($N = 7$).

Results: Meta-analysis of brain activation associated with RH tactile stimulation (whole-brain studies) revealed large clusters of activation in the left primary somatosensory cortex (S1) and bilaterally in the secondary somatosensory cortex (S2; including parietal operculum) and supramarginal gyrus (SMG), as well as the left anterior cingulate. Comparison between findings from RH whole-brain and ROI studies revealed activation as expected, but restricted primarily to S1 and S2 regions. Further, preliminary analyses of LH stimulation studies only, revealed two small clusters within the right S1 and S2 regions, likely limited due to the small number of studies. Contrast analyses revealed the one area of overlap for RH and LH, was right secondary somatosensory region.

Conclusions: Findings from the whole-brain meta-analysis of right hand tactile stimulation emphasize the importance of taking into consideration bilateral activation, particularly in secondary somatosensory cortex. Further, the right parietal operculum/S2

OPEN ACCESS

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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *13 September 2018*
Accepted: *10 December 2018*
Published: *10 January 2019*

Citation:
Lamp G, Goodin P, Palmer S, Low E, Barutchu A and Carey LM (2019) Activation of Bilateral Secondary Somatosensory Cortex With Right Hand Touch Stimulation: A Meta-Analysis of Functional Neuroimaging Studies. Front. Neurol. 9:1129. doi: 10.3389/fneur.2018.01129

region was commonly activated for right and left hand tactile stimulation, suggesting a lateralized pattern of somatosensory activation in right secondary somatosensory region. Implications for further research and for possible differences in right and left hemispheric stroke lesions are discussed.

Keywords: ALE "activation likelihood estimation", meta-analysis, brain activation, sensation, hand, touch, secondary somatosensory cortex

INTRODUCTION

Somatosensory function is crucial for daily life, guiding our interactions with the world around us through the detection, discrimination and recognition of body sensations (1). Somatosensation is important not only for perception, but also for goal-directed action (2, 3). For example, somatosensation contributes to the fundamental pinch grip-lift-and hold task (4) and is important in dexterous movement of the hand (5). Following stroke, reduced functional arm use is contributed to by motor *and* somatosensory deficits. Somatosensory impairment has a negative impact on grasp and manipulation of objects (6) and is associated with reduced arm use (7). Further, somatosensory brain regions have been implicated in motor recovery (8). It has been suggested that somatosensory processing for the guidance of action can be dissociated from the processing that leads to perception (2). Here we focus on brain regions involved in somatosensation, specifically tactile stimulation of the hand, without motor confounds.

The neuroanatomy of somatosensory processing is well established through a large body of lesion, post-mortem, animal and structural neuroimaging studies (9–12). Reproducible functional activation in the contralateral primary somatosensory cortex (S1) has been demonstrated in healthy controls when asked to perceive a touch stimulus to their fingertips (13). Technological advances in recent years have even allowed mapping of individual fingers to corresponding areas of S1 (14) and the temporal acuity of anticipation of a tactile stimulus originating in the ipsilateral S1 (15).

Different patterns of activation and lateralization emerge when examining somatosensory processing in the secondary somatosensory cortex (S2). Median nerve stimulation has been shown to activate bilateral S2 regions, including parietal operculum, regardless of the hand being stimulated, but only the contralateral S1 (16). This has also been seen in other stimulation studies. Lee et al. (17) recently examined the differential neural activations associated with vibrotactile, pressure and temperature stimulation of right palm, showing common activation in the contralateral S1 and bilateral S2/insula regardless of stimulation type. Bilateral S2 region activation has also been seen with vibrotactile stimulation irrespective of other cognitive demands (18). It has been suggested that serial somatosensory processing occurs from contralateral S1 to contralateral S2 in response to electrical stimulation, but when stimulation becomes more intense or painful there is an increase in hemispheric integration (19). A meta-analysis of studies examining the functional role of S2 in somatosensory processing divided the area into OP1 (parietal operculum 1), OP2, OP3, and OP4 (10). While OP1 is reported to represent the human homolog of macaque area S2 and was generally more responsive to pure somatosensory (tactile) stimuli (10), overall the areas were all implicated in different somatosensory processes (20). A thorough review of the functional role of S2, from the bi-laterality of activation with unilateral stimulation, to the mapping of the hand area spread of OP1-OP4, has been provided by Eickhoff et al. (10).

When examining the literature it becomes clear that the functional activation of somatosensory processing in the brain is still a developing area. There are various stimulation techniques to investigate reflexive neural activity, for example vibrotactile stimulation (18, 21) as opposed to MNS median nerve stimulation (16, 22, 23), that can yield different results. Somatosensory stimuli are applied to various body parts, including the face, upper limb, and lower limb (10, 24), but may not be performed on each hand separately (25, 26). Finally, studies have often been confounded by motor contributions to the task, e.g., involving movement intention and/or execution (27–29).

Our aim was to characterize and synthesize the somatosensory brain activation network during touch sensation, with potential influence of motor contributions eliminated. We employed the ALE meta-analytic technique to provide a statistically-based likelihood estimation of the brain regions that are consistently activated during tactile stimulation of the hands. Firstly, studies were limited to those that involved only tactile stimulation of the right (RH) or left hand (LH) separately in order to allow interpretation of networks that account for hemispheric dominance. Following this, studies which incorporated any motor movements during the stimulation task were excluded, to address confounding motor influence during somatosensory task performance. Lastly, to characterize neural correlates specific to touch sensation, studies involving other somatosensory modalities, such as pain or proprioception, were excluded.

METHODS

Identification of Studies for Meta-Analysis

The meta-analysis of neuroimaging studies was conducted according to the PRISMA statement and recorded using the suggested checklist (30). A thorough literature search was conducted using Web of Science database (conducted December 12, 2017) and the following search terms: (fMRI OR MRI OR PET OR "functional magnetic resonance imaging" OR "positron emission tomography" OR neuroimaging OR "brain imaging" OR "neural activation") AND (somatosen* OR sens* OR tactile) AND (hand OR "upper limb" OR finger) AND (health* OR control). These papers were then crosschecked with

papers identified in the Sleuth functional database (31–33). The Sleuth database was searched for "somesthesis perception" in the behavioral domain and for "activation only" studies. These were reviewed using the strict inclusion criteria (see **Figure 1**).

Activation Likelihood Estimation Meta-Analysis

The meta-analysis was performed using Activation Likelihood Estimation (ALE) on the activation voxel coordinates reported by the selected study (34–36). Analyses were conducted using GingerALE (version 2.3.6) (37) software (downloaded from http://brainmap.org/ale), with coordinates in Montreal Neurological Institute (MNI) space (38, 39). Coordinates reported in Talairach space (40) were converted to MNI space using the "icbm2tal transform" (41, 42). To minimize within-experiment and within-group effects we utilized the modified algorithm described in Turkeltaub, Eickhoff (36) and, thus, were able to include multiple contrasts from within the one study. The calculated ALE map had a cluster forming threshold of $p < 0.001$ with 1000 permutations, corrected for multiple comparisons using the Family Wise Error (FWE) $p < 0.05$ (20, 37, 43, 44). Contrast and conjunction analyses were calculated to compare activation associated with task type, first by creating an image of two tasks pooled together (e.g., RH and LH) with an uncorrected threshold of $p < 0.01$ at 10,000 permutations, and then subtracting each original task analysis

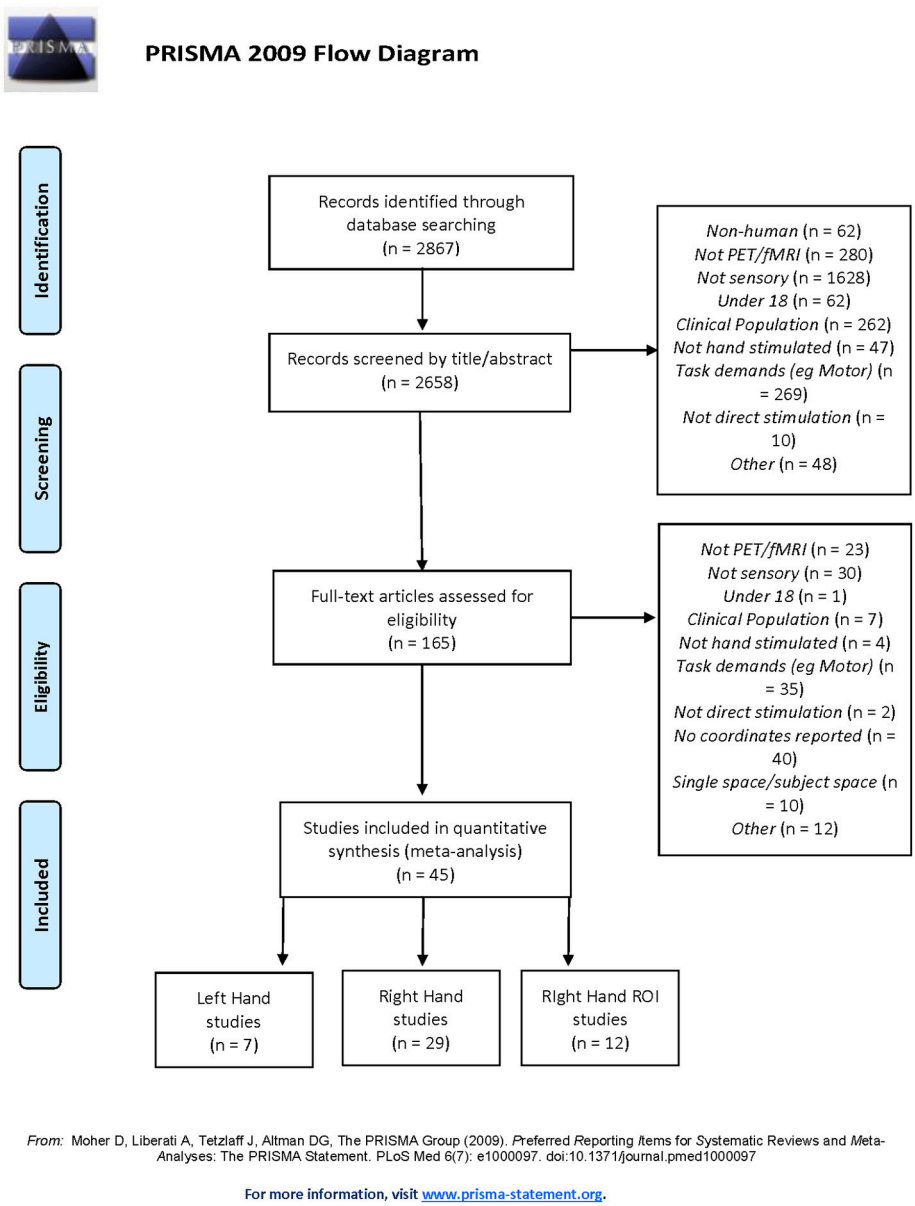

FIGURE 1 | PRISMA Flowchart of selection criteria for including and excluding studies.

TABLE 1 | Studies included in the meta-analysis ($n = 45$) and reported participant and task information, separated by task category.

References	*N*	Age M (SD); min-max	Sex M:F	Handedness	Stimulus type	Stimulus Location	Attended	Response required	fMRI/PET
Right Hand stimulation Whole-Brain (*N* = 29)									
Borstad et al. (52)	10	39–82	5:5	9RH, 1LH	Brush stroke	Index finger	Y	N	fMRI
Bjornsdotter et al. (53)	22	19–35	13:9	NR	Brush stroke	Palm	Y	N	fMRI
Brodoehl et al. (54)	34	21–71	17:17	RH	Compressed air	Fingers 1-3	Y	N	fMRI
Brodoehl et al. (55)	10	23.1 (1.54)	0:10	RH	Compressed ait	Fingers 1-5	Y	N	fMRI
Brodoehl et al. (56)	32	21–71	15:17	RH	Compressed air	Fingers 1-5	Y	N	fMRI
Burton et al. (57)	11	19–25	5:6	RH	Textured surface	Digits 2-3	Y	Y (after scan)	fMRI
Carey et al. (13)*	5	52–76	3:2	RH	Texture grids	Fingertips	Y	Y (after scan)	PET
Chung et al. (58)	21	24.19 (2.71)	NR	RH	Band pressure	Index finger	Y	N	fMRI
Chung et al. (59)	21	24.19 (2.17)	NR	RH	Band pressure	Index finger	Y	N	fMRI
Gelnar et al. (27)	9	18-NR	NR	RH	Vibration	Fingers 2-5	Y	N	fMRI
Godde et al. (60)	10	18–30	8:2	RH	Vibration	Fingers	Y	N	fMRI
Hagen et al. (61)*	18	37 (12)	11:7	RH	Von Frey	Index finger	Y	N	PET
Hlushchuk and Hari, (62)	10	23–33	7:3	NR	Compressed air	Index, middle, ring fingers	Y	N	fMRI
Kavounoudias et al. (63)	10	31.4 (10.7)	2:8	RH	Textured surface	Whole hand	Y	N	fMRI
Kitada et al. (64)	5	23–25	5:0	RH	Pressure	First 2 fingers	Y	Y	fMRI
Kitada et al. (65)	14	23–26	12:2	RH	Tactile grids	2 Fingers	Y	N	fMRI
Kwon et al. (66)	10	25.20 (2.49); 22–29	5:5	RH	Rubber brush	Dorsum	Y	N	fMRI
Lee et al. (17)	10	27.8 (4.1); 23–34	8:2	NR	Vibratory brush	Palm of right hand	y	N	fMRI
Malinen et al. (67)	10	20–32	6:4	RH	Vibration	Fingers 2-3	NR	NR	fMRI
McGlone et al. (68)	10	18–26	0:10	RH	Brush stroke	Palm	NR	NR	PET
Nebel et al. (69)	12	28.7 (7.6)	0:12	NA	Vibration	Hand	NR	N	fMRI
Ozcan et al. (70)*	12	22–35	8:4	11RH, 1LH	Compressed air	Fingertips	N	N	fMRI
Planetta and Servos, (71)	10	25 (1)	3:7	RH	Pressure	Fingertips	NR	NR	fMRI
Rolls et al. (72)	9	28 (NR)	5:4	RH	Textured surface	Hand	NR	NR	fMRI
Ruben et al. (73)	8	21–31	6:2	NR	Electrical stimulation	Digit 2 and 5	NR	NR	fMRI
Schurmann et al. (74)	13	22–39	9:4	RH	Vibration; Compressed air	Hand; Fingers	Y	N	fMRI
Summers et al. (75)	6	20–33	6:0	RH	Vibration	Digit 2	Y	N	fMRI
Yoo et al. (76)	13	21–38	8:5	RH	Von Frey brush	Index finger	Y	N	fMRI
Young et al. (77)	10	21–32	6:4	RH	Textured surface	Hand	Y	N	fMRI
Right Hand stimulation Region of Interest (ROI) studies (*N* = 12)									
Blankenburg et al. (78)	8	25–39	7:1	RH	Electrical stimulation	Third finger and palm	NR	N	fMRI
Blatow et al. (79)	12	25–59	5:7	RH	Vibration	Digits 1 and 2	Y	Y	fMRI
Blatow et al. (80)	16	21–51	8:8	RH	Vibration	Digits 1 and 2	NR	NR	fMRI
Burton et al. (81)	12	28.3 (12.8)	8:4	RH	Vibration	Index finger	Y	Y	fMRI
Deuchert et al. (82)	8	23–26	4:4	RH	Von Frey monofilaments	Thenar eminence	Y	Y	fMRI
Dresel et al. (83)	6	24–39	2:4	5RH, 1LH	Electrical stimulation	2 and 5th finger	N	N	fMRI
Eickhoff et al. (10)	14	25.6 (3.4)	7:7	RH	Brush stroke	Fingers	Y	Y	fMRI

(Continued)

TABLE 1 | Continued

References	*N*	Age M (SD); min-max	Sex M:F	Handedness	Stimulus type	Stimulus Location	Attended	Response required	fMRI/PET
Hlushchuk and Hari, (62)	6	20–30	2:4	RH	Compressed air	Palm	NR	NR	fMRI
Huang and Sereno, (84)	9	23–33	6:3	NR	Compressed air	Digits 2,3,4	Y	N	fMRI
Kobayashi et al. (85)	10	18–22	0:10	RH	Textured surface	Palm	Y	N	fMRI
Martuzzi et al. (86)	10	20–35	10:0	RH	Stroke	Finger tips	Y	N	fMRI
Nelson and Chen, (87)	12	25–66	4:8	RH	Vibration	Fingertip	Y	N	fMRI
Left Hand stimulation Whole-Brain (*N* = 7)									
Ackerley et al. (88)	12	18–35	12:0	NR	Brush stroke	Palm	Y	N	fMRI
Carey et al. (13)*	5	33–80	2:3	RH	Texture grids	Fingertips	Y	Y (after scan)	PET
Case et al. (89)	26	24.8 (7); 19–43	11:15	RH	Brush stroke	Palm and back of hand	Y	N	fMRI
Hagen et al. (61)*	12	39 (13)	6:6	11RH, 1LH	Von Frey	Index finger	Y	N	PET
Maldjian et al. (90)	5	28–40	4:1	RH	Vibration	Each finger pad	NR	NR	fMRI
Ozcan et al. (70)*	12	22–35	8:4	11RH, 1LH	Compressed air	Fingertips	N	N	fMRI
Wacker et al. (91)	13	22–35	9:4	12RH, 1LH	Vibration	Index finger	Y	N	fMRI

**Studies contributing data to both RH and LH stimulation Whole-Brain analyses.*

from the pooled image in an iterative process (45, 46). Contrast analyses permitted identification of regions of difference between groups while conjunction analyses quantify regions of overlap. To maximize accurate localization and interpretation, images created in GingerALE were also imported into the SPM Anatomy Toolbox (47–49) to permit localization of the ALE images with 3-dimensional probabilistic cytoarchitectonic mapping (50, 51). This regional cytoarchitectonic classification of ALE maps complements the GingerALE localization that uses peak MNI co-ordinates.

RESULTS

A total of $n = 45$ studies were determined to be suitable for inclusion (see **Table 1**). Of the 45 studies, 29 were used to perform the RH whole-brain meta-analysis, seven were used for the LH whole-brain meta-analysis (three studies involved stimulation of both LH and RH independently), and 12 studies examined RH stimulation in a ROI analysis.

As can be seen in **Table 1**, for the 29 RH whole-brain studies, a total of $n = 375$ participants were included ($n = 173$ males, however $n = 3$ studies did not report sex) aged 18–76 years. The RH ROI studies included $n = 123$ participants ($n = 63$ males) aged 18–66 years. The seven LH studies included $n = 85$ participants ($n = 52$ males) aged 18–80 years. The most common form of stimulation was vibration ($n = 12$ studies), followed by compressed air ($n = 8$), textures ($n = 7$), brush stroke ($n = 7$), Von Frey filaments ($n = 4$), and pressure ($n = 4$).

The RH whole-brain studies, RH ROI studies and the LH whole-brain studies were analyzed separately, as presented in **Table 2** and **Figure 2**. For the RH whole-brain stimulation studies, the contralateral (left) primary and secondary somatosensory areas were significant, with a large cluster containing the parietal operculum (92), somatosensory (93), and motor (94) cortices. The ipsilateral (right) secondary somatosensory cortex, S2, was also significant, largely comprising the parietal operculum (92) and inferior parietal cortex (95, 96), in addition to a small cluster in the anterior cingulate. The RH ROI studies revealed visually smaller contralateral (left) clusters in the primary and secondary somatosensory regions, with a smaller ipsilateral (right) cluster within S2. The contralateral (left) clusters were separated into a large superior cluster containing the primary somatosensory (93) and motor (94) cortices, and a smaller inferior cluster containing primarily the parietal operculum (92). The ipsilateral (right) cluster contained similar areas to RH whole brain, namely the parietal operculum (92) and inferior parietal cortex (95, 96). With the small number of LH stimulation studies, only two clusters were significant in the contralateral (right) primary (containing somatosensory (93) and motor (94) cortices) and secondary somatosensory regions [primarily parietal operculum (92)] and primary auditory cortex (97) (**Table 2**).

Contrast analyses were then performed, as presented in **Table 3** and **Figure 3**. When contrasted with the LH whole-brain studies, RH whole-brain studies revealed two clusters in the contralateral (left) primary and secondary somatosensory areas. The largest cluster contained primary somatosensory (93, 98) and motor (94) cortices, while the smaller cluster contained primarily the auditory cortex (97), insula (99), and parietal operculum (92). When contrasted with RH whole-brain studies, the LH whole-brain studies activated three small clusters in S1 quite similar to those found in the standalone LH whole-brain analysis, all containing primary somatosensory areas (93, 98). In our analysis of conjoined areas (i.e. areas of overlap) for RH and LH whole-brain studies, only one significant cluster

TABLE 2 | Anatomical location, summary statistics and MNI co-ordinates of ALE identified areas for RH whole-brain, RH ROI and LH whole-brain studies (Extrema ALE value, FWE cluster corrected $p < 0.05$, uncorrected $p < 0.001$).

SPM Anatomy Toolbox region location	MNI GingerALE peak location	Extrema value	Size	*x*	*y*	*z*
RH WHOLE-BRAIN STUDIES (30 CONTRASTS, 334 FOCI)						
Left parietal operculum (OP) Area OP3 (VS), area OP4 (PV), and area OP1 (S2)	Left primary somatosensory area (S1); Insula (BA 13)	0.061623	17,784	−48	−20	20
Left Area 1, Area 3b, and Area 4a	*Left S1; postcentral gyrus (BA 2)*	*0.035296*		*−54*	*−20*	*48*
Left Area 3b, Area 1, and Area 4a	*Left S1; postcentral gyrus (BA2)*	*0.028759*		*−44*	*−26*	*58*
Not assigned in probability maps	*Left Insula (BA 13); claustrum*	*0.021434*		*−38*	*−12*	*4*
Left Area OP4 (PV)	*Left primary motor area (M1); insula (BA 13)*	*0.016304*		*−44*	*−8*	*10*
Not assigned in probability maps	*Left par opercularis (BA 44); insula (BA 13)*	*0.015817*		*−40*	*4*	*10*
Right area OP1 (S2), area OP4 (PV), and area TE 1.0	Right supra marginal gyrus (SMG, BA 40); insula (BA 13)	0.039009	6,032	56	−22	20
Right area PFcm (inferior parietal lobe, IPL), and Area OP1 (S2)	*Right superior temporal area (BA 22); insula (BA 13)*	*0.021011*		*56*	*−34*	*18*
Right Area PFcm (IPL) and Area PF (IPL)	*Right IPL, SMG (BA 40)*	*0.017283*		*56*	*−38*	*28*
Right area PFop (IPL), area PFt (IPL), and area 3b	*Right S1; postcentral gyrus (BA 2)*	*0.015576*		*60*	*−20*	*32*
Left area 33	Left cingulate gyrus (BA 24, 32)	0.022505	896	−4	14	36
RH ROI STUDIES (12 CONTRASTS, 93 FOCI)						
Left area 1, area 4a	Left S1; postcentral gyrus (BA 2)	0.025885	6520	−50	−18	52
Left area 4a and area 3b	*Left M1; postcentral gyrus (BA 3)*	*0.017133*		*−40*	*−28*	*60*
Left area 4a and 3b	*Left M1; postcentral gyrus (BA 3)*	*0.015225*		*−42*	*−22*	*58*
Left area OP1 (S2), area TE 1.0, and area PFop (IPL)	Left postcentral gyrus, SMG, BA 40)	0.014924	2,296	−54	−26	20
Left area OP4 (PV), area OP3 (VS), and area OP1 (S2)	*Left S1; insula (BA 13)*	*0.012088*		*−50*	*−20*	*20*
Area OP3 (VS) and Area OP4 (PV)	*Left M1; Insula (BA 13)*	*0.007544*		*−42*	*−12*	*16*
Right Area OP1 (S2), Area PFcm (IPL), and Area PFop (IPL)	Right IPL, SMG (BA 4)	0.012395	1,840	54	−26	24
Right area OP1 (S2) and area OP4 (PV)	*Right SMG (BA 40); insula (BA 13)*	*0.011046*		*58*	*−18*	*20*
Right area OP4 (PV)	*Right S1, postcentral gyrus (BA 43)*	*0.007434*		*60*	*−8*	*14*
LH WHOLE-BRAIN (7 CONTRASTS, 53 FOCI)						
Right Area 1, Area 3b, and Area 4p	Right primary somatosensory area (S1); postcentral gyrus (BA2)	0.013074	3,176	54	−20	44
Right Area 3b, Area 4p, and Area 4a	*Right S1; IPL (BA40), postcentral gyrus*	*0.010481*		*40*	*−34*	*60*
Right Area 1 and Area 3b	*Right S1; postcentral gyrus (BA 3)*	*0.009132*		*44*	*−24*	*64*
Right Area 1, Area 3b, and Area PFt (IPL)	*Right S1; postcentral gyrus (BA 3)*	*0.008071*		*62*	*−18*	*36*
Right Area 4p, Area 3b, and Area 3	*Right S1; IPL (BA 40)*	*0.007689*		*36*	*−34*	*52*
Not assigned in probability maps	*Right M1; precentral gyrus (BA 4)*	*0.007664*		*44*	*−12*	*60*
Right area OP4 (PV), area OP1 and area TE 1.0	Right supramarginal gyrus (SMG: BA 40); Insula (BA 13)	0.016235	1,392	52	−16	16

MNI, Montreal Neurological Institute; ALE, Activation Likelihood Estimation; RH, Right Hand; ROI, Region of Interest; LH, Left Hand; FEW, Family Wise Error; SPM Anatomy Toolbox location based on 3 dimensional probabilistic cytoarchitectonic maps (47–51); MNI GingerALE peak location based on anatomical location of peak MNI co-ordinate from the GingerALE software; (OP), Parietal Operculum; OP3 (VS), Ventral Somatosensory; OP4 (PV), Parietal Ventral; OP1 (S2), Second Somatosensory; Area TE 1.0, Central Primary Auditory Cortex (PAC); PFcm, IP within Parietal Operculum; IPL, Inferior Parietal Lobe; PF, Caudal inferior parietal cortex (IPC); PFop, Rostro-ventral IPC; PFt, Dorsal IPC; BA, Brodmann Area. Locations in italics refer to areas within the larger clusters (i.e. sub clusters identified).

was present, in the right secondary somatosensory region, primarily parietal operculum areas OP1, OP3 and OP4 (92). There were no significant differences in the contrast analysis between RH whole-brain studies and RH ROI studies. However, when the two groups were conjoined, significant common regions of activation were identified, with clusters revealed in the left primary (93) and secondary somatosensory areas (92), and the right secondary somatosensory area (92), including OP1.

DISCUSSION

In two important ways our ALE meta-analysis allowed us to examine the brain regions consistently activated during tactile

stimulation of the hands in order to characterize functional somatosensory regions and networks, without the influence of motor function. Firstly, the meta-analysis allowed us to characterize and compare areas involved in right hand and left hand tactile stimulation studies separately. Secondly, it revealed the similarities and differences between functional activation studies that focus on specific brain regions (RH ROI studies) and what is actually occurring throughout the brain (RH whole-brain studies). Unfortunately very few studies ($n = 7$) examined LH stimulation separate to the RH and without the influence of motor activity, making a statistical comparison between the hands difficult and exploratory.

For the RH whole-brain stimulation studies ($n = 29$) not only did we find two large clusters in the contralateral (left) primary (93) and secondary [specifically within parietal operculum areas OP1, OP3 and OP4 (92)] somatosensory cortices as expected, but activation was also revealed in the ipsilateral (right) secondary somatosensory region involving OP1 and OP4 (92) in addition to the anterior cingulate. Bilateral activation of secondary somatosensory S2 region, involving parietal operculum (92) to unilateral stimulation of the right hand is consistent with previous reports (100). From the few LH studies included, two small but significant clusters were revealed in the contralateral (right) S1 and S2. While each hand had significantly greater activation in the contralateral S1 and S2 in comparison to the other hand, the only significant area of overlap was in the right S2, specifically OP1, OP3 and OP4 (92). Lateralized differences have been reported for different sensory modalities, with right hemisphere being more spatially oriented toward the dorsal perceptual/sensory systems (101). Overlap in right S2 is consistent with hemispheric asymmetry involving right-hemisphere-based bilateral representation of the body (101), right-sided asymmetry for tactile processing (102) and robust bilateral responses to unilateral stimulation in S2 (100). Due to the difference in numbers of studies included for each hand, this comparison is considered exploratory and highlights the need for more studies to examine LH tactile stimulation separately. Nevertheless, it is an interesting trend and could have significant implications for better understanding somatosensory function and dysfunction.

Activation in the contralateral S1, when using a tactile stimulus on the hand, is quite consistent with previous research (13, 14). The pattern of activation shown in the RH whole-brain studies is consistent with research showing contralateral S1 activation only, *and* studies that have shown bilateral activation in S2 regardless of the hand being stimulated (16, 17, 103). It is surprising that bilateral S2 activation was not seen for the meta-analysis of LH studies also. However, this may have been attributable to the low number of studies stimulating the LH alone.

The role of S2 both contralateral and ipsilateral to the hand being stimulated is particularly interesting and may have important implications. The secondary somatosensory cortex of nonhuman primates is located on the parietal operculum, and the anatomical cytoarchitectonic maps of OP 1-4 of the human parietal operculum correlate with the functionally defined human somatosensory cortex (92), with OP 1 constituting the putative human homologue of area S2 (92). Further, OP1 is closely connected with the parietal networks for higher order somatosensory processing, while OP 4 is more closely integrated

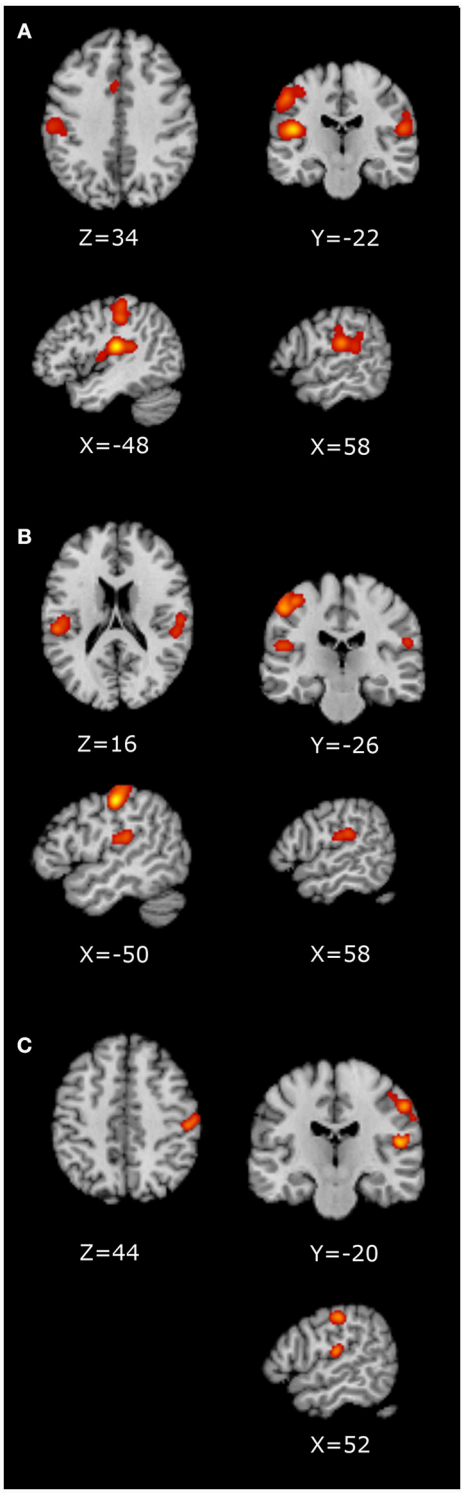

FIGURE 2 | ALE Images displayed in neurological convention. **(A)** RH whole-brain ALE; **(B)** RH ROI ALE; **(C)** LH whole-brain ALE.

TABLE 3 | Anatomical location, summary statistics and MNI coordinates of ALE identified areas for contrast analyses: RH Whole-Brain greater than LH Whole-Brain, LH Whole-Brain greater than RH Whole-Brain, RH Whole-Brain conjoined with LH Whole-Brain, and RH Whole-Brain conjoined with RH ROI studies ($p < 0.01$, 10,000 p-value permutations, 100 mm cluster threshold).

SPM Anatomy Toolbox region location	MNI GingerALE peak location	Extrema value	Size	x	y	z
RH WHOLE-BRAIN GREATER THAN LH WHOLE-BRAIN STUDIES						
Left area 3b, area 2 and area 4p	Left Inferior parietal lobe (IPL), supramarginal gyrus (SMG: BA 40)	3.719017	4,168	−45	−28	44
Left area 4p, area 4a, and area 3a	*Left S1: postcentral gyrus (BA 2)*	*3.540084*		*−49*	*−25*	*50*
Left area 4a and area 1	*Left S1; postcentral gyrus (BA 2)*	*3.352795*		*−52*	*−19*	*53*
Left area TE 1.0, area Ig2, and area TE 1.1	Left transverse temporal gyrus (BA 41)	3.890592	3,488	−39	−22	17
Left area TE 1.0, area TE 1.1, and area OP1 (S2)	*Left transverse temporal gyrus (BA 41)*	*3.719017*		*−45*	*−26*	*16*
Left area Ig2, area TE 1.2, and area TE 1.0	*Left S1; insula (BA 13)*	*3.352795*		*−44*	*−18*	*12*
Not assigned in probability maps	*Left S1; postcentral gyrus (BA 2)*	*3.011454*		*−44*	*−20*	*28*
LH WHOLE-BRAIN GREATER THAN RH WHOLE-BRAIN STUDIES						
Right area 3b and area 2	Right S1: IPL (BA 40)	2.597153	296	40	−38	60
Right area 3b, area 4p, and area 2	*Right S1; IPL (BA 40)*	*2.582808*		*36*	*−36*	*54*
Not assigned in probability maps	*Right S1; postcentral gyrus (BA 40)*	*2.483769*		*40*	*−30*	*58*
Right area 1 and area 3b	Right postcentral gyrus (BA 3)	2.894304	288	45	−26	58
Right area 1 and area 3b	Right postcentral gyrus (BA 3)	2.911238	280	48	−22	56
Right area 1 and area 3b	*Right postcentral gyrus (BA 3)*	*2.847963*		*52*	*−20*	*52*
Right area 3b and area 4a	*Right postcentral gyrus (BA 2)*	*2.575829*		*48*	*−18*	*54*
Not assigned in probability maps	*Right postcentral gyrus (BA 40)*	*2.536396*		*47*	*−21*	*50*
RH WHOLE-BRAIN STUDIES CONJOINED WITH LH WHOLE-BRAIN STUDIES						
Right area OP4 (PV), area OP1 (S2), and area OP3 (V5)	Right SMG BA 40); insula (BA 13)	0.016235	688	52	−16	16
RH WHOLE-BRAIN CONJOINED WITH RH ROI STUDIES						
Left area 3b, area 4a, and area 1	Left S1; postcentral gyrus (BA 2)	0.025433	4,400	−50	−18	50
Not assigned in probability maps	*Left M1; postcentral gyrus (BA 3)*	*0.017133*		*−40*	*−28*	*60*
Not assigned in probability maps	*Left M1; postcentral gyrus (BA 3)*	*0.015225*		*−42*	*−22*	*58*
Left area OP1 (S2), area TE 1.0, and area OP4 (PV)	Left postcentral gyrus, SMG (BA 40)	0.014924	2,144	−54	−26	20
Not assigned in probability maps	*Left S1; insula (BA 13)*	*0.012088*		*−50*	*−20*	*20*
Not assigned in probability maps	*Left M1; insula (BA 13)*	*0.007544*		*−42*	*−12*	*16*
Right area OP1 (S2) and area OP4 (PV)	Right IPL, SMG (BA 40)	0.012395	1,632	54	−26	24
Not assigned in probability maps	*Right insula (BA 13), SMG (BA 40)*	*0.011046*		*58*	*−18*	*20*

MNI, Montreal Neurological Institute; ALE, Activation Likelihood Estimation; RH, Right Hand; ROI, Region of Interest; LH, Left Hand; SPM Anatomy Toolbox location based on 3 dimensional probabilistic cytoarchitectonic maps (47–51); MNI GingerALE peak location based on anatomical location of peak MNI co-ordinate from the GingerALE software; Area TE 1.0 - Central Primary Auditory Cortex (PAC); Ig2 - Granular Insula area 2; TE 1.1 - Medial PAC; TE 1.2 - Lateral PAC; OP4 (PV) - Parietal Ventral; OP1 (S2) – Second Somatosensory; OP3 (VS), Ventral Somatosensory; BA, Brodmann Area. Locations in italics refer to areas within the larger clusters (i.e. sub clusters identified).

with areas responsible for basic sensorimotor processing and action control (104). Bilateral secondary somatosensory cortex, in particular, has demonstrated a role in complex integrative processes of stimulus elaboration and attention following stimulation of right hand (105). Tame, Braun (103) have demonstrated bilateral activation in both S1 and S2 regardless of which hand was stimulated, suggesting that these areas may be involved in integrating somatosensory input from both sides of the body. Some may attribute the involvement of ipsilateral S2 to a more cognitive role in sensory processing, and while it is important to consider the cognitive aspects of sensorimotor control, such as planning and strategy (106), bilateral S2 activation has been demonstrated in somatosensory studies regardless of the level of cognitive demand (18).

The involvement of S2 is particularly interesting in the context of aging, somatosensory dysfunction, and sensory rehabilitation. Age-related changes in activation have been seen, with decreased activation in S2 with tactile stimulation evident in elderly participants who are known to experience behavioral decline in somatosensory thresholds (54). The relationship of bilateral S2 with tactile sensation must also be considered in fields such as stroke research, where the location of the lesion has been demonstrated to impact both the type of somatosensory dysfunction (107), and also the ability to recover after stroke (108). Our finding of overlap in activation of right secondary somatosensory region for RH and LH tactile stimulation, may have particular relevance after stroke. For example,

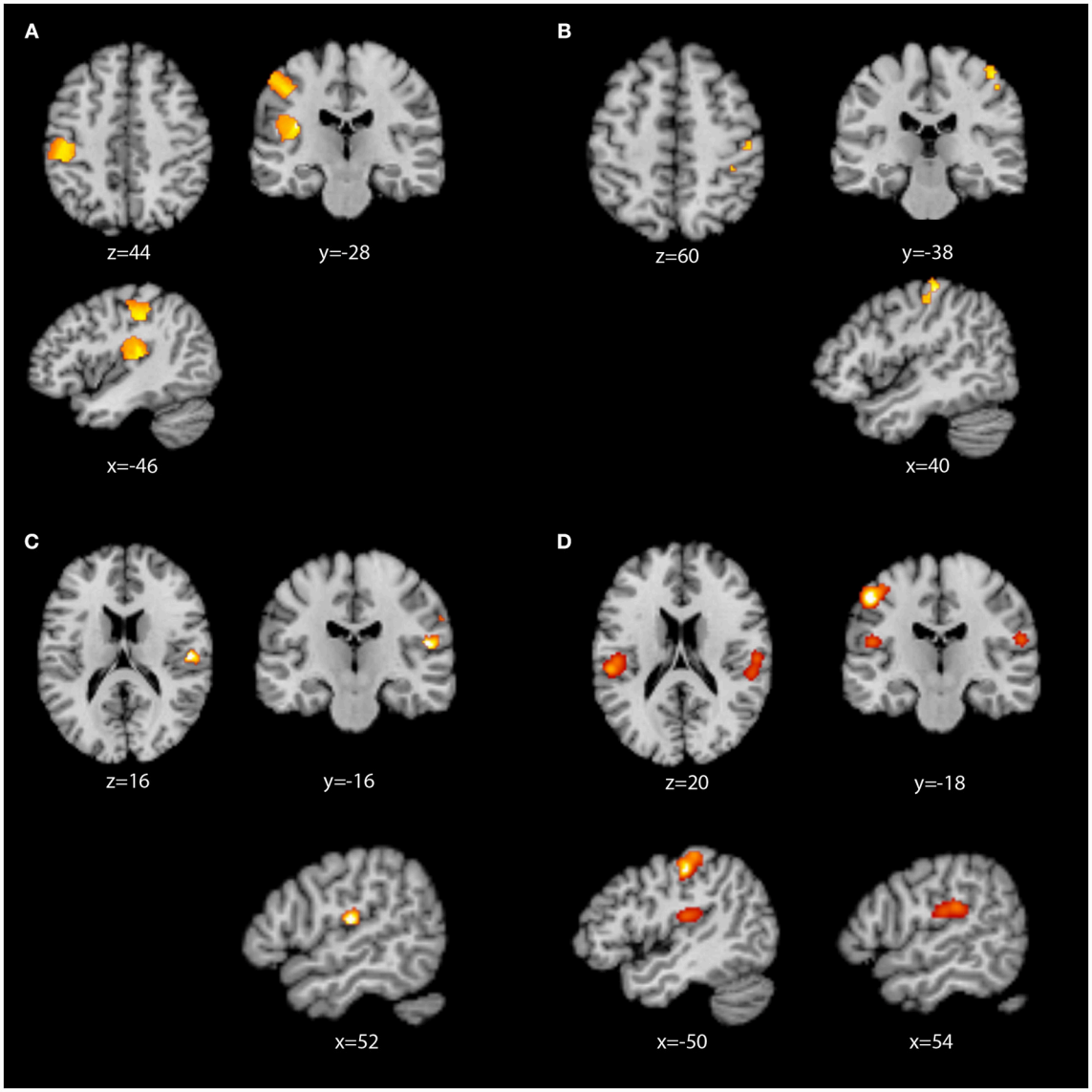

FIGURE 3 | ALE images displayed in neurological convention. **(A)** RH whole-brain activation greater than LH whole-brain activation; **(B)** LH whole-brain activation greater than RH whole-brain activation; **(C)** RH whole-brain conjoined with LH whole brain activation; **(D)** RH whole-brain conjoined with RH ROI activation.

a stroke survivor with an infarct in the right hemisphere affecting S2 might not only experience the typically expected impairment of sensation in the contralateral hand (i.e., LH), but also impairment in the ipsilateral right hand; as has been described clinically (2). Further, recent evidence of altered functional connectivity in stroke survivors with impaired touch sensation following left or right hemisphere lesions, highlighted increased laterality indices in ipsilateral (contralesional) S2 relative to healthy controls following lesion of either hemisphere (109). Further, functional connectivity research has demonstrated that an increase in connectivity from contralesional S2 to contralesional thalamus correlates with better somatosensory function 6-months post-stroke (110).

Evaluation of the RH ROI studies ($n = 12$) revealed that only contralateral (left) S1 and bilateral S2 were examined by studies which predefined the areas thought to be involved in somatosensory processing of the hand. In comparison, the RH whole-brain studies also revealed anterior cingulate activation, and much larger clusters were involved with tactile stimulation. This suggests that when researchers set out to examine the functional activation of a tactile stimulus, if they limit the focus to a-priori areas, this may not capture the entire neural functional process related to the sensation. Anterior cingulate activation may play a significant role in sensory processing. For example, pleasant human touch is represented in anterior cingulate cortex (111). In addition, while attention differentially modulates signal amplitudes in the human somatosensory cortex,

at higher intensities activation is also seen in the anterior cingulate cortex, consistent with attention to tactile stimuli in the current studies (112). It has been suggested that Von Economo (spindle) neurons found in cingulate cortex (113), and linked with insula, may have a role as part of a salience network (114). Network analyses identify anterior cingulate as a hub region and common co-activation of anterior cingulate and insula support the interpretation of a saliency network devoted to the integration of information from internal and external sensory environments (115). Further, interhemispheric connections between bilateral thalami occur via the anterior cingulate (113) and healthy controls show interhemispheric functional connectivity between a number of regions associated with somatosensory processing, including anterior cingulate (107), highlighting the contribution of both hemispheres and the broader somatosensory system. Interestingly, cingulate cortex has also been implicated in rats sensory recovery after lesions (116).

Other areas identified in this meta-analysis included inferior parietal lobe, insula, supramarginal gyrus and temporal lobe. Inferior parietal lobe (IPL) of the right hemisphere was identified for both RH whole-brain and ROI analyses. The location included OP1 and OP4. IPL has been associated with multi-modal sensory information integration (117, 118) and is reported to be part of the larger somatosensory network (119). The insula was also identified using the GingerALE peak maps, although this region was frequently assigned to the parietal operculum using the Anatomical toolbox. The insula has been identified as having a role in recognition, perception and learning in functional models of somatosensory processing (2). S2 is reciprocally connected with granular fields of the insula, reported to be devoted to somatic processing in monkeys (120). The close proximity of locations highlight the importance of the combined parietal opercular-insula region. Supramarginal gyrus is similarly located close to the parietal operculum/S2 region. The SMG is part of the somatosensory association cortex which has a role in interpretation of tactile sensory information as well as in perception of space and limbs location (121). Right SMG was found for RH whole-brain, RH ROI and LH whole-brain, and for the conjoined analyses. Right SMG is associated with spatial processing (121), consistent with tasks requiring localization of stimuli and/or involving spatial features of textures. Activation of left temporal gyrus, including auditory cortex and granular insula area 2, was greater in RH than LH whole-brain studies. Left temporal cortex has been linked with structural and semantic knowledge of body representation (122).

Each of the regions identified above have been implicated in stroke tactile impairment and recovery, potentially highlighting their broader importance. For example, change in functional connectivity from ipsilesional right S1 to right inferior parietal lobe was found in stroke survivors with impaired touch sensation compared to healthy controls (109). In addition, increased interhemispheric connectivity between the S2 region of interest and somatosensory association cortex (involving insula, parietal operculum and SMG) and temporal gyrus was found in healthy age-matched controls compared to stroke survivors with tactile deficits (109). Further, following tactile training, patients with lesions of sensory thalamus and/or internal capsule demonstrated activation in ipsiliesional insula, extending to the temporal pole, and supramarginal gyrus post-intervention (108). Interestingly, the regions identified have a role in the broader interpretation of tactile stimuli, including multi-modal integration, perception and learning, spatial processing and semantic knowledge and appear to be accessed as part of a wider somatosensory network.

There are limitations to this meta-analysis when examining the demographic information regarding the participants (see **Table 1**). Most of the LH studies (with the exception of one) included young participants (18–43 years). Aside from this, the cohorts were fairly well controlled, with the majority being RH dominant, and with tasks controlled for motor and other influences. Variable naming across studies can also contribute to confusion with interpretation. For example, terms such as secondary somatosensory cortex, secondary somatosensory region and secondary somatosensory area are often used interchangeably, although differences have been defined (10). To maximize accuracy and comparison across studies and broader literature in the field, we have reported on the MNI co-ordinates and peak location ALE results as well as the Anatomy Toolbox regional activation results.

The aim of this meta-analysis was to determine the convergence of foci reported from functional neuroimaging studies of touch sensation, separate to motor contributions and/or confounds. The findings advance our understanding of the separate, but potentially complementary, contributions of brain regions involved in processing touch sensation. Given the role of somatosensation and the somatosensory system in goal-directed actions of the upper limb and recovery after stroke, in depth knowledge of the role of key regions in the network is critical. The importance of bilateral S2 activation with right hand touch stimulation is highlighted, with a potential lateralization of activation in right S2 for right and left hand stimulation. This has implication for possible differences in unilateral vs. bilateral patterns of somatosensory impairment following right or left hemisphere lesion stroke. It may also identify a region with scope to contribute to recovery.

In conclusion, while research has established a role for S1 and S2 contralateral to the hand being stimulated (13, 14), this meta-analysis has demonstrated the need to also examine the bilateral activation in S2 with right hand stimulation in order to further delineate the role of this area in tactile processing. Additional studies examining LH tactile processing separate to the RH would be beneficial to further examine whether this same pattern of activation is seen. These two advances in understanding would in turn further research into somatosensory dysfunction and rehabilitation.

AUTHOR CONTRIBUTIONS

LC conceived the study. GL, LC, EL, and AB contributed to the design of the study. GL, SP, EL, and AB conducted the search and extraction of data. GL and PG conducted the meta-analysis. GL and LC interpreted the findings and drafted the manuscript. All authors critically reviewed and revised the manuscript for

important intellectual content, provided approval for publication and agree to be accountable for all aspects of the work.

FUNDING

We acknowledge financial support for conduct of the research from the James S. McDonnell Foundation 21st Century Science Initiative in Cognitive Rehabilitation - Collaborative Award (#220020413). We also acknowledge support from the National Health and Medical Research Council of Australia (NHMRC) Project grant (#1022694), Career Development Award (#307905) Centre of Research Excellence (#1077898) and Partnership grant (#1134495).

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Conflict of Interest Statement: The 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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 04 January 2019
doi: 10.3389/fneur.2018.01105

Short Intracortical Inhibition During Voluntary Movement Reveals Persistent Impairment Post-stroke

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Objective: Short intracortical inhibition (SICI) is a $GABA_A$-mediated phenomenon, argued to mediate selective muscle activation during coordinated motor activity. Markedly reduced SICI has been observed in the acute period following stroke and, based on findings in animal models, it has been posited this disinhibitory phenomenon may facilitate neural plasticity and contribute to early motor recovery. However, it remains unresolved whether SICI normalizes over time, as part of the natural course of stroke recovery. Whether intracortical inhibition contributes to motor recovery in chronic stroke also remains unclear. Notably, SICI is typically measured at rest, which may not fully reveal its role in motor control. Here we investigated SICI at rest and during voluntary motor activity to determine: (1) whether $GABA_A$-mediated inhibition recovers, and (2) how $GABA_A$-mediated inhibition is related to motor function, in the chronic phase post-stroke.

Methods: We studied 16 chronic stroke survivors (age: 64.6 ± 9.3 years; chronicity: 74.3 ± 52.9 months) and 12 age-matched healthy controls. We used paired-pulse transcranial magnetic stimulation (TMS) to induce SICI during three conditions: rest, submaximal grip, and performance of box-and-blocks. Upper-extremity Fugl-Meyer Assessment and Box-and-Blocks tests were used to evaluate motor impairment in stroke survivors and manual dexterity in all participants, respectively.

Results: At rest, SICI revealed no differences between ipsilesional and contralesional hemispheres of either cortical or subcortical stroke survivors, or healthy controls (P's $>$ 0.05). During box-and-blocks, however, ipsilesional hemisphere SICI was significantly reduced ($P = 0.025$), especially following cortical stroke ($P < 0.001$). SICI in the ipsilesional hemisphere during box-and-blocks task was significantly related to paretic hand dexterity ($r = 0.56$, $P = 0.039$) and motor impairment ($r = 0.56$, $P = 0.037$).

Conclusions: SICI during motor activity, but not rest, reveals persistent impairment in chronic stroke survivors indicating that inhibitory brain circuits responsible for motor coordination do not fully normalize as part of the natural history of stroke recovery. Observation that reduced SICI (i.e., disinhibition) is associated with greater motor impairment and worse dexterity in chronic hemiparetic individuals suggests the response considered to promote neuroplasticity and recovery in the acute phase could be maladaptive in the chronic phase post-stroke.

Keywords: $GABA_A$, inhibition, motor control, SICI, stroke

OPEN ACCESS

Edited by:
Martin Lotze,
University of Greifswald, Germany

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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *04 September 2018*
Accepted: *03 December 2018*
Published: *04 January 2019*

Citation:
Ding Q, Triggs WJ, Kamath SM and Patten C (2019) Short Intracortical Inhibition During Voluntary Movement Reveals Persistent Impairment Post-stroke. Front. Neurol. 9:1105. doi: 10.3389/fneur.2018.01105

INTRODUCTION

GABAergic inhibitory brain circuits are important to motor control (1–6). These inhibitory circuits are suggested to prevent co-activation of separate motor cortical regions in animal models (1) and are implicated in selective muscle activation during dexterous motor tasks in humans (1–6).

Paradoxically, reduced GABAergic activity, or disinhibition, is considered relevant to early motor recovery following stroke (7–10). This argument stems from observations in a mouse model of acute stroke that excessive $GABA_A$-mediated tonic inhibition is reduced by blockage of extrasynaptic $GABA_A$ receptors (11). Functional recovery of forelimb and hindlimb motor control is associated with this reduced inhibition (11). It is thus reasoned that disinhibition of $GABA_A$ activity enhances neuroplasticity and promotes functional reorganization of perilesional tissue contributing to functional recovery (12). As a result, reduced GABAergic activity, or disinhibition, is also believed to be relevant to early motor recovery following stroke in humans (7–10). However, due to differences in both the underlying biology and measurement of GABAergic activity, it remains unclear how well results from animals models can be generalized to humans.

The role of cortical disinhibition in the ipsilesional hemisphere (IH) becomes even less clear in the chronic phase post-stroke when an alternative motor network has become established (8, 13–15). Current views on stroke rehabilitation emphasize means to increase IH cortical excitability [i.e., non-invasive brain stimulation (NIBS)] in both acute and chronic stroke survivors with expectation this approach will improve upper limb motor function (16–20). Recent meta-analyses of NIBS clinical trials report unsatisfactory outcomes; while IH cortical excitability can be increased, it does not appear to be effectively translated to functional improvements in the paretic arm (21, 22). However, these studies focus on cortical excitability without consideration of the role of intracortical inhibitory circuits in motor control. Of note, Marconi et al. (14) found intervention-related improvements in motor function in chronic stroke survivors correspond with increased intracortical inhibition. Similar results have been reported by Liepert et al. (13). Together, these observations suggest enhancement of intracortical inhibitory activity in the chronic phase post-stroke may contribute to remodeling of the residual motor network (14) and promote motor recovery more effectively than a further loss of inhibition (13). Given limited evidence to support these suggestions, the role of intracortical inhibition in motor recovery in chronic stroke remains unclear.

Short intracortical inhibition (SICI), induced using paired-pulse transcranial magnetic stimulation (TMS), reflects activity of $GABA_A$-mediated inhibitory circuits (23–25). The literature suggests SICI is reduced in the IH acutely (i.e., within a month) post-stroke (7, 8, 10, 26), but may return to normal levels chronically (i.e., >6 months) (15, 27, 28). Beyond these fundamental observations, the current literature discussing SICI post-stroke lacks a common thread. For example, differences in the magnitude of IH SICI have been reported between cortical and subcortical stroke by some (13, 27) but not all (8, 10, 26, 28) investigators. Inconsistencies are also found in the relationship between paretic hand motor function and IH SICI. For example, Honaga et al. (28) reported that motor function and SICI were inversely related in chronic stroke survivors (i.e., lower-functioning individuals tend to show disinhibition), while Ferreiro de Andrade et al. (29) recently reported the opposite. Still other studies report no correlation between SICI and motor function in chronic stroke (8, 13, 27). The influence of lesion location on SICI is also unclear. For example, SICI has been found to be more disrupted in the early phase following cortical vs. subcortical stroke (27, 30). However, it has also been reported that lesion location does not influence IH $SICI_{rest}$ in chronic stroke (8, 10, 26, 28).

Such inconsistencies in detecting SICI may stem from multiple confounding factors. For one, SICI is usually measured at rest, particularly in stroke survivors. A few studies have measured SICI during motor preparation in stroke surviors (31, 32). However, since GABAergic circuits are implicated in motor function, SICI measured at rest ($SICI_{rest}$), or prior to movement, may not elicit the same phenomenon as SICI measured during production of motor activity ($SICI_{active}$). Another key factor, motor-evoked potential (MEP) size, is more variable at rest than during voluntary muscle contraction (33). To our knowledge, no published study has measured SICI during muscle contraction or motor activity (i.e., $SICI_{active}$) in stroke survivors.

Here we investigated the relationship between SICI and motor function in the chronic phase post-stroke to determine whether IH SICI is normalized as part of the natural history of recovery. We studied individuals with hyper-chronic stroke sequelae at rest and during active motor tasks to investigate: (1) whether SICI is normalized, (2) whether recovery of SICI differs between cortical and subcortical stroke survivors, and (3) the relationship of IH SICI during motor activity ($SICI_{active}$), relative to healthy controls. We anticipated IH $SICI_{active}$ would be reduced in stroke survivors, especially following cortical stroke. These results have potential implications for both understanding the process of motor recovery and identifying rehabilitation strategies to promote recovery following stroke.

METHODS

Subjects

We studied sixteen chronic stroke survivors and twelve age-matched healthy controls. Stroke survivors meeting the following criteria were included: (1) evidence of a single, monohemispheric stroke (with confirmatory neuroimaging) ≥6 months prior to enrollment with (2) nominal ability to form and release a power grip and transfer small objects as required by the Box and Blocks Test (BBT) (34). Healthy, age-matched adults

Abbreviations: AMT, active motor threshold; B&B, box & blocks task; BBT, box and blocks test; CH, contralesional hemisphere; FDI, first dorsal interosseus; IH, ipsilesional hemisphere; ISI, interstimulus interval; MEP, motor-evoked potential; MEP/EMG, the ratio of S2 MEP size over the mean prestimulus EMG activity; MoCA, Montreal cognitive assessment; MVC, maximal voluntary contraction; NIBS, Non-invasive Brain Stimulation; RMT, resting motor threshold; SICF, short intracortical facilitation; SICI, short intracortical inhibition; TMS, transcranial magnetic stimulation; UE FMA, upper-extremity component of the Fugl-Meyer Motor Function Assessment.

with no history of stroke or chronic neurological impairment were studied as reference control subjects. All participants were screened for eligibility to receive TMS (35) and excluded if: using medications that reduce seizure threshold; pregnant; or any implanted device or metal that might be affected by the magnetic field generated by TMS was present. Additional study exclusion criteria were: presence of cognitive impairment as defined by inability to comprehend and follow three step commands; corrected vision <20/20; or history of seizure disorder. Stroke survivors were classified as cortical or subcortical stroke if the lesions involved cortical areas in any vessel distribution or affected only subcortical areas, respectively. Demographic characteristics are reported in **Tables 1**, **2**.

All study procedures were approved by University of Florida Health Science Center Institutional Review Board (IRB-01) and carried out in conformity with the standards of the Declaration of Helsinki. Prior to enrollment all participants provided written informed consent.

Clinical Assessments

Motor impairment in stroke survivors was assessed using the upper extremity component of the Fugl-Meyer Motor Assessment (UE-FMA) (36) and the Modified Ashworth Scale (MAS) (37). All participants were assessed with the Edinburgh Handedness Inventory, to determine laterality (38), and the BBT (34), to assess manual dexterity. The Montreal Cognitive Assessment (MoCA) was also administered in all participants to characterize cognitive function (39).

Force Measurements

We tested maximal voluntary isometric power grip (MVC) in both hands of stroke survivors and the non-dominant hand of healthy controls. Custom grip dynamometers instrumented with capacitive load cells (iLoad Mini MFD-200 & DQ-1000A, Loadstar Sensors, Fremont, California) were used to measure isometric power grip force in the "standard" position (40) with real-time force feedback displayed on a television screen (Samsung, TruSurround HD, Dolby Digital, 48 inches). Three MVC trials were interspersed with rest intervals (2 min); the peak value was carried forward as MVC for each hand.

EMG Recordings

MEPs were collected by recording surface EMG from the first dorsal interosseus (FDI) using the Surface EMG for Non-Invasive Assessment of Muscles (SENIAM) guidelines for electrode placement (41). Participants were seated in a comfortable chair with the back and neck supported. EMG signals were sampled at 2 kHz using LabChart (Version 7 Pro, AD instruments, Colorado Springs, Colorado, U.S.A.) via a laboratory analog-to-digital interface (PowerLab 16/35, AD instruments, Colorado Springs, Colorado, U.S.A.). EMG data were written to disc for offline analysis.

Transcranial Magnetic Stimulation (TMS)

TMS was performed using two Magstim stimulators connected by a Bi-stim module (Magstim 200^2 & BiStim^2, The Magstim Company Ltd, Dyfed, Wales, UK). TMS was applied over primary motor cortex using a figure-of-eight-shaped coil (70 mm diameter) positioned tangentially 45° from midline to induce a posterior-anterior current in the target hemisphere. Participants were asked to rest while determining the optimal scalp position for eliciting maximal responses in contralateral FDI (i.e., "hotspot"). Resting motor threshold (RMT) was determined experimentally as the lowest stimulation intensity that produced MEPs ≥50 μV in >50% of consecutive stimulations (42) during rest, and active motor threshold (AMT) as the lowest stimulation intensity that produced MEPs ≥100 μV in >50% of consecutive stimulations while gripping at 10% MVC (43). Neuronavigation (BrainSight, Version 2, Rogue Research Inc., Montreal, Quebec, Canada, 2006) was used to maintain coil position over the hotspot and monitor its stability. Coil positioning error was controlled at <5 mm displacement and <3° relative to target. Stimulations were delivered at ≤0.1 Hz.

SICI was induced using paired-pulse TMS [i.e., conditioning (S1)—test (S2) stimuli delivered at a fixed interstimulus interval (ISI)]. During study parameterization, ISIs were tested (range 2–6 ms, 0.5 ms increments, randomized order) to identify the ISI producing maximal inhibition for each subject and hemisphere (44, 45). In the rest condition S1 was set at stimulator output equal to 80% RMT (23); during active motor tasks S1 was set at 70% AMT (46). S2 was adjusted across tasks to the stimulator intensity producing an MEP between 0.5 and 1 mV peak-to-peak during task performance (46).

We defined "SICI non-responders" for cases where $SICI_{rest}$ could not be induced using any ISI. Such atypical $SICI_{rest}$ (i.e., inability to induce inhibition) has been reported among older adults (47, 48), thus to eliminate this potential confounding factor, "SICI non-responders" were excluded from further analysis. This exclusion involved three healthy control participants, both hemispheres of one individual (subcortical) and the contralesional hemispheres (CH) of three stroke survivors (two cortical, one subcortical).

Task-Dependent SICI

SICI was induced in three motor conditions: at rest ($SICI_{rest}$), during submaximal grip ($SICI_{grip}$), and during box & blocks (B&B) ($SICI_{B\&B}$). At rest, the arm was positioned in 5–10° of shoulder flexion, 10–15° shoulder abduction, and 90° elbow flexion, with the forearm and wrist in neutral supported by an armrest. Participants were instructed to completely relax. EMG signals displayed on a computer screen were used to provide feedback and assist participants in keeping the arm and hand muscles quiet. During grip, participants produced constant submaximal (10% MVC) isometric power grip with force feedback displayed visually as a target zone (10 ± 2% MVC) within which the participant was instructed to maintain force. The standard arm position was maintained during gripping (40, 49) with an arm support. Prior to testing, participants practiced using visual feedback to maintain the force trace within the target zone. TMS was applied when the force trace was stable and maintained in the target zone. During SICI testing, participants gripped for up to 20 s; 3–4 stimulations were delivered during each trial. Note, the B&B task condition differs slightly from the BBT, referenced above, used for assessment of dexterity. During

TABLE 1 | Participants demographic and clinical characteristics.

	Age, years	Sex	Paretic side	Handedness (premorbid in stroke)	Months after stroke onset	FMA (0–66)	MAS (0–28)	BBT (P or ND arm)	MoCA (0–30)
	Mean ± *SD* (range)	**Male/Female**	**Right/Left**	**Right/Left**	**Mean ± *SD* (range)**	**Mean ± *SD* (range)**	**Mean ± *SD* (range)**	**Mean ± *SD* (range)**	**Mean ± *SD* (range)**
Cortical stroke ($n = 8$)	65.1 ± 11.1 (49–81)	7/1	5/3	8/0	88.3 ± 57.8 (6–170)	58.0 ± 10.1 (38–66)	3.8 ± 8.0 (0–23)	37.6 ± 11.4 (21–49)	24.8 ± 5.7 (16–30)
Subcortical stroke ($n = 8$)	62.6 ± 7.7 (53–77)	7/1	2/6	8/0	60.3 ± 46.9 (7–175)	55.6 ± 10.1 (38–66)	4.3 ± 7.4 (0–21)	33.8 ± 10.2 (16–47)	27.3 ± 3.6 (21–30)
Healthy controls ($n = 12$)	60.6 ± 8.8 (51–80)	7/5	n/a	12/0	n/a	n/a	n/a	51.2 ± 11.4 (31–75)	27.7 ± 2.5 (22–30)

UE FMA refers to upper-extremity component of the Fugl-Meyer Motor Function Assessment, indicating motor impairments in stroke survivors (36). MAS refers to modified Ashworth scale, indicating spasticity in stroke survivors (37). BBT refers to box and blocks test, measuring manual dexterity (34). MoCA refers to Montreal cognitive assessment. P arm refers to paretic arm in stroke survivors. ND arm refers to non-dominant arm in healthy controls. No differences in age were revealed between cortical, subcortical stroke and control groups. No difference in chronicity, UE FMA, MAS, BBT, or MoCA was revealed between cortical and subcortical stroke groups.

TABLE 2 | Participant characteristics.

Subject number	Age (years)	Sex	Paretic hand	Chronicity (mos)	Type of stroke	Lesion location	UE FMA
Stroke 01	53	M	R	28	Ischemic	Posterior internal capsule; subcortical	58
Stroke 02	64	M	R	170	Ischemic	Frontal lobe and posterior parietal lobe; cortical	49
Stroke 03	58	M	L	34	Ischemic	Temporal/parietal lobe; cortical	38
Stroke 04	77	M	L	34	Ischemic	Thalamus; subcortical	66
Stroke 05	62	M	L	150	Ischemic	Posterior internal capsule; subcortical	38
Stroke 06	63	F	L	93	Ischemic	Internal capsule; subcortical	66
Stroke 07	81	M	R	143	Hemorrhagic	Temporal/parietal lobe; cortical	66
Stroke 08	74	M	R	70	Ischemic	Parietal lobe and insula; cortical	58
Stroke 09	67	M	R	66	Hemorrhagic	Periventricular white matter, centrum semiovale; subcortical	62
Stroke 10	66	M	L	80	Ischemic	Putamen and periventricular white matter; subcortical	44
Stroke 11	59	M	L	24	Ischemic	Posterior internal capsule; subcortical	55
Stroke 12	70	F	L	47	Hemorrhagic	Parietal/temporal lobe; cortical	65
Stroke 13	54	M	L	7	Hemorrhagic	Putamen and periventricular white matter; subcortical	56
Stroke 14	49	M	L	127	Ischemic	Temporal/frontal/parietal lobe; cortical	66
Stroke 15	53	M	R	110	Ischemic	Frontal/temporal/parietal lobe; cortical	57
Stroke 16	72	M	R	6	Ischemic	Insular; cortical	65

UE FMA refers to upper-extremity component of the Fugl-Meyer Motor Function Assessment. M refers to male, and F refers to female. L refers to left, and R refers to right.

B&B, participants transferred blocks between halves of a divided box at their preferred pace. The box and blocks task involves repeated reach, grasp, transfer, and release of a standard object, thus is considered an assay of functional movement. Attainment of maximal thumb-index finger aperture during hand pre-shaping is recognized as an invariant characteristic of reach-to-grasp movements (50). Therefore, to assure all participants were stimulated at the same stage of movement, we applied TMS concurrently with acquisition of maximal finger-thumb aperture during the reach-to-grasp stage.

Experimental Procedures

All procedures were conducted in a single session. TMS testing was performed in both hemispheres in stroke survivors and the non-dominant hemisphere in healthy controls. SICI testing followed TMS parameterization to determine RMT, AMT, S2, and ISI. In stroke survivors, IH and CH were tested in random order. Task order was randomized by subject; within each task conditioned and unconditioned stimuli (20 each) were block randomized (four stimuli per block).

Data Analysis

Data Reduction

MEPs were analyzed offline using custom written Matlab scripts (MATLAB R2011b, The MathWorks, Natick, Massachusetts, U.S.A.). EMG data were demeaned, filtered (4th order Butterworth, 10–500 Hz), and signal averaged over 20 trials per condition. SICI was quantified by calculating 1 – the ratio of

conditioned MEP_{area}/unconditioned MEP_{area} (C/U ratio) where positive values indicate inhibition and negative values indicate disinhibition (51). EMG during the 100 ms period preceding the stimulus was analyzed offline to determine the magnitude of background EMG activity during muscle contraction (46). The ratio of S2 MEP size to background EMG activity (MEP/EMG) was also calculated.

Statistical Analysis

To address our primary question, whether IH SICI is normalized in chronic stroke, data analysis focused on IH SICI with participants grouped by lesion location (i.e., cortical, subcortical). Statistical analyses were performed using IBM SPSS Statistics 22 (SPSS Inc., Chicago, IL, USA). Data were found to meet the normality assumption using the Kolmogorov-Smirnov test.

For stroke survivors, mixed design [Hemisphere(2) × Task(3) × Lesion location(2)] ANOVA, with repeated measures on Hemisphere and Task, was used to analyze SICI and S2 MEP size. Background EMG and MEP/EMG were analyzed using similar mixed design [Hemisphere(2) × Task(2) × Lesion location(2)] ANOVA, with repeated measures on Hemisphere and Task. Subsequently, each hemisphere of stroke survivors was compared separately against the control group using mixed design [Group(2) × Task(3)] ANOVA with repeated measures on task. Within each hemisphere, comparisons were performed between cortical stroke, subcortical stroke, and controls using mixed design [Group(3) × Task(3)] ANOVA with repeated measures on task. All data met the Sphericity assumption, which was tested using Mauchly's test. Based on suggestions of current statistical literature, *post-hoc* comparisons, with Bonferroni correction for multiple comparisons, were conducted regardless of F-test results (52–55). Effect sizes (Cohen's d for two group comparisons, where Effect sizes = 0.2 are considered small, 0.5 medium, and ≥0.8 large; or Cohen's f for comparisons between more than two groups, where 0.1 is considered small, 0.25 medium and ≥0.4 large) (56) were also computed for all multiple comparisons.

RMT, AMT and ISI were each compared between hemispheres in stroke survivors using paired *t*-tests; each hemisphere was then compared with the control group using independent *t*-tests. Mixed design [Group(3) × Task(3)] ANOVA was used to analyze neuronavigation target errors in both hemispheres of stroke survivors and the control group, with repeated measures on task.

Pearson correlations were used to investigate the relationship between motor function scores and SICI, S2 MEP size, background EMG and MEP/EMG during each task. Statistical significance was established at $P < 0.05$.

RESULTS

Neuronavigation displacement and angle errors both fell within the target range (<3 mm and <5°). Displacement error was consistent between groups, hemispheres, and across tasks (*P*'s > 0.05). Angle error was somewhat greater during B&B compared to rest and grip (*P*'s < 0.02) without differences between groups or hemispheres (**Table 3**). No significant differences in RMT, AMT, or ISI were revealed between hemispheres or groups (*P*'s > 0.05).

TABLE 3 | Neuronavigation target error.

	Displacement error (mm)			Angle error (°)		
	Rest	Grip	B and B	Rest	Grip	B and B
IH	1.49 (±0.64)	1.48 (±0.51)	1.86 (±0.77)	2.64 (±1.40)	2.71 (±1.25)	3.76 (±1.51)*
CH	1.50 (±0.39)	1.59 (±0.38)	1.81 (±0.56)	2.59 (±1.07)	2.44 (±0.87)	3.36 (±1.52)*
Controls	1.37 (±0.89)	1.43 (±0.72)	1.56 (±0.63)	2.61 (±1.00)	2.43 (±1.02)	3.19 (±1.59)*

*Data presented are mean(±SD). *indicates significant between-task differences (P < 0.05). Displacement error was minimal (<3 mm) and consistent between groups, hemispheres and across tasks (P > 0.05). Angle error was somewhat greater during B and B compared to rest and grip (P's < 0.02), but within our targeted range (<5°); no group or hemisphere differences were revealed. CH, contralesional hemisphere; IH, ipsilesional hemisphere; B and B, box and blocks task.*

Group means for ISI, S2 MEP size, background EMG, and MEP/EMG are reported in **Table 4**. These three parameters were evaluated for significant differences across tasks to determine whether variations in general motor excitability or MEP size, specifically, influence SICI. Responses were generally consistent between hemispheres and groups across tasks. No significant differences were revealed between hemispheres, or between cortical stroke, subcortical stroke and healthy controls during any task (*P*'s > 0.05). Furthermore, in stroke survivors IH S2 MEP size, mean prestimulus EMG, and MEP/EMG during grip and B&B were not significantly correlated with clinical severity (e.g., UE FMA and BBT) (*P*'s > 0.05). These results indicate variations in background EMG or MEP size are not likely confounding factors contributing to differences in SICI across tasks.

SICI by Hemisphere

No significant differences were revealed between hemispheres in stroke survivors, or between the CH and controls in any task (*P*'s > 0.05). Comparison between the IH and the control group revealed significant main effects of Task [$F_{(2, 42)} = 3.86$, $P = 0.029$] and Group [$F_{(1, 21)} = 11.65$, $P = 0.003$] (**Figure 1**). Follow up comparisons revealed that during active tasks, SICI in the IH was lower than controls; this difference approached significance during grip ($P = 0.094$, $d = 0.76$) and reached significance during B&B ($P = 0.025$, $d = 1.09$). At rest, there was no significant difference in SICI between IH and controls ($P > 0.05$, $d = 0.46$). In addition, IH $SICI_{B\&B}$ was significantly reduced compared with $SICI_{rest}$ ($P = 0.028$, $d = 0.63$). In the control group, however, no differences in SICI were revealed across tasks ($P > 0.05$, $f = 0.39$). In the CH, although there was a significant main effect of Task ($F_{(2, 20)} = 3.91$, $P = 0.37$, $f = 0.62$), no significant differences in SICI across tasks were revealed in *post-hoc* comparisons (*P*'s > 0.05, *d*'s < 0.7) (**Figure 1**).

SICI by Lesion Location

Our primary analysis, comparison between IH of cortical and subcortical stroke and healthy controls (**Figure 2**), revealed

TABLE 4 | ISI, S2 MEP size, prestimulus EMG activities, and MEP/EMG ratio.

	ISI (ms)	S2 MEP size (μV)			Mean prestimulus EMG acitvity (μV)		MEP/EMG	
		Rest	Grip	B and B	Grip	B and B	Grip	B and B
IH	3.25 (±0.91)	557.87 (±487.36)	548.73 (±327.20)	636.35 (±4014.51)	36.99 (±27.71)	37.24 (±37.31)	26.67 (±25.90)	24.48 (±18.59)
CH	3.06 (±1.17)	587.36 (±383.36)	747.48 (±576.44)	561.53 (±349.91)	71.08 (±58.68)	34.09 (±13.66)	16.86 (±20.44)	17.33 (±9.78)
Controls	2.95 (±0.64)	555.92 (±390.23)	464.63 (±323.37)	775.18 (±294.60)	68.27 (±39.10)	27.42 (±7.42)	10.02 (±12.25)	26.69 (±10.49)

Data presented are mean (±SD). All parameters were generally consistent across hemispheres and groups in each task. ISI, interstimulus interval; MEP/EMG, the ratio of S2 MEP size to prestimulus EMG; CH, contralesional hemisphere; IH, ipsilesional hemisphere; B and B, box and blocks task.

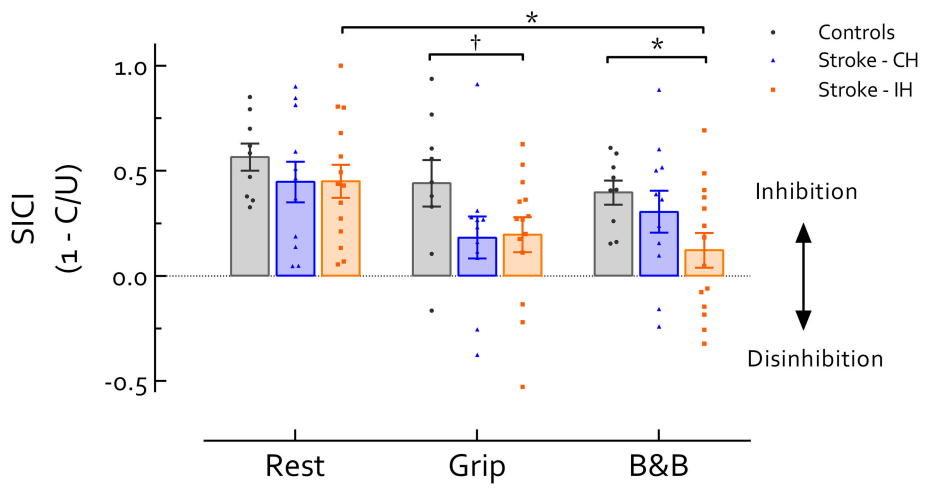

FIGURE 1 | Short intracortical inhibition (SICI) across tasks and hemispheres. Data presented are group mean ±SEM. * indicates significant differences ($P < 0.05$). † indicates differences approaching statistical significance ($P < 0.1$). No significant difference was revealed between IH and CH in stroke survivors. During grip and B and B, IH SICI was reduced compared with healthy controls ($P = 0.094$ during grip and 0.025 during B and B). Additionally, IH SICI was significantly reduced during B and B compared with rest ($P = 0.028$). In CH or healthy controls no difference in SICI was revealed across tasks. Of note, background EMG activity, S2 MEP size, and MEP/EMG were not significantly different between controls and Stroke IH during either grip or B and B, reducing likelihood that differences in motor excitability contribute to differences in SICI between controls and IH in stroke. CH, contralesional hemisphere; IH, ipsilesional hemisphere; B and B, box and blocks task; MEP, motor-evoked potential. MEP/EMG refers to the ratio of S2 (unconditioned) MEP size to mean prestimulus EMG activity.

main effects of Task [$F_{(2, 40)} = 5.19$, $P = 0.01$] and Group [$F_{(2, 20)} = 12.04$, $P < 0.001$]. Follow up comparisons revealed that SICI was significantly lower during grip and B&B in cortical stroke than controls (P's = 0.03 and 0.012, d's = 1.23 and 1.74, respectively); while at rest, no difference in SICI was revealed across groups ($P > 0.05$, $f = 0.23$). In cortical stroke, $SICI_{grip}$ ($P = 0.04$, $d = 0.77$) and $SICI_{B\&B}$ ($P = 0.017$, $d = 0.82$) were significantly reduced compared with $SICI_{rest}$. In subcortical stroke, no differences in SICI were revealed across tasks ($P > 0.05$, $f = 0.37$) (**Figure 2**).

Relationship Between Motor Performance and SICI

Paretic hand BBT scores were highly correlated with the UE-FMA in all stroke survivors ($r = 0.95$, $P < 0.0001$). Thus, due to the known ceiling effect of the FMA (57, 58), we used the BBT to evaluate stroke survivors and controls on the same continuum of motor function. Using data from stroke survivors' IH and healthy controls we found $SICI_{B\&B}$ was positively correlated with BBT score ($r = 0.57$, $P = 0.005$) (**Figure 3**). Within only stroke survivors, IH $SICI_{B\&B}$ was also positively correlated with paretic hand BBT score ($r = 0.56$, $P = 0.039$). When the stroke group was separated by lesion location, the intercept of this relationship was significantly higher in cortical than subcortical stroke ($P = 0.01$) (**Figure 4**). IH $SICI_{B\&B}$ was also positively correlated with FMA ($r = 0.56$, $P = 0.037$) (not illustrated). However, no significant correlations were revealed between IH $SICI_{rest}$ or $SICI_{grip}$ and behavioral parameters (i.e., paretic hand BBT score or FMA) and SICI in the CH or in healthy controls.

DISCUSSION

To our knowledge, this is the first study to measure SICI during motor activity in stroke survivors. Our primary findings are: (1) when measured at rest, IH SICI appears to be normalized in chronic stroke; but (2) when measured during motor activity, IH SICI is reduced, reflecting motor disinhibition, especially following cortical stroke or in the presence of severe motor impairment; (3) when S1 intensity is adjusted to induce

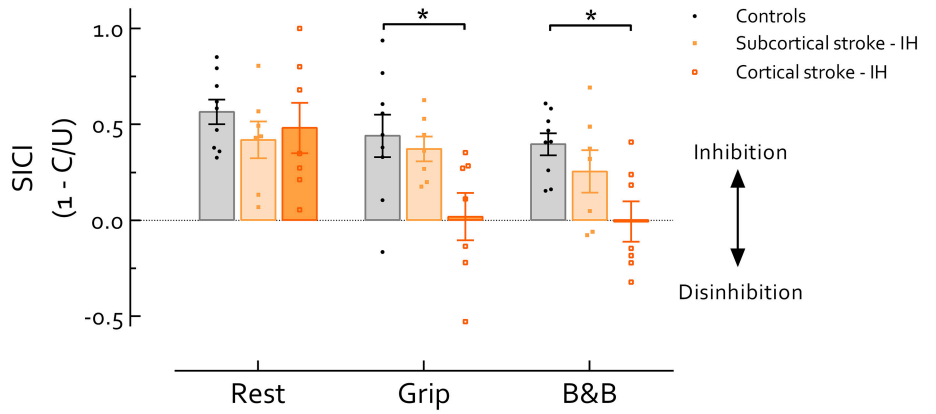

FIGURE 2 | Short intracortical inhibition (SICI) in the IH in stroke survivors and healthy controls. Data presented are group mean ±SEM. * indicates significant difference ($P < 0.05$). During grip and B and B, SICI was significantly reduced in cortical stroke compared with healthy controls (P's = 0.03 and 0.012, respectively). Across tasks, SICI in cortical stroke was significantly reduced during grip and B and B compared with rest (P's = 0.04 and 0.017, respectively). Of note, background EMG activity, S2 MEP size, and MEP/EMG were not significantly different among groups during either grip or B and B, reducing likelihood that differences in motor excitability contribute to group-differences in SICI. IH, ipsilesional hemisphere; B and B, box and blocks task; MEP, motor-evoked potential. MEP/EMG refers to the ratio of S2 (unconditioned) MEP size to mean prestimulus EMG activity.

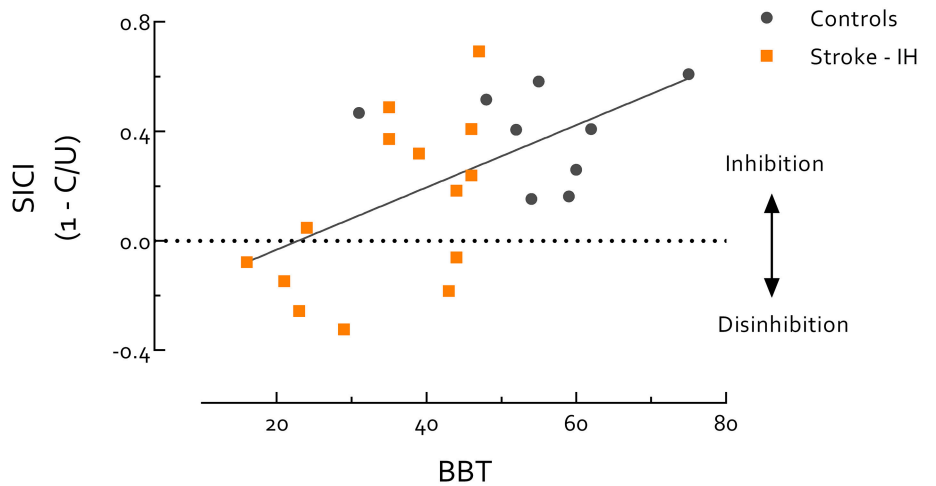

FIGURE 3 | Short intracortical inhibition (SICI) measured during box and blocks task (B and B) is significantly correlated with Box and Blocks Test (BBT) score. Correlation includes all participants, stroke survivors and healthy controls, and all participants were evaluated on the same continuum. Most healthy controls showed better performance in BBT than stroke survivors, but there is also a region of overlap in BBT between healthy controls and stroke survivors. Individuals with better motor performance (i.e., healthy controls or high-functioning stroke survivors) tend to have more SICI during B and B, while individuals with poor motor performance (i.e., low-functioning stroke survivors) tend to have reduced SICI in IH during B and B ($r = 0.57$, $P = 0.005$). This result indicates that SICI-related inhibitory circuits may play an active role in coordinated motor activity. Of note, background EMG activity, S2 MEP size, and MEP/EMG during B and B were not significantly correlated with BBT score, therefore do not contribute to the correlation between SICI and BBT score. IH, ipsilesional hemisphere; MEP, motor-evoked potential. MEP/EMG refers to the ratio of S2 (unconditioned) MEP size to mean prestimulus EMG activity.

maximal inhibition, $SICI_{rest}$ and $SICI_{active}$ are similar in healthy individuals.

SICI Measured at Rest

IH $SICI_{rest}$ Appears to be Normalized in Chronic Stroke

Consistent with previous studies reporting normalization of IH $SICI_{rest}$ by 6 months post-stroke (27, 28), we observed the magnitude of IH $SICI_{rest}$ was similar between age-matched healthy controls, cortical, and subcortical stroke survivors. Furthermore, no differences were revealed between cortical and subcortical stroke in $SICI_{rest}$.

CH $SICI_{rest}$ also appeared to be similar to healthy controls. Results regarding CH $SICI_{rest}$ in chronic stroke remain inconsistent in the current literature. Similar to our findings, Shimizu et al. (30) reported that CH SICI returns to normal within 6 months following both cortical and subcortical stroke. However, Honaga et al. (28) reported that CH SICI remains

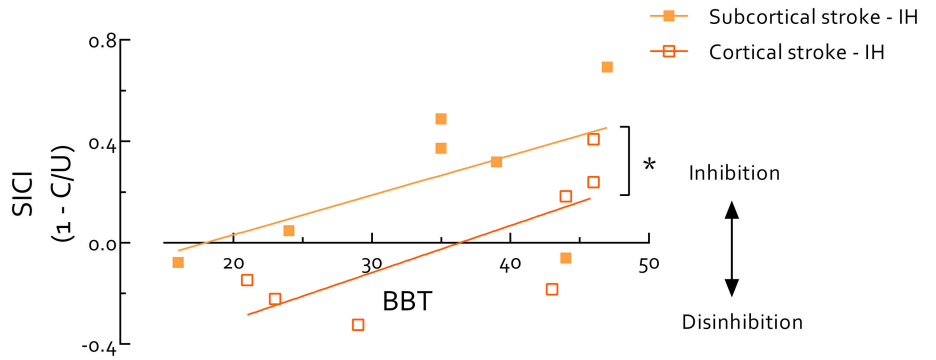

FIGURE 4 | Short intracortical inhibition (SICI) in ipsilesional hemisphere measured during performance of box and blocks (B and B) correlates with box and blocks test (BBT) score in the paretic hand in stroke survivors. *indicates significant difference ($P < 0.05$). Overall correlation reveals an association between SICI during movement and motor function ($r = 0.56$, $P = 0.039$). BBT scores span a similar range between cortical and subcortical stroke survivors, but the intercept is significantly lower ($P = 0.01$) in cortical stroke indicating systematically reduced SICI during B and B compared to subcortical stroke. Of note, background EMG activity, S2 MEP size, and MEP/EMG during B and B were not significantly correlated with BBT score, therefore do not contribute to the correlation between SICI and BBT score. IH, ipsilesional hemisphere; MEP, motor-evoked potential. MEP/EMG refers to the ratio of S2 (unconditioned) MEP size to mean prestimulus EMG activity.

reduced 6 months following cortical, but returns to normal following subcortical stroke. Dissimilarities between Honaga et al.'s (28) results and ours may stem from differences in chronicity of stroke survivors studied [~2 years (28) vs. ~6 years, present study]. It is possible that if CH $SICI_{rest}$ is normalized, it may occur over a wider time span following stroke than previously suggested.

Confounding Influences on SICI, Measured at Rest

While we observed "SICI non-responders" in both stroke and control groups, it remains unclear whether absence of SICI reflects the range of normal physiological variation or represents a pathological phenomenon (47, 48). Important to the current study, however, inability to induce $SICI_{rest}$ may influence the function of SICI-related inhibitory circuits during motor activity, making it difficult to compare $SICI_{active}$ between "SICI non-responders" and individuals exhibiting normal $SICI_{rest}$. Therefore, we excluded the hemispheres (28, 32, 59) in which we were unable to induce $SICI_{rest}$ at any ISI. Factors influencing the magnitude and presence of $SICI_{rest}$ are complex and explanation for occurrence of four "SICI non-responders" among the larger sample is beyond the scope of the present study. However, methods to induce SICI were consistent across all participants, suggesting individual physiologic differences contribute to the phenomenon of "SICI non-responders."

Variability in MEP size influences the presence and magnitude of SICI (60) and is much higher at rest than during voluntary muscle contraction (33) likely reflecting a fluctuating physiological state at rest (61). MEP size, and by extension SICI, are influenced by many physiological factors including: attention (62), speech (61), motor imagery (63–66) and movement observation (67–69), which are difficult to control when measuring neurophysiological responses at rest. Recognized inconsistencies in the existing SICI literature may stem from increased variability when SICI is measured at rest. Measuring SICI during controlled motor activity may stabilize the level of background neural drive across individuals, thereby reducing variability in SICI, and improving the likelihood of detecting genuine group or task differences.

While previous studies have suggested that IH SICI returns to normal in the chronic phase of stroke recovery (27, 28), this conclusion is based on studies in which SICI was measured at rest. Such results contribute to the impression that GABAergic inhibitory circuit function is ultimately normalized after stroke. However, since GABAergic inhibitory circuits have been found to contribute to selective muscle activation during coordinated motor tasks (2–5), SICI evoked at rest may not be the optimal methodology to assess functional recovery of this inhibitory network in chronic stroke.

SICI During Motor Activity

Compared with healthy controls, IH $SICI_{active}$ was reduced in chronic stroke. Importantly, S2 MEP size and background EMG during motor tasks were similar across groups, thus are unlikely to contribute to this group difference in SICI. Additionally, we found reduced IH $SICI_{active}$ revealed significant influences of lesion location and motor function.

Lesion Location

Whether lesion location influences IH $SICI_{rest}$ remains controversial. We found both IH $SICI_{grip}$ and $SICI_{B\&B}$ were reduced in chronic stroke compared with healthy controls, especially following cortical stroke. Because SICI is suggested to be of cortical origin (23), it is reasonable to speculate that SICI-related inhibitory circuits are more likely to be disrupted in cortical than subcortical stroke. Indeed, it has been reported that SICI is more affected in the early phase following cortical vs. subcortical stroke (27, 30), but it has also been reported that lesion location does not influence IH $SICI_{rest}$ more than 1 month post-stroke (8, 10, 26, 28). In the chronic phase however, differences between cortical and subcortical stroke are less clear, particularly whether and how GABAergic inhibitory circuits are normalized over time and how they function during motor

activity. Activity of SICI-related circuits is argued to prevent unwanted muscle activation (2, 3) contributing to production of fractionated activity in intrinsic hand muscles (4–6). Therefore, greater activity in these circuits can be expected during both precision grip and B&B tasks. Although lesion location may not influence $SICI_{rest}$ in the chronic phase following stroke, it appears to influence $SICI_{active}$.

During grip, participants were asked to produce and maintain a stable, submaximal force level with visual feedback. SICI-related inhibitory circuits may contribute to this type of motor activity by inhibiting excessive muscle activation. During B&B, TMS was delivered concurrently with achieving maximal finger-thumb aperture prior to grasping a block. At this point in movement preparation, the velocity and direction of finger movements are carefully controlled, thus likely involve inhibitory activity to coordinate finger movements. Our observation of reduced $SICI_{active}$ in cortical stroke suggests dysfunction of inhibitory GABA circuits during this coordinated motor activity. Although apparently normal at rest, our findings indicate the function of inhibitory GABAergic circuits may not be fully recovered following stroke, especially following cortical stroke.

Motor Function

Across all participants, our results revealed a positive correlation between $SICI_{B\&B}$ and motor function scores, implicating $SICI_{B\&B}$ as a functional correlate of motor performance. In lower-functioning stroke survivors, $SICI_{B\&B}$ is markedly reduced, or wholly deficient. Of note, no significant correlation was revealed between motor function and $SICI_{rest}$ or $SICI_{grip}$. There are two possible explanations for the correlation between paretic arm motor function and $SICI_{B\&B}$: greater impairment of SICI-related brain circuits in lower-functioning individuals, or differences in the relative muscle contraction level during B&B.

Relative contraction level

Relative contraction level is an important consideration when measuring $SICI_{active}$ and a possible explanation for reduced $SICI_{B\&B}$ observed in low functioning individuals. While the absolute force requirement of B&B is constant and the grip force required for lifting a light object should be similar for stroke survivors and healthy adults (70), it is possible that a higher relative muscle contraction level was required during B&B in low-functioning individuals. The importance of this distinction is that SICI tends to be decreased at contraction levels >10% MVC (46) due to: reduced GABAergic inhibition, superimposition of concurrent facilitation from increased spinal motoneuron excitability (46, 71), or recruitment of short intracortical facilitation (SICF) (46), leading to less net inhibition. The confounding influence of SICF can be eliminated by setting S1 at 70% AMT (46) as was done in the current study. Increased spinal motoneuron excitability, as occurs with higher background contraction force, causes I-wave facilitation (72), specifically observed as increased I1 and reduced I3 contributions to MEPs (71, 72). During higher level muscle contraction (>10–15% MVC) later I-waves (i.e., I3) are not required to generate a test MEP size of 1 mV (46, 71, 72). Importantly, SICI acts mainly on the I3 wave with little influence on the I1 wave (71, 73, 74). Thus, less SICI is observed at higher contraction levels because there are fewer I3 waves to suppress (46).

Additionally, it has been suggested that when S1 = 70% AMT, low level muscle contraction (i.e., 0–10% MVC) does not influence SICI (46). The mass of each wooden block is ∼10 g (∼0.1 N) translating to a minimum grip force requirement of ∼0.1 N. The magnitude of safety margin for lifting a light object is considered to be similar between stroke and healthy adults (70). Therefore, although not directly measured here, grip force is usually low (0.5–1 N) when grasping and lifting a small wooden block (70, 75, 76), well <10% MVC in most, if not all, participants studied here. Furthermore, our results revealed no significant correlations between motor function and S2 MEP size, background EMG, or MEP/EMG during B&B. Taken together, it is unlikely that SICI was strongly influenced by the relative contraction levels during B&B. Therefore, our observed correlation between $SICI_{B\&B}$ and motor function is more likely due to impaired GABAergic inhibition in lower-functioning individuals.

Effects of motor impairment

As mentioned above, while $SICI_{active}$ has not been measured in stroke survivors, correlations between $SICI_{rest}$ and motor impairment post-stroke have been previously investigated producing conflicting results (13, 28, 29). Honaga et al. (28) observed that chronic stroke survivors who exhibit more $SICI_{rest}$ (i.e., more inhibition) tend to have better paretic arm motor function. Recently, Ferreiro de Andrade et al. (29) reported an opposite correlation, while still other studies report no correlation between SICI and motor function in chronic stroke survivors (8, 13, 27). Such inconsistent results may indicate that $SICI_{rest}$ does not accurately reflect the function of GABAergic inhibitory circuits as they relate to motor control. Similarly, our $SICI_{rest}$ results did not differentiate between control and stroke, or between high and low functioning stroke survivors. In contrast, $SICI_{active}$ clearly differentiated between healthy controls and stroke survivors. While maintenance of stable, low level grip force may involve activity of GABAergic inhibitory circuits, power grip itself does not require individuated finger movements or place high demands on selective muscle activation. Consistent with this premise, our data show that $SICI_{grip}$ was generally similar across stroke survivors, regardless of functional level. The B&B task, however, involves manual dexterity and finger coordination, arguably the types of movements in which GABAergic inhibitory circuits are actively involved. The robust association demonstrated between motor function scores and $SICI_{B\&B}$, included all participants—healthy and stroke regardless of lesion location—strongly suggesting both a role of $GABA_A$-mediated inhibition in motor control and a functional consequence of deficient SICI in low functioning stroke survivors.

SICI Across Tasks With Adjusted Conditioning Stimulus

We adjusted conditioning stimulus (i.e., S1) intensity between rest and active motor tasks to induce maximal SICI in each condition (4, 23, 46, 77–79). Our results contrast with most

other studies that use the same S1 intensity across tasks and show reduced SICI during muscle contraction compared with rest (4, 77–79). Instead, our results reveal similar $SICI_{rest}$ and $SICI_{active}$ in healthy adults.

It is well-recognized that the magnitude of SICI depends critically on S1 intensity (23, 42, 46, 80, 81). Variation of S1 intensity at a given S2 intensity typically reveals a *U*-shaped relationship in SICI magnitude (23, 42, 80, 81) (**Figure 5**) with the lowest point of this U-curve ascribed to increasing recruitment of inhibitory interneurons that contribute to SICI (81). While the mechanism responsible for the high end of this curve is less clear, it has been suggested that SICF-related brain circuits are recruited and superimpose with inhibition thus reducing SICI magnitude (24, 42, 81). S1 intensity has also been reported to have differential influences on $SICI_{rest}$ and $SICI_{active}$ (46, 82), producing different *U*-shaped curves between resting and active muscle contraction. At rest, the S1 intensity which induces maximal inhibition falls around 80% RMT (or 100% AMT) (23, 25, 46, 80, 81); but during muscle contraction, this curve is left-shifted with the low point falling at 70% AMT (46) (**Figure 5**). Our goal in the present study was to induce maximal SICI in each task which motivated the decision to vary S1 intensity between 80% RMT for the resting condition and 70% AMT during active motor tasks.

To our knowledge, maximal SICI—at the putative low point of the U-curves—has not previously been reported. Using this method, we observed no differences between $SICI_{rest}$ and $SICI_{active}$ in healthy individuals. This is a novel finding suggesting that maximal SICI is similar whether induced at rest or during motor activity. We acknowledge that most other studies use the same absolute S1 intensity during both rest and active muscle contraction and, consistent with Ortu et al. (46), report reduced $SICI_{active}$ compared with $SICI_{rest}$. Due to this methodological difference, it is not possible to directly compare modulation of SICI across tasks between ours and other studies. However, we posit that our experimental approach maximally engages GABAergic inhibitory circuits in each condition, revealing reduced $SICI_{active}$ in the IH even in the hyper-chronic stage post-stroke. Because only one S1 intensity was tested in each task it remains unclear whether a horizontal or vertical shift in the U-curve caused the reduction in IH $SICI_{active}$ post-stroke; further studies are needed to answer this question. Regardless, our data contrast with the literature suggesting that SICI normalizes as part of the natural history of motor recovery. Deficits in the function of inhibitory circuits remain in chronic stroke and likely affect task-dependent regulation of motor circuits during active task performance.

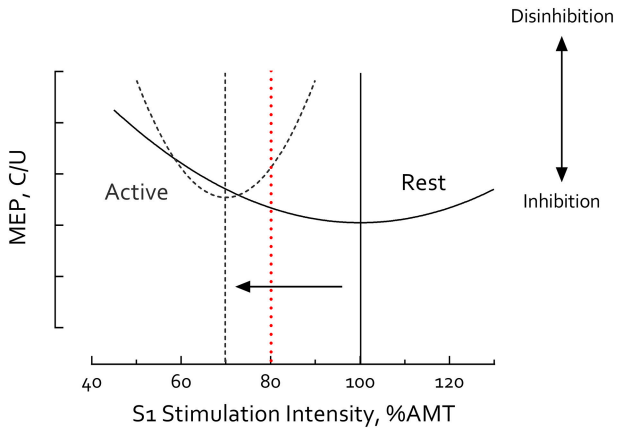

FIGURE 5 | S1 Intensity-Short intracortical inhibition (SICI) relationship differs between rest and motor activity. Illustrative curves constructed using results compiled from published data obtained in healthy adults (23, 46, 80, 81). S1 Intensity-SICI curve is left-shifted during motor activity (dashed line) compared to rest (solid line). Vertical lines mark the minima of each curve. At rest, the low point of the U-shaped curve (i.e., the S1 intensity inducing maximal inhibition) falls ∼100% active motor threshold (AMT) or 80% resting motor threshold (RMT) (23, 25, 46, 80, 81); but during muscle contraction, the curve is left-shifted with the low point falling ∼70% AMT (arrow) (46). Using S1 = 80% RMT at rest and 70% AMT during active tasks the current study revealed no significant differences between $SICI_{rest}$ and $SICI_{active}$ in healthy controls suggesting these parameters induced maximal SICI in both conditions. Other studies have used the same S1 intensity (≥80% AMT) in both rest and active conditions (e.g., 80% AMT, red dashed line) (4, 77–79). In such cases, observation of reduced SICI during muscle contraction is not surprising, due to comparisons at different points of the resting and active S1-SICI curves. MEP, motor-evoked potential. C/U refers to conditioned MEP/unconditioned MEP. Greater C/U ratio indicates less SICI and disinhibition.

Clinical Implications

Observation in animal models that blockage of extrasynaptic $GABA_A$ receptors is related to increased cortical plasticity and functional recovery acutely following stroke (11) contributes to expectation that a similar reduction in GABAergic inhibition is critical to motor recovery in the early phase post-stroke in humans (7–10). As a result current views on stroke rehabilitation emphasize means to increase IH cortical excitability (i.e., NIBS, intensive paretic limb rehabilitation, etc.) in both acute and chronic stroke survivors (16–19). Effects of these rehabilitative interventions are, however, limited. Furthermore, only a sub-set of stroke survivors are able to benefit (21, 22).

Our findings implicate an important role for GABAergic intracortical inhibition in motor recovery, at least in the chronic phase post-stroke, and may explain why therapeutically increasing IH cortical excitability regardless of individual's baseline neurophysiological state does not always contribute to a beneficial functional outcome. Demonstration of a relationship between net cortical excitability and strength (83, 84) contributes to the ostensible premise that increased IH cortical excitability may be related to strength improvement following stroke (85, 86). However, performance of dexterous motor tasks requires activity of intracortical inhibitory circuits to gate, or shape, motor excitability in response to task demands. As a result, increased cortical excitability alone cannot be expected to improve dexterous motor function.

Despite findings in the extant literature (2–6, 13, 14), the importance of intracortical inhibitory circuits to motor recovery post-stroke remains under-appreciated in neurorehabilitation. This oversight is possibly due to the belief that SICI is normalized during the natural course of stroke recovery and therefore is not associated with motor function in chronic stroke survivors. Our results suggest that inconsistencies in the current SICI literature in stroke survivors likely result from insensitivity of $SICI_{rest}$, and furthermore that $SICI_{active}$ is more sensitive for

revealing motor impairment post-stroke. By measuring maximal SICI during motor activities, our results reveal that activity of GABAergic brain circuits is not normalized, even in the hyper-chronic phase following stroke. Moreover, reduced GABAergic activity (e.g., disinhibition) in stroke survivors negatively impacts motor function. Inhibitory circuit function may therefore serve as a physiological biomarker of unfulfilled motor recovery in the chronic phase post-stroke.

Limitations

We acknowledge limitations of the present study. Stimulations were delivered manually during B&B, at the point of maximum finger-thumb aperture during grasp preparation. In future work, an instrumented device to trigger stimulations in conjunction with a movement event could improve experimental consistency. While muscle fatigue may influence SICI (87, 88), tasks were tested in randomized order, therefore differences across tasks observed here are unlikely to result from fatigue. The sample size in this study is relatively small, but this limitation is mitigated somewhat by normal distribution of data and large effect sizes. We recommend future studies involve a larger number of stroke survivors in various phases of stroke recovery to confirm and extend our findings.

Conclusion

In conclusion, this is the first study to measure $SICI_{active}$ in stroke survivors. Although differences in $SICI_{rest}$ were not revealed between chronic stroke survivors and healthy controls, IH $SICI_{active}$ was reduced post-stroke and IH $SICI_{B\&B}$ was significantly associated with paretic arm motor function. Taken together, our results suggest that the functionality of GABAergic inhibitory networks remains altered, even in the chronic phase post-stroke, and may impede execution of dexterous motor tasks.

DATA AVAILABILITY STATEMENT

The datasets generated and analyzed for this study are available by request from the corresponding author.

AUTHOR CONTRIBUTIONS

CP and WT designed the experiment. SK, QD, and CP conducted the experiments. QD and SK reduced and analyzed data. QD, CP, and WT interpreted the data. QD, CP, WT, and SK wrote the manuscript.

FUNDING

VA Rehabilitation Research & Development—Research Career Scientist Award (F7823S, Patten), VA Brain Rehabilitation Research Center of Excellence (B6793C). University of Florida Graduate School Fellowships (QD, SK).

ACKNOWLEDGMENTS

We thank Emily Maltby, Anjanie Pandey for assisting with data collection.

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Conflict of Interest Statement: The 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.

frontiers in Neurology

REVIEW
published: 11 December 2018
doi: 10.3389/fneur.2018.01082

Arm Ability Training (AAT) Promotes Dexterity Recovery After a Stroke—a Review of Its Design, Clinical Effectiveness, and the Neurobiology of the Actions

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Arm Ability Training (AAT) has been specifically designed to promote manual dexterity recovery for stroke patients who have mild to moderate arm paresis. The motor control problems that these patients suffer from relate to a lack of efficiency in terms of the sensorimotor integration needed for dexterity. Various sensorimotor arm and hand abilities such as speed of selective movements, the capacity to make precise goal-directed arm movements, coordinated visually guided movements, steadiness, and finger dexterity all contribute to our "dexterity" in daily life. All these abilities are deficient in stroke patients who have mild to moderate paresis causing focal disability. The AAT explicitly and repetitively trains all these sensorimotor abilities at the individual's performance limit with eight different tasks; it further implements various task difficulty levels and integrates augmented feedback in the form of intermittent knowledge of results. The evidence from two randomized controlled trials indicates the clinical effectiveness of the AAT with regard to the promotion of "dexterity" recovery and the reduction of focal disability in stroke patients with mild to moderate arm paresis. In addition, the effects have been shown to be superior to time-equivalent "best conventional therapy." Further, studies in healthy subjects showed that the AAT induced substantial sensorimotor learning. The observed learning dynamics indicate that different underlying sensorimotor arm and hand abilities are trained. Capacities strengthened by the training can, in part, be used by both arms. Non-invasive brain stimulation experiments and functional magnetic resonance imaging data documented that at an early stage in the training cortical sensorimotor network areas are involved in learning induced by the AAT, yet differentially for the tasks trained. With prolonged training over 2 to 3 weeks, subcortical structures seem to take over. While behavioral similarities in training responses have been observed in healthy volunteers and patients, training-induced functional re-organization in survivors of a subcortical stroke uniquely involved the ipsilesional premotor cortex as an adaptive recruitment of this secondary motor area. Thus, training-induced plasticity in healthy and brain-damaged subjects are not necessarily the same.

Keywords: stroke, arm, training, rehabilitation, plasticity

OPEN ACCESS

Edited by:
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Reviewed by:
Bruce H. Dobkin, University of California, Los Angeles, United States
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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *19 September 2018*
Accepted: *27 November 2018*
Published: *11 December 2018*

Citation:
Platz T and Lotze M (2018) Arm Ability Training (AAT) Promotes Dexterity Recovery After a Stroke—a Review of Its Design, Clinical Effectiveness, and the Neurobiology of the Actions. Front. Neurol. 9:1082. doi: 10.3389/fneur.2018.01082

MOTOR DEFICITS OF STROKE SURVIVORS WITH MILD TO MODERATE ARM PARESIS

Arm paresis post stroke shows a bi-modal distribution. Many stroke survivors have either severe arm paresis and are only able to use their arms functionally in everyday life to a very limited extent, if at all, or mild to moderate arm paresis with the ability to use their paretic arm for functional tasks, yet with a lack of dexterity (1, 2). Thus, the motor control deficits of these subgroups are quite different and hence so too are their therapeutic needs.

Clinically, stroke survivors with mild to moderate arm paresis have reduced strength and endurance of their paretic arm and are functionally limited by a lack of speed, accuracy and co-ordination of arm, hand, and finger movements and a lack of dexterity when handling objects. Key to understanding any functional deficits and the need and opportunities to improve function by training is a focused analysis of the specific motor control deficits involved in this clinical syndrome. A way to do this is to test various domains of sensorimotor control that have been shown to be independent by factorial analysis (3, 4).

When motor performance of healthy people across various tasks has been analyzed by factorial analysis certain independent arm motor abilities have been documented. These are different independent sensorimotor capacities that together contribute to our skilfulness in everyday life. What are these abilities? They are our ability to make fast selective wrist and finger movements (wrist-finger speed), to manipulate small objects (finger dexterity) or larger objects (manual dexterity) efficiently, our ability to keep our arm steady (steadiness), to move our arm quickly and precisely to an intended target (aiming), or to move it under constant visual control along a line (tracking) (5).

When tested among stroke survivors with mild to moderate arm paresis all these abilities are deficient, indicating the complex nature of sensorimotor control deficits in this clinical condition (6, 7).

THE ARM ABILITY TRAINING AS A "TAILOR-MADE TRAINING" TO MEET SPECIFIC REHABILITATION DEMANDS

The Arm Ability Training (AAT) was designed to train all these sensorimotor abilities and thus to meet the specific rehabilitation demands of this subgroup of stroke survivors (8, 9). The eight training tasks collectively cover these affordances (**Figure 1**).

Other factors thought to enhance motor learning were incorporated in the design of the AAT (5):

Repetition: The training has a highly repetitive structure. It has long been known that the establishment of motor skills needs repetition-mediated practice (10).

Variability-of-practice: The different training tasks are each constructed to have a varying task difficulty. Thus, the brain needs to generate and regulate variation in motor control across and within the training tasks, which together with the repeated structure and the explicit intention to improve performance promotes motor learning (11).

Focus of attention, type and distribution of augmented feedback: During the training, patients are encouraged to continuously improve their speed and accuracy, i.e., their performance (as opposed to patterns of joint motion); to promote this emphasis they receive verbal instructions and are intermittently given their results during training sessions (8). This strategy helps focus the attention on the behavioral task as opposed to the movement pattern, and also focuses on the training goal, which is to not only repeat training tasks, but also to improve performance (12).

Overall, the training addresses the motor control deficits both in a targeted way and comprehensively, i.e., across abilities, and does so with a training structure that supports motor learning. Neuroscience knowledge about the specific motor control deficits which characterize this clinical syndrome is thus embedded in the training structure and combined with a high "density" of othertraining aspects that support motor learning and recovery of sensorimotor control for stroke survivors with mild to moderate arm paresis.

A practical description of the AAT has been provided in Platz (13).

CLINICAL EFFECTIVENESS OF THE ARM ABILITY TRAINING

The clinical effectiveness has been tested with two single-blind randomized controlled studies (RCT) (8, 14), one being a multi-center study (14). In addition, the data have been synthesized for stroke survivors in an individual patient data meta-analysis (15).

The first RCT tested the efficacy of the AAT with a sample of traumatic brain injury (TBI) and stroke patients with arm paresis (8). Seventy-four patients were enrolled, 60 (45 stroke patients, 15 with TBI) completed the study; 37 patients were available for an additional 1-year follow-up. During a 3-week intervention period participants received either no AAT ($n = 20$), AAT without knowledge of results ($n = 20$), or AAT with knowledge of results ($n = 20$). The time needed for tasks resembling the arm activities in daily life (Test Evaluant les Membres superieurs des Personnes Agees, TEMPA) (16) and a kinematic analysis of aimed movements were the main outcome measures. After the period of training, the improvement rates were greater among patients who had received the AAT compared to the controls. The mean change score for all TEMPA tasks was 41.4 vs. 12.8 s ($p = 0.0012$), for unilateral TEMPA tasks 16.5 vs. 4.2 seconds ($p = 0.0036$); and for the ballistic component of aimed movements 96 vs. 20 ms ($p = 0.0115$). Whether the AAT was performed with or without knowledge of results had no discernable effect. At the 1-year follow-up there was still an advantage for those who had previously received the AAT. This RCT therefore documented that the AAT provided as "add-on" therapy reduced focal disability associated with mild central arm paresis after TBI and stroke (with a long-term effect).

Further, a multi-center RCT compared the effects of (a.) passive arm and hand splinting with active arm motor training

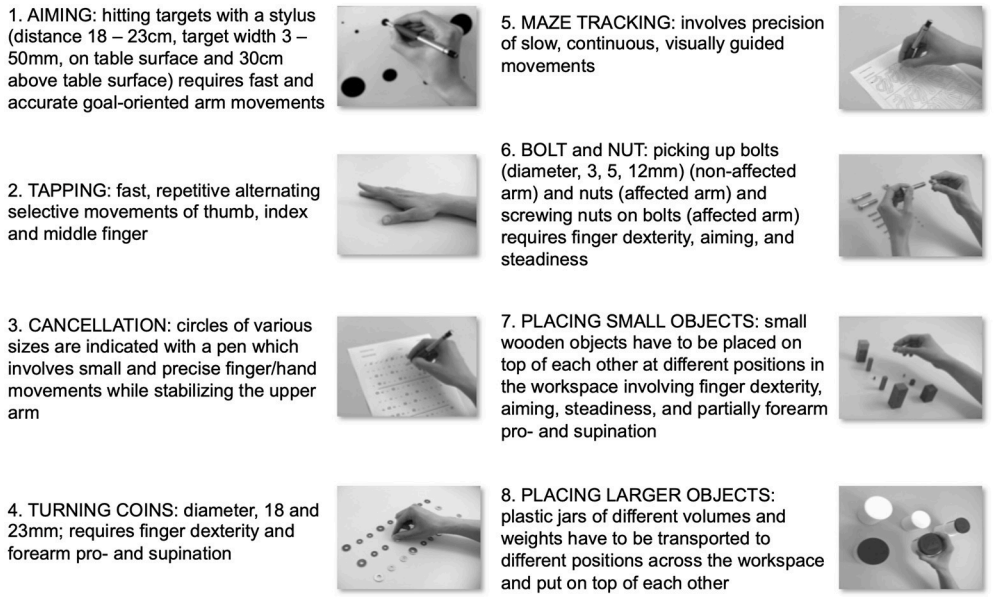

FIGURE 1 | Training tasks of the Arm Ability Training. Description of the eight training tasks of the Arm Ability Training (AAT) that are repetitively exercised daily. Together they train various independent arm and hand sensorimotor abilities. During the AAT sensorimotor performance is trained at its individual limit. Further aspects thought to promote motor learning are a high repetition rate of trained tasks, variation in the difficulty of training tasks, and the augmented feedback provided in the form of intermittent knowledge of the results.

that could be either (b.) individualized best conventional therapy (CONV) or (c.) standardized impairment-oriented training (IOT) in 148 subacute stroke patients with mild to severe arm paresis (14). Participants received 45 min of additional daily arm therapy over 3 to 4 weeks as either (a.), (b.), or (c.). For patients who had severe arm paresis IOT was provided as Arm BASIS training (9), for those who had mild arm paresis it was provided as AAT.

For participants with severe arm paresis the Fugl-Meyer arm motor score (17, 18) testing the selective movement capacity was the primary outcome measure, for participants with mild arm paresis it was the TEMPA time scores (16). Pre–post changes were analyzed to assess the immediate training effects and pre−4 weeks follow-up changes were used to assess any long-term effects. Both per-protocol and intention-to-treat analyses indicated greater improvement rates for participants who had received IOT as treatment compared to best conventional therapy (Fugl-Meyer, arm motor scores: IOT +12.3, CONV +9.2 points; TEMPA: IOT 31.1 s, CONV 20.5 s; $P = 0.0363$); and again, for mildly affected patients, i.e., those receiving the AAT superior long-term effects were shown. Since both of these groups (CONV and IOT) had received the same therapeutic time the specific focus of the active training seemed more important for motor recovery than the intensity (therapy time). The comprehensive modular IOT approach induced motor recovery to a higher degree than best conventional treatment and did so for a broad range of arm paresis post stroke, i.e., from mild to severe arm paresis.

A meta-analysis of individual patient data confirmed the clinical effectiveness of the AAT for stroke patients who have mild to moderate arm paresis, with a greater effect on motor recovery (focal disability) compared to other active motor rehabilitation or none and a moderate differential effect size in favor of AAT (15): Motor recovery (arm/hand function) (standardized mean difference (SMD) for pre-post change scores) in the AAT group was 0.51 standard deviations higher (95% confidence interval (95% CI); 0.11 to 0.91 higher) ($P = 0.0133$; 2 studies, 125 participants).

Both the training's effectiveness and its superiority compared to time-equivalent conventional therapy for stroke patients who have mild to moderate arm paresis are noteworthy and need to be compared to the effectiveness of other arm rehabilitation techniques. Training-based therapies that had been tested in post-stroke arm rehabilitation over the last decades include the constrained-induced movement therapy (CIMT), task-oriented training, bilateral training, mirror therapy, neuromuscular electrical stimulation (NMES) and, arm-robot-therapy. Most of these are clinically useful for stroke survivors with severe arm paresis (i.e., bilateral training, mirror therapy, neuromuscular electrical stimulation (NMES) and arm-robot-therapy), but not for mild to moderate arm paresis like the AAT. The CIMT is useful for stroke survivors with mild to moderate arm paresis, but is indicated for a subgroup who—in spite of their capacities to use their affected arm—do not use their affected arm in daily life or do so only to a rather limited extent. This occurs as a result of learning early on post stroke that the arm will not be useful for daily life activities and consequently a learnt non-use of the affected arm is developed and retained even though the arm might have recovered in the meantime. In this situation CIMT is clinically effective; it can reverse the learnt non-use and induce

more and adequate use of the affected arm in daily life (19). The AAT, however, is applicable to stroke survivors with mild to moderate arm paresis independent of the presence of learnt non-use. The therapy which has the biggest overlap with the AAT in terms of the target population is the task-oriented training. Here, the conceptual idea is that when training tasks resemble the activities of daily life, the brain is comprehensively engaged during training, and hence might have adequate stimuli to re-learn arm motor skills. The clinical evidence for task-oriented training in arm rehabilitation post stroke is, however, relatively weak. A large US-based multicentre RCT that randomized 361 subacute stroke patients with moderate arm impairment who then either received 30 h of task-oriented training over 10 weeks, or time-equivalent conventional occupational therapy, or monitored occupational therapy only, did not reveal any statistically or clinically relevant differences between these groups both when assessed after the intervention and during the follow-up up to 12 months post stroke (20). Hence, it was not possible to substantiate an effect of task-oriented training on arm function in this large clinical trial. A Cochrane review documented low-quality evidence that repetitive task training improves arm function (SMD 0.25, 95% CI 0.01 to 0.49; 11 studies, 749 participants) and hand function (SMD 0.25, 95% CI 0.00 to 0.51; eight studies, 619 participants) with a small effect (SMD $<$ 0.40) (21). These comparisons were no longer statistically significant in sensitivity analyses that removed studies with a high or unclear risk of bias for allocation concealment, questioning the stability of the effects when accounting for risk of bias.

But why should task-oriented training be clinically less effective than the AAT? Since no head-to-head comparison is available the evidence needs to be treated with caution and as indirect. Nevertheless, the reason for the observed discrepancy in clinical effectiveness between the two approaches might be that task-orientation is neither a necessary nor a sufficient training characteristic for determining the clinical effectiveness in that patient population. As will be pointed out below, the AAT (which does also systematically involve handling objects) has a variety of characteristics that are not genuine characteristics of a task-oriented training, and which can systematically promote motor learning and motor recovery in stroke survivors. While the evidence thus far shows a clinically relevant lasting effect for subacute stroke survivors with mild to moderate arm paresis receiving AAT, it is also important to report on the limitations of the available evidence. The total number of participants in RCTs testing the AAT's effectiveness is lower than would be needed to enable a precise estimate of its therapeutic effects (i.e., $<$400). Thus, the estimate of the magnitude of its effect could well change when further trials become available for a meta-analysis. In addition, the reported evidence has been generated during the subacute phase of stroke and inpatient rehabilitation. A low drop-out rate [2% drop-outs among participants randomized to IOT in the biggest multicentre trial (14)] indicates a high acceptability of the IOT interventions tested in that situation. Nevertheless, we do not have evidence for the training's acceptability and effectiveness when applied in the chronic stage and in an ambulatory situation.

SENSORIMOTOR LEARNING INDUCED BY THE ARM ABILITY TRAINING

Given the clinical effectiveness of the AAT and its superiority for the therapeutic domain of focal disability recovery after a stroke what are the neurobiological mechanisms of its action?

Motor skill acquisition is generally thought to be dependent on specific repeated practice with an "initial phase" of rapid improvement within single sessions of practice caused by strategic adaptation and behavioral response selection for a motor task and a "slow phase" of gradual improvement with a (true) increase in motor performance, i.e., improved capability of the motor system with an improved speed-accuracy relationship rather than a functional adaptation within the limits of a constant level of performance only (speed-accuracy trade-off) (10).

In healthy subjects motor learning has previously been investigated with various types of motor tasks, e.g., discrete, serial, or continuous tasks and various modifying conditions such as massed vs. distributed practice, different degrees of variability-of-practice, and the type and distribution of feedback given (5). This knowledge has been explicitly embedded in the structure of the AAT and hence it is of interest to assess (physiologically) whether and to what degree motor learning can be achieved with AAT.

We performed a number of studies with the AAT, addressing the behavioral question of its effects on sensorimotor learning in healthy subjects. While the training was designed in such a way as to have a high chance of inducing comprehensive motor learning (within and across abilities), it is worthwhile testing whether it actually achieves this goal. Such knowledge has significant translational significance. A robust induction of motor learning in healthy subjects with measurable effects on dexterity could be a key element in terms of its clinical effectiveness. Stroke survivors with mild to moderate arm paresis, for whom the AAT has been "tailor-made" can use their arms in everyday life, but are less dexterous. Accordingly, their brain is confronted with the same motor control affordances as healthy subjects are and they can cope, but at a lower level of performance than healthy subjects.

While this type of translational research, i.e., the effects of a "therapeutic" training in healthy subjects, has not usually been conducted for other arm rehabilitation therapies, it can be regarded as a relevant research milestone for safeguarding the development of clinically effective therapy.

The AAT Induces Substantial Sensorimotor Learning

In several experiments it has repeatedly been shown that the AAT promotes considerable and robust sensorimotor learning in healthy right-handed adults training their left non-dominant arm (22–26). As participants in the AAT have to comply with the precision demands, which are made explicit for each of the eight training tasks (**Figure 1**), any training-induced sensorimotor learning is reflected in the reduced time needed to fulfill work packages given for each training task. When the duration for each work package is standardized for baseline values (= 1.0 at baseline) the time needed to fulfill the work packages after 5 days

of daily training (∼60 min) has been shown to decrease to 0.79 (95% CI 0.73 to 0.84) ($P < 0.0001$) (14) to 0.72 (95% CI; 0.71 to 0.74) ($P < 0.0001$) (16) on average (across tasks), denoting a 20 to 30% improvement after training. After 10 days an improvement rate of ∼30% has been documented (26), and after 16 days ∼34% ($P < 0.0001$) (15) which resembles a typical learning curve for motor learning.

Thus, the AAT induced a considerable repetition-mediated increase in performance (speed and accuracy) with incremental gains in motor performance following prolonged daily practice (10).

The AAT Induces Learning for Different Sensorimotor Abilities

Across the eight different AAT training tasks the improvement rates and thus the learning dynamics were consistently different (22–25) with tapping showing the least improvement; e.g., after 16 days of daily training the improvement in performance ranged from 0.77 (95% CI; 0.72 to 0.81) for tapping to 0.60 (95% CI; 0.51 to 0.69) for nuts and bolts (23), and thus improvement rates varied across AAT tasks from 23 to 40% on average. This is noteworthy since the tasks had been deliberately chosen to collectively address different (independent) sensorimotor abilities and thereby to achieve an effect on sensorimotor performance in daily life which was as broad as possible. Different learning dynamics across tasks do support the assumption that they addressed different control affordances.

To test this notion more specifically, a principal component analysis (PCA) for all behavioral data was performed in one of the experiments (24). Data from the eight AAT tasks, 4 work packages per task and day for 5 days [except for work package 1 on day 1] were used and thus 19 variables per task for 18 participants. The PCA revealed a meaningful 8-component solution and thus a high degree of independence for subsets of variables. The total communality estimate for the model was 123.4, the communalities for each factor ranged from 12.4 to 20.9. In addition, a considerable to high loading of each AAT task on just one (each) of the 8 components was observed.

Taken together, the PCA indicated a high degree of independence of the behavioral data across the arm ability tasks for the repeated measurements taken during the training while the data for each arm ability task during the period of training loaded highly on just one of eight different independent components. This observation further supports the notion that the AAT trains different sensorimotor abilities and might well be a reason for its (superior) clinical effectiveness.

While motor learning research in healthy subjects typically focusses on one of several types of motor tasks, e.g., a discrete, serial, or continuous task (5, 27), here we have proof that the parallel repeated and prolonged practice of different motor tasks both addresses a variety of independent affordances ("abilities") and induces a substantial improvement in performance level (i.e., motor learning) across these tasks and hence "abilities." This observation has again significant translational relevance as it shows that the AAT induces the intended *comprehensive* motor learning and thus is a good candidate for assisting the recovery of stroke survivors with mild to moderate arm paresis who have been shown to have performance deficits across these "abilities" (4).

The AAT Induces Both Limb-Dependent and Limb-Independent Sensorimotor Learning

Another behavioral observation is noteworthy. While only the left arm and hand had been trained in the aforementioned experiments with healthy participants, there was, again consistently (when assessed) a partial transfer of motor learning to the non-trained right hand. This was evident when it was used to perform the AAT tasks after the course of training (compared to baseline assessment) (23, 25, 28). E.g., after 10 days AAT the improvement rate for the trained left hand was 30% ($P < 0.001$) and 19% for the non-trained right hand ($P < 0.001$) indicating a common proportion of 63% for both hands (25). Looking at the pattern of improvement for either hand over 3 weeks (assessed once per week) and for each AAT task separately gave the impression of a qualitatively similar task-specific pattern of improvement for both hands (varying across tasks) with a partial benefit for the non-trained right hand (23). Further, effects of the AAT on the non-trained right hand were not only been observed for the trained AAT tasks, but also when the right hand was assessed with a standard assessment of finger dexterity, the Nine-Hole-Peg-Test, NHPT (29) after a course of AAT (22–24). After 3 weeks (16 days) of AAT the improvement rate for the NHPT were on average 13 and 14% for the left and right hand, respectively, ($P = 0.0006$; effect size $d = 0.90$) (average time needed for the NHPT: baseline right hand 16.7 s, 95% CI 15.3 to 18.0; left hand 17.4 s, 95% CI 16.2 to 18.6; week 3 right hand 14.3 s, 95% CI 13.3 to 15.3; left hand 15.1 s, 95% CI 14.1 to 16.1) (23).

Taken together, these observations suggest that the AAT trains in part sensorimotor capacities that can be used by either hand, i.e., which are end-effector (limb) independent. Biologically it makes sense that the complex nature of the training not only uses brain processes that are tightly linked to the contralateral sensorimotor system for each limb, but also to activities of brain networks that support sensorimotor control for either limb.

In the literature such a transfer of skill has been shown from a trained to a non-trained finger with a finger tracking task applied over a week (30). And more comparably, a transfer of finger dexterity to the non-trained dominant right hand has also been shown when healthy subjects trained handwriting with their left hand for 15 days (31).

TRAINING-INDUCED PLASTICITY

The behavioral evidence therefore points to a diversity of sensorimotor processes that are improved by this training, i.e., "abilities." They show training-induced improvements to a varying extent and with a partial transfer of effects to the non-trained arm. Given this knowledge it would be of interest to learn about the involvement and particularly any differential involvement of cerebral regions and network "nodes"

during AAT-induced learning for the various abilities and how this might change over time. The significant motor learning that could be behaviourally observed with prolonged repeated practice must be associated with changes in how the brain performs motor control for these tasks (and abilities), i.e., training-induced plasticity.

Effects of AAT-induced Sensorimotor Learning Can be Modified by Non-invasive Cortical Brain Stimulation

To probe the involvement of sensorimotor cortical areas in AAT-induced motor learning tests were conducted to determine whether AAT-induced learning could be altered by inhibitory or excitatory non-invasive brain stimulation (22–24).

The first experiment used an excitability reducing, inhibitory rTMS protocol (continuous theta burst stimulation with a total of 600 stimuli, cTBS-600) (22). The hypothesis was that at an early stage in the AAT, i.e., during the first few days of training, cortical sensorimotor areas contralateral to the trained arm would be involved in motor learning, and if so, learning dynamics could experimentally be reduced by an inhibitory non-invasive brain stimulation. To test this experimentally seven healthy young subjects trained their left non-dominant arm with the AAT once a day for 5 days. cTBS-600 was applied between the first and second half of individual AAT sessions on four consecutive days (days 2 to 5 of the experiment). With permutation of the order, for each participant cTBS-600 was applied to either the primary motor cortex (M1), supplementary motor area (SMA), premotor cortex (PMC), or primary somatosensory cortex (S1) during one session. The specific objectives were to test whether the motor learning dynamics within sessions could negatively be influenced by cTBS-600, and if so whether the stimulation site (M1, S1, PMC, or SMA) mattered and whether effects were different for the different AAT tasks. The effect on motor learning was analyzed with intra-session effects which examined how cTBS-600 affected motor improvement from the 1st to the 2nd half of each training session. On average these intra-session improvement rates had been in the range of 2%. It was then analyzed whether cTBS modified these rates. For this purpose, effects of cTBS-600 to one site was compared to the data from all other sites. Overall, cTBS-600 to S1 had a more detrimental effect on motor learning than stimulation to the other sites (M1, PMC, S1) ($P = 0.0432$; effect size d = 1.04; absolute differential detrimental effect for cTBS over S1: +0.9%).

This is perhaps not unexpected since the AAT tasks do involve sensorimotor integration. A reverse experimental approach, i.e., peripheral electrical somatosensory stimulation of the fingertips of the trained hand prior to the AAT increased the training gain achieved over 10 days by 3.4% (on average 32.9% improvement rate with somatosensory priming vs. 29.5% without) ($P = 0.044$; effect size d = 0.77) (26).

Back to the cTBS-experiment (22): There were also effects that were specific for individual AAT tasks. Tapping was most affected by cTBS-600 to M1 ($P = 0.0341$; effect size d = 2.73) and aiming as well as placing large objects by cTBS-600 to PMC ($P = 0.0249$; effect sizes d = 2.97 and $P = 0.0249$; d = 1.21, resp.). Thus, improvement of fast isolated finger movements was most affected by cTBS-600 to M1, while any improvement of motor behavior that involved the navigation of the arm in extrapersonal space was most affected by cTBS-600 to PMC.

The experiment was repeated with twelve right-handed AAT-naive volunteers who, however, had a prolonged course of 3 weeks AAT (instead of 5 days). In this experiment, when the same cTBS-600 applications were used in the final 3rd week of training, no cTBS-effects on learning dynamics within the session could be corroborated (23).

Overall, the results of these two experiments would suggest that motor learning with the AAT involves the cortical areas S1, M1, and PMC critically during the first days of training and much less so after extended training over a few weeks.

This observation is in line with both animal and human data assessing cortical involvement during prolonged motor learning. Picard et al. (32) documented a decreased activation of the primary motor cortex (M1) in monkeys when performing highly over-trained internally-generated sequences of reaching movements most likely indicating a higher synaptic efficacy achieved by prolonged training. Wymbs and Grafton (33) observed an overall and skill-specific decrease in the contralateral primary sensorimotor cortex and premotor regions including PMC and SMA as well as the posterior parietal cortex with prolonged finger sequence learning.

Thinking along these lines, it was also of interest to find out whether the reverse intervention, i.e., an excitatory non-invasive brain stimulation to one of these areas could enhance the AAT-induced training effect. For this purpose, eighteen healthy young subjects trained their non-dominant left arm with the AAT once a day for 5 days using (24). In this case an excitatory form of rTMS, i.e., intermittent theta burst stimulation, iTBS-600 was used for priming purposes. Participants were assigned to three groups that received either (A) sham stimulation with a placebo-coil to the right M1, (B) iTBS-600 to the right M1, or (C) iTBS-600 to the right S1 on days 2 to 5 of the experiment. There was a numerically small, yet statistically significant difference in favor of subjects who received iTBS compared to sham stimulation for 4 days directly prior to the AAT: The final level of performance at the end of training was on average 0.72 across the arm ability tasks for the group receiving iTBS compared to 0.74 for the sham group ($P = 0.0285$), indicating a differential benefit in improvement rate of 2%. Differences between iTBS to either M1 or S1 could not be corroborated statistically in this experiment. There was, however, a generalization of the effect of iTBS on motor learning to the non-trained finger dexterity task, the NHPT, specifically for the trained left hand ($P = 0.0414$). The pre-post improvement was 13% on average for the left hand NHPT performance among those receiving iTBS, but only 7% among those receiving sham stimulation.

Thus, priming with iTBS-600 to either M1 or S1 enhanced motor learning during the AAT.

In the literature, the effects of non-invasive brain stimulation have been variable (34). The reported observations are nevertheless consistent and in agreement with experiments with single motor learning sessions where iTBS priming was associated with enhanced motor learning, e.g., for ballistic thumb

movements (35) and dexterity after complex training involving a dexterity task, tapping, tracking and a pegboard task (36).

AAT-induced Changes in Cerebral Activation During Motor Tasks

The behavioral evidence that (a.) substantial sensorimotor learning is induced by the AAT, (b.) the fact that different sensorimotor abilities are addressed and their capacities enhanced by the training, and (c.) the evidence from both inhibitory and excitatory non-invasive brain stimulation experiments that different cortical areas are involved in sensorimotor learning early during the AAT (first week of daily training), but presumably less so at later stages (e.g., after a couple of weeks of training) all require functional imaging data to elucidate the cerebral activation patterns associated with (sensori)motor tasks and their evolution after a course of AAT, i.e., training-induced plasticity.

Cerebral Activation Patterns Before and After AAT in Healthy Volunteers

For this purpose, fifteen healthy subjects trained their non-dominant left arm for 2 weeks (11 training sessions) with the AAT (25). Functional magnetic resonance imaging, fMRI was performed with three non-trained motor tasks that were performed with both of the participants' hands, i.e., both the trained left and also the non-trained right hand: (A) Participants had to clench their fist with a strength of 33% of their maximum voluntary contraction at a rate of 1 Hz. (B) A finger sequence task with 12 responses of the index, middle, ring, or small finger was performed according to a visual presentation of numbers (corresponding to the digits, i.e., 2 to 5), again with a frequency of 1 Hz. (C) Writing involved copying 10 words in cursive handwriting; individually, the same writing speed was used at pre and post test fMRI.

MRI data were collected before and after 2 weeks of AAT for 14 participants using a 3 Tesla MRI scanner (Magnetom Verio, Siemens, Erlangen, Germany) equipped with a 32-channel headcoil.

After the training period there was a substantial improvement in performance for the AAT tasks (∼30% on average) ($P < 0.001$) with a partial transfer to the non-trained right arm (∼19% on average) ($P < 0.001$). In addition, the motor tasks used for fMRI also showed improved performance, for both hands in the case of the finger sequence task and for the (trained) left hand with regard to the writing task.

Regarding the fMRI data, only statistically corroborated effects are described here (without individual *P*-values). Activation maps for the main effects and conjunctions were FWE-corrected over the whole brain; training effects were analyzed with a region of interest approach, corrected for multiple comparisons, FWE-corrected.

A decrease in activation when the trained arm was used after the training was observed for the finger sequence tasks in the ipsilateral S1 (BA1, 2, 3), bilateral SMA (BA 6), ipsilateral superior parietal lobe (SPL; BA 5 and BA 7) and inferior parietal sulcus (IPS, BA 40) as well as the dorsolateral prefrontal cortex (dlPFC, Brodman area, BA 8). For the writing tasks a decrease was found in the ipsilateral posterior cerebellar hemisphere (Larsell H VIIA; crus 1).

An increase in activation when the trained arm was used after the training was found in the contralateral pallidum and bilateral putamen for the fist clenching task (see **Figure 2A**) and the left anterior cerebellar hemisphere (Larsell H VI) for the writing task.

For the non-trained right hand, a decrease in activation during the finger sequence task was documented in the ipsilateral in SPL (BA 5), contralateral cerebellar hemisphere (Larsell H VI and VIIA) as well as the ipsilateral cerebellar vermis (VI and VIIIA).

In summary, after 2 weeks of AAT with the non-dominant left arm the fMRI data showed complex changes in motor-task related activation, i.e., a reduced activation in ipsilateral S1, parietal cortical areas, the SMA bilaterally, and the dlPFC with a finger sequence task, and the lateral cerebellar hemisphere with the writing task. An increase of activation in the striatum was found for the fist clenching task and the anterior cerebellum for the writing task. Thus, cortical motor and non-motor area activation decreased over time, whereas cerebellar anterior hemisphere and striatum activity became more prominent after prolonged sensorimotor training with the AAT. Further, related to the different sensorimotor affordances of the motor tasks used in the scanner, changes in brain network activations were different. These observations are in good agreement with the notion that the AAT induces learning for different sensorimotor abilities and hence training-induced plasticity in the cerebral networks providing these capacities.

Overall, the data is consistent with known cortical-basal ganglia-cerebellar networks involved in human motor learning (38) and corresponding knowledge about motor control, motor skill acquisition and related neuroplasticity from animal studies (27, 39). Previous observations of human motor learning, likewise, showed more prominent cortical involvement in early motor learning and a gradual shift of acquired skill representation to more subcortical activity in motor cortico-striatal and cortico-cerebellar networks with more prolonged training (33, 40, 41). The increase in activation in the striatum with the fist clenching task might mirror an aspect of reinforcement learning by the "sensorimotor" striatum, while the increased cerebellar hemisphere with improved writing for the trained left arm presumably indicates learning based on error signals (27).

For the translational research aspect it is important to note that the complex parallel motor training schedule with the AAT shows typical previously known aspects of the neurobiology of motor learning, i.e., training-induced cerebral plasticity. Furthermore, training-induced brain plasticity manifested itself even with motor tasks that had not been trained, validating the notion that when training tasks address "abilities" comprehensively, motor learning generalizes to untrained tasks (that draw on the same underlying set of "abilities") and hence change their cerebral activation pattern accordingly.

Cerebral Activation Patterns Before and After AAT in Subcortical Stroke Patients

Given the cerebral re-organization associated with the AAT in healthy volunteers it is of interest to know whether these changes could likewise be observed in stroke survivors who

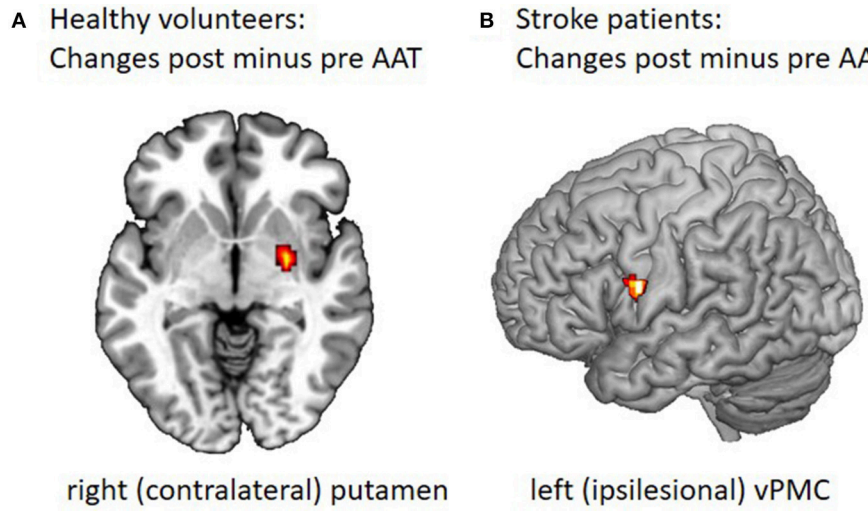

FIGURE 2 | Changes in motor task-related cerebral activation after the Arm Ability Training. **(A)** FMRI data were collected before and after 2 weeks of AAT for 14 healthy participants using a 3 Tesla MRI scanner (25). For the fist clenching task participants were trained to press the ball with the target force being 33% of maximal voluntary and a target rate of 1 Hz. The post minus pre comparison showed increased contralateral putamen and pallidum and ipsilateral putamen activation for fist clenching after training. The ipsilateral putamen activation is to be found at another z-direction height (here z = 0). **(B)** Twelve patients in the subacute phase from 2 to 9 weeks after a mild to moderate motor stroke were recruited for a combined AAT (15 one hour sessions over 3 weeks) and fMRI study during their inpatient rehabilitation stay (37). FMRI during an active and a passive motor task for the affected and unaffected hand was performed before and after a 3 week course of AAT during inpatient rehabilitation. The figure shows the change in activity over time observed in vPMC as measured for the active hand grip task when performed with the affected hand, post minus pre contrast, displayed on a segmented template (Collins Brain).

have survived a subcortical stroke leaving them with a mild to moderate arm paresis and who then receive a 3 week course of AAT.

For this purpose, 12 stroke survivors with mild to moderate are paresis were recruited for a combined AAT (15 one hour sessions over 3 weeks) and fMRI study during their inpatient rehabilitation stay in the subacute stage of recovery (37). Improvement in performance after the training was assessed with both the AAT tasks and conventional hand motor tests [NHPT, Box-and-Block Test, BBT (42)]. The AAT (combined with other rehabilitation efforts) resulted in considerable performance improvements, both in the trained tasks (mean execution time for AAT tasks was reduced on average by 27.7%, $P < 0.001$), and other hand motor functions (NHPT: average time needed to perform the NHPT decreased by 25.2%, $P < 0.007$; BBT: number of blocks moved in the BBT increased by 20.9% on average, $P < 0.001$).

For the parallel fMRI investigation there was a non-trained active and also a passive task used. The active task was a fist clenching task; performance at pre and post-test was kept constant in terms of both force and frequency. For the passive movement task, wrist flexion-extension movements were performed at a rate of 1 Hz with a pneumatically driven splint.

Statistical note for the fMRI data analyses: For the region of interest analyses M1, S1, SMA, dorsal PMC, ventral PMC, and the cerebellum on either side were included. Only statistically corroborated effects corrected for multiple comparisons [p(FWE) < 0.05] are described here (without individual *P*-values).

The active tasks performed with the non-affected hand activated M1, SMA, dPMC, vPMC, S1 and cerebellum in both hemispheres both in the pre-test and post-test. When performed with the affected hand, M1, SMA, dPMC, S1, and cerebellum were activated before the training while there was an additional bilateral vPMC activation after the training. The analysis of longitudinal fMRI changes corroborated a specific effect for the affected hand and the active task only: there was an increase of vPMC activation over time (see **Figure 2B**). Furthermore, only the analysis for the affected hand performing the active task post training indicated a stronger bilateral vPMC activation than healthy subjects.

These results point toward a need for additional recruitment of this secondary motor network area for survivors of subcortical strokes with mild to moderate arm paresis, in order to improve their performance levels.

In general, our knowledge about training-induced cerebral re-organization for stroke survivors with arm paresis is still limited. A small cohort study with 12 acute subcortical stroke patients with moderate to severe hand paresis who received very early mobilization and task-oriented physical therapy indicated that hand motor recovery was associated with a highly lateralised ipsilesional primary sensorimotor cortex activation on fMRI (43). In a substudy of two multi-centere clinical trials with chronic stroke survivors receiving either robotic or intensive conventional therapy for 6 to 12 weeks resting state connectivity was responsive to treatment, showing an increase in affected primary motor cortical connectivity to other frontal motor areas (44). In another small cohort

study (10 chronic stroke participants) mental practice over 10 weeks induced both motor performance improvements for the affected hand and associated increases in bilateral primary sensorimotor and premotor activation (45). A systematic review (8 studies, 164 participants) addressing the question of whether bilateral arm training is associated with training-induced plasticity in stroke patients could, however, not corroborate a consistent pattern of cerebral re-organization (46). These examples indicate that training-related changes in the cortical activation and connectivity pattern had been reported for primary sensorimotor and secondary motor areas, yet had been variable. Reasons for this heterogeneity might be that the participants included had been diverse in terms of their stroke characteristics or level of impairment or that the interventions themselves and their effects had been variable. In our study (37) a selective group of patients,who were subacute subcortical stroke survivors with mild to moderate paresis, received a standardized training and showed both clinically relevant motor recovery and an increase in vPMC activation during movements of the affected hand post training. In that constellation vPMC seemed to be an important network node for motor recovery.

CONCLUSIONS

The AAT has been specifically designed to meet the needs of subjects with acquired brain injury with mild to moderate arm paresis and a lack of "dexterity" in everyday life causing focal disability. It explicitly addresses the lack of sensorimotor efficiency across various arm abilities as documented for this subgroup of stroke survivors by (a.) training these abilities, (b.) training sensorimotor performance at the individual limit as well as further aspects known to promote motor learning, i.e., (c.) a high repetition rate of trained tasks, (d.) variation in the difficulty of the training tasks, and (e.) augmented feedback provided in the form of intermittent knowledge of results. The inherent external focus of attention created by the constant drive for improved performance (speed and accuracy) beyond the current individual limit as opposed to a self-centered, non-ambitious "quality of movement"-focus, together with the intermittent provision of results, the almost uniformly experienced improvement of performance within training sessions and from day to day and hence the enhanced expectancy for further success are all likely to direct attention to the task and the training goal and enhance goal-action coupling during the AAT (12). These aspects are strong facilitators for the repetition-mediated improvement of performance, i.e., motor learning (10). The implemented constant change of affordances within tasks (variability of task difficulty) and the shift between tasks which train different sensorimotor abilities is a learning experience for the brain with a high need to generate and increasingly efficiently regulate motor variability, a situation that makes motor skill acquisition highly likely (11).

The clinical effectiveness for stroke patients in the subacute phase with mild to moderate arm paresis was able to be shown by two fairly large single blind randomized controlled trials: The AAT improved sensorimotor efficiency with ADL-like arm activities with a long-term effect. And, it has been shown to be superior to therapeutic time-equivalent "best conventional" therapy.

With regard to the neurobiology of the training, behavioral training data from experiments with healthy subjects training their non-dominant left arm with the AAT over a period of 1 to 3 weeks confirmed that the AAT induces substantial motor learning, with generalization to a non-trained dexterity task and partial transfer to the non-trained arm indicating partially endeffector-independent resources that were improved by the training. The data further supports the notion that the AAT induces motor learning across different independent sensorimotor abilities, a fact that may well be of paramount importance for its clinical effectiveness. Motor learning processes induced by the AAT involved distributed cortico-subcortical networks with task-specific variation of the relevance of cortical areas (as shown for M1, PMC and S1) and a change with less cortical involvement and more basal ganglia and cerebellar activation after prolonged training indicating a consolidation process. All these findings contribute to our understanding of how the substantial increase in motor performance is induced by the training.

It could be shown that the ipsilesional vPMC played a specific role in training-induced plasticity and recovery for patients with subcortical stroke in the subacute phase with mild to moderate arm paresis who received the AAT for 3 weeks and showed a substantial clinical improvement.

In summary, the AAT is a complex motor training tailor-made for stroke survivors with mild to moderate arm paresis; it is intentionally designed to contain a "high density" of aspects that are relevant for achieving substantial training-induced recovery from focal disability. Its structure supports intrinsic motivation and a focus on motor learning and effectively strengthens various sensorimotor arm and hand abilities with long-term effects. The training-induced recovery of arm abilities is based on functional re-organization of related cortico-subcortical cerebral networks with a partially bilateral organization and an adaptive recruitment of the ipsilesional ventral premotor cortex among stroke survivors.

AUTHOR CONTRIBUTIONS

TP designed and wrote the manuscript. ML critically revised it for intellectual content and clarity of presentation.

FUNDING

The authors are grateful to the public sponsors who generously supported this research over the years (BMBF, DFG), and the BDH, Bundesverband Rehabilitation e.V. (charity with focus neuro-disabilities) who supports the neurorehabilitation research of TP. Neither sponsor had influence on the decision to publish or any content of the manuscript.

ACKNOWLEDGMENTS

The authors wish to thank the many team members who contributed to the cited work over the last few decades, the healthy volunteers and stroke survivors who participated in the studies as well as the public sponsors (BMBF, DFG) and a charity for neuro-disabilities (BDH Bundesverband Rehabilitation e.V.) who generously supported this research over the years.

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Conflict of Interest Statement: TP received grants from the German ministry for education and research (BMBF) for clinical trials assessing the effectiveness of the AAT, provides AAT teaching courses for therapists and training material. ML and TP received jointly received grants from the German research community (DFG) for the rTMS and fMRI experiments cited. Thus, both authors have a personal link to the work presented.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 29 November 2018
doi: 10.3389/fneur.2018.01020

Does Resting Motor Threshold Predict Motor Hand Recovery After Stroke?

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Background: Resting Motor threshold (rMT) is one of the measurement obtained by Transcranial Magnetic Stimulation (TMS) that reflects corticospinal excitability. As a functional marker of the corticospinal pathway, the question arises whether rMT is a suitable biomarker for predicting post-stroke upper limb function. To that aim, we conducted a systematic review of relevant studies that investigated the clinical significance of rMT in stroke survivors by using correlations between upper limb motor scores and rMT.

Methods: Studies that reported correlations between upper limb motor function and rMT as a measure of corticospinal excitability in distal arm muscle were identified via a literature search in stroke patients. Two authors extracted the data using a home-made specific form. Subgroup analyses were carried out with patients classified with respect to time post-stroke onset (early *vs.* chronic stage) and stroke location (cortical, subcortical, or cortico-subcortical). Methodological quality of the study was also evaluated by a published checklist.

Results: Eighteen studies with 22 groups ($n = 508$ stroke patients) were included in this systematic review. Mean methodological quality score was 14.75/24. rMT was often correlated with motor function or hand dexterity ($n = 15/22$, 68%), explaining on average 31% of the variance of the motor score. Moreover, the results did not seem impacted if patients were examined at the early or chronic stages of stroke. Two findings could not be properly interpreted: (i) the fact that the rMT is an independent predictor of motor function as several confounding factors are well-established, and, (ii) whether the stroke location impacts this prediction.

Conclusion: Most of the studies found a correlation between rMT and upper limb motor function after stroke. However, it is still unclear if rMT is an independent predictor of upper limb motor function when taking into account for age, time post stroke onset and level of corticospinal tract damage as confounding factors. Clear-cut conclusions could not be drawn at that time but our results suggest that rMT could be a suitable candidate although future investigations are needed.

Systematic Review Registration Number: (https://www.crd.york.ac.uk/prospero/): ID 114317.

Keywords: stroke, Transcranial Magnetic Stimulation, corticopinal excitability, motor function, outcome

OPEN ACCESS

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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *19 August 2018*
Accepted: *12 November 2018*
Published: *29 November 2018*

Citation:
Rosso C and Lamy J-C (2018) Does Resting Motor Threshold Predict Motor Hand Recovery After Stroke? Front. Neurol. 9:1020. doi: 10.3389/fneur.2018.01020

INTRODUCTION

Upper limb motor function, and more specifically hand motor function is difficult to predict in stroke survivors. Although recent clinical papers pointed out the predictive value of the proportional recovery rule, meaning that patients will recover about 70% of the lost function, this rule is seriously challenged by the prediction of the most severe ones (1, 2) in whom different profiles of recovery ranging from nearly no improvement to tremendous one have been observed. Indeed, researchers and clinicians are still struggling to explain these different patterns of recovery. In this context, developing and implementing biomarkers in stroke recovery research is more than ever challenging (3, 4). As regards post-stroke upper limb motor function, corticospinal excitability measured by Transcranial Magnetic Stimulation (TMS) has been identified as a possible biomarker. Some reviews already attempted to define the predictive value of TMS-induced Motor Evoked Potentials (MEPs) in arm motor function (5, 6). In contrast, resting Motor Threshold (rMT), i.e., the minimum amount of energy necessary to evoke a MEP in the relaxed target muscle has been less studied. In this paper, we review the clinical significance of corticospinal excitability, using rMT and not the MEPs amplitude, in stroke patients. This work is divided into two parts. The first one deals with the general principles of measuring rMT, its variability and values in stroke. The second part is a systematic review of relevant studies that investigated the clinical significance of rMT in stroke by the means of correlations between upper limb motor scores and rMT.

RESTING MOTOR THRESHOLD AS A MEASURE OF CORTICOSPINAL EXCITABILITY

Definition

According to the International Federation of Clinical Neurophysiology (IFCN), rMT is defined as the lowest stimulus intensity (expressed as a percentage of maximal stimulator output-MSO) required to induce a MEP with a peak-to-peak amplitude of at least 50 microvolts in 5 out of 10 consecutive trials in the relaxed target muscle (7).

The motor threshold depends on the excitability of several neural elements, which are excited by TMS and propagate the elicited action potential including the cortico-cortical axons, their excitatory synaptic contacts with the corticospinal neurons, the initial axon segments of the corticospinal neurons (8) but also the spinal cord structures (9, 10).

MT Variability and Influential Factors

Both intra (between repeated stimulation sessions within the same subject) and inter-individual variability (between-subjects) of TMS-induced MEP are well-known and contribute to the overall heterogeneity of the measurement (11).

For inter-individual variability, one critical factor is the coil-to-cortex distance (12, 13). When targeting the hand motor area, the coil-to-cortex distance is defined as the shortest distance between the scalp and the hand knob area of the primary motor cortex and is critical in determining the amount of energy required to depolarize the corticospinal tract (CST).

The role of age is still a matter of debate. Whereas, it has been documented that rMT decreases with age (14) a recent meta-analysis reports the opposite effect, i.e., increased rMT with age (15). Among the possible other factors of inter-individual variability, drugs intake are of importance. Indeed, Voltage-Gate Sodium Channels antiepileptic drugs, i.e., carbamazepine, phenytoin, and lamotrigine increase rMT, i.e., these drugs reduce CST excitability. In contrast, ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist that indirectly facilitates glutamate neurotransmission dose-dependently decreases rMT, i.e., it increases CST excitability (16).

Intra-individual variability corresponds to the intrinsic fluctuations of the excitability of cortical and spinal neurons that cause trial-to-trial variability in MEP amplitude (17). While physiological noise introduces some uncertainties and cannot be eliminated (18), other technical and physiological variables should be kept constant during rMT measurements such as the level of arousal or the time of the session during the day (rMT being sensitive to the nycthemeral cycle). From a technical point of view, the type and size of the coil have to be kept constant. Thus, smaller coils give higher rMT, as well as circular coils *vs.* figure-of-eight shape coils (17). Coil orientation (delivering posterior-anterior, lateromedial, anteroposterior currents), pulse waveform (i.e., monophasic or biphasic) and type of stimulators are also known to affect the rMT (19, 20).

However, when these factors are controlled, the intraclass coefficient of the intra-individual variability of rMT is good (21).

Impact of Stroke on MT

Stroke affects corticospinal excitability and, as a result, the rMT. A recent review summarized the neurophysiological effects of stroke on rMT [see (22) for further details]. Briefly, the rMT is higher in the affected hemisphere when compared to the unaffected one or to healthy subjects. The exact time course of rMT after stroke is not well-known. It probably reduces over time after stroke but remains higher in the affected hemisphere (AH) with respect to the unaffected hemisphere (UH) at the chronic stage. For the UH, the meta-analysis of McDonnell et al. (22) found no differences in rMT when compared to healthy controls (22 studies, 821 participants), regardless of the stage of stroke (i.e., early or chronic).

rMT AS A BIOMARKER OF STROKE HAND FUNCTION

Definition of a Biomarker

According to a recent consensus paper (3, 4), a stroke recovery biomarker can be defined as "an indicator of disease state that can be used as a measure of underlying molecular/cellular processes that may be difficult to measure directly in humans."

A biomarker could be used (i) to understand outcome/impairment or, (ii) to predict a future outcome or recovery (defined as the change in the clinical score) or a treatment response. We propose to review whether rMT,

measured by TMS, can be considered as a biomarker according to this definition.

Systematic Review of the Literature

Aims

The overall goal of this review is to determine whether rMT can act as a biomarker that could (i) understand impairment (UI), (ii) predict the outcome (PO), and (iii) predict recovery (PR) of the distal upper limb motor function after stroke. We did not focus on treatment response. We defined a study as UI if the measure of rMT and the clinical scores were obtained at the same time point. We defined PO if the rMT was measured at T1 and scores were obtained later (T2), and PR, if rMT was collected at T1 and motor scores at T1 and T2 (i.e., PR represents the changes in the motor scores between T2 and T1).

Methods

PRISMA and PICOS checklists are available in the **Supplementary Material** available on line. This systematic review has been registered to PROSPERO (https://www.crd.york.ac.uk/prospero/), ID 114317.

Search strategy

The search strategy was formulated in broader terms voluntarily, in order to ensure exhaustivity. The Mesh terms "transcranial magnetic stimulation" AND "stroke" were combined. We searched the following databases from inception until June 2018: Medline and EMBASE. The language was restricted to English. The number of articles corresponding to these Mesh terms was 1798.

Studies were then included if (i) TMS was used to investigate ipsilesional rMT in participants with a confirmed diagnosis of stroke of any type, with or without comparison to healthy controls, (ii) rMT was collected in hand or forearms muscles (if rMT was recorded from multiple muscle groups, only the distal arm muscle data were included), (iii) motor upper limb or hand function was evaluated at the time of the TMS session or later and, (iv) individual patient data (with rMT and motor scores) were available even though the primary aim of the publication was not to investigate rMT but rather other TMS parameters.

Studies were excluded if (i) rMT was recorded from the proximal arm muscles (i.e., biceps brachii) or from lower limb/pharyngeal/trunk muscles, (ii) motor threshold was collected under active condition (i.e., during a contraction of the target muscle), (iii) rMT was collected after an intervention (i.e., novel rehabilitation techniques, after non-invasive brain stimulation such as repetitive TMS…) and, (iv) the sample size was less than 5 patients, including case reports.

Two researchers ran each database search independently and then compared findings. Search results duplicates were removed. The same two researchers screened the search findings for eligibility, using article titles and abstracts, for the inclusion of appropriate participants, and measurements. When it was unclear if the study met all of the inclusion criteria on the initial title/abstract screening, the full text was obtained and assessed for eligibility.

Data extraction and management

One author extracted data from the included studies using a standardized data extraction form specifically designed for this review. Extracted data included the following information from the methods section of the articles: aim of the study (UI, PO, PR), detailed description of the participants (age, sex, type and location of stroke, time since post-stroke onset, motor scores), research methods (type and size of the coil, target muscle) and type of the motor score. The correlation coefficient between rMT and motor scores, the R2 and the statistical significance were recorded when available.

Subgroup analyses

We planned *a priori* subgroup analyses to compare results from (i) acute (within 7 days) *vs.* subacute (within 3 months after stroke onset) *vs.* chronic phase (more than 3 months) and, (ii) the location of stroke (subcortical *vs.* cortical *vs.* cortico-subcortical).

Risk of bias

Risk of individual bias: methodological quality assessment. We extracted information on the methodological quality of each study included in our systematic review. For this methodology quality assessment, two reviewers independently assessed the quality of each study using the checklist designed by Chipchase et al. (23) for TMS studies. This checklist was modified, as in McDonnell et al. (22). Four items were removed because they related to paired-pulse TMS paradigms, an additional one because it dealt with healthy participants and a last one because it assessed repetitive sessions within the same subjects. As a result, a total quality score of 24 was obtained. We coded the studies as low (score > 16), unclear (scores ranging from 9–16) or high risk (score ≤ 8) of bias.

Risk of Bias inherent to group analysis. We considered all potential sources of bias in the conduct of our systematic review, such as recruitment bias, publication bias and selection bias.

Results

Descriptions of the included studies (Figure 1, Tables 1, 2)

Of the 20 studies included for analysis (Flow chart: **Figure 1**), two studies reported the same stroke patients (24, 25), so the more recent study was selected (25). One study (43) was discarded because of methodological issues (no information about rMT definition and TMS equipment used for recording was provided). Eighteen studies were included depicting a total of 508 stroke patients. Two studies reported separated groups in the main text: the first one (27) reported two groups (subacute vs. chronic) and the second one (33) four groups according to the infarct location. As a result, 22 samples from 18 studies were included in this review (25–42). We further referenced throughout the following as a number of samples and not studies for clarity. Among these 22 samples, 20 samples reported the correlation between rMT and motor scores in the main text. For two of them, we computed correlation, based on the individual patient data, using Spearman rank coefficients.

The purpose of identifying samples was to understand impairment (UI–$n = 18$), predict outcome (PO–$n = 4$), and

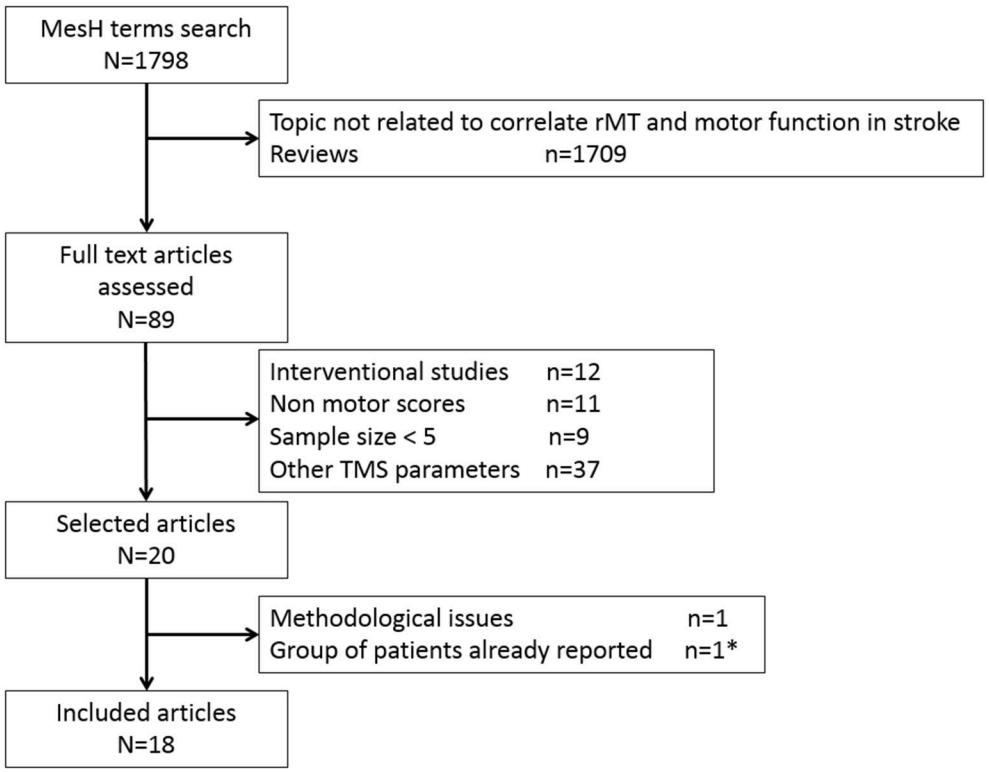

FIGURE 1 | Flow chart of the systematic review process. * Ward et al. (24) was excluded to keep the more recent study (25).

predict recovery (PR–$n = 2$). Two samples investigated both UI and PO or UI and PR.

The clinical characteristics of stroke patients are displayed in **Figure 2**. As regards TMS measurements (**Table 2**), First Dorsal Interosseus (FDI) was the distal muscle recorded in 17 samples, Extensor Carpis Radialis (ECR) in 2, Abductor Pollicis Brevis (APB) in 2 and Abductor Digiti Minimi (ADM) in 1 sample. Motor function and hand dexterity were assessed using several clinical scores (see **Table 1**).

Correlations between motor distal upper limb function and rMT

Mean rMT was 61 ± 13%MSO (SD) on the AH and 51 ± 9%MSO on the UH. Seventeen samples reported that it was not possible to elicit MEP on the AH (mean proportion of the patients without MEPs: 24 ± 21%). When MEPs could not be evoked, so that rMT could not be determined, authors assigned to rMT an arbitrary value of 100% MSO in 4 samples, 110% in one sample and 120% in one sample. In some samples ($n = 3$), patients without MEP on the AH were excluded from the analysis.

Fifteen samples found a significant correlation between motor scores and rMT, with R2 ranging from 12 to 64% (mean: 31%) whereas 7 samples found no significant correlations. Regardless of the value of the correlation, the fact that rMT was an independent predictor of motor function is of importance. This point was raised in only four samples ($n = 75$), by adjusting the model according to well-known confounding factors (i.e., age, time post stroke onset or other TMS parameters) but the correlation between motor scores and rMT remained significant.

Subgroup analyses

Early vs. chronic patients. We divided our samples into three categories: acute (<7days), subacute (7 days to 3 months) and chronic (>3 months). **Table 3** displays the values of rMT, the proportion of patients without MEP and the correlations between motor scores and rMT. It is worth noting that results dealing with the acute period must be taken with caution given: (i) the small number of both samples ($n = 2$) and patients ($n = 43$), and (ii) the possible bias in the recruitment of these acute patients (who are likely less severe to be able to handle TMS measurements). For these reasons, we focused the analysis on the comparison of subacute *vs.* chronic stroke patients. On the AH, rMT was higher at the subacute *vs.* chronic phase but the difference did not reach significance (p: 0.15). On the UH, rMT was unchanged. The proportion of patients who did not exhibit MEP decreased from 34 to 17% ($p < 0.001$) between the subacute *vs.* chronic stage, suggesting that some MEPs might reappear during recovery. When rMT correlated to motor scores, the proportion of variance of the motor score explained by the rMT was around 30% in both stages.

Location of stroke. Samples reporting either individual patient data (25, 26, 40) or samples with location subgroups analyses (33) were analyzed in order to investigate whether stroke location (cortical-C, cortico-subcortical-CSC, subcortical-SC)

TABLE 1 | Clinical characteristics of the patients included.

Study	*N*	Purpose	I/H	Location SC/C/SCS/BS	TPSO(months)	Stage	Age	Motor scores	Lost FU
Bastings et al. (26)[ch]	12	PI	12/0	6/0/6/0	14	C	na	Frenchay	
Brouwer et al. (27)[su]	14	PI	9/5	7/0/7/0	96	C	62	Tapping,MVC	
Brouwer et al. (27)	14	PI	11/3	6/0/8/0	1.4	S	67	Tapping, MVC	
Borich et al. (28)	36	PI	36/0	36/0/0/0	na	C	65	BBT	
Cakar et al. (29)	22	PI	22/0	3/10/9/0	na	C	64	Tapping, Brunnstom	
Freundlieb et al. (30)	12	PO	12/0	6/3/1/0	0.08	A	68	FM, JTI, 9HPT	2
Huynh et al. (31)	31	PO	na	17/14/0/0	0.2	A	64	FM	14
Jo et al. (32)	113**	PO	84/29**	75/21/0/17**	0.4**	S	58	FM	0
Liepert et al. (33)[a]	7	PI	na	0/7/0/0	na	S	73	GS, 9HPT	
Liepert et al. (33)[b]	13	PI	na	13/0/0/0	na	S	67	GS, 9HPT	
Liepert et al. (33)[c]	13	PI	na	13/0/0/0	na	S	63	GS, 9HPT	
Liepert et al. (33)[d]	10	PI	na	0/0/0/10	na	S	71	GS, 9HPT	
Pennisi et al. (34)	40	PI	40/0	40/0/0/0	na	C	64	MRC, 9HPT	
Shiner et al. (35)	9	PI	6/3	na	17	C	54	BBT, GS, FM	
Simis et al. (36)	35	PI	na	10/23/0/2	15	C	62	FM	
Stinear et al. (37)	46	PR	46/0	32/2/7/5	0.43	S	67	FM, ARAT	0
Takechi et al. (38)	24	PI/PO	10/14	24/0/0/0		S	64	FM,JTI, GS	
Takeuchi et al. (38)	38	PI	na	18/20/0/0	50	C	62	FM	
Thibaut et al. (39)	55	PI	49/6	na	31	C	62	FM	
Veldema et al. (40)	18	PI/PR	18/0	6/3/6/1	1.7	S	70	ARAT, WMFT	9
Ward et al. (25)	9	PI	na	8/0/0/0	11.5	C	48	9HPT	
Swayne et al. (41)	10	PI	10/0	5/1/3/0	na	S	58	9HPT	

*** Of the 113 patients, MEPs were elicited only in 40 patients (only them were used for correlation).*

N, number; I, ischemic stroke; H, hemorrhagic stroke; SC, subcortical; C, cortical; CSC, cortico-subcortical; BS, Brainstem; TPSO, time post-stroke onset; C, chronic; A, acute; S, subacute; PI, predict impairment; PO, predict outcome; PR, predict recovery; na, not available; BBT, Box and block test; FM, Fugl Meyer; GS, grip strength; MVC: maximal voluntary contraction; ARAT, Action Research Arm Test; 9HPT, 9-hole peg test; JTT, Jebsen Taylor test; WMFT, Wolf motor function test; FU, follow-up.

[a]group of patients with cortical lesions.

[b]group of patients with basal ganglia lesions.

[c]group pf patients with internal capsule lesions.

[d]group of patients with brainstem lesions.

ch: chronic stage group of Brouwers et al. (27); su: subacute stage group of Brouwers et al. (27).

impacts rMT values or its correlation with motor scores. As reported in **Table 4**, the results were quite heterogeneous, with no clear pattern indicating that rMT values relate to a specific location of stroke. In all these groups (C, CSC, SC), rMT in the AH was higher than in the UH. Although Liepert et al. (33) reported that the correlation between rMT and motor scores was only present in lesions involving the corticospinal tract at the subcortical level (internal capsule and pons) and not at the cortical level, these results were not confirmed by others. Indeed, Jo et al. (32) reveal no significant difference between each lesion site with respect to the stroke location classified as cortical, subcortical and brainstem. Overall, it is not possible to draw any conclusion on the potential impact of stroke location on rMT predictive value or its correlation with motor scores.

Risk of bias

Risk of individual bias: methodological quality assessment. All studies were assessed using the checklist designed by Chipchase et al. (23). The average quality score was 14.75 (SD: 2.53, ranging from 9 to 19). Two studies scored less than half the total score (i.e., 12) (36, 39). Five studies had a low risk (28%), 13 were unclear (72%) and none was rated with a high risk.

Risk of bias inherent to group analysis. As regards recruitment bias, all studies included patients with first-ever stroke with motor impairments. However, some of these added more inclusion criteria, especially for the type of stroke [i.e., lacunar in Pennisi et al. (34)] or for the severity of the motor deficits [at least 10 degrees of wrist extension for Simis et al. (36) and Thibaut et al. (39)]. These more stringent criteria could limit the extrapolation of these results. Publication bias may be caused, at least in part, by journal editors and reviewers who are more likely to accept studies with statistically significant results. Finally, there are others (methodological) biases given that confounding factors have not been taken into consideration.

Discussion

This systematic review provided two main findings. First, rMT often correlated with motor function or hand dexterity. Second, the results did not seem impacted by the duration of the disease (i.e., early or chronic stages). Two findings could not be properly interpreted: (i) the fact that rMT is an independent predictor

TABLE 2 | TMS measurements characteristics.

Study	Muscle	Type coil	Size coil	MEP size for determining rmt (microvolts)	Absence of MEP at T1	rMT AH	rMT UH	Imputation
Bastings et al. (26)	FDI	8-Coil	na	na	3 (25%)	70	67	Yes
Brouwer et al. (27) ch	FDI	8-Coil	80	50	2 (14%)	76	63	No
Brouwer et al. (27) su	FDI	8-Coil	80	50	3 (21%)	85	63	No
Borich et al. (28)	ECR	8-Coil	70	na	2 (6%)	43	41	No
Cakar et al. (29)	ADM	parabolic	na	50	na	50	37	No
Freundlieb et al. (30)	FDI	na	na	na	3 (25%)	35	38	No
Huynh et al. (31)	APB	circular	90	200	6 (19%)	66	58	Yes
Jo et al. (32)	FDI	8-Coil	70	50	73 (65%)**	51	na	No
Liepert et al. (33)[a]	FDI	8-Coil	na	50	na	56	46	na
Liepert et al. (33)[b]	FDI	8-Coil	na	50	na	55	44	na
Liepert et al. (33)[c]	FDI	8-Coil	na	50	na	50	45	na
Liepert et al. (33)[d]	FDI	8-Coil	na	50	na	59	45	na
Pennisi et al. (34)	FDI	circular	90	20	0 (0%)	48	42	No need
Shiner et al. (35)	FDI	circular	125	50	4 (44%)	na	na	Yes
Simis et al. (36)	FDI	na	na	50	3 (9%)**	na	na	No need
Stinear et al. (37)	ECR	8-Coil	70	70	10 (22%)	71	45	Yes
Takechi et al. (38)	FDI	8-Coil	90	50	10 (42%)	74	47	No
Takeuchi et al. (42)	FDI	8-Coil	70	50	20 (53%)**	52	52	No
Thibault et al. (39)	FDI	8-Coil	70	50	3 (5%)	C1: 59. C2 : 73	C1 : 52. C2 : 55	No
Veldema et al. (40)	APB	8-Coil	70	50	10 (56%)	86	64	Yes
Ward et al. (25)[b]	FDI	8-Coil	70	50	0 (0%)	58	Na	No need
Swayne et al. (41)	FDI	8-Coil	70	50	0 (0%)	64	42	Yes

*** (excluded from analysis).*

FDI, First Digital Interosseus; APB, Abductor Pollicis Brevis; ADM, Abductor Digiti Minimi; Na, not available; C1, center 1; C2, center 2; MEP, motor evoked potential; rMT, resting motor threshold; AH, affected hemisphere; UH, unaffected hemisphere.

[a]group of patients with cortical lesions.

[b]group of patients with basal ganglia lesions.

[c]group pf patients with internal capsule lesions.

[d]group of patients with brainstem lesions; ch: chronic stage group of Brouwers et al. (27); su, subacute stage group of Brouwers et al. (27). Imputation, imputation of MT in patients without MEPs.

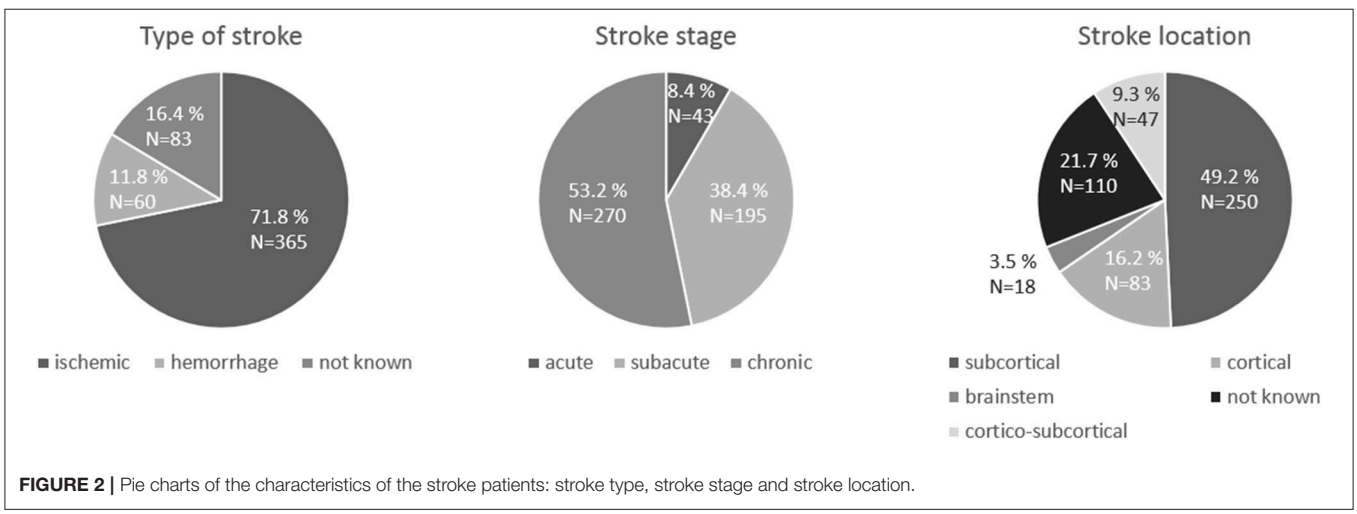

FIGURE 2 | Pie charts of the characteristics of the stroke patients: stroke type, stroke stage and stroke location.

of motor function given that several confounding factors are well-known and, (ii) whether the stroke location impacts this prediction.

MT as a predictor of upper limb motor function

Fifteen samples (68%) found a correlation between upper limb motor function and MT, wherein four of these confirmed

TABLE 3 | Resting motor threshold and correlation with clinical score with respect to time post-stroke onset.

	Acute *N* = 43	Subacute *N* = 195	Chronic *N* = 270	*P*-value S *vs.* C
rMT AH (% MSO)	51 ± 22	65 ± 13	58 ± 13	0.15
rMT UH (% MSO)	48 ± 14	49 ± 8	50 ± 11	0.90
MEP– (%)	22 ± 4	34 ± 24	17 ± 20	<0.001
Samples with non-significant correlations	2/2 (100%)	3/10 (30%)	2/10 (20%)	0.62
R2 (in samples with significant correlations)	–	30 ± 14	32 ± 18	0.69

S, Subacute; C, chronic; AH, affected hemisphere; UH, unaffected hemisphere; MEP-, patients in whom it was not possible to elicit MEP; MSO, Maximal stimulator output.

TABLE 4 | TMS characteristics of the four studies (seven samples) examining the impact of location on the correlation between rMT and motor scores.

	C *N* = 11	SC *N* = 46	CSC *N* = 12	BS *N* = 12
rMT AH (%MSO)				
Liepert et al. (33)	56 ± 12	53 ± 12	_	59 ± 11
Ward et al. (25)	_	57 ± 19	_	53 ± 2
Bastings et al. (26)	_	73 ± 17	82 ± 26	_
Veldema et al. (40)	96 ± 9	89 ± 19	78 ± 19	_
rMT UH (%MSO)				
Liepert et al. (33)	46 ± 6	45 ± 10	_	45 ± 8
Ward et al. (25)	_	_	_	_
Bastings et al. (26)	_	67 ± 12	68 ± 23	_
Veldema et al. (40)	54 ± 7	71 ± 19	60 ± 7	_

C, cortical; SC, subcortical; CSC, corticosubcortical; BS, brainstem; AH, affected hemisphere; UH, unaffected hemisphere; MSO, Maximal Stimulator Output.

it was an independent predictor using regression analysis. Among the seven samples in which no correlation was found to be significant, two were collected at the acute stage (<7 days).

rMT corresponds to the threshold where the pyramidal tract responds to the magnetic stimulus. However, the basic neurophysiology of rMT is incompletely understood regarding the generation of transmembrane excitation and is still a matter of debate (44). The hypothesis that could explain why rMT is correlated to motor function could be that it integrates many pieces of information about the structural and the functional integrity of the motor system. One current and a somehow logical statement is that rMT reflects the properties of the corticospinal tract. In one study (45), rMT was independently explained (R2: 13%) by the radial diffusivity in the internal capsule, suggesting that the coherence of the fiber orientation determines the intensity needed to produce a MEP. rMT has been shown to be correlated with the white matter properties of the premotor, motor, and prefrontal regions, supporting the hypothesis that fractional anisotropy is a surrogate marker of the organization of the cortico-cortical connections that may facilitate the depolarization of the primary motor cortex (M1) cells (46).

Second, as rMT reflects the neuronal membrane excitability, it strongly relates to the orientation and structure of the pyramidal cells within M1. Indeed, modeling studies have shown that individual cortical anatomy has a major impact on TMS-induced electrical field distributions (47–49). It has also been demonstrated that field strength significantly enhanced when currents run approximately perpendicular to the local orientation of the gyri (17, 50).

However, rMT could depend, not only on the neuronal membrane excitability by itself but also on the interactions of the vicinity on these cells (premotor and somatosensory cortices) that could modify the state of excitability. This statement is reinforced by the fact that TMS suffers from a poor spatial resolution. Using Dynamical Causal Modeling, an MRI technique that allows making inference between regions during a task, Sarfeld et al. (51) demonstrated that the higher the excitability of left M1 the stronger the coupling between left supplementary motor area and M1. In line with these results, we demonstrated in a previous study (52) that rMT was in part explained by the functional connectivity of the premotor cortex and M1. These results underlined the major role of the premotor areas and the cortico-cortical connections toward M1 in the excitation of the CST fibers (through trans-synaptic pathways).

Finally, if rMT integrates the information from M1 itself, and from the surrounding regions at the cortical level, it is also susceptible to synaptic influences at the spinal level. The corticomotoneuronal pathway is a disynaptic route where the first neuron makes its junction spinal motoneurons. Obviously, MEPs are influenced not only by the excitability of the corticospinal cells but also by the excitability of the spinal motoneurons to which they project (9, 10). It represents the sum of the events at all these synapses as well as the spinal postsynaptic excitability. Overall, this determines whether corticospinal cells are activated and synchronized.

Together, these suggest that altered rMT could relate to motor function outcomes.

To summarize, our results support the view that rMT could be a suitable biomarker of post-stroke motor function as it responds to the definition recently published as "an indicator of disease state that can be used as a measure of underlying molecular/cellular processes that may be difficult to measure directly in humans." This statement applies for the subacute and the chronic phase. This conclusion cannot be extrapolated to the acute phase, where the sample sizes were too small.

MT and stroke location

We could not draw a meaningful conclusion about whether location of stroke influences or not the association between rMT and motor outcome. If most of the samples reported stroke locations, only few of them performed subgroup analyses between cortical, subcortical and cortico-subcortical lesions.

Liepert et al. (33) reported a significant association between rMT and motor function only in lesions involving the CST at the subcortical level. This was explained by the fact that rMT was significantly higher in subcortical lesions whereas it did not

differ with respect to the UH for lesions encompassing M1 or the basal ganglia. These results were supported by others. According to Freundlieb et al. (30), purely subcortical lesions are more likely to globally disrupt efferent motor pathways and thereby to raise rMTs. This could be explained by the susceptibility to ischemia which could differ for low *vs.* high rMT pyramidal cells. There are also some reports in which (at least in the early post-stroke phase) rMT is higher in patients with subcortical compared to cortical ones (53, 54). Indeed, Delvaux et al. (55) reported near normal rMT in a group of patients studied the first day after a mainly cortical stroke (55). It may be that a subcortical lesion damaging a large number of densely packed fibers can compromise responsiveness to TMS more than a cortical lesion that often damages patchy areas of survived tissue. However, Catano et al. (56) found no clear association during the first 3 months post-stroke between rMT and lesion location (56). As this latter, when we reported rMT from the three other samples that provided individual patients data and allow us to analyse the rMT according to stroke location, we could not find a clear pattern of high rMT for subcortical and normal rMT for cortical strokes.

Limitations

As in all systematic review, and especially those who include studies with small sample sizes, our results should be taken with caution mainly because of methodological purposes. For example, from a technical perspective, most of our samples used 70 mm 8-shape coils but some used coils of different shapes and sizes that could influence the absolute value of the rMT. The definition of rMT was relatively homogeneous and in accordance with the IFCN definition (7) except in Huynh et al. (31). The number of trials was 5 out of 10 in 19 samples (86%). Second, the lack of individual patients data reported hampered us for more advanced statistics, and further analyses. Only four studies reported data for each patient for a total of 76 patients. Finally, the type of motor scores was quite heterogeneous. Some of them measured gross motor function (such as the Fugl-Meyer) while others measured fine dexterity (i.e., finger tapping, 9HPT) (57). We were not able to perform subgroups analysis according to gross or fine motor function assessment because of the small sample of studies included.

CONCLUSION

The results of this systematic review support the need for future work regarding the rMT as a potential biomarker of post-stroke upper limb motor function. Most of the studies found a correlation between rMT and clinical scores. However, it is still unclear if rMT is an independent predictor of upper limb motor function when taking into account for age, time post-stroke onset and level of CST damage as the main confounding factors. Clear-cut conclusions could not be drawn at that time but our results suggest that rMT could be a suitable candidate although future investigations are needed.

AUTHOR CONTRIBUTIONS

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

ACKNOWLEDGMENTS

We thank Eric Moulton for proofreading the English of our manuscript.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.01020/full#supplementary-material

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Conflict of Interest Statement: The 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.

frontiers in Neurology

BRIEF RESEARCH REPORT
published: 22 October 2018
doi: 10.3389/fneur.2018.00883

Measuring Habitual Arm Use Post-stroke With a Bilateral Time-Constrained Reaching Task

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Background: Spontaneous use of the more-affected arm is a meaningful indicator of stroke recovery. The Bilateral Arm Reaching Test (BART) was previously developed to quantify arm use by measuring arm choice to targets projected over a horizontal hemi-workspace. In order to improve clinical validity, we constrained the available movement time, thereby promoting more spontaneous decision making when selecting between the more-affected and less affected arm during the BART.

Methods: Twenty-two individuals with mild to moderate hemiparesis were tested with the time-based BART in three time-constraint conditions: no-time constraint, medium, and fast conditions. Arm use was measured across three sessions with a 2-week interval in a spontaneous choice block, in which participants were instructed to use either the more-affected or the less-affected arm to reach targets. We tested the effect of time-constraint condition on the more-affected arm use, external validity of the BART with the Actual Amount of Use Test (AAUT), and test-retest reliability across the three test sessions.

Results: The fast condition in the time-based BART showed reduced use of the more-affected arm compared to the no-time constraint condition ($P < 0.0001$) and the medium condition ($P = 0.0006$; Tukey *post hoc* analysis after mixed-effect linear regression). In addition, the fast condition showed strong correlation with the AAUT ($r = 0.829$, $P < 0.001$), and excellent test-retest reliability (ICC = 0.960, $P < 0.0001$).

Conclusion: The revised BART with a time-restricted fast condition provides an objective, accurate, and repeatable measure of spontaneous arm use in individuals with chronic stroke hemiparesis.

Keywords: stroke, hemiparesis, arm use, habitual choice, decision making

OPEN ACCESS

Edited by:
Pavel Lindberg, INSERM U894 Center de Psychiatrie et Neurosciences, France

Reviewed by:
Denise Taylor, Auckland University of Technology, New Zealand
Agnes Roby-Brami, Institut National de la Santé et de la Recherche Médicale (INSERM), France

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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *15 May 2018*
Accepted: *01 October 2018*
Published: *22 October 2018*

Citation:
Kim S, Park H, Han CE, Winstein CJ and Schweighofer N (2018) Measuring Habitual Arm Use Post-stroke With a Bilateral Time-Constrained Reaching Task. Front. Neurol. 9:883. doi: 10.3389/fneur.2018.00883

INTRODUCTION

Spontaneous use of the more-affected upper extremity post-stroke is often lower than would be expected from impairment levels (1, 2), with low use associated with a reduced quality of life (3). Besides the common therapy goal of improving motor performance of the more-affected arm/hand, an additional approach would be to influence the decision-making system (4), with the aim to improve use of the more-affected arm/hand.

The three instruments commonly used for measuring spontaneous arm/hand use in the natural environment are the Motor Activity Log [MAL; (5)], the Actual Amount of Use Test [AAUT; (6)], and accelerometers (7, 8). These instruments are not ideal, however: the MAL relies on self-reported ratings from memory; the AAUT cannot be administered repeatedly once participants recognize that they are being tested, thereby revealing its covert nature; and accelerometers only provide overall activity, and thus not a direct measure of functional arm use.

We previously developed a simple and objective assessment tool, the Bilateral Arm Reaching Test (BART) to address these limitations (1). With BART, arm use is measured in a *spontaneous choice block*, in which participants are instructed to choose either the more-affected or the less-affected arm to reach displayed targets on a table. Although arm use as assessed with BART showed good test-retest reliability, it was only moderately correlated with the AAUT (1). In seeking to improve BART, we sought a better way to capture real-world spontaneous arm use. We turned to previous research in decision-making (9–11). Contemporary decision models posit that choices between potentially rewarding actions are driven by a combination of a goal-oriented system and a habitual system. The goal-directed system is called "model-based" because individuals learn through experience, and then mentally simulate, models of the decision environment to prospectively evaluate the outcomes of possible actions. In contrast, the habitual system is "model-free," because choice is performed via direct comparison of expected rewards for each potential action (12). Mental simulations in the goal-directed system is a time-consuming process. As a result, performing choices under time-pressure enhances expression of the time-insensitive habitual system (13). For this reason, we modified BART by adding a short time-constraint condition to the experimental paradigm.

The aim of this study was to accurately quantify arm/hand use post-stroke with the time-based BART system. We hypothesized that a reduction of available decision time would reduce affected arm use. In addition, we reasoned that affected arm use in the time-constrained condition would more strongly correlate with arm use as assessed by the covert AAUT than arm use without time constraint.

MATERIALS AND METHODS

Participants

Twenty-two right-handed stroke participants with chronic stroke and mild to moderate upper extremity impairments were recruited as part of a sub-cohort of the DOSE phase 1 randomized controlled trial (NCT 01749358). Here, we only included baseline BART data, that is, data obtained before the DOSE intervention. Inclusion criteria were: (1) ischemic or intraparenchymal hemorrhagic stroke without intraventricular extension with confirmatory neuroimaging more than 180 days (6 months) after onset; (2) Age $\geq$21 and no upper limit; (3) impaired arm/hand motor function indicated by the Fugl-Meyer motor and coordination score no less than 19 out of 66 on the total motor score (14); (4) no arm/hand neglect as determined by Albert Test; (5) Mini-Mental State Examination (MMSE) score >24/30; and (6) no previous or current musculoskeletal injury or conditions that limited arm/hand use. We excluded participants if they were left-handed or could not reach the farthest straight-ahead target in the BART display (30 cm away from the home position; see below). The study was approved by the Human Research and Review Committee of the University of Southern California and each participant signed an informed consent.

Experimental Setup and Task

The time-based BART system consists of a computer, an overhead projector illuminating virtual targets on a table surface, two magnetic sensors placed on the index finger of each hand, and a seat belt to prevent compensational trunk movements during reaching (**Figure 1A**). The detailed physical set up is described in our previous study (1). At each trial, a virtual target (white disk, 2 cm in diameter) appeared at one of 35 possible target locations (**Figure 1B**). There were three movement duration conditions with three levels of time constraint: a no-time constraint, a medium time constraint, and a fast time constraint condition (**Figure 1C**). Whereas in the no time constraint condition, targets did not disappear until they were captured, in the fast and medium conditions, targets disappeared after movement onset following condition-dependent and target-dependent time constraints: 350–580 ms in the fast condition and 500 ms longer for all targets (i.e., 850–1,080 ms) in the medium condition. The target-dependent time constraints, which were estimated using previous reaching data from non-disabled participants, account for longer movement times for far away targets and for targets that require coordinated elbow and shoulder movements [see **Figure 1B** and (15)].

Each time-constraint condition consisted of a spontaneous choice block to measure spontaneous arm use and a forced choice block to measure performance of the investigator-specified limb (**Figure 1C**). Here, we only report results from the spontaneous choice blocks, which was always given before the forced choice blocks to prevent bias in hand use. In the spontaneous choice block, participants were free to choose either the more-affected or the less-affected arm to reach each target, with two trials per target (i.e., 70 trials per block). In each spontaneous choice block condition, we measured use in by counting the number of targets successfully captured using the more-affected arm, within the time constraint.

For the medium and fast speed conditions, a reminder block (similar to the spontaneous choice block, 35 trials per block) was provided before the spontaneous choice block (**Figure 1C**). Participants were asked to reach the targets as rapidly and accurately as possible throughout all conditions and blocks. Participants performed three BART sessions, with a 2-week interval between sessions.

Clinical Assessments

We used the Actual Amount of Use Test (AAUT), specifically, the AAUT quality of movement scale (QOM) to assess spontaneous use of the arm/hand (6, 16). From a videotaped record acquired without the participants' awareness (i.e., covert administration),

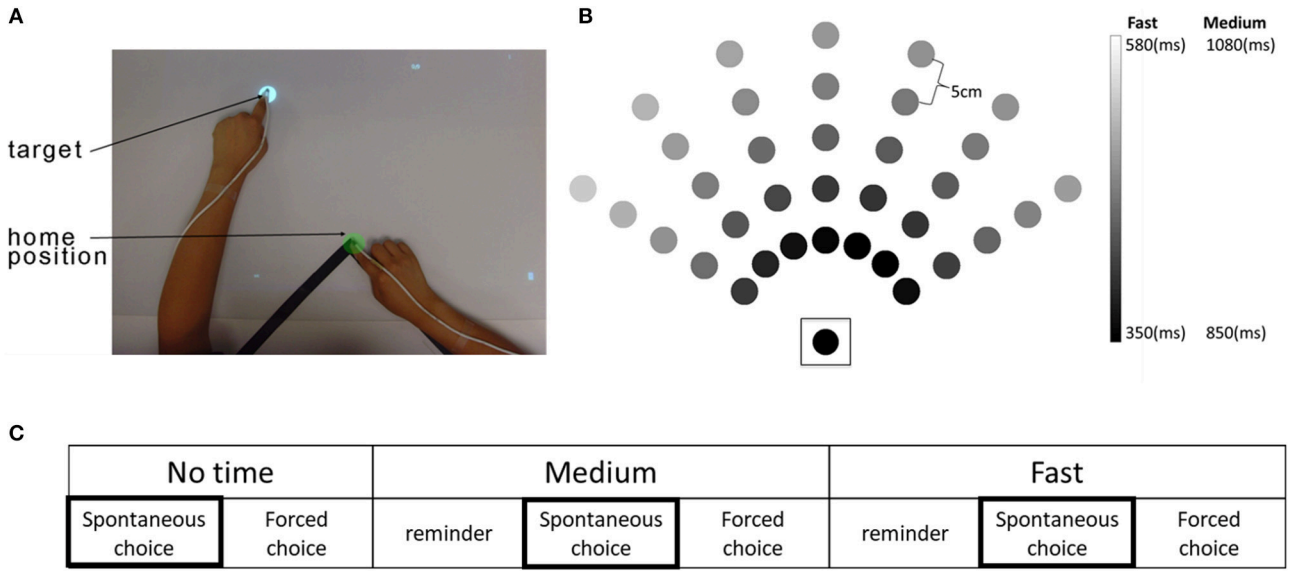

FIGURE 1 | The time-based Bilateral Arm Reaching Test (BART), target location, and experimental protocol. **(A)** Participants sat in a chair with a trunk-restraining belt. A magnetic sensor attached to the tips of each index finger. Home position and target are shown in green and white colors, respectively. **(B)** BART workspace with 35 targets (the home position is enclosed by a square). Movement duration constraints for each target varied as a function of target distance and angle. Shading shows the time constraints for each target in the medium and the fast conditions. **(C)** The experimental protocol. Each condition was presented in a spontaneous choice (participant chooses the arm/hand for the reach) and forced choice (investigator determines the arm/hand for the reach) block. A reminder block was given before the spontaneous choice block for both medium and fast conditions. Arm use/choice in the three spontaneous choice blocks was used for data analysis.

the trained and standardized evaluator scored the participants' spontaneous arm use behavior during 14 upper-extremity daily tasks, such as opening a file folder, and writing on and folding up a piece of paper. The QOM score for each item was averaged over the 14 tasks (6).

Statistical Analysis

The effect of the time constraint on arm use was analyzed using mixed effect models with condition (no time-, medium-, and fast-constraint) as fixed factors and participants as a random factor. *Post-hoc* analyses were performed using Tukey's test, which corrects for multiple comparisons. External validity for the no time, medium, and fast conditions, for the third test session was tested using correlations with the AAUT QOM. Test-retest reliability for the time-based BART was assessed using intraclass correlation coefficients (ICCs) for the three test sessions (test 1, 2, and 3). Significance threshold was set at $P = 0.05$, and statistics were run using customized code in R and MATLAB. All results are reported as average ± SEs.

RESULTS

Demographic information and stroke-specific characteristics are provided in **Supplementary Table 1**. **Figure 2A** shows the number of times the more-affected arm was successfully used across the three conditions. More-affected arm use decreased in the fast- (18.9 ± 2.9) compared to the medium- (27.5 ± 1.9) and compared to the no time constraint-condition (30.7 ± 1.8; $P < 0.0001$ between the fast- and no time constraint-condition, $P = 0.0006$ between the fast- and medium-condition).

Arm use computed in the fast condition was strongly correlated with AAUT QOM use score ($r = 0.829$, $P < 0.001$, Pearson correlation; **Figure 2B**). In contrast, arm use in the medium condition showed a moderately strong correlation with AAUT QOM ($r = 0.538$, $P = 0.009$, Spearman correlation), and arm use in the no-time constraint condition showed no significant correlation ($r = 0.363$, $P = 0.096$, Spearman correlation).

The fast condition showed excellent test-retest reliability (ICC = 0.960, $P < 0.0001$; **Figure 2C**). In contrast, the medium- and no time constraint conditions showed lower reliability (ICC for the medium condition: 0.815, $P < 0.0001$ and no time constraint condition: 0.691, $P < 0.0001$).

DISCUSSION

Our primary aim was to objectively quantify use of the more-affected arm during targeted reaching movements using a novel, theoretically-motivated, temporally-constrained version of BART in individuals post-stroke. Our results demonstrate that individuals in the chronic stage post-stroke with mild to moderate hemiparesis decrease their use of the more-affected arm in the fast condition, compared to the other two, less time constrained (no-time- and medium time constraint), conditions. In addition, and in support of our hypothesis, we found a strong and significant correlation between arm use measured in the fast time-constrained condition and arm use assessed with an often-used clinical tool, the AAUT QOM. Thus, the time-based BART appears to reflect an accurate assessment of real-world arm use. Compared to the original BART, this time-based BART may

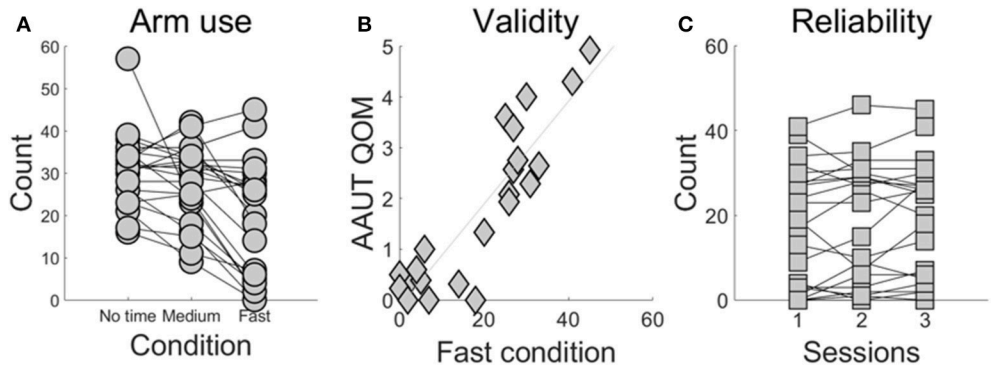

FIGURE 2 | BART assessment of use as a function time constraint condition **(A)**, external validity of the fast condition **(B)**, and test-retest reliability of the fast condition **(C)**. **(A)** Use of the more-affected arm in the fast condition is lower than use in the no time constraint and the medium condition ($P < 0.001$). Each line represents a participant post-stroke tested in the three conditions and each dot represents the number of targets that each subject successfully reached using the more-affected arm. **(B)** Arm use scores the fast condition and from the AAUT QOM show excellent correlation ($r = 0.829$, $P < 0.001$). **(C)** The fast condition shows excellent test-retest reliability (ICC = 0.960, $P < 0.0001$).

represent a more ecologically valid measure of arm choice/use, because it nudges the participant into decision-making under time pressure; a situation previously shown to enhance the expression of the habitual choice system (13).

Arm choice is a flexible and dynamic process that depends on the task environment. Previous research with non-disabled participants shows that arm choice is modulated by the task demands. For instances, (i) introduction of an abrupt force on one hand quickly reduces the choice of that hand for action (17), (ii) a reduction in target size leads to a reduced choice of the non-dominant hand (18), and (iii) a decreased success rate for one hand yields reduced choice of that hand (19). Additionally, individuals who are recovering from a stroke use their more-affected arm less as tasks became more challenging (20). In the time-based BART, the time constraint puts pressure on movement time as well as decision time. It is known that faster reaching is more challenging than reaching at preferred speed (21). Our results therefore indicate that, under time constraint, individuals with stroke decrease use of their more affected arm to maximize success with the task.

Thus, the time-based BART appears to be a viable alternative to the AAUT, because it captures use of the arm/hand objectively and repeatedly in chronic stroke survivors with mild to moderate arm/hand motor impairment. In addition, BART is easy to administer and requires minimal training.

However, additional testing is needed before the time-based BART can be used to replace the AAUT in the general stroke population for three reasons. First, we included a relatively small number of individuals chronically post-stroke, specifically, those with mild to moderate motor impairments. Second, because of the difficulty in recruiting pre-stroke left-hand dominant participants, we only included right-hand dominant individuals. Finally, because the no time constraint condition was presented first, participants may have accumulated fatigue by the time they experienced the fast condition (22). Thus, we cannot rule out the possibility that fatigue may have influenced use/choice of the more-affected arm in the fast condition. Nevertheless, we chose to start with the no time constraint condition in order to prevent "zero-use" of the more-affected arm in the fast condition, something we observed in our pilot studies, for some participants, regardless of capability to reach targets successfully.

Finally, given that the time-based BART assesses aiming movement, whereas the AAUT assesses both arm and hand movements that involve grasp manipulation or stabilization, and bi-manual tasks, one may question the validity findings. We offer four possible explanations: (i) the fast condition in the time-based BART provides an accurate expression of the habitual system for arm choice, in large part due to the time pressure which prevents full engagement of the goal-oriented system, (ii) the AAUT, by its covert nature, captures habitual and spontaneous use of the more-affected arm, (iii) both the BART and AAUT evaluate the speed and accuracy of the more-affected arm, (iv) the habitual system for arm choice is not well tuned to the specific task requirements. In contrast, the goal-oriented choice system would be, via simulation of the motor system, well-tuned to specific motor actions. Further work is needed to formally test these possibilities.

AUTHOR CONTRIBUTIONS

SK designed the study, piloted the study, ran the study, analyzed the data, wrote the manuscript; HP adapted the computer code, piloted the study; CH wrote the initial computer code, provided advice to the design; CW designed the study, wrote the manuscript; NS designed the study, wrote the manuscript.

FUNDING

Research reported in this publication was supported by the National Institute of Neurological Disorders And Stroke of the National Institutes of Health under Award Numbers R01 HD065438 and R56 NS100528. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

ACKNOWLEDGMENTS

The authors want to thank Drs. Jim Gordon and John Monterosso for their comments on an earlier draft.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2018.00883/full#supplementary-material

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Conflict of Interest Statement: The 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.

frontiers in Neurology

ORIGINAL RESEARCH
published: 11 October 2018
doi: 10.3389/fneur.2018.00854

Predicting Training Gain for a 3 Week Period of Arm Ability Training in the Subacute Stage After Stroke

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Background: Biomarkers for gains of evidence based interventions for upper limb motor training in the subacute stage following stroke have rarely been described. Information about these parameters might help to identify patients who benefit from specific interventions and to determine individually expected behavioral gains for a certain period of therapy.

Objective: To evaluate predictors for hand motor outcome after arm ability training in the subacute stage after stroke selected from known potentially relevant parameters (initial motor strength, structural integrity of the pyramidal tract and functional motor cortex integrity).

Methods: We applied the arm ability training (AAT) over 3 weeks to a subpopulation of stroke patients with mild arm paresis, i.e., in 14 patients on average 4 weeks after stroke. The following biomarkers were measured before therapy onset: grip strength on the affected hand, transcranial magnetic stimulation recruitment curve steepness over the primary motor hand area [slope ratio between the ipsilesional hemisphere (IH) and contralesional hemisphere (CH)], and diffusion weighted MRI fractional anisotropy (FA) in the posterior limb of the internal capsule (PLIC; determined as a lateralization index between IH and CH). Outcome was assessed as the AATgain (percentage improvement over training). The "Test d'Evaluation des Membres Supérieurs de Personnes Âgées" (TEMPA) was assessed before and after training to test for possible associations of AAT with activity of daily living.

Results: A stepwise linear regression identified the lateralization index of PLIC FA as the only significant predictor for AAT-gain ($R^2 = 0.519$; $P = 0.029$). AAT-gain was positively associated ($r = 0.59$; $P = 0.028$) with improvement in arm function during daily activities (TEMPA).

Conclusions: While all mildly affected patients achieved a clinically relevant therapeutic effect, pyramidal tract integrity nevertheless had a modifying role for clinical benefit.

Keywords: subacute stroke, pyramidal tract integrity, upper limb motor function, arm ability training, recruitment curve steepness, diffusion weighted imaging, diffusion tractography, longitudinal

OPEN ACCESS

Edited by:
Yves Vandermeeren, Université Catholique de Louvain, Belgium

Reviewed by:
Laurence Dricot, Université Catholique de Louvain, Belgium
Robbert-Jan Van Hooff, Zealand University Hospital, University of Copenhagen, Denmark

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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *24 April 2018*
Accepted: *21 September 2018*
Published: *11 October 2018*

Citation:
Lotze M, Roschka S, Domin M and Platz T (2018) Predicting Training Gain for a 3 Week Period of Arm Ability Training in the Subacute Stage After Stroke. Front. Neurol. 9:854. doi: 10.3389/fneur.2018.00854

INTRODUCTION

Hand motor outcome is one of the clinically most important parameters after stroke and about half of stroke survivors remain to be significantly delayed in distal pinch grip performance (1) 3 months after stroke. In order to understand mechanisms of motor recovery processes for evidence based interventions the identification of parameters able to predict motor gain during training is an important strategy. This might help to identify patients who are responding best for a given therapy and is an important step on the way for individualized therapy planning using biomarkers. It has been suggested before (2), that predictive parameters for upper limb outcome after stroke might be related to three aspects of motor system integrity: the initial motor performance (e.g., motor score), the functional integrity of the motor system [e.g., quantified by motor recruitment of hand muscles, indicated with motor evoked potential (MEP) amplitude height using transcranial magnetic stimulation (TMS)], and the structural integrity of the motor system [for white matter connectivity for instance the fractional anisotropy (FA) of the pyramidal tract at the height of the posterior limb of the internal capsule (PLIC)]. All these aspects contribute to the PREP1 algorithm (Predict Recovery Potential; Version 1) suggested for upper limb outcome prognosis from the subacute stage after stroke (3).

With respect to the motor outcome used for prediction, it is important to consider that those patients who are left with good motor performance initially are those who are leaving therapy near to normal (4, 5). Contrarily, those patients who are strongly impaired initially have a wider range for motor gain, i.e., no ceiling effect. Compared to the level of performance after training, gain might be better suited to indicate benefit by a given therapy approach in damaged patients. In addition, training gain directly expresses the effect of a specific training and according to the proportional recovery model it is likely to detect training effects among both more and less severely affected patients (6).

Secondly, TMS induced MEP amplitude is a clinically valid method for predicting motor outcome in patients after stroke (3, 7). The recruitment of motor assemblies in an increasing stimulus intensity protocol (recruitment curve steepness) and its ratio between the affected and the non-affected hemisphere has been described to be a valuable monitor for corticospinal integrity (8, 9).

Thirdly, PLIC FA has been reported in several studies to show a predictive value for motor impairment for the acute (10) to subacute (between 1 week and 3 months after onset) stage after stroke [for a recent review see (11)]. An earlier study determined the relevance of PLIC FA for Fugl-Meyer score gain after a 3 week of robotic therapy upper limb intervention (12). Riley et al. reported relevance of PLIC FA only of the part interconnected with the primary motor cortex (M1) and the dorsal premotor cortex (dPMC). Other compartments such as those interconnecting the supplementary motor area (SMA) or the ventral premotor cortex (vPMC) showed no relevance for impairment outcome.

We measured these three biomarkers before an impairment-oriented training (IOT) during inpatient rehabilitation therapy in the subacute stage after stroke on a number of stroke survivors with mild hand motor affection.

For IOT we applied the arm ability training (AAT), an evidence based training recommended for stroke patients with mild to moderate upper limb impairment and dexterity deficits (13). AAT was performed for a period of 3 weeks in the subacute stage after stroke (4 weeks on average). The predictive power of the three biomarkers for AAT gain was assessed using a stepwise linear regression. In order to assess the relevance of gain with training tasks for arm use during daily activities we correlated AAT-gain with those scored with the TEMPA, a timed measure of (non-trained) tasks resembling daily life activities (14).

METHODS

Participants

Overall 19 patients were recruited from the BDH Neurorehabilitation Center in Greifswald. All patients had been diagnosed with a first-ever unilateral supratentorial anterior circulation ischemic stroke. To be eligible for the motor training patients had to be able to grasp smaller objects and to move their arm against gravity [with a score of $\geq$3 at the Medical Research Council (MRC) scale for pinch grip and $\geq$4 for shoulder abduction and elbow flexion respectively with notable impairment (15)]. Other inclusion criteria were: (1) first ischemic supratentorial anterior circulation stroke, (2) unilateral upper limb impairment (3) no contraindications for MRI and TMS (e.g., ferromagnetic devices, epilepsy) (4) older than 18 years, (5) 2 weeks to 4 months after stroke, (6) no other neurological or psychiatric diseases, (7) no current pregnancy, (8) being able to consent for study participation (e.g., no severe cognitive impairment). Five patients initially recruited did not complete the study procedures and were drop-outs. Reasons for drop-out had been: inpatient rehabilitation therapy was not longer covered by health insurance, an additional stroke occurred, agoraphobia in the scanner tube, and lack of compliance. Complete data sets of 14 patients were included in the analysis (11 were male, 3 female; age 59.71 $\pm$ 12.10 years; range = 33–74 years; 12 right-handed; average score of handedness 82.6 $\pm$ 33.72 according to the Edinburg handedness inventory (16), Mini Mental Status (MMS) averaged on 27.00 $\pm$ 2.32, National Institutes of Health Stroke Scale [NIHSS (17)] with 2.64 $\pm$ 1.78, and lesion size was 7.09 $\pm$ 15.15 ccl (see lesion map on **Figure 1**, **Table 1**). With respect to initial motor impairment the Motricity Index (MI) Upper Extremity Score (17) ranged with 77–92 and the NIH stroke scale (NIHSS) ranged with 0–6, both indicating mild to moderate impairment. In addition, the REsistance to PAssive movement Scale [REPAS, arm score (18)] indicated mostly no spasticity (range 0–2). Patients were included 2 to 9 weeks after stroke (on average 4.61 $\pm$ 1.93 weeks).

Participants provided written informed consent and the study was approved by the Ethics Committee of the University Medicine Greifswald (BB51/07a).

Outcome Measure

We selected increase in AAT performance for the affected upper limb as measure of training gain. Duration (seconds) of

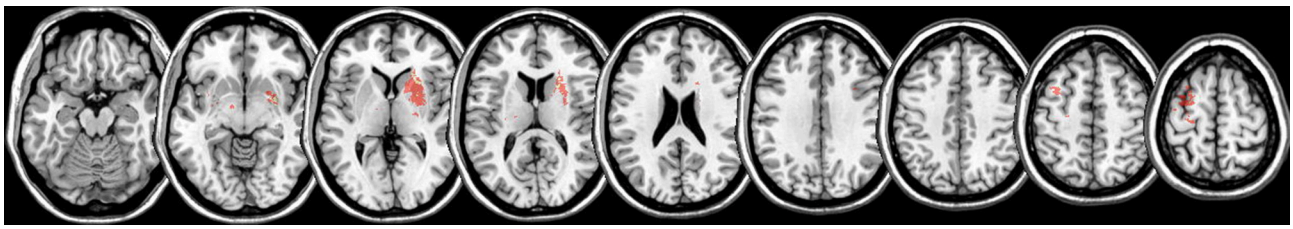

FIGURE 1 | Lesion map. Lesion mapping (color coded in red) overlay on the MNI reference brain for all 14 patients investigated. Predominantly right subcortical and left hemispheric cortical lesions are seen.

TABLE 1 | Demographic and clinical data of stroke patients.

Subject	Age	Gender (male/female)	Time since stroke (weeks)	Lesion hemis-phere	Lesion location[a] and volume (ccl)	MMST[b]	REPAS[c]	NIHSS[d]	MI[e]
1	65	m	2	Left	sc; put (0.2)	30	2	2	79
2	57	m	5	Left	sc; pt; ic (0.3)	27	1	1	92
3	45	m	5	Right	sc; pt; ic (0.6)	30	0	2	85
4	73	m	6	Left	c; M1; S1; parieto-temporal (57.5)	24	1	5	85
5	52	f	4	Left	sc; pt (1.2)	23	0	5	84
6	54	m	2.5	Left	sc; ec (0.3)	28	0	1	77
7	73	m	6	Left	sc; pt (3.4)	27	2	0	85
8	73	f	4.5	Left	sc, pt (1.0)	23	0	2	77
9	52	f	3	Right	sc; ic; put (11.0)	27	0	1	84
10	62	m	3	Left	sc, pt;(0.8)	28	0	6	84
11	74	m	4.5	Right	sc; pt; ic; put (14.4)	27	0	4	77
12	33	m	9	Left	sc; pt; ic (0.9)	30	0	3	77
13	57	m	3	Left	sc; pt; ic; put (6.1)	27	2	2	85
14	66	m	7	Right	sc; pt; ic; ec; put (2.2)	27	0	3	77

[a] *lesion location: sc, subcortical; c, cortical; ic, internal capsule; pt, pyramidal tract; ec, external capsule; M1, primary motor cortex; S1, primary sensorimotor cortex; put, putamen.*
[b] *MMST, mini mental status test.*
[c] *REPAS, resistance to passive movement scale, affected arm.*
[d] *NIHSS, National institutes of health stroke scale.*
[e] *MI, Motricity index.*

performance pre minus post was calculated, averaged over all 8 AAT tasks, and expressed individually as percent performance increase.

Associations of Outcome Measure Gain With Changes in Activities of Daily Living (ADL)

Transfer to non-trained tasks involving affected upper extremity arm use resembling activities of daily living was assessed as improvement in the TEMPA time score (14), documented before and after training.

General Study Design

Patients were preselected by SR within the first days when they entered the rehabilitation hospital. Our study occupational therapist (SR) and one of the neurologists (TP or ML) visited the patients for suitability for AAT training. When the patient consented to participate predictive parameters were assessed and intervention was started within 3 days. Intervention was provided for 3 weeks and post training measurement was completed within less than 3 days of training completion. **Figure 2** provides an overview on the study design.

Motor Training

Inpatient rehabilitation therapy was individualized to account for individual therapeutic goals for different domains (cognition, speech and language, arm rehabilitation, rehabilitation of stance, balance and gait, and psychological counseling). Overall, therapy amounted on average for 10 h therapy/week. In addition, all participants received the Arm Ability Training (AAT) 1 h per weekday for 3 weeks. This repetitive and standardized training targets different sensorimotor abilities such as fast finger movements, arm-hand steadiness, aiming, visuomotor tracking, and dexterity of the affected arm and hand (13). The AAT has been shown to be an effective training for mild to moderate arm paresis after stroke (18, 19). Training comprised eight different tasks for the affected arm and hand: aiming,

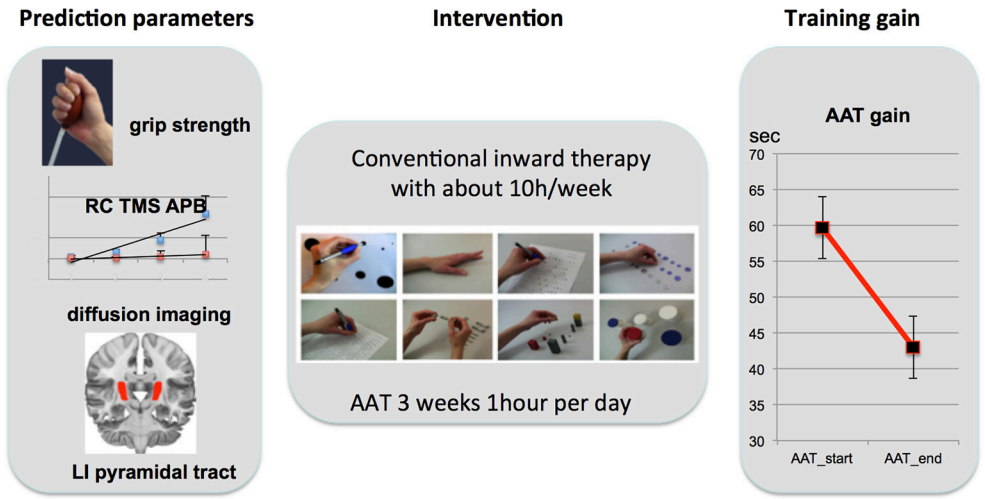

FIGURE 2 | Study Design. **Left**: Prediction parameters were selected from three different levels of motor integrity: motor function (grip strength), motor cortex neurophysiology [ratio of RC slope between the IH (red) and CH (blue); schematic plot of all participants; standard error indicated with lines over average plots; APB, abductor pollicis brevis], and structural integrity of the pyramidal tract (PT; lateralization index of fractional isotropy: LI_{FA}). Intervention (AAT; **middle**) was highly standardized in this trial with 1 h 5 days a week over 3 weeks. After 3 weeks of training motor gain was assessed with percentage improvement (**right**: decrease in execution time averaged over all 8 AAT tasks).

tapping, crossing circles, turning coins, labyrinth, nuts and bolts, placing small objects, placing large objects. The tasks were repetitively trained in blocks; four blocks for each task, each lasting approximately 1 min. At the first day of training, the individual number of repetitions within 1 min for each task and block was determined for every patient based on the patient's individual motor capacities and kept constant for the following training days. Time needed for the execution of each of the eight trained tasks was recorded daily by the therapist (SR). Improved performance was indicated by reduced execution time keeping accuracy demands of the tasks constant. For the pre assessment before training we averaged the first two AAT-testing runs for each subtest. For the post evaluation we averaged the last 2 measurements of day 15 for each subtest. Performance feedback was given verbally and visually as intermittent knowledge of result in order to maintain motivation.

MRI Data Acquisition

We used a 3T MRI-scanner (Verio, Siemens, Erlangen, Germany) with a 32 channel head coil. T1-weighted imaging for lesion mapping was carried out using a sagittal 3D MPRAGE with 176 slices, a spatial resolution of $0.98 \times 0.98 \times 1$ mm^3. The field of view was 250×250 mm^2 corresponding to an acquisition matrix of 256×256. Repetition time was 1690 ms, echo time 2.52 ms, total acquisition time 3:50 min. In both sequences GRAPPA with a PAT factor of 2 was used. In addition, we applied a Siemens MDDW (Multi Directional Diffusion Weighting) sequence with the following parameter setup: voxel size: $1.8 \times 1.8 \times 2.3$ mm^3, 55 slices, 1 acquisition and 64 directions. One b0-volume was measured and $b = 1000$ s/mm^2 was used for the diffusion-weighted images. TR was 10500 ms, TE: 107 ms and the total scan time was 12 min. No acquisition matrix interpolation was used.

MRI-Data Evaluation

Lesion Volumes

Lesion volumes were calculated by manually drawing the border of the lesion in the high-spatial-resolution T1-weighted image for each slice and by calculating the resulting volume (cc) with MRIcro (http://www.mccauslandcenter.sc.edu/crnl/mricro). Overlay of ROIs was visualized using Non Parametric Mapping (NPM; Chris Rorden; Vers. 2013).

DWI Data Evaluation

After conversion of the MDDW diffusion data to the NIFTI format, the FSL (v5.0.6) tool EDDY_CORRECT was used to correct for eddy-current and motion-related artifacts, including an appropriate correction of the diffusion gradient vector table. One participant (patient 14) had to be excluded from further DTI-analysis because of movement artifacts. The FSL-tool DTIFIT was used to calculate the diffusion tensor as well as related measures such as fractional anisotropy. Additionally, the individual T1 images were coregistered to their respective DWI data and, after skull stripping, (non-) linearly transformed to MNI space using FSL FLIRT and FNIRT. The combined inverse of the final non-linear transformation (DWI->T1->MNI) was created, allowing for a reverse-normalization of MNI space atlases or regions-of-interest into the individual subject space (20).

The binary ROIs of the pyramidal tract (posterior limb of the internal capsule, PLIC) [JHU Whitematter Label Atlas, (21, 22)] were transformed from MNI space into subject space using the

aforementioned inverse transformation and for each ROI the mean FA values were extracted.

The lateralization index for the fractional anisotropy between the ipsilesional and contralesional hemisphere were calculated as suggested before [(LI= FA_{IH}-FA_{CH})/(FA_{IH}+FA_{CH}); (9, 23, 24)].

FSL PROBTRACKX was used to differentiate compartments in the PLIC deriving from different seeds. Five cortical target regions were selected: vPMC [sphere of 10 mm around the cluster (MNI-coordinates: −48, 3, 21) showing an fMRI-increase over AAT in the same participants (25)], the dPMC, M1, S1were chosen from the Human Motor Area Template (26) and superior parietal lobe (SPL) from the Anatomy toolbox for SPM (27).

TMS-Measurement

Each participant's T1- MRI and head and brain surface models were used for stereotaxic co-registration of the participant's brain with the TMS coil. This enabled online neuroanatomic control of coil positioning during TMS assessment. Patients were seated in a reclining chair and instructed to remain relaxed. Surface electromyography (EMG) from participants' abductor pollicis brevis (APB) muscle was monitored using the motor evoked potential unit of (Dantec Keypoint® by Alpine Biomed ApS, Skovlunde, DK). Application of TMS was performed with a 75 mm figure-8 passively cooled coil (MCF-B65) and the MagPro X100 Magnetic Stimulator and (MagVenture A/S, Farum, DK). The TMS coil was oriented tangentially to the scalp with the handle pointing back and away from midline at 45° during stimulation of both primary motor cortices (M1).

The latency and amplitude of the M -waves were used as measures of α motoneuron excitability. M waves and MEPs were recorded from silver chloride surface electrodes overlying the APB muscle of each hand. M-waves were elicited using supramaximal electrical stimulation of the median nerve at the wrist. The resting motor threshold (RMT) and recruitment curves (RCs) were used as measures of corticomotor excitability. Relaxation was monitored by visual feedback of the EMG signal within sweeps of 100 ms from stimulus onset. After amplification and band-pass filtering (2 Hz to 10 kHz) the EMG signal was digitized and stored for off-line analysis. The RMT for each hand was defined as the minimum stimulus intensity that produced MEPs $>$ 50 μV in at least 5 of 10 consecutive trials. RCs were derived from the MEP amplitude obtained at 90, 110, 130, and 150% of RMTs, from 8 valid stimuli per intensity. Individual trials were examined, and any traces showing voluntary EMG activity or artifacts were discarded. The MEP amplitude was measured peak to peak from the average of 8 valid trials. MEP amplitudes for the RC were normalized to M-wave amplitude. MEP-amplitudes for the recruitment curves (RC) were divided by M-Wave-amplitude for each hand to provide a corrected MEP recruitment curve from the affected hemisphere of each patient [method adopted from Ward et al. (8)]. The slope of RC was determined from the line of best fit using least squares. We used the proportional relation (RC slope ratio) between the affected and the unaffected hemisphere, because we intended to express the decrease of motor recruitment instead of absolute values [again adopted from Ward et al. (8)].

Statistical Approach

All tests were performed with SPSS (Statistical Package for the Social Sciences; PASW-Statistics Version 21). Bilaterally assessed motor scores were tested for differences between affected and unaffected hand. As REPAS and MI are not interval scaled, these were tested with Wilcoxon paired tests, grip strength was tested using a pairwise *t*-test.

Associations of training gain were assessed with percentage AAT improvement and change scores of time needed to perform the different TEMPA tasks using Pearson correlation. Both scores were tested for significant differences between pre and post easurements using a paired *t*-test (AAT) or Wilcoxon paired *t*-tests (TEMPA affected and unaffected hand).

We tested for effects between the four TMS-measurements of recruitment curve steepness using a two by two rmANOVA with the factors TIME (pre, post) and SIDE (ipsilesional, contralesional).

For prediction of training gain (percentage AAT improvement) we first calculated Pearson correlations between each possible predictor and training gain. This analysis was restricted to those patients with complete assessments for all three aspects of motor integrity (grip strength, TMS-steepness ratio, LI_{FA} PLIC). In addition, these variables were entered into a stepwise linear regression analysis (probability to enter in the model $p = 0.05$; probability to leave the model $p = 0.10$) to determine an overall prediction model for training gain.

Furthermore, DTI-FA values for the differentiated PLIC compartments, i.e., connected to dPMC, vPMC, M1, S1, and superior parietal cortex were compared between the hemispheres using paired *t*-tests.

RESULTS

Motor Performance

Initially we found a marked difference in all motor parameters between the affected and unaffected hand: grip strength [$t_{(13)} = 5.72$; $p < 0.001$], REPAS ($z = 2.25$; $p = 0.024$) and MI ($z = 3.74$; $p < 0.001$). Arm ability training showed an overall average gain of 27.79 ± 4.70% from day 2 to day 15 which represents a relevant gain over time [$t_{(13)} = 20.07$; $p < 0.001$]. The time needed to perform the TEMPA tasks improved over time for the affected side (13.16 s; $z = 3.30$; $p = 0.001$) but not for the unaffected (1.96 s; $z = 1.85$; n.s.). Improvement in AAT and TEMPA for the affected upper limb were positively associated ($r = 0.59$; $p = 0.028$; see **Figure 3**).

TMS-Parameters

When testing for changes over time and differences between sides for the variable RC-steepness we found no significant effect, neither for time ($F = 0.33$; $p = 0.58$), nor for side ($F = 2.10$; $P = 0.18$), and no interaction (time * side: $F = 3.64$; $P = 0.089$).

Diffusion Tractography

FA-values between pyramidal tracts as measured at the height of the internal capsule/posterior limb differed significantly, i.e., were lower on the affected side (ipsilesional hemisphere, IH: 0.59 ± 0.066; contralesional hemisphere, CH: 0.68 ± 0.032;

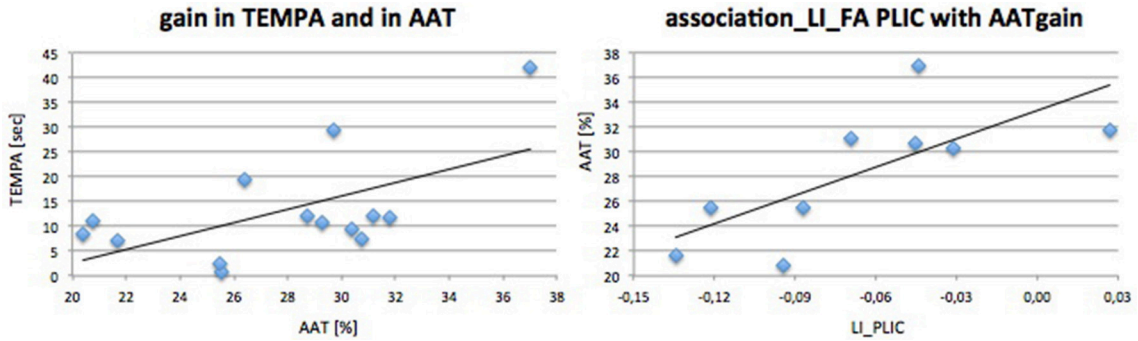

FIGURE 3 | Performance gain associations. Associations and linear regression plot of trained (AAT gain) and ADL (TEMPA)-motor score gain (**left**) and AAT gain with DTI FA PLIC (**right**).

$t_{(12)} = 4.59$; $p = 0.001$). Variability of PLIC FA-values was larger in the IH (SD = 0.066) than in the CH (SD = 0.032) illustrating the impact of lesion on PLIC FA.

When differentiating the pyramidal tract into subunits from five different motor regions such as dPMC, vPMC, M1, S1, and superior parietal cortex (see **Figure 4**) we found that only the compartments from dPMC and M1 differed between hemispheres regarding their FA values [dPMC: $t_{(13)} = 4.58$; $p_c = 0.005$; M1: $t_{(13)} = 3.39$; $p_c = 0.025$]. When testing for similarity of variances using a Levene Test (correcting for 5 comparisons) we found larger variances for the tract from the M1-seed ($F = 9.42$; pcorr = 0.025) and the tract from the vPMC-seed ($F = 11.06$; pcorr = 0.015) for the ipsilesional hemisphere compared to the contralesional.

Correlation of Initial Biomarkers With Motor Outcome After Treatment

Initial motor performance (grip strength) was negatively associated with AAT gain ($r = -0.68$; $p = 0.021$) indicating that those who were most impaired in hand flexion strength progressed best during training. LI_{FA} PLIC was positively associated with AAT gain ($r = 0.80$; $p = 0.005$). TMS steepness ratio was not associated with AAT gain. Outcome parameter and prediction parameters were independent of age or time since stroke.

Stepwise Linear Regression Analysis

FA asymmetry of the pyramidal tract was the only significant predictive factor for the primary outcome parameter (AAT gain: $R^2 = 0.519$; $t = 2.75$; $p = 0.029$, $\beta = 0.72$). Other factors (grip strength, TMS RC ratio) had no additional predictive value for training gain. No predictive value was observed when using the FA of each single compartment of the PLIC as a predictor for AAT gain.

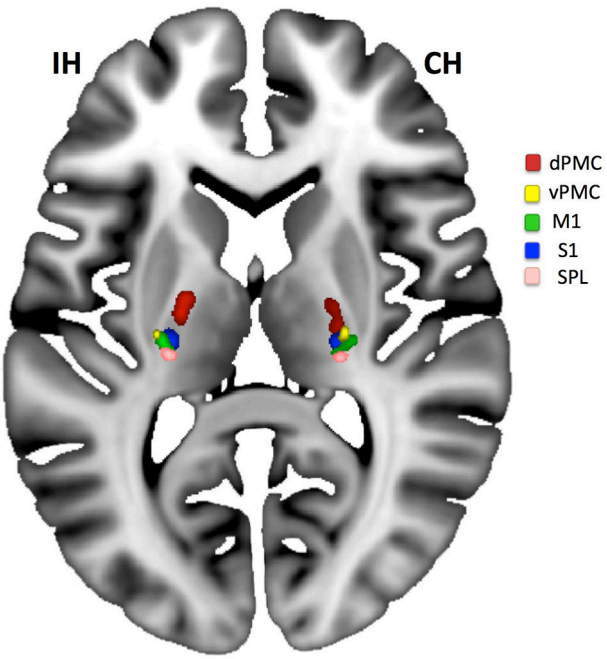

FIGURE 4 | Compartments of the PLIC. Compartments of PLIC calculated for the ipsilesional (IH) and contralesional (CH) hemisphere for all patients and overlaid on the MNI-reference brain. An area on the IH with lesion caused tract loss can be located between dPMC (red) and M1 (green)/S1 (blue). Only dPMC and M1 (if corrected for 5 comparisons) showed a significant decrease in FA when IH was compared to CH.

DISCUSSION

Our study identified that the pyramidal tract integrity was predictive for arm ability training gain for individuals in the subacute stage after stroke with a mildly impaired upper limb. Other factors tested had no relevant predictive effect on the primary outcome parameter. Training gain was positively associated with improvements observed with the TEMPA, a test resembling activities of daily living performed indicating a good generalization of recovered upper limb function by AAT to non-trained arm activities.

The data raises the question whether a lack of pyramidal tract integrity limits therapeutic achievement in absolute terms or would necessitate a longer span of therapy for a comparable achievement of high arm and hand motor function.

Other groups already reported the importance of pyramidal tract integrity for upper limb motor outcome in the subacute stage after stroke (7, 28). The asymmetry of fractional anisotropy within the posterior limb of the internal capsule expressed as a lateralization index (LI) is a robust quantitative parameter for assessing the intactness of the cortico-spinal tract (28). Tracts from the dorsal (dPMC) and ventral (vPMC) premotor cortex, the supplementary motor area (SMA), M1 and primary somatosensory cortex (S1), and superior parietal cortex are passing through this structure (29) enabling a global assessment of asymmetry in patients with only small lesions of the pyramidal tract. Our study extended the importance of PLIC integrity for patients in a subacute stage with only mild impediment of the upper limb function.

We applied a highly standardized, clinically effective, comprehensive and repetitive arm training over a period of 3 weeks (18, 19). It is noteworthy that we observed substantial behavioral gains across a set of different sensorimotor (AAT) tasks that involve different abilities with different learning dynamics (30) and different cortical network nodes (31). And yet, for all these tasks that showed parallel improvement over the course of 3 weeks in these stroke patients, the integrity of the efferent pathway determined about 50% ($R^2 = 0.519$) of the magnitude of recovery. While cortico-subcortical networks (32) are critically involved in learning induced by the AAT, the intactness of the corticospinal tract is highly relevant for any improvement of sensorimotor efficiency (33).

The impairment of primarily components of M1 and dPMC of the PLIC [see also (34)] was verified by a probabilistic differentiation of pyramidal tract compartments: only these two compartments showed relevant ipsilesional decrease. However, for all five compartments, the ipsilesional hemisphere descriptively showed a larger variance in FA-values indicating the impact of pathology on the FA-values which was absent for the contralesional hemisphere.

The moderate lesion load was due to our patient selection with inclusion of subjects with mild upper extremity paresis who are known to benefit from the AAT. In addition we applied the FA-PLIC asymmetry since this measure has been solidly proven before to be associated with upper limb motor outcome (9, 24). In consideration of the patients selection (optimal for AAT therapy), the lesions of patients were diverse (see **Figure 1**). This might well be the reason for no predictive value of a single compartment of the PLIC (see **Figure 4**) but an overall effect in stepwise linear regression for AAT gain instead.

In a recent meta-analysis the authors concluded that over different TMS-studies the affected hemisphere showed higher MEP-thresholds than the unaffected hemisphere or those observed in healthy controls (HC). In contrast, the unaffected hemisphere was not different in MEP compared to HC (35). We here used a lateralization index as suggested before (8, 9) and corrected for peripheral pathology (M-wave) to focus on central pathology following stroke. In spite of these normalization and correction processes TMS-parameters indicating M1 functional integrity showed no predictive value for therapeutic gain in our setting.

Although initial grip strength showed a negative association with AAT gain, indicating that those who are starting training with more strength impairment have more capacity to improve comprehensive motor function over time, it had no predictive value for AAT gain in stepwise linear regression. Strength of the affected hand has been demonstrated to be a valuable predictor in many upper limb motor outcome studies for the subacute stage after unilateral stroke [for extension (3); for flexion (36)]. However, Xu et al. (37) demonstrated that whereas strength predominantly recovers in the first 4 weeks after stroke other parameters such as independent movements of fingers, essential for precise movements as trained in the AAT, are recovering constantly over a longer period of about 3 months. Given the fact that our patients were included after 4.61 weeks after stroke on average, recovery of strength might have taken place already after inclusion of patients. This might well had an impact on the sensitivity of strength as a predictive measure.

Another explanation for our results might be that grip strength and PLIC integrity are both measures related to corticospinal tract integrity and that PLIC integrity had been the measure more directly linked to our outcome as also indicated by the univariate analyses. This again might be related to the fact that our measure of PLIC integrity integrated other relevant aspects such as dPMC connectivity in addition to M1 connectivity. Similarly, while M1 is crucial for motor learning and has its role with sensorimotor learning during the AAT (31), cortico-subcortical connectivity seemed to be more relevant as modifier of clinical benefit by the training, again presumably by its relevance for sensorimotor integration and learning (32).

The present work has some limitations. The usage of stepwise regression is suboptimal for the evaluation of biomarkers in small samples. Larger samples might be more sensitive for investigating the predictive value of TMS-parameters for motor gain associated with effective motor training for upper limb impairment after stroke. In addition, without a control group with no AAT we cannot conclude that changes observed were caused by the special impairment oriented training procedure. Subscore analysis of the eight different movement types trained in the AAT might differentiate even better who is profiting from which subtype of AAT. However, the small sample size did not allow for a further differentiation of analysis in subtests. The total AAT gain does, however, resemble an overall improvement in sensorimotor efficiency (30) which can be considered an important and clinically relevant information.

CONCLUSION

In a subgroup of stroke patients with mild arm paresis we demonstrated the predictive relevance of fractional anisotropy lateralization of the PLIC for the gain in a 3 week arm ability training. The training improved upper limb function on average by 27% and showed a significant positive association with improvement in arm function during daily activities. Especially for the early phase of training (first days) sensorimotor integration is extremely important for achieving gain in motor training (31, 32, 38). In addition, dPMC and vPMC

are especially important for gaining motor recovery after subcortical stroke [for dPMC (39, 40); for vPMC (25)]. A decrease of affected hemisphere pyramidal tract FA is therefore associated with impairment in sensorimotor integration hampering relearning of motor function especially in the early phase of training. In view of the limited number of subjects our data need to be interpreted cautiously. More longitudinal studies on evidence based interventions are needed with larger patient cohorts to not only understand the most robust predictors for arm ability outcome but also to find strategies for objective therapy decisions for individuals with motor impairment in an early stage after stroke.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the International Neuroscience Community and the German Community for Neurology. The protocol was approved by the Ethics Board of the University Medicine, Greifswald. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

AUTHOR CONTRIBUTIONS

ML and TP designed and supervised the study. SR performed the patient selection and training. MD and ML evaluated the data. All authors wrote the manuscript.

FUNDING

The study was funded by a grant from the German Research Community (DFG Lo795/7-1).

ACKNOWLEDGMENTS

We would like to thank Ulrike Horn for helpful comments on the manuscript.

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Conflict of Interest Statement: The 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.

The reviewer LD and handling Editor declared their shared affiliation.

frontiers in Neurology

ORIGINAL RESEARCH
published: 24 July 2018
doi: 10.3389/fneur.2018.00597

Predicting Gains With Visuospatial Training After Stroke Using an EEG Measure of Frontoparietal Circuit Function

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OPEN ACCESS

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Reviewed by:
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Shirley Ryan AbilityLab, United States

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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: 06 May 2018
Accepted: 04 July 2018
Published: 24 July 2018

Citation:
Zhou RJ, Hondori HM, Khademi M, Cassidy JM, Wu KM, Yang DZ, Kathuria N, Erani FR, Dodakian L, McKenzie A, Lopes CV, Scacchi W, Srinivasan R and Cramer SC (2018) Predicting Gains With Visuospatial Training After Stroke Using an EEG Measure of Frontoparietal Circuit Function. Front. Neurol. 9:597. doi: 10.3389/fneur.2018.00597

The heterogeneity of stroke prompts the need for predictors of individual treatment response to rehabilitation therapies. We previously studied healthy subjects with EEG and identified a frontoparietal circuit in which activity predicted training-related gains in visuomotor tracking. Here we asked whether activity in this same frontoparietal circuit also predicts training-related gains in visuomotor tracking in patients with chronic hemiparetic stroke. Subjects ($n = 12$) underwent dense-array EEG recording at rest, then received 8 sessions of visuomotor tracking training delivered via home-based telehealth methods. Subjects showed significant training-related gains in the primary behavioral endpoint, Success Rate score on a standardized test of visuomotor tracking, increasing an average of 24.2 ± 21.9% ($p = 0.003$). Activity in the circuit of interest, measured as coherence (20–30 Hz) between leads overlying ipsilesional frontal (motor cortex) and parietal lobe, significantly predicted training-related gains in visuomotor tracking change, measured as change in Success Rate score ($r = 0.61$, $p = 0.037$), supporting the main study hypothesis. Results were specific to the hypothesized ipsilesional motor-parietal circuit, as coherence within other circuits did not predict training-related gains. Analyses were repeated after removing the four subjects with injury to motor or parietal areas; this increased the strength of the association between activity in the circuit of interest and training-related gains. The current study found that (1) Eight sessions of training can significantly improve performance on a visuomotor task in patients with chronic stroke, (2) this improvement can be realized using home-based telehealth methods, (3) an EEG-based measure of frontoparietal circuit function predicts training-related behavioral gains arising from that circuit, as hypothesized and with specificity, and (4) incorporating measures of both neural function and neural injury improves prediction of stroke rehabilitation therapy effects.

Keywords: stroke, rehabilitation, electroencephalography, augmented reality, parietal lobe, motor, therapy, coherence

INTRODUCTION

Stroke remains a leading cause of adult disability. A number of treatment modalities are under study to improve outcomes, particularly for arm motor deficits, which are present in >80% of patients with stroke (1). These efforts are complicated by the fact that stroke is a heterogeneous condition, and so restorative therapies are not likely to benefit from a one-size-fits-all approach. Therefore, an intense area of research is the evaluation of methods to identify the target population for post-stroke restorative therapies.

One approach to identifying predictors of treatment response emphasizes measuring brain function at the circuit level. Measures of functional connectivity reliably correspond to behavioral deficits (2–5) and after stroke such measures can predict spontaneous (6) and treatment-related recovery (7–10). Furthermore, combining anatomical measures of injury with functional connectivity measurement improves the predictive value compared to either alone (9–12).

The current study extended this approach by providing training that targeted a specific neural circuit in order to test whether baseline function of a specific frontoparietal circuit predicts training-related gains in a behavior arising from that circuit's function. The motor-parietal circuit targeted in the current study was identified in a prior study of healthy subjects (13) that identified predictors of training-related gains in visuomotor tracking skill, a behavior central to many forms of rehabilitation therapy after stroke. In that study, a measure of coherence in the high beta band (20–30 Hz), recorded at rest using dense-array EEG, between leads overlying left primary motor area (M1) and a left parietal area (PAR) was a strong predictor of motor skill acquisition, exceeding the information provided by baseline behavior and demographic data.

The primary hypothesis of the current study was that high beta coherence in the same frontoparietal circuit, measured using identical EEG acquisition and analysis methods as in the prior study (13), would again predict training-related gains in visuomotor tracking skill. *Coherence is of interest* because it is considered to be a measure of functional connectivity between two brain regions. Coherence is estimated from EEG electrodes overlying the corresponding regions (14). Coherence ranges from zero to one, with a coherence value near one indicating EEG signals have similar phase and amplitude difference at all time points, and a coherence value near zero indicating signals have a random difference in phase and amplitude. Although coherence has been widely adopted in EEG studies as a surrogate marker of communication between cortical neural sources (14), there is potential that an observed increased in coherence may result from increased input from a tertiary common neural source (14, 15). Changes in coherence after stroke are thus seen as changes in functional connectivity and might result from a combination of injury (to cortical EEG sources or to white matter tracts connecting them) or from functional changes—a distinction examined in the current report. *The frontoparietal circuit is of interest* because of its established importance to visuomotor tracking, a behavior that is important to many activities of daily living and rehabilitation therapy regimens. Parietal cortex has direct and indirect anatomical connections with the precentral gyrus (16–19), which transmit information form parietal operations that include locating of the arm in space in a body-centered coordinate system (16, 20), processing spatial components of movement (21, 22), and transforming sensory information into information appropriate for action and thus providing visuomotor transformations (23) in relation to the dorsal visual stream (24) and in support of visuomotor tracking (25). The specific EEG leads defining the specific parietal-motor circuit of interest were defined in our prior study (13). *The high beta frequency range (20–30 Hz) is of interest* because it was informative in the prior study (13), and because it is known to be the frequency band most closely associated with function of the human motor system (26–28). The current study is focused on patients with stroke, among whom it is known that injury effects can be associated with changes in the distribution and magnitude of beta coherence (29–32).

The population evaluated in the current study was patients with chronic hemiparetic stroke. Training consisted of a 5-day protocol focused on visuomotor tracking, and was provided using augmented reality games, an approach we have found feasible in stroke survivors (33, 34). Three secondary hypotheses were (a) that training results would generalize but only to other visuomotor tracking assessments; (b) that incorporating a measure of anatomical injury would improve the relationship between circuit function and behavior; and (c) that only the hypothesized frontoparietal circuit would predict training-related gains, i.e., function of other circuits would not predict gains and thus current predictor findings would have specificity.

METHODS

Study Overview

Subjects meeting entry criteria (see **Table 1**) were recruited from the community via advertisements. Those meeting entry criteria underwent a 5-day protocol consisting of (a) testing at baseline, (b) training on visuomotor tracking skill across eight sessions, and (c) testing post-training Testing consisted of visuomotor tracking assessment plus a resting EEG recording. The first training session occurred at the lab in UC Irvine following baseline assessments. The second training session occurred later that same day (Day 1), and the remaining six training sessions were twice/day over the next 3 days (Days 2–4) and took place in the subject's home. Subjects returned to the lab on Day 5 for post-training assessments.

The primary behavioral endpoint of this study was the ability to successfully track a moving target, calculated as the Success Rate (SR) score and expressed as percent change over time (i.e., from pre-training to post-training). The secondary behavioral endpoint was the percentage of error a patient made tracking the moving target, referred to as Error Rate (ER) score.

This study was carried out in accordance with the recommendations of, and the protocol was approved by, the University of California, Irvine Institutional Review Board. All subjects gave written informed consent in accordance with the Declaration of Helsinki.

TABLE 1 | Entry and exclusion criteria.

Entry Criteria	Exclusion Criteria
Age > 18 years	Significant difficulty maintaining attention or understanding instructions
Prior diagnosis of stroke, radiologically confirmed	Advanced liver, kidney, heart, or lung disease
English speaking	Major neurological, psychiatric, or medical disease
Arm weakness arising from stroke	Co-existing diagnosis having a major effect on arm/hand function
Able to attend and participate in all visits and sessions	Unable to successfully perform the test exercise examples
Ability to move at least 3 blocks over 60 s on the Box & Block test using the paretic arm	

Subject Characteristics

A total of 12 subjects were studied (**Table 2**). There was 1 female and 11 males. All were right-handed. The infarct affected the left brain in seven and right brain in five. No subject was receiving concurrent occupational or physical therapy. Average years of education was 16.1 ± 3.1. The stroke was ischemic in 10 and hemorrhagic in two. The infarct (**Figure 1**) injured the hand area of primary motor cortex in four subjects, among whom 9.4 ± 10.0% of this region was injured. The infarct injured the parietal lobe in three of these subjects, among whom superior parietal lobule injury averaged 27.1 ± 26.3% and inferior parietal lobule injury averaged 13.3 ± 10.4%. Subjects had mild to moderate motor impairment at baseline, e.g., median Box and Blocks score was 13 [IQR = 7–20], which was 18.2% [IQR 8.6–27.8] of age/gender-adjusted normal values (35).

The AR system set up in each subject's home operated correctly throughout the week. All but one subject completed all eight visuomotor training sessions. One subject skipped a single home-based session due to a schedule conflict. Although subjects were instructed to perform only two training sessions each day, one subject performed an extra three sessions during the week.

Behavioral Assessments

At the baseline visit (Day 1), prior to any visuomotor skill testing or training, demographic data were recorded, as was handedness (36). Depression was scored using the Geriatric Depression Scale (37), which ranges from 0 to 15, with higher scores indicating greater depression and with a score of 5 or higher suggesting depression. Manual dexterity was measured using the Box & Blocks Test (38), which counts the number of blocks transferred across a table and over an obstacle by the paretic arm during 60 s.

Subjects also underwent serial behavioral testing, once at the baseline visit (Day 1) and again post-training (Day 5); for any given subject, a single examiner performed all assessments. Next, subjects were scored on three tests of visuospatial skill: (1) *The Symbol Digit Modalities Test*, which assesses divided attention, visual scanning, tracking, and motor speed (39). Subjects are given a score sheet in which they match symbols to corresponding digits. Subjects are given a 10-item practice before beginning the actual test. The test consists of 110 symbols and subjects are given 90 s to complete as many as possible, in sequential order. (2) *The Bells Test* (40), which assesses visual inattention. Subjects view a score sheet with 35 bells hidden among 14 possible distracter items. Subjects are instructed to circle as many bells on the scoring sheet as possible, with no time limit. The primary measure for the Bells Test is the number of bells circled; time to completion is also measured secondarily. (3) *The Benton Judgment of Line Orientation Short Form* (41), which assesses spatial perception and orientation. Subjects are presented with 30 items and for each compare the orientation of two lines displayed in a booklet to a fan of all possible line orientations. Both lines have to be correctly identified to be considered a correct response. Items were ordered based on difficulty and subjects would move up in difficulty to establish a basal rate of 6 correct items plus a ceiling rule of 6 incorrect items. As a broad test of cognitive status, subjects also completed the Trailmaking A & B tests (42); for Trailmaking A, subjects were given 2 min to complete the test, and for Trailmaking B subjects were given 4 min. Computerized testing of reaction time (mean of 20 runs) was also obtained.

EEG Studies

EEG Acquisition

Dense-array EEG was acquired at two time points. The first was at the Day 1 baseline visit and was used to address the primary study hypothesis. The second was at the Day 5 post-training visit and was used to examine a secondary hypothesis regarding change in EEG in relation to training-related behavioral gains. Awake, resting-state EEG was acquired for 180 s. Data were collected using a 256-lead Hydrocel net at 1,000 samples/s with a high input impedance Net Amp 300 amplifier and Net Station 4.5.3 software (ElectricalGeodesics, Inc., Eugene, OR). EEG signal was referenced to Cz during recording and re-referenced to the average of all leads for analysis. EEG signal was recorded without bandpass filters. During EEG acquisition, participants were instructed to hold still with the forearms resting on the anterior thigh and to direct their gaze at a fixation cross.

EEG Analysis

EEG data were exported to Matlab (R2015a, MathWorks, Inc., Natick, MA) for preprocessing. The continuous EEG signal was low-pass filtered at 50 Hz, segmented into non-overlapping 1-s epochs, and detrended. Visual inspection and independent components analysis were used in combination to remove extra-brain artifacts from the EEG, as described previously (13). This included removing epochs contaminated by overt muscle activity, eye blinks, eye movements, and heart rhythms (43).

Next, EEG data underwent an Infomax ICA decomposition [EEGLAB (44)]. Components that only occurred in one channel or with high activity in 35–50 Hz frequency band, as typified by muscle artifact, were automatically rejected. Of the remaining components, amplitude topography, frequency spectra, and component time series were inspected to identify eye blinks, eye movements, and heart rhythms, and were removed.

TABLE 2 | Subject characteristics.

Baseline (Pre-Training)		Post-Training scores	Percent change over one week	
			Value	*P*
Age	63.8 ± 10.7			
Time post stroke (months)	35 ± 26			
Infarct volume (cc)	17.2 ± 25.3			
Geriatric depression score	2.4 ± 2.2			
Box & blocks score	14.9 ± 11.8			
Symbol digit modality test (out of 110)	34.3 ± 10.7	36.2 ± 13.8	12.7 ± 13.0	0.004
Bells test (Total number circled out of 35)	31.1 ± 6.3	34 ± 1.8	14.8 ± 29.4	0.039
Bells test (Time in seconds)	203.5 ± 54.4	172.6 ± 71.8	−11.2 ± 37.4	0.37
Benton judgment of line orientation (out of 30)	24.8 ± 4.8	25.3 ± 5.4	1.6 ± 9.4	0.57
Trailmaking A (Time in seconds)	49.6 ± 30.1	48.5 ± 34.3	−4.5 ± 15.4	0.38
Trailmaking B (Time in seconds)	107.7 ± 67.8	97.6 ± 74.3	−11.2 ± 27.8	0.25
Success rate score	60.5 ± 11.5	74.0 ± 13.2	24.2 ± 21.9	0.003
Error rate score	32.1 ± 5.3	26.5 ± 5.8	16.7 ± 16.9	0.01

All subjects completed all 25 Trailmaking A and B targets. Values are mean ± SD. P refers to significance of change over 1 week.

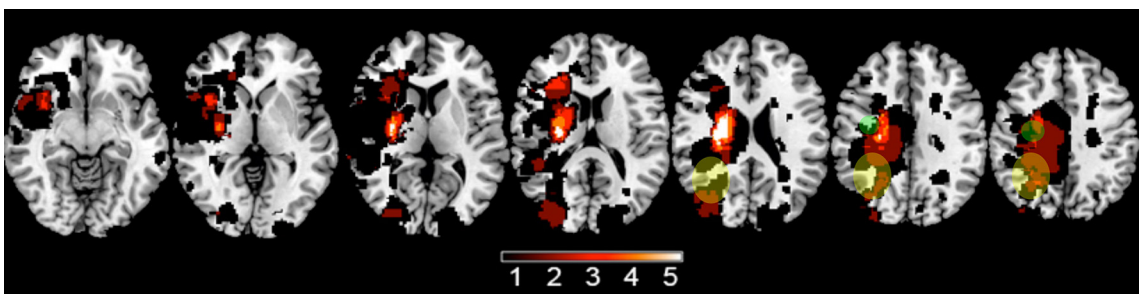

FIGURE 1 | A lesion overlay plot shows the 12 infarcts among study subjects. The color bar indicates the number of subjects with an infarct at any given brain pixel. The green circles approximate the location of the iM1 region analyzed, and the yellow ellipses approximate the location of the iPAR region.

Extraction of EEG Coherence Measures

The primary EEG endpoint was coherence between a seed region, consisting of leads overlying ipsilesional hand of primary motor cortex (iM1), and an ipsilesional parietal lobe region (iPAR), measured in the high beta (20–30 Hz) band. The iPAR region contained 21 leads over the lateral PAR area and was identified in a prior EEG study as the area for which high beta band coherence with M1 predicted learning during visuospatial skill training in healthy young subjects (13). The iM1 seed region included C3 and the six immediately surrounding electrodes. Secondary EEG measures were high beta coherence between iM1 and leads overlying either (a) contralesional PAR, (b) contralesional M1, (c) ipsilesional frontal/dorsal premotor cortex, (d) ipsilesional prefrontal cortex, (e) ipsilesional medial PAR, and (f) as a negative control ipsilesional primary visual cortex.

Visuomotor Tracking Skill Training

Augmented Reality System

Subjects sat with their paretic forearm on a desk onto which moving virtual targets were presented, and as part of game play had to track the targets to earn points. Subjects were introduced to the system and had the first training sessions during the baseline visit, then the same system was delivered to the subject's home, where subjects underwent seven additional training sessions over 4 days.

The augmented reality (AR) approach used for visuomotor tracking skill training enabled subjects to interact in the real world tabletop workspace with virtual objects projected by a computer (45). The AR system consisted of a (1) computer (Dell Latitude E5420 laptop running Windows 7 Home Premium with Intel Core i5-2430M CPU @ 2.40 GHz and 4 GB RAM), (2) camera (PlayStation Eye), (3) projector (AAXA LED Android Pico Projector) that presented onto the tabletop images that were rapidly updated according to camera data, (4) chair, (5) table, and (6) LED-and infrared-equipped splint that the subject donned then moved around the tabletop. Before starting each session, subjects placed onto the paretic forearm a wrist splint that had two co-localized lights fixed on its superior aspect (**Figure 2**). One was an infrared (IR) light that allowed the camera to locate the splint's location on the tabletop, tracking hand movements in real time to drive game play, and the other was

a red LED light that allowed the patient to see the precise spot that served as the cursor during game play. IR light data was fed to the computer, allowing the projector to provide tabletop game images that varied in real time according to the subject's game play movements. The projector was mounted 39″, and the camera 35″, above the table using an aluminum stand, generating a projected image size of 18 3/8″ × 29″ upon the table.

Baseline Testing

On Day 1, each subject was tested to define the optimal speed for visuomotor tracking learning. The subject donned the splint and then played a tracking game for which the speed of the tracked target increased across successive rounds. The target moved in a cloverleaf pattern, and the subject was instructed to move their paretic hand as fast as possible while keeping the red LED over the target. Error was calculated as the Euclidean distance between the pixel representing the center of the splint's IR light (i) and the center of the target (j): $[(x_i\text{-}x_j)^2+(y_i\text{-}y_j)^2]^{0.5}$. A distance <32 pixels was considered a success. The success rate for each round was calculated by dividing the total number of successful instances by the total number of instances. Across successive rounds, the speed of target movement was plotted against success rate, generating a sigmoidal curve for which the left tail asymptote was too simple/no error, and the right tail asymptote was too hard/maximum error. An individual subject's training speed was defined at 60% of the speed associated with maximum error.

Next, having defined the subject's training speed, a baseline test of visuomotor tracking skill was given, and repeated three times. The target moved in the same cloverleaf pattern as above, with each run of this test lasted 90 s.

The six games were then explained to the subject, including the target to be tracked in each game. The subject was taught how to independently don the wrist splint and how to initiate a training session on the computer. Next, the subject performed the first training session (see below) in the lab, under supervision. A member of the study team then delivered and setup the visuomotor tracking training system in the subject's home.

Eight Training Sessions Spanning 4 Days

The first training session was on Day 1, in the lab, following baseline testing. The remaining sessions were in the subject's home. The second training session was one on Day 1, at least 4 h after the first. Training sessions 3–8 were on Days 2–4, during which subjects were instructed to perform one training session in the morning and one in the evening with a minimum 4-h break between sessions. During each training session, subjects played each of the 6 games in succession. Training sessions lasted 20–30 min, depending on the subject's designated playing speed.

Repeat Testing Post-training

On Day 5, the subject returned to the lab. The same test of visuomotor tracking skill from Day 1 was again performed and again repeated three times, using the same individualized speed as at baseline. A member of the study team then removed the visuomotor tracking training system from the subject's home. Compliance with training at sessions was determined offline, once the system was returned to the lab.

Augmented Reality Games

For all six games (**Figure 2**), subjects were instructed to move the paretic hand to maintain the red LED over that game's target. Games were played at the subject's designated speed (see above). Each game lasted 3–5 min, with exact duration varying according to the subject's designated playing speed. All of these games were developed specifically for this experiment, and they contained enough instrumentation to collect all necessary data.

(1) Paparazzi game: Subjects were to maintain the splint's red LED atop a white limousine that drove around the table surface, and also stopped intermittently. The car glowed yellow when the subject was on target. When stopped, a celebrity photo was revealed and cheers were played if the subject was on target >60% of the time.

(2) Frog game: Subjects controlled the movements of a frog and were to keep the frog on a lily pad that moved across the tabletop. The lily pad turned bright green when the frog was on target. Intermittently a bubbling sound played, foreshadowing the appearance of a crocodile on the lily pad. Subjects were instructed to move away from the lily pad when the crocodile appeared.

(3) Map game: Subjects were to keep the LED atop a helicopter as it moved a circuitous route across a map of the continental USA. The helicopter stopped intermittently. If subject was able to stay on target >60% of the time prior to a stop, music played and images were displayed that were related to the city at which the helicopter was stopped.

(4) Mario game: Subjects controlled the movements of a Mario character to follow a gold coin as it moved around the bottom 2/3 of the projection. The top 1/3 of the projection had a moving green gift box. At various times, the gold coin disappeared as the green box opened to reveal either a sack of coins or a red monster. The subjects were instructed to move toward the sack of coins and away from the red monster.

(5) Outline game: Subjects maintained the splint LED atop a simple target displayed on the table that moved along a path that outlined a simple line drawing. Each round displayed 1 of 20 simple line drawings. Once the drawing was complete, the actual outlined shape was presented alongside the subject's attempt. Four shapes were outlined each round of game play.

(6) UFO game: Subjects maintained the splint LED atop a UFO as it flew around a background of space and the Earth. If subjects stayed on the UFO >60% of the time, the UFO exploded; if not, the Earth exploded.

Visuomotor Tracking Skill Performance Measures

The primary visuomotor tracking skill behavioral measure was the SR score, modeled after our prior approach to AR training (34). The SR score was determined by calculating the Euclidean distance between the pixel representing the center of the IR light and the center of the target. As during baseline testing, a distance <32 pixels was considered a success. This was repeated 30 times/s, and the final SR score for a given game was the proportion of assessments that were a success * 100. A

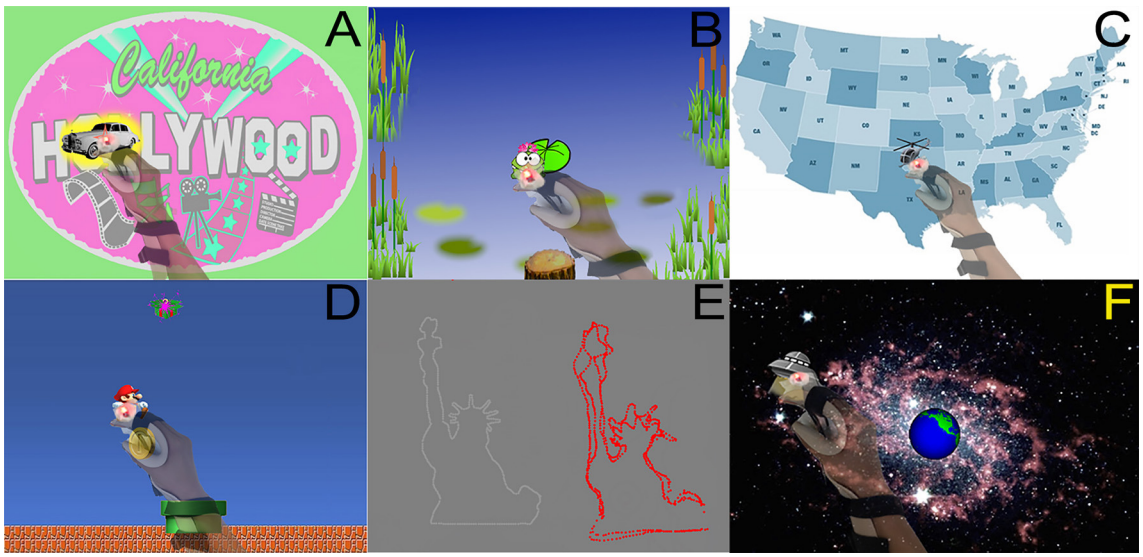

FIGURE 2 | (A) Paparazzi game, whereby subject maintained the splint's red LED light over the white limousine. The yellow highlight around the car indicates that the subject is currently on the target. **(B)** Frog game, whereby a frog controlled by the subject's movements was to be kept on a lily pad. The lily pad turned bright green when the frog was on target. **(C)** Map game, during which the subject kept the LED over the flying helicopter as it traveled a circuitous route across the continental USA. **(D)** Mario game, whereby a Mario character controlled by the splint follows a gold coin and moves toward or away from a green gift box depending on the contents of the box when they are revealed. **(E)** Outline game, whereby a subject used the splint LED to carefully follow a target as it outlined 1 of 20 different shapes (such as the Statue of Liberty). After each round, the actual outlined shape (in white) was presented alongside the subject's attempts (in red). **(F)** UFO game, whereby the splint LED followed a UFO to prevent it from destroying the Earth.

secondary tracking skill behavioral measure was the ER score, which weighted each Euclidean distance by the magnitude of the distance.

MRI Data

Images demonstrating the index infarct were retrieved from medical records. Images available consisted of a clinical MRI in seven subjects (T2-weighted images and DWI) and a research MRI in five subjects (T1-weighted images), which in all cases were sufficient to visualize and outline the infarct (see **Figure 1**). Using methods described previously (46), a mask of each subject's stroke was generated by outlining the infarct in MRIcron. Masks were transformed into MNI stereotaxic space using FSL then binarized. Infarct volume was calculated, then the extent to which each infarct overlapped with two regions of interest [motor cortex (precentral gyrus) and parietal lobe (superior and inferior parietal lobules)] (47) was determined for each subject.

Statistics

Bivariate analyses were used to determine correlation in ROI-based brain-behavior relationships. Statistical significance was set at $p < 0.05$. Nonparametric statistical analyses were employed because many measures were not normally distributed and could not be transformed to normality, thus analyses focused on correlation or prediction employed the Spearman rank correlation coefficient and analyses focused on within subject change over time employed the Wilcoxon signed rank test. A secondary analysis reanalyzed the primary study hypothesis excluding four subjects who had damage to either brain region (M1 or PAR lobe) from which the primary EEG outcome measure was derived. Statistical analyses were performed using JMP 8.0.2.

RESULTS

Baseline Visuomotor Tracking Performance

Baseline score for the primary endpoint, SR score, was 60.5 ± 11.5%. Baseline score for the secondary endpoint, ER score, was 32.1 ± 5.3%. Baseline SR and ER scores were related ($r = -0.90$, $p < 0.001$).

Change in Tracking Performance Across the Week of Visuomotor Training

Subjects showed significant gains after training on the home-based AR system. Mean SR score increased (improved) to 74 ± 13.2% after training, a relative gain of 24.2 ± 21.9% ($p = 0.003$). Likewise, mean ER score fell (improved) to 26.5 ± 5.8% after training, a relative change of 16.7 ± 16.9% ($p = 0.01$). Change in SR score and in ER score were significantly related ($r = 0.94$, $p < 0.0001$).

Several other behavioral measures also showed significant change over time. Of the three visuospatial tasks tested before and after training, two showed significant improvement: Symbol Digit Modality score improved by 4.2 ± 3.8, a 12.7% relative improvement ($p = 0.004$), and the number of bells circled on the Bells Test rose by 2.9 ± 5.1, a 14.8% improvement ($p = 0.039$). Change in the score on the Benton Judgment of Line Orientation was 0.42 ± 2.1

(1.6% relative change) and was not significant ($p = 0.57$). Change over time in Trailmaking A time, Trailmaking B time, and reaction time was also not significant ($p \geq 0.25$).

Predicting Change in Visuomotor Tracking Performance

Data support the primary study hypothesis: individual gains in visuomotor tracking performance from baseline to post-training were significantly predicted by the hypothesized EEG-based measure of frontoparietal connectivity in the high beta band that was measured at baseline. Specifically, coherence between leads overlying iM1 and iPAR in the high beta band correlated with training-related gains in visuomotor tracking such that greater iM1-iPAR coherence at baseline predicted greater % change in the primary behavioral outcome measure, % change in SR score ($r = 0.61$, $p = 0.037$, **Figure 3**, black dots and gray dots). The same EEG measure showed a similar but non-significant relationship with the secondary behavioral outcome measure, % change in ER score ($r = 0.52$, $p = 0.084$). To further understand these relationships, we examined iM1-iPAR high beta coherence at baseline in relation to baseline, rather than training-related change in, tracking performance; baseline iM1-iPAR high beta coherence was not related to baseline SR score or baseline ER score ($p > 0.9$). We also examined whether change in high beta coherence between iM1-iPAR across the week of training correlated with change in tracking performance and it did not, neither for % change in SR score ($r = -0.38$, $p = 0.23$) nor % change in ER score ($r = -0.40$, $p = 0.20$).

To determine if injury to cortical regions underlying electrodes influences findings, we excluded four subjects with damage to either of the brain regions (iM1 or iPAR) in which coherence predicted training-related gains. When these four subjects were excluded, the strength of the relationship between baseline EEG iM1-iPAR high beta coherence and visuomotor tracking gains measured as change in SR score increased ($r = 0.81$, $p = 0.015$, **Figure 3**, black dots only). A similar strengthening of the relationship was found for the secondary endpoint, ER score, when excluding these four subjects but this did not reach significance ($r = 0.62$, $p = 0.10$).

As a control, we further hypothesized that prediction of training-induced gains in visuomotor tracking would be specific to connectivity in this ipsilesional frontoparietal circuit. To test this, we examined whether coherence in other circuits, both intra-hemispheric and inter-hemispheric, predicted the % increase in SR score, and none of these other circuits did ($p > 0.1$, **Table 3**).

As a further control, we explored the performance of coherence in the hypothesized iM1-iPAR circuit as a predictor but using other frequency bands besides the primary band of interest (high beta, 20–30 Hz). We found that M1-PAR coherence at baseline did not significantly predict % change in SR score in the theta ($r = 0.11$, $p = 0.73$), alpha ($r = 0.13$, $p = 0.7$), or low beta ($r = 0.52$, $p = 0.087$) frequency bands, but did predict % change in SR score in the delta band ($r = 0.62$, $p = 0.032$).

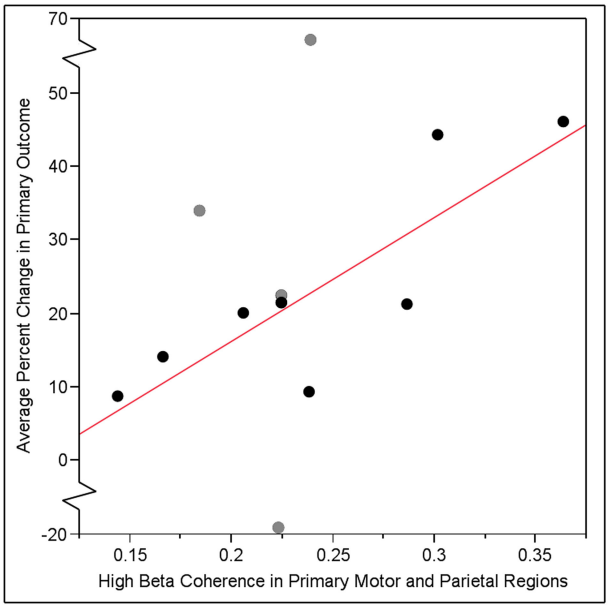

FIGURE 3 | Training-related gain in visuomotor tracking, defined as the % change in SR score, pre- vs. post-training, increased linearly as a function of baseline coherence in the high beta band (20–30 Hz) between leads overlying ipsilesional primary motor cortex (iM1) and ipsilesional parietal lobe (iPAR) region identified by our group in a prior study (13) of visuomotor tracking training. The relationship between baseline EEG iM1-iPAR coherence and subsequent training-related gains was significant across all 12 subjects ($r = 0.61$, $p = 0.037$). When analysis was repeated excluding the four subjects (gray dots) who had injury to either iM1 or iPAR, this relationship was strengthened ($r = 0.81$, $p = 0.015$).

DISCUSSION

Stroke is a heterogeneous condition, making difficult the task of identifying those patients who are most likely to benefit from a given restorative therapy, and underscoring the need for predictors of individual treatment response. The current focus was on visuomotor skills, which are relevant to many activities of daily living and are often a focus of stroke rehabilitation. Here we addressed the need for clinical predictors by testing the hypothesis that, among a cohort of patients with chronic hemiparetic stroke, training-related gains in a visuomotor tracking task can be predicted by an EEG-based measure of frontoparietal circuit function that is known (13) to predict training-related gains in healthy subjects. The data support this hypothesis, finding that visuomotor tracking training significantly improves visuomotor performance after stroke, and that an EEG-based measure of frontoparietal circuit function predicts the training-related behavioral gains arising from this circuit, as hypothesized, and with specificity, i.e., behavioral gains were predicted only when examining EEG activity in the hypothesized brain circuit.

The primary study hypothesis focused on prediction using a measure of brain function, coherence in the high beta (20–30 Hz) band within a frontoparietal circuit. Measures of brain function can provide information about neurological status and

TABLE 3 | Baseline EEG prediction of training-related gain in visuomotor tracking.

Coherence metric	*r*	*p*-value
iM1-iPAR	0.61	0.037
iM1-cPAR	0.20	0.53
iM1-cM1	0.36	0.25
iM1-iPMd	−0.06	0.86
iM1-iPf	0.36	0.25
iM1-iMedPr	0.49	0.11
iM1-iV1	−0.02	0.93

Coherence was measured in the high beta band (20–30 Hz) and is reported for all 12 subjects. Training-related gain in visuomotor tracking is defined as the % change in SR score, pre- vs. post-training. Abbreviations indicate leads overlying: iM1, ipsilesional hand area of primary motor cortex; iPAR, ipsilesional parietal lobe region identified by our group in a prior study (13) of visuomotor tracking training; cPAR, contralesional parietal lobe region; cM1, contralesional primary motor cortex; iPMd, ipsilesional frontal/dorsal premotor cortex; Pf, ipsilesional prefrontal cortex; iMedPr, ipsilesional medial parietal area; iV1, ipsilesional primary visual cortex.

its change over time beyond what can be learned from measures of brain structure or behavior, for example, providing a unique source of insights in settings ranging from genetic risk (48) to severe neural injury (49, 50). The current study focused on an EEG-based measure of brain function that was established in a prior study of healthy controls. In that study (13), brain activity was recorded in 17 healthy young subjects during 3 min of rest then examined in relation to training-related gains in right arm visuomotor tracking skill. A partial least squares regression model found that left M1 high beta band coherence, particularly with left PAR area, was a strong predictor of visuomotor skill acquisition, with most of the prediction arising from significant left M1-parietal coherence ($r = 0.58$, $p < 0.05$). In that study, these EEG-based findings exceeded the predictive value provided by baseline behavior and demographics. Based on this, coherence between leads overlying iM1 and iPAR was hypothesized to predict paretic arm training-related gains in visuomotor skill. The data support the primary study hypothesis, with a similar relationship ($r = 0.61$, $p = 0.037$) identified in the current cohort of subjects with chronic hemiparetic stroke. This finding must be interpreted in light of the fact that the results in **Figure 3** are in part driven by the two patients who had the highest baseline coherence and the highest training-related behavioral gains. A weakness of the current study was the absence of a control group. An inactive control could provide insights into the main effect of time, while an active control group performing a different training task could provide insights that are more specific to visuomotor processing. Current results focused on the iM1-iPAR coherence in the high beta frequency band, but a secondary analysis found that results were also significant with delta frequency coherence. Although measures of delta band power are generally associated with neural injury, considerably less is known regarding delta band coherence, and so this finding suggests that delta range coherence may be a useful measure of motor system function worthy of further study in the context of brain plasticity.

The brain functional measure of interest was activity within a specific frontoparietal circuit. Current results reinforce that measures of circuit activity provide behaviorally relevant insights into a network's functional status in the setting of stroke (9, 51–54). EEG coherence between two brain regions likely reflects their functional connectivity, though the influence of common drive from a third brain region cannot be excluded (14, 15). Findings were specific to the hypothesized iM1-iPAR circuit (**Table 3**), consistent with known visuomotor functions of these brain areas in relation to the content of training (16, 20–25).

Incorporating measures of both neural function and neural injury improves prediction of stroke rehabilitation therapy effects. Anatomical details are important when evaluating physiology-behavioral relationships (9, 54), and so the relationship between iM1-iPAR coherence and training-related gains in visuomotor skill was reexamined excluding patients with injury to either iM1 or iPAR. Despite reducing sample size, removing these four patients increased the significance of the relationship between baseline EEG and training-related gains, highlighting the importance of measuring stroke-related injury to regions for which function is being assessed. Change in high beta band iM1-iPAR coherence did not correlate with training-related gains in visuomotor skill, consistent with a prior study that found that resting EEG is a better predictor than it is a biomarker of change (31). That resting EEG data predicts gains from 1 week of training but does not change in parallel with training suggests that resting EEG measures correspond to features of functional brain organization that are highly stable and do not rapidly change. This may be because the type of brain plasticity needed to change EEG coherence over time requires a large dose of training; a change in EEG coherence requires a change in two brain areas' relationship, and this may be a complex neural task. Consistent with this, in a study where subjects received 28 days, rather than 4 days, of training, we did find that measures of high beta coherence with iM1 changed in parallel with training-related behavioral gains (10). Inter-subject variability in neural plasticity over time or Type II error might have also contributed to the observed lack of association found between change in iM1-iPAR coherence and change in % SR score over time.

Increasing evidence supports the utility of using computer-based games to provide rehabilitation that improves outcomes after stroke (55–57). The current study used augmented reality, in which virtual objects are projected into the real world, to drive visuomotor skill training through 6 games (**Figure 2**). An augmented reality approach has several potential advantages that can enhance post-stroke therapy, for example, patients can interact with any object that can be displayed in their visual field, safely, in a game-play context. Augmented reality also has potential advantages compared to rehabilitation-focused games played on a typical computer monitor, as an augmented reality approach can decrease cognitive demands, such as a visuospatial transformation from third-person to first-person space (34). These games were implemented using home-based telehealth methods, building on an approach that we have described previously (58). The current study found significant training-related gains in a visuomotor tracking task and so highlights the utility of an augmented reality gaming approach as part of stroke rehabilitation, and provides

preliminary evidence supporting home-based augmented reality gaming.

The behavior at the center of training, visuomotor tracking, was selected in part because of its clinical relevance to many functional tasks (59). One key area of focus during stroke rehabilitation involves visuomotor behaviors such as reaching and grasp, as these are essential for many activities of daily living. The current study had subjects train on a novel augmented reality gaming system that focused on gross arm movement and reaching. Guided reaching tasks have been shown to involve the posterior parietal cortex (60–62), and here we have found this region to be an important element within the frontoparietal circuit that predicted improvement in our motor tracking task. The validation of the importance of this frontoparietal circuit in visuomotor tasks could have implications for stroke rehabilitation. The current form of visuomotor training was associated with generalization, i.e., two of the three tests of visuospatial skill also improved (**Table 2**), although a non-treated control group would be needed to insure that this was not in part attributable to learning effects from repeated testing. Being able to target specific circuits has been shown by our group as a possibility of rehabilitation to optimize motor recovery outcomes (63, 64).

Predictors are important in designing individual rehabilitation treatment programs after stroke, providing measures that stratify patients into clinically useful categories (65, 66). The current study focused on EEG measures of functional connectivity, but other forms of connectivity such as structural connectivity may also be useful (67, 68). EEG is a useful tool, particularly for studies of the motor system (13, 31, 69). Compared to other imaging-based prediction techniques, EEG has potential advantages such as low cost, good safety, and high accessibility in complex medical settings. The current study found that an EEG-based measure, high beta band coherence within a frontoparietal circuit function at rest, predicted training-related visuospatial behavioral gains arising from that circuit, with specificity. Ultimately, such findings may lead to broader incorporation of functional brain measurements into the management of stroke rehabilitation.

AUTHOR CONTRIBUTIONS

RZ and JC: study design, data collection, data analysis, and writing; HH, MK, LD, AM, CL, and WS: study design; KW, FE, and NK: data collection; DY: data analysis; RS and SC: study design, data analysis, and writing.

FUNDING

This work was funded by grants from the American Heart Association (13GRNT16990060) and from the National Institutes of Health (K24 HD074722, UL1 TR001414, and T32 AR047752).

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Conflict of Interest Statement: The 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.

frontiers in Neurology

SYSTEMATIC REVIEW
published: 25 June 2018
doi: 10.3389/fneur.2018.00472

Kinematic Components of the Reach-to-Target Movement After Stroke for Focused Rehabilitation Interventions: Systematic Review and Meta-Analysis

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OPEN ACCESS

Edited by:
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Reviewed by:
Margit Alt Murphy, Institute of Neuroscience and Physiology, The Sahlgrenska Academy, University of Gothenburg, Sweden
Denis Mottet, University of Montpellier 1, France

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Specialty section:
This article was submitted to Stroke, a section of the journal Frontiers in Neurology

Received: *08 March 2018*
Accepted: *31 May 2018*
Published: *25 June 2018*

Citation:
Collins KC, Kennedy NC, Clark A and Pomeroy VM (2018) Kinematic Components of the Reach-to-Target Movement After Stroke for Focused Rehabilitation Interventions: Systematic Review and Meta-Analysis. Front. Neurol. 9:472. doi: 10.3389/fneur.2018.00472

Background: Better upper limb recovery after stroke could be achieved through tailoring rehabilitation interventions directly at movement deficits.

Aim: To *identify potential; targets for therapy by* synthesiz*ing* findings of differences in kinematics and muscle activity between stroke survivors and healthy adults performing reach-to-target tasks.

Methods: A systematic review with identification of studies, data extraction, and potential risk of bias was completed independently by two reviewers. Online databases were searched from their inception to November 2017 to find studies of reach-to-target in *people-with-stroke* and healthy adults. *Potential* risk-of-bias was assessed using the Down's and Black Tool. Synthesis *was undertaken via*: (a) meta-analysis of kinematic characteristics utilizing the standardized mean difference (SMD) [95% confidence intervals]; and (b), narrative synthesis of muscle activation.

Results: Forty-six studies met the review criteria but 14 had insufficient data for extraction. Consequently, 32 studies were included *in the meta-analysis*. Potential risk-of-bias was low for one study, unclear for 30, and high for one. Reach-to-target was investigated with 618 *people-with-stroke* and 429 healthy adults. *The meta-analysis* found, in all areas of workspace, that *people-with-stroke had*: greater movement times (seconds) e.g., SMD 2.57 [0.89, 4.25]; lower peak velocity (millimeters/second) e.g., SMD −1.76 [−2.29, −1.24]; greater trunk displacement (millimeters) e.g. SMD 1.42 [0.90, 1.93]; *a more curved reach-path-ratio* e.g., SMD 0.77 [0.32, 1.22] and reduced movement smoothness e.g., SMD 0.92 [0.32, 1.52]. In *the* ipsilateral and contralateral workspace, *people-with-stroke exhibited*: larger errors in *target* accuracy e.g., SMD 0.70 [0.39, 1.01]. In contralateral workspace, stroke survivors had: reduced elbow extension and shoulder flexion (degrees) e.g., elbow extension SMD −1.10 [−1.62, −0.58] and reduced shoulder flexion SMD −1.91 [−1.96, −0.42]. Narrative synthesis of muscle activation found that *people-with-stroke, compared with healthy adults,*

exhibited: delayed muscle activation; reduced coherence between muscle pairs; and use of a greater percentage of muscle power.

Conclusions: This first-ever meta-analysis of the kinematic differences between people with stroke and healthy adults performing reach-to-target found statistically significant differences for 21 of the 26 comparisons. *The differences identified and values provided are potential foci for tailored rehabilitation interventions to improve upper limb recovery after stroke.*

Keywords: stroke rehabilitation, reaching, upper limb, kinematics, movement performance

INTRODUCTION

Reaching is essential for everyday activities such as drinking, *using a touch screen or operating buttons on an elevator*. Rehabilitation therefore gives emphasis to regaining reaching ability through evidenced-based task-specific training. *Many people after stroke have upper limb disability, for example: approximately 48% of a consecutive admissions sample at three days after stroke(1); and 65% of individuals with severe stroke not regaining the ability to reach and grasp everyday objects despite participation in rehabilitation (2).*

There are many different therapy approaches available to clinicians to progress upper limb motor function. An alternative to best conventional therapy is offered by impairment-orientated therapy (3). This impairment-orientated training involves targeting interventions at the movement control deficits underlying difficulty and inability to perform everyday functional tasks. Therefore, a precursor to continuing investigation of impairment-orientated training is to identify the exact movement control deficits experienced by stroke survivors.

Movement control deficits can be identified by kinematic assessment providing sensitive, objective and reliable measurement (4–9). Therefore, kinematic assessment can be used to identify movement control deficits as targets for impairment-orientated training after stroke. Indeed, reaching kinematics has been studied widely in both healthy populations (10–12) and in people after stroke (13–16). Even more information can be gained by combining kinematics with measurement of muscle activity (17). For example, electromyography (EMG) provides neurological measures such as spatial-temporal patterns of muscle activity for enhanced understanding of the movement control (*kinematics and muscle activity*) underlying the performance of everyday tasks (18).

Knowledge of the kinematics of all forms of reaching (4, 19) and more specifically, coordination of reach and grasp components (20), has been drawn together in narrative reviews. These reviews are valuable as they provide an expert overview of the kinematics of reaching activity. However, narrative reviews have potential for bias in at least two aspects: identification of the primary studies included (selection bias); and the possibility that synthesis is influenced by author opinion (expert opinion bias). A robust systematic review is required to minimize the risk of potential bias. In addition, review of the neural components of reaching is required alongside the kinematics.

To understand reaching impairment we need to consider the different forms of reaching required for everyday activity e.g., reach-to-target (operate elevator buttons), reach-to-release (put can on shelf); reach-to manipulate (cut paper with scissors); and reach-to-pull (open cupboard). In addition, reaching activity takes place in many workspace areas including: above the head, behind the trunk and to the contralateral side of the reaching upper limb. Diverse forms of reaching for performance of everyday tasks require the ability to utilize different spatial-temporal patterns of muscle activity and limb segment orientations (4, 19). Indeed, kinematic characteristics vary depending on the reaching task and goal (21, 22). A prerequisite for development of impairment-orientated rehabilitation, therefore, requires knowledge of the movement

TABLE 1 | The search strategy used to search the database MEDLINE as example of electronic searches.

Upper extremity OR arm OR hand
(upper limb).tw
Stroke.tw
"range of motion, articular"/ph
Movement/ph
Muscle, skeletal/ph
Motor skills/ph
arm/ph
Exp Muscle contraction (includes isotonic contraction, isometric contraction and excitation contraction coupling)
(muscle activation OR co?contraction OR motor control).tw
(grasp* OR reach* OR grip* OR pinch* OR limb transport).tw
Exp psychomotor performance (includes motor skills and performance analysis)
Electromyograph* OR transcranial magnetic stimulation OR biomechanics
(co?contraction OR EMG OR motor evoked potential OR biomechanic* OR electromyograph* or kinematic* OR object manipulation).tw
(1) OR (2)
(15)AND (3)
(4) OR (5) …OR (11)
(12) OR (13) OR (14)
(16) AND (17) AND (18)
Limits: individuals > 18 years of age; human; English Language

Tw, text word; ph, physiology.

control deficits underlying difficulty performing everyday reaching tasks to enable therapy to be targeted at what needs to change.

The aims of this systematic review were to: (1) systematically synthesise the differences between individuals with stroke and healthy adults for the *kinematics and muscle activations* of

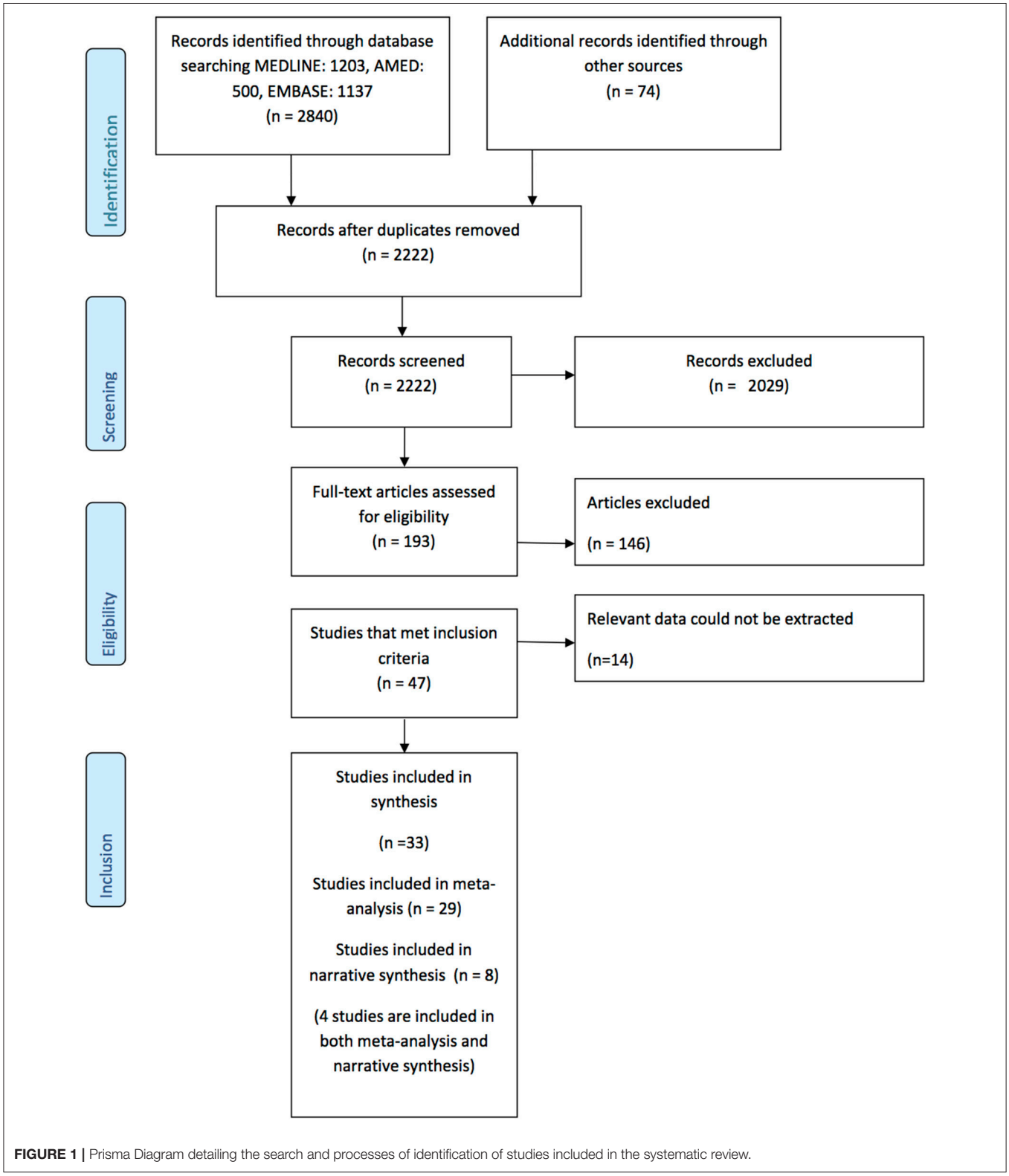


FIGURE 1 | Prisma Diagram detailing the search and processes of identification of studies included in the systematic review.

reach-to-target; and (2) determine the potential influence of object location on the differences in *kinematics and muscle activity*. Reach-to-target was chosen because it is the precursor component of most everyday upper limb tasks *and is essential for many daily activities such as a using touch screen (tablet, computer), turning on/off light switch, and using a doorbell, or elevator*.

METHODS

The systematic review methodology was based on guidelines by the Cochrane Collaboration (23). Two reviewers worked independently at each stage: title and abstract screening, full text screening, assessment of potential risk of bias, and data extraction. Each reviewer recorded their assessment on a pre-agreed proforma. If there were disagreements the two reviewers referred to the original document in question. If agreement could not be reached then a third researcher was consulted.

Searching for Studies

The search strategy was developed in collaboration with a research librarian. The search was limited to studies published in the English language. The search terms used included: reaching, upper limb, kinematics, biomechanics, movement analysis, electromyography, and stroke. The terms were a combination of MeSH and non-MeSH terms used as text words. Three online databases were searched: MEDLINE, AMED, and EMBASE; the databases were searched from their inception to November 2017. Due to the differences between databases the search strategy was modified for each individual database; an example of the search strategy used for MEDLINE is in **Table 1**. In addition, the reference lists of relevant papers were hand searched for potential articles that were not retrieved in the electronic search.

Study Eligibility Criteria

Types of Studies

All study designs were included except for single case studies, and reviews. Included studies of people after stroke also needed to investigate healthy adults (control) completing identical reach-to-target tasks.

Types of Participants

The participants in eligible studies had to be at least 18 years of age. For people after stroke there were no limitations placed on lesion location, time since ictus, or number of strokes. Healthy adult participants needed to have no diagnosis of a neurological or musculoskeletal disorder that could potentially influence movement control or reaching.

Types of Reaching Tasks

Studies were eligible if reaching to a target was assessed with the paretic upper limb of the people after stroke and either upper limb of the healthy adult participants. Specific exclusion criteria were: reach-to-grasp of an object, tapping, tracing, drawing tasks, or reaching with the non-paretic limb (stroke survivors).

Types of Measures

Eligible studies employed kinematic assessment (motion analysis); muscle activity (electromyography, EMG); and/or corticospinal pathway excitability (transcranial magnetic stimulation, TMS) during the reach-to-target task.

Identification of Studies

Studies were assessed as not relevant, probably relevant, or relevant. Title and abstract were screened together. For those studies deemed as either relevant or probably relevant their full texts were then screened (23, 24). Those studies which met the eligibility criteria were included in this review.

Potential Risk of Bias

The majority of included studies used observational designs, therefore, the Downs and Black tool was used to assess potential risk of bias (25). The tool was modified by using just the criteria pertinent to potential risk of bias of observational study designs (23, 26). For example: the removal of questions relating to randomization, group allocation, and group concealment (26–28).

Data Extraction

The data extracted were: number of participants, participants' age, time since stroke, reach-to-target task description, use of trunk restraint, upper limb motor ability, kinematic characteristics (e.g., velocity), EMG data (e.g., muscle activity). Some included studies evaluated the effect of an intervention. For these, only the baseline data (pre-intervention) were extracted. For studies in which the published data were unclear or missing then the authors were emailed to request clarification/more details.

Synthesis

A meta-analysis was undertaken for measures where two or more included studies reported measurement values of the same movement characteristic. A narrative synthesis was performed if there was insufficient similarity across included studies.

If a study included data for multiple reach-to-target tasks one task was selected to be included in the meta-analysis. The task selected was the one most similar to the rest of the studies in the meta-analysis. For example, reaching at a self-paced speed versus fast speeds, tasks in which reaching distances were most similar, and most similar grip (23).

The meta-analysis used the Cochrane Statistical package, RevMan 5.2, to compare the group means and standard deviations of the kinematic characteristics of people after stroke and healthy adult participants. The heterogeneity of data was assessed using the I^2 statistic and interpreted as low for a value $\leq 25\%$, high for a value of $\geq 75\%$ and moderate for all values in between (23, 29, 30). If heterogeneity was low a fixed effect model was used; if heterogeneity was moderate or high a random effects model was used (23, 30). The standardized mean difference (SMD) was calculated (23).

TABLE 2 | Characteristics of included studies investigating reach-to-target in multiple anterior areas of the workspace.

Study	Participants	Time since stroke	Reaching task	Kinematic measures	Muscle activity measures
(44)	**S:** 8; Age: 50 ± 16 **C:** 6; Age: 46 ± 16	65 ± 36 months (32–120 months)	Initial target 20 cm from sternum; final targets 35 cm from initial target and 45° to either side of initial target (ipsilateral and contralateral workspace); reach between initial and distal targets Arm support: no Movement speed: fast Trunk restraint: with and without	Movement time Movement smoothness Joint range of motion Compensatory trunk movement Inter-joint coordination	No
(48)	**S:** 9; age 61.4 ± 14.1 **C:** 7; age: 47.2 ± 16.6	3–9 months	Initial target central position then each to a target placed 30 cm from the participant in the ipsilateral, central, and contralateral workspace Arm support: robotic exoskeleton Movement speed: self-selected Trunk restraint: not reported	Execution time Movement smoothness Achievement of target Inward/outward movement time Joint angles Interjoint coordination	Co-contraction ratio of the triceps, biceps, and deltoid (anterior and posterior)
(50)	**S:** 10; age: 71.6 ± 10.4 **C:** 10; age: 68.6 ± 8.7	2.7 ± 1.8 months	Reach to a target in the central, ipsilateral, and contralateral workspace 14 cm from the initial position Arm support: robotic exoskeleton Movement speed: not reported Trunk restraint: not reported	Target accuracy Trajectory or movement straightness	No
(52)	**S:** 16; age: 30–85 **C:** 4; age: 24–39	9 months to 6 years	Reach to targets arranged in 5 rows by 15 columns separated by 12°; reaching to targets was random; initial position thumb on umbilicus Arm support: Wrist splinted Movement speed: self-selected Trunk restraint: yes	Trajectory Velocity Movement smoothness	No
(54)	**S:** 15; age: 59.0 ± 15.4 (30–80) **C:** 12; age: 53.3 ± 17.1	11–101 months	Reach in a physical environment and virtual environment to six targets arranged in a 2 row by 3 column grid in all areas of the anterior workspace in a random order; the distance between participant and the targets were the length of the participant's arm + 50 mm; the target were both above and below shoulder height Arm support: no Movement speed: fast Trunk restraint: not reported	Precision Velocity Trajectory (straightness) Joint range of motion Trunk displacement and rotation Interjoint coordination	No
(55)	**S:** 10; age: 60.9 ± 6.6 **C:** 9; age: 57.8 ± 5.9	2–10 months	Holding a vertical handle (pointer diameter of 3 cm) reach forward 36 cm from initial location and reach lateral 48 cm from initial location. Arm supported: yes, arm brace on smoothed motion plane Movement speed: fast Trunk restraint: not reported (told to move as fast as possible without moving their trunk)	Velocity Reaction time Duration (movement time) Trajectory	EMG of pectoralis clavicular, anterior deltoid, posterior deltoid, biceps, triceps long and lateral head, brachioradialis.

(Continued)

TABLE 2 | Continued

Study	Participants	Time since stroke	Reaching task	Kinematic measures	Muscle activity measures
(59)	**S:** 18; age 65.2 ± 9.8 **C:** 8; age 58.6 ± 7.0	2–36 months	Reach to targets (30 mm x 30mm squares) suspended from the ceiling in the ipsilateral, central, and contralateral workspace; target distance was beyond arm's length. The central target was 150 mm above the level of the shoulder; the ipsilateral and contralateral targets were 300 mm to either side of the central target at shoulder height (150 mm lower than the central target). Arm support: no Movement speed: not reported Trunk restraint: no	Velocity Trajectory Joint angles Trunk displacement and rotation Smoothness (number of velocity peaks)	No
(62)	**S:** 7; age: 64.4 ± 13.5 **C:** 7; age: 64.8 ± 11.4	6–37 months	Reach with a wooden dowel to a target at knee height at 160% of arm's length and retrieve a magnetic disc with the dowel in the contralateral and ipsilateral workspace Arm support: no Movement speed: self-selected Trunk restraint: no	Trajectory Joint coordination Joint configuration variance Timing of hand and trunk movement	No
(63)	**S:** 16; age: Left hemisphere damage group: 57 (46–79) right hemisphere damage: 48 (28–78) **C:** 10; age 41 (25–69)	1–27 months	Reach to 9 targets with the palm of the hand; 6 arranged on a table 60% and 90% of arm's length; 3 targets above the table at 90% of arm's length in the central, ipsilateral, and contralateral workspace. Arm support: no Movement speed: self-selected Trunk restraint: no	Velocity Number of velocity peaks (smoothness) Trajectory (curve index)	No
(16)	**S:** 16, age: left hemisphere damage group 57 (46–79), right hemisphere damage group: 48 (28–78) **C:** 10,; age: 41 (25–69)	1–27 months	Reach to 9 targets with the palm of the hand, 6 targets were arranged on the table 60% and 90% of arm's length; 3 targets above the table at 90% of arm's length in the central, ipsilateral, and contralateral workspace. Arm support: no Movement speed: self-selected Trunk restraint: no	Velocity Trajectory (curve index) Trunk displacement Trunk angular rotation, flexion and torsion	No
(13)	**S:** 18; age: 48.8 ± 11.8 **C:** 9 age: 41 (29–71)	0.25 to 15 years	Reach using a pointer to 9 targets; 6 arranged on a table 65% and 90% of arm's length; 3 targets above the table at 90% of arm's length in the central, ipsilateral, and contralateral workspace. Arm support: wrist Splint Movement speed: self-selected Trunk restraint: yes	Velocity Trajectory (curve index) Principle component analysis Precision Joint motion (degrees of freedom of arm joints and scapula)	No

(Continued)

TABLE 2 | Continued

Study	Participants	Time since stroke	Reaching task	Kinematic measures	Muscle activity measures
(67, 68) (side of brain damage)	**S:** 14; age 59.5 ± 12.9 (R hemisphere stroke) & 58.9 ± 9.73 9 (L hemisphere stroke) **C:** 6; age 63.8 ± 14.4	R hemisphere stroke 33.2 ± 28.9 months L hemisphere stroke 65.0 ± 33.3	Reach to six targets (3.8 cm sphere) in the ipsilateral and contralateral workspace at a distance of 8 am 16 cm, and 24 cm from the initial start position. Reaches were made without vision. Arm support: Wrist and finger splint to provide support and maintain pointing posture Movement speed: fast Trunk restraint: no Virtual Reality task reaching from the initial positon in front of chest to 6 targets in the ipsilateral and contralateral workspace 8 cm, 16 cm, and 24 cm from initial position. Reaches were made without vision. Arm support: wrist and finger splint to provide support and maintain pointing posture Movement speed: fast Trunk restraint: no	Movement time (a &b) Error/accuracy (a & b) Velocity (a &b) Time to peak velocity (a) Movement distance (a)	No
(69)	**S:** 6; age 71.8 ± 5.4 **C:** 10; age 71.2 ± 5.8	14 to 37 days	Reach to 8 targets placed around a circumference with a radius of 0.14 m. The robot used was the InMotion2 Arm support: Robotics (InMotion 2) Movement speed: not reported Trunk restraint: yes	Trajectory	Muscle synergies

S, individuals with stroke and c, control participants.

TABLE 3 | Characteristics of included studies investigating reach-to-target task in the contralateral workspace.

Study	Participants	Time since stroke	Reaching task	Kinematic measures	Muscle activity measures
(46)	**S:** 9; age: 54 ± 14 **C:** 9; age: 43 ± 18	2–17 months	Initial target by ipsilateral thigh final target in the contralateral workspace at shoulder height just beyond arms reach; reaches make without vision every 5th trial open eyes to assess final arm position Arm support: no Movement speed: self-selected Trunk restraint: not reported	Movement time Trajectory Error Interjoint coordination# Angular joint motions	No
(14)	**S:** 18; age: 54 ± 17 **C:** 10; age: 43 ± 18	3–17 months	Initial target by ipsilateral thigh final target in the contralateral workspace at shoulder height just beyond arms reach Arm support: no Movement speed: fast Trunk restraint: not reported	Movement time Joint angles Trunk displacement Trajectory Error/accuracy Velocity	No
(14)	S: 20; age: 53.5 ± 16.4 **C:** 10; age: 43.3 ± 18.2	3–17 months	Initial target by ipsilateral thigh final target in the contralateral workspace at shoulder height just beyond arms reach; completed task without vision, every 5th trial open eyes to assess final arm position Arm support: no Movement speed: fast Trunk restraint: not reported	Movement time Coefficient of variability Error Coefficient of variability, Temporal segmentation, Joint ROM Trunk displacement and rotation	No
(45)	**S:** 37; 3 groups age: 1:55.7 ± 15.4 2: 59.1 ± 17.9 3: 64.5 ± 14.1 **C:** 10; age 43.3 ± 18.2	Group 1: 12.1 ± 4.9 Group 2: 11.4 ± 6.3 Group 3: 11.1 ± 5.9 months	Initial target by ipsilateral thigh final target in the contralateral workspace at shoulder height just beyond arms reach Arm support: no Movement speed: fast Trunk restraint: not reported	Movement time Precision (accuracy) Segmentation (smoothness) Velocity variability	No

S, individuals with stroke and c, control participants.

TABLE 4 | Characteristics of included studies investigating reach-to-target in the ipsilateral workspace.

Study	Participants	Time since stroke	Reaching task	Kinematic measures	Muscle activity measures
(5)	**S:** 8 age 53 ± 8 (SE) **C:** 4; age 28 ± 2.5	46.2 ± 41.5 (12–154) months	Reach from hand on thigh to a target placed 15 mm in front of participant at shoulder height Arm support: no Movement speed: self-selected Trunk restraint: no	Movement time Joint angles Velocity Normalized jerk (measure of smoothness)	No
(56)	**S:** 28; age: 52.2 ± 11.7 **C:** 18; age: 52.1 ± 11.9	19.6 ± 16.3 months	Seated at a table reach to a bell placed in the midsagittal plane shoulder width apart placed at 90 or 125% of arm's length Arm support: no Movement speed: fast Trunk restraint: no	Joint angular changes (shoulder, elbow, trunk)	No
(57)	**S:** 10, age: 58 ± 10 (41–76) **C:** 5 age and sex-matched to stroke participants	>6 months post stroke	In standing reach to a target ball located 5 cm past the outstretched paretic arm of each participant Arm support: no Movement speed: fast Trunk restraint: no	None	EMG activity of: anterior deltoid, middle deltoid, biceps brachii, tibialis anterior, soleus, and sternocleidomastoid Joint ROM
(36)	**S:** 20; age: 60.9 ± 6.1 **C:** 10; age: 61.0 ± 9.0	4.3 ± 2.6 years	Reach to a target with the index finger located at shoulder height within arm's reach Arm support: no Movement speed: fast Trunk restraint: yes	Joint angles Velocity Directness Segmentation Skewness	Muscle activity patterns
(60)	**S:** 8; age 60.5 ± 5 **C:** 10; age 51.5 ± 5	1–10 years	Reaching toward a 0.5 L bottle of water placed in the scapular plane (ipsilateral workspace) at arm's length. Participants had to reach touch the bottle (not grasp) and return. Arm support: no Movement speed: self-selected & fast Trunk restraint: not reported	Velocity Trunk displacement	EMG muscle activity onset
(65)	**S:** 30; age 63.2 ± 12.4 **C:** 30 age matched	29 (6–120) months	Bilateral task of reaching to switches in the ipsilateral/lateral workspace (relative to the reaching arm) 24 cm from the start position and hit a target mounted switch. Arm support: no Movement speed: fast Trunk restraint: not reported	Movement time Reaction time Velocity Trajectory Interlimb coupling	No
(66)	**S:** 11; age 66.1 ± 15.5 **C:** 11; age 51.6 ± 14.5	22.1 ± 13.5 months	Reach to a target 1.3 times arm length in the ipsilateral workspace without vision. There were trials with trunk movement and with trunk movement restrained. Arm support: no Movement speed: not reported Trunk restraint: Trunk free trials and trunk restrained trials	Trajectory Interjoint coordination	No

(Continued)

TABLE 4 | Continued

Study	Participants	Time since stroke	Reaching task	Kinematic measures	Muscle activity measures
(70)	**S:** 29; age 63.9 ± 11.7 **C:** 9; age 58.4 ± 13.1	2 time points 8.7 days and 108.7 days after stroke	Reach to touch a 40mm diameter target placed at 90% of arms' length in the ipsilateral workspace at shoulder height Arm support: no Movement speed: fast Trunk restraint: yes	Velocity Trajectory Endpoint error Movement time	Muscle activation patterns EMG muscle activation onset time Modulation ratio
(71)	**S:** 46; age 63.9 ± 13.2 **C:** 10; age 59.1 ± 12.5	9.2 ± 4.2 days	Reach to touch a 40mm diameter target placed at 90% of arms' length in the ipsilateral workspace at shoulder height Arm support: no Movement speed: fast Trunk restraint: yes	Velocity Endpoint error trajectory	No

s, individuals with stroke and c, control participants.

RESULTS

Identification of Studies

The flowchart describing the results of the search is provided the PRISMA diagram **Figure 1**. In summary, 2,222 records were identified after duplicates were removed. Following title, abstract, and full text screening 46 studies met the inclusion criteria, however, 14 were subsequently excluded because the relevant data could not be extracted (9, 31–43). Therefore, there are 33 studies included in the synthesis (5, 7, 13, 14, 16, 44–71). There were two pairs of studies that reported two reaching tasks in the same cohort (16, 63, 67, 68) so participants were only counted once in any particular meta-analysis.

Included Studies

Observational designs were used by 27 of the 32 studies and five studies used experimental designs (5, 45, 47, 48, 61, 69). The included studies investigated reach-to-target with 618 people after stroke and 429 healthy adult participants. The mean number (standard deviation, SD) of individuals per included study was 17.2 ± 9.9 people after stroke and 11.9 ± 9.3 control participants.

Participants

The mean age (SD) of: people after stroke was 58.4 ± 9.3 years whilst healthy adult participants were a mean (SD) of 54.0 ± 10.0 years. The mean time after stroke, calculated from the data reported, was 25.6 ± 23.1 months. Full details of participants are provided in **Tables 2–5** according to the placement of the target in the workspace.

Reach-To-Target Task

The reach-to-target task varied across studies. Heterogeneity was present in: the target distance; target size; target location; reaching speed; trunk restraint; and use of vision for reaching. A description of the reaching tasks, grouped by the location of the target in the workspace, is provided in **Tables 2–5**. Location of the target in the workspace was considered the pertinent grouping variable because of the expectation of related differences in joint angles, joint trajectories and spatial-temporal patterns of muscle activity.

Outcome Measures

The methods of data collection, kinematic, and EMG outcomes assessed across all studies were diverse. The kinematic characteristics most frequently assessed were: movement time; peak velocity; reach-path-ratio/trajectory; movement smoothness; target accuracy; joint range of motion; and trunk contribution to movement. The EMG-derived assessments most frequently made were: muscle coupling; muscle onset time; and the percentage of muscle used.

Risk of Potential Bias

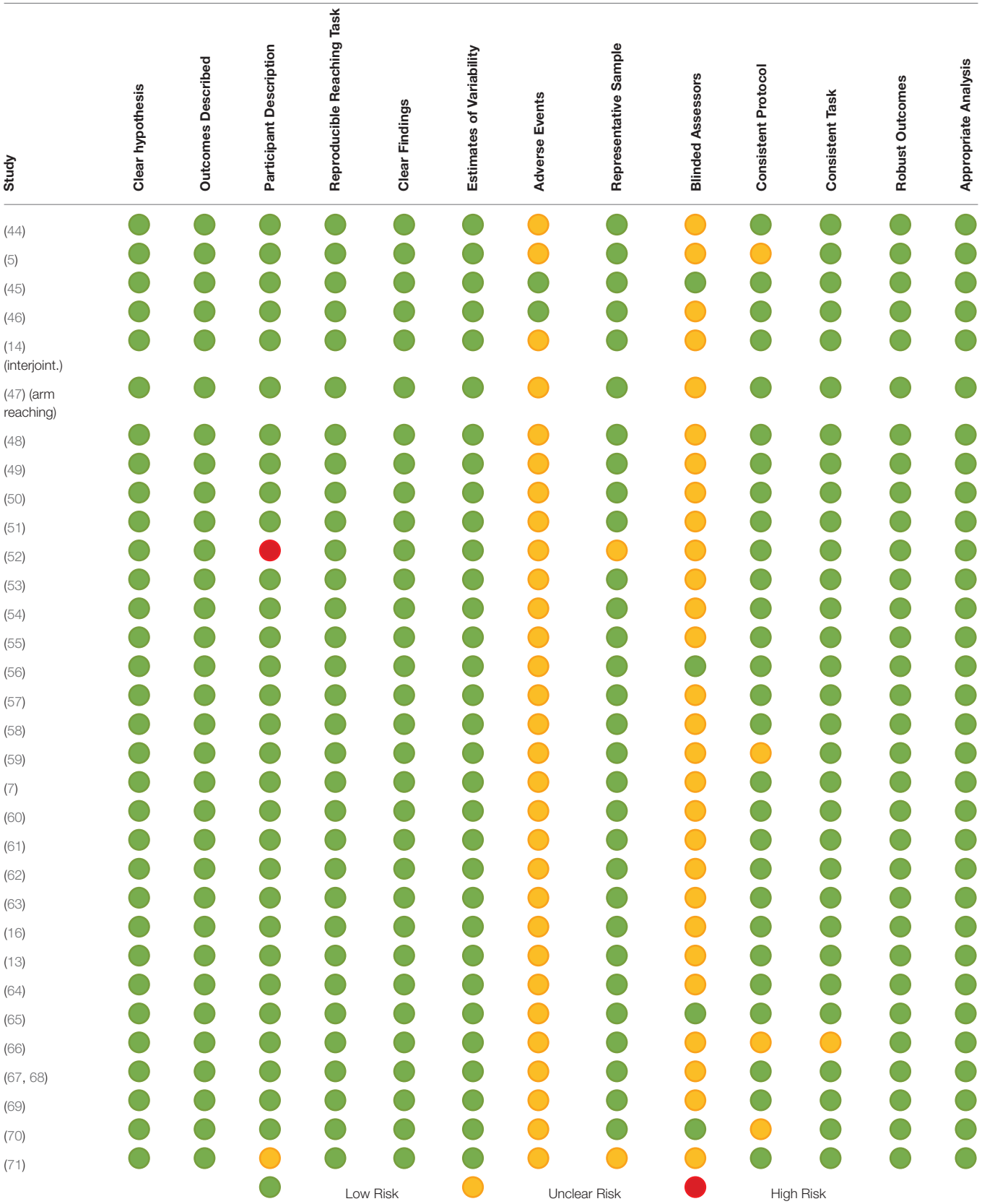
The detailed assessment of risk of potential bias is provided in **Table 6**. In summary, one study (45) had a low risk of bias across all 13 items of the modified Downs and Black tool (**Table 6**). There was only one study that was judged to have a high risk of bias for one item (52). This was for participant description. Most of the risk of potential bias was due to unclear reporting of

TABLE 5 | Characteristics of included studies investigating reach-to-target in the central workspace.

Study	Participants	Time since stroke	Reaching task	Kinematic measures	Muscle activity measures
(49)	**S:** 10; age 59.3 ± 9.3 **C:** 10; age 64.1 ± 10.5	7–107 months	Two tasks: reach up or reach down beyond functional arm length 115%. The target height for reaching down was 30 cm from the floor and reaching up was between shoulder and nipple height. Participants had to reach between their lap and the upper/lower targets Arm support: yes Movement speed: fast Trunk restraint: no	Movement time	Muscle coordination via mode vectors and PCA
(51)	**S:** 25; age 64.8 ± 15.9 **C:** 25; age 63.1 ± 16.0	31.5 ± 55 months	Reach to a target 14 cm from the initial position in the central workspace. Arm support: Robotic exoskeleton (REAplan) Movement speed: self-selected Trunk restraint: yes	Accuracy Velocity Trajectory (straightness)	No
(53)	**S:** 11; age: 62.7 ± 11.2 **C:** 8; age: 60.6 ± 6.3	39.4 ± 27.7 (12–94) months	Reach to a target 14 cm from initial position (target displayed on LCD screen) Arm support: deactivated robot exoskeleton Movement speed: self-selected Trunk restraint: yes	Trajectory Peak force and mean force during reaching	EMG amplitude Timing of EMG (muscle) activation
(7)	**S:** 18; age: 67.6 ± 8.1 **C:** 9; age: 57.2 ± 6.7	7–174 months	Reach to a target placed within 80% of arm's length in the participant's midline Arm support: no Movement speed: self-selected & fast Trunk restraint: no	Movement time Velocity Trajectory (index of curvature) Trunk displacement	
(61)	**S:** 14; age: 55.9 ± 11.6 **C:** 14; age: 55.1 ± 9.0	"sub-acute phase"	Unilateral or bilateral task of reaching to a target in front of the body in the central workspace 20 cm from start position Arm support: no Movement speed: fast Trunk restraint: not reported	Movement time Accuracy	
(64)	**S:** 30; **C:** 30 Age: stroke and healthy 67 (4-–86)	29 (6–120) months	Reach forward to hit a switch (in midline) under 3 conditions: unimanual: paretic & non-paretic, and bimanual. Target location was determined such that the action required no more than 15 degrees of elbow extension and 90 degrees of shoulder flexion. Arm support: no Movement speed: fast Trunk restraint: yes	Reaction time Movement time Velocity	

s, individuals with stroke, c, control participants.

TABLE 6 | Potential risk of bias of included studies assessed using the modified Down's and Black Tool.



(a) adverse events during the studies and (b) the use of assessors blinded to the intervention/task being investigated.

There were seven studies in which the experimental protocol differed for people after stroke and healthy adult participants (9, 61, 63, 69, 72, 73). This was primarily because people after stroke were receiving some rehabilitation and thus had pre/post assessments whereas the healthy adult participants had one assessment only. The reach-to-target task protocols did not differ, thus as the review is utilizing baseline data only this difference in protocol does not impact on the findings and does not contribute to potential bias.

Synthesis

The synthesis is grouped by workspace location of the target for reach-to-target: central, ipsilateral, contralateral and multiple. Data from 27 of the 32 studies were included in the meta-analysis. The narrative synthesis included data from 8 of the 32 studies.

Meta-Analysis of Kinematic Data

Meta-analysis was possible for the kinematic characteristics of: peak velocity; movement time; reach-path-ratio; smoothness of movement; elbow range of motion (extension); shoulder range of motion (flexion); accuracy; trunk contribution during reaching; and trunk rotation during reaching. Two or more included studies investigated these characteristics. Twenty-six meta-analyses were undertaken. The heterogeneity of the meta-analyses, as measured by the I^2 statistic, was low ($I^2 = \leq 25\%$) for 10, moderate ($I^2 = 26$–74%) for 13, and high ($I^2 \geq 75\%$) for three (**Figures 2**–**8**).

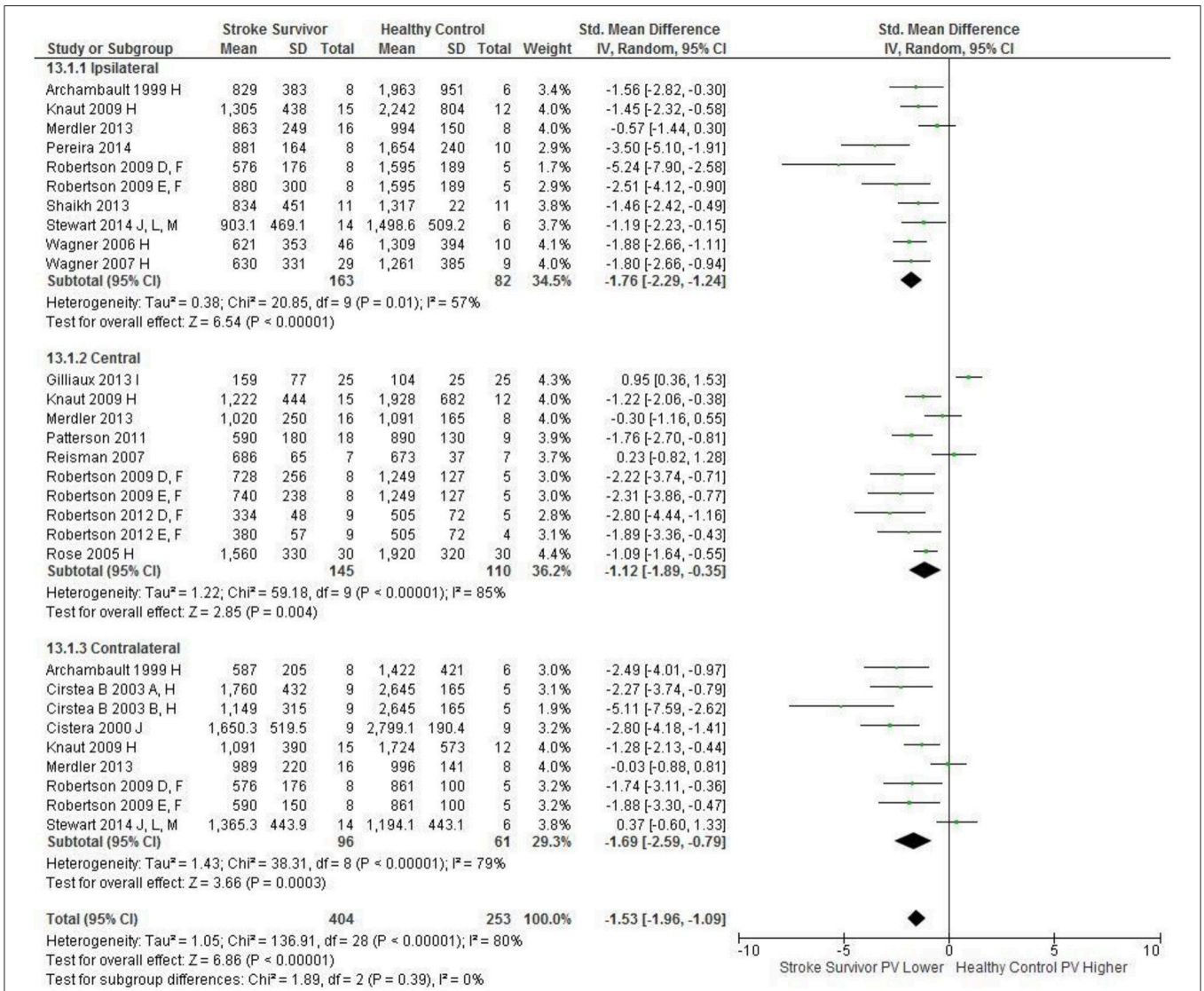


FIGURE 2 | The standardized mean difference (SMD) of peak velocity (mm/s) during reach-to-target in the: ipsilateral, central, and contralateral workspace. D, right hemisphere stroke; E, left hemisphere stroke; F, target placed 90% of arm's length; H, fast speed; I, robotics; J, reaches without vision; L, 24 cm target distance; M, virtual environment.

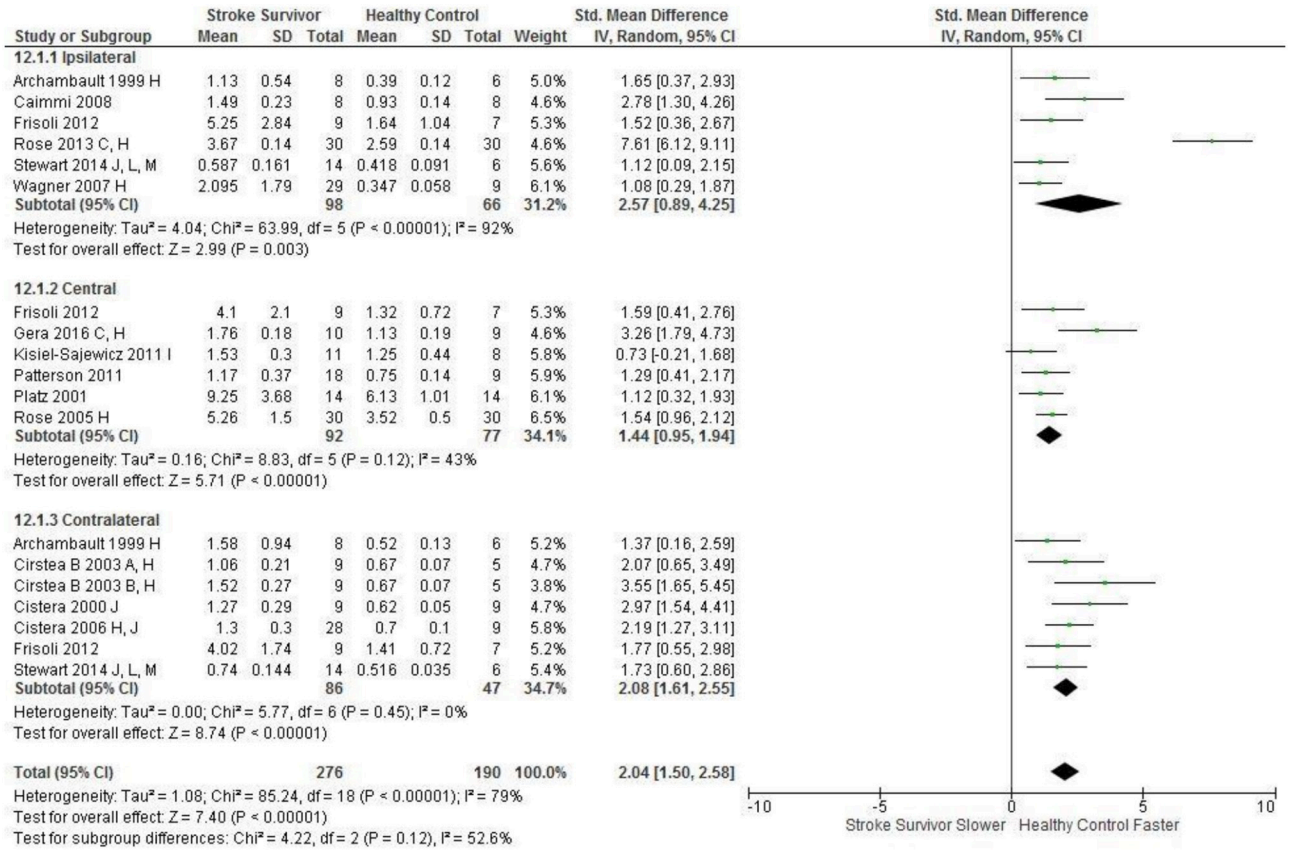


FIGURE 3 | The standardized mean difference (SDM) of movement time (s) during reach-to-target in the: ipsilateral, central, and contralateral workspace. A, mild motor impairment; B, moderate motor impairment; C, bilateral task; F, target placed 90% of arm's length; C, bimanual task; H, fast speed; I, robotics; J, reaches without vision; L, 24 cm target distance; M, virtual environment.

An overview of the meta-analyses is provided in **Table 7** and details in **Figures 2–8**. In summary, 21 of the 26 meta-analyses found significant differences in kinematics between stroke survivors and control participants.

The SMD (95% CIs) for the significant differences in kinematic characteristics between people after stroke and healthy adult participants ranged from: −1.76 (−2.29, −1.24) for peak velocity in the ipsilateral workspace to 2.57 (0.89, 4.25) for movement time in the ipsilateral workspace. *Individuals with stroke demonstrated lower peak velocities and longer movement times in all areas of the workspace (**Figures 2**, **3**). A more curved reach-path-ratio associated with less efficient reaching was demonstrated by individuals with stroke (**Figure 4**) as well as less smooth more segmented movement due to a greater number of velocity peaks in all areas of the workspace (**Figure 6**). Individuals with stroke demonstrated greater trunk displacement during reaching (**Figure 5**), less upper limb range of motion in all areas of the workspace (**Figure 7**) and reduced reaching accuracy (**Figure 8**).*

The non-significant differences between people after stroke and healthy adults for kinematics during reaching were: elbow extension in the central workspace SMD = −0.41 [−1.10, 0.28]; target accuracy in the central workspace SMD = 0.52 [−0.30, 1.34]; trunk rotation in the contralateral workspace SMD = 0.74 [−0.17, 1.54], trunk rotation in the ipsilateral workspace SMD = −0.07 [−0.50, 0.36]; and shoulder flexion in the central workspace SMD = −0.95 [−2.08, 0.19].

Narrative Synthesis of Muscle Activity Data

The muscles most frequently investigated were the: triceps, biceps, deltoid (anterior, posterior, and middle), trapezius, pectoralis, and latissimus dorsi. Six studies investigated interaction between muscle pairs (48, 53, 69, 70, 72, 74). Also investigated were muscle activation patterns (58, 60), muscle timing (57, 60), and the percentage of muscle activity used in relation to the maximal voluntary contraction (MVC) (55, 58, 69, 70).

There were comparable findings across studies. For example, compared to healthy adult participants the people after stroke used a greater percentage of MVC (58, 70), higher background muscle activity (55, 69), a reduced level of coherence between antagonistic muscle pairs (48, 53, 74), and prolonged co-contraction between muscles after achieving the task (55).

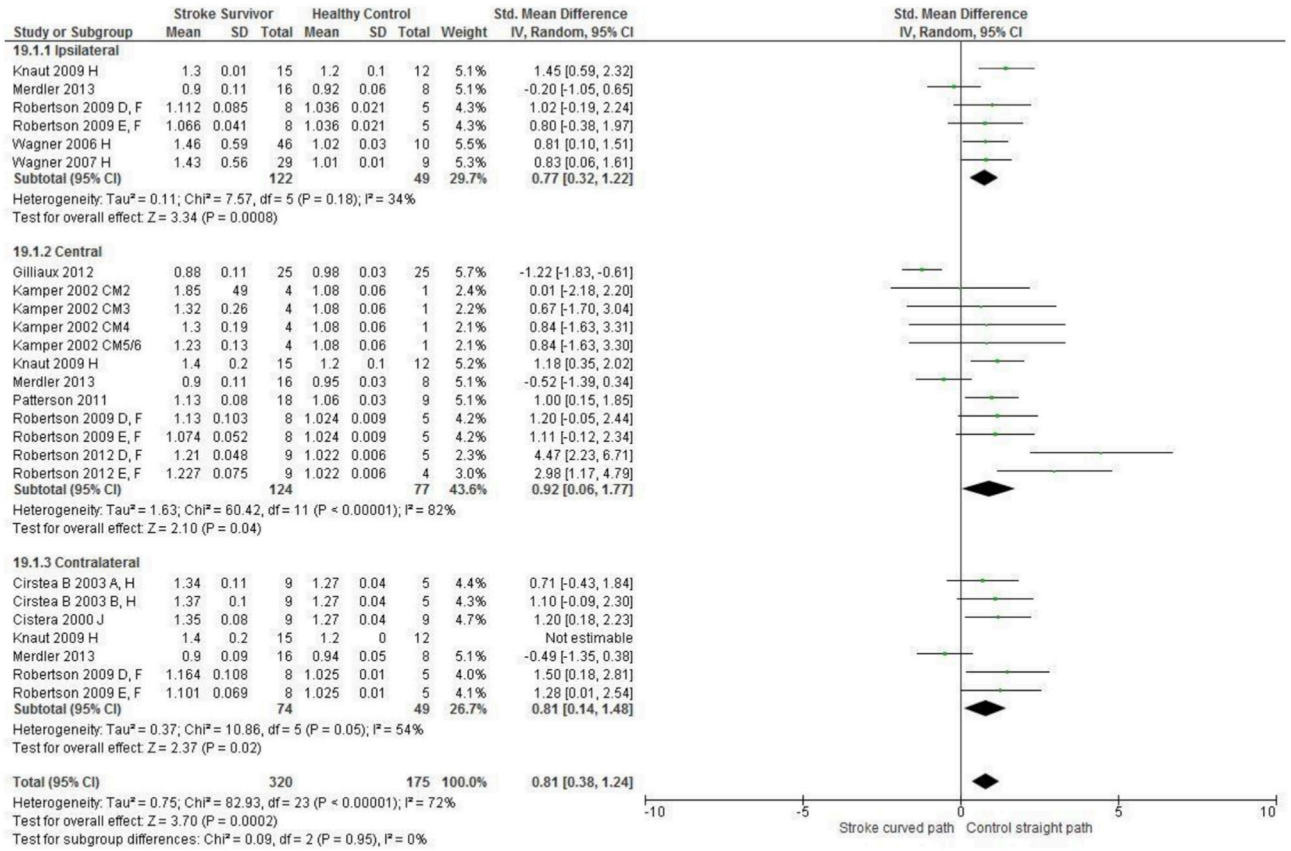


FIGURE 4 | The standardized mean difference (SDM) of reach-path ratio in the: ipsilateral, central, and contralateral workspace. A, mild motor impairment; B, moderate motor impairment; D, right hemisphere stroke; E, left hemisphere stroke; F, target placed 90% of arm's length; H, fast speed; J, reaches without vision; CM, Chedoke-McMaster Stroke Assessment Scale; and corresponding stage (2–6).

There were also differences between studies. For example, delayed onset of muscle activation in stroke survivors compared to healthy adult participants (57, 60, 74), contrasts with findings of no significant difference between the two groups (53).

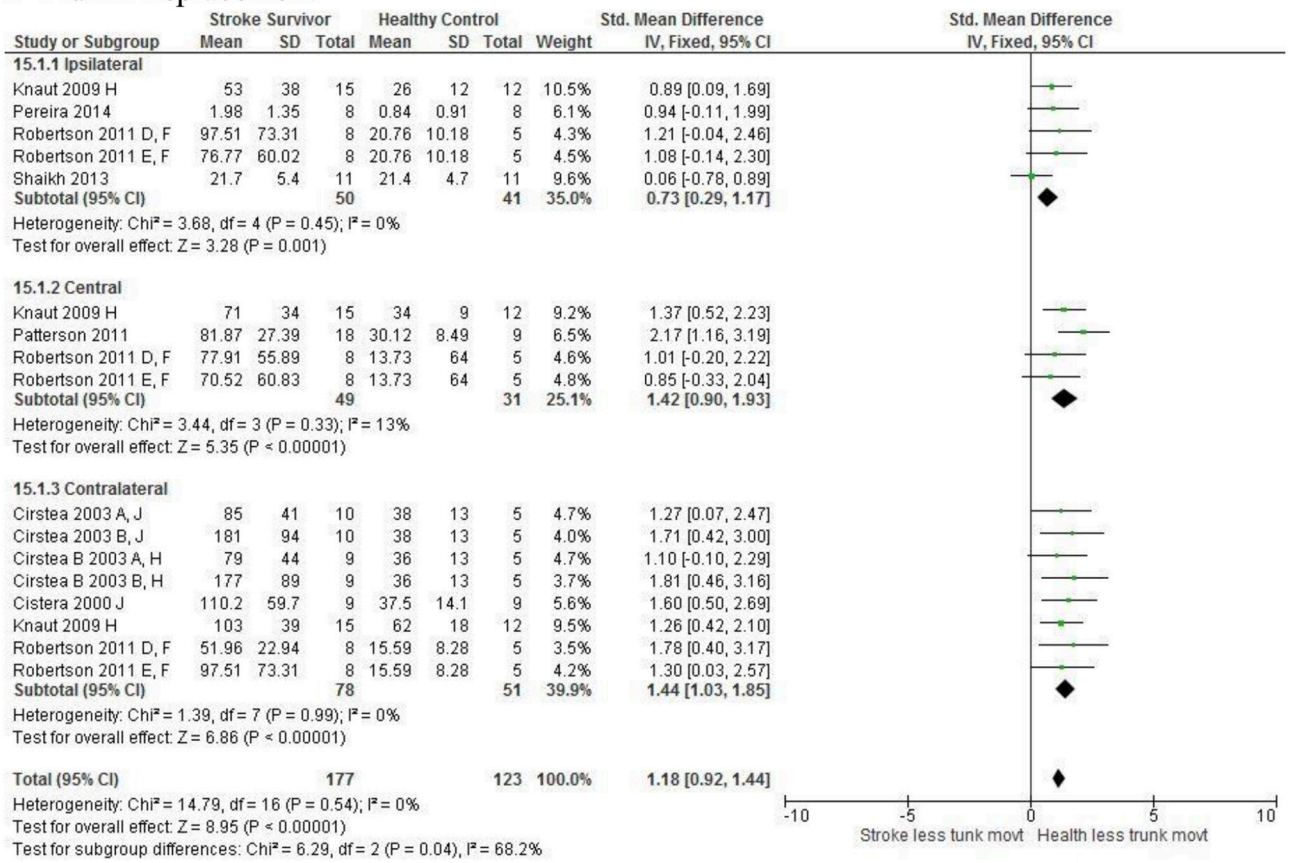
The synthesis also suggests that just examining one aspect of muscle activity might not be sufficient for identification of potential therapy targets after stroke. For example, people after stroke and healthy adult participants were found to utilize a similar number of muscle synergies during reaching (69, 72). But, a notable difference was that healthy adult participants during arm abduction and flexion recruited the anterior deltoid and pectoralis major whereas people after stroke recruited additional muscle of the brachioradialis and brachial (69).

DISCUSSION

The meta-analysis reported here found that people after stroke, compared with healthy adult participants, demonstrate: longer movement time, decreased peak velocity, greater trunk contribution, less smooth movement, and a more curved reach path when performing reach-to-target in all areas of the workspace. Furthermore, people after stroke exhibit less accurate reaches and decreased elbow extension reaching *to objects* in the ipsilateral and contralateral workspace; and less shoulder flexion when reaching in the contralateral and ipsilateral workspace. *Object location in the workspace influenced joint range of motion and target accuracy such that there were no differences between individuals with and without stroke in the central workspace.* These kinematic elements of movement skill are potential targets for rehabilitation therapy.

The narrative analysis reported here suggests that compared with healthy adult participants, people after stroke performing reach-to-target: use a greater percentage of MVC, have higher background muscle activity, and decreased coherence between muscle pairs. Meta-analysis was precluded by heterogeneity between included studies therefore caution needs to be used in considering these elements of movement skill as potential targets for rehabilitation therapy.

The meta-analysis finding reported here are applicable to individuals with stroke that exhibit similar levels of motor function to those individuals within the studies e.g., have the motor control to reach and point (mild to moderate upper limb deficits).



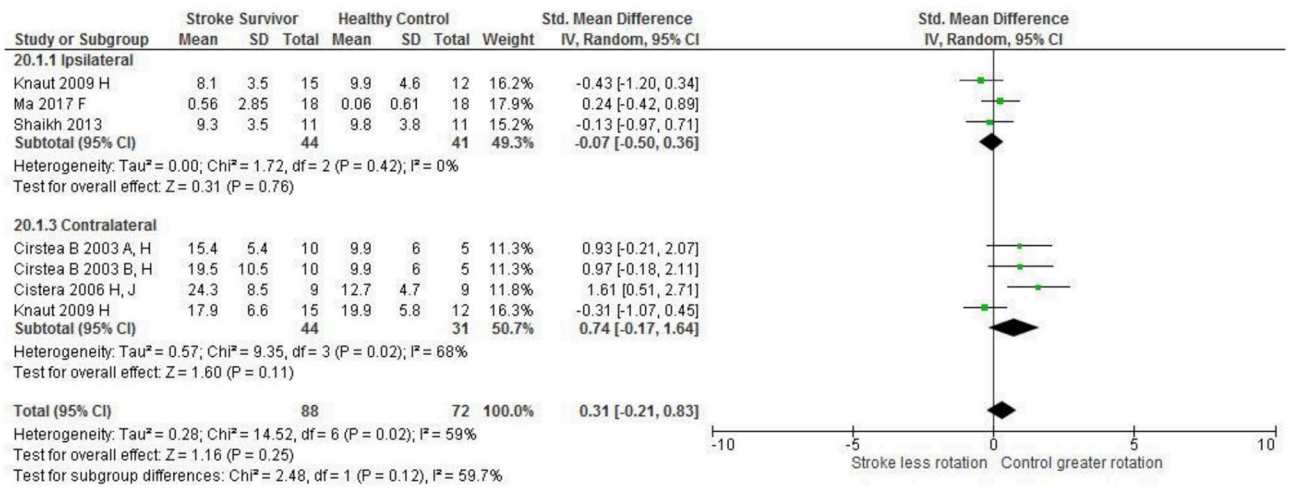


FIGURE 5 | The standardized mean difference (SDM) of trunk displacement (mm) during reach-to-target in the ipsilateral, central, and contralateral workspace. A, mild motor impairment; B, moderate motor impairment; C, bilateral task; D, right hemisphere stroke; E, left hemisphere stroke; F, target placed 90% of arm's length; H, fast speed; LK robotics; J, reaches without vision.

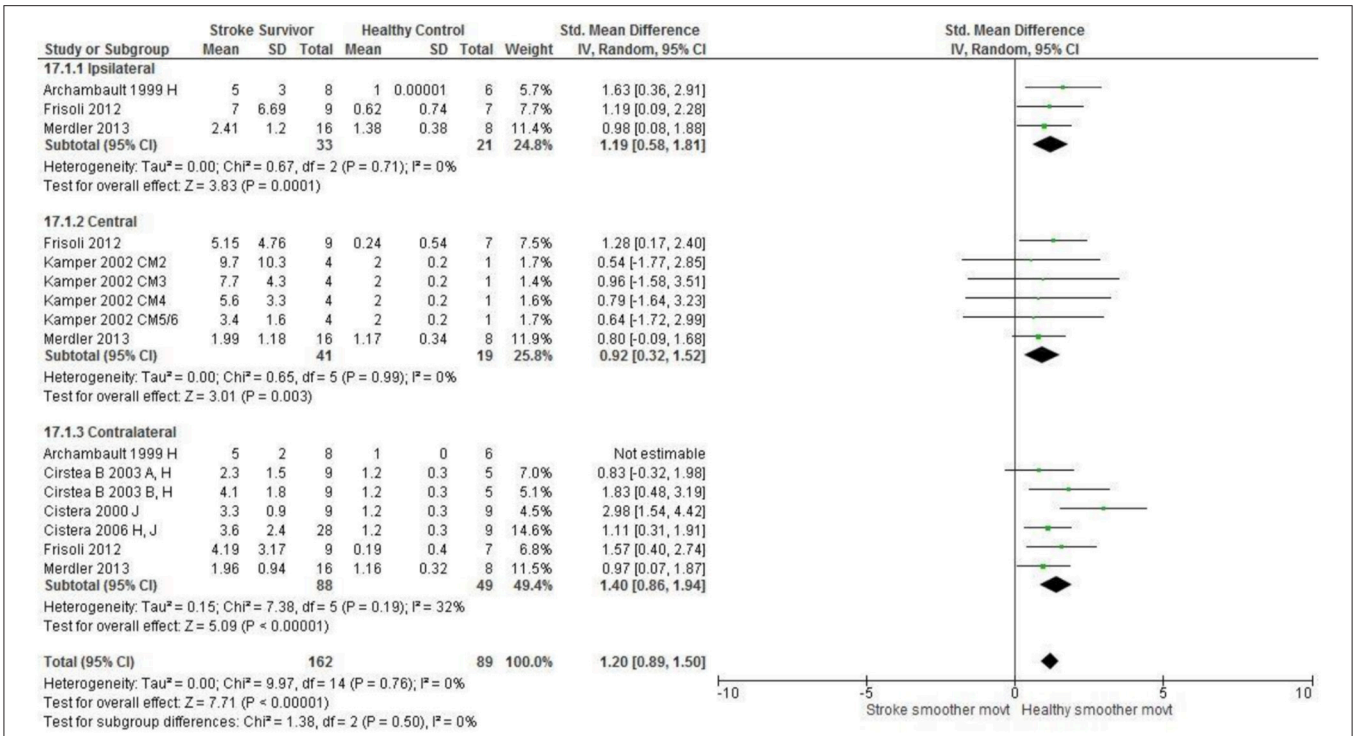


FIGURE 6 | The standardized mean difference (SDM) of movement smoothness during reach-to-target in the ipsilateral, central, and contralateral workspace. A, mild motor impairment; B, moderate motor impairment; H, fast speed; I, robotics; J, reaches without vision; M, virtual environment; CM, Chedoke-McMaster Stroke Assessment Scale; and corresponding stage (2–6).

Comparison With Earlier Published Findings

Interpretation of the present findings needs to be made considering the risk of potential bias of included studies. Most items were assessed as low risk; however, there was one area of one study assessed as high risk. Overall there was unclear reporting of both adverse events and blinded assessment for most included studies. The influence of these indications of risk of potential bias is debatable. It is reasonable to propose that reporting adverse events is irrelevant to this review because most included studies did not investigate an intervention and for those that did, only the baseline measures were included. It is also possible that unclear reporting of blinded assessment is not directly relevant to the results of this systematic review as measures derived from kinematic assessment and EMG are objective. However, the risk of potential bias from unclear reporting of blinded assessment remains if the same researcher conducted the assessments and those conducting processing and statistical analysis of the movement data. So, caution remains in respect of unclear reporting of blinded assessment. Otherwise, there is mostly low risk of potential bias and therefore the meta-analysis results are considered to be strong.

The identified kinematic differences during reach-to-target are mostly in accordance with previous narrative reviews (4, 19, 20). However, the study reported here is the first-ever meta-analysis of reach-to-target, using a systematic literature search unlike two of the earlier reviews (4, 20) and employed a systematic approach for reviewers to identify relevant studies and extract data unlike any of the earlier reviews (4, 19, 20). The results therefore are less likely to be confounded by reviewer bias than the earlier reviews. The results reported here provide the kinematic differences, and their variances, during reach-to-target performed by people after stroke and healthy adult participants. Objective reference values that could be used for target setting for upper limb rehabilitation after stroke can also be derived from this review. Consequently, the review reported here has provided additional knowledge to that provided in the earlier narrative reviews. Especially as the earlier reviews examined a variety of tasks involving reaching (19); reach-to-grasp rather than reach-to-target; and did not specify the aspects of reaching that were reviewed. This difference between reviews is important as it has been known for some time that kinematic characteristics differ between different reaching tasks (21, 22, 75).

Unlike the earlier narrative reviews (4, 19, 20) the review has examined EMG-derived measures of reach-to-target. It is possible that reduced coherence between muscles contributes to the kinematic differences between individuals with and without stroke such as reduced peak velocity and decreased movement smoothness. Suchc an association has been found between a reduced number of muscle synergies and reduced gait speed after stroke which was subsequently correlated with walking dysfunction (76).

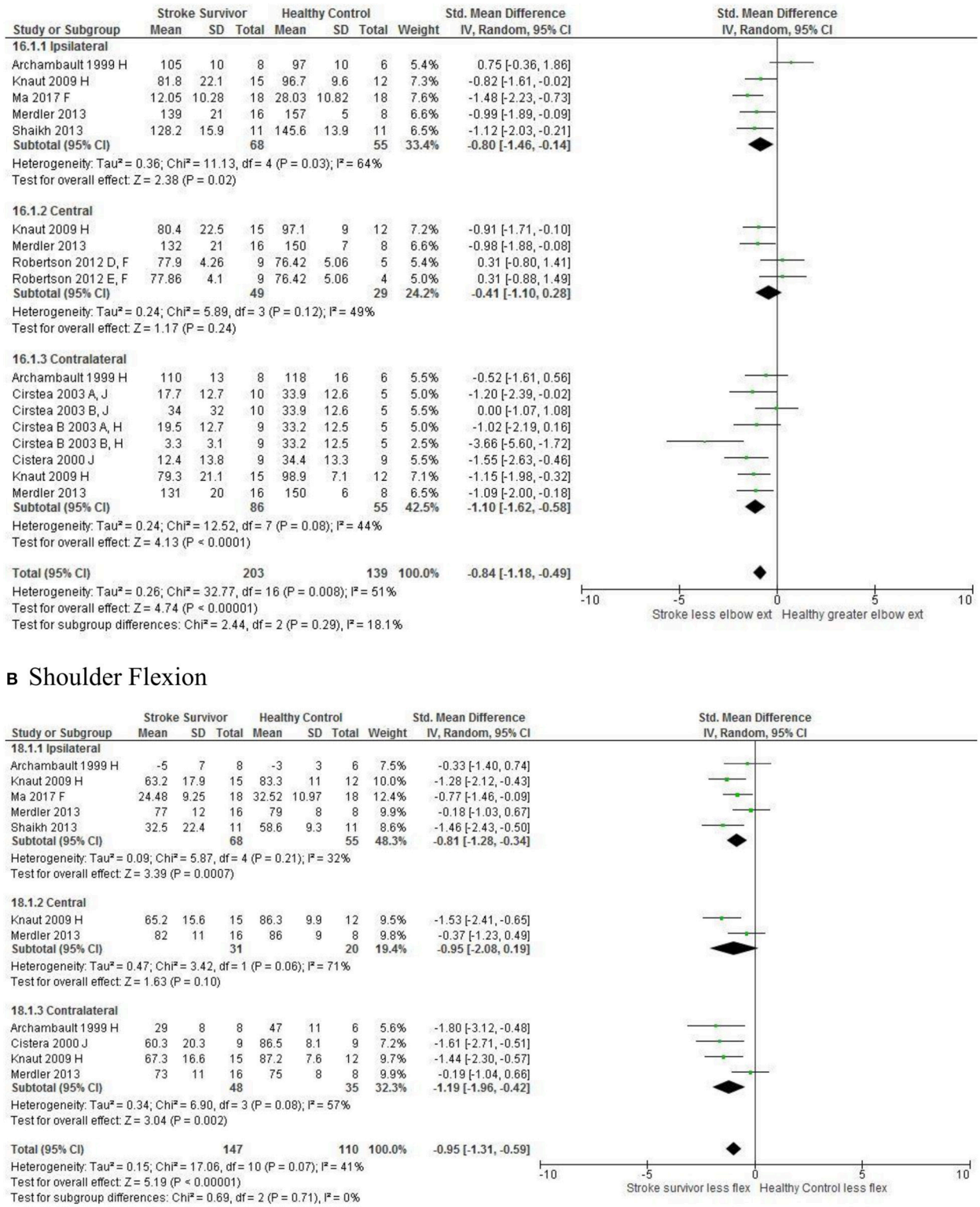


FIGURE 7 | The standardized mean difference (SDM) of joint kinematics in the ipsilateral, central, and contralateral workspace. D, right hemisphere stroke; E, left hemisphere stroke; F, target at 90% of arm's length; H, fast speed; J, reaches without vision.

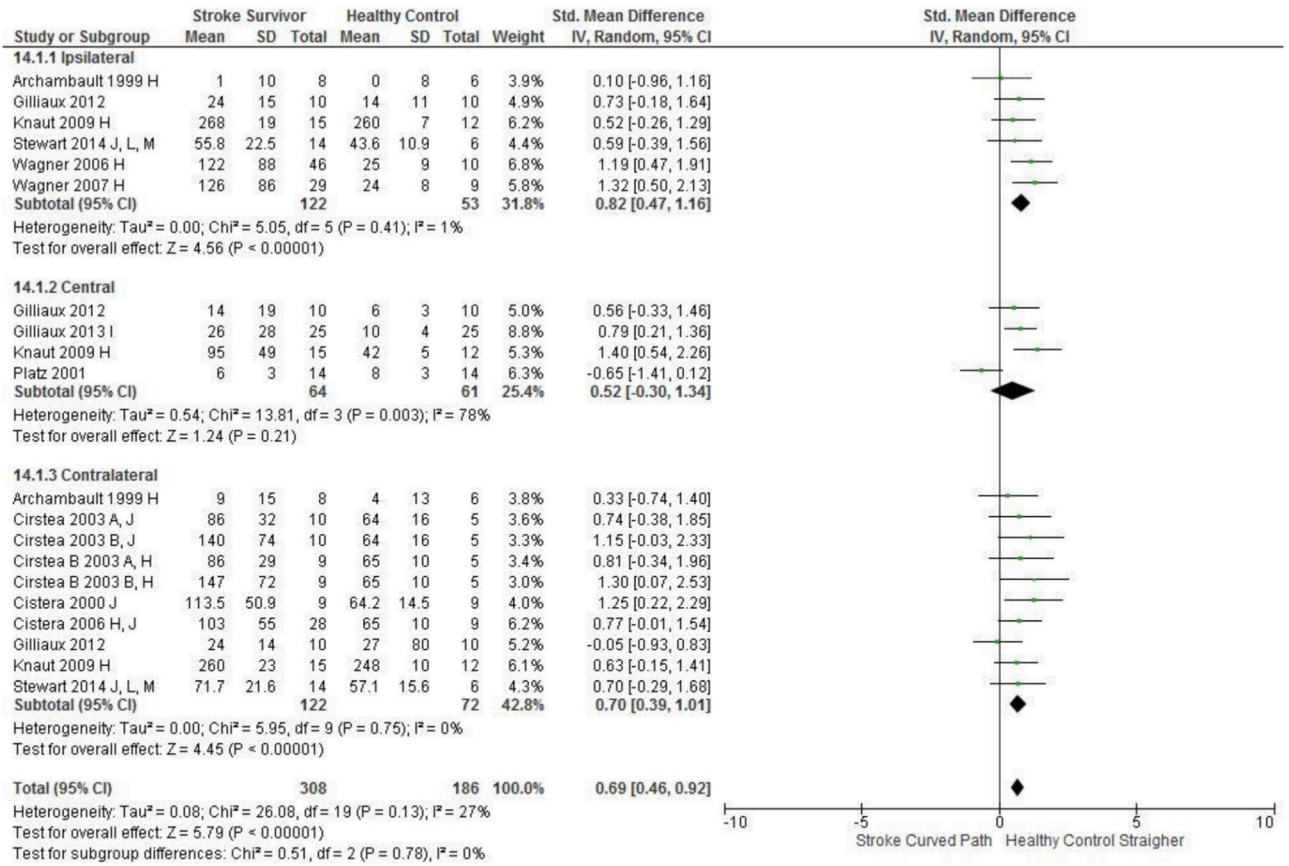


FIGURE 8 | The standardized mean difference (SDM) of accuracy (mm) in the ipsilateral, central, and contralateral workspace. A, mild motor impairment; B, moderate motor impairment; C, bilateral task; H, fast speed; I, robotics; J, reaches without vision; M, virtual environment.

This review found conflicting findings for timing of muscle activation. One study identified no difference in muscle onset time in comparison to control participants (53). Whereas, another found that individuals with stroke have delayed muscle onset/activation (57, 60, 74). Clearly this is an area for future research.

Interestingly 12 reach-to-target studies included reaching into the contralateral workspace. Yet healthy adults, when given the option to use their preferred arm to reach to target in any area of the workspace, utilize ipsilateral reaches rather than contralateral reaches during spontaneous activity (left arm for left targets, and right arm for (77) right targets) (34, 78, 79). Potential explanations for preferred ipsilateral reaches are that contralateral reaches are less biomechanically efficient thus require greater energy (79). *Workspace location had minimal influence on the differences in kinematics between individuals with stroke and control with there being consistent significant differences in all areas of the workspace. However, in the central workspace there were no differences in shoulder/elbow range of motion or accuracy between individuals with and without stroke. This could be due to the joint combinations needed to reach to the central workspace (e.g. elbow extension with shoulder adduction) are part of the flexor synergy in individuals with stroke, an often used movement pattern (77).*

Strengths and Limitations

The studies included in the systematic review were heterogeneous, for example: the reaching task; movement speed; object location; use of trunk restraint; upper limb motor ability of individuals with stroke; and varied time since stroke. The I^2 statistic demonstrated that of the 26 meta-analyses three meta-analyses had high heterogeneity ($I^2 \geq 75\%$) reach-path-ratio (central workspace), peak velocity (central workspace), and movement time in the ipsilateral workspace. The remaining twenty three meta analyses exhibited low (10/26) and moderate heterogeneity (13/26) (23, 30). Evaluation of the forest plots demonstrates that many of the confidence intervals are overlapping and the mean differences fall on the same side of the line of no effect (23, 30) suggesting the studies are comparable. However the possibility remains that combing heterogeneous studies with in a meta-analysis could be a limitation as the findings may be biased (23).

There are two additional potential limitations to this review. First, limitation of the search to articles published in the English language. However, a strength is that the search strategy was

TABLE 7 | Summary of the meta-analyses of the kinematic characteristics of reach-to-target.

Kinematic characteristic and area of workspace	Number of participants	SMD [95% CI]	Stroke participants compared to control participants
Peak velocity: Central	Stroke = 145, Control = 110	−1.12 [−1.90, −0.35]*	↓
Peak velocity: Ipsilateral	Stroke = 163, Control = 82	−1.76 [−2.29, −1.24]*	↓
Peak velocity: contralateral	Stroke = 96, Control = 61	−1.69 [−2.59, −0.79]*	↓
Movement time: Central	Stroke = 92, Control = 77	1.44 [0.95, 1.94]*	↑
Movement time: Ipsilateral	Stroke = 98, Control = 66	2.57 [0.89, 4.25]*	↑
Movement time: Contralateral	Stroke = 86, Control = 47	2.08 [1.61, 2.55]*	↑
Reach path tatio: Central	Stroke = 124, Control = 77	0.92 [0.06, 1.77]*	↑
Reach path ratio: Ipsilateral	Stroke = 122, Control = 49	0.77 [0.32, 1.22]*	↑
Reach path ratio: Contralateral	Stroke = 74, Control = 49	0.81 [0.14, 1.48]*	↑
Trunk contribution: Central	Stroke = 49, Control = 31	1.42 [0.90, 1.93]*	↑
Trunk contribution: Ipsilateral	Stroke = 50, Control = 41	0.73 [0.29, 1.17] *	↑
Trunk contribution: Contralateral	Stroke = 78, Control = 51	1.44 [1.03, 1.85]*	↑
Smoothness of movement: central	Stroke = 41, Control = 19	0.92 [0.32, 1.52]*	↓
Smoothness of movement: Ipsilateral	Stroke = 33, Control = 21	1.19 [0.58, 1.81]*	↓
Smoothness of movement: contralateral	Stroke = 88, Control = 49	1.40 [0.86, 1.94]*	↓
Elbow extension: Central	Stroke = 49, Control = 29	−0.41 [−1.10, 0.28]	↔
Elbow extension: Ipsilateral	Stroke = 68, Control = 55	−0.80 [−1.46, −0.14]*	↓
Elbow extension: Contralateral	Stroke = 86, Control = 55	−1.10 [−1.62, −0.58]*	↓
Shoulder flexion:Central	Stroke = 31, Control = 20	−0.95 [−2.08, 0.19]	↔
Shoulder flexion: Ipsilateral	Stroke = 68, Control = 55	−0.81 [−1.28, −0.34]*	↓
Shoulder flexion: Contralateral	Stroke = 48, Control = 35	−1.19 [−1.96, −0.42]*	↓
Accuracy: Contralateral	Stroke= 122, Control = 72	0.70 [0.39, 1.01]*	↑
Accuracy: Ipsilateral	Stroke = 122, Control = 53	0.82 [0.47, 1.16]*	↑
Accuracy: Central	Stroke = 64, Control = 61	0.52 [−0.30, 1.34]	↔
Trunk rotation: Contralateral	Stroke = 44, Control = 31	0.74 [−0.17, 1.64]	↔
Trunk rotation: Ipsilateral	Stroke = 44, Control = 41	−0.07[−0.50, 0.36]	↔

*A fixed effect model was used if $I^2 \leq 25\%$, and a random effects model was used if $I^2 > 26$ %. SMD, standardized mean difference; 95%CI, 95% confidence intervals; * indicates significant difference in SMD between individuals with stroke and control participants; ↑, significantly greater in individuals with stroke; ↓, significantly decreased in individuals' with stroke; and ↔, no differences between individuals' with stroke and control participants.*

robust and carried out in multiple data-bases. The second limitation is that participants with stroke had to have sufficient upper limb motor function to complete the reaching task, so, the findings may not be applicable to those with severe paresis.

CONCLUSION

This first-ever meta-analysis of the kinematics of reach-to-target by people with stroke and healthy adults performing reach-to-target found 21 elements that could provide targets for impairment-orientated therapy for better upper limb recovery. *Of the kinematic characteristics, object location influenced joint range of motion and target accuracy*.The findings also quantify the differences which should inform measurement of the efficacy of rehabilitation. Subsequent studies need to investigate whether tailoring therapy at the identified differences reported here, does enhance upper limb recovery after stroke.

AUTHOR CONTRIBUTIONS

KC led the conception, design, analysis and interpretation of this systematic review, prepared the initial drafts of the report, provided approval for publication of the content and agreed to be accountable for all aspects of the work. NK made

substantial contributions to the conception, design, analysis and interpretation of this systematic review, contributed to drafts of the report, provided approval for publication of the content and agreed to be accountable for all aspects of the work. AC made substantial contributions to the conception, design, analysis and interpretation of this systematic review, contributed to drafts of the report, provided approval for publication of the content and agreed to be accountable for all aspects of the work. VP made substantial contributions to the conception, design, analysis and interpretation of this systematic review, contributed to drafts of the report, prepared the final version of this report, provided approval for publication of the content and agreed to be accountable for all aspects of the work.

FUNDING

No external funding was provided for the systematic review reported here which was undertaken as part of the Ph.D. studies of KC (first author).

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