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Review Article

# Been there, done that, so what's next for arm and hand rehabilitation in stroke?

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**Abstract**.
**BACKGROUND:** The extraordinary advances in technology such as body-worn sensors, health information technologies, technological advances in neuroimaging, and computational approaches to predictive modelling using biomarkers offers considerable promise to literally transform our thinking, our approach to the problem, and the design of future clinical trials about arm and hand rehabilitation after stroke.
**OBJECTIVE:** To provide a focused review that considers the past, present and future of arm and hand rehabilitation in stroke.
**METHOD:** We organized this perspective into three parts: 1) Past– we summarize the past decade of the clinical trial enterprise in neurorehabilitation, 2) Present– we provide a brief review of three research areas where mechanistic studies that rely on uniquely human neural circuits provide a basis for promising intervention tools, and 3) Future–we highlight three unique research domains that are likely to provide the biggest impact on the future of post-stroke arm and hand recovery.
**RESULTS:** The past has not been a complete failure—in particular, the EXCITE RCT put arm and hand rehabilitation on the map. Unfortunately, the majority of clinical trials that followed were based on an immature science of neurorehabilitation. We got drawn in by the seductive preclinical animal model work which suggested that dose and intensity of task-oriented training was the most important ingredient for fostering recovery in humans. While dose, and intensity are clearly important, they are of little value unless the stroke survivor is engaged, motivated, and the neural infrastructure provides enough resource to allow the recovery process. Recently, we noticed an increase in mechanistic and theory-driven studies, findings from which will not only advance our understanding of critical brain-behavior mechanisms, but will provide a more mature science moving into the future.
**CONCLUSIONS:** The good news is that there is evidence that we learned from the past and have invented a future that appears to be much more exciting and promising than the past.

Keywords: Arm and hand rehabilitation, stroke recovery, neural networks, biopsychosocial factors

## 1. The past: The clinical trial enterprise in neurorehabilitation intervention studies

Over the past decade, there have been approximately nine moderate- to large-scale non-pharmacologic stroke recovery trials with a focus on rehabilitation. The majority of these trials tested the superiority of a particular evidence-based intervention, but returned negative/neutral results, with no difference in outcome between the experimental intervention and an appropriate control. These nine intervention trials include the EXCITE (Extremity Constraint-Induced Movement Therapy Evaluation) trial (Wolf et al., 2006) the VA-Robot trial (Lo et al., 2010), the LEAPS (Locomotor Experience Applied Post Stroke) trial (Duncan et al., 2011), the EVEREST (Epidural Electrical Stimulation for Stroke Rehabilitation) trial (Levy et al., 2016), the AVERT (A Very Early Rehabilitation) trial (AVERT, 2015), the EXPLICIT (Explaining Plasticity after

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Stroke) trial (Kwakkel et al., 2016), the ICARE (Interdisciplinary Comprehensive Arm Rehabilitation Evaluation) trial (Winstein, Wolf, et al., 2016), the Dose-response trial (Lang et al., 2016) and ATTEND (Family-led Rehabilitation after Stroke in India) trial (Lindley et al., 2017). Of these non-pharmacologic, evidence-based intervention trials including one using electrical epidural cortical stimulation (i.e., EVEREST), only EXCITE and AVERT saw significant differences in the primary outcome compared to a usual care group. Of these two, only EXCITE was focused on arm and hand recovery.

EXCITE was the first large-scale phase III efficacy trial of a stroke rehabilitation intervention which paved the way for many of the intervention trials to follow (Luft & Hanley, 2006; Wolf et al., 2006). From a contemporary perspective, the EXCITE trial findings are not particularly surprising, given that the trial was designed to compare 1 year outcomes of those with mild to moderate upper extremity impairment who receive 2 weeks of intensive constraint-induced movement therapy (i.e., 6 hr/day) to a delayed control group. At the time, a no-therapy control group, was considered an acceptable comparison group, particularly one that on average was 6 months post-stroke and generally, beyond the time window for receiving formal rehabilitation services.

While the EXCITE trial provided an important inaugural boost to the stroke rehabilitation trial enterprise, the practicality of such an intensive program of constraint-induced movement therapy, one which required a 6 hr/day investment from a trained clinician and willing patient, was simply not realistic, making EXCITE a well-regarded efficacy trial, but with minimal effectiveness evidence to follow (Taub, Lum, Hardin, Mark, & Uswatte, 2005). In fact, there were a number of modified Constraint-Induced Movement Therapy (CIMT) studies (Levine & Page, 2004; Page & Levine, 2007; Page, Levine, & Leonard, 2005; Page, Sisto, Johnston, & Levine, 2002); and more recently, a study (Gauthier et al., 2008) compared two versions of CIMT training, one with traditional elements of constraint-induced therapy, including intensive in-laboratory practice (task practice and "shaping" behavior with progressive practice) of the more impaired arm using functional tasks for 3 hours daily for 10 consecutive weekdays, restraint of the less-impaired arm for approximately 90% of waking hours, and what was termed a "transfer package" for an additional half-hour every training day with review of daily arm use and problem-solving to overcome perceived barriers to arm use at home. This version of CIMT was compared to one with all elements *except* the transfer package. Remarkably, CIMT with transfer package was superior to CIMT without transfer package. In fact, evidence indicated that the CIMT group with transfer package showed both structural brain changes in grey matter of sensory and motor regions and hippocampus, and large behavioral changes in real-world arm function, while the group receiving CIMT without the transfer package did not exhibit grey matter increases, and showed reduced improvements in motor activity. These results imply that it was not so much the volume and progression of task practice itself that drove brain and motor activity changes but the efforts to contextualize arm use to the patient's natural environment.

On the other hand, the more recent efficacy and safety of very early mobilization within 24 h of stroke onset (AVERT) trial used a parallel-group design for which physiologically eligible participants were randomized to either a usual stroke-unit care alone group or a very early mobilization in addition to usual care group. The primary outcomes for efficacy and safety revealed that fewer patients in the very early mobilization group had a favorable outcome compared with those in the usual stroke-unit care group [46% vs 50%]. Since then the AVERT group has published the results of a pre-specified dose-response analysis to provide practical guidance for clinicians on the timing, frequency and amount of mobilization following acute stroke (Bernhardt, Churilov, et al., 2016). To date, there are no moderate- to large-scale studies similar to AVERT that are focused on very early mobilization of the upper extremity. A close comparison is the phase II VECTORS trial (Dromerick et al., 2009) that determined that CIMT was as effective but not superior to an equal dose of standard therapy during inpatient stroke rehabilitation. In fact, a higher intensity of CIMT resulted in less motor improvement at 90 days, indicating an inverse dose-response relationship.

Taking stock of the rehabilitation and recovery clinical trial enterprise in stroke and considering the issues and opportunities, the Rehab and Recovery workgroup of the National Institutes of Health StrokeNet identified eight specific issues to address to move stroke recovery and rehabilitation research forward (Cramer et al., 2017). While a number of issues raised by the workgroup were pragmatic in nature (e.g., post-acute stroke care delivery), we chose one in particular to highlight— "social and personal factors can have a high impact on stroke recovery in humans, affect pragmatic aspects of subject retention in trials, and are not well modelled in preclinical research"—because it underscores the challenges of translating preclinical research into human stroke recovery research (Adkins, Schallert, & Goldstein, 2009; Corbett, Jeffers, Nguemeni, Gomez-Smith, & Livingston-Thomas, 2015).

In the next section, we begin to tackle the translation problem and discuss studies of intervention tools—those that rely on neural networks emergent from human brain studies—that use more ecologically valid paradigms and shed light on the poorly understood human condition of stroke (Corbetta et al., 2015; Edwardson et al., 2017). Given that the dose hypothesis emerged from preclinical animal model work, we move beyond dose per se to understand the paretic limb in context with both the environment and the individual.

## 2. The present: Beyond dose toward promising intervention tools that rely on neural networks

### *2.1. Mirror feedback and the action observation network*

There is some evidence that mirror feedback is potentially a powerful intervention tool to facilitate recovery of paretic arm movement and activate brain areas that have been down-regulated after stroke. Recent work has used the Dynamic Causal Modeling (DCM) approach to distinguish between two theoretical neural mechanisms that might mediate the mirror feedback effect (Saleh, Yarossi, Manuweera, Adamovich, & Tunik, 2017). The potential neural mechanisms mediating mirror feedback are: transfer of information between bilateral motor cortices; or recruitment of regions comprising an action observation network which in turn modulates the motor cortex. The authors used a clever experimental design whereby they used event-related fMRI to capture neural activity while 14 chronic stroke survivors performed goal-directed finger flexion movements with their less affected hand while observing real-time visual feedback of the corresponding (veridical) or opposite (mirror) hand in virtual reality. Using DCM, 30 plausible network models were tested—the winning model supported the indirect hypothesis—that mirror feedback-based activation of the motor cortex may be attributed to engagement of a contralateral (contralesional) action observation network.

A complimentary study by Garrison and colleagues (Garrison, Aziz-Zadeh, Wong, Liew, & Winstein, 2013) used functional magnetic resonance imaging (fMRI) to measure activity in motor-related brain regions during action observation. Twelve participants with chronic middle cerebral artery stroke and moderate to severe dominant (right) hand paresis, and 12 matched right-handed non-disabled participants observed precision reach-to-grasp actions (e.g. lift pencil) made using the left and right hand. Observed actions were difficult or impossible for participants with stroke to perform using the paretic right hand, but easy to perform using the non-paretic left hand. All participants performed the actions using each hand to the best of their ability after the MRI. Overall, for non-disabled participants, left- more than right-hand action observation engaged cortical motor regions and more so in the right hemisphere; whereas for participants with stroke, right (paretic) hand more than left hand action observation engaged cortical motor regions, and more so in the damaged left hemisphere. Importantly, activity in the motor system during action observation is related to motor capability to perform the observed actions, such that longer movement times (more impaired) using the paretic right hand, are associated with greater activity during right hand action observation in the inferior frontal gyrus of the left lesioned hemisphere. Results suggest that despite chronic non-use, cortical representations of the paretic limb in the damaged motor cortex are preserved and may be accessed by action observation in stroke rehabilitation.

Finally, a recent cohort study used a within-subject design to investigate whether action observation training with immediate physical practice improves upper-limb function after stroke. Fourteen chronic stroke survivors were assessed at baseline, followed by participation in 2 weeks of relaxation-sham plus physical practice (control) and reassessed immediately after. Thereafter, this same cohort participated in 2 weeks of action observation training coupled with immediate physical practice (intervention), followed by a final assessment. Duration of each action observation video sequence (priming exposure) was 30 s immediately followed by practice of the observed motor task. Sugg and colleagues (Sugg, Muller, Winstein, Hathorn, & Dempsey, 2015) found significant improvements in control and intervention phases on primary outcome measures—Upper Extremity Fugl-Meyer Motor Assessment (FMA) and Functional Test of the Hemiparetic Upper Extremity (FTHUE)—as well as secondary outcome measures of self-perceptions of arm use. Gains in the primary outcomes were greater during the intervention phase than during the control phase (relaxation-sham plus physical practice). Interviews with participants highlighted the added value of watching an actor perform the movement before physically attempting to perform the action. This study provides preliminary evidence of the additive value of action observation plus physical practice over relaxation-sham plus physical practice. There appears to be capacity for further recovery of upper-limb function in chronic stroke that persists at least in the short term and when the participant is guided through action observation. While Sugg and colleagues did not measure a neural correlate such as the action observation network, their behavioral research was designed with the assumption that such a network would be engaged by the intervention and thereby enhance recovery.

Taken together, these three studies provide evidence that mirror feedback and action observation are promising recovery-supportive intervention tools that may depend upon emergent neural networks that could be tapped for future development. We come back to this notion in the *Future* section where we discuss the concept of "detour circuits".

### 2.2. Bimanual coordination and training

Indeed, a defining feature of real world arm use is that the two hands work cooperatively in order to interact with the environment and achieve functional goals, e.g. buttoning a shirt, cutting food etc. The lack of engagement in functional activities after stroke may therefore be arguably related to diminished bimanual coordination, and may subsequently lead to a vicious cycle of functional decline (Kantak, Jax, & Wittenberg, 2017). While a return to prior levels of real world bimanual use, and thus a return to function, is desirable after a stroke, the means to achieve this through appropriate therapy remain an open question. Bilateral training, by definition, allows simultaneous engagement of two hands, a characteristic feature of arm use in the real world.

Naturally, the last two decades have seen a tremendous growth in the number of small clinical and experimental studies investigating the effects of bilateral training in stroke survivors. As with most training paradigms, the goal of bilateral training in many of these studies was to reduce paretic arm impairment, improve functional outcomes, and possibly improve participation-level outcomes (i.e., arm use). Before delving into the specific findings of these studies, it is important to recognize that many of them were not designed as randomized controlled trials. Additionally, several of them either combined bilateral therapy with other interventions such as unilateral therapy, neuromuscular stimulation, or administered bilateral therapy through either robotic (Bi-Manu-Track, MIME etc.) or gaming interfaces (Wii-Fit, Razer Hydra etc.). Of these several variants, one of the promising and relatively well-studied interventions is the Bilateral Arm Training with Rhythmic Auditory Cueing (BATRAC) (Whitall, Waller, Silver, & Macko, 2000).

The BATRAC involves rhythmic non-goal-oriented repetitions of bilateral arm movements and is based on the fundamental principle of frequency-dependent inter-limb coupling (Amazeen, Schmidt, & Turvey, 1995; Rose & Winstein, 2013; Schmidt, Shaw, & Turvey, 1993), which is thought to allow entrainment of the paretic arm by the non-paretic arm. Whitall et al. (2000) reported that 20 minutes of BATRAC, 3 days/week for 6 weeks reduced paretic arm impairment (Fugl-Meyer Assessment score), improved function (Wolf Motor Function test time score), and increased self-reported arm use (University of Maryland Arm Questionnaire for Stroke) in chronic hemiparetic participants, and these gains were sustained over 8 weeks (Whitall et al., 2000). In a follow-up study, the group found that compared to 12 weeks of unilateral training alone, a combined training protocol with 6 weeks each of BATRAC and unilateral task-oriented training led to greater improvements in the above-mentioned outcomes (McCombe-Waller et al., 2014). Apart from its effects as standalone and combined therapy, bilateral training has also been found to be an effective "primer" to conventional therapy (Stinear, Barber, Coxon, Fleming, & Byblow, 2007; Stoykov & Stinear, 2010). For example, a form of rhythmic bilateral training (APBT) in which active movements of the non-paretic arm caused simultaneous passive mirror movements of the paretic arm was found to enhance effects of conventional therapy, making those who receive such priming 3 times more likely to reach their recovery potential.

On the other hand, there is some evidence that bilateral therapy may not be any more effective in reducing impairment or improving function compared to conventional therapy (Seegelke, Hughes, Wunsch, van der Wel, & Weigelt, 2015; Whitall et al., 2011; Wu, Yang, Chen, Lin, & Wu, 2013). For example, in a study that compared much higher doses (>90 minutes/day, 5 days/week for 4 weeks) of robot-administered bilateral and unilateral training, it was found that bilateral therapy alone was not superior to unilateral training, at least not in improving function or self-reported use; however the bilateral group demonstrated less compensatory trunk movement during arm reaching (Wu et al., 2013). A similar study comparing therapist-administered unilateral and bilateral therapy found that improvements in function as assessed by the Action Research Arm Test (ARAT) were equivalent between the two groups, except certain dexterous functions for which unexpectedly, the bilateral therapy group demonstrated significantly better outcomes (Morris et al., 2008). Noteworthy to the comparison between unilateral and bilateral training is that even though measured by similar clinical outcomes, the two have been found to target different regions of the brain in effecting these changes, with relatively greater bi-hemispheric involvement in those who receive bilateral therapy (Luft et al., 2004).

On the whole, in evaluating the present state of the science in this area, two issues emerge: First, and most important, it is essential for us as a scientific community to acknowledge that in order to best understand the effects of bilateral training, we ought to first understand the factors crucial to bimanual behavior after stroke, and by so doing identify subsets of patients who might be best suited for bilateral training. As indicated in a review by one of the authors (Rose & Winstein, 2004) and reaffirmed by others since (McCombe Waller & Whitall, 2008), with regards to the application of bilateral training for post-stroke rehabilitation, there exists, most decidedly, a "set of specific patient and task characteristics." Thus, in the interest of designing robust future investigations of the effect of such training, it behooves us to first and foremost understand these phenotypic profiles. Second, as mentioned previously, the quality of evidence that exists in this area is low and perhaps a reflection of the relatively nascent scientific understanding of bilateral training. Most of these studies were not conducted as RCTs, and those that were suffered from flaws in the study design including allocation concealment, blinding, and baseline differences. Moreover, small and inhomogeneous samples and inconsistent definitions of bilateral training further prevent generalization.

Taken together, the evidence for bilateral training is somewhat mixed, but we are optimistic about the future as the scientific foundation for this intervention matures. Next, in the *Future* section, we discuss bilateral training from two viewpoints: as a promising intervention for engaging detour circuits, and from the perspective of identifying unique subgroups of responders—each in its own way providing insight into how this intervention might work.

### *2.3. Learned non-use and biopsychosocial factors*

One of the most impenetrable problems challenging full recovery after stroke is non- or limited spontaneous use of the paretic limb in the natural environment (Mayo, Wood-Dauphinee, Cote, Durcan, & Carlton, 2002). While motor capability has long been thought to be the primary factor that determines paretic limb use, recent work suggests that after controlling for motor impairment, 'non-use' behavior can be explained in part by one's limited expectations for task success and low confidence in task performance (Salbach et al., 2006; Stewart & Cramer, 2013). Comprehensive rehabilitation programs with adequate resources, dose, and duration are essential aspects of stroke care in the post-acute ambulatory setting (Winstein, Stein, et al., 2016). A limitation of traditional rehabilitation models is that rehabilitation is largely relegated to training in clinic-based settings with after care primarily dependent upon paper-based home exercise programs.

Limited use of the paretic hand after stroke can severely constrain an individual's activity and participation and lead to further functional degradation (Kleim & Jones, 2008) (Hidaka, Han, Wolf, Winstein, & Schweighofer, 2012). Clinical practice as well as research has focused on improving motor capability of the paretic hand to promote spontaneous use in the natural environment (Sterr, Freivogel, & Schmalohr, 2002; Edward Taub et al., 1993; Wolf et al., 2006). Kleim and Jones highlighted the benefit of "use" in rehabilitation after brain damage, fueled in part by growing evidence of experience-dependent neuroplasticity (Kleim & Jones, 2008; Nudo, Milliken, Jenkins, & Merzenich, 1996). The potential for central nervous system recovery with persistent practice and use of paretic limbs is far greater than previously suspected. If the use of the paretic limb is limited or absent, further functional decline is likely to ensue, leading to higher levels of disability and limited community reintegration. This scenario depicts a perpetual cycle of decline that accounts for many disabling conditions including stroke (Hidaka et al., 2012). Therefore, clinicians and researchers have devoted tremendous efforts to develop rehabilitative interventions, such as intense task-specific training (e.g., Constraint-Induced Movement Therapy-CIMT (Edward Taub et al., 1993; Edward Taub, Uswatte, Mark, & Morris, 2006; Wolf et al., 2006) that are used to promote paretic hand use, with the goal to maximize motor recovery and break the perpetual cycle of decline.

The implicit assumption behind current approaches is that improved motor capability after these motor-based interventions will automatically promote spontaneous functional use of the paretic hand in the natural environment. However, the non-use phenomenon signifying the sub-optimal use of the paretic hand threatens the validity of this assumption (Sterr et al., 2002; Stewart & Cramer, 2013). In essence, the motor improvements that patients achieve in therapy when they are 'forced' to perform tasks with the paretic hand are seldom maintained or generalized into the natural environment unless the therapy includes a "transfer package". (Gauthier et al., 2008) Previously, we described Gauthier and colleagues' study in the *Past* section of this perspective. The importance of the transfer package over and above the volume of task practice highlights the importance of linking the stroke survivors' preferences, values, and perceptions to the goals of practice—the transfer package contextualizes and personalizes the training to each individual. Most importantly, the transfer package addresses a critical blind spot in current healthcare reform (Rosenbaum, 2013) and one we introduced earlier in connection with the rehabilitation clinical trial enterprise, namely, personal and social factors and their tremendous impact on recovery in humans. We turn to this issue next.

An early study reported that 52% of patients post-stroke did not incorporate the paretic hand in performing daily activities at home even though they had demonstrated the capability in the rehabilitation unit (Andrews & Stewart, 1979). A more recent study revealed that individuals only spontaneously choose and used their paretic hand for 22% of the activities in the Actual Amount of Use Test (Chen, Wolf, Zhang, Thompson, & Winstein, 2012) even though the motor capability was sufficient to perform all the activities (Sterr et al., 2002). Even in those patients with full motor recovery (as indicated by the full score of the Fugl-Meyer Upper Extremity Assessment, FM), 27% reported reduced hand use in daily activities (Stewart & Cramer, 2013). Although stroke survivors are aware of the importance of paretic hand use (Barker & Brauer, 2005), 65% of stroke survivors report limitation in incorporating their paretic hand into daily activities (Mayo, Wood-Dauphinee, Côté, Durcan, & Carlton, 2002).

Han and colleagues provided specific evidence that the non-use phenomenon cannot be fully explained by motor capability. The difference between what people can do and what people actually did was not correlated with residual motor capability (Han et al., 2013). Chen (2011) found a similar result in which participants' motor capability (as measured by the FM, the time subscale of the Wolf Motor Function Test, and the reaching movement time of the paretic hand) was not predictive of paretic hand use in target reaching (Chen, 2011). Instead, relative self-efficacy, a comparative measure of confidence between pairs of targets in the workspace predicted the probability of choosing the paretic hand for reaching (Chen, Lewthwaite, Schweighofer, & Winstein, 2013). Recent work from our group (Yi-An Chen, unpublished Dissertation, 2017) demonstrated that social-cognitive factors (i.e., social interaction and self-efficacy) play an essential role in post-stroke hand use behavior in the natural environment. Motor capability, although an important factor, is not the only thing that influences the use of the paretic hand post-stroke. With the real-time measures of ecological momentary assessment (EMA), positive social interaction was found to be predictive of an individuals' hand movement as measured by accelerometry. Self-efficacy was also shown to have a lagged effect on unimanual paretic hand movement after controlling for motor capability. That is, individuals were more likely to use the paretic hand at a subsequent time if they had greater self-efficacy of that hand at the present time interval (Chen et al., 2017, manuscript in preparation). For Yi-An Chen's project, we used EMA (i.e., probed 6x/day) over a 5-day period in the home environment. In spite of the fact that we were not providing feedback as would be the case with Ecological Momentary Intervention (EMI), the simple act of responding to the EMA probe 6 times/day induced a small but significant increase in paretic arm use. This alone, suggests that the development of EMIs that target the putative modifiers and essential factors of hand use such as self-efficacy and social support are important considerations for future research, particularly that conducted in the natural environment.

Further, there is substantial evidence that feedback provided in real-time and in natural settings, such as EMI, is effective in changing health behaviors (Jean, Swendsen, Sibon, Fehér, & Husky, 2013; Liao, Intille, & Dunton, 2014; Shiffman, Stone, & Hufford, 2008). Positive task-based EMIs can be used to improve self-efficacy, and consequently, reverse paretic limb non-use. However, clinicians and researchers currently lack the tools to accurately and continuously monitor patients' arm use behavior while providing high-quality, relevant EMIs in the natural setting. With recent advances in technology and specifically wearable sensors, this limitation will soon be overcome (Dobkin, 2017). In the *Future* section, we return to the opportunity to leverage advances in health information technology to engage patients, monitor outcomes and optimize rehabilitation interventions.

## 3. The future: Promising directions for the field

Given the plethora of empirical studies, particularly on the intervention side and the paucity of well-developed theories to stimulate research, we focus in this section on new and promising theoretical models that we believe have the potential to motivate future research. A repeating theme in these future directions is to tailor rehabilitation to each individual by adopting a more patient-centered approach to both clinical research and clinical trial design. Figure 1 illustrates the stages of increasing evidence for arm and hand recovery we chose to highlight here. Beginning with clinical trials of complex interventions, as we did, is in sharp contrast to the recommendation of scholars in the field of health improvement where evidence develops in stages and begins with a strong theoretical and preclinical foundation (Campbell et al., 2000). In this section, we highlight three domains of science with tremendous potential to inform future hypothesis-driven studies as well as the clinical trial enterprise. (Fig. 1).

### *3.1. Accessing and engaging detour circuits*

The potential for motor recovery after stroke has been repeatedly shown to, at least in part, depend on the preservation of neural infrastructure, particularly, the corticospinal tract (Boyd et al., 2017; Feng et al., 2015; Milot & Cramer, 2008; Stinear et al., 2007). Fortunately, owing to its inherent structural and functional redundancy, the nervous system has the tremendous capability to adapt to a variety of physical and environmental stressors, including neural structure agenesis (Milner & Jeeves, 1979), tissue resections (Gazzaniga, 1995; Sperry, 1965), and even injuries (Sörös, Teasell, Hanley, & Spence, 2017). Our premise is that accessing functional 'detour circuits' in the brain, such as those with efferent routes through the contralesional corticospinal system (contralesional hemisphere and ipsilateral tracts), allows for such adaptability after stroke. We borrow the analogy of detour circuits from Jankowska and Edgley (see Jankowska & Edgley, 2006 for an excellent review). In this section, we present the evidence—both phenomenological and interventional—for accessing and engaging functional neural networks, specifically those that access contralesional corticospinal pathways, using brain-computer interfaces (BCI) and non-traditional training paradigms described earlier, such as mirror feedback and action observation, and bilateral training.

In humans, there is strong phenomenological evidence to support the idea of bi-hemispheric input especially to proximal muscles of the upper extremities (Perez, Butler, & Taylor, 2014) via crossed and uncrossed corticospinal tracts. Outputs of the ipsilateral tracts are manifest in the behavioral phenomenon of motor irradiation or motor overflow, evidence for which dates back to the early 1960s, when Cernacek observed that voluntary contraction of muscles of one arm elicited unintended contractions of the homologous muscles of the opposite arm (Cernacek, 1961). This effect seems to be pronounced during developmental years, i.e. $<8-9$ years (Cohen, Taft, Mahadeviah, & Birch, 1967; Lazarus & Todor, 1987), and reemerges after a neurologic injury, such as stroke, varying directly with the severity of impairments (Nelles, Cramer, Schaechter, Kaplan, & Finklestein, 1998). Similarly, neurophysiologic studies using transcranial magnetic stimulation (TMS) have reported that the EMG output from the inactive (ipsilateral) hand is reproducible in non-disabled adults by mere observation of the active hand in a mirror, but not at rest (Garry, Loftus, & Summers, 2005). The presence of ipsilateral output has been confirmed numerous times in individuals post-stroke using TMS (Alagona et al., 2001; Caramia et al., 2000; Johansen-Berg et al., 2002; Schwerin, Yao, & Dewald, 2011; Werhahn, Conforto, Kadom, Hallett, & Cohen, 2003). In one report, maximal pulses over the premotor region of the unaffected hemisphere resulted in an MEP response in the ipsilateral hand (Alagona et al., 2001). This was later confirmed in multiple studies pointing to the involvement of contralesional non-M1 regions in post-stroke motor recovery (Bestmann et al., 2010; Fridman et al., 2004).

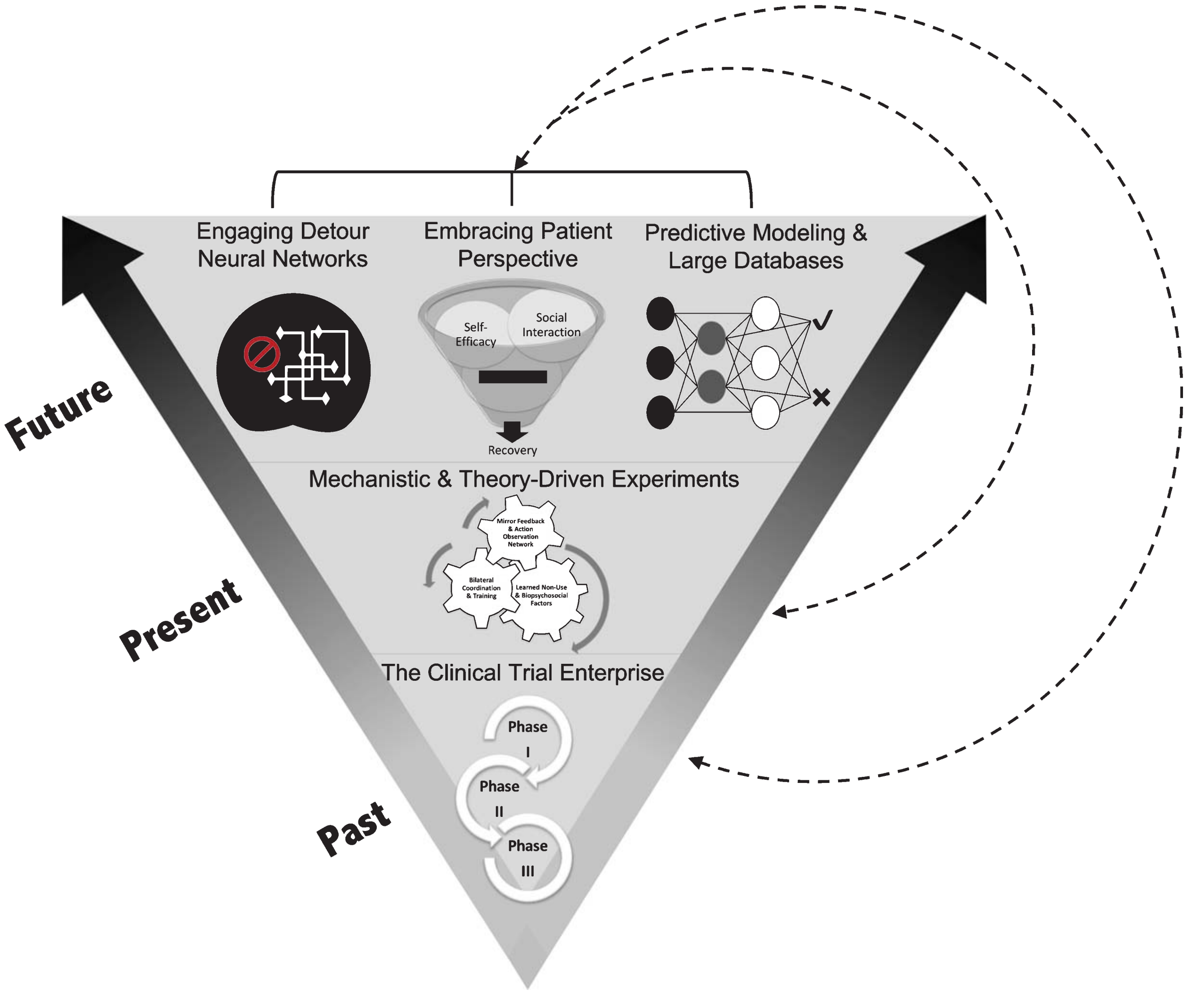


Fig. 1. Conceptual Model: Past, Present and Future of Post-Stroke Arm and Hand Recovery. The future of arm and hand recovery after stroke is illustrated using a historic perspective that began with the past dominated by a predominantly failed clinical trial enterprise. In recognition of the immature scientific foundation, there is presently a growing body of mechanistically conceived, hypothesis-driven clinical studies. The future holds considerable promise with opportunities to explore and engage detour circuits, integrate quantitative and qualitative methods, and use predictive models and large databases to advance knowledge in this field. The bi-directional arrows highlight the importance of an iterative process between theory, modelling, exploratory trials, and definitive and pragmatic randomized controlled trials that provide an informed and strategic approach to building the evidence behind clinical practice for post-stroke arm and hand recovery.

More evidence for the presence and engagement of detour circuits after stroke comes from interventional studies. (Buetefisch et al., 2015; Bundy et al., 2017; Luft et al., 2004, Lindenberg et al., 2010). Luft and colleagues found that, compared to unilateral training alone, those individuals who received bilateral training showed greater activation of the contralesional sensorimotor cortex and ipsilesional cerebellum, as well as the anterior cingulate cortex, providing initial evidence for the role of ipsilateral detour circuits using bilateral training (Luft et al., 2004). In a recent feasibility study, Bundy and colleagues demonstrated that by implementing an EEG-based brain control interface (BCI) on the contralesional hemisphere, chronic stroke survivors were able to drive an actuated finger exoskeleton to produce a 3-finger pinch, which with practice, led to further functional improvements in the paretic hand. Improvements in function positively correlated with the rate of change in BCI accuracy, suggesting that those who were able to acquire better control using the contralesional hemisphere showed greater improvements on the ARAT (Bundy et al., 2017). Lastly, as mentioned previously, by modeling effective connectivity in an event-related fMRI study it was shown that mirror feedback-based action observation induced greater activations of the action observation network of the contralesional hemisphere, including premotor and supplementary motor areas as well as temporal-parietal regions (Saleh et al., 2017; Sugg et al., 2015).

We conclude with the idea that accessing and engaging detour circuits after stroke, located in the contralesional hemisphere and accessing spared ipsilateral pathways, is indeed possible, and might optimize cooperative exchange of information between the two hemispheres. With current innovation in neuroimaging methods and neuroprosthetic technology such as BCI, we are entering a new age with opportunities to develop and implement hypothesis-driven clinical research studies to tap the recovery-supportive mechanisms afforded by viable detour circuits.

### *3.2. Embracing the patient's perspective*

Our premise is that the process of neurorehabilitation is complex and multifaceted, but importantly, for success, it requires a genuine collaboration between the patient and the clinician or caregiver to effect optimal recovery (Wulf & Lewthwaite, 2016). This collaborative relationship must be defined by the unique perspective of each patient. By doing so, we acknowledge the importance of the individual patient's values, goals, perspectives, and capacity. Rehabilitation scientists can design what arguably is a scientifically sound intervention that is evidence-based and even with preliminary data supporting its efficacy, but if the patient does not value the target outcome, does not fully engage in the therapy, or does not expect the intervention to succeed, the likelihood of success is poor.

A recent systematic review of stroke survivors' experiences of physical rehabilitation reported negative experiences that included disempowerment, boredom and frustration (Luker, Lynch, Bernhardsson, Bennett, & Bernhardt, 2015; Rosenbaum, 2013). The authors suggest that rehabilitation could be improved by increasing activity within formal therapy and in free time, fostering patients' autonomy through genuinely patient-centered care, and more effective communication and information. It is our view that future rehabilitation research including clinical trials will need to seamlessly incorporate patient values, goals, perspectives, and capacity into the trial design and outcomes. Integration of quantitative and qualitative methods into the next generation of RCTs of complex interventions for arm and hand recovery should be an imperative (Campbell et al., 2000). We return to the issue raised earlier "social and personal factors can have a high impact on stroke recovery in humans... and are not well modelled in preclinical research". One noted exception is the work of Dale Corbett using enriched rehabilitation, a combination of environmental enrichment and task-specific therapy, a proxy for "social and personal factors" in the rodent model (Corbett et al., 2015).

Recent efforts to develop consensus statements for rehabilitation and recovery research is an important first step (Bernhardt, Borschmann, et al., 2016). Just as Rosenbaum argued for overcoming the blind spots in health care reform, the rehabilitation clinical trialist must overcome the blind spots concerning the complexity of rehabilitation and recovery research (Rosenbaum, 2013). The evidence for the importance of engagement and motivation, confidence, autonomy, and social-relatedness in stroke rehabilitation and recovery is mounting from both clinical research (Danks, Pohlig, Roos, Wright, & Reisman, 2016; French, Moore, Pohlig, & Reisman, 2015; Lewthwaite, Chiviacowsky, Drews, & Wulf, 2015; (Winstein & Kay, 2015; Wulf, 2007; Wulf, Lewthwaite, Cardozo, & Chiviacowsky, 2017) and recent computational models (Han, Arbib, & Schweighofer, 2008; Hidaka, Han, Wolf, Winstein, & Schweighofer, 2012).

As we embrace individual patient differences in clinical practice, we must harness that variability in our intervention studies and not expect "one size to fit all". For example, recent research in persons post-stroke suggests that improving balance self-efficacy may augment walking capacity and translate to improved walking activity in the community (Danks et al., 2016). Similarly, while the primary outcome of the ICARE trial was negative (Winstein, Wolf, et al., 2016), the secondary outcome analysis found that the Accelerated group achieved greater participant-perceived recovery at the end of therapy time point, including in physical function, strength, health (EQ5D VAS), motor activity, and reintegration to normal living. The Accelerated group gains were sustained, while the usual therapy groups eventually achieved the same level of outcome by end of study, roughly 8 months later (Lewthwaite et al., 2018). These findings reflecting participant perspectives represent specific qualitative and personalized domains of recovery that are not routinely captured by the typical quantitative outcomes such as arm motor performance (i.e., the primary outcome) but are valued by the patient and as such contribute to their overall quality of life (Barker, Gill, & Brauer, 2007; Edwards, Hahn, Baum, & Dromerick, 2006; Reuben & Tinetti, 2012; Sabini, Dijkers, & Raghavan, 2013; Taule & Råheim, 2014).

The disabling consequences of stroke, including limitations imposed by hemiparesis, strongly reduces the quality of life (World Health Organization, 2001). Importantly, the cycle of decline (i.e., increased dependence, reduced activity, disempowerment, and isolation) can be prevented with the proper patient-centered education and rehabilitation intervention (Luker et al., 2015). In a recent issue of NEJM/catalyst, Neil Wagle speaks to the importance of pragmatic trials (measuring what matters) and postulates that patient-reported outcomes (PROs) are the "missing link in defining a good outcome" (Wagle, 2016). This is because PROs capture quality-of-life issues that are most important to our patients and why they seek our care. By focusing on PROs as a core component of clinical care, clinicians can use them to improve an individual's care as well as improve the care more generally for a given diagnostic group.

Recent lively discussions about the means for fostering patient engagement while remaining time- and cost-effective have motivated the development of new health information technology (IT) strategies for collecting and using patient-reported outcome (PRO) measures in practice (Black, 2013). Current perspectives claim that biometric measurement devices such as wireless scales are the most effective technologies in patient engagement initiatives followed closely by apps (Pedan, Saxon, 2017). Further, when asked where is the greatest potential for technology to enable patient engagement and improve health, leaders in the healthcare industry responded by emphasizing a closer clinician-patient relationship and true communication; others pointed to improved continuity of care between in-person visits; and yet others highlighted the integration of every day behaviors (e.g., medication, exercise) that can be easily tracked by the user (Pedan, Saxon, 2017; Dobkin, 2017). Given that digital health hinges on patient engagement, there has been emphasis on the need for more flexible health care interactions that digital innovations can provide, but at the same time we need to consider issues of computer literacy, access and trust. As with any new patient engagement technology, one size does not fit all; we must address the many challenges in a thoughtful and realistic manner. Our position is that new health IT that enables real-time collection of PROs can be developed and used effectively to promote shared decision-making, for patient engagement in a personalized plan of care, to provide patient-specific education about recovery potential, and to acknowledge and encourage progress, thereby promoting self-confidence and autonomy in the recovery process (Stone, 2007; Wulf & Lewthwaite, 2016). Finally, the integration of quantitative and qualitative methods in the development of randomized controlled trials of complex interventions is long overdue in the area of post-stroke arm and hand recovery (Campbell et al., 2000).

### *3.3. Toward prediction and leveraging large databases*

Finally, as we learn from our past and present and move into the future, we must strive to ground the clinical practice of neurorehabilitation in sound scientific theory (Kantak et al., 2017; Krakauer, Ghazanfar, Gomez-Marin, MacIver, & Poeppel, 2017). In this regard, we believe that predictive modeling of behavior in a hypothesis-driven manner will aid meaningful research inquires and beget new scientific theories that will drive effective neurorehabilitation into the future.

Clinicians, rehabilitation specialists, and clinical scientists would all agree that predicting recovery or response to therapy, while extremely important (Collins & Varmus, 2015; Stinear, Byblow, Ackerley, Barber, & Smith, 2017), is notoriously difficult to achieve, especially in small inhomogeneous samples that are typical in most clinical studies. With a myriad of factors playing into an individual's variability in motor performance and recovery, we must be cognizant that not every form of training will yield the same results in any sample of individuals, and that a select subset may benefit more or less depending on their unique set of characteristics. For instance, it has been found that responsiveness to bilateral therapy, particularly an improvement in function depended on hand dominance and side of stroke lesion (McCombe-Waller, Whitall, 2005), a factor previously shown to be crucial for unilateral arm use (Han et al., 2013; Rinehart, Singleton, Adair, Sadek, & Haaland, 2009; Schweighofer et al., 2015) and consistent with a recent observational analysis of bilateral motor behavior (Varghese & Winstein, 2017, manuscript in preparation). Therefore, incorporating the best of our understanding regarding patient characteristics will be key in customizing our approach to rehabilitation and maximizing therapy gains.

Recent advances in predictive modeling of moderate-to-large clinical datasets have greatly contributed to our understanding and ability to predict recovery after stroke, especially in the acute stages. An example of this is the algorithm for Predicting REcovery Potential or PREP (Stinear, Barber, Petoe, Anwar, & Byblow, 2012; Stinear, Byblow, Smith, Ackerley, & Barber, 2017). By using a multi-modal approach and combining outcomes that traverse measurement scales, i.e. clinical/behavioral, neurophysiological, and neuroanatomical, the PREP algorithm provides a comprehensive profile of subgroups that are most likely to recover at 3 months after stroke. Recently, Stinear and colleagues provided evidence that use of the PREP algorithm within the clinical workflow served to modify therapy content and increased rehabilitation efficiency after stroke without compromising clinical outcome during inpatient rehabilitation (Stinear et al., 2017). Although we have made significant strides in predicting recovery in the acute stages, similar approaches for predicting efficacy of recovery-supportive training and compensatory motor behaviors (Jones, 2017) in chronic stroke remain far less explored, and point to areas that might be ripe for future exploration.

Central to the pursuit of predictive modeling of bio-behavioral data after stroke is our ability to utilize large databases via data sharing platforms and establish standards for clinical and experimental datasets (Kwakkel et al., 2017; Saver et al., 2012). One example of recent efforts to create a large-scale database for the analysis and modeling of neuroimaging, genetic and behavioral data is the ENIGMA Consortium (Enhancing Neuro Imaging Genetics through Meta-Analysis: http://enigma.ini.usc.edu/ongoing/enigma-stroke-recovery/). The ENIGMA Stroke Recovery consortium is an international collaboration of 20 research sites working in the field of stroke rehabilitation and recovery and aims to develop accurate, specific and sensitive predictive models of stroke recovery using neuroimaging and clinical and behavioral data (Liew et al., 2017). There is great utility for such initiatives as is evidenced by our recent understanding of translational stroke models in humans, viz. that a key differentiating factor between animal models of stroke and the human clinical condition is that the latter is predominantly subcortical in nature (Corbetta et al., 2015). By characterizing structural and functional deficits specific to human stroke, database systems like ENIGMA may help define new directions for stroke rehabilitation interventions.

Clearly, the advent of big data and sophisticated computing has made it possible to apply highly advanced quantitative methods such as predictive modeling and machine learning algorithms to large datasets, and while this is without a doubt an opportunity for the future scientist in neurorehabilitation, we must tread thoughtfully and carefully. The necessity for informed theory (Krakauer et al., 2017) and its application to these datasets cannot be overstated. As effective as these can be, conducting quantitative and qualitative analyses without an informed a-priori hypothesis may mislead the field into an unproductive use of time and resources. Conversely, a clear vision and a strong scientific premise to be tested will reveal informative and interpretable results.

## 4. Summary

For arm and hand recovery, the past–dominated by a premature clinical trial enterprise– emerged out of an immature science, ignited by a revolution in neuroscience on the one hand, and an oversimplified scientific premise that dose and intensity of task-specific practice was the essential ingredient to foster arm and hand recovery (Winstein, Lewthwaite, Blanton, Wolf, & Wishart, 2014). As fortune would have it, the failure of a majority of the large-scale RCTs has propelled us into the present filled with a growing body of mechanistic and theory-driven clinical investigations, some of which have already shown promise. The future brings ample opportunities for exploring the use of detour circuits, integrating quantitative and qualitative (i.e. patient-reported outcomes) methods into the next generation of clinical trials and advancing knowledge through well-informed predictive models and large databases such as ENIGMA. Figure 1 highlights the iterative process illustrated with the bi-directional arrows built into the system that provide an informed and strategic approach to building the evidence behind clinical practice for post-stroke arm and hand recovery.

## Conflict of interest

None to report.

## References


Adkins, D. L., Schallert, T., & Goldstein, L. B. (2009). Poststroke treatment: Lost in translation. *Stroke; a Journal of Cerebral Circulation*, *40*(1), 8-9. http://doi.org/10.1161/STROKEAHA.108.534248

Alagona, G., Delvaux, V., Gérard, P., De Pasqua, V., Pennisi, G., Delwaide, P. J., ... Maertens de Noordhout, a. (2001). Ipsilateral motor responses to focal transcranial magnetic stimulation in healthy subjects and acute-stroke patients. *Stroke; a Journal of Cerebral Circulation*, *32*(6), 1304-1309. http://doi.org/10.1161/01.STR.32.6.1304

Amazeen, P. G., Schmidt, R. C., & Turvey, M. T. (1995). Frequency detuning of the phase entrainment dynamics of visually coupled rhythmic movements. *Biological Cybernetics*, *72*(6), 511-518. http://doi.org/10.1007/BF00199893

Andrews, K., & Stewart, J. (1979). Stroke recovery: He can but does he? *Rheumatol Rehabil*, *18*(1), 43-48. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/424667

AVERT. (2015). Efficacy and safety of very early mobilisation within 24h of stroke onset (AVERT): A randomised controlled trial. *The Lancet*, *6736*(15), 1-10. http://doi.org/10.1016/S0140-6736(15)60690-0

Barker, R. N., & Brauer, S. G. (2005). Upper limb recovery after stroke: The stroke survivors' perspective. *Disabil Rehabil*, *27*(20), 1213-1223.

Bernhardt, J., Borschmann, K., Boyd, L., Thomas Carmichael, S., Corbett, D., Cramer, S. C., ... Ward, N. (2016). Moving rehabilitation research forward: Developing consensus statements for rehabilitation and recovery research. *International Journal of Stroke*, *11*(4), 454-458. http://doi.org/10.1177/1747493016643851

Bernhardt, J., Churilov, L., Ellery, F., Collier, J., Chamberlain, J., Langhorne, P., ... AVERT Collaboration Group. (2016). Prespecified dose-response analysis for A Very Early Rehabilitation Trial (AVERT). *Neurology*, *86*(23), 2138-2145. http://doi.org/10.1212/WNL.0000000000002459

Bestmann, S., Swayne, O., Blankenburg, F., Ruff, C. C., Teo, J., Weiskopf, N., ... Ward, N. S. (2010). The Role of Contralesional Dorsal Premotor Cortex after Stroke as Studied with Concurrent TMS-fMRI. *Journal of Neuroscience*, *30*(36), 11926-11937. http://doi.org/10.1523/JNEUROSCI.5642-09.2010

Black, N. (2013). Patient reported outcome measures could help transform healthcare. *BMJ*, *346*(jan28 1), f167-f167. http://doi.org/10.1136/bmj.f167

Boyd, L. A., Hayward, K. S., Ward, N. S., Stinear, C. M., Rosso, C., Fisher, R. J., ... Cramer, S. C. (2017). Biomarkers of stroke recovery: Consensus-based core recommendations from the Stroke Recovery and Rehabilitation Roundtable. http://dx.doi.org/10.1177/1747493017714176.

Bundy, D. T., Souders, L., Baranyai, K., Leonard, L., Schalk, G., Coker, R., ... Leuthardt, E. C. (2017). Contralesional Brain-Computer Interface Control of a Powered Exoskeleton for Motor Recovery in Chronic Stroke Survivors. http://doi.org/STROKEAHA.116.016304 [pii]

Campbell, M., Fitzpatrick, R., Haines, A., Kinmonth, A. L., Sandercock, P., Spiegelhalter, D., & Tyrer, P. (2000). Framework for design and evaluation of complex interventions to improve health. *BMJ*, *321*(7262), 694-696. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=10987780

Caramia, M. D., Palmieri, M. G., Giacomini, P., Iani, C., Dally, L., & Silvestrini, M. (2000). Ipsilateral activation of the unaffected motor cortex in patients with hemiparetic stroke. *Clinical Neurophysiology*, *111*(11), 1990-1996. http://doi.org/10.1016/S1388-2457(00)00430-2

Cernacek, J. (1961). Contralateral Motor Irradiation-Cerebral Dominance. *Archives of Neurology*, *4*(2), 165. http://doi.org/10.1001/archneur.1961.00450080047005

Chen, S. (2011). The influence of self-efficacy on recovery of spontaneous arm use in hemiparetic stroke, Dissertation, University of Southern California-Di.

Chen, S., Lewthwaite, R., Schweighofer, N., & Winstein, C. J. (2013). Discriminant validity of a new measure of self-efficacy for reaching movements after stroke-induced hemiparesis. *J Hand Ther*, *26*(2), 116-122.

Chen, S., Wolf, S. L., Zhang, Q., Thompson, P. A., & Winstein, C. J. (2012). Minimal detectable change of the actual amount of use test and the motor activity log: The EXCITE Trial. *Neurorehabil Neural Repair*, *26*(5), 507-514.

Chen, Y.-A., Lewthwaite, R., Monterosso, J. R., Fisher, B. E., Schweighofer, N., & Winstein, C. J. (n.d.). Mobile-based ecological momentary assessment of paretic hand use and related person-centered measures: Feasibility and validity, (Manuscript in preparation).

Cohen, H. J., Taft, L. T., Mahadeviah, M. S., & Birch, H. G. (1967). Developmental changes in overflow in normal and aberrantly functioning children. *The Journal of Pediatrics*, *71*(1), 39-47. http://doi.org/10.1016/S0022-3476(67)80228-2

Collins, F. S., & Varmus, H. (2015). A New Initiative on Precision Medicine. *New England Journal of Medicine*, *372*(9), 793-795. http://doi.org/10.1056/NEJMp1500523

Corbett, D., Jeffers, M., Nguemeni, C., Gomez-Smith, M., & Livingston-Thomas, J. (2015). Lost in translation. In *Progress in brain research* (Vol. 218, pp. 413-434). http://doi.org/10.1016/bs.pbr.2014.12.002

Corbetta, M., Ramsey, L., Callejas, A., Baldassarre, A., Hacker, C. D., Siegel, J. S., ... Shulman, G. L. (2015). Common behavioral clusters and subcortical anatomy in stroke. *Neuron*, *85*(5), 927-941. http://doi.org/10.1016/j.neuron.2015.02.027

Cramer, S. C., Wolf, S. L., Adams, H. P., Chen, D., Dromerick, A. W., Dunning, K., ... Broderick, J. P. (2017). Stroke Recovery and Rehabilitation Research. *Stroke*, *48*(3), 813-819. http://doi.org/10.1161/STROKEAHA.116.015501

Danks, K. A., Pohlig, R. T., Roos, M., Wright, T. R., & Reisman, D. S. (2016). Relationship Between Walking Capacity, Biopsychosocial Factors, Self-efficacy, and Walking Activity in Persons Poststroke. *Journal of Neurologic Physical Therapy*, *40*(4), 232-238. http://doi.org/10.1097/NPT.0000000000000143

Dobkin, B. H. (2017). A Rehabilitation-Internet-of-Things in the Home to Augment Motor Skills and Exercise Training. *Neurorehabilitation and Neural Repair*, *31*(3), 217-227. http://doi.org/10.1177/1545968316680490

Dromerick, A. W., Lang, C. E., Birkenmeier, R., Wagner, J. M., Miller, J. P., Videen, T. O., ... Edwards, D. F. (2009). Very Early Constraint-Induced Movement during Stroke Rehabilitation (VECTORS): A single-center RCT. *Neurology*, *73*, 195-201.

Duncan, P. W., Sullivan, K. J., Behrman, A. L., Azen, S. P., Wu, S. S., Nadeau, S. E., ... Hayden, S. K. (2011). Body-weight-supported treadmill rehabilitation after stroke. *The New England Journal of Medicine*, *364*(21), 2026-2036. http://doi.org/10.1056/NEJMoa1010790

Edwards, D. F., Hahn, M., Baum, C., & Dromerick, A. W. (2006). The impact of mild stroke on meaningful activity and life satisfaction. *Journal of Stroke and Cerebrovascular Diseases*, *15*, 151-157. http://doi.org/10.1016/j.jstrokecerebrovasdis.2006.04.001

Edwardson, M. A., Wang, X., Liu, B., Ding, L., Lane, C. J., Park, C., ... Dromerick, A. W. (2017). Stroke Lesions in a Large Upper Limb Rehabilitation Trial Cohort Rarely Match Lesions in Common Preclinical Models. *Neurorehabilitation and Neural Repair*, 154596831668879. http://doi.org/10.1177/1545968316688799

Feng, W., Wang, J., Chhatbar, P. Y., Doughty, C., Landsittel, D., Lioutas, V.-A., ... Schlaug, G. (2015). Corticospinal tract lesion load: An imaging biomarker for stroke motor outcomes. *Annals of Neurology*, *78*(6), 860-870. http://doi.org/10.1002/ana.24510

French, M. A., Moore, M. F., Pohlig, R., & Reisman, D. (2015). Self-efficacy Mediates the Relationship between Balance/Walking Performance, Activity, and Participation after Stroke. *Topics in Stroke Rehabilitation*, *9357*(July), 1-7. http://doi.org/10.1080/10749357.2015.1110306

Fridman, E. A., Hanakawa, T., Chung, M., Hummel, F., Leiguarda, R. C., & Cohen, L. G. (2004). Reorganization of the human ipsilesional premotor cortex after stroke. *Brain*, *127*(4), 747-758. http://doi.org/10.1093/brain/awh082

Garrison, K. A., Aziz-Zadeh, L., Wong, S. W., Liew, S.-L., & Winstein, C. J. (2013). Modulating the motor system by action observation after stroke. *Stroke*, *44*(8), 2247-2253.

Garry, M. I., Loftus, A., & Summers, J. J. (2005). Mirror, mirror on the wall: Viewing a mirror reflection of unilateral hand movements facilitates ipsilateral M1 excitability. *Experimental Brain Research*, *163*(1), 118-122. http://doi.org/10.1007/s00221-005-2226-9

Gauthier, L. V, Taub, E., Perkins, C., Ortmann, M., Mark, V. W., & Uswatte, G. (2008). Remodeling the Brain: Plastic Structural Brain Changes Produced by Different Motor Therapies After Stroke * Supplemental Material. *Stroke*, *39*(5), 1520-1525. http://doi.org/10.1161/strokeaha.107.502229

Gazzaniga, M. S. (1995, February). Principles of human brain organization derived from split-brain studies. *Neuron*. Cell Press. http://doi.org/10.1016/0896-6273(95)90280-5

Han, C. E., Kim, S., Chen, S., Lai, Y.-H., Lee, J.-Y., Osu, R., ... Schweighofer, N. (2013). Quantifying arm nonuse in individuals poststroke. *Neurorehabilitation and Neural Repair*, *27*(5), 439-447. http://doi.org/10.1177/1545968312471904

Hidaka, Y., Han, C. E., Wolf, S. L., Winstein, C. J., & Schweighofer, N. (2012). Use it and improve it or lose it: Interactions between arm function and use in humans post-stroke. *PLoS Comput Biol*, *8*(2), e1002343.

Jankowska, E., & Edgley, S. A. (2006). How Can Corticospinal Tract Neurons Contribute to Ipsilateral Movements? A Question With Implications for Recovery of Motor Functions. *The Neuroscientist*, *12*(1), 67-79. http://doi.org/10.1177/1073858405283392

Johansen-Berg, H., Rushworth, M. F. S., Bogdanovic, M. D., Kischka, U., Wimalaratna, S., & Matthews, P. M. (2002). The role of ipsilateral premotor cortex in hand movement after stroke. *Proceedings of the National Academy of Sciences of the United States of America*, *99*(22), 14518-14523. http://doi.org/10.1073/pnas.222536799

Jones, T. A. (2017). Motor compensation and its effects on neural reorganization after stroke. *Nature Publishing Group*, 1-14. http://doi.org/10.1038/nrn.2017.26

Kantak, S., Jax, S., & Wittenberg, G. (2017). Bimanual coordination: A missing piece of arm rehabilitation after stroke. *Restorative Neurology and Neuroscience*, *35*(4), 347-364. http://doi.org/10.3233/RNN-170737

Kleim, J. A, & Jones, T. A. (2008). Principles of experience-dependent neural plasticity: Implications for rehabilitation after brain damage. *Journal of Speech, Language, and Hearing Research: JSLHR*, *51*(1), S225-S239. http://doi.org/10.1044/1092-4388(2008/018)

Krakauer, J. W., Ghazanfar, A. A., Gomez-Marin, A., MacIver, M. A., & Poeppel, D. (2017). Neuroscience Needs Behavior: Correcting a Reductionist Bias. *Neuron*, *93*(3), 480-490. http://doi.org/10.1016/j.neuron.2016.12.041

Kwakkel, G., Lannin, N. A., Borschmann, K., English, C., Ali, M., Churilov, L., ... Bernhardt, J. (2017). Standardized Measurement of Sensorimotor Recovery in Stroke Trials: Consensus-Based Core Recommendations from the Stroke Recovery and Rehabilitation Roundtable. *Neurorehabilitation and Neural Repair*, *31*(9), 784-792. http://doi.org/10.1177/1545968317732662

Kwakkel, G., Winters, C., van Wegen, E. E. H., Nijland, R. H. M., van Kuijk, A. A. A., Visser-Meily, A., ... EXPLICIT-Stroke Consortium. (2016). Effects of Unilateral Upper Limb Training in Two Distinct Prognostic Groups Early After Stroke: The EXPLICIT-Stroke Randomized Clinical Trial. *Neurorehabilitation and Neural Repair*, *30*(9), 804-816. http://doi.org/10.1177/1545968315624784

Lang, C. E., Strube, M. J., Bland, M. D., Waddell, K. J., Cherry-Allen, K. M., Nudo, R. J., ... Birkenmeier, R. L. (2016). Dose response of task-specific upper limb training in people at least 6 months poststroke: A phase II, single-blind, randomized, controlled trial. *Annals of Neurology*, *80*(3), 342-354. http://doi.org/10.1002/ana.24734

Lazarus, J.-A. C., & Todor, J. I. (1987). Age Differences In The Magnitude Of Associated Movement. *Developmental Medicine & Child Neurology*, *29*(6), 726-733. http://doi.org/10.1111/j.1469-8749.1987.tb08817.x

Levine, P., & Page, S. J. (2004). Modified constraint-induced therapy: A promising restorative outpatient therapy. *Top Stroke Rehabil*, *11*(4), 1-10. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15592985

Levy, R. M., Harvey, R. L., Kissela, B. M., Winstein, C. J., Lutsep, H. L., Parrish, T. B., ... Venkatesan, L. (2016). Epidural Electrical Stimulation for Stroke Rehabilitation: Results of the Prospective, Multicenter, Randomized, Single-Blinded Everest Trial. *Neurorehabilitation and Neural Repair*, *30*(2), 107-119. http://doi.org/10.1177/1545968315575613

Lewthwaite, R., Winstein, C.J., Lane, C.J., Blanton, S., Wagenheim, B.R., Nelsen, M.A., Dromerick, A.W., Wolf, S.L. (2018). Accelerating Stroke Recovery: Body Structures and Functions, Activities, Participation, and Quality of Life Outcomes From a Large Rehabilitation Trial. Neurorehabilitation and Neural Repair, 32(2), 150-165. http://doi.org/10.1177/1545968318760726

Liao, Y., Intille, S. S., & Dunton, G. F. (2014). Using ecological momentary assessment to understand where and with whom adults' physical and sedentary activity occur. *Int J Behav Med*, *22*(1), 51-61.

Liew, S.-L., Jahanshad, N., Aziz-Zadeh, L., Birbaumer, N., Borich, M., Boyd, L., . . . Thompson, P. M. (2017). Abstract 14: Effects of Lesion Laterality on Post-Stroke Motor Performance: An ENIGMA Stroke Recovery Analysis. *Stroke*, *48*(Suppl 1).

Lindley, R. I., Anderson, C. S., Billot, L., Forster, A., Hackett, M. L., Harvey, L. A., . . . Sebastian, I. (2017). Family-led rehabilitation after stroke in India (ATTEND): A randomised controlled trial. *The Lancet*, *390*(10094), 588-599. http://doi.org/10.1016/S0140-6736(17)31447-2

Lo, A. C., Guarino, P. D., Richards, L. G., Haselkorn, J. K., Wittenberg, G. F., Federman, D. G., . . . Peduzzi, P. (2010). Robot-assisted therapy for long-term upper-limb impairment after stroke. *N Engl J Med*, *362*(19), 1772-1783. http://doi.org/10.1056/NEJMoa0911341

Luft, A. R., & Hanley, D. F. (2006). Stroke recovery–moving in an EXCITE-ing direction. *JAMA*, *296*(17), 2141-2143. http://doi.org/10.1001/jama.296.17.2141

Luft, A. R., McCombe-Waller, S., Whitall, J., Forrester, L. W., Macko, R., Sorkin, J. D., . . . Hanley, D. F. (2004). Repetitive Bilateral Arm Training and Motor Cortex Activation in Chronic Stroke. *JAMA*, *292*(15), 1853. http://doi.org/10.1001/jama.292.15.1853

Luker, J., Lynch, E., Bernhardsson, S., Bennett, L., & Bernhardt, J. (2015). Stroke Survivors' Experiences of Physical Rehabilitation: A Systematic Review of Qualitative Studies. *Archives of Physical Medicine and Rehabilitation*. http://doi.org/10.1016/j.apmr.2015.03.017

Mayo, N. E., Wood-Dauphinee, S., Cote, R., Duncan, L., & Carlton, J. (2002). Activity, participation, and quality of life 6 months poststroke. *Arch Phys Med Rehabil*, *83*(8), 1035-1042. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12161823

McCombe Waller, S., & Whitall, J. (2008). Bilateral arm training: Why and who benefits? *NeuroRehabilitation*, *23*(1), 29-41.

McCombe Waller, S., Whitall, J., Jenkins, T., Magder, L. S., Hanley, D. F., Goldberg, A., & Luft, A. R. (2014). Sequencing bilateral and unilateral task-oriented training versus task oriented training alone to improve arm function in individuals with chronic stroke. *BMC Neurology*, *14*, 236. http://doi.org/10.1186/s12883-014-0236-6

Milner, A. D., & Jeeves, M. A. (1979). A Review of Behavioural Studies of Agenesis of the Corpus Callosum. In *Structure and Function of Cerebral Commissures* (pp. 428-448). London: Macmillan Education UK. http://doi.org/10.1007/978-1-349-03645-5_36

Milot, M.-H., & Cramer, S. C. (2008). Biomarkers of recovery after stroke. *Current Opinion in Neurology*, *21*(6), 654-659. http://doi.org/10.1097/WCO.0b013e3283186f96

Morris, J. H., van Wijck, F., Joice, S., Ogston, S. A., Cole, I., & MacWalter, R. S. (2008). A Comparison of Bilateral and Unilateral Upper-Limb Task Training in Early Poststroke Rehabilitation: A Randomized Controlled Trial. *Archives of Physical Medicine and Rehabilitation*, *89*(7), 1237-1245. http://doi.org/10.1016/j.apmr.2007.11.039

Neil W. Wagle, MD, M. (2016). Implementing Patient-Reported Outcome Measures (PROMs). *NEJM Catalyst*, 1-2. Retrieved from http://catalyst.nejm.org/implementing-proms-patient-reported-outcome-measures/

Nelles, G., Cramer, S. C., Schaechter, J. D., Kaplan, J. D., & Finklestein, S. P. (1998). Quantitative Assessment of Mirror Movements After Stroke. *Stroke*, *29*(6), 1182-1187. http://doi.org/10.1161/01.STR.29.6.1182

Nudo, R. J., Milliken, G. W., Jenkins, W. M., & Merzenich, M. M. (1996). Use-dependent alterations of movement representations in primary motor cortex of adult squirrel monkeys. *J Neurosci*, *16*(2), 785-807.

Page, S. J., & Levine, P. (2007). Modified Constraint-Induced Therapy in Patients With Chronic Stroke Exhibiting Minimal Movement Ability in the Affected Arm. *PHYS THER*. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=17472950

Page, S. J., Levine, P., & Leonard, A. C. (2005). Modified constraint-induced therapy in acute stroke: A randomized controlled pilot study. *Neurorehabil Neural Repair*, *19*(1), 27-32. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15673841

Page, S. J., Sisto, S., Johnston, M. V., & Levine, P. (2002). Modified constraint-induced therapy after subacute stroke: A preliminary study. *Neurorehabil Neural Repair*, *16*(3), 290-295. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=12234091

Pedan, C.J., & Saxon, L.A. (2017). Patient engagement: Digital technology to engage patients: Ensuring access for all. NEJM Catalyst, 1–2. Retrieved from https://catalyst.nejm.org/digital-health-technology-access/

Perez, M. A., Butler, J. E., & Taylor, J. L. (2014). Modulation of transcallosal inhibition by bilateral activation of agonist and antagonist proximal arm muscles. *Journal of Neurophysiology*, *111*(2), 405-414. http://doi.org/10.1152/jn.00322.2013

Rinehart, J. K., Singleton, R. D., Adair, J. C., Sadek, J. R., & Haaland, K. Y. (2009). Arm use after left or right hemiparesis is influenced by hand preference. *Stroke*, *40*(2), 545-550. http://doi.org/10.1161/STROKEAHA.108.528497

Rose, D. K., & Winstein, C. J. (2004). Bimanual Training After Stroke: Are Two Hands Better Than One? *Topics in Stroke Rehabilitation*, *11*(4), 20-30. http://doi.org/10.1310/NCB1-JWAA-09QE-7TXB

Rose, D. K., & Winstein, C. J. (2013). Temporal Coupling Is More Robust Than Spatial Coupling: An Investigation of Interlimb Coordination After Stroke. *Journal of Motor Behavior*, *45*(4), 313-324. http://doi.org/10.1080/00222895.2013.798250

Rosenbaum, L. (2013). The whole ball game–overcoming the blind spots in health care reform. *The New England Journal of Medicine*, *368*(10), 959-962. http://doi.org/10.1056/NEJMms1301576

Sabini, R. C., Dijkers, M. P., & Raghavan, P. (2013). Stroke survivors talk while doing: Development of a therapeutic framework for continued rehabilitation of hand function post stroke. *J Hand Ther*, *26*(2), 124-130; quiz 131. http://doi.org/10.1016/j.jht.2012.08.002

Saleh, S., Yarossi, M., Manuweera, T., Adamovich, S., & Tunik, E. (2017). Network interactions underlying mirror feedback in stroke: A dynamic causal modeling study. *NeuroImage: Clinical*, *13*, 46-54. http://doi.org/10.1016/j.nicl.2016.11.012

Saver, J. L., Warach, S., Janis, S., Odenkirchen, J., Becker, K., Benavente, O., . . . National Institute of Neurological Disorders and Stroke (NINDS) Stroke Common Data Element Working Group, for the N. I. of N. D. and S. (NINDS) S. C. D. E. W. (2012). Standardizing the structure of stroke clinical and epidemiologic research data: The National Institute of Neurological Disorders and Stroke (NINDS) Stroke Common Data Element (CDE) project. *Stroke*, *43*(4), 967-973. http://doi.org/10.1161/STROKEAHA.111.634352

Schmidt, R. C., Shaw, B. K., & Turvey, M. T. (1993). Coupling dynamics in interlimb coordination. *Journal of Experimental Psychology: Human Perception and Performance*, *19*(2), 397-415. http://doi.org/10.1037/0096-1523.19.2.397

Schweighofer, N., Xiao, Y., Kim, S., Yoshioka, T., Gordon, J., & Osu, R. (2015). Effort, success, and nonuse determine arm choice. *Journal of Neurophysiology*, *114*(1), 551-559. http://doi.org/10.1152/jn.00593.2014

Schwerin, S. C., Yao, J., & Dewald, J. P. A. (2011). Using paired pulse TMS to facilitate contralateral and ipsilateral MEPs in upper extremity muscles of chronic hemiparetic stroke patients. *Journal of Neuroscience Methods*, *195*(2), 151-160. http://doi.org/10.1016/j.jneumeth.2010.11.021

Seegelke, C., Hughes, C. M. L., Wunsch, K., van der Wel, R., & Weigelt, M. (2015). Frames of reference in action plan recall: Influence of hand and handedness. *Experimental Brain Research*, *233*(10), 2801-2812. http://doi.org/10.1007/s00221-015-4350-5

Shiffman, S., Stone, A. A., & Hufford, M. R. (2008). Ecological momentary assessment. *Annu Rev Clin Psychol*, *4*, 1-32. http://doi.org/10.1146/annurev.clinpsy.3.022806.091415

Sörös, P., Teasell, R., Hanley, D. F., & Spence, J. D. (2017). Motor recovery beginning 23 years after ischemic stroke. *Journal of Neurophysiology*, *118*(2), 778-781. http://doi.org/10.1152/jn.00868.2016

Sperry, R. W. (1965). Brain Bisection and Mechanisms of Consciousness. In *Brain and Conscious Experience* (pp. 298-313). Berlin, Heidelberg: Springer Berlin Heidelberg. http://doi.org/10.1007/978-3-642-49168-9_13

Sterr, A., Freivogel, S., & Schmalohr, D. (2002). Neurobehavioral aspects of recovery: Assessment of the learned nonuse phenomenon in hemiparetic adolescents. *Arch Phys Med Rehabil*, *83*(12), 1726-1731.

Stewart, J. C., & Cramer, S. C. (2013). Patient-reported measures provide unique insights into motor function after stroke. *Stroke*, *44*(4), 1111-1116. http://doi.org/10.1161/STROKEAHA.111.674671

Stinear, C. M., Barber, P. A., Coxon, J. P., Fleming, M. K., & Byblow, W. D. (n.d.). Priming the motor system enhances the effects of upper limb therapy in chronic stroke. http://doi.org/10.1093/brain/awn051

Stinear, C. M., Barber, P. A., Petoe, M., Anwar, S., & Byblow, W. D. (2012). The PREP algorithm predicts potential for upper limb recovery after stroke. *Brain*, *135*(Pt 8), 2527-2535. http://doi.org/10.1093/brain/aws146

Stinear, C. M., Barber, P. A., Smale, P. R., Coxon, J. P., Fleming, M. K., & Byblow, W. D. (2007). Functional potential in chronic stroke patients depends on corticospinal tract integrity. *Brain*, *130*(1), 170-180. http://doi.org/10.1093/brain/awl333

Stinear, C. M., Byblow, W. D., Ackerley, S. J., Barber, P. A., & Smith, M.-C. (2017). Predicting Recovery Potential for Individual Stroke Patients Increases Rehabilitation Efficiency. *Stroke*, *48*(4), 1011-1019. http://doi.org/10.1161/STROKEAHA.116.015790

Stone, A. (2007). *The Science of Real-Time Data Capture*. Oxford University Press.

Stoykov, M. E., & Stinear, J. W. (2010). Active-passive bilateral therapy as a priming mechanism for individuals in the subacute phase of post-stroke recovery: A feasibility study. *American Journal of Physical Medicine & Rehabilitation*, *89*(11), 873-878. http://doi.org/10.1097/PHM.0b013e3181f1c31c

Sugg, K., Muller, S., Winstein, C., Hathorn, D., & Dempsey, A. (2015). Does Action Observation with Immediate Physical Practive Improve Hemiparetic Upper-Limb Function in Chronic Stroke? *Neurorehabilitation & Neural Repair*, 1-11. http://doi.org/10.1177/1545968314565512

Taub, E., Lum, P. S., Hardin, P., Mark, V. W., & Uswatte, G. (2005). AutoCITE: Automated delivery of CI therapy with reduced effort by therapists. *Stroke*, *36*(6), 1301-1304. Retrieved from http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&dopt=Citation&list_uids=15879335

Taub, E., Miller, N. E., Novack, T. A., Cook, E. W., Fleming, W. C., Nepomuceno, C. S., ... Crago, J. E. (1993). Technique to improve chronic motor deficit after stroke. *Arch Phys Med Rehabil*, *74*(4), 347-354.

Taub, E., Uswatte, G., Mark, V. W., & Morris, D. M. (2006). The learned nonuse phenonmenon: Implications for rehabilitation. *Eura Medicophys*, *42*(3), 241-255.

Taule, T., & Råheim, M. (2014). Life changed existentially: A qualitative study of experiences at 6-8 months after mild stroke. *Disability and Rehabilitation*, 1-13. http://doi.org/10.3109/09638288.2014.904448

Varghese, R., & Winstein, C. J. (manuscript in preparation). *Factors Associated with Bilateral Arm Use in Chronic Stroke*.

Waller, S. M., Whitall, J., Mccombe, S., & Uini-, W. (2005). Hand dominance and side of stroke affect rehabilitation in chronic stroke. *Clinical Rehabilitation*, *19*(September 2005), 544-551. http://doi.org/10.1191/0269215505cr829oa

Werhahn, K. J., Conforto, A. B., Kadom, N., Hallett, M., & Cohen, L. G. (2003). Contribution of the ipsilateral motor cortex to recovery after chronic stroke. *Annals of Neurology*, *54*(4), 464-472. http://doi.org/10.1002/ana.10686

Whitall, J., Waller, S. M., Silver, K. H. C., & Macko, R. F. (2000). Repetitive Bilateral Arm Training With Rhythmic Auditory Cueing Improves Motor Function in Chronic Hemiparetic Stroke. *Stroke*, *31*, 2390-2395. http://doi.org/10.1161/01.STR.31.10.2390

Whitall, J., Waller, S. M., Sorkin, J. D., Forrester, L. W., Macko, R. F., Hanley, D. F., ... Luft, A. (2011). Bilateral and unilateral arm training improve motor function through differing neuroplastic mechanisms: A single-blinded randomized controlled trial. *Neurorehabilitation and Neural Repair*, *25*(2), 118-129. http://doi.org/10.1177/1545968310380685

Winstein, C. J., & Kay, D. B. (2015). Translating the science into practice: Shaping rehabilitation practice to enhance recovery after brain damage. In N. Dancause & S. Rossignol (Eds.), *Sensorimotor rehabilitation: At the crossroads of basic and clinical sciences* (Vol. 218, pp. 331-360). Amsterdam, The Netherlands: Elsevier B.V. http://doi.org/10.1016/bs.pbr.2015.01.004

Winstein, C. J., Lewthwaite, R., Blanton, S. R., Wolf, L. B., & Wishart, L. (2014). Infusing motor learning research into neurorehabilitation practice: A historical perspective with case exemplar from the Accelerated Skill Acquisition Program. *Journal of Neurologic Physical Therapy*, *38*(3), 190-200. http://doi.org/doi:10.1097/NPT.0000000000000046.

Winstein, C. J., Stein, J., Arena, R., Bates, B., Cherney, L. R., Cramer, S. C., ... Zorowitz, R. D. (2016). Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart

Association/American Stroke Association. *Stroke; a Journal of Cerebral Circulation*. http://doi.org/10.1161/STR.0000000000000098

Winstein, C. J., Wolf, S. L., Dromerick, A. W., Lane, C. J., Nelsen, M. A., Lewthwaite, R., ... Azen, S. P. (2016). Effect of a Task-Oriented Rehabilitation Program on Upper Extremity Recovery Following Motor Stroke: The ICARE Randomized Clinical Trial. *JAMA*, *315*(6), 571-581. http://doi.org/10.1001/jama.2016.0276

Wolf, S. L., Winstein, C. J., Miller, J. P., Taub, E., Uswatte, G., Morris, D., ... Nichols-Larsen, D. (2006). Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: The EXCITE randomized clinical trial. *JAMA: The Journal of the American Medical Association*, *296*, 2095-2104. http://doi.org/10.1001/jama.296.17.2095

World Health Organization. (2001). *International Classification of Functioning, Disability, and Health*. *World Health Organization*.

Wu, C., Yang, C., Chen, M., Lin, K., & Wu, L. (2013). Unilateral versus bilateral robot-assisted rehabilitation on arm-trunk control and functions post stroke: A randomized controlled trial. *Journal of NeuroEngineering and Rehabilitation*, *10*(1), 35. http://doi.org/10.1186/1743-0003-10-35

Wulf, G. (2007). Self-controlled practice enhances motor learning: Implications for physiotherapy. *Physiotherapy*, *93*(2), 96-101. http://doi.org/10.1016/j.physio.2006.08.005

Wulf, G., & Lewthwaite, R. (2016). Optimizing performance through intrinsic motivation and attention for learning: The OPTIMAL theory of motor learning. *Psychonomic Bulletin & Review*, *23*(5), 1382-1414. http://doi.org/10.3758/s13423-015-0999-9

Wulf, G., Lewthwaite, R., Cardozo, P., & Chiviacowsky, S. (2017). Triple play: Additive contributions of enhanced expectancies, autonomy support, and external attentional focus to motor learning. *The Quarterly Journal of Experimental Psychology*, 1-9. http://doi.org/10.1080/17470218.2016.1276204