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Behavioral and neurophysiological mechanisms underlying motor skill learning in patients with post-stroke hemiparesis

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HIGHLIGHTS

- Learning of motor skills with the paretic arm is relatively intact after unilateral stroke.
- Learning improves the control of the paretic arm for the practiced skill.
- Learning augments ipsilesional corticospinal excitability and reduces transcallosal inhibition from contra- to ipsilesional motor cortex.

ABSTRACT

Objective: Given the presence of execution deficits after stroke, it is difficult to determine if patients with stroke have deficits in motor skill learning with the paretic arm. Here, we controlled for execution deficits while testing practice effects of the paretic arm on motor skill learning, long-term retention, and corticospinal excitability.
Methods: Ten patients with unilateral stroke and ten age-matched controls practiced a kinematic arm skill for two days and returned for retention testing one-day and one-month post-practice. Motor skill learning was quantified as a change in speed–accuracy tradeoff from baseline to retention tests. Transcranial magnetic stimulation (TMS) was used to generate an input–output curve of the ipsilesional motor cortex (M1), and measure transcallosal inhibition from contralesional to ipsilesional M1.
Results: While the control group had greater overall accuracy than the stroke group, both groups showed comparable immediate and long-term improvements with practice. Skill improvements were accompanied by greater excitability of the ipsilesional corticospinal system and reduced transcallosal inhibition from contralesional to ipsilesional M1.
Conclusions: When execution deficits are accounted for, patients with stroke demonstrate relatively intact motor skill learning with the paretic arm. Paretic arm learning is accompanied by modulations in corticospinal and transcallosal mechanisms.
Significance: Functional recovery after stroke relies on ability for skill learning and the underlying mechanisms.

1. Introduction

Skilled actions of daily life such as reaching across a busy table to pick a coffee mug are often performed with accurate, yet fast and efficient arm movements. Such complex skilled actions require optimization of speed *and* accuracy; and rely on efficient planning and execution (Begliomini et al., 2014; Fang et al., 2015; Orban de Xivry et al., 2017; Stewart et al., 2013). Following a neurological insult such as stroke, skilled arm movements are greatly impaired in the paretic (weaker) arm such that task performance is slow, inaccurate and fragmented (Cirstea et al., 2003; Levin, 1996; Liu et al., 2013; Shaikh et al., 2014; Silva et al., 2014). Arm rehabilitation is predicated on the premise that practice leads to improvements in speed, accuracy and control of the weaker arm (Huang and Krakauer, 2009; Krakauer, 2006). However, the behavioral and neurophysiologic mechanisms underlying complex skill learning of the paretic arm remain largely unknown in patients with

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unilateral stroke. Determining the motor control changes may provide insights into recovery or compensatory mechanisms underlying practice-induced performance improvements. Identifying neurophysiologic changes associated with complex skill learning in patients with stroke will likely inform neuromodulation strategies aimed to augment motor recovery.

Motor learning studies in stroke survivors to date have investigated motor adaptation (Quattrocchi et al., 2017; Schaefer et al., 2009; Takahashi and Reinkensmeyer, 2003), simple reaching movements (Park et al., 2016), sequence learning (Boyd et al., 2007; Boyd and Winstein, 2001; Carey et al., 2007; Meehan et al., 2011), often with the nonparetic arm (Boyd et al., 2007; Boyd and Winstein, 2003, 2001; Schaefer et al., 2009; Winstein et al., 1999). Motor adaptation involves a short-term modification of a well-learned motor behavior to reduce perturbation-induced error (Krakauer and Mazzoni, 2011). In contrast, sequence learning involves acquisition of a new series of discrete movements that are already present in the learner's repertoire (Karni et al., 1998). While adaptation and sequence learning studies have provided important insights in cognitive-motor capabilities in patients with stroke, these tasks do not best reflect the processes engaged in learning of complex real world motor skills. Relearning real-world motor skills after stroke involves reacquisition of movements/movement combinations that are currently not a part of patients' movement repertoire (Dipietro et al., 2012; Krakauer and Mazzoni, 2011; Shmuelof and Krakauer, 2014). Improvements in adaptation and sequence learning are often characterized by changes in accuracy (reduction in error) OR change in movement/reaction time. Given the well-known inverse relationship between speed and accuracy (speed–accuracy tradeoff), quantifying motor skill learning using either speed *or* accuracy, as has been done in many studies, can be problematic. That is, an improvement in one measure (speed or accuracy) with little change or deterioration of the other may indicate skill learning *or* simply a performance change to a different part of an unchanged speed–accuracy tradeoff. Recently, we and others have quantified motor skill learning by examining a relatively long-term shift in the speed–accuracy tradeoff (SAT) with motor practice (McGrath and Kantak, 2016; Reis et al., 2009; Shmuelof et al., 2012) in able-bodied individuals.

Another important index of skill learning is that it leads to improved motor control of the paretic arm following practice. That means, the learned skill is smoother and has less fragmented movements after practice (Shmuelof et al., 2012). For point-to-point reaching movements, improved control has been quantified as a reduction in the number of submovements, which are thought to be basic subunits of movement. Reduction in the number of submovements indicates improved planning with lesser requirement for feedback-based corrections. It is not known if practice of a complex skill with the paretic arm leads to lesser submovements and smoother skill performance, particularly if the skills are complex. In particular, this question has clinical significance to delineate if practice-induced improvements in the paretic arm are associated with improved control or are a reflection of compensatory processes.

Following stroke, patients have varying degrees of execution deficits in the weaker arm (Roh et al., 2013; Wagner et al., 2006). These execution deficits (e.g. weakness, fractionated movements) pose an additional challenge in studying motor skill learning. On one hand, motor execution deficits as well as stroke-induced disruption of learning-related neural networks may impair learning of motor skills. Alternately, these execution deficits may simply mask otherwise intact motor learning in these patients. For example, many previous studies have controls and patients move to a specific target distance common to both groups, and demonstrate different learning rates between controls and stroke (Fleming et al., 2016; Meehan et al., 2011; Schaefer et al., 2009). It cannot be discerned if the slow learning rates are indeed due to learning deficits or are a result of impaired motor execution. Therefore, to make inferences about learning in patients with stroke, the motor execution deficits need to be disentangled when determining performance changes with practice. While one way to circumvent the "execution vs. learning problem" is to test practice effects on the nonparetic arm, it is not clear if findings of the nonparetic arm can be generalized to the paretic arm, an issue relevant to rehabilitation. Another way to account for execution deficits may be to scale the motor skill to the capacity of the paretic arm. For example, in our previous study, we scaled the extent of the complex reaching goals to the participants' maximum reach distance (McGrath and Kantak, 2016). Thus, any differences in skill acquisition could then be predominantly attributed to deficits in learning, rather than execution limitations.

Practice-induced improvements in skill performance are implemented by reorganization of ipsilesional and contralesional neural networks that include the motor cortices (M1s) and cerebellum (Müller et al., 2002; Shmuelof et al., 2014). Planning and coordinating novel muscle synergies with precise timing engage the fronto-cerebellar and motor cortico-cerebellar circuits (Cantarero et al., 2015; Seidler and Noll, 2008; Shmuelof et al., 2014; Wadden et al., 2013). With repetitive practice, the new skilled action becomes represented in the motor cortex, which supports improved motor performance (Kantak et al., 2010; Shmuelof et al., 2014). Following injury to the corticospinal tract, the spared motor cortex is shown to reorganize with practice to support improved motor behavior (Harris-Love et al., 2011; Meehan et al., 2011; Nudo et al., 1996a, 1996b). However, the precise changes in the motor corticospinal excitability that accompany complex motor skill learning are unknown in patients with stroke. Transcranial magnetic stimulation (TMS) has been used to characterize the input–output characteristics of the motor corticospinal system. Changes in motor evoked potential (MEP) size (output) as a function of TMS intensity (input) allows an evaluation of excitability of a broad range of corticospinal neurons including those who may be a part of the "subliminal fringe", but change their excitability through trans-synaptic projections during learning (Devanne et al., 1997; Harris-Love et al., 2011; Jensen et al., 2005; Perez et al., 2004). Motor recovery after stroke is also associated with changes in the contralesional M1 as well as the transcallosal connections from contralesional to ipsilesional M1 (Harris-Love et al., 2011). Studies have demonstrated that motor recovery of the weaker arm is associated with reduced transallosal inhibition (TCI) from the contralesional to ipsilesional M1 (Davidson and Tremblay, 2013; Harris-Love et al., 2016). While complex skill learning is a critical component of arm rehabilitation, it is not known how ipsilesional M1, contralesional M1 and transcallosal interactions between the two M1s change with complex skill learning.

In this preliminary study, we investigated behavioral and neurophysiologic changes associated with complex motor skill learning in patients with unilateral stroke compared to neurologically-intact control participants. We controlled for the execution deficits by normalizing the motor skill demands to each participant's maximal capability. Behavioral changes were quantified at baseline; immediately, one-day and one-month after motor practice. First, we determined if practice of the new skill with the paretic arm led to improvements in the speed–accuracy tradeoff. Second, we determined if practice improved the paretic arm control for the skill by quantifying changes in submovements and smoothness of skill performance. Third, in select patients with stroke, we used TMS to determine the practice-induced changes in the input–output characteristics of the ipsilesional corticospinal pathway projecting to the paretic triceps, excitability of the con-