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Reviews and perspectives

Movement-dependent stroke recovery: A systematic review and meta-analysis of TMS and fMRI evidence

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Abstract

Evidence indicates that experience-dependent cortical plasticity underlies post-stroke motor recovery of the impaired upper extremity. Motor skill learning in neurologically intact individuals is thought to involve the primary motor cortex, and the majority of studies in the animal literature have studied changes in the primary sensorimotor cortex with motor rehabilitation. Whether changes in engagement in the sensorimotor cortex occur in humans after stroke currently is an area of much interest. The present study conducted a meta-analysis on stroke studies examining changes in neural representations following therapy specifically targeting the upper extremity to determine if rehabilitation-related motor recovery is associated with neural plasticity in the sensorimotor cortex of the lesioned hemisphere. Twenty-eight studies investigating upper extremity neural representations (e.g., TMS, fMRI, PET, or SPECT) were identified, and 13 met inclusion criteria as upper extremity intervention training studies. Common outcome variables representing changes in the primary motor and sensorimotor cortices were used in calculating standardized effect sizes for each study. The primary fixed effects model meta-analysis revealed a large overall effect size (ES = 0.84, S.D. = 0.15, 95% CI = 0.76–0.93). Moreover, a fail-safe analysis indicated that 42 null effect studies would be necessary to lower the overall effect size to an insignificant level. These results indicate that neural changes in the sensorimotor cortex of the lesioned hemisphere accompany functional paretic upper extremity motor gains achieved with targeted rehabilitation interventions.

Keywords: Meta-analysis; TMS; fMRI; Neural plasticity; Stroke; Motor recovery

Contents

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1. Introduction

Over 750,000 individuals experience a new stroke every year in the United States (American-Heart-Association, 2005). The majority have enduring reductions in contralateral arm and hand function that interfere with their ability to perform goal-oriented activities (Kwakkel, Wagenaar, Twisk, Lankhorst, & Koetsier, 1999; Nakayama, Jorgensen, Raaschou, & Olsen, 1994) and capacity for vocational pursuits. Understanding how to promote motor recovery of arm and hand function after stroke, therefore, is a major challenge for stroke rehabilitation.

The recovery of motor skills post-stroke relies on altering how the brain controls movement. According to Rossini and Pauri, there are multiple and diffuse colonies of neurons that contribute to the large repertoire of movement strategies available to an individual (Rossini & Pauri, 2000). Flexible functional neural ensembles are created from these colonies to control the execution of the various movement patterns that are embedded in the various activities that the individual performs. Damage to some of these neurons from stroke requires the brain to create alternative functional ensembles with the neurons that are still viable after the stroke. This has been postulated to occur via the unmasking of latent synaptic connections because of the down-regulation of inhibitory mechanisms and synaptogenesis (Rossini & Pauri, 2000), both within the lesioned hemisphere and in the intact hemisphere. Thus, recruitment of both spared neurons in the lesioned hemisphere and undamaged neurons in the intact hemisphere may be used to control the execution of movements after stroke.

The role of the intact hemisphere in the recovery of arm and hand function after stroke has long been controversial. Although still not completely understood, recent research suggests that motor recovery improvements are associated with decreased reliance on recruitment of the intact hemisphere and increased engagement in the lesioned hemisphere (Calautti, Leroy, Guincestre, Marié, & Baron, 2001; Marshall et al., 2000; Traversa, Cicinelli, Bassi, Rossini, & Bernardi, 1997; Traversa, Cicinelli, Pasqualetti, Filippi, & Rossini, 1998; Turton, Wroe, Trepte, Fraser, & Lemon, 1996). These findings indicate that conditions that promote greater neural plasticity within and recruitment of the lesioned hemisphere are likely to foster greater functional recovery of the upper limb. Typically, triggering such neural plasticity changes is the goal of motor rehabilitation for the arm and hand post-stroke, thereby, facilitating the gains in motor capabilities that result in an increased ability to perform daily activities.

Over the past decade, there has been an increasing amount of evidence from basic science indicating that behavioral (i.e., activity-dependent) experiences alter how the brain controls movement after stroke. Nudo et al. demonstrated that squirrel monkeys with small cortical lesions who were given intensive therapy for the paretic upper limb demonstrated altered cortical motor maps (Nudo, Milliken, Jenkins, & Merzenich, 1996) in the lesioned hemisphere. Specifically, cortical representations of the hand were spared as well as representations in the peri-lesional tissue that had not subserved hand functions prior to the stroke. Control monkeys with the same types of lesions who did not receive therapy lost the representation of the paretic hand (Nudo, Milliken, et al., 1996). In addition, other researchers have shown the neural plasticity-promoting effects in the lesioned hemisphere of behavioral experiences in animals (Black, Isaacs, Anderson, Alcantara, & Greenough, 1990; Comery, Stamoudis, Irwin, & Greenough, 1996; Jones, Chu, Grande, & Gregory, 1999; Kleim, Jones, & Schallert, 2003; Plautz, Milliken, & Nudo, 2000). The majority of these studies have examined changes in primary sensorimotor cortex with motor rehabilitation when the sensorimotor cortex of animals has been lesioned (Black et al., 1990; Comery et al., 1996; Gonzalez et al., 2004; Jones et al., 1999; Kleim et al., 2003; Plautz et al., 2000).

However, lesions induced in these rat or monkey models are usually dissimilar to lesions experienced by humans. These animal model lesions are typically small with grey matter damage compared to the more extensive white matter damage commonly seen in humans (Nudo, Wise, SiFuentes, & Milliken, 1996). Moreover, how the size of the lesion impacts the capacity for neural plasticity is unknown. Further, evidence is lacking concerning the impact of therapies on either function or neural structure when the fiber tracts from cortical neurons are damaged. Therefore, whether changes in engagement in the sensorimotor cortex occur in humans after stroke currently is an area of much research interest.

Recently, there have been a number of studies investigating whether the neural changes in the lesioned hemisphere observed with therapy post-stroke in animals also occurs in humans (Boroojerdi, Battaglia, Muellbacher, & Cohen, 2001; Brouwer & Ambury, 1994; Carey et al., 2002; Cramer, 2004; Cramer, Finklestein, Schaechter, Bush, & Rosen, 1999; Cramer et al., 1997; Devanne, Lavoie, & Capaday, 1997; Foltys et al., 2003; Jang et al., 2003, 2005; Johansen-Berg et al., 2002; Könönen et al., 2005; Koski, Mernar, & Dobkin, 2004; Levy, Nichols, Schmalbrock, Keller, & Chakeres, 2001; Liepert, Bauder, et al., 2000; Liepert, Graef, Uhde, Leidner, & Weiller, 2000; Liepert, Uhde, Graf, Leidner, & Weiller, 2001; Lindberg, Schmitz, Forssberg, Engardt, & Borg, 2004; Luft et al., 2004; Muellbacher et al., 2002; Nelles, 2004; Nelles, Jentzen, Jueptner, Muller, & Diener, 2001; Newton et al., 2002; Park, Butler, Cavalheiro, Alberts, & Wolf, 2004; Platz et al., 2005; Schaechter et al., 2002;