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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 ($E.S. = 0.84$, $S.D. = 0.15$, $95\% \text{ C.I.} = 0.76 - 0.93$). 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

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,

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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; Jang et al., 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; Seitz, Butefisch, Kleiser, & Homberg, 2004; Sonde, Bronge, Kalimo, & Viitanen, 2001; Stinear & Byblow, 2004; Wittenberg et al., 2003). Most these studies tested only small numbers of subjects and used a variety of techniques and methods to measure neural plasticity changes that may have occurred with therapeutic behavioral experiences. Under such conditions, drawing valid conclusions about therapy-induced (movement dependent) neural changes is challenging.

Conducting a meta-analysis offers a systematic, objective method for summarizing the neural plasticity evidence from a variety of studies and determining an overall effect size. Therefore, using the meta-analytic technique, we asked whether motor rehabilitation (i.e., activity-dependent movement training) for the upper extremities produces neural plasticity changes in the motor cortex of the lesioned hemisphere. We investigated lesioned hemisphere effects because of the research showing that increased recruitment of neurons from the motor cortex of this hemisphere mediates functional motor recovery. The specific question asked; does neural plasticity evidence accrue across various movement-dependent training protocols?

2. Method

2.1. Subjects: study selection and inclusion/exclusion criteria

The exhaustive search for stroke references focused on neural plasticity and therapy studies in individual journal articles, review papers, book chapters, as well as two computerized databases: (1) PubMed (1966 to 2006) and (2) Cochrane Reviews (2007). Key search words were stroke, cerebrovascular accident, upper extremity hemiparesis, neural plasticity, transcranial magnetic stimulation (TMS), functional magnetic resonance imaging (fMRI), imaging, rehabilitation training effects, and motor recovery. In addition, the reference lists of articles obtained through these searches were scrutinized for additional articles not found during the searches. Lastly, we searched again using the names of the authors of previously identified articles.

Our literature search identified 28 relevant training studies that quantified neural plasticity changes for further analysis to determine if inclusion in this meta-analysis was appropriate (Brouwer & Ambury, 1994; Carey et al., 2002; Cramer, 2004; Cramer et al., 1999; Cramer et al., 1997; Foltys et al., 2003; Jang et al., 2003; Jang et al., 2005; Johansen-Berg et al., 2002; Könönen et al., 2005; Koski et al., 2004; Levy et al., 2001; Liepert, Bauder et al., 2000; Liepert, Graef et al., 2000; Liepert et al., 2001; Lindberg et al., 2004; Luft et al., 2004; Muellbacher et al., 2002; Nelles, 2004; Nelles et al., 2001; Newton et al., 2002; Park et al., 2004; Platz et al., 2005; Schaechter et al., 2002; Seitz et al., 2004; Sonde et al., 2001; Stinear & Byblow, 2004; Wittenberg et al., 2003). For meta-analysis inclusion, each article was originally examined for changes in neural representation measured in four areas of interest: (1) primary motor cortex (M1), (2) supplementary motor area, (3) dorsal premotor area, and (4) cingulate area. We

decided to further analyze only those studies that included the primary motor or combined sensorimotor cortices (henceforth referred to as the sensorimotor cortex) because examining the 28 studies revealed that these areas of the cortex were the most frequently reported sites.

Moreover, limiting our selection criteria to only the *sensorimotor cortex* represented a common area to all identified studies. A final criterion involved *stroke treatment rehabilitation*; to evaluate the contribution toward motor recovery and neural representation changes that may have occurred, patients must have received an intervention (i.e., movement-dependent training) protocol specifically for the paretic upper extremity that was provided for at least two training sessions between the pretest and posttest regardless of the type or intensity of the intervention.

According to the above stated criteria and consistent with meta-analysis techniques, 15 studies (Brouwer & Ambury, 1994; Cramer, 2004; Cramer et al., 1999; Cramer et al., 1997; Foltys et al., 2003; Johansen-Berg et al., 2002; Levy et al., 2001; Liepert, Graef et al., 2000; Lindberg et al., 2004; Nelles, 2004; Newton et al., 2002; Park et al., 2004; Seitz et al., 2004; Sonde et al., 2001; Wittenberg et al., 2003) were excluded from the initial list of articles because 10 were not designed as rehabilitation studies (Brouwer & Ambury, 1994; Cramer, 2004; Cramer et al., 1999; Cramer et al., 1997; Foltys et al., 2003; Liepert, Graef et al., 2000; Nelles, 2004; Newton et al., 2002; Seitz et al., 2004; Sonde et al., 2001), four articles used unique analyses and data displays that made it impossible to calculate standardized effect sizes (Johansen-Berg et al., 2002; Levy et al., 2001; Lindberg et al., 2004; Wittenberg et al., 2003), and one was a case study (Park et al., 2004). The 13 remaining studies (Carey et al., 2002; Jang et al., 2003; Jang et al., 2005; Könönen et al., 2005; Koski et al., 2004; Liepert, Bauder et al., 2000; Liepert et al., 2001; Luft et al., 2004; Muellbacher et al., 2002; Nelles et al., 2001; Platz et al., 2005; Schaechter et al., 2002; Stinear & Byblow, 2004) used upper extremity training as a rehabilitation treatment while testing stroke subjects in both the sub-acute and chronic stages of recovery. The necessary data from the 13 treatment studies were extracted by two authors and separately confirmed by the other three authors of this meta-analysis. Moreover, the meta-analysis authors were in unanimous agreement on the coding for the sensorimotor cortices as well as the outcome measures of neural representations.

Table 1 lists the studies, grouped by type of experimental paradigm, included in the current meta-analysis and summarizes relevant characteristics for each study. Across the 13 studies, 166 subjects were tested, the average age of the subjects was 58.77 years (S.D. = 5.23), and mean number of months post stroke was 26.71 (S.D. = 21.47). Lesion location was isolated in the left hemisphere for 77 subjects and the right hemisphere for 64.

Four experimental paradigms were used to evaluate neural plasticity changes pre/post rehabilitation (training) intervention: (1) TMS = 6; (2) fMRI = 5; (3) positron emission tomography (PET) = 1; and (4) single photon emission computerized tomography (SPECT) = 1. TMS measures the distribution and excitability of the corticospinal neurons subserving particular muscles. In TMS, the magnetic field produced by a magnetic coil is placed over the motor cortex excites the underlying pyramidal neurons. When enough pyramidal neurons are activated, alpha motor neurons in the spinal cord are depolarized, generating a motor evoked potential in the subserved muscles. In contrast, fMRI, PET and SPECT all measure neural activation indirectly via the increases or decreases of cerebral blood flow that is associated with increased or decreased neural activation. PET and SPECT measure the uptake of radioactive tracers, given prior to scanning, that are carried in the cerebral blood whereas fMRI measures the balance of oxygenated and deoxygenated hemoglobin. Additionally, testing tasks varied for each experimental paradigm. TMS, PET, and SPECT data were collected while the participants were at rest or while the paretic limb was passively moved, while in the fMRI studies, participants actively flexed and/or extended with their paretic fingers or elbows.

Table 2 displays the treatment durations and protocols for each study in our meta-analysis. The durations ranged from 10 to 60 hours, and across the studies, the number of hours of treatment averaged 32 (S.D. = 17.13). This represents a substantial amount of intervention directed to upper extremity function not typically provided in clinical settings. For instance, in a study of six inpatient rehabilitation facilities across the United States, patients received on average approximately 11 hours of occupational therapy (Richards et al., 2005). Nearly 3 of the 11 hours of therapy were directed to improving upper extremity movements, representing a mean of only 2.67 hours of therapy devoted to upper extremity activities in typical post-stroke inpatient rehabilitation.

2.2. Establishing outcome measures

To accurately compare the studies and determine the overall training effects as contributing to the changes in neural representations post stroke, common outcome measures were selected, and the results of each measure were standardized. The types of paradigms used to measure activation included TMS, fMRI, PET, and SPECT. Specific outcome measures varied across the techniques and the range of dependent/outcome measures reported in this set of studies (e.g., laterality index, the number of active voxels, area of perfusion, center of gravity displacement, motor evoked potential threshold, area of brain activation, and volume of brain activation) shows a substantial amount of variability. To avoid the potential bias that occurs when using multiple measures from a single study, only one outcome measure per study was selected. Our *a priori* primary outcome measure for the five fMRI studies was the number of active voxels. However, two studies did not report values for the number of active voxels, consequently, closely related measures, laterality index and volume of brain activation, were selected. For five of the six TMS studies, the chosen dependent measures were motor evoked potential amplitude and motor evoked active positions/locations; the sixth study reported map volume. The outcome measure for the PET study was regional cerebral blood flow signal intensity, and the SPECT experiment recorded area of perfusion.

Neural representation baseline data for each subject and outcome measure were recorded during pretesting, before the treatment intervention. These baseline values were compared to the neural representations recorded post treatment to determine changes in activation levels. This within-subjects analysis was necessary because seldom were neural representation control data reported in the 13 qualified studies. Conducting a within-subjects meta-analysis (i.e., baseline values versus post-treatment values) is statistically robust and consistent with the meta-analysis literature.

2.3. Data synthesis

As stated by Rosenthal et al. (2001), a meta-analysis has two important and complimentary functions in synthesis and analysis (Rosenthal, Hiller, Bornstein, Berry, & Brunell-Neuleib, 2001). The synthesis function involves describing the properties of the collection of studies (effect sizes) as a whole, including central tendency, variability, and overall significance. Whereas the analysis function involves finding factors (i.e., moderator variables that account for differences in the collection of effect sizes (Rosenthal et al., 2001).

Consistent with these meta-analysis functions, we calculated Cohen's *d* on individual effect sizes for the 13 neural plasticity movement-dependent training studies. This accepted and robust meta-analysis effect size calculation is a within-subjects technique for each individual study that determines the difference between a treatment group's baseline (pretest) and posttest scores, and divides the value by the pooled standard deviation (Cohen, 1988; Rosenthal, 1995; Rosenthal & DiMatteo, 2001; Rosenthal et al., 2001; Rosenthal & Rubin, 2003). Furthermore, to ensure consistency in the meta-analytic technique for examining potential

heterogeneity across studies a fixed effects model was selected (Sutton, Abrams, Jones, Sheldon, & Song, 2000; Thompson, 1998).

Moreover, the effect size of the studies with small samples sizes were weighted by the reciprocal of its variance to determine the overall corrected mean effect size (Hedges & Olkin, 1985). This procedure was conducted for two reasons: (1) to avoid an inflated effect size that would result if the findings from the small-sample studies had as much weight as the findings from larger sample studies, and (2) to ensure a precise corrected mean effect size with smaller variances receiving a larger weight in the overall group mean (Hedges & Olkin, 1985; Rosenthal, 1995; Rosenthal & DiMatteo, 2001; Sutton et al., 2000).

A third accepted and applied meta-analytic procedure is to evaluate the contribution of moderating variables (Hedges & Olkin, 1985; Sutton et al., 2000). One moderating variable question of the current meta-analysis concerned the potential difference in the neural plasticity evidence found by the different experimental paradigms. In the included studies, 11 of the 13 either used TMS or fMRI to map the brain before and after therapy. Thus, a separate analysis examined these 11 studies split into two potential moderating variable groups: 6 TMS studies and 5 fMRI studies.

2.4. Fail-safe analysis

Given that all of the current 13 neural plasticity with motor rehabilitation studies were published, and that many studies had to be excluded on the basis of insufficient data available for the meta-analysis, a fail-safe analysis was conducted. This technique accounts for any potential publication bias effect in the meta-analysis by quantifying the number of studies with null effects that would be necessary to lower the calculated effect size to an insignificant level. Fail-safe analyses have become accepted conventional procedures in meta-analyses (Hedges & Olkin, 1985; Rosenthal, 1995; Sutton et al., 2000).

2.5. Quality assessment

Consistent with suggestions by Jadad et al. and Moher et al., the quality of each study was assessed on three criteria: (1) randomization, (2) double blinding, and (3) withdrawals or drop outs (Jadad et al., 1996; Moher, Schulz, & Altman, 2001). Randomization was noted if the subjects were either randomly placed into a treatment or control group or if the treatment was randomly assigned to the subjects. The current analysis revealed that six studies completed randomization. Concerning the double blind criteria, the rating scale varied from 0 – 2: 0 = not described or inappropriate, 1 = single blind, and 2 = double blind. The third quality assessment involved dropout guidelines. For this analysis, seven studies had at least one subject drop out (total = 20 subjects). As shown in Table 3, these criteria did not indicate an optimal quality assessment, but this is representative of early phase clinical trials.

3. Results

3.1. Mean effect size

The meta-analysis indicated a significant overall mean effect size of 0.84 (S.D. = 0.15) with a 95% confidence interval ranging from 0.76 to 0.93. These values indicate that the cumulative effect size is a large effect as well as significant (Cohen, 1988; Rosenthal, 1995; Rosenthal & DiMatteo, 2001). This large overall effect was based on 13 neural plasticity and motor rehabilitation studies with 98 treatment subjects out of 166 total subjects (i.e., treatment and control groups). Across the studies, the individual effect sizes ranged from a low of -0.54 to a high of 1.95. Table 4 shows the individual weighted effect sizes with lower and upper limit confidence intervals for each study. Examining the confidence intervals indicated that 10 of 13 the studies found evidence supporting increased engagement of the damaged hemisphere.

3.2. Fail-safe analysis

The fail-safe analysis determined that 42 null effect studies/findings were necessary to lower the calculated effect size to an insignificant level. In considering publication bias, this conventional procedure indicates that a relatively large number of studies with null effects are required to reduce the large overall weighted effect size indicating neural plasticity associated with movement-oriented rehabilitation.

3.3. Homogeneity test

Consistent with meta-analytic recommendations, the variability of the weighted effect sizes was determined (Rosenthal & DiMatteo, 2001). This accepted procedure determines whether the results reflect a single underlying effect or a distribution of effects (Hedges & Olkin, 1985; Rosenthal, 1995; Rosenthal & DiMatteo, 2001; Sutton et al., 2000). For the current meta-analysis, the distribution of the effect sizes was homogeneous as revealed by the Q statistic, $\chi^2(12) = 16.15, p > 0.05$.

3.4 Moderating variable analysis

Given that two predominant experimental paradigms for measuring neural representations (i.e., TMS and fMRI) were tested in 11 studies, a specific technique could be a potential moderating variable. Thus, a separate meta-analysis was conducted on these 11 studies. The analysis failed to reveal a significant moderator effect. The motor cortex changes in the six TMS studies were equivalent to the changes reported in the five fMRI studies.

In addition, the varying outcome measures were compared to determine if motor cortex changes differed across the methods. The one-way ANOVA failed to differentiate the multiple outcome measures.

4. Discussion

The current meta-analysis determined whether participating in stroke motor rehabilitation targeting the paretic upper extremity was associated with increased recruitment or engagement of the lesioned hemisphere. The identified large effect size demonstrates that neural plasticity changes in the motor cortex of the lesioned hemisphere accompany functional motor gains achieved with such targeted therapy. Increases in hemisphere engagement were evidenced by both increases in the area of the brain subserving paretic arm movement and greater signal strengths of physiological measures. These effects were found in the sensorimotor cortex of the lesioned hemisphere.

Increased engagement in the lesioned hemisphere with an activity-based intervention is consistent with studies of natural recovery from stroke which show that individuals with better functional recovery of their upper extremity activate primarily the lesioned hemisphere when using the paretic arm (Calautti et al., 2001; Marshall et al., 2000; Traversa et al., 1997; Traversa et al., 1998; Turton et al., 1996). The significance of these findings contributes to the argument that targeted upper extremity therapy post-stroke can facilitate increased engagement of the lesioned hemisphere during paretic arm movements in individuals with chronic stroke.

Further, the current increased excitatory findings are consistent with the animal research showing that behavioral experience leads to neural plastic changes in the lesioned hemisphere. Nudo et al. (Nudo, Milliken et al., 1996) and other researchers (Jones et al., 1999; Kleim, Lussnig, Schwarz, Comery, & Greenough, 1996; Kleim, Vij, Ballard, & Greenough, 1997) demonstrated increased protein synthesis, gene activation, and synaptogenesis in the lesioned hemisphere with motor practice of the paretic limb.

The favorable overall effect of upper extremity training in promoting increased activation in the lesioned hemisphere is compelling even with the inherent limitations of the meta-analysis technique. The fact that we only included studies in which a targeted upper extremity intervention was provided rather than including studies in which subjects engaged in traditional rehabilitation is a conservative approach to investigating the ability of behavioral experience to promote neural plasticity in the lesioned hemisphere. While the intervention dosing in the included studies was greater than that typically experienced in stroke rehabilitation (Boroojerdi et al., 2001), it may be that these neural events could be triggered by other therapy protocols where there was less upper extremity-directed therapy. Therefore, not including studies that provided traditional rehabilitation interventions minimized a potential spurious and inflated overall effect size.

Given that we included only published articles with a treatment component in this meta-analysis and multiple studies had to be discarded because of insufficient reporting of outcomes, we conducted a fail-safe analysis to determine the potential of missed studies that could possibly change our results. The analysis indicated that 42 articles demonstrating no change in activation of the lesioned hemisphere would need to exist to change our findings. This large fail-safe number further strengthens our conclusions that motor practice (i.e., movement-dependent training) is associated with increased engagement in the lesioned motor cortex.

However, not all studies of neural plasticity following motor training that reported increased motor recovery also reported an increased engagement in the lesioned hemisphere. Some have found general decreases in activation in the motor system (Ward, Brown, Thompson, & Frackowiak, 2003) while others have found increased activation (Kopp et al., 1999; Koski et al., 2004) in the contralesional rather than the lesioned hemisphere. The reasons why some individuals increasingly engage the intact hemisphere to control the paretic upper extremity as recovery happens while for others greater recovery is associated with increased lesioned hemisphere activation is not clear. Location and the size of the lesion may be one of the critical elements. Fujii and Nakada demonstrated that individuals whose lesions damaged most of the sensorimotor and its corticospinal tract experienced increased engagement of the contralesional hemisphere as they recovered motorically (Fujii & Nakada, 2003). Delineating how the brain responds to behavioral experience based on individual characteristics is an important direction for future studies of therapy efficacy.

Granted, a major weakness in the human neural plasticity literature is the large variability in methodology for examining the neural plasticity associated with stroke recovery and the effects of motor training. A variety of different experimental paradigms have been used for measuring neural representations: TMS, fMRI, serial optical tomography, SPECT, and near infrared spectroscopy. Within each paradigm, there is no consensus on methods for measuring these physiological changes in the motor cortex. Measures of neural representation status include, but are not limited to, the number of active voxels, laterality indices, center of gravity coordinates, the correlation between neural changes and functional improvements, motor evoked potential thresholds and amplitudes, and perfusion indices. Which are the best measures for answering specific questions about the nervous system are still being debated. For example, only recently have investigators suggested that the recruitment curve is the most sensitive and reliable TMS measure for assessing neural plasticity and this measure has not yet found widespread adoption among researchers (Boroojerdi et al., 2001; Devanne et al., 1997). Moreover, none of the TMS studies included in this meta-analysis measured recruitment curves.

Most importantly, we must keep in mind that the maps obtained with TMS are not identical to those obtained with fMRI. TMS typically produces one hotspot, where the coil is located, with the ability to produce MEPs declining the farther from this spot in 360° (Lotze, et al., 2003). In contrast, fMRI characteristically detects multiple maxima with the center of gravity located

between them. Krings reported that the mean offset of TMS maps compared to fMRI maps was 0.6 cm (Krings et al., 2001). Frequently, the TMS map is more widespread and uniform in shape than the fMRI map. Three viable explanations for differences in map sizes and locations include (a) disparity between the two methods in terms of the underlying physiological mechanisms, (b) relationship of the coil position in activating the underlying cortical tissue (TMS) (Lotze et al., 2003), and (c) measurement of which neurons could activate a given muscle (excitability of these tissues: TMS) versus which neurons actually activate a given muscle during a task (fMRI). The importance of a particular muscle to task completion and the muscle's activation threshold (e.g. proximal muscles have higher thresholds and, therefore, their maps may differ depending on the level of TMS stimulation) is not completely understood (Petersen, Pyndt, & Nielsen, 2003). Thus, attempting direct comparisons of map sizes and areas between different imaging techniques is precarious without additional clarification and understanding. However, investigating concordance in measures of general brain region involvement in motor control, as we did in the present meta-analysis, may be more beneficial. Moreover, despite the differences between the two methodologies, findings from the current meta-analysis indicated that both techniques showed greater involvement of the lesioned motor cortex in the control of the paretic upper extremity after movement-dependent training.

Further variability involves the tasks used during testing in that tasks vary considerably across studies. Usually, TMS is administered while the person is at rest, although some researchers have asked the person to make a voluntary contraction during stimulation. Concerning the task-sensitive fMRI methodology, tasks have ranged from passive movements of one joint of the arm to active movement of a single finger. This task issue is critical during rehabilitation trials because the BOLD signal may increase when more attention is paid to the movement (Binkofski et al., 2002; Johansen-Berg & Matthews, 2002; Kopp et al., 1999), when task complexity requires greater effort (Catalan, Honda, Weeks, Cohen, & Hallett, 1998), or when the speed of the movements are increased (Fujii & Nakada, 2003; Jancke, Specht, Mirzazade, & Peters, 1999). These findings raise interesting questions about how to use fMRI to measure therapy gains because a high number of clinicians and patients are most interested in motor capabilities while completing complex tasks in a shorter length of time. Discussing this issue is beyond the scope of this paper, but this situation points out the importance of carefully selecting an experimental paradigm to control for these potential confounds to minimize such extraneous variability and allow researchers to draw valid conclusions about neural plasticity.

Thus, the variability in studies of neural plasticity creates considerable difficulty in synthesizing the results of these studies. However, given that the current meta-analysis found high concordance across the studies, regardless of technique and methodology used, this systematic review demonstrates an important finding: increased engagement within the lesioned hemisphere after the completion of an upper extremity rehabilitation program.

In summary, the current meta-analysis findings provide clean support for the argument that increased upper extremity motor functions from movement activity-based stroke rehabilitation therapies occur in the presence of neural plastic changes in the lesioned hemisphere. These neural plastic changes occurred in individuals who were primarily in the chronic stage of recovery (> 1 year post stroke). Such findings lend credence to the postulate that behavioral movement experiences can function as effective stroke interventions (Cauraugh & Summers, 2005; Krakauer, 2006; Moher et al., 2001; Schaechter, 2004; Seitz et al., 2004). Certainly, the various types of movement-dependent training specifically designed for the upper extremity (i.e., 10 different therapies) and treatment durations (i.e., 13 different durations; mean treatment = 32 hours; median = 28 hours) provided in the studies included in this meta-analysis improved motor capabilities, and associated changes in the motor cortex were evidenced. These findings

should be helpful to rehabilitation researchers and clinicians while the merits of the therapeutic use of transcranial magnetic stimulation are debated (Ridding & Rothwell, 2007).

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Table 1
Characteristics of each study used in the meta-analysis. Studies are listed in chronological order, earliest to latest.

Study	Total N	Mean Age: Years	Lesion Location	Mean Time Post Stroke (Months)	Experimental Paradigm
Liepert, Bauder, et al., 2000	13	56.7	11 Left 2 Right	58.8	TMS
Liepert et al., 2001	9	59.7	3 Left 6 Right	1.4	TMS
Muellbacher et al., 2002	7	58	5 Left 2 Right	37.0	TMS
Stinear & Byblow, 2004	9	62	6 Left 3 Right	16.2	TMS
Koski et al., 2004	10	59	4 Left 6 Right	30.0	TMS
Platz et al., 2005	28	61.5	16 Left 12 Right	1.1	TMS
Luft et al., 2004	21	61.5	7 Left 14 Right	50.3	fMRI
Jang et al., 2003	4	50	2 Left 2 Right	12.2	fMRI
Carey et al., 2002	19	65.7	6 Left 4 Right	56.4	fMRI
Jang et al., 2005	10	59.8	2 Left 3 Right	13.8	fMRI
Schaechter et al., 2002	9	57	3 Left 1 Right	12.5	fMRI
Nelles et al., 2001	15	65.5	7 Left 3 Right	N/A	PET
Könönen et al., 2005	12	47.7	5 Left 6 Right	34.0	SPECT

Table 2

Study comparisons for treatment duration (daily/weekly and total hours), and specific treatment protocol.

Study	Treatment Duration: Daily/Weekly	Treatment Duration: Total Hours	Treatment Protocol
Liepert, Bauder, et al., 2000	6 hours/day 8 days	48	CIMT
Liepert et al., 2001	1 st week CT 2 nd week CIMT: 60 minutes/day	10	CT & CIMT
Muellbacher et al., 2002	90 minutes/day Mean 35 days	52.5	Pinching Task and Anesthesia
Stinear & Byblow, 2004	1 hour/day 28 days	28	Bilateral Movements
Koski et al., 2004	90 minutes/day Group 1: 1–2 days/week Group 2: 4 days/week	13	Task Practice
Platz et al., 2005	CT & 45 minutes extra therapy 4 weeks	35	CT & ABT
Luft et al., 2004	60 minutes/day 3 days/week 6 weeks	18	BATRAC
Jang et al., 2003	4 days/week 4 weeks	10.5	Practice 6 Tasks
Carey et al., 2002	60 minutes/day 2–5 days/week 4–10 weeks	14 (mean)	Index Finger Flexion/Extension Computer Task
Jang et al., 2005	60 minutes/day 5 days/week 4 weeks	20	Task-oriented Virtual Reality Training
Schaechter et al., 2002	4 hours/day 10 days	40	CIMT
Nelles et al., 2001	45 minutes/session 4 sessions/day 3 weeks	45	Task-oriented Repetitive Training
Könönen et al., 2005	6 hours/day 5 days/week 2 weeks	60	CIMT

Note. CT = conventional therapy; CIMT = constraint-induced movement therapy; BATRAC = bilateral arm training with rhythmic auditory cuing; ABT = arm BASIS training

Table 3
Quality assessments for each study included in the meta-analysis.

Study	Random Assignment	Not Described	Single Blind	Double Blind	Drop Outs
Liepert, Bauder, et al., 2000	0	0	1	0	3
Liepert et al., 2001	0	0	1	0	0
Muellbacher et al., 2002	0	0	0	0	1
Stinear & Byblow, 2004	1	0	1	0	0
Koski et al., 2004	0	0	0	0	1
Platz et al., 2005	1	0	1	0	7
Luft et al., 2004	1	0	1	0	5
Jang et al., 2003	0	0	0	0	0
Carey et al., 2002	1	0	0	0	2
Jang et al., 2005	1	0	1	0	0
Schaechter et al., 2002	0	0	0	0	0
Nelles et al., 2001	1	0	1	0	1
Könönen et al., 2005	0	1	0	0	0

Table 4
Summary statistics for the 13 studies included in the meta-analysis.

Study	Testing Task	Outcome Measure	Exper. Paradigm	Weighted Effect Size	Confidence Intervals(95%)
Liepert et al., 2000	Relax Abductor Pollicis Brevis muscle	Number of MEP Active Positions	TMS	1.950	1.613
Liepert et al., 2001	Relax Abductor Pollicis Brevis muscle	Number of MEP Active Positions	TMS	1.680	1.322
Muelbacher et al., 2002	Relax Flexor Pollicis Brevis muscle	MEP Amplitude	TMS	0.782	0.302
Stinear & Byblow, 2004	Relax Flexor Carpi Radialis muscle	Map Volume	TMS	0.585	0.271
Koski et al., 2004	Relax 1 st Dorsal Interossei, Abductor Pollicis Brevis or Abductor Digiti Minimi muscles	MEP Amplitude	TMS	0.492	0.180
Platz et al., 2005	Relax Abductor Pollicis Brevis muscle	Number of MEP Active Positions	TMS	0.034	-0.014
Luft et al., 2004	Active elbow flexion/extension	Volume of Brain Activity	fMRI	1.125	0.793
Jang et al., 2003	Active finger flexion/extension	Laterality Index	fMRI	1.094	0.351
Carey et al., 2002	Active finger flexion/extension tracking	Number of Active Voxels	fMRI	0.852	0.490
Jang et al., 2005	Active elbow flexion/extension	Number of Active Voxels	fMRI	.498	-0.065
Schaechter et al., 2002	Active finger flexion/extension	Number of Active Voxels	fMRI	-0.538	-1.244
Nelles et al., 2001	1/2 trials- relax 1/2 trials-passive elbow flexion/extension	rCBF Signal Intensity	PET	1.870	1.039
Könönen et al., 2005	Relax all muscles	Area of Perfusion	SPECT	0.914	0.671

Note. Exper. = Experimental; rCBF = regional cerebral blood flow; MEP = motor evoked potential; confidence intervals were calculated with standard error values.

Overall Weighted Effect Size	S.D.	Confidence Interval (95%)	Q Statistic	Fail-Safe N
0.842	0.152	0.759 – 0.925	16.14	41.70