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

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CRD summary
This meta-analysis evaluated the effects of upper extremity motor rehabilitation on neural plasticity changes in the motor cortex of the lesioned hemisphere in patients recovering from stroke. The authors concluded that the large effect size suggested that functional motor gains can be achieved. Given some methodological weaknesses in the review process, the reliability of the authors' conclusions is unclear.

Authors' objectives
To determine if activity-dependent movement training for the upper extremity produces neural plasticity changes in the motor cortex of the lesioned hemisphere of patients recovering from stroke.

Searching
PubMed and The Cochrane Library, and journal articles, review papers and book chapters, were searched. The database search covered the years 1966 to 2007. Search terms were reported. Reference lists of retrieved articles were searched. A citation search was conducted using the names of the authors of the identified studies.

Study selection
Before-and-after stroke rehabilitation studies that quantified neural plasticity changes in the sensory motor cortex were eligible for inclusion. Case studies and studies that did not report enough data to allow the calculation of standardised effect size were excluded from the meta-analysis. Studies were eligible for inclusion if treatment was movement-dependent training of any type and intensity, targeted the paretic upper extremity of stroke patients and was provided during at least two sessions between pre-test and post-test. Included studies evaluated the effects in stroke patients in the subacute and chronic stages of recovery, conventional therapy, constraint-induced movement therapy (CIMT), pinching task and anaesthesia, bilateral movements, task practice, arm BASIS training (ABT), bilateral arm training with rhythmic auditory cuing (BATRAC), practice 6 tasks, Index Finger Flexion/Extension Computer Task, Task-oriented Virtual Reality Training and Task-oriented Repetitive Training. The average duration of treatment was 32 hours. Included patients with left and right hemisphere lesions were included. Participants had a mean age of 58.77 years and were a mean of 26.71 months post-stroke. The primary outcome was changes in neural activation levels. Included measures were: functional magnetic resonance imaging (fMRI), transcranial magnetic stimulation (TMS), positron emission tomography (PET) and single photon emission computed tomography (SPECT). Data from testing tasks were collected with the patients at rest or while the paretic limb was passively moved for TMS, PET and SPECT. Data were collected during active movement of the paretic limb in fMRI studies. Various indicators of changed neural activity were reported in the paper.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
The quality of the included studies was assessed by adequacy of randomization, double blinding and withdrawals and drop-outs with a validated tool (Jadad and Moher).

The authors do not state how many reviewers performed the validity assessment.

Data extraction
Since outcomes were measured with different techniques, common outcomes were chosen and the results were standardised. Data were extracted in order to calculate the mean effect size and 95% confidence interval (CI). Baseline neural representations and post-treatment data were collected to determine changes in activation level. The authors...
calculated Cohen’s d on individual effect size for the included studies.

Data were extracted by two authors and independently confirmed by the other three authors.

**Methods of synthesis**
The authors conducted a within-subject meta-analysis that compared the baseline values with the neural representations recorded post-treatment across several treatments. The effect sizes of the studies with small sample sizes were weighted by the reciprocal of its variance to determine the overall corrected mean effect size. A fixed-effects model was used for the meta-analysis. A failsafe analysis was conducted to control for potential publication bias by quantifying the number of studies with null effect that would be necessary to lower the calculated effect size to an insignificant level. A moderating variable analysis was undertaken to evaluate the contribution of different techniques used to measure outcomes by examining the 11 studies that used TMS or fMRI split into two potential moderating variable subsets. Homogeneity among effect size of included studies was tested using the Q statistic.

**Results of the review**
Thirteen before-after studies were included in the meta-analysis (n=166). Six studies were randomized (n=102). Six studies were not randomized (n=52). One did not describe the method of assignment (n=12). Seven studies were single blinded, and seven studies had at least one subject drop out. The sample size of included studies was less than or equal to 10 in seven studies and less than or equal to 15 in 10 studies.

**Neuroplasticity changes:** The meta-analysis (98 participants) showed a statistically significant overall mean effect size of 0.84 with standard deviation of 0.15 (95% CI 0.76 to 0.93), which indicated a large effect of motor rehabilitation on neural plasticity changes in the lesioned hemisphere. The Q statistic showed that the distribution of effect sizes was homogeneous Χ² (12) =16.15, p>0.05. The moderating variable analysis did not reveal any significant moderator effect.

A fail-safe analysis found that 42 null effect studies were necessary to reduce the effect size to a non-significant level.

**Authors' conclusions**
In patients in the chronic stage of recovery from stroke (mostly more than one year post-event), neural plasticity changes in the motor cortex of the lesioned hemisphere accompanied functional motor gains achieved with motor rehabilitation therapy.

**CRD commentary**
The review addressed a well-defined question in terms of interventions, outcomes and study designs. Two electronic databases were searched, but no apparent attempt was made to locate unpublished literature and this could have introduced publication bias. However, the authors conducted a fail-safe analysis to check for potential publication bias. The authors did not report how many reviewers conducted the selection of studies, therefore, it was impossible to known if bias and error were avoided. Validity was assessed with a validated scoring system and the scores were reported for each study; however, the authors did not report how many reviewers participated in the validity assessment, which made it difficult to know whether bias and error was avoided. Data extraction was carried out in duplicate and checks by the other authors minimised the risk of bias. The characteristics of individual studies are presented clearly. The use of within-subject meta-analysis may have been appropriate given the variability among the included studies, although any potential threats to internal validity were not fully discussed. The small sample size of included studies increased the likelihood that larger trials may contradict the results of this meta-analysis. Given some potential methodological weaknesses in the review process, together with the inclusion of small sample sizes contained within a limited number of studies, the extent to which the authors’ conclusion is reliable was unclear.

**Implications of the review for practice and research**
**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that delineating how the brain responded to behavioural experience according to individual characteristics was an important direction in future research of therapy efficacy.
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