



# AOTA Evidence Briefs

## Stroke: Focused Questions

*\*A product of the American Occupational Therapy Association's Evidence-Based Literature Review Project*

### SFQ #2

## **What is the evidence that challenging demands (therapy, activity, or sensory stimulation) on the brain reorganize brain function after stroke, beyond spontaneous recovery?**

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### **Findings of Review Articles**

Nudo and Friel (1999) reviewed the studies done from 1983 to 1998 on human stroke patients and experimental animals. They concluded that the cerebral cortex can be altered functionally by specific motor experiences. After stroke, compensatory changes inevitably occur in the functional organization of the uninjured, surrounding cortical tissue and in more distant cortical tissue, and the two variables—motor experience and injury—interact in such a way that the first can modulate the effects of the second. Intensive, task-specific practice with the impaired limb is the type of motor experience to which Nudo and Friel were referring.

Nudo, Plautz, and Frost (2001) reviewed the literature from 1964 to 2000 to determine the specific types of behavioral experiences that induce long-term changes in the remaining, intact cortical tissue of adult animals. They concluded that those experiences were the ones that entail development of new motor skills. “The close correspondence between acquisition of new motor skills and alterations in the physiology of motor cortex circuitry is now becoming firmly established” (p. 1005). Repetitive unskilled movements that did not involve motor learning did not produce changes in motor representation in the rat or monkey cortices. Furthermore, if monkeys were left to recover from cortical **lesion** (see *Glossary*) spontaneously (without behavioral training or encouragement to use the affected limb), the representation of the remaining, undamaged hand was decreased in size. “Behavioral experience and cortical injury interact such that motor use can adaptively modulate the plasticity process that inevitably occurs after cortical injury” (p. 1013).

Nudo, Plautz, and Frost noted that “**synaptogenesis**” (see *Glossary*) that occurred as a result of learning appeared to be specific to the cortical area serving the part of the limb involved in the task. They further noted that long-term behavioral training resulted in alterations in **sensorimotor** (see *Glossary*) maps—for example, the maps of the skilled hand of string instrument players, the reading hand of Braille readers, or the skilled hand of badminton players. Classen, Liepert, Wise, Hallett, and Cohen (1998—Level III) reported that the phenomenon occurred after only a brief amount of time—30 minutes of repeated practice of a single, specific movement—and was reversed after 30 minutes of nonuse.

In a 1998 review of studies on the cortical mechanisms of recovery after stroke, Hallett, Wassermann, Cohen, Chmielowska, and Gerloff discussed the manifestation and degradation of cortical activity. They noted that the patterns of use (e.g., those used by Braille readers—the particular motor patterns that Braille reading involves) enlarged the cortical representation of the relevant movement used in the activity and that disuse (no training after stroke) resulted in reductions of cortical representations.

In 2001, Hallett again noted that use affects brain maps, citing the work of Pascual-Leone (2001), who taught normal study participants to play a particular 5-finger exercise on the piano. They practiced 2 hours per day for 5 days. As they became more skilled, the size or excitability of the motor representation of the hand increased. After 1 week of

not practicing, the maps of cortical output returned to baseline and remained stable. Pascual-Leone also found that, in the group of participants who continued to practice and whose performance continued to improve, the maps of motor output showed an initial plateau, then a slow decrease. “Skill acquisition [though not skill maintenance] is associated with a change in the pattern of activation of the executive structures” (p. 320). Hallett noted that if the weakened limb is not exercised after stroke (or after an experimentally induced lesion, in the case of animals), then the representational area of the limb is further limited because of the disuse.

In their review of the literature, Schallert, Leasure, and Kolb (2000) focused on the direct interaction between behavioral experience and structural changes associated with plasticity and degeneration. They noted that enriched, varying environments requiring an animal with a cortical lesion to solve motor problems were associated with brain reorganization. The effect of an enriched environment appeared to depend on the social milieu. That is, rats housed alone in enriched environments did not recover as did those housed together. From this observation, the reviewers hypothesized that the social situation increased the activity level of the animals, making it more likely that they would encounter motor problems. This seemed to be the case in that rats housed alone that were induced to be active within an enriched, changing environment showed recovery and brain activation. The reviewers concluded “sheer physical exercise in the absence of enrichment [opportunity to solve motor problems] does not produce impressive effects on postinjury recovery of locomotor function” (p. 1519). The mechanisms by which an enriched environment produces its effects on behavior have yet to be determined.

Fisher and Sullivan (2001), both physical therapists, reviewed the literature regarding brain reorganization and the characteristics of rehabilitation following stroke that promoted functional recovery as opposed to compensation. The characteristics that were associated with brain reorganization were specific, intensive, and complex movements required to solve motor problems and attain goals, as opposed to repetition of simple movements or reliance on the unaffected limb. Repetition of simple movements was found to be ineffective for synaptogenesis in rats, compared with acrobatic (complex) movement training. Learning resulted in new synapses being formed, whereas exercise induced only new blood vessels.

Fisher and Sullivan concluded that exercise (repetition of simple movements) does not appear to produce structural changes in the brain, but physical activity coupled with cognitive stimulation (development of new movement strategies) does. Reliance on the unaffected limb and the concurrent disuse of the affected limb result in a decrease of activation of the brain areas associated with the affected limb.

## Findings of Selected Studies

With the recent advent of noninvasive methods of studying cortical activity, researchers have looked at the cortices of human stroke patients for structural changes that occur as a result of use. Their studies have indicated that specific practice to develop new motor skills bring about changes in the motor cortex of the participating patients.

For example, in a randomized controlled study, Carey et al. (2002—Level I) studied improvement of finger movement accuracy and concurrent brain reorganization of volunteers who were in the chronic stage of stroke and volunteers who were well and elderly. In each of these cohorts, half of the participants were randomly assigned to the treatment group and half to the **control group** (see *Glossary*). The stroke participants assigned to the control group crossed over to a treatment period after the 4- to 7-week control period. The training involved using finger flexion and extension to track **sine waves** (see *Glossary*) of various shapes and frequencies that were displayed on a computer screen. Training was intensive (18–20 sessions, 45–60 minutes per session), and the training tasks were varied to require active problem-solving and attention to feedback by the participant. Brain reorganization was mapped using scores derived from analysis of data from **functional magnetic resonance imaging (fMRI)** (see *Glossary*).

The tracking accuracy of the stroke participants improved **significantly** (see *Glossary*) after treatment, and this improvement transferred to a significant improvement on a test of gross dexterity (Box & Block Test). As a result of training, the brain organization changed from **ipsilateral** (see *Glossary*) control to significantly more **contralateral** (see *Glossary*) control, which was similar to the control evidenced by the well-elderly participants.

In another randomized controlled trial, Nelles, Jentzen, Jueptner, Müller, and Diener (2001—Level I) studied the effects of an intensive course of training of the impaired arm versus a less-intensive generalized therapy to improve movement of severely hemiparetic arms of patients after **subcortical stroke** (see *Glossary*). The training of the

impaired arm required the patients to attempt to move it in all degrees of freedom to reach in different directions. The treatments lasted 45 minutes per session, 4 sessions per day, for 3 weeks, as compared with one 45-minute session per day for 3 weeks for the control treatment. Control treatment included range-of-motion exercises, soft tissue mobilization, and stretching. After the 3 weeks, brain scans of the experimental group showed significantly greater activation of the motor cortex compared with the control group. The experimental group also gained more on the clinical measure of recovery, the Upper Extremity subtest of the Fugl–Meyer Motor Function Test. However, the difference between groups was not significant, probably because there were too few subjects (only 10) for adequate statistical power to detect differences. Whether the improvement in brain activation was due to the nature of the training or the intensity of the training, however, cannot be discerned from this study.

Liepert, Graef, Uhde, Leidner, and Weiller (2000—Level III) found that the cortical motor-output area of the abductor pollicis brevis (APB) was significantly greater immediately after 1 hour of physical therapy than it was immediately before therapy. The training session included grasp and pinch exercises and movements of the individual fingers (not aimed at accomplishing an activity) during which the patient was expected to pay attention to joint perception. Although the motor output area of the affected hemisphere was significantly greater after treatment than before, 1 day after treatment, the effect was lost. Although 7 of the 9 study participants showed improvement on the Nine-Hole Peg Test, the difference was **not significant** (see *Glossary*).

The researchers concluded that even after a training session of 1 hour, changes could be demonstrated in the brains of people who had experienced a stroke. Because this experiment was carried out in 1 day, the complicating factor of spontaneous recovery was controlled.

### Findings of Selected Studies

Fisher and Sullivan (2001) cited constraint-induced therapy (CIT) as an intervention that requires the patient to develop new movement strategies for the affected extremity. Several studies have examined the effects of CIT on brain reorganization. For example, Liepert, Bauder, Miltner, Taub, and Weiller (2000—Level III) investigated whether massed, concentrated practice of functional tasks with the affected arm by 13 stroke patients would result in changes of the motor cortex. The treatment protocol was that of CIT, in which the patients with some voluntary movement of the wrist and fingers agreed to have their unaffected arm restrained for 90% of the day for 2 weeks and to participate in 6 hours of daily practice of activities that required use of the affected limb with increasingly finer control.

Clinically, the treatment significantly improved the amount of use of the affected limb (as measured by the Motor Activity Log) after treatment, compared with a control period of no treatment before CIT. The researchers reported significant “massive” changes in the size of the cortical motor output map after treatment compared with before. They also found a small, nonsignificant decrease of the motor map associated with the restrained limb. Together, these changes balanced the hemispheres more normally. The study was well controlled, except for loss of participants (23%–38% lost over time).

Using the same methodology, Liepert, Uhde, Gräf, Leidner, and Weiller (2001—Level III) studied whether intensified physical therapy (modified CIT) would induce a reorganization of the motor cortex in subacute stroke patients. They compared modified CIT with conventional physical therapy aimed at improving gait, activities of daily living, and **cognition** (see *Glossary*). Nine patients received 1 week of conventional physical therapy and then 1 week of conventional physical therapy plus modified CIT. The modification in the CIT, in addition to reduction of the duration to 1 week instead of the usual protocol of 12 days over a 2-week period, was an individually negotiated amount of time for wearing the forearm splint daily. It varied from 30% of waking hours to 85%, with an average of 58%. There was no mention in the report of behavioral training of the affected extremity during CIT, as is commonly reported in other studies.

No significant improvements were noted for the 1 week of conventional therapy. On the other hand, the size of output area in the affected hemisphere increased significantly after the 1 week of conventional physical therapy plus CIT. Accompanying this change was a significant improvement in dexterity as measured by the Nine-Hole Peg Test. **Effect sizes** (see *Glossary*) were large ( $r > .64$ ). The researchers concluded that a combination of conventional physical therapy and forced-use therapy is significantly more effective than conventional physical therapy alone in bringing about brain reorganization and motor recovery of the affected hand.

In a poorly reported study, Kopp, Kunkel, Muhinickel, Villringer, Taub, and Flor (1999—Level III) tested whether brain reorganization changed as a result of intensive CIT (6 hours a day for 2 weeks) applied to 4 volunteer patients in the chronic stage of stroke recovery. Although clinical measures “showed significant improved use” (p. 808; no scores or statistics were reported) after treatment, brain localization of finger movements did not change after treatment compared with before treatment. Localization of movements of the paretic right hands did change to the ipsilateral (undamaged) side after a 3-month period of no treatment.

This study offers weaker evidence than those cited previously because of the small number of participants; their heterogeneity; the lack of **randomization** (see *Glossary*) or a control condition; and the failure to test the results statistically. It is included because the originator of CIT, Dr. Edward Taub, was one of the study’s coauthors, and it is one of the few studies that examined brain reorganization in relation to CIT.

## Summary

Although the evidence is limited to studies with small samples of highly screened stroke participants and community-dwelling volunteers, when the results are taken together, there is evidence that challenging demands (therapy, activity, or environmental stimulation) on the brain reorganize brain function after stroke beyond spontaneous recovery. Challenges that require the brain to engage in problem-solving and new learning are associated with increased size of the cortical maps corresponding to the body part being used to solve the motor problem. On the other hand, according to the anecdotal report of Pascual-Leone (2001), after the problem is solved and the skill is learned, the cortex no longer expands with continued practice. Perhaps deeper parts of the brain take over the motor control, but that is not known at this time.

The intensity of training also appears to be a factor in brain reorganization, although Liepert, Graef, et al. (2000—Level III) did demonstrate that significant changes occurred in the size of the motor output area of the affected hemisphere after only a brief period of exercise. Challenging demands, as opposed to repetition of simple movements, reorganize the brain areas concerned with motor function after stroke.

## Clinical Application

Strong evidence supports structuring therapy to provide the patient with occupations and environments that challenge him or her to repetitively solve motor problems to help the brain reorganize after stroke. Brain reorganization appears to correlate with improved motor performance, although this evidence is sparse and needs further study.

## Glossary

**cognition**—“the act or process of knowing, including both awareness and judgment” (*Merriam-Webster’s Collegiate Dictionary*, 10th ed., s.v.).

**contralateral**—relating to the opposite side, as when paralysis occurs on the side opposite to that of the lesion.

**control group**—a group that received special attention similar to that which the treatment group received, but did not receive the treatment.

**effect size** (Cohen’s  $r$ )— a measure of clinical significance. It provides information about the magnitude of effect of the treatment. Although related to significance, it is not as influenced by the size of the sample. Therefore, it is possible to have an outcome on which the treatment had a large effect (e.g., the treatment group improved a lot more than the control group) and still have a nonsignificant result. If the results have a large effect but no significance, this means that this effect may be sample specific and not generalizable outside the study. There are many different types of effect sizes. What is reported here is Cohen’s  $r$ . Cohen’s  $r$  can be interpreted in a manner similar to a Pearson’s correlation coefficient:

| Effect size $r$ | Size of the effect |
|-----------------|--------------------|
| <0.09           | Negligible         |
| 0.10 – 0.29     | Small              |
| 0.30 – 0.49     | Medium             |
| >0.50           | Large              |

Note: Cohen, J. (1977). *Statistical power analysis for behavioral sciences*. New York: Academic Press.

**functional magnetic resonance imaging (fMRI)**—computer-enhanced radiologic procedure for clearly examining the structures of the body.

**Functional resonance imaging (fMRI)** is the same procedure applied to the head and conducted while the subject is doing some functional task. The fMRI indicates which brain areas are active or inactive for particular tasks or parts of a task.

**ipsilateral**—on the same side; e.g. paralytic symptoms occurring on the same side as the brain lesion causing them.

**lesion**—“an abnormal change in structure of an organ or part due to injury or disease” (*Merriam-Webster Medical Dictionary*, s.v.).

**nonsignificant (or no significance)**—A statistical term that refers to study findings that are likely to be due to chance differences between the groups rather than to other factors (e.g., the treatment of interest). A nonsignificant result is not generalizable outside the study. Like significance, a nonsignificant result does not indicate the clinical effect. Often studies will show nonsignificant results, yet the treatment group’s mean will be better than the control group’s. This is usually referred to as a *trend in the right direction*. Because significance is closely determined by sample size, nonsignificant results would often become significant if the sample size were increased.

**randomization**—the practice of assigning participants to either the treatment or control group using random allocation. Random allocation methods include flipping a coin or using a random number table. Randomization is meant to prevent the possibility that the experimenter might subconsciously let his or her opinions and preferences influence into which group a participant goes. Randomization also helps to ensure that the two groups are essentially equal on many demographic variables, although randomization does not always create equal groups.

**sensorimotor**—“of, relating to, or functioning in both sensory and motor aspects of bodily activity” (*Merriam Webster’s Collegiate Dictionary*, 10th ed., s.v.).

**significance (or significant)**—a statistical term; refers to the probability that the results obtained in the study are not due to chance but to some other factor (such as the treatment of interest). A significant result is one that is likely to be generalizable to populations outside the study.

Significance should not be confused with *clinical effect*. A study can be statistically significant without having a very large clinical effect on the sample. For example, a study that examines the effect of a treatment on a client’s ability to walk, may report that the participants in the treatment group were able to walk significantly longer distances than the control. However, if you read the study you may find that the treatment group was able to walk, on average, 6 feet, while the control group was able to walk, on average, 5 feet. While the outcome may be statistically significant, a clinician may not feel that a 1-foot increase will make his or her client functional.

**sine wave**—a wave form of a single constant frequency and amplitude that continues for all time.

**subcortical stroke**—the location of the lesion is in levels of the central nervous system lower than the cortex (e.g., the tracts or basal ganglia or white matter, etc.).

**synaptogenesis**—formation of new synapses (electrochemical connections between neurons).

## References

### Articles Ranked for Level of Evidence

- Carey, J. R., Kimberley, T. J., Lewis, S. M., Auerbach, E. J., Dorsey, L., Rundquist, et al. (2002). Analysis of fMRI and finger tracking training in subjects with chronic stroke. *Brain*, *125*, 773–788.  
**Level IC2c:** Randomized controlled trial, less than 20 participants per condition, moderate internal validity, low external validity.
- Nelles, G., Jentzen, W., Jueptner, M., Müller, S., & Diener, H. C. (2001). Arm training induced brain plasticity in stroke studied with serial positron emission tomography. *NeuroImage*, *13*, 1146–1154.  
**Level IC3c:** Randomized controlled trial, less than 20 participants per condition, low internal validity, low external validity.
- Liepert, J., Bauder, H., Miltner, W. H. R., Taub, E., & Weiller, C. (2000). Treatment-induced cortical reorganization after stroke in humans. *Stroke*, *31*, 1210–1216.  
**Level IIIC2c:** Nonrandomized controlled trial—one group (one treatment) pretest and posttest, less than 20 participants per condition, moderate internal validity, low external validity.
- Liepert, J., Graef, S., Uhde, I., Leidner, O., & Weiller, C. (2000). Training-induced changes of motor cortex representations in stroke patients. *Acta Neurologica Scandinavica*, *101*, 321–326.  
**Level IIIC2c:** Non-randomized controlled trial—one group (one treatment) pretest and posttest, less than 20 participants per condition, moderate internal validity, low external validity].
- Liepert, J., Uhde, I., Gräf, S., Leidner, O., & Weiller, C. (2001). Motor cortex plasticity during forced-use therapy in stroke patients: A preliminary study. *Journal of Neurology*, *248*, 315–321.  
**Level IIIC2c:** Nonrandomized controlled trial—one group (one treatment) pretest and posttest, less than 20 participants per condition, moderate internal validity, low external validity.
- Classen, J., Liepert, J., Wise, S. P., Hallett, M., & Cohen, L. G. (1998). Rapid plasticity of human cortical movement representation induced by practice. *Journal of Neurophysiology*, *79*, 1117–1123.  
**Level IIIC3c:** Nonrandomized controlled trial—one group (one treatment) pretest and posttest, less than 20 participants per condition, low internal validity, low external validity.
- Kopp, B., Kunkel, A., Muhinickel, W., Villringer, K., Taub, E., & Flor, H. (1999). Plasticity in the motor system related to therapy-induced improvement of movement after stroke. *NeuroReport*, *10*, 807–810.  
**Level IIIC3c:** Nonrandomized controlled trial—one group (one treatment) pretest and posttest, less than 20 participants per condition, low internal validity, low external validity.

### Articles for Focused Questions (not ranked)

- Fisher, B. E., & Sullivan, K. J. (2001). Activity-dependent factors affecting poststroke functional outcomes. *Topics in Stroke Rehabilitation*, *8*, 31–44.
- Hallett, M. (2001). Plasticity of the human motor cortex and recovery from stroke. *Brain Research Reviews*, *36*, 169–174.
- Hallett, M., Wassermann, E. M., Cohen, L. G., Chmielowska, J., & Gerloff, C. (1998). Cortical mechanisms of recovery of function after stroke. *NeuroRehabilitation*, *10*, 1331–1342.
- Nudo, R. J., & Friel, K. M. (1999). Cortical plasticity after stroke: Implications for rehabilitation. *Revue Neurologique*, *155*, 713–717.
- Nudo, R. J., Plautz, E. J., & Frost, S. B. (2001). Role of adaptive plasticity in recovery of function after damage to motor cortex. *Muscle and Nerve*, *24*, 1000–1019.
- Pascual-Leone, A. (2001). The brain that plays music and is changed by it. *Annals of the New York Academy of Science*, *930*, 315–329.
- Schallert, T., Leasure, J. L., & Kolb, B. (2000). Experience-associated structural events, subependymal cellular proliferative activity, and functional recovery after injury to the central nervous system. *Journal of Cerebral Blood Flow and Metabolism*, *20*, 1513–1528.

## Further Reading

- Borlongan, C. V. (2000). Motor activity-mediated partial recovery in ischemic rats. *NeuroReport*, *11*, 4063–4067.
- Kleim, J. A., Barbay, S., Cooper, N. R., Hogg, T. M., Reidel, C. N., Rempel, M. S., et al. (2002). Motor learning-dependent synaptogenesis is localized to functionally reorganized motor cortex. *Neurobiology of Learning and Memory*, *77*, 63–77.
- Levy, C. E., Nichols, D. S., Schmalbrock, P. M., Keller, P., & Chakeres, D. W. (2001). Functional MRI evidence of cortical reorganization in upper-limb stroke hemiplegia treated with constraint-induced movement therapy. *American Journal of Physical Medicine and Rehabilitation*, *80*, 4–12.
- Liepert, J., Miltner, W. H. R., Bauder, H., Sommer, M., Dettmers, C., Taub, E., et al. (1998). Motor cortex plasticity during constraint-induced movement therapy in stroke patients. *Neuroscience Letters*, *250*, 5–8. [Level IIIC3c: Non-randomized control trial—one group (one treatment) pretest and posttest, less than 20 participants per condition, low internal validity, low external validity].
- Mulder, T., & Hochstenbach, J. (2001). Adaptability and flexibility of the human motor system: Implications for neurologic rehabilitation. *Neural Plasticity*, *8*, 131–140.
- 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. *Journal of Neuroscience*, *16*, 785–807.
- Tillerson, J. L., Cohen, A. D., Philhower, J., Miller, G. W., Zigmond, M. J., & Schallert, T. (2001). Forced limb-use effects on the behavioral and neurochemical effects of 6-hydroxydopamine. *Journal of Neuroscience*, *21*, 4427–4435.
- Trexler, L. E. (1998). Volitional control of homonymous hemianopsia: A single case study. *Neuropsychologia*, *36*, 573–580.
- Xerri, C., Merzenich, M. M., Jenkins, W., & Santucci, S. (1999). Representational plasticity in cortical area 3b paralleling tactual-motor skill acquisition in adult monkeys. *Cerebral Cortex*, *9*, 264–276.
- Xerri, C., Merzenich, M. M., Peterson, B. E., & Jenkins, W. (1998). Plasticity of primary somatosensory cortex paralleling sensorimotor skill recovery from stroke in adult monkeys. *Journal of Neurophysiology*, *79*, 2119–148.

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