AOTA Evidence Briefs

Stroke: Focused Questions

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

SFQ #1

What occurs in the brain during recovery after stroke (so-called spontaneous recovery)?

Spontaneous recovery is the recovery that occurs with no specific therapeutic intervention (Nudo, 1999). Recovery from stroke involves hemodynamic changes (reduction of swelling or resorption of blood), recovery of neural mechanisms (brain plasticity), and recovery of behaviors, all of which occur at independent rates (Small, Hlustik, Noll, Genovese, & Solodkin, 2002— Level II). Spontaneous recovery is probably due to the resolution of edema (a hemodynamic phenomenon) and recovery of the function of neural tissues that were **ischemic** (see *Glossary*) but not destroyed (Hallett, 2001).

Findings of Review Articles

Hallett, Wasserman, Cohen, Chmielowska, and Gerloff (1998) and Hallett (1999, 2001) reviewed and summarized the research concerning the cortical mechanisms of recovery of motor function. Although several mechanisms have been identified in animals and humans, knowledge of the exact mechanisms is incomplete (Hallett et al., 1998; Nudo, 1999). The mechanisms identified include the following:

1. Changes in the balance of excitation and inhibition (unmasking of neurons in an extensive, existing, inactive network formerly kept in check by inhibition)—The balance of positive and negative electrical charges on the neurons not normally involved in the function are changed, making them more likely to be activated for the function.
2. Strengthening or weakening of synapses (electrochemical connections between neurons) already present through long-term potentiation (changes in the electrical charges that make neurons more likely to be active).
3. Change in the excitability of neuronal membranes (Hallett, 2001).
4. Sprouting of new axon (efferent fiber from the neuron cell body) terminals, "synaptogenesis" (formation of new synapses) (Humm, Kozlowski, James, Gotts, & Schallert, 1998).

The first two mechanisms (unmasking of inactive neurons and changes in electrical charges of active neurons) are bioelectrical in nature and account for rapid changes that occur within milliseconds to hours following a **lesion** (see *Glossary*). Sprouting of axons and formation of new synapses are anatomical changes that occur over weeks to months following a lesion. Growth of **dendrites** (see *Glossary*), which precedes formation of new synapses, depends on the use of the limb (Hallett, 2001; Nudo, 1999). Documentation of reorganization of **cortical representational maps** (see *Glossary*) indicates that, during use, areas other than those commonly involved in motor control of the affected limb are recruited (e.g., the **ipsilateral** [see *Glossary*]; **primary sensorimotor** [see *Glossary*] **cortex**; and the **contralateral** [see *Glossary*] cerebellum).

Although these mechanisms have been discovered in animals and humans, each individual is different, and generalities cannot be made (Hallett et al., 1998). The best recovery is seen when the affected limbs are used (Nudo, Wise, SiFuentes, & Milliken, 1996—Level III) and when the corticospinal tract (the conduit of neural activity from the cortex to the spinal nerves) is preserved (Feydy et al., 2002—Level II; Hallett et al., 1998). This corresponds to the observation by Gresham, Duncan, Stason, et al. (1995) that those patients with stroke who benefited from motor therapy were those who demonstrated some voluntary motor control of the affected limb before therapy. Indeed, in many

studies (e.g., Miltner, Bauder, Sommer, Dettmers, & Taub, 1999—Level III), such voluntary motor control is a prerequisite for initiating constraint-induced therapy.

Findings of Selected Studies

A few studies provide primary evidence of the reorganization of cortical representation. Nudo and Milliken (1996—Level II) made **focal ischemic infarcts** (see *Glossary*) in the primary motor cortex governing distal forelimb movement of adult squirrel monkeys. The researchers demonstrated that, immediately following the lesion, the representational maps in the digit and wrist–forearm areas of the cortex were decreased in the animals that had not been retrained to use the affected limb. In other words, fewer cortical neurons were controlling the affected limb. The affected paw on the side opposite to the lesion showed marked, but transient, inability to pick up food pellets that corresponded to the widespread reduction in the extent of the area of digital representation in the cortex.

Nudo et al. (1996—Level III) studied the effects of rehabilitation on adult squirrel monkeys. They trained the monkeys to do a skilled hand task (feeding from small wells) before they imposed the infarcts. Five days following surgery, the monkeys began the same training procedure (rehabilitation) as before surgery, but with their unaffected arms restrained by a jacket. Training continued until performance by 3 out of the 4 monkeys was as good as before the lesion. Comparison of cortical representational maps showed that the area of movement representation did not differ significantly between the rehabilitated and spontaneously recovered control monkeys of the Nudo and Milliken study. There was, however, a **significantly** (see *Glossary*) greater representation of the hand in the cortices of the retrained monkeys, compared with the representation of the hand of the control monkeys. In fact, in the spontaneously recovered monkeys, there was a loss in the digital representational area that was not seen in the retrained monkeys.

Feydy et al. (2002) studied cortical mechanisms of recovery over 6 months in 14 people with **hemiplegia** (see *Glossary*) (7 who had experienced right hemisphere damage and 7 who had experienced left) secondary to ischemic infarct of the middle cerebral artery. The participants acted as their own controls, that is, movement consequences of the unaffected upper limb were compared with those of the affected upper limb, while all variables unique to each person remained the same. During **functional magnetic resonance imaging (fMRI)** (see *Glossary*), the participants opened and closed their hands into a fist at the same pace on each side. Those who could not do so, repetitively flexed and extended their elbow or adducted and abducted their shoulder. In addition, Wallerian degeneration (degeneration of the axons that have been severed from their cell bodies) of the corticospinal tract was measured. When the participants were performing with the unaffected limb, the cortical activation always involved the contralateral sensorimotor cortex (SMC), with little or no variation within or between sessions. This was similar to reports from normal participants. In addition, bilateral activation of the supplementary motor areas (SMA), with some variability, was present in most participants.

When the participants were performing with the affected limb, two patterns of activation were detected: (a) *recruitment*—defined as extension of activation into cortical areas not activated by movements of the unaffected hand, such as the ipsilateral SMC and SMA, and the frontal premotor and superior parietal areas and (b) *focusing*—the opposite of recruitment, defined as inhibition of cortical areas formerly recruited excessively over time. If the primary motor area (M1) had been spared, the pattern seen was focusing, but if the M1 area or its connections had been damaged, the brain continued to recruit sites bilaterally.

These patterns of activation were unrelated to degree of recovery in the participants studied. Wallerian degeneration, on the other hand, was significantly related to the degree of functional recovery. Feydy et al. (2002) concluded that functional recovery depends not on the type of plasticity but on the amount of remaining fibers in the impaired corticospinal tract. If too few fibers of the corticospinal tract remain active, only scant messages from the remodeled cortex reach the muscles that bring about movement.

Marshall et al. (2000) studied 7 persons who had experienced a purely motor stroke and reported a similar change in brain reorganization over time, from extensive involvement of the ipsilateral motor centers immediately after stroke to a more focused pattern of contralateral control 3–6 months following stroke.

In a well-controlled study that related behavioral recovery to brain reorganization, Small et al. (2002) tested 12 relatively young patients (average age 54 years) with acute strokes of various locations in the brain. They tested the par-

ticipants 4 times during their first 6 months of recovery. The researchers hypothesized that in the course of stroke recovery, brain activation would increase in one or more of four primary sites: The primary motor cortex (M1) ipsilateral to the impaired hand, the primary motor cortex (M1) contralateral to the impaired hand, the cortical regions functionally connected to the impaired M1, particularly the supplemental motor area (SMA) and the lateral premotor cortices, and the cerebellum (CRB). Further, they hypothesized that behavioral (functional) motor recovery would correlate with the neurobiological changes such that better recoverers, but not poorer recoverers, would demonstrate these changes.

All the participants were able to perform finger-to-thumb opposition. Behavioral tests were grip and pinch strength testing by dynamometry and the Nine-Hole Peg Test (timed fine motor performance). Brain activation was tested with fMRI while the participants did finger-to-thumb opposition and wrist flexion and extension in time to a regular auditory signal. The extensor digitorum was monitored bilaterally using electromyography to verify that the patient did not contract the finger extensors of the unaffected side which would activate motor cortical areas bilaterally as has been noted in normal people. No contractions were detected. This possible variable had not been controlled in other studies. All participants improved on all 3 measures, but on the basis of improvement scores (defined as the difference between the best and the worst performance in the impaired hand), those with greater-than-average improvement were classified as "better recoverers" and those with poorer-than-average improvement were classified as "worse recoverers."

The researchers tested the volume of brain activation during use of the impaired hand using a five-way analysis of variance (ANOVA). The five factors were as follows:

1. Participant group: better or worse recoverer
2. Task: finger or wrist task
3. Brain region:
    a. Primary sensory and motor cortex (SM1)
    b. Pre-motor cortex (PM)
    c. Supplementary motor and cingulate motor corticies (M2/3)
    d. Cerebellum (CRB).The group with better recovery differed from the group with worse recovery in the regional pattern of activation among the four regions listed above, regardless of task or time since stroke. Further analysis showed that a single activation accounted for the effect: the good recoverers had significantly more activation in the ipsilateral cerebellum than did poor recoverers. Activation in the M1 contralateral to hand movement, which is pronounced during movements of the paretic hand, did not differ between better and worse recoverers.

Increased activity in the ipsilateral CRB was significantly, but weakly, correlated to improvement on the Nine-Hole Peg Test over time. The researchers concluded that the degree of recovery from motor stroke is significantly correlated with activation of the CRB ipsilateral to the impaired, moving hand.

Cramer et al. (1997—Level II) also studied recovered patients. Their research question was: Is the activation of the area where the stroke occurred, the SMA, or the motor regions of the unaffected hemisphere increased, as determined by fMRI, in 10 patients who had recovered hand movements after stroke compared with 9 healthy people who acted as controls? The answer was yes. In the control group, index-finger tapping produced activation in many brain areas consistent with prior fMRI studies of healthy group. The areas of brain activation were not significantly different between recovered stroke patients and control group, although the stroke patients activated the areas to a significantly greater extent. The researchers noted that motor recovery after stroke is accompanied by increased activity in the unaffected sensorimotor cortex, which is usually present but less active during performance of a simple task in healthy brains. The more complex the task attempted, the more activated this area. It appears that, in the view of the now-damaged brain, doing once-simple tasks is complex. It is known that stroke patients require greater effort to use paretic muscles (Brodal, 1973; Hallett et al., 1998).

Summary

In summary, the brain appears to reorganize after injury, but without use of an affected limb, the cortical representation of that limb is decreased. Reorganization consists of changes in dendrites and axons, recruitment of motor areas surrounding or contralateral to the lesion, and neurochemical changes (Hallett, 2001; Johansson, 2000).

The studies reported here are primarily observational in nature. They involved small samples of animals and humans. The instrumentation was sophisticated, complicated, and time-consuming to apply, and that probably accounts for the small samples. Small sample or non-parametric statistics have been appropriately applied in these studies.

In contrast, one experimental study was reported by Humm et al. (1998). The researchers assigned 53 rats to one of two conditions: a condition in which they received a real operation (an infarction) or a condition in which they received a sham operation and then randomly assigned them to conditions in which they were casted in various ways. The assessor of functional recovery was **"blind"** (see *Glossary*) to (unaware of) group assignment. Evaluation in the other studies was probably not blinded (the authors did not report whether or not it was), because each participating animal or human was studied intensely and the infarcted condition would have been obvious.

Humm et al. found that forced overuse of the affected forelimb (by casting the entire unaffected forelimb) of rats during the first 7 days following surgical lesioning of the forelimb SMC significantly lowered the volume of remaining brain tissue (i.e., it expanded the neural injury) and greatly interfered with restoration of function, as compared with sham-anesthetized rats and those casted after the 7th day. Forced overuse of the affected limb in the second 7 days caused no effect on lesion size but interfered with restoration of function. The mechanism for these functional deficits is not known. In their discussion Humm et al. noted that there is "no established time course of post-traumatic neural events in relation to vulnerability to behavioral intervention in humans that would allow for comparison with that of rats" (p. 291). They conclude that "the most opportune time at which to begin rehabilitation following injury, and at what intensity such rehabilitation must be conducted, remains unknown" (p. 291).

A precautionary note is emerging in the literature, related to early motor training or overuse. Excess usage has been associated with exaggeration of cortical injury in animals (Humm et al., 1998; Nudo, 1999; Nudo & Milliken, 1996; Nudo, Wise, et al., 1996; Risedal, Zeng, & Johansson, 1999—Level II). The phenomenon has not yet been studied in humans. Johansson (2000), a coauthor of one of these studies, advises, "I do not think that these animal data should make us change the policy of early mobilization of stroke patients. Housing animals in an enriched environment, which may correspond to early mobilization, has no aggravating effects" (p. 227).

Clinical Application

These studies found that spontaneous recovery (recovery without treatment) did not enhance brain reorganization. The use of the affected limb in functional tasks did modify brain reorganization. These findings suggest that having the patient attempt to use the affected limb in daily activities as much as possible after a stroke would be beneficial to brain recovery, within the limits that recovery is to be regained. ■

Glossary

blinded/blinding—the practice of keeping members of the research study unaware of which group a participant is assigned to (treatment or control) in the study. *Single blinding* usually refers to keeping study participants unaware of whether they are receiving the experimental or the sham treatment. *Double blinding* usually refers to keeping the participants and those who are administering the treatment unaware of who is receiving the experimental and who is receiving the sham treatments. In some cases, where it is impossible to blind those administering treatment, the individuals who are administering the outcome measures can be blinded to group status.

Studies in which blinding does not occur can have significant biases. When the participants know that they are receiving the experimental treatment, they often get better because they think they ought to (this is often referred to as the "placebo effect"). When researchers know that a participant is receiving the experimental treatment, they often subconsciously favor those participants when evaluating them on outcome measures. For instance, when timing a participant in the treatment group, researchers may unknowingly stop the watch a little faster or slower so the treatment participant seems to do better.

contralateral—side opposite the affected limb in this case.

cortical representational maps—diagrams of the cortex, determined by computer-assisted radiological examination or electrical stimulation, that designate the particular places of the cortex responsible for movement of particular body parts.

dendrites—balancing protoplasmic processes that conduct impulses toward the body of a nerve cell.

focal ischemic infarcts—circumscribed lesions caused by deprivation of the blood supply carrying oxygen to the cells in that particular area.

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

hemiplegia—"total or partial paralysis of one side of the body that results from disease of or injury to the motor centers of the brain" (*Merriam-Webster Medical Dictionary*, s.v.).

ipsilateral—same side as affected limb in this case.

ischemic—deprived of blood and oxygen.

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

primary sensorimotor cortex—section of the brain responsible for voluntary movement.

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.

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Articles Ranked for Level of Evidence

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Level IIC1: Nonrandomized controlled trial—two groups, less than 20 participants per condition, high internal validity, external validity not reported.

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Level IIIC2: Nonrandomized controlled trial—one group (one treatment) pretest and posttest, less than 20 participants per condition, moderate internal validity, external validity not reported. (Structured abstract not available).

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