Published in final edited form as:

J Commun Disord. 2011 ; 44(5): 515–520. doi:10.1016/j.jcomdis.2011.04.004.

Neural bases of recovery after brain injury

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Abstract

Substantial data have accumulated over the past decade indicating that the adult brain is capable of substantial structural and functional reorganization after stroke. While some limited recovery is known to occur spontaneously, especially within the first month post-stroke, there is currently significant optimism that new interventions based on the modulation of neuroplasticity mechanisms will provide greater functional benefits in a larger population of stroke survivors. To place this information in the context of current thinking about brain plasticity, this review outlines the basic theories of why spontaneous recovery occurs, and introduces important principles to explain the effects of post-stroke behavioral experience on neural plasticity.

Learning outcomes—Readers will be able to: (a) explain the three classic theories to explain spontaneous recovery after focal brain injury, (b) explain the neurophysiological effects of post-injury rehabilitative therapy on functional organization in motor cortex, (c) readers will be able to describe some of the variables that impact the effects of post-stroke behavioral experience on neuroplasticity, and (d) readers will be able to explain some of the current laboratory-based approaches to modifying brain circuits after stroke that might soon be translated to human application.

Keywords

stroke; plasticity; recovery; rehabilitation

1. Introduction

Stroke remains near the top of the list of causes of death and disability worldwide, despite numerous attempts to reduce the risks associated with this devastating neurological event. There are now about 800,000 strokes per year in the United States, and since age is one of the most important single risk factors, this number is expected to escalate significantly in the near future due to our aging population (Lloyd-Jones et al., 2010). Thrombolytic therapy using tissue plasminogen activator has demonstrated substantial benefit for reducing disability after thrombotic/embolic strokes, which account for about 85% of all strokes. However, relatively few patients are eligible to receive tPA therapy due to its narrow window of effectiveness, recently extended to 4.5 hours post-event (Lansberg, Bluhmki, & Thijs, 2009; Uchino, Massaro, Jovin, Hammer, & Wechsler, 2010).

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Due to the devastating physical and emotional toll of stroke on individuals, and its economic impact to society in caring for disabled stroke survivors, basic and clinical scientists have long sought effective means to restore function in the sub-acute and chronic phases following stroke. Our increased understanding of the mechanisms underlying brain plasticity both in normal and injured brains has led to an increased focus on developing post-stroke therapies that target underlying plasticity mechanisms. While few such therapies have yet to advance to large-scale Phase III clinical trials, there are currently several approaches that have the potential to result in clinically-significant improvements in standard outcomes measures.

Since current and future stroke therapies rely on the ability to alter brain organization in adaptive ways, current theories of recovery are briefly reviewed. A few of the rules that govern plasticity in the brain, especially in the cerebral cortex, are then proposed. The challenges in translating such rules from animal models to human stroke are emphasized. Finally, new device-based therapies that aim to maximize the brain's ability to reorganize adaptively are discussed.

2. Theories of recovery

Determining that a particular therapeutic intervention has a significant effect on outcome measures after stroke can be challenging since substantial functional recovery can occur spontaneously, especially in the first month post-stroke. Thus, before attributing change scores in outcome measures to the intervention of interest, proper control groups employing so-called "standard and usual care" must be employed in clinical trials. Maintaining a truly standard and uniform control intervention remains one of the most challenging aspects of conducting clinical trials in rehabilitation.

It is widely held that spontaneous recovery occurs due to three principal mechanisms. First, substantial evidence exists to support the theory of diaschisis, and its reversal, following focal injury to the brain (Feeney & Baron, 1986). Intact brain regions, well outside of the ischemic core, undergo reduced metabolism and blood flow. There appears to be a specific reduction in those intact brain regions that are connected with the injury core. However, since this process is reversible over the ensuing days and weeks, it is thought that at least some of the early functional recovery observed in both animal models and human stroke survivors must be due to the reversal, or resolution, of diaschisis. Second, while individuals improve on functional outcome measures, some have questioned whether true recovery ever occurs (Krakauer, 2006). For example, reduced time to complete a motor task on say, a Fugl-Meyer assessment, could be described as functional improvement but may belie the fact that compensation with the proximal and axial muscles may contribute to propelling the limb forward in the attempt to reach for an object. While this is arguably a functional improvement, significant impairment may still remain if one examines the kinetics and kinematics of the movement patterns.

Finally, it is now thought that the brain undergoes substantial physiological and neuroanatomical reorganization following injury (Nudo, 2006). Mechanisms such as long-term potentiation and long-term depression alter the physiological responses in intrinsic neuronal networks. Excitatory and inhibitory neurotransmitter levels are altered. Anatomical changes, such as alteration in dendritic branching, axonal sprouting, and synaptogenesis, can occur surprisingly fast. To a limited extent, the injury triggers neurogenesis in certain portions of the brain. How these various changes contribute to the recovery process, either adaptively or maladaptively, is still under investigation. However, it is clear that they occur quickly after injury and are sustained over at least several weeks, if not months. Further, the process of compensation discussed above almost certainly involves neurophysiological and

neuroanatomical plasticity to establish and maintain compensatory movement patterns. The remainder of this review will focus on some of the emerging principles of plastic reorganization that may have impact on designing rehabilitative interventions.

3. Temporal contiguity hypothesis

Early experiments in the somatosensory cortex of non-human primates provided strong evidence that neurophysiological maps in the cerebral cortex can be modified by experience, even in adulthood (Jenkins, Merzenich, Ochs, Allard, & Guic-Robles, 1990). The normal somatotopic map of the body surface in the primary somatosensory cortex (S1) is a distorted representation of the distribution of cutaneous receptors in the periphery. The distortion is due largely to the much higher density of receptors on the fingertips and lips, resulting in an exaggerated representation of these body parts. Within the map of the hand the individual finger representations are highly orderly, with the thumb represented more laterally and the little finger represented more medially. Within each finger representation, multi-unit recordings demonstrate that cortical neurons in layer 4 typically respond to only one fingertip surface. The border between adjacent fingers is quite narrow. Thus, recording neuronal activity from a microelectrode may reveal that neurons respond to stimulation of a small receptive field on one fingertip, say the middle finger. Moving the microelectrode a short distance on the surface, say 100 microns, reveals neurons that respond to stimulation of a small receptive field on the ring finger. This normal, orderly representation is thought to be maintained because the receptors on any given fingertip are typically stimulated at the same time, and thus, their inputs to the cortex are highly correlated. The probability of any two adjacent fingers being stimulated at the same time is much lower, and thus, correlated inputs to the cortical representations of two fingertips occurs with relatively low frequency. These observations have led to the “temporal contiguity hypothesis”, which suggests that the normal, orderly representation of the body surface is maintained by temporal coincidence of the component inputs.

One way to test this hypothesis experimentally is to suture two adjacent digits together, creating a digital syndactyly (Clark, Allard, Jenkins, & Merzenich, 1988). This greatly increases the probability that inputs from adjacent digits will be stimulated together in time. After 2 to 3 months, the resulting cortical representations are far from normal. Over a relatively large expanse of cortex along the border between the joined digits, one finds neurons that respond to stimulation of both fingertips. In other words, receptive fields span the suture line and extend onto both digits. This is not a result of peripheral sprouting of receptor afferents but reorganization in the cortex presumably due to the increased temporal contiguity of inputs from the two fingertips.

The temporal contiguity hypothesis can also be extended to motor cortex. In the typical motor map in primary motor cortex (M1), the representation of muscles and joint movements is not as orderly as the representation of skin surfaces in S1. Due to the divergence of corticospinal (CS) neurons to multiple motor neuron pools in the spinal cord, and the overlap of differently projecting CS neurons in M1, the typical somatotopic order is maintained only on a gross scale. That is, the face representation is located most laterally, the hand representation somewhat more medially, and the foot representation (and tail representation, in non-human primates) more medial still. However, on a finer scale, that is, within the hand representation, movement maps appear as a complex mosaic pattern but with the most distal muscles represented in the center of the hand map (Nudo, Jenkins, Merzenich, Prejean, & Grenda, 1992).

As in S1, experience can distort the hand map in a manner predicted by the temporal contiguity hypothesis. After training monkeys on a skilled reach-and-retrieval task, joint

movement combinations used conjointly, or in close temporal sequence, come to be represented over larger territories (Nudo, Milliken, Jenkins, & Merzenich, 1996). The specific patterns that emerge are highly idiosyncratic and related to the particular movement pattern that an individual monkey adopts when learning the task. That is, a monkey that retrieves small food items with the hand using a finger flexion/wrist extension combination will develop a much larger representation of finger flexion/wrist extension combinations in M1, as revealed using microelectrode stimulation techniques. Interestingly, these multi-joint movements are evoked by stimulation in M1 with much lower current levels than single joint movements in the same motor map. It is hypothesized that the representation of specific joint synergies is an emergent property of M1 that results from motor skill acquisition. As motor skills are acquired, the component joint movements are initially performed discretely. As skill develops, the transition from one joint movement to another becomes obscured until the entire movement composition is performed in one smooth pattern (Plautz, Milliken, & Nudo, 2000). Multi-joint representations in M1 reflect this acquired skill, and may underlie the ability to perform the task quickly and smoothly.

4. Post-injury retraining

It is reasonable to assume that if the healthy adult brain is capable of altering its function and structure in association with skill acquisition that the injured brain may accomplish functional recovery utilizing similar mechanisms in spared brain tissue. Studies in both animal models and in human stroke survivors have demonstrated that structural and functional alterations in spared cortical tissue occur over an extended time period after the event (Dancause et al., 2005; Cramer, 2010). Neurophysiological studies using microelectrode mapping techniques, neuroanatomical studies using immunocytochemical and tract-tracing techniques, as well as non-invasive imaging and stimulation studies have shown excitability changes, spontaneous map reorganization, and dendritic and axonal sprouting.

Importantly, the changes that occur appear to depend upon post-injury behavioral experience. For example, in monkeys that do not receive rehabilitative intervention after a small ischemic lesion in M1, spared hand representations next to the injury contract, and are taken over by more proximal (elbow/shoulder) representations. However, if beginning about 4 to 5 days after the event monkeys are subjected to one hour per day of repetitive training on a pellet retrieval task, the hand map contraction is prevented. In some cases, the spared hand representation expands into the adjacent proximal representations (Nudo, Wise, SiFuentes, & Milliken, 1996). This result would seem to support the vicariation hypothesis espoused by Glees and Cole in the 1950s (Glees & Cole, 1949). Parallel results have been demonstrated using TMS in humans (Liepert, Graef, Uhde, Leidner, & Weiller, 2000). In order to encourage monkeys to engage in the rehabilitative training after M1 injury using the impaired hand, monkeys can be placed into jackets with a long sleeve extending the length of the forelimb on the less-affected side with a mitten on the end. This is a procedure similar to that used in constraint-induced movement therapy in humans (Wolf et al., 2006).

5. What is the metric for rehabilitation dose?

In attempting to translate findings from animal experiments in stroke recovery to human stroke survivors, it is clear that the rehabilitative training paradigms are very different. In animal models it is usually necessary to pre-train the animals on a particular task in order to develop a stable baseline. Then, after injury, the same task is typically used to assess recovery. Especially in rodent models, few behavioral tasks that are difficult enough to display chronic deficits can be accomplished without prior training. Thus, in animal models, we usually are examining the rate of re-learning of a highly stereotypical task.

Further, the number of repetitions in a post-injury rehabilitation session is typically quite high in animal experiments compared with human post-stroke therapy sessions. In monkey studies demonstrating neurophysiological benefits of rehabilitative training on a pellet retrieval task the number of repetitions (successful retrievals) per session was about 300, and two sessions were conducted per day (Nudo, Wise, SiFuentes, & Milliken, 1996). In a recent observational study of typical therapy sessions in human stroke survivors the average number of functional upper extremity repetitions during sessions in which functional movements was observed was 32, an order of magnitude less than in the animal studies (Lang et al., 2009; Birkenmeier, Prager, Lang, 2010). The discrepancy is actually much greater since functional movements only occurred in about half of the observed sessions and the number of repetitions was divided among 2 to 4 activities. Thus, if the number of repetitions is an important metric for the dose of a rehabilitative training regimen, one can conclude that standard stroke rehabilitation in human stroke survivors is probably under-dosed.

6. Distributed networks and brain plasticity

Understanding neuroplastic mechanisms that underlie recovery after stroke involves not only the peri-infarct tissue but the entire network of sensorimotor structures indirectly affected by the injury. Neuronal populations that are normally interconnected reciprocally with the damaged area are most likely to be involved in the reorganization process since (a) major targets of their projecting axons are destroyed, and (b) they are at least partially deafferented by virtue of the degeneration of axonal projections from the injured zone. To model these network-related changes, we have begun to examine the relationship between primary motor cortex (M1) and the premotor cortex. The premotor cortex, specifically the ventral premotor cortex (PMv), has reciprocal connections with M1, its principal output target. In monkeys after an ischemic infarct in the hand representation in M1, the hand representation in PMv expands in a linear manner with respect to the size of the M1 injury. In addition, new corticocortical projection patterns are formed. Within five months after injury, PMv establishes novel reciprocal connections with the hand area of S1 (Dancause et al., 2005). While the underlying molecular triggers to axonal sprouting are still under investigation, it is clear that neuronal populations in PMv, as well as other cortical motor areas normally interconnected with M1, display increases in growth-related proteins such as vascular endothelial growth factor within a few days after injury (Stowe et al., 2007; Li et al., 2010). Novel corticospinal projection patterns from spared motor regions also occur (McNeal et al., 2010).

It now appears that structural and functional alterations in corticocortical circuitry after stroke is not limited to animal models nor is it limited to upper extremity representations. Using diffusion tensor imaging to infer anatomical changes in white matter tracts in human stroke survivors, Schlaug and colleagues have demonstrated significant alterations in the arcuate fasciculus, which interconnects Wernicke's area in the parietal lobe with Broca's area in the frontal lobe. The changes were induced by the delivery of intonation therapy, which improved the motor speech function in these individuals (Schlaug, Marchina, & Norton, 2009).

Since animal models have demonstrated structural and functional changes in spared network relationships after stroke, and neuroimaging studies in humans have found parallel evidence for axonal remodeling, it may be possible to use neuroimaging data as a surrogate marker for the effects of various rehabilitative therapies after stroke. Alternatively, it may be possible to use neuroimaging data to select those patient populations that are more inclined to benefit from a particular therapy.

7. Activity-dependent stimulation

Since structural and functional plasticity is modulated by experience, and since temporal coincidence appears to drive specific network changes, it may be possible to artificially couple the discharge of neuronal populations to affect their functional or structural connectivity. It has been demonstrated that functional relationships can be built in the intact adult nervous system by artificially driving temporal sequences of inputs and outputs of cortical modules, at least over short distances. It has been demonstrated in primates that action potentials recorded from one cortical module can be used to drive microstimulation of another cortical module that is located 1–2 mm away (Jackson, Mavoori, & Fetz, 2006). Following several weeks of entrainment, the two disparate modules had similar output properties. Thus, temporal coupling of different regions of the brain or spinal cord conceivably could be manipulated to induce reciprocal connectivity. This hypothesis is now being explored in several laboratories.

8. Conclusion

Modern studies examining brain repair after stroke have matured from a nascent beginning in the mid-1990s to a mature science examining mechanisms from the molecular to behavioral levels of analysis. Many fundamental questions still need to be addressed, but indications are that more effective interventions to improve functional recovery after stroke, even in the chronic phase, are just on the horizon.

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Appendix A. Continuing education

1. Principal theories of why spontaneous recovery of function occurs during the first few weeks post-stroke include:
 - a. Tissue reperfusion
 - b. Edema reduction
 - c. Reversal of diaschisis
 - d. Neurogenesis
 - e. Secondary degeneration
2. Motor skill training with the hand after stroke is associated with
 - a. Progressive differentiation of motor representations
 - b. Increased representation of proximal movements

- c. Cognitive impairment
 - d. Expansion of remaining hand representations
 - e. Increased mirror-movements
- 3. The temporal contiguity hypothesis
 - a. suggests that orderly representation of the body surface is maintained by temporal coincidence of the component inputs
 - b. predicts that the motor cortex has a precise representation of individual muscles
 - c. was rejected by results of digital syndactyly experiments
 - d. suggests that all parts of the somatosensory cortex fire in synchrony
 - e. does not apply to motor cortex
- 4. The number of repetitions of upper extremity tasks in a typical therapy session in human stroke survivors is about
 - a. 10
 - b. 30
 - c. 90
 - d. 300
 - e. 1000
- 5. Intonation-based speech therapy after stroke
 - a. Appears to increase white matter volume in the arcuate fasciculus
 - b. Benefits only left hemisphere language function
 - c. Disrupts orofacial representations in the cortex
 - d. Is effective primarily in early development
 - e. Is counterproductive in non-fluent aphasia

Answer key: 1-c; 2-d; 4-a; 4-b; 5-a