Applying Basic Neuroscience to Aphasia Therapy: What the Animals Are Telling Us

Kristen A. Keefe
National Institutes of Mental Health, Bethesda, MD

Advances in basic neuroscience have increased our knowledge about the neural processes underlying learning and memory and the cortical reorganization that occurs in response to environmental demands and cortical injury. This article provides a selective review of published studies conducted in animals that examine functional and structural substrates of neural plasticity in the adult mammalian brain, and discusses the implications of this knowledge for aphasia therapy. The processes and constraints identified in the studies reviewed can be used to refine and justify current aphasia therapies, as well as to design additional behavioral interventions.

Basic neuroscience research in animals has demonstrated the presence of marked cortical reorganization in the adult mammalian brain in response to behavioral manipulations, alterations in sensory input, and cortical injury. Such changes likely subserve learning and memory and contribute to the functional recovery following central nervous system injury. In addition to subserving recovery, these changes also are likely to contribute to the residual deficits that are encountered. As Kandel (1985) observes, "The cortical maps of an adult, and indeed the whole adult sensory system, are probably subject to constant modification on the basis of use or activity....Insofar as social intervention...works, it must work by acting on the brain, and quite likely on the connections between nerve cells" (pp. 830–831). If we can wed our knowledge of the types of changes that occur in the brain in response to behavioral events and neural injury and the mechanisms that underlie them with our understanding of the nature of language processing in the brain and how it is disrupted by nervous system injury, then the behavioral interventions that we use to treat aphasia may be more effective. What do we know, from the basic neuroscience literature, about the changes that occur in the brain as a consequence of behavioral experience and injury and the mechanisms that may underlie them? What are the animals telling us?

Normal Sequelae of Stroke

Stroke leads to acute, primary changes in the nervous system tissue receiving its blood supply from vessels that are occluded or that rupture. These primary changes are a consequence of the loss of oxygen and glucose delivery to the tissue and, if prolonged and severe enough, lead to cell death in the affected area. Obviously, this cell loss will contribute to behavioral deficits, the nature of the deficits being a function of the processes that previously had been subserved by the now-infarcted tissue.

Whereas the primary damage occurring in response to stroke will occur over a matter of hours to days and then become static, numerous secondary processes that continue to evolve over time are set into motion as a consequence of the primary damage. Such secondary changes include: (a) transneuronal degeneration, in which areas receiving neuronal input from or providing neuronal input to the infarcted area degenerate due to the loss of the connections; (b) denervation supersensitivity, in which neurons that have lost most of their input from the infarcted area become increasingly sensitive to any residual input being received from that area; (c) resolution of diaschisis, the temporary loss of electrical activity in areas remote from, yet functionally connected to, the infarcted tissue; and (d) collateral sprouting, in which axons from nearby neurons establish new axonal contacts on the neurons that have lost their input from the infarcted area. These secondary lesion-induced changes will contribute to the behavioral recovery and residual deficits that are observed (and that change) over time. Importantly, because these processes develop over a longer time-course than do the primary changes associated with the stroke, the organization and function of a patient's brain a few days after injury will be different from that a few weeks after injury and, presumably, a few months after the injury as well. Therefore, the deficits observed and the interventions required may be different.

The secondary changes that occur in conjunction with the primary damage caused by a stroke highlight the plasticity of the adult brain. Although regeneration of lost neurons and their afferent and efferent connections does not occur, the brain does undergo a remarkable degree of change in response to such damage. In addition, adaptations to environmental and behavioral influences occur in the adult brain as well; some of these are similar to those seen in response to damage. The behavioral outcome after stroke, then, will be a function of: (a) the organization of the individual's brain at the time of the stroke, (b) the tissue affected by the primary infarct, (c) the secondary neuronal changes that occur in response to the primary injury, and (d) the effects of environmental and behavioral influences on the postinjury function and organization of the brain. There is nothing that the aphasiologist can do about the first three of these factors. But the fourth factor, i.e., the fact that the behavioral experiences of an individual clearly affect cortical organization and function, provides the basis for the important role that aphasia therapy has in determining language outcome after stroke. Our goal should be to expand and to capitalize on our understanding of the basic neurophysiology underlying these processes in order to design the most effective treatment approaches.

Neural Substrates Underlying Adult Brain Plasticity

Although it has been said that "you can't teach an old dog new tricks,"

learning clearly occurs throughout the lifespan. Data from studies in animals indicate that this lifelong ability to learn is accompanied by continued neural plasticity in the adult brain. This plasticity in the adult mammalian brain is realized at a number of levels, from the synapse to the system and, presumably, reflects the neural processes that underlie the learning, memories, and other behavioral changes that we all experience. To the extent that the adult brain is capable of reorganization in response to behavioral and environmental influences, understanding the types of plastic changes that occur and what governs those changes can be important for refining and designing behavioral interventions for aphasia, because the interventions will undoubtedly influence the structure and function of patients' brains.

Changes in Nervous System Synaptic Function

Long-Term Potentiation

Perhaps the most popular neural explanation at present for learning and memory is the concept of long-term potentiation (LTP). LTP, first described in the early 1970s (Bliss & Lomo, 1973; Bliss & Gardner-Medwin, 1973), is a rapidly induced and sustained increase in the efficiency of neural transmission at a given synapse. That is, an incoming signal produces a greater response in the postsynaptic neuron after LTP than it did before. The phenomenon of LTP, although first described in the hippocampus, is observed throughout the neocortex as well, being most readily induced in layers II/III, the site of most cortico-cortical connections (Tsumoto, 1990). This enhancement of the effectiveness of a synaptic connection typically is studied in slices of the brain, where it is produced by stimulation of the input pathways to a neuron. The fact that manipulations that alter the induction of LTP also affect learning on behavioral tasks (Barnes et al., 1994; Castro, Silbert, McNaughton, & Barnes, 1989; Davis, Butcher, & Morris, 1992; Morris, 1989; Morris, Anderson, Lynch, & Baudry, 1986) suggests that this phenomenon is not an artifact of the experimental manipulations typically used to study it, but, rather, a likely neural substrate for learning and memory formation. LTP also demonstrates properties similar to those needed for learning or memory formation to occur, such as associativity. That is, stimulation of one input will potentiate the synaptic response produced by stimulation of another convergent input if the two stimuli are given in close temporal proximity to each other, a process known as associative

or heterosynaptic LTP (Levy & Steward, 1979; McNaughton, Douglas, & Goddard, 1978). For example, in the motor cortex, LTP of neurons in layers II/III can be induced by high-frequency stimulation of the inputs from the somatosensory cortex (Iriki, Pavlides, Keller, & Asanuma, 1989). Stimulation of the thalamic input to those same neurons, while exciting the neurons, fails to induce LTP. However, when the stimulation of the thalamic input is coincident with stimulation from the somatosensory cortex, the response of the motor cortex neurons to the subsequent thalamic input is enhanced.

Implications for Aphasia Therapy

Presuming that LTP, or a phenomenon like it, contributes to plastic changes observed in the adult brain, then heeding the constraints of this mechanism in designing or refining behavioral therapies, should enhance the outcome. For example, LTP might be the neural mechanism underlying the effects of deblocking or stimulation therapies, with the input from the intact modality to a given neuron or population of neurons enhancing the effectiveness of the synapses remaining from the impaired modality to those same neurons. If such a scenario is true, then because both heterosynaptic LTP and classical conditioning show similar temporal constraints (Robinson, 1986), optimizing the temporal relation between the presentation of stimuli in the intact and impaired modalities should be important for improving the likelihood that the impaired modality regains its function. In addition, presenting input from more than one intact modality, or increasing the intensity (saliency) of the stimulus in the impaired modality, should improve the probability for recovery, as the conditions of stimulus presentation inducing LTP can determine the extent of the cortical area that is influenced (Lee, Weisskopf, & Ebner, 1991).

Contribution of LTP to Pharmacological Influences on Therapy

The induction and expression of LTP also is affected by pharmacological manipulations, providing a possible basis for the ability of such manipulations to both positively and negatively affect the outcome of behavioral training. For example, stimulation of noradrenergic receptors can produce an enhancement of synaptic transmission and increase the degree of long-term potentiation induced by stimulation of afferent fibers in both the hippocampus and cerebral cortex

(Brocher, Artola, & Singer, 1992; Klukowski & Harley, 1994). This enhancement of synaptic transmission by norepinephrine might underlie the ability of psychostimulants, such as amphetamine, to enhance learning and recovery from brain injury. Furthermore, because this effect is mediated by beta adrenergic receptors, it might be possible to fine-tune the pharmacological adjuvants that are used with aphasia therapy.

Whereas activation of noradrenergic receptors facilitates LTP and memory, stimulation of γ-amino-butyric acid (GABA) type A receptors blocks the induction of LTP (Cerro, Jung, & Lynch, 1992; Izquierdo, 1994). This GABA-A-mediated inhibition of LTP has been presented as a mechanism by which benzodiazepines, such as diazepam (valium), impair memory function in humans (Cerro et al., 1992). Therefore, evaluating the effectiveness of the behavioral therapies used to treat aphasic patients should take into consideration the effects that drugs acting at these receptor systems may be having.

Changes in Nervous System Structure

Influence of Environmental Tasks on Dendritic Branching

Evidence for plasticity in the adult nervous system is available not only from examination of the function of synapses within a given area, but also from examination of the structure of the cortex. Studies have shown that when animals are placed in an enriched environment or trained to navigate mazes, there are increases in dendritic area in the visual cortex (Greenough & Bailey, 1988; Greenough, Juraska, & Volkmar, 1979; Volkmar & Greenough, 1972) and in the number of synapses per neuron (Juraska, Greenough, Elliott, Mack, & Berkowitz, 1980).

These learning- or environment-induced changes in cortical structure are highly associated with the specific task demands imposed, as evidenced by the observation that rats trained to reach with one forepaw had larger dendritic fields in the forelimb region of the contralateral sensorimotor cortex (Greenough, Larson, & Withers, 1985). Unfortunately, the mechanisms underlying these structural changes in the central nervous system, as well as the parameters critical for promoting their ocurrence, remain largely undefined, making it difficult at present to extrapolate from these data in normal animals to treatment approaches (but see below).

Influence of Central Nervous System Damage on Dendritic Branching

After damage to the cortex, there also is an increase in the number of dendritic branches on neurons in brain regions connected to the damaged area, suggesting that similar processes mediate both experience- and damage-induced changes in the adult central nervous system. This increase in dendritic branching is seen not only in the cortex on the same side as the lesion (Kolb & Gibb, 1991), but also in the contralateral cortex as well (Jones & Schallert, 1992, 1994; Kozilowski & Schallert, 1994). In the work by Kolb and Gibb (1991), damage to the prefrontal cortex of adult rats led to enhanced dendritic arborization in pyramidal neurons of layers II and III of the cerebral cortex. Because the dendrites of neurons in these layers of cortex receive input primarily from axons originating elsewhere in the cortex, the changes observed by Kolb and colleagues presumably were secondary to the altered input to that area from the prefrontal cortex. Likewise, Jones and Schallert (1994) reported increased dendritic arborization in pyramidal cells of the opposite, homotopic cortex after damage to the adult motor cortex. In both groups of animals, there were initial behavioral deficits that improved over time. The data suggest that these changes in dendritic branching are important for the recovery of function and that behavioral interventions play an important role in determining the outcome from central injury. In the work by Schallert and colleagues, the cortical injury led to impaired use of the contralateral forelimb by the rats. As a result, they relied more heavily on the limb ipsilateral to the damaged cortex for postural support, feeding, and other tasks. Over time, this over-reliance on the unimpaired limb decreased and use of the impaired limb increased and improved. The dendritic branching in the hemisphere contralateral to the lesion increased with a time course similar to that observed for the over-reliance on the good limb, and then decreased slightly, although not back to normal levels, coincident with increased use of the impaired limb. What is most interesting from the standpoint of the use of behavioral interventions for treating brain injury is the observation that prohibiting the rats from using the intact limb and forcing them to use the impaired limb prevented the increase in dendritic arborization and produced persistent impairments in the behavioral recovery (Jones & Schallert, 1994; Kozilowski & Schallert, 1994). Such findings suggest that behav-ioral manipulations clearly influence the functional outcome of recovery from brain injury, and that this influence is reflected in changes in the structure and function of the central nervous system.

Implications for Aphasia Therapy

The data from Schallert's group also suggest that forced use of the impaired limb is detrimental to functional recovery, raising the question of whether aphasia therapy centered on use of impaired modalities or practice of deficient skills might be less efficacious or actually deleterious to the recovery process. Fortunately, other studies suggest a more positive influence of task-specific training (Barth, Irish, & Barbay, 1994). For example, after motor cortex lesions in monkeys, functional recovery was greatest in animals receiving stimulation and specific training of the affected limbs rather than the unaffected limbs. The reason for the impaired function as a result of behavioral intervention in the studies by Schallert and others (Jones & Schallert, 1994; Kozilowski & Schallert, 1994) is not clear. However, it may relate to the extent to which the rodents required the use of their intact limb to provide a supportive foundation from which appropriate use of the impaired limb could be started. When the intact limb was immobilized, forcing the animal to use the impaired limb for all tasks, the ability to use that limb in an effective manner may have been compromised. Task-specific training, as used in the other studies, presumably facilitates effective use of the impaired structure or modality. These data and the interpretation suggest that therapies can be beneficial if they practice the impaired skills or modalities in the way they are to be used in the "recovered" state. However, the data also suggest that the wrong therapy may be worse than no therapy at all, highlighting the need to further our understanding of aphasic deficits and how to treat them.

Future Directions

While it is clear that there are changes in dendritic structure in the cortex after injury and that these changes are in some way associated with recovery of behavioral function, the stimulus for enhanced dendritic branching, how the increase in dendritic branching affects nervous system function and behavior, and how behavioral treatments facilitate the positive aspects of this response remain unknown. Evidence suggests that injury alone may not be sufficient to maximally stimulate dendritic sprouting. For example, in the study by Jones and Schallert (1994), restricting the use of the ipsilateral (intact) forelimb resulted in less dendritic branching, suggesting that some aspect of the behavior was critical for the process. Conversely, forced use of one limb in neurologically intact animals did not lead to increased dendritic branching in the contralateral motor cortex, suggesting that damage to the other cortex was critical for the branching as well, although the data reviewed above demonstrate increases in dendritic branching due to behavioral challenges alone. To the extent that similar neurophysiological responses underlie alterations in dendritic branching in response to both behavioral demands and cortical injury, then these influences are likely to interact to determine the CNS changes that occur after cortical injury, as well as the functional outcome. Basic neuroscience needs to increase our understanding of what produces such changes and determines their extent. Interestingly, both LTP and the increases in dendritic branching are evident primarily in layers II and III of the cortex. LTP has been associated with changes in synaptic structure (Desmond & Levy, 1990; Geinisman, Toledo-Morrell, & Morrell, 1991), and recent data show increases in the expression of certain cytoskeletal proteins, such as activity-regulated cytoskeletal protein (Lyford et al., 1995) with LTP, raising the possibility that a mechanism such as LTP may precipitate the enhanced dendritic branching.

Changes in Nervous System Networks

Influence of Sensory Input on Cortical Maps

Perhaps the most elegant examples of how behavioral interventions lead to reorganization of the normal adult cortex are those studies examining the receptive fields of cortical neurons after manipulations of sensory input. To examine these changes, electrodes are implanted in primary or secondary areas of cortex, and the response of neurons to sensory stimulation is recorded. In the normal animal, neurons responding to stimulation of a given area of the body are localized to the same area of somatosensory cortex, giving rise to a topographic representation of the body surface in the receptive field maps. When sensory nerves from a particular part of the body are cut or digits are amputated so that the sensory input from that body part to the brain is removed, the area of the cortex that was responsive to the affected body part becomes responsive to stimulation of another neighboring body part (Merzenich et al., 1983; Merzenich et

al.. 1984; Pons et al.. 1991). Evidence from imaging studies for such cortical reorganization in humans with arm amputations shows a shift in the focus of cortical activation; electroencephalograph studies show enhanced evoked potentials in response to stimulation of the face toward the hand representation area of the somatosensory cortex (Elbert et al., 1994). Although it has been argued that the shift in receptive field maps may be incomplete and limited by the extent of innervation of that area of cortex by other brain areas such as the thalamus (Jenkins, Merzenich, & Recanzone, 1990), other data suggest that the reorganization may be more complete and less restricted in the extent of the cortical area involved (Pons et al., 1991). Several factors may influence the extent of cortical reorganization. First, the area examined may be critical. Primary and secondary cortical areas may show more limited reorganization than association cortex because of more limited inputs to the former (Jenkins & Merzenich, 1987; Pons, Garraghty, & Mishkin, 1988). Most views of cortical reorganization hold that the changes reflect modifications of synaptic connections already present. Therefore, the amount of change should be limited by the nature and extent of the existing afferent connections. Second, the amount of time elapsed from when the alteration in input occurs to when the reorganization is examined may be important. In the studies by Merzenich and colleagues, receptive fields typically were examined within months after the sensory manipulation, whereas in the study by Pons and others, electrophysiological recordings took place 12 years after the loss of sensory input. One implication of these studies is that reorganization in the brain in response to a static alteration can continue over years and may contribute to the prolonged time course of recovery of function after nervous system injury.

Influence of Environmental Tasks on Cortical Maps

Changes in the functional organization of the cortex in adults, as evidenced by changes in receptive field maps, are also seen in response to behavioral interventions in animals. For example, Merzenich and colleagues trained monkeys to touch a device that delivered cutaneous stimulation to their fingers in order to obtain a food reward (Jenkins, 1990). The increased stimulation of those fingers over several months led to an increase in the area of somatosensory cortex in which the fingers were represented and a decrease in the average size of a neuron's receptive field in those areas. Such changes conceivably

lead to improved discrimination ability. In fact, monkeys trained on a tactile frequency discrimination task show increased cortical representation for the area of skin stimulated during training and sharpening of the responsiveness of neurons in that area to sensory stimuli. These changes are associated with improved performance on the task (Recanzone, Merzenich, & Jenkins, 1992; Recanzone, Merzenich, Jenkins, Grajski, & Dinse, 1992; Recanzone, Merzenich, & Schreiner, 1992). Such task-related changes are not restricted to somatosensory cortex. Training of monkeys on an auditory frequency discrimination task increased the size of the cortical representation for the trained frequencies in the primary auditory cortex (Recanzone, Schreiner, & Merzenich, 1993). Likewise, stimulation of the whiskers in rats increases the representation of those whiskers in the cortex (Kossut, 1992).

Implications for Aphasia Therapy

There are several important aspects of the behaviorally driven cortical reorganization described by Merzenich and his colleagues that may be relevant to the refinement and development of treatment approaches. First, the changes in cortical representation observed in the animals occurred in response to intense training; for instance, more than 300 trials per day over the course of several weeks or 1.5–2 hours of differential stimulation per day for 4.5 months (Jenkins, 1990; Wang, Merzenich, Sameshima, & Jenkins, 1994). Although the necessity for such intense schedules of training has not been established, these studies raise the possibility that therapeutic intervention may need to be as intense if such central changes underlie recovery. Second, the cortical changes induced by repetitive stimulation of the hand in monkeys were reversed to the "normal" pattern of representation after the behavioral task was stopped (Jenkins et al., 1990). To the extent that the "normal" pattern of representation in the cortex reflects the sum of the daily behaviorally relevant events occurring in an individual's life, then the language behaviors addressed in the treatment setting must be ones that are carried over to and used outside of treatment if the cortical reorganization is to be maintained, or the behavioral therapy must be continued so that the cortical changes that it induces and that underlie behavioral recovery persist. Third, in those studies in which monkeys were trained to make tactile or auditory frequency discriminations, changes in cortical representation

occurred only when the monkeys were required to make the discriminations in that modality. That is, application of the same auditory or tactile stimuli to monkeys did not result in cortical reorganization in the auditory or somatosensory cortex, respectively, if the animal was attending to another modality at the same time. These findings suggest that a patient's focused attention to the treatment task may be critical if the desired cortical reorganization is to take place; that is, passive language stimulation and therapeutic exercises may be largely ineffective. Finally, in the study on the effects of auditory discrimination training, it was observed that there was no improvement in discrimination ability or changes in cortical representation for nontrained frequencies, suggesting that generalization did not occur (Recanzone et al., 1993). More research using training procedures that promote response generalization is needed to explore the impact of such training and behavior on cortical organization.

Influence of Central Nervous System Damage on Cortical Maps

Neocortical reorganization, as reflected in alterations in cortical maps, is seen following cortical injury. It likely contributes both to recovery of behavioral function as well as to certain aspects of the residual deficits. For example, when the hand area of primary somatosensory cortex in primates is lesioned, the skin surfaces formerly represented in that area of cortex are subsequently represented in adjacent, preserved areas of the primary somatosensory cortex (Jenkins et al., 1990). As a consequence of this reorganization, the receptive field size of neurons in the remaining cortex becomes larger, resulting in coarser representation of the skin surface, an effect opposite to that encountered in the cortex of monkeys trained on behavioral tasks or sustaining a loss of peripheral sensory input. Lesions of the primary somatosensory cortex also affect more distant cortical areas, in particular the secondary somatosensory cortex in which the same body part was represented (Pons et al., 1988). Twenty-four to 48 hours after lesioning of the primary cortex, the corresponding area of the secondary somatosensory cortex was completely unresponsive to stimulation of the hand or other body parts, indicating that the activity of neurons in this cortical region is driven by neurons in primary somatosensory cortex, rather than by thalamic inputs as had previously been thought. Months after such a lesion, however, no area of the secondary soma-

tosensory cortex was unresponsive, and the initially unresponsive area of the secondary cortex was responsive to stimulation of the foot. The representation of other body parts was not significantly altered, and the hand was not represented despite evidence from other studies that the hand does come to be re-represented in the primary somatosensory cortex. The parameters determining the nature of this reorganization are not known.

Further Implications for Aphasia Therapy

What are the implications of these lesion-induced changes in cortical organization for behavioral outcomes after stroke? First, the coarser cortical representation that occurs as a consequence of the decreased area of representation for a given input should result in deficits in discrimination ability and thereby contribute to the residual deficits observed after stroke. Because specific training can enhance cortical representation for a specific input and decrease the receptive field sizes of neurons in that area, then behavioral therapy should offset at least some of this lesion-induced loss of discrimination ability and facilitate recovery. It seems that this can be accomplished without compromising the response of the reorganized cortical areas to their original inputs. Classical conditioning involving the whiskers of rats leads to an increase in the area of representation of the stimulated whiskers in the cortex, so that they activate areas of cortex previously responsive only to input from other whiskers. However, these reorganized areas of cortex continue to be responsive to their original primary inputs (Kossut & Siucinska, 1994). The broader receptive fields of neurons and coarser representations after cortical injury also predict that the saliency of and differences between stimuli presented to patients through their impaired modalities should be enhanced, to aid the patient in making the necessary discriminations. Second, as emphasized by Merzenich and colleagues (1987), cortical reorganization and the recovery that it presumably subserves can occur only if the areas of cortex receiving qualitatively similar input survive. Thus, awareness of the extent of the cortical lesion and the nature of the cortical areas affected (i.e., primary, secondary, association) will be important for determining the degree to which recovery may be expected. Third, the loss of cortico-cortical afferents may be responsible for diaschisis, with its resolution reflecting the topographic reorganization that occurs. The fact that secondary cortex may fail to become

responsive once again to its original input, even though that input once again becomes represented in primary somatosensory cortex, raises the possibility that despite reorganization in one brain area that might facilitate recovery, disordered representations in "downstream" cortical areas may contribute to the deficits observed after cortical injury and preclude behavioral recovery. Gaining a better understanding of the processes that determine which surviving inputs come to predominate in a given area of cortex, and the time course over which such changes occur, may lead to the development of interventions that can promote more beneficial reorganization.

Conclusion

Although the field of neuroscience currently provides much evidence from animal studies for the tremendous plasticity of the adult cortex, it is just beginning to unravel the critical parameters of behavioral interventions and cortical injury that lead to these changes. Also in their infancy are the investigations of the underlying neurophysiological and neuroanatomical processes that lead to the restructuring and reorganization that occurs. The data already acquired provide some guidelines to be considered in the refinement and justification of currently used aphasia therapies, as well as in the design of new ones, and undoubtedly will offer more as the processes underlying neural plasticity are further defined. As the field of clinical aphasiology can benefit from the basic neurosciences, so too can the basic neurosciences benefit from the field of aphasiology. It is hoped that experiments exploring the neurophysiological bases by which behavioral interventions affect cortical organization and function after CNS damage will be designed with the ideas and concerns of clinicians at their center.

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Contact author: Kristen A. Keefe, Department of Pharmacology and Toxicology, 112 Skaggs Hall, University of Utah, Salt Lake City, UT 84112