Neural Compensations After Lesion of the Cerebral Cortex

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ABSTRACT

Functional improvement after cortical injury can be stimulated by various factors including experience, psychomotor stimulants, gonadal hormones, and neurotrophic factors. The timing of the administration of these factors may be critical, however. For example, factors such as gonadal hormones, nerve growth factor, or psychomotor stimulants may act to either enhance or retard recovery, depending upon the timing of administration. Nicotine, for instance, stimulates recovery if given after an injury but is without neuroprotective effect and may actually retard recovery if it is given only preinjury. A related timing problem concerns the interaction of different treatments. For example, behavioral therapies may act, in part, via their action in stimulating the endogenous production of trophic factors. Thus, combining behavioral therapies with pharmacological administration of compounds to increase the availability of trophic factors enhances functional outcome. Finally, anatomical evidence suggests that the mechanism of action of many treatments is through changes in dendritic arborization, which presumably reflects changes in synaptic organization. Factors that enhance dendritic change stimulate functional compensation, whereas factors that retard or block dendritic change block or retard compensation.

KEYWORDS

recovery, synaptogenesis, psychomotor stimulants, therapy, neurotrophic factors

INTRODUCTION

One of the challenges for behavioral neuroscience is to find ways to stimulate the brain to compensate for injury to the cerebral cortex. One of the obstacles to compensation, however, is that functions are relatively localized in the cerebral cortex. Indeed, during the 100 years that followed Broca’s first paper in 1861 showing cerebral localization of language, the concept of functional localization dominated the neurological sciences. The bulk of the evidence emphasized the synaptic connectivity of cerebral areas, with the general implication that the brain was largely hard-wired. There is little doubt, for example, that functions of the occipital cortex are dependent upon visual input and appropriate output connections. It is thus impractical to imagine that the somatosensory cortex would be able to participate in the recovery of visual functions. The last 25 years has shown a marked change in thinking, however, as it is now clear that the cerebrum is capable of considerable plasticity. The challenge is to find a way to stimulate the remaining parts of localized neural circuits to do ‘more with less’. On the surface,
given that cerebral regions are already presumably working to capacity, this would seem to be an insolvable problem. But there have been clues for over 100 years that cerebral organization may be at least somewhat flexible. For example, it has been known since the late 1800s that damage to the left hemisphere of children does not necessarily lead to permanent language deficits. As early as 1877, Barlow reported on a young boy who had a serial lesion of the left and then right frontal lobe. The boy was initially aphasic after a left-side lesion but recovered, only to become aphasic again after a right-side lesion. Even Broca was aware that children might not be so dependent on the left frontal operculum and wrote,

_I am convinced that a lesion of the left third frontal convolution, apt to produce lasting aphemia [aphasia] in an adult, will not prevent a small child from learning to talk_ (Finger & Almli, 1988, p. 122).

More recent research has shown not only that Broca was correct, but it has provided an explanation for how the brain is able to accomplish this. For example, Rasmussen and Milner (1977) showed that infants with unilateral injury to the anterior speech zone shift language to the opposite hemisphere (e.g., Buckner & Petersen, 2000; Kinsbourne, 1971; Vallar, 1990). Thus, it appears that at least some functions can show compensation by recruiting the intact, opposite hemisphere. But what about the possibility of the residual regions in the injured hemisphere showing some form of compensatory change? Although this is apparently less common, there is accumulating evidence that some degree of functional compensation is possible from the activation of perilesion regions of the injured hemisphere, both in patients and laboratory animals (e.g., Glees & Cole, 1950; Jenkins & Merzenich, 1987). Furthermore, computer modeling has shown the possibility of functional compensation in the cortical response to focal damage (Reggia et al., 2000).

In sum, although there is little doubt that there is considerable localization of function in the cerebral cortex, there has been a rediscovery of the ideas that the brain may be flexible after an injury (for a historical review see Benton & Tranel, 2000). With the recognition that some form of functional compensation is possible after cerebral injury, we are left with two fundamental questions. First, what are the neural mechanisms underlying the observed compensatory changes? Second, is it possible to enhance these changes and thus potentiate recovery? These questions have guided our research program and will be the focus of the remainder of this article.

**BACKGROUND AND ASSUMPTIONS**

As we begin, we must first consider several assumptions that underlie our thinking about brain structure and function. First, it is assumed that the structural properties of neurons, such as the amount of dendritic space or the number of synapses, reflect their function. It follows that changes in the structure of neurons will reflect changes in the function of neurons and, ultimately, behavior. Second, it is assumed that many, and perhaps most, gross neuronal changes will be visible using light microscopy and appropriate histological stains. It is generally assumed in the literature that evidence of change is most likely to be found at the synapse and that synaptic changes can be measured by the analysis of either pre- or postsynaptic structure. Although synapses can only be visualized using electron microscopic methods, it is possible to infer the presence of synapses by the presence of either axonal terminals or dendritic space. In our studies, we have chosen to use an adaptation of the Golgi technique. A major advantage of the Golgi technique is that a small
percentage of neurons (1% to 5%) are stained and these neurons are stained completely. It is thus possible to draw the individual neurons and to quantify the amount of dendritic space available, as well as the location and density of dendritic spines. The latter measures are used because they can be taken as estimates first of the total space for synapses (i.e., dendritic length) and of the density of excitatory synapses (i.e., spine density). It is estimated that about 95% of excitatory synapses are located on dendrites and most of those are found on spines (e.g., Buell & Coleman, 1985).

Third, it is assumed that changes in neuronal structure reflect changes in connectivity. These changes are unlikely to involve novel connections from regions that were not previously connected but rather an enhancement or deterioration of existing connections. Nicoll and Blakemore (1993) estimated that roughly 70% of the excitatory synapses on any layer II/III pyramidal cells are derived from pyramidal cells in the near vicinity. It is reasonable to predict, therefore, that most changes in cortical connectivity result from changes in connections with neighboring neurons.

Fourth, it is assumed that most recovery of function will be mediated by cortical circuitry. Decorticated rats show virtually no functional recovery, even if the decortication is achieved shortly after birth (e.g., Kolb & Whishaw, 1981). Furthermore, anatomical studies have shown little or no evidence of reorganization of connections in decorticated rats (e.g., Kolb et al., 1984). Finally, rats with hemidecortication early in life do show functional compensation, but this is correlated with changes in the dendritic structure and connections of neurons in the intact hemisphere rather than in subcortical structures (Kolb et al., 1992).

Fifth, it is assumed that functional improvement after cortical injury is most likely to represent compensation rather than actual recovery of the original behavior. This assumption is consistent with the concept of functional localization noted earlier. Nevertheless, from a practical clinical perspective it matters little whether the brain is performing a behavioral function in the same way that it did prior to injury. The real goal is to stimulate the brain to produce behaviors that will allow a person to resume at least a partially normal lifestyle.

CORTICAL PLASTICITY AND FUNCTIONAL COMPENSATION AFTER FRONTAL LOBE INJURY

There is considerable evidence that rats with neocortical lesions do show spontaneous return of some lost behaviors if the lesion is small. For example, Whishaw (2000) has shown in an elegant series of studies that rats with small motor cortex lesions are initially severely impaired in skilled forelimb reaching tasks but over a 15-day period they show significant improvement (see also Rowntree & Kolb, 1997). Animals with larger lesions show far less return of function, however, and when it occurs, it may take many weeks or months to stabilize (e.g., Kolb et al., in press). A similar result can be seen in rats with bilateral removal of the medial frontal cortex. For example, Kolb (1995) showed that there is improvement in maze performance but not skilled motor behavior, after bilateral medial frontal lesions in rats. If the lesions are made very large, however, there is no compensation even for the spatial maze performance (e.g., Kolb & Gibb, 1991). Subsequent Golgi analyses have revealed that if there is functional improvement, there is an initial decrease in dendritic arborization in perilesion regions (i.e., pyramidal neurons in adjacent sensorimotor cortex), and this decrease is later followed by an increase that is temporally locked to the functional improvement. (A parallel result is seen after lesions in the hippocampal system as
well [Steward, 1991]). Thus, it seems likely that the observed recovery is supported, at least in part, by the reorganization of intrinsic cortical circuits. We hasten to point out, however, that this reorganization is insufficient to influence recovery of skilled motor sequences or of species typical behaviors (e.g., food hoarding, nest building, social behavior). Nevertheless, the brain-behavior correlation with at least some functional compensation is encouraging and suggests that treatments that increase the dendritic changes might also enhance functional improvement.

One circumstance under which there is a better functional outcome occurs when cortical injury occurs at particular times during development. Perhaps the best known studies on the effects of early brain injury on behavior were those performed by Margaret Kennard in the late 1930s (e.g., Kennard, 1942). She made unilateral motor cortex lesions in infant and adult monkeys. The behavioral impairments in the infant monkeys were milder than those in the adults, which led Kennard to hypothesize that there had been a change in cortical organization in the infants and these changes supported the behavioral recovery. In particular, she hypothesized that if some synapses were removed as a consequence of brain injury, “others would be formed in less usual combinations” and that “it is possible that factors which facilitate cortical organization in the normal young are the same by which reorganization is accomplished in the imperfect cortex after injury” (Kennard, 1942; 239). Kennard’s findings were seductive because they were consistent with the evidence noted above that infants with left hemisphere damage were not aphasic. On the other hand, there were dissenting views that suggested that early brain damage might actually be worse, or at least no better, than later injury (e.g., Hebb, 1947; Goldman, 1974). One clear hypothesis from these studies is that whatever conditions allow substantial functional recovery after infant injury should be associated with one type of synaptic reorganization (presumably reflecting an increase in total synapses), whereas those conditions that do not allow recovery or make the outcome worse should be associated with synaptic loss. In order to test this hypothesis, we removed the frontal cortex of different groups of rats at various ages ranging from embryonic day 18 (the gestation period of a rat is about 22 days), through infancy and adolescence (e.g., Kolb, 1995). The behavioral results can be illustrated by the skilled reaching and spatial navigation performance of rats with removal of the frontal cortex on embryonic day 18 (E18), postnatal day 1 (P1), P5, P10, or P90 (i.e., adult). In the former task, rats are trained to reach through a slot to grasp food (Whishaw, 2000) whereas in the spatial task the rats are trained to find a hidden platform in a swimming pool (Morris, 1981). Figure 1 shows that rats with lesions on day 1 show severe deficits relative to control animals, whereas rats with lesions on day P5 or in adulthood show intermediate deficits, and those with E18 or P10 lesions show no deficit at all. Similar results are also seen when the motor, posterior parietal, posterior cingulate, or occipital cortex are damaged at similar ages (e.g., Kolb et al., 2000; 1987). Subsequent Golgi analysis showed that those groups that show functional restitution also show an increase in dendritic arborization and/or spine density (e.g., Kolb & Gibb, 1993; Kolb et al., 1997) (see Fig. 2).

The results of our developmental studies therefore show three important points.

1. It is the precise developmental age at the time of cortical injury that is important in predicting recovery in the rat. Damage during the period of neurogenesis, which in the rat cortex is from about E12 to E20, appears to be associated with a good functional outcome (see also Hicks & D’Amato, 1961); damage in
the first week of life, which is a time of neural migration and the initiation of synaptic formation, is associated with a dismal outcome; damage in the second week of life, which is a time of maximal astrocyte generation and synapse development, results in an excellent functional outcome; and, damage after 2 weeks leads to progressively more severe chronic behavioral loss. A similar pattern of results can be seen in parallel studies of the effects of cortical lesions in kittens by Villablanca and his colleagues (e.g. Villablanca et al., 1993).

2. Given that recovery is especially poor after injury during the first few days of life, it should be possible to initiate treatments that will improve this dismal outcome. We shall see that there are.

3. The changes in synaptic organization that we have seen most likely reflect a remodeling of intrinsic connectivity of the cortex and do not reflect changes in the organization of cortico-subcortical connections.

In order to examine the possibility that there might also be changes in cortical connectivity with other structures, we used retrograde tracing techniques to map the cortical-cortical, cortical-thalamic, and cortical-fugal pathways after frontal or motor cortex lesions on days 1 or 10. The results were surprising as animals with frontal lesions on day 1 showed massive changes in cortical connectivity but these animals had the worst behavioral outcome (Kolb et al., 2001a; 2001b; Kolb et al., 1994). Furthermore, we showed that the abnormal pathways did not reflect the creation of new connections so much as they reflected a failure of pruning of connections that are normally discarded during development. This was demonstrated by our finding that newborn
animals have extensive aberrant pathways that die off during the first week of life. If the cortex is damaged during this time, however, some of these pathways fail to die off, leaving the animal with abnormal circuitry that is not seen in normally developing animals. Some of this unusual circuitry could prove helpful after an injury, but given that normal animals shed such circuitry, it seems likely that it could prove equally disadvantageous to maintain such circuitry. Indeed, both hypotheses are confirmed. Rats with infant motor cortex lesions do show sparing of some motor skills (Whishaw & Kolb, 1988) but apparently at the price of impairments in other cognitive functions (e.g. Kolb et al., 2000). Subsequent identification of the motor representation in the cortex showed that the motor map had moved into posterior cortex (Kleim et al., unpublished). It therefore seems likely that the presence of abnormal corticofugal pathways after early cortical injury may be as disruptive as it is helpful, a concept that Teuber (1975) referred to as 'crowding'.
TABLE 1
Modification of the effects of frontal cortical injury

| Treatment | Result | Basic reference |
|-----------|--------|-----------------|
| A. Adult injury | | |
| Complex housing after lesion | Functional recovery: reversal of neuronal atrophy | Kolb & Gibb, 1991 |
| NGF | Functional recovery reversal of neuronal atrophy | Kolb et al., 1997 |
| bFGF | Functional recovery | Witt-Lajeunesse & Kolb, unpublished |
| Nicotine | Functional recovery | Brown et al., 2000a; 2000b |
| B. Infant Injury | | |
| Tactile stimulation after P4 lesion | Functional recovery: reversal of neuronal atrophy | Kolb & Gibb, 2001 |
| Complex housing after P1-5 lesion | Functional recovery | Kolb et al., unpublished |
| Prenatal nicotine before P3 lesion | Functional recovery | McKenna et al., 2000 |
| bFGF after P3 lesion | Functional recovery | Kolb et al., 2000 |

Stimulating plasticity and recovery after cortical injury in adults

Rehabilitative programs have been widely used for decades to treat people with cortical injury but to date, few well-controlled clinical studies document either the benefits, if any, from these programs or the conditions under which maximum benefits can be expected. Nonetheless, it is generally assumed that recovery should be stimulated by either some sort of rehabilitative therapy, pharmacotherapy, or a combination. We have undertaken a series of studies in which we systematically examined these three possibilities by investigating the following:

1. the effects of specific rehabilitative training versus more generalized experience;
2. the effects of neurotrophic factors with and without rehabilitative training; and
3. the effects of a psychomotor stimulant (nicotine) (see Table 1).

The results of our studies reveal three basic results.
1. First, placing animals in complex environments stimulates the recovery of motor functions, whereas training animals daily on a skilled motor task is without benefit (e.g. Kolb & Gibb, 1991; Whishaw, 2000; Witt-Lajeunesse & Kolb, unpublished). Consider the following example.
In one study we manipulated postoperative experience of animals with unilateral motor cortex lesions, which produced severe deficits in skilled fore-limb use, by providing one of two different treatments. In the first, the animals were trained daily to reach through bars to obtain food (see Whishaw, 2000, for details). In the second, they were placed for 24 hours a day in complex environments, in which there were novel stimuli and ample opportunity for both sensory and motor stimulation. In both cases, the animals were tested biweekly on a series of motor tasks over a 12-week period. The results showed that whereas animals in the complex environments showed significant functional compensation over the postoperative period, those animals that were trained daily showed no benefit whatsoever (Witt-Lajeunesse & Kolb, unpublished). It is interesting to note here that placing animals in complex environments has been shown to increase the production of neurotrophic factors, such as basic Fibroblast Growth Factor (bFGF), whereas simple training does not appear to have such an action (e.g., Gomez-Pinilla, et al., 1998). Thus, it is possible that behavioral treatments could alter recovery indirectly through their action on the production of neurotrophic factors.

2. Second, the administration of neurotrophic factors stimulated functional improvement. In particular, Nerve Growth Factor (NGF) stimulated partial restitution of motor functions after unilateral motor cortex stroke (Kolb et al., 1997). In contrast, treatment with bFGF did not enhance recovery unless animals also received daily training on a skilled motor task (see Fig. 3). In other words, whereas neither
rehabilitative training nor bFGF worked alone, in combination they produced significant functional recovery.

3. Third, treating animals both pre- and post-injury with the psychomotor stimulant nicotine stimulated recovery of spatial learning after medial frontal and hippocampal lesions, respectively (Brown et al., 2000a,b). Treating animals only post-operatively was less effective, although there was still significant benefit. Pretreatment alone with nicotine was without any benefit. The nicotine results parallel other findings that another psycho-motor stimulant, amphetamine, also has been reported to facilitate functional recovery (e.g. Feeney & Sutton, 1987; Goldstein & Hulsebosch, 1999).

From our Golgi studies summarized earlier, we would predict that the treatments that stimulate functional recovery also stimulate dendritic growth. Although our anatomical analyses are as yet incomplete, we have preliminary evidence that this is indeed the case. We have shown, for example, that housing lesion animals in complex environments produced widespread increases in dendritic arborization of cortical neurons (e.g., Kolb & Gibb, 1991). Similarly, NGF infusion stimulated widespread increases in dendritic arbor and spine density in pyramidal cells in rats with cortical lesions, and this was correlated with functional compensation (Kolb et al., 1997) (see Fig. 4).

Finally, we have shown that repeated injections of nicotine stimulated large changes in dendritic arborization in prefrontal cortex and nucleus accumbens of otherwise normal animals (Brown & Kolb, 2001). We have not yet examined the neurons in nicotine-treated lesion animals, but our prediction is that nicotine stimulates compensatory dendritic growth in animals with cerebral lesions in adulthood.

Fig. 4: Examples of layer V pyramidal cells taken from the motor cortex (Fr2) of a saline-treated sham and lesion rat (left) and an NGF-treated sham and lesion rat (right). The inset illustrates spine density in a typical terminal tuft from the basilar fields. (After Kolb et al., 1997).
Stimulating plasticity and recovery after cortical injury in infants

Because the animal with a cortical lesion in the first days of life is functionally devastated in adulthood and because it shows atrophy of cortical neurons, we anticipated that such animals should benefit the most from therapeutic interventions. Furthermore, given that we knew that the infant brain is particularly plastic after injury around 10 days of age, we reasoned that the brain would be especially responsive to other experiences at this age as well. This proved to be the case. In one series of studies, animals were given frontal or posterior parietal lesions at 4 days of age, following by tactile stimulation until weaning. Tactile stimulation with a small paintbrush for 15 minutes, three times per day, for just 10 days permanently alters the morphological and neurochemical structure of the cortex of normal animals but has even bigger effects on the cortex of an injured brain (Kolb & Gibb, unpublished). Thus, rats with tactile stimulation show an unexpectedly large attenuation of the behavioral deficits of cerebral injury as a result of this rather brief ‘therapy’. In fact, the rats with posterior parietal lesions on day 4 showed substantial recovery of performance in various spatial and motor tasks, such as skilled reaching. This is a stunning reversal of a devastating functional loss normally seen in animals with such injuries at this age. Analysis of the brains showed a reversal of the atrophy of the remaining cortical neurons normally associated with such early lesions. Thus, a treatment that reversed the dendritic atrophy after perinatal lesions also reversed the severe functional disturbance from the early lesion.

In parallel studies, we have placed rats that had cortical lesions in the first week of life in complex environments for 3 months, beginning at the time of weaning or in adulthood. The animals placed in the environments as juveniles showed a dramatic reversal of functional impairments that was correlated with increased cortical thickness (e.g. Kolb & Elliott, 1987). The dramatic improvement in the animals with the earliest injuries carries an important message for it suggests that even the young animal with substantial neural atrophy and behavioral dysfunction is capable of considerable neuroplasticity and functional recovery in response to behavioral therapy. When animals with similar injuries were placed into enriched environments as adults they showed a less impressive reversal of functional losses, although they did show marked reversal of dendritic atrophy (Kolb et al., 2001). The brain thus appears to be capable of considerable environment-mediated modification after early injury, although the timing of the postinjury therapy does appear to make some difference (Table 2). Perhaps the synaptic organization of the remaining brain can be more easily remodeled if the reorganization occurs while the brain is still developing, whereas it is more difficult to remodel a brain with infant injuries once the synaptic organization has stabilized in adulthood.

One reasonable question we might ask is just how complex or enriched environments for rats relate to environmental stimulation for children. In particular, it seems likely that standard laboratory housing for rats is rather sterile compared to the usual environment of feral rats so if we try to generalize to humans we are left wondering how stimulating an environment would have to be in order to induce functional changes in human infants. One way to answer this question is to consider what animals do in the complex environments. They are provided with novel objects to interact with every few days; they get a lot of sensory input and motor activity as they move about the compounds; and, they have considerable social experience as they live in groups of six to eight other animals. The experience is thus perceptually and socially stimulating, motorically demanding, and is
continuous for several weeks or months. Although we do not know which aspects of this experience are the most important, our guess is that all contribute because they stimulate different types of brain activity. Thus, our best guess as we generalize to human infants is that therapies would include perceptual stimulation, including novelty, as well as social interaction and motor activities.

In view of our findings that both neurotrophic factors and nicotine could stimulate functional recovery after cortical injury, we also asked whether such treatments might influence functional recovery after cortical injury in infancy.

In one series of studies, rats were given bilateral frontal lesions on postnatal day 3 and then given daily injections of bFGF for a week (Kolb et al., 2000). This treatment led to a dramatic improvement in functional outcome that was equivalent to that seen in animals placed in complex environments at weaning. In another series of experiments, female rats were implanted with minipumps that subcutaneously infused nicotine throughout their pregnancy. The infants were given frontal lesions on postnatal day 3, but no further treatment with nicotine. Again, there was a significant benefit to nicotine treatment, although in this case it was nicotine that was administered before the cortical injury and, indeed, before birth (McKenna et al., 2000). We have not yet completed our Golgi analyses of the bFGF and nicotine-treated brains, but the prediction is clear: the treated animals are expected to show a reversal of the dendritic atrophy that normally characterizes the brain with cortical injury in the first few days of life.

In sum, the infant-damaged brain is especially responsive to both behavioral and pharmacological treatments that are initiated in infancy. Importantly, in the one study in which behavioral treatment was initiated in adulthood, there was a significantly attenuated functional benefit. This latter result implies that therapeutic programs should be initiated early after cortical injury in infants if they are to be effective in leading to significant functional compensation. Our finding that prenatal nicotine treatment can influence recovery from later brain injury is intriguing and leads us to wonder how other prenatal events might influence functional recovery from cortical injury either in infancy or adulthood and, additionally, whether such events might interact with postnatal treatments.

Stimulating neurogenesis after cortical injury

Although we have emphasized changes in remaining cortical neurons after injury, recent advances in our understanding of the nature of stem cell activity in the postnatal brain (e.g. Gould et al., 1999; Weiss et al., 1998) leads one to question whether it might be possible to stimulate neurogenesis after cortical injury. In the course of studying the effect of restricted lesions of the medial frontal cortex or olfactory bulb, we discovered that, in contrast to lesions elsewhere in the cerebrum, midline telencephalic lesions on postnatal day 7 to 12 led to the spontaneous regeneration of the lost regions, or at least partial regeneration of the lost regions (Fig. 5). Similar injuries either before or after this temporal window did not produce such a result. Analysis of the medial frontal region showed that the area contained newly generated neurons that formed at least some of the normal connections of this region (Kolb et al., 1998). Furthermore, animals with this regrown cortex appeared virtually normal on many, although not all, behavioral measures (Kolb et al., 1997). Additional studies showed that if we removed the regrown tissue, functional recovery was eliminated (Temesvary et al., 1998). Parallel studies found that it was possible to block regeneration of the tissue with prenatal injections of the mitotic marker bromodeoxyuridine (BrdU), and in this case there was no recovery of function (Kolb et al., 1998), a result that implies that the regrown tissue was supporting recovery. Thus, in
the absence of the regrown tissue, either because we blocked the growth or because we removed the tissue, function was lost.

Our findings that neurogenesis could spontaneously occur, at least under special circumstances, following cortical lesions in infancy have led us to ask whether it might be possible to induce neurogenesis in adulthood. Indeed, there are now several reports that stem cell activity is stimulated after cerebral injury in rats (e.g., Altman & Bayer, 1993). We approached this problem by infusing a cocktail of neurotrophic factors (including epidermal growth factor, bFGF, and NGF) into the lateral ventricles of animals given either unilateral or bilateral cortical lesions. The results have been at once both stimulating and disappointing. In particular, we have found that the neurotrophic cocktail does stimulate massive generation of undifferentiated cells that migrate to the lesion site but, to our chagrin, these cells fail to differentiate and ultimately die (Kolb et al., 1998). Furthermore, behavioral studies have found no evidence
of any functional benefit. Thus, although it is clear that it is possible to mobilize the brain to generate new cells, we have not yet been able to stimulate the brain to generate functioning neurons. Note however, that our earlier studies showed that a combination of neurotrophic factors and behavioral therapy was more effective in stimulating functional recovery than either treatment alone, so it is possible that experience may interact with the neurotrophic treatments to encourage cell differentiation and functional improvement. This remains to be seen.

CONCLUSIONS

One of the most intriguing questions in behavioral neuroscience concerns the manner in which the brain, and especially the neocortex, can modify its structure and ultimately its function throughout one's lifetime, and in particular in response to an injury. As the preceding review has suggested, the injured cortex can be modified by various treatments, and this modification is modulated by various factors. Several basic conclusions can be extracted.

- Experience alters the synaptic organization of the cortex. It is possible to visualize with a light microscope the morphological changes in the cortex that reflect synaptic modification. The neuronal changes can be quantified as increases or decreases in the amount of dendritic arborization, as well as in the density of dendritic spines.
- There can be compensatory plastic changes in the brain following brain injury that are similar in kind to those observed when animals learn from experience. These injury-induced changes are also age-dependent and are thought to reflect the age-related recovery observed after brain injury at different times throughout the lifetime. For example, animals with cortical injuries in the first week of life show decreased dendritic arborization that is associated with a poor functional outcome. In contrast, animals with cortical injuries in the second week of life show increased dendritic arborization and a good functional outcome.
- Changes in synaptic organization are correlated with changes in behavior. Animals with extensive dendritic growth relative to untreated animals show facilitated performance on many types of behavioral measures, especially measures of cognitive activity. Animals with dendritic atrophy show severe behavioral impairments and little functional recovery.
- The similarity between the plastic changes in the brain in response to injury or experience suggests that there may be basic mechanisms of synaptic change in the mammalian cortex that are used in many forms of synaptic plasticity. This is an encouraging possibility, for it allows hope that we will be able to improve recovery from cerebral injury by taking advantage of the innate mechanisms that the brain uses for other forms of plasticity.
- Injury-induced changes in cortical structure are modified by experience. Furthermore, brains that show the least change in response to a cortical injury appear to be the most responsive to experience. For instance, animals with neonatal brain injuries show a poor functional outcome and an atrophy of cortical neurons, but these animals show dramatic functional recovery and marked synaptic growth in response to environmental manipulations. This is encouraging for it suggests that behavioral therapies should be especially helpful in reversing some of the devastating consequences of brain damage in the latter periods of prenatal development in human infants.
- Not all experiences are equally effective in changing behavior after cortical injury. Training
animals on specific motor patterns, such as skilled reaching, is not effective in facilitating recovery. In contrast, placing animals in complex environments in which they have varied social, sensory, and motor experiences, is effective in stimulating recovery.

- Neurotrophic factors influence plastic changes in the cortex. More importantly in the current context, the production of neurotrophins is influenced by experience. Thus, one reason why behavioral therapies may be effective in changing the brain is that the behavioral changes brought about by specific experiences actually stimulate the brain to produce neurotrophins. This link between behavior, neurotrophins, and plasticity requires further study, especially in the context of designing therapies for restitution of function.

- Psychomotor stimulants, such as nicotine, are effective in stimulating functional recovery after cortical injury, either in infancy or in adulthood. Nicotine is most effective when it is administered both before and after injury, although there is a beneficial effect of just postinjury administration.

- It is possible to generate new neurons after cortical injury and, at least in infancy, these neurons are capable of supporting functional recovery. It remains to be seen if new neurons can function after cortical injury in adult animals.

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