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### **SECTION 1**

Principles of cognitive neurorehabilitation

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### **Introduction to Section 1**

#### Gordon Winocur

Cognitive neurorehabilitation is predicated on two fundamental principles: (1) that the brain has within it an inherent plasticity that enables it to recover from damage that gives rise to cognitive impairment, and (2) that individuals have the capacity to make behavioral adjustments necessitated by changing circumstances. At the same time, the development of the field rests on recognition of and adherence to other essential principles. Foremost are those principles that guide the conduct and assessment of research that ultimately fuels the development of successful rehabilitation programs. Too often, these principles receive insufficient attention and, as a result, the foundations on which treatment programs rest can be a little shaky. It is appropriate then that the first section of this book, which is intended to be comprehensive and broader in scope than the first edition, is devoted to some of the over-riding principles that are central to cognitive neurorehabilitation, and to its continued development as a form of clinical practice within rehabilitation medicine.

The first two chapters cover neuroplasticity and the brain's potential for reorganization in ways that make optimal use of residual resources in promoting cognitive recovery. Kolb and Gibb review principles that govern brain plasticity and factors that affect its expression following regional damage. In describing some of the cellular and physiological mechanisms underlying plasticity, Kolb and Gibb make the important point that the level of analysis must depend on the questions being asked. This has important implications for cognitive

neurorehabilitation. For example, an understanding of alterations at the neuronal or neurotransmitter level are critical to the development of pharmacological therapies, whereas an appreciation of reorganisation of neural circuitry through neuroimaging, may be more relevant to designing behavioral therapies that invoke the use of appropriate strategies. The chapter broadly reviews research that demonstrates that brain plasticity is influenced by a wide range of factors that include age, etiology of damage, and type of experiences. Kolb and Gibb end with the interesting observation that brain plasticity may not always work in the patient's interest and cite, as an example, counter-productive changes that occur in relation to developmental disorders. This is important for cognitive neurorehabilitation because brain-damaged individuals often develop maladaptive responses and their neurophysiological imprint must be overcome for rehabilitation to proceed successfully.

In their chapter, Hunter and McEwen focus on the relationship between adverse life experiences and chronic dysregulation of the neuroendocrine axis which, combined, increase the risk of various diseases (e.g., type 2 diabetes, stroke), that include cognitive impairment as part of their symptomatology. Attention is directed to stress-induced abnormal release of adrenal steroids (e.g., cortisol) and their toxic effects on brain regions such as the hippocampus. In contrast, there may be benefits from treatment with gonadal steroids (e.g., androgens, estrogens). Hunter and McEwen acknowledge the controversy in this area but also remind us of the considerable evidence linking such treatment to

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positive effects on dendritic growth and synaptic function in the hippocampus. Under some circumstances, the authors suggest, this form of cognitive therapy may be warranted. Hunter and McEwen assess the potential for pharmacologic treatment of cognitive problems that are related to metabolic disorders and, in line with other contributors (e.g., Kolb and Gibb; Dawson and Winocur; Dixon, Garrett and Bäckman) stress the importance of combining such interventions with a healthy lifestyle, physical exercise, and a psychosocial environment that is both stimulating and supportive.

Consistent with the brain's capacity for reorganization is the principle of compensation, whereby cognitive abilities are recovered through a combination of adaptive changes in brain function and behavior. Dixon et al. provide a lucid account of conditions that give rise to compensatory approaches and the mechanisms by which compensation is mediated. On a cautionary note, they point out that, because of constraints and diminished resources resulting from damage to functional systems, successful compensation in one area may entail losses in other areas. Because these losses may have negative consequences, they must be taken into account in rehabilitation programs aimed at promoting compensation. As well, Dixon et al. emphasize the important interplay between compensation that occurs between neural and behavioral levels, and the need for them to influence each other if optimal benefits are to be achieved. The authors cite several studies of behavioral training-induced cognitive improvements and, importantly, provide related evidence that such improvements are accompanied by stable and long-lasting biological changes. Dixon et al. further underscore the importance of compensation to rehabilitation practice by arguing for the universality of the process and its relevance to different types of injury and abnormality.

Ultimately, progress in neurorehabilitation practice will flow from quality research and this is the focus of Rodriguez and Rothi's thought-provoking chapter. The authors acknowledge the randomized control trial (RCT) as the gold standard in rehabilitation research. At the same time, they argue that exploratory studies have a rightful place in the investigative process and, properly conducted, can even help to shape RCTs, rendering them more informative in the larger picture. A substantial portion of the chapter is devoted to Rothi's multistage model for conducting neurorehabilitation research. According to the model, in the initial discovery stage, clear hypotheses are proposed and evaluated at the basic science level. This stage might involve animal models or normal humans but, in the second, translation stage, the research is extended to the targeted populations. The third, innovation, stage entails exploratory clinical study using the principles established in stages 1 and 2. At this point, a treatment should be ready for a phase I clinical trial (evaluation/formalization stage), in which optimal conditions are created for demonstrating a treatment effect. A positive outcome would lead to a more rigorous phase II trial (efficacy stage) that would take into account effect sizes and possibly involve multiple sites. A phase III clinical trial (effectiveness stage) would then be conducted to establish the full potential of the treatment program. Finally, it is necessary to consider issues related to delivery of the program and its impact, taking into account practical considerations such as costs and benefits.

Cicerone takes on a similar cause in his probing chapter. He too acknowledges the important advances made through RCTs and, like Rodriguez and Rothi, argues that there are important benefits to be derived from other approaches. He suggests, for example, that observational studies may be even more useful than RCTS in certain situations - such as evaluating behaviors that have a relatively low rate of occurrence, or in assessing naturally occurring services. Cicerone's position is that we need more good RCTs in neurorehabilitation research and, to achieve that, investigators must strive to avoid design pitfalls which occur all too frequently. As examples, he cites unsuccessful randomization, failure to employ double-blind designs and maskedoutcome assignments, and inadequate long-term follow-up. Moreover, it is important to be cognizant of the need to report fully all relevant procedures, provide information on treatment compliance and

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> treatment integrity, and, in the interest of reproducibility, to use accessible outcome measures. The chapters by Cicerone and Rodriguez and Rothi contain important messages and provide a valuable road-map for conducting scientifically rigorous rehabilitation research that ultimately will lead to improved treatment programs and better outcomes.

> As Kolb and Gibb point out in their chapter, a critical consideration in evaluating cognitive neurorehabilitation programs is in the selection of outcome measures and this is the focus of Lincoln and Nair's chapter. They begin by emphasizing the need to distinguish between impairments induced by brain damage and changes in functional performance - neurorehabilitation may be effective in improving performance without necessarily affecting the fundamental impairment. If assessment focused exclusively on cognitive impairment (as measured by standard cognitive tests), the benefits of the program may not be fully appreciated or even detected. In selecting cognitive instruments for measuring outcome, Lincoln and Nair emphasize established criteria (e.g., reliability, validity, sensitivity to program-induced change and practicality) and, in addition, remind us that not all tests are well suited for assessing outcome. Some are better suited as screening or diagnostic instruments. They go on to review strengths and weaknesses of assessment techniques in various cognitive domains (e.g., attention, memory, executive function). The authors also underscore the need for ecologically valid tests but caution that sometimes such tests (e.g., the Rivermead Behavioral Memory Test) only indirectly measure performance in everyday activities. Finally, they point out that, although participation in a wide range of activities in a social context is the ultimate aim of cognitive neurorehabilitation, few measures of participation rate actually exist, and that progress in this area must be considered a research priority.

In Chapter 3 of this section, Stuss and Binns bring into focus the fundamental principle of behavioral variability, as it applies to cognitive neurorehabilitation. It is well established that cognitively impaired patients can be extremely variable in the expression of their cognitive problems. It follows that variability should be taken into account routinely in assessing recovery or the effects of cognitive neurorehabilitation. Yet, it is not and, as Stuss and Binns point out, to assess outcome in a single snapshot in time, runs the risk of masking benefits or, conversely, giving an exaggerated impression of improvement. Because it is so tempting to mistakenly conclude positive effects following a single assessment, Stuss and Binns label variability as a "silent disorder." Their highly enlightening chapter is particularly informative on intra-individual variability, which typically receives less attention than inter-individual variability. They discuss various ways of measuring intra-individual variability (e.g., between-task scatter; within-task dispersion), as well as mediating factors (e.g., structural - fatigue, rhythmic changes; task demands; personality; age). They also provide insights into possible mechanisms and, in the process, distinguish between frontal lobe-mediated, general control processes, and damage-specific control processes that are said to be regulated by brain regions associated with the functions affected. The chapter ends with a description of individual cases that dramatically make the authors' point that variability is a critical index of cognitive impairment that must be factored into neurorehabilitation programs and treatment assessment. It remains to be seen, of course, whether variability measurement will prove practical in diagnosis and in assessing outcome. Nevertheless, in convincingly showing that increased variability is an inherent part of the pathology associated with cognitive impairment and the recovery process, Stuss and Binns have made a strong case for investigating the possibilities.

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### Principles of neuroplasticity and behavior

Bryan Kolb and Robbin Gibb

#### Introduction

Behavioral neuroscience spent much of the twentieth century seeking the fundamental rules of cerebral organization. One underlying assumption of much of that work was that there is constancy in cerebral organization and function, both between and within mammalian species (e.g., Kaas, 2006). One unexpected principle to emerge, however, was that although there is much constancy in cerebral functioning, there is remarkable variability as well. This variability reflects the brain's capacity to alter its structure and function in reaction to environmental diversity, thus reflecting a capacity that is often referred to as brain plasticity. Although this term is now commonly used in psychology and neuroscience, it is not easily defined and is used to refer to changes at many levels in the nervous system ranging from molecular events, such as changes in gene expression, to behavior (e.g., Shaw & McEachern, 2001). The relationship between molecular or cellular changes and behavior is by no means clear and is plagued by the problems inherent in inferring causation from correlation. Nonetheless, we believe that it is possible to identify some general principles of brain plasticity and behavior. As we do so we will attempt to link these principles to potential clinical implications.

#### Assumptions underlying brain plasticity

As we consider the principles of brain plasticity, we need to consider five underlying assumptions that will color our perspective.

#### Brain plasticity takes advantage of a basic, but flexible, blueprint for cerebral organization that is formed during development

The process of brain development is a remarkable feat of nature. Billions of neurons and glia must be generated, they must migrate to their correct locations, and they must form neuronal networks that can underlie functions that range from as simple as postural reflexes to complex thought. Although a complete genetic blueprint for neuronal organization might be possible for a simple creature like the nematode Caenorhabditis elegans, which has a total of 302 neurons, it is not remotely possible for the mammalian brain to have a specific blueprint (Katz, 2007). The best that nature can be expected to do is to produce a rough blueprint of cerebral organization that must be shaped by experience in order for animals to exploit specific ecologies, including cultures. The disadvantage of such flexibility is that it is possible to make errors, but this problem is certainly outweighed by the advantage of having a brain that can learn complex motor or perceptual skills that could scarcely have been anticipated by evolution thousands or even millions of years before.

#### Cerebral functions are both localized and distributed

One of the great issues in the history of brain research relates to whether functions are discretely localized in the brain (for a review, see Kolb & Whishaw, 2001). The resolution to this debate was important because the degree of localization of

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> function places constraints on the potential extent of functional plasticity. The more distributed a function, the greater the likelihood that the neural networks underlying the function will be flexible after a brain injury. As we enter the twenty-first century it is clear that functions are at once localized and distributed. Consider language. Although there are discrete language zones in the cortex, language is much more distributed across the cortex than would have been expected from the classical neurologists (e.g., Geschwind, 1972). But there are limits to distributed functions, especially in the sensory systems. For example, information coming to the occipital lobe travels from the eye to subcortical areas, then to Visual area 1 (V1) where it is processed, and then is sent on to other visual regions such as V2 and on to V3 etc. If V1 is only partially damaged, V2 will still receive some input and can function, albeit not normally. Further, after partial damage, neural networks in V1 and V2 could reorganise and possibly facilitate some type of functional improvement. But if V1 is completely (or substantially) damaged, downstream visual areas, such as V2, will not be provided with appropriate inputs and no amount of reorganization in V2 could generate functional recovery. The partial localization of functions thus places significant constraints upon plasticity and recovery of function.

## Changes in the brain can be shown at many levels of analysis

Although it is ultimately the activity of neuronal networks that controls behavior, and thus changes in neuronal network activity that are responsible for behavioral change, there are many ways to examine changes in the activity of networks. Changes may be inferred from global measures of brain activity, such as in the various forms of *in vivo* imaging, but such changes are far removed from the molecular processes that drive them. Changes in the activity of networks likely reflect changes at the synapse but changes in synaptic activity must result from more molecular changes such as modifications in channels, gene expression, and so on. The problem in

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studying brain plasticity is to choose a surrogate marker that best suits the question being asked. Changes in potassium channels may be perfect for studying presynaptic changes at specific synapses that might be related to simple learning in invertebrates (e.g., Kandel, 1979; Lukowiak *et al.*, 2003; Roberts & Glanzman, 2003) but are impractical for understanding sex differences in language processing. The latter might best be studied by *in vivo* imaging or postmortem analysis of cell morphology (e.g., Jacobs *et al.*, 1993). Neither level of analysis is "correct." The appropriate level must be suited for the research question at hand.

One convenient surrogate for synaptic change in laboratory studies of brain and behavior is dendritic morphology. In this type of study entire neurons are stained with a heavy metal (gold, silver or mercury) and the dendritic space is calculated (Figure 1.1). It is assumed that by knowing the space available for



**Figure 1.1.** Example of a Golgi-Cox stained pyramidal cell from layer III of the parietal cortex of the rat. A. Higher power magnification showing spines on an apical branch. B. Higher power magnification showing spines on a basilar branch. (Photograph courtesy of Grazyna Gorny.)

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synapses it is possible to infer associations between synaptic organization and behavior - notwithstanding the problems inherent in correlational studies discussed below. The studies of Jacobs and Scheibel (Jacobs et al., 1993; Jacobs & Scheibel, 1993) provide a good example. These researchers examined the dendritic morphology of pyramidal neurons in postmortem brains of people whose educational and employment history was known. Comparison of synapse numbers in the posterior speech zone of people with university education, high-school education, or less than high-school education showed that there were progressively more synapses on the neurons from brains with more education. The study cannot tell us why this correlation is present but it tells us that there is some relationship between experience and synaptic organization.

#### To be functionally meaningful, changes reflecting brain plasticity must persist for at least a few days

Changes in neuronal activity related to brain plasticity may be of limited duration, perhaps in the order of seconds or milliseconds. While such changes are interesting in their own right, we are focusing our attention on longer-lasting changes that persist for at least a few days. This is a practical assumption as we think about how experiences might be related to chronic behavioral changes seen after brain injury or with addiction.

#### Correlation is not a four-letter word

By its very nature, behavioral neuroscience searches for neuronal correlates of behavior. Some of these changes are directly associated with behavior but others are more ambiguous. Consider an example. If an individual is given a psychoactive drug we may see an obvious acute behavioral change such as increased motor activity. If the drug is taken repeatedly, we may see that there is an escalating increase in the drug-dependent hyperactivity, a phenomenon referred to as *drug-induced behavioral sensitisation*. If we were to look for changes in the brain

that were related to the observed sensitization we might find a change in synapse number in some discrete brain region such as the nucleus accumbens (NAcc). Both the behavioral change and the synaptic change are correlates of the drug administration. But what is the relationship between the behavioral and synaptic change? We can conclude that the drug caused the behavioral change but it is less clear that the drug directly caused the neuronal change. Perhaps the behavioral change caused the neuronal change or maybe both were related to some other change in the brain. Thus, a common criticism of studies trying to link neuronal changes to behavior is that "they are only correlates." This is true but it is hardly a reason to dismiss such studies. The task is to try to break the correlation by showing that one change can occur without the other. The presence of such evidence would disconfirm causality but, unfortunately, the failure to break the correlation is not proof of causation. Ultimately the proof would be in showing how the synaptic changes arose, which would presumably involve molecular analysis such as a change in gene transcription. For many studies this would be an extremely difficult challenge and often impractical. It is our view that once we understand the "rules" that govern neuronal and behavioral change, we will be better able to look for molecular changes. Furthermore, we argue that a certain level of ambiguity in the degree of causation is perfectly justifiable at this stage of our knowledge. Understanding the precise mechanism whereby the synaptic changes might occur is not necessary to proceed with further studies aimed at improving functional outcome.

#### Principles of brain plasticity

Although it is presumptuous to try to identify basic principles of brain plasticity when so much is still unknown, we believe that the progress over the past decade allows us to begin to identify some of the rules underlying brain plasticity. These principles should be seen as a work in progress that will

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undoubtedly be expanded and further demonstrated over the next decade.

### When the brain changes, this is reflected in behavioral change

The primary function of the brain is to produce behavior but behavior is not constant. We learn and remember, we create new thoughts or images, and we change throughout our lifetime. All of these processes require changes in neural networks. It follows that whenever neural networks change, behavior, including mental behavior, will also change. A corollary of this principle is that in order to change behavior we must change the brain. This latter idea is especially important as we search for treatments for brain injuries or diseases.

### Plasticity is found in all nervous systems and the principles are conserved

Even the simplest animals, such as the nematode C. elegans, can show simple learning that is correlated with neuronal plasticity (e.g., Rose & Rankin, 2001). Similarly, there is now an extensive literature showing neuronal and other changes in invertebrates such as sea snail Aplysia during simple learning, including associative learning. Furthermore, it now has become clear that both simple and complex nervous systems show both pre- and postsynaptic changes and that the changes are remarkably similar (e.g., Rose & Rankin, 2001). There is reason to believe, for example, that there are NMDA-like changes in learning in both mammals and invertebrates (e.g., Roberts & Glanzman, 2003). The details of the postsynaptic second messengers may differ in simple and complex systems but the general principles appear to be conserved across both simple and complex animals.

## The brain is altered by a wide range of experiences

Virtually every experience has the potential to alter the brain, at least briefly. It now has been shown that a wide variety of experiences can also produce **Table 1.1.** Factors affecting the synaptic organization of the normal brain

Factor	Reference
Sensory and motor experience	Greenough & Chang, 1989
Task learning	Greenough & Chang, 1989
Gonadal hormones and stress hormones	Stewart & Kolb, 1988
Psychoactive drugs (e.g., stimulants, THC)	Robinson & Kolb, 2004
Neurotrophic factors (e.g., NGF, bFGF)	Kolb <i>et al.</i> , 1997
Natural rewards (e.g., social interaction, sex)	Fiorino & Kolb, 2003
Aging	Kramer <i>et al.</i> , 2004
Stress	McEwen, 2005
Anti-inflammatories (e.g., COX-2 inhibitors)	Silasi & Kolb, 2007
Diet (e.g., choline)	Meck & Williams, 2003
Electrical stimulation: kindling	Teskey <i>et al.</i> , 2001
Long-term potentiation	Ivanco <i>et al.</i> , 2000
Direct cortical stimulation	Teskey <i>et al.</i> , 2004

enduring changes, ranging from general sensorymotor experience to psychoactive drugs to electrical brain stimulation (see Table 1.1). The bulk of these studies have used morphological techniques such as electron microscopy or Golgi-like stains and have shown that experience-dependent changes can be seen in every species of animals tested, ranging from fruit flies and bees to rats, cats and monkeys (for a review see Kolb & Whishaw, 1998). Consider a few examples.

When animals are placed in complex environments rather than simple laboratory cages, within 30 days there is about a 5% increase in brain weight and cortical thickness, an increase in cortical acetylcholine and neurotrophic factors (e.g., nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), fibroblast growth factor-2 (FGF-2)), as well as changes in physiological properties of neurons such as those measured in studies of

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long-term potentiation (LTP) (for a review see Kolb & Whishaw, 1998). Although most studies have focused on neocortical changes, similar changes can also be seen in hippocampus and striatum (e.g., Comery *et al.*, 1996; Juraska, 1990). The anatomical and physiological changes are associated with improved performance on tests of both motor and cognitive behaviors and although the data are correlational, it is generally assumed that the morphological changes are responsible for the facilitation in behavior.

Experience-dependent changes in the brain do not require procedures as intense as complex housing, however. Increased social experience selectively increases synapses in the orbital frontal cortex (Fiorino & Kolb, 2003; Hamilton et al., 2003). We have also seen that tactile stimulation either in infancy or adulthood alters cells in sensorimotor cortex (e.g., Gibb & Kolb, submitted a,b). This latter treatment has also been used in animals with cortical injuries to stimulate dendritic growth and facilitate functional recovery. Although there is little evidence that exercise can enhance plasticity in the normal brain, there is growing evidence that it can facilitate plastic changes in the injured lab animal and human brain (e.g., Gibb et al., 2005; Kramer et al., 2006).

A final example can be seen in the effects of psychoactive drugs. Robinson & Kolb (1999a) showed that repeated doses of amphetamine or cocaine given to rats produced a persisting increase in dendritic length and spine density localized to the medial prefrontal cortex (mPFC) and NAcc but not to adjacent sensorimotor cortical regions. It now appears that repeated doses of all psychoactive drugs, including prescription drugs, change neuronal morphology. The details of drug-induced morphological changes vary with the drug but the general principle is that psychoactive drugs alter neuronal morphology in the cerebrum and this can be seen both in dendritic measures as well as in a variety of more molecular measures (for a review, see Hyman et al., 2006). Once again, the relationship between the behavioral changes, such as drug-induced behavioral sensitization, and the altered neuronal networks has yet to be proven but there is little doubt that the chronic effects of drug use are not neutral to cerebral functioning. The ability of drugs to alter neuronal morphology may be important for rehabilitation because drugs can be combined with behavioral treatments such as rehabilitation therapy, including cognitive therapy (e.g., Gonzalez *et al.*, 2006).

Taken together the examples described above illustrate the power of experience in modulating cerebral networks and in facilitating remodeling stimulated by behavioral therapies. Although experience is likely more effective in remodeling neural networks as they are repairing after injury, improvement still can occur late after injury (e.g., Hodics *et al.*, 2006). Psychomotor stimulants may provide a powerful way of reinstigating cerebral plasticity late after injury to facilitate the effectiveness of behavioral therapies.

#### Plastic changes are age-specific

When weanling, adult or senescent rats were placed in a complex environment, we had anticipated that we would find larger changes in the younger animals but to our surprise, we found a qualitative difference in the neuronal response to the same experience. Thus, whereas rats at all ages showed an increase in dendritic length and branching in neocortical pyramidal cells after complex housing, rats placed in the environments as infants showed a decrease in spine density whereas young adult or senescent rats showed an increase in spine density (Kolb et al., 2003a). A similar drop in spine density was found in later studies in which newborn rats were given tactile stimulation with a soft brush for 15 min, three times daily over the first 10 days of life (Kolb & Gibb, submitted).

The obvious question is whether the behavioral effects to the complex housing are the same depending upon the age at experience. Our early results suggest that there is an advantage in both cognitive and motor tasks and that it does not matter when the experience occurred. There are clearly different ways to organize neuronal networks to

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enhance both motor and cognitive behaviors. This point is important as we consider treatments for brain dysfunction – there may be many ways to facilitate recovery.

# Early events, including prenatal events, can influence the brain throughout life

Our finding that early postnatal experiences could alter neuronal organization led us to ask if prenatal experiences might also alter cerebral organization. In one study pregnant dams were placed in complex environments for 8 hours a day prior to their pregnancy and then throughout the 3 week gestation. (In different studies the dams were in the environments during the day or night but it made no difference.) Analysis of the adult brains of their infants showed a decrease in dendritic length and an increase in spine density in adulthood (Gibb et al., submitted). We were surprised both that there was a large effect of prenatal experience and that it was qualitatively different than experience either in the juvenile period or in adulthood. More recently we have shown that a variety of *prenatal* experiences alter brain organisation in adulthood including prenatal tactile stimulation (i.e., stimulation of the pregnant dam), exercise during pregnancy, prenatal stress and psychoactive drugs. All of these experiences also chronically alter motor and cognitive functions, with the precise effect varying with the different experiences (for a review see Kolb et al., in press).

Although we do not know how these *prenatal* changes might influence the effect of *postnatal* experiences, it is clear that prenatal experiences produce chronic effects on brain organization and behavior. One is reminded here of the idea of cognitive (or neural) reserve as being key factors in the onset of dementias (e.g., Stern, 2006). Might early life events influence cognitive reserve in adulthood or senescence?

#### Plastic changes are area dependent

Although we are tempted to expect plastic changes in neuronal networks to be fairly general, it is becoming

clear that many experience-dependent changes are highly specific. The clearest examples can be seen in neuropsychological studies in which animals are trained on cognitive or motor tasks. For example, rats trained on a visuospatial task show specific changes in visual cortex whereas rats trained on motor tasks show specific changes in motor cortex (e.g., Greenough & Chang, 1989; Kolb & Cioe, submitted; Withers & Greenough, 1989). Such taskdependent specific changes are reasonable in view of the relative localization of functions in the cortex. But not all area-dependent changes are so easily predicted. Consider two examples.

We noted above that the effect of psychoactive drugs appeared to be selective to regions that receive dopaminergic innervation. We therefore were surprised to find that the orbitofrontal cortex (OFC), another region that receives dopaminergic innervation, showed drug-induced changes that are opposite to those in mPFC and NAcc (Robinson & Kolb, 2004). Thus, whereas psychomotor stimulants increased dendritic length and spine density in the mPFC, they decreased the same measures in the OFC. The contrasting effects of these drugs on the two prefrontal regions are puzzling given the similarity in thalamic and other connections of the two regions (e.g., Uylings et al., 2003). Curiously, there also are differential effects of gonadal hormones on the two prefrontal regions as well: mPFC neurons have more synaptic space in males whereas OFC neurons have more space in females (Kolb & Stewart, 1991). Although we do not yet know what such differences mean behaviorally, there can be little doubt that the differential response of two such similar cortical regions to drugs and hormones must be important in understanding their functions.

#### Plastic changes are time-dependent

There is growing evidence that plastic changes are not constant and can change over time. The clearest example comes from drug studies. For example, although there are large increases in spine density and dendritic length 2 weeks after cessation of cocaine administration, these changes slowly disappear over a