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Searching for the principles of brain plasticity and behavior

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ABSTRACT

An important development in behavioral neuroscience in the past 25 years has been the demonstration that the brain is far more flexible in structure and function than was previously believed. Studies of laboratory animals have provided an important tool for understanding the nature of brain plasticity and behavior at many levels ranging from detailed behavioral paradigms, electrophysiology, neuronal morphology, protein chemistry, and epigenetics. Here we seek a synthesis of the multidisciplinary work on brain plasticity and behavior to identify some general principles on how the brain changes in response to a wide range of experiences over the lifetime.

1. Introduction

Although the idea that experience can modify brain structure is not new (e.g., Ramony Cajal, 1928) evidence demonstrating what changes occur and why they occur has really only become available in the past 25 years. There is now an extensive literature correlating neuronal and other changes with behavioral changes in species as diverse as insects and humans. Our goal here is to identify some general principles of brain plasticity and behavior and to summarize the factors that best illustrate the relationship between brain plasticity and behavior in mammals.

2. Assumptions

As we search for the principles of brain plasticity, we will make three fundamental assumptions. First, we assume that changes in the structure or operation of the brain will be correlated with behavioral changes. The primary function of the brain is to produce behavior but behavior is constantly changing. Although minute-to-minute changes in behavior, such as changing one's mind about choices for dinner, likely do not reflect meaningful brain changes, plastic changes related to behavior can be both short-term as well as long-term. For example, some memories are relevant only for the next few minutes whereas others may be important for years (e.g., Tetzlaff, Kolodziejski, Markelic, & Worgotter, 2011). Although the details of what synaptic changes might occur at different time scales are poorly understood, single neurons can show persisting changes in postsynaptic potentials or firing rates that could underlie brief memories. In contrast, long-lasting memories likely result from structural changes such as the growth of new synapses and associated neural networks. Both types of

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plastic changes are associated with behavioral changes but in quite different ways.

Second, changes in the brain can be shown at many levels of analysis as summarized in Table 1. The choice of level will depend upon the question being posed and the species being studied. For example, if a researcher is interested in brain changes associated with skilled motor learning in people, the level might be neural imaging, possibly to identify motor maps. In contrast, if the question is related to motor learning in a laboratory animal, the level could be invasive such as cellular recording or postmortem measures of neuronal morphology. There is no "correct" or "best" level. Studies need to be done at many levels to thoroughly understand brain plasticity and behavior. But we must be wary of being too reductionistic. Understanding the operation of calcium channels may be very important for developing drugs to facilitate recovery from brain injury but is not going to be too helpful in understanding how we generate language.

Third, although correlation does not demonstrate causation, behavioral neuroscience is, by its nature, correlational. Some behavior–brain correlations likely do reflect causation whereas others are more ambiguous. Consider an example. If we give an animal a psychoactive drug, which produces symptoms of Parkinson's disease within hours, the brain changes induced by the drug can be presumed to be the cause of the behavioral changes. But, if we do the same study and measure changes in synaptic organization in the striatum several days later, we cannot be certain what caused what. We can conclude that the drug changed the brain and behavior, but it is less clear that the drug directly caused the neuronal changes in the striatum or that the neuronal changes are related to the behavioral changes. Or, they may both be related to some other change in the brain that was caused by the drug. This ambiguity in causal relationships often leads to the criticism that studying brain plasticity and behavior is really "only studying correlations". This may be true but this is not a reason to dismiss the studies. Given our current general ignorance over the principles of brain plasticity we believe that some level of ambiguity will be inevitable.

3. General principles of plasticity

It is, of course, presumptuous for us to claim to understand the general principles of brain plasticity when so little is known about the fundamental phenomena at play. Nonetheless, we believe that the time is right to reflect on what is known and try to identify some of the "rules". These rules should be seen as a work in progress that hopefully will provide a framework for progress.

Table 1 – Levels of analysis.

1. Behavior
2. Neural imaging
3. Maps – invasive and noninvasive
4. Physiology (e.g., LTP, unit recording)
5. Neuronal morphology
6. Genetics and epigenetics
7. Proteins and other molecules

3.1. *Plasticity is found in all nervous systems and the principles are conserved*

Although most current work on brain plasticity is conducted on mammals, many of the early ideas regarding plasticity came from the study of invertebrates (e.g., Bailey & Kandel, 2008) and other nonmammals, such as birds (e.g., Horn, 2004). We now know that all animals, including very simple ones like *Caenorhabditis elegans*, can show various forms of learning, which is correlated with neuronal plasticity (e.g., Ardiel & Rankin, 2010). This plasticity includes both pre- and postsynaptic changes that are remarkably similar to those observed in animals with much more complex nervous systems. There are certainly differences in the details, such as the nature of gene expression changes and changes in second messengers, but the general principles appear to be conserved across diverse phyla. The conservation of principles allows researchers to use a wide range of models to search for the neural mechanisms of plasticity in humans.

3.2. *The primary form of plasticity is a change in neuronal network organization*

We have noted that plasticity can be studied at many levels, but an overriding principle is that behavioral change is related to specific gain and elimination of synapses within ensembles of connections (e.g., Caroni, Donato, & Muller, 2012). The cause of the synaptic change is ultimately related to gene expression and related molecular events, but it is the synaptic change that is most related to behavior. One common erroneous assumption is that positive behavioral change, such as learning, is related to adding synapses whereas negative behavioral change, such as that related to stress, is related to losing synapses. In fact, most behavioral change is related to both the addition and the subtraction of synapses within a network of neurons. One exception may be the neuronal changes related to dementia, which are likely mostly synaptic loss.

3.3. *There are three general types of plasticity*

Three types of plasticity can be distinguished in the normal brain: experience-expectant, experience-dependent, and experience-independent (Black, Greenough, & Wallace 1997; Shatz, 1992). *Experience-expectant* plasticity largely occurs during development. For different brain systems to develop they require specific types of experience. A good example is the development of ocular dominance columns found in the primary visual cortex. These alternating columns provide a mechanism for the inputs from the left and right eyes to be combined to produce binocular vision. Wiesel and Hubel (1963) showed that if one eye is kept closed after birth in kittens, the open eye expands its territory leading to shrinkage of the column related to the closed eye. When the closed eye is eventually opened, its' vision is compromised.

Experience-independent plasticity is also largely a developmental process. It is impractical for the genome to specify the connectivity of every connection in development. Instead, the brain is designed to produce a rough structure in which there is an overproduction of neurons, and later, connections, that

are sculpted in response to internal and external events. A good example of experience-independent plasticity is the development of the eye-specific layers of the lateral geniculate nucleus (LGN) of the cat (Campbell & Shatz, 1992). Axons arriving from the retina eventually terminate in separate layers in the LGN but they initially also send axonal branches to the layer for the other eye. In order to segregate the layers correctly, the retinal ganglion cells spontaneously fire so as to correlate their firing with nearby cells but independent of those in the other eye. Cells that fire together increase their connections whereas those out of synch weaken their connections and eventually die out. This type of plasticity, which is independent of external sensory input, allows the nervous system more precision in connectivity without requiring overwhelmingly complex genetic instructions.

Finally, *experience-dependent* plasticity reflects changes in the brain that are needed to modify neuronal ensembles that are already present. Experience-dependent plasticity can be seen in a variety of situations such as when animals learn problems (e.g., Greenough & Chang, 1989), when topographic maps expand or shrink in response to experience (e.g., Blake et al., 2002), when animals receive intense environmental manipulations (e.g., Greenough & Chang, 1989), in response to abnormal experiences such as psychoactive drugs (e.g., Robinson & Kolb, 2004) or injury (e.g., Kolb, 1995). These types of experiences both increase and decrease synapse numbers, often in the same animals, but in different brain regions (see below). The key points are that the synaptic changes are all dependent on experiences and they reflect modifications of a basic phenotype shaped by development. It is important to note that although it is often assumed that experience-dependent plasticity largely reflects the addition of synapses, it may be seen both in the addition and/or pruning of synapses.

3.4. *Similar behavioral change can be correlated with different plastic changes*

A variety of experiences, and especially early experiences, have long-lasting effects on later plasticity. For example, complex housing produces wide-spread changes in the brain, which are correlated with enhanced motor and cognitive behaviors (see review by Kolb & Whishaw, 1998). But, the brain changes are not consistent. For example, when rats are placed in complex environments beginning in adulthood, there are increases in spine density throughout sensory and motor cortex (Kolb, Gibb, & Gorny, 2003a, 2003b), but just the opposite happens when the animals are placed in the environments at weaning, namely a decrease in spine density. Yet both experiences enhance performance in skilled reaching tasks. The contrasting neural correlates of behavioral change are even clearer in animals with cerebral lesions. We used postinjury tactile stimulation to facilitate recovery from medial prefrontal lesions in infancy (Kolb & Gibb, 2010). The treatment enhanced motor and cognitive performance in both the control and lesion groups relative to untreated animals. Our expectation was that the synaptic changes would be similar too but they were not. For example, whereas there was an *increase* in spine density in cortical pyramidal neurons in animals with perinatal prefrontal lesions, there was a *decrease* in sham operates. Of course, we do not know if the changed spine density actually had anything to do with the behavioral changes – the behavioral changes may have been related to plastic changes that we did not measure. But, we do know that the same experience had very different effects in the normal and injured brain.

3.5. *Plasticity is age-dependent*

As we noted above, the same complex housing experience can differentially affect synaptic plasticity depending on the age of the experience. Many other examples can be seen in the plastic changes that follow cerebral injury at different ages. If the cerebral cortex of rats is injured in the first few days after birth versus the second week of life there are dramatically different behavioral and anatomical outcomes as summarized in Table 2 (Kolb & Gibb, 2007) (see also parallel effects of early cortical injury in kittens, Villablanca, Hovda, Jackson, & Infante, 1993). Injury from days 1–5 has devastating consequences on behavior, with the effect generally being worse the earlier the injury. In contrast, damage in the second week of life allows remarkable sparing of function: There is nearly normal performance on cognitive tests and partial recovery of motor performance. The good behavioral outcomes from the later injuries is associated with several plastic changes including increased dendritic length and spine density, and in some cases, regeneration of the lost tissue. It is possible to block these plastic changes by pretreating animals with Bromo-deoxy-Uridine (BrdU), a label used to identify dividing cells, at embryonic days 12–14 (Kolb, Peterson & Gibb, 2012). Animals with the BrdU treatment do not show sparing of function, suggesting that the neurogenesis and synaptic changes support the behavioral outcome.

Lesions to other cortical regions including motor cortex, posterior cingulate cortex, visual, and temporal cortex, show similar age-dependent effects on behavior as well as correlated dendritic changes. There is spontaneous regeneration only after posterior cingulate lesions, however (Gonzalez, Gibb, & Kolb, 2002) and the functional recovery following motor, parietal, and temporal lesions is less than that seen

Table 2 – Summary of the effects of medial prefrontal injury at different ages.

Age at injury	Result	Basic reference
P1–6	Small brain, dendritic atrophy Dismal functional outcome	Kolb and Gibb (1990)
P7–12	Dendrite and spine growth Cortical regrowth Functional recovery	Kolb and Gibb (1990) Kolb, Gibb, Gorny, and Whishaw (1998)
P35	Dendritic and spine growth Functional recovery	Nemati and Kolb (2012)
P55	No dendritic or spine growth Poor functional outcome	Nemati and Kolb (2012)
P120	Dendritic atrophy, then regrowth Partial return of function	Kolb (1995)

after the frontal and posterior cingulate lesions. It is possible to stimulate neurogenesis, however, by providing subcutaneous injections of the neurotrophic factor, Fibroblast Growth Factor-2 (FGF-2) following day 10 motor cortex lesions (e.g., Monfils et al., 2006). Similar injections after day 3 lesions are without effect. And, as in the spontaneous regeneration after prefrontal lesions, injections of BrdU on E12 prevent the regeneration and the functional recovery (Monfils et al. 2006).

Age-dependent plasticity is not just related to early cerebral injury. Nemati and Kolb (2010) compared the effects of motor cortex injury at postnatal day 35 and 55. Whereas the rats with lesions on day 35 had significant motor deficits on a battery of motor tasks, rats with day 55, but not day 35, lesions showed nearly complete recovery, which was correlated with dendritic hypertrophy in the pyramidal neurons in the remaining sensorimotor cortex in the day 55 operates.

In contrast to the age-related plasticity after motor cortex lesions at day 35 versus day 55, just the opposite was found for medial frontal lesions: day 35 showed good recovery and dendritic hypertrophy whereas day 55 did not (Nemati & Kolb, 2012). The contrasting effects of motor and prefrontal lesions was quite unexpected and is likely due to differences in plasticity in different regions related to differences in maturation rate during adolescence, although this remains to be proven.

In sum, the brain's response to experience varies with precise age. The rules that govern these age-dependent differences are poorly understood but likely reflect the processes underlying brain development, which is far more prolonged than had previously been appreciated (see Petanjek et al., 2011).

3.6. *Plastic changes are brain-region dependent*

It is not surprising that specific experiences might affect some brain regions and not others but what is unexpected is the finding that an experience can produce qualitative differences in plastic changes in different brain regions in the same animal. For example, when one compares the effects of amphetamine on the medial prefrontal and orbital prefrontal cortex, parietal cortex, nucleus accumbens, CA1 of the hippocampus, and the dentate gyrus in rats the effects are wildly different (Crombag, Gorny, Li, Kolb, & Robinson, 2005). Thus, whereas neurons in the medial prefrontal cortex, nucleus accumbens, and CA1 show increased spine density, neurons in the orbital frontal cortex show a decrease in spine density (see Fig. 1). Mychasiuk, Muhammad, Ilnytsky, and Kolb (2013) compared gene expression in medial prefrontal cortex, orbital prefrontal cortex, and nucleus accumbens following 14 days of amphetamine or nicotine administration. Although there were many changes in gene expression, there was virtually no overlap across the three structures. Similarly, when Mychasiuk et al. (2012b) examined the effects of prenatal stress on gene expression in hippocampus and medial prefrontal cortex they found over 100 genes changed in each region but there was virtually no overlap in which genes changed. Using one structure or the other (or blood) as a surrogate marker for epigenetic change throughout the brain is clearly misleading.

Region-specific changes are not just seen in the effects of drugs. Comeau, McDonald, and Kolb (2010) reported that both complex housing and the learning of a spatial nonmatch-to-sample task produced opposite changes in dendritic branching and spine density in medial and orbital prefrontal cortices. Similarly, Liston et al. (2006) found opposite changes in response to stress. Indeed, one recurring theme is that experience-dependent changes in medial and orbital prefrontal cortex tend to be opposite – increases in one region are associated with decreases in the other. The likely reason is a difference in gene expression (Mychasiuk et al., 2013) but it is unclear what is responsible for this difference.

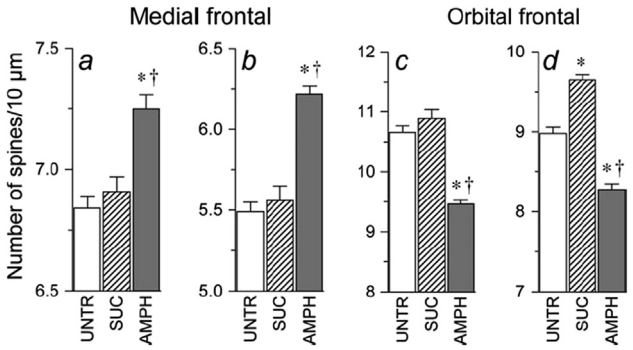

Fig. 1 – Summary of the contrasting effects of amphetamine on the medial frontal and orbital frontal cortex. Abbreviations: UNTR = untrained; SUC = trained to bar press for sucrose; AMPH = trained to bar press for amphetamine. (After Crombag et al., 2005).

3.7. *Plastic changes can be cortical-layer specific*

The cerebral cortex is formed by about six layers, which are organized in vertical columns that span the layers (e.g., Kolb & Whishaw, 2009). It is usually presumed that the column is the functional unit of the cortex and thus changes that occur in one layer would be expected to reflect changes across the column. However, just as different cortical regions can express opposite changes, so can cortical layers within a specific region. The first clear example of this was observed in the brains of animals who had developed a condition known as kindling. Kindling refers to the progressive intensification of electrographic and behavioral seizure activity with repeated stimulation and is thus a model of brain sensitization (for a review see Teskey, 2001). Kindling is an extremely robust example of plasticity and would be expected to be associated with neuronal morphological correlates. When stimulated, many cerebral structures, including hippocampus, amygdala, and cortex show kindling-related synaptic changes. What was unexpected, however, is that when the cortex is stimulated, different layers of the cortex change differently as shown in Fig. 2. Thus, kindling results in an initial dendritic hypertrophy in layer V but hypotrophy in layer III. With time, layer V basilar dendrites reverse their changes and become hypotrophic whereas the layer III dendrites return to baseline levels (Teskey et al., 2006). Given that cortical columns have long been thought to act as unit (Mountcastle, 1997), it was generally assumed that there would be a singular change in synaptic space across the column but this is not the case. Such layer-specific changes are not unique to brain stimulation studies,

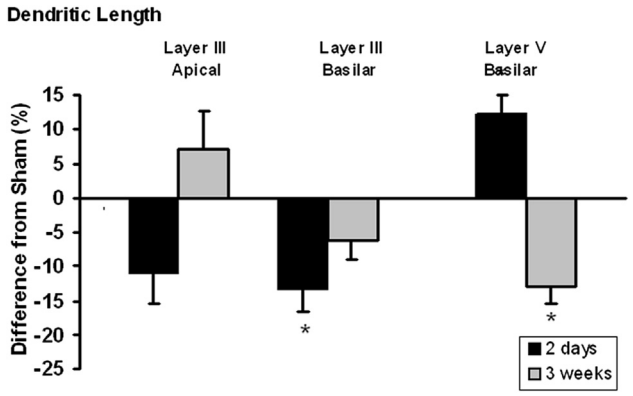

Fig. 2 – Quantification (mean ± SEM) of the effect of 25 sessions of kindled seizures at either 2 days (black), or 3 weeks (gray) following the last seizure on layer III apical, layer III basilar, and layer V basilar dendritic length in pyramidal cells in frontal cortex (area Fr1). Kindling induction was associated with significant decreases in dendritic length in both apical and basilar fields in layer III but significant increases in layer V following the last seizure. At 3 weeks kindling was associated with a significant increase in layer III and a decrease in layer V. * indicates a significant difference from implanted controls, $p < .05$. (After Teskey et al., 2006).

however. We have found parallel findings in studies of the brains of rats learning various neuropsychological tasks (Comeau et al., 2010; Kolb, Cioe, & Comeau, 2008). We interpret these data as evidence that layers III and V have different and perhaps opposing roles in at least some forms of plasticity.

3.8. *Plastic changes are time-dependent*

As we saw above, plastic changes related to kindling change over time and there are many more examples. For example, when rats are placed in complex environments there is a transient increase in dendritic length in medial prefrontal cortex that can be seen after four days of complex housing but has disappeared after 14 days. In contrast, sensory cortex shows no obvious signs of change after 4 days but exhibits clear, and seemingly permanent, changes after 14 days (Comeau et al., 2010). These changing patterns of ensemble organization are likely related to changes in gene expression. For example, Rampon et al. (2000) found that there are different sets of genes expressed acutely and chronically in response to complex housing.

Time-dependent changes may also reflect a slow loss of experience-dependent plasticity. Repeated exposure to cocaine produces large changes in dendritic arborization and spine density observed two weeks after the last drug exposure (Robinson & Kolb, 1999a, 1999b) but these changes gradually disappear and are not visible four months later (Kolb, Gorny, Li, Samaha, & Robinson, 2003). In contrast, when rats are given morphine and the brains are examined immediately after drug cessation, there is an increase in dendritic arborization in nucleus accumbens (Ballesteros-Yanez et al., 2007) but a month later the changes are just the opposite (Robinson & Kolb, 1999b).

Time-related changes in synaptic organization can be quite prolonged. For example, during development there is an overproduction of synapses, especially in prefrontal cortex, which are slowly pruned beginning in adolescence and continuing well into the latter part of the third decade in humans (Petanjek et al., 2011). Similar results can also be seen in rats (Milstein et al., 2013) and are likely true of other cortical regions as well (e.g., Huttenlocher & Dabholkar, 1997).

Time-dependent synaptic changes can also be seen after cerebral injury. Kolb and Gibb (1993) made medial prefrontal lesions in rats at either 1 or 10 days of age. The animals were trained on a spatial learning task at 22–25 days or at 52–55 days and the brains were harvested for analysis on following completion of the training. Brain-injured animals in the earlier age group were impaired regardless of the age at injury. In contrast, the day 10 operates were essentially normal in performance when tested at the later age whereas the day 1 operates were still as impaired as in the earlier time period. When we looked at the dendritic changes, the lesion groups in the earlier testing groups both showed *hypotrophy* of pyramidal cells in the cortex whereas the day 10, but not the day 1, operates showed *hypertrophy* after day 55 training. The compensatory synaptic changes related to the functional recovery took several weeks to develop.

3.9. *Plasticity is related to the relevance of an experience to the animal*

Some behaviors can be learned in one trial whereas others appear to be impossible to learn. For example, food aversions are often related to a single incidence of an illness, a phenomenon referred to as taste aversion learning. If animals encounter a food with a novel flavor that is paired with illness, there is an immediate and persistent aversion to the taste. This learning usually requires only a single trial. This type of learning is obviously relevant to the animal and the brain is clearly prepared to make certain associations (Yamamoto, Shimura, Sako, Yasoshima, & Sakai, 1994). Imprinting in young fowl is similar (e.g., Lorenz, 1970). Horn and his colleagues have shown that visual imprinting in chick's is correlated with immediate changes in the hyperstriatum, including an increase in dendritic length but a decrease in spine density, increased NMDA receptor density, increased immediate early gene expression, and more (e.g., Horn, 1998; Horn, Nicol, & Brown, 2001; Solomonia, Kotorashvili, Kiguradze, McCabe, & Horn, 2005). The unique feature of Horn's results is the speed whereby they occur, which matches the speed of the behavioral imprinting.

3.10. *Plasticity is related to the intensity or frequency of experiences*

Although some learning can occur in a single trial (see above), most learning is much slower and requires multiple exposures to experiences. The slower behavioral change likely reflects a slow change in neurons as well. Although we are unaware of any relevant studies related to task learning, there is evidence that repeated doses of psychoactive drugs produce a cumulative change in dendritic organization. For example, Kolb, Gorny, et al. (2003) compared the effects of 0, 2, 12, and 44

daily doses of amphetamine and found an escalating change in spine density with added doses (Fig. 3). Curiously, the increase was not linear with the increase between 2 and 12 doses being about the same as that between 12 and 44 doses. This is probably to be expected given that as we learn information, there is a decreasing benefit of more practice.

A different form of intensity-related plasticity can be seen in the effects of direct electrical brain stimulation. Thus, whereas high frequency stimulation (25–200 Hz) produces long-term potentiation (i.e., postsynaptic potentiation), low frequency stimulation leads to long-term depression (i.e., reduced potentiation) (e.g., Cain, 2001; Teyler, 2001). The two different forms of stimulation lead to the activation of different postsynaptic signaling pathways and a host of different plastic changes (e.g., Teyler, 2001).

3.11. *Changes in neuronal organization reflect changes in gene expression, which can be passed on through generations*

We have noted that plastic changes in behavior and neuronal morphology are associated with specific changes in gene expression (e.g., Mychasiuk et al., 2012a, 2012b, 2013). More interesting, however, is that experiences in parents prior to conception of their offspring can be associated with changes in gene expression in the brains of the offspring. For example, Mychasiuk et al. (2012b) placed male rats in complex environments for 28 days before mating the males with females. The offspring of the complex-environment housed-males showed a significant decrease in gene methylation, reflecting the increased expression of about 1000 genes (Fig. 4). More surprising, however, was that the gene expression changes were remarkably similar to those observed in the offspring of females who were housed in similar complex environments while pregnant.

3.12. *Experience-dependent changes interact*

Life is not about singular experiences but rather is made up of hundreds of serial experiences that vary in intensity. It is thus not surprising that experiences will interact, a phenomenon referred to as metaplasticity (Abraham & Bear, 1996). Consider a couple of examples. If rats are exposed to psychomotor

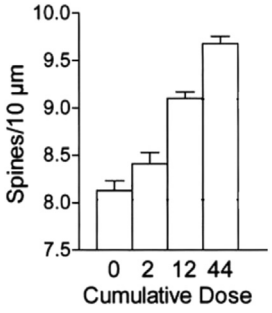

Fig. 3 – A comparison of the effects of repeated amphetamine treatment on spine density in spiny neurons of the nucleus accumbens. Spine density rises with additional doses but the increase is not linear. (Modified from Kolb et al., 2003).

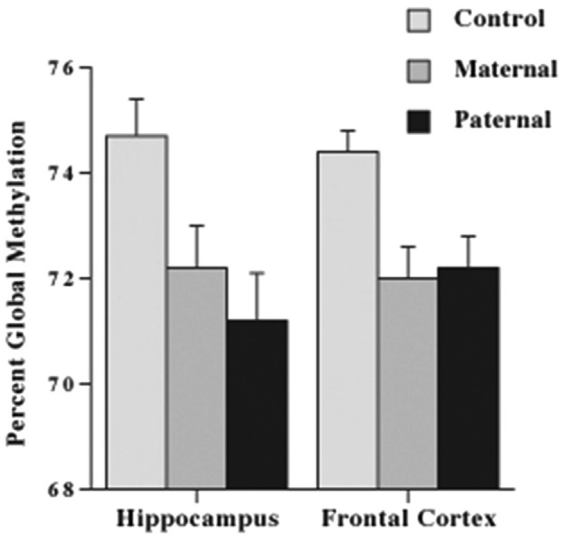

Fig. 4 – The effect of maternal or paternal complex housing of gene methylation. (After Mychasiuk et al., 2012b).

stimulants (amphetamine, cocaine, or nicotine), neurons in many cerebral regions are altered in an areal-dependent manner (see Robinson & Kolb, 2004). If animals are later placed in complex environments, there is an unexpected interaction. Not only do neurons in drug-altered regions such as prefrontal cortex not change but neither do neurons in regions such as parietal cortex that were not directly changed by the drugs (e.g., Kolb, Gorny, et al. 2003). A similar, although less dramatic, effect can be seen if the experiences are reversed. Hamilton and Kolb (2005) placed rats in complex environments before giving them repeated doses of nicotine. The effects of the nicotine were markedly attenuated by the earlier complex housing, although the drug did still alter the brain. Similarly Gonzalez et al (2003) trained rats on a skilled forelimb task while treating the rats with nicotine. When the rats were later trained on a different skilled reaching task, but not on the drug, there was an interference with the new learning. The behavioral disruption was correlated with differential changes in dendritic morphology.

Even prenatal experiences can modify the response to psychoactive drugs later in adulthood. For example, prenatal stress or prenatal tactile stimulation modify the effect of amphetamine in adulthood (Muhammad & Kolb, 2011; Muhammad, Hossain, Pellis, & Kolb, 2011). Although it is easy to conclude that the early experiences directly changed the later drug effects, there are other explanations. For example, both prenatal experiences alter juvenile play behavior and the manipulation of juvenile play behavior also changes the brain's response to psychomotor stimulants (Himmler, Pellis, & Kolb, 2013). Hence, we can conclude that experiences interact but just how they interact to change the brain is much less clear.

3.13. *Virtually every experience has the capacity to alter the brain and behavior, at least briefly*

Data continue to accumulated demonstrating that all behavioral changes can be correlated with plastic changes in the

brain at some level (see Table 3). Of course, few studies would be published that fail to show such changes because it could always be argued that the investigators used the wrong measure or looked in the wrong place in the brain. Nonetheless, we prefer to focus on the wide range of experiences that have been shown to change the brain and behavior. A thorough review of all the examples is well beyond the scope of this article and has been the topic of books (e.g., Shaw & MacEachern, 2001).

3.14. *Plasticity can be maladaptive*

Although there is natural tendency to think of plasticity as a positive influence on brain organization, there are many examples of plasticity having negative effects on brain and behavior. For example, we have seen that psychoactive drugs produce many changes in neuronal morphology. It is reasonable to suggest that some of the maladaptive behavior of drug addicts could be related to the drug-related changes, especially in prefrontal cortex.

Another example is phantom limb pain, which refers to perceived pain in a body part that has been amputated (Baranauskas, 2001). Once thought to be a mental disorder, evidence has grown to show that it is likely a result of plastic changes both at the periphery and in the central nervous system (Flor, Nikolajsen, & Jensen, 2006). Thus, both human and lab animal studies have shown hyperexcitability of neurons in the dorsal horn of the spinal cord that is believed to result from the amputation. Supraspinal changes are also reported in the brainstem, thalamus, and especially the cortex.

There are many other examples of maladaptive plasticity including epilepsy (Teskey, 2001), dystonia (Byl, Nagajaran, & McKenzie, 2003), and dementia (Mattson, Duan, Chan, & Guo, 2001). Furthermore, many early experiences such as severe environmental deprivation are associated with a wide range of pathological effects in both brain and behavior, the best example being seen in the brain and behavioral effects in Romanian orphans (Nelson, Fox, & Zeanah, 2013).

3.15. *Understanding normal plasticity gives us a cue to repairing the abnormal brain*

Although our understanding of the rules governing plasticity in the normal brain are in their infancy, it is our working hypothesis that understanding plastic changes in the normal brain will inform treatments of the abnormal brain. Our basic assumption is that experiences that change the normal brain will likely produce similar, and hopefully even larger, changes in the injured brain. This is often the case but not always. Consider a recent example. It has been shown tactile stimulation in early development has a profound effect on neural organization and behavior (e.g., Richards, Mychasiuk, Kolb, & Gibb, 2012) so we anticipated that tactile stimulation might be a good treatment for brain injury, and especially perinatal brain injury. It is. But we were surprised to discover that the synaptic changes in normal and brain-injured animals were qualitatively different. Specifically, whereas there was a *decrease* in spine density in cortical pyramidal neurons in sham operates, which was correlated with enhanced motor and cognitive skills, there was an *increase* in animals with perinatal prefrontal injuries. Nevertheless, the latter animals showed remarkable functional recovery in both cognitive and motor behaviors (e.g., Kolb & Gibb, 2010).

Notwithstanding this type of unexpected outcome, the general conclusion we can reach is that factors that enhance cognitive and motor functions in otherwise normal animals generally improve functional outcome following brain injuries related to a range of etiologies in both infant, adolescent, and adult laboratory animals (see Tables 4 and 5). We hasten to

Table 3 – Factors affecting the synaptic organization of the normal brain.

Factor	Example reference
1. Sensory and motor experience	Greenough and Chang (1989)
2. Task learning	Comeau et al., 2010
3. Gonadal hormones	Mychasiuk, Gibb, and Kolb, 2012a
4. Psychoactive drugs	Robinson and Kolb (2004)
5. Neurotrophic factors (e.g., NGF, FGF-2)	Monfils, Driscoll, Vavrek, Kolb, and Fouad (2008)
6. Natural rewards (e.g., sex; social interaction, play)	Fiorino and Kolb (2003) Bell, Pellis, and Kolb (2010)
7. Prenatal experiences	Muhammad and Kolb (2011)
8. Preconceptual experiences	Mychasiuk et al. (2012b)
9. Aging	Kramer, Bherer, Colcombe, Dong, and Greenough (2004)
10. Stress	McEwen (2005)
11. Anti-inflammatories (e.g., COX-2 inhibitors)	Silasi and Kolb (2007)
12. Diet (e.g., choline)	Meck and Williams (2003)
13. Electrical stimulation:	
Kindling	Teskey et al. (2006)
LTP	Monfils, VandenBerg, Kleim, and Teskey (2004)
LTD	Monfils and Teskey (2004)
Surface cortical stimulation	Adkins, Hsu, and Jones (2008)

Table 4 – Factors enhancing recovery from the injured adult brain.

Factor	Basic reference
Behavioral therapies	
Constraint-induced therapy	Byl et al., 2003
Voluntary forced use movement therapy	Livingston-Thomas et al., 2013
Complex housing	Biernaskie and Corbett, 2001
Tactile stimulation	Gibb, Gonzalez, Wegenast, and Kolb, 2010
Pharmacotherapies	
Psychomotor stimulants	Feeney and Sutton, 1987
Inosine	Chen, Goldberg, Kolb, Lanser, and Benowitz, 2002
Antibodies to Nogo-A	Papadopoulos et al., 2006
FGF-2	Witt-Lajeunese, 2001
NGF	Kolb, Cote, Ribeiro-da-Silva, and Cuello, 1997
Anti-inflammatories	Silasi and Kolb, 2007
Cell-based therapies	
EGF and erythropoietin (EPO)	Kolb et al., 2007
Electrical stimulation	
Cortical surface	Teskey, Flyunn, Goertzen, Monfils, and Young, 2003

Table 5 – Factors enhancing recovery from the injured young brain.

Factor	Basic Reference
Behavioral therapies	
Complex housing at weaning (after P1–7 injury)	Kolb and Elliott, 1987
Complex housing in adulthood (after P5 injury)	Comeau, Gibb, Hastings, Cioe, and Kolb, 2008
Complex housing prenatally (before P3 injury)	Gibb, 2004
Prenatal complex housing (before P3 injury)	Gibb, 2004
Tactile stimulation postinjury	Kolb and Gibb, 2010
Tactile stimulation prenatally	Gibb, 2004
Pharmacotherapies	
FGF-2 (after P4 frontal or parietal lesion)	Comeau, Hastings, and Kolb, 2007
FGF-2 (after P35 motor cortex lesion)	Nemati and Kolb, 2012
FGF-2 (neurogenesis induced after P10 lesion)	Monfils et al., 2006
FGF-2 (after P7 hypoxia-ischemia)	Williams, 2010
Gonadal hormones	Kolb and Stewart, 1995
Nicotine (after P7 hypoxia-ischemia)	Williams, 2010
Diet	Halliwell, 2011

point out, however, that there is no evidence that any treatment can completely restore behavior to its preinjury level of competency.

4. Conclusion

One of the key properties of the nervous system is its capacity to change after in response to experience. We have attempted to identify some general principles of brain plasticity and behavior and to summarize the factors that best illustrate the relationship between brain plasticity and behavior in mammals. Our review of the literature is somewhat arbitrary and biased towards our own work but we believe that we have provided a framework that others might find useful as we search for an understanding of brain plasticity and behavior.

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