# 11.

# ENVIRONMENTAL INFLUENCES ON PREFRONTAL DEVELOPMENT

Allyson P. Mackey, Rajeev D. S. Raizada, and Silvia A. Bunge

## INTRODUCTION

It takes only a few years for a human child's sensory cortex to develop its full functionality. By contrast, it takes over two decades of experience and growth before prefrontal cortex (PFC) reaches its full maturity (Casey, Giedd, & Thomas, 2000; Fuster, 2002). A variety of studies have provided evidence that this prolonged period of development makes the PFC particularly sensitive to environmental influences—not only during the prenatal period and infancy, but also during childhood and adolescence (Andersen & Teicher, 2008; Crews, He, & Hodge, 2007). Among adults, as among children, there is a high degree of variability in cognitive functions that rely on PFC, including working memory (Vogel & Machizawa, 2004; Vogel, McCollough, & Machizawa, 2005) and cognitive control (Braver, Cole, & Yarkoni, 2010; Kane & Engle, 2002). Research on development and plasticity can provide important insights regarding the origins of individual differences in PFC-dependent cognitive functions. In this chapter, we focus on the role of the environment in shaping the development of the PFC—for better or for worse.

There is substantial evidence that the development of PFC can be hindered by a variety of environmental factors, including chronic stress as well as physical and psychosocial deprivation. However, there is also a growing body of research showing that various interventions could have a positive influence on brain development or at least mitigate the effects of negative influences. In this chapter, we review key concepts related to brain plasticity and environmental influences. We then provide an overview of research in humans and other animals that provides evidence for both negative and positive influences on prefrontal development. Finally, we point to several questions in this area of research that are ripe for investigation.

## THE BRAIN IS MORE PLASTIC THAN WE ONCE THOUGHT

A recurring pattern in the history of neuroscience is that brain areas once thought to be static and nonplastic have gradually been discovered to be dynamic and malleable. For decades, sensory cortex was believed to be unchangeable after the end of the critical period, until the pioneering work of researchers such as Merzenich, Kaas, and Taub and colleagues demonstrated large plastic changes in adult animals. In humans, the range of skills that have been shown to be amenable to training has extended from low-level perceptual learning (Karni & Bertini, 1997; Sagi & Tanne, 1994) to visuomotor skill acquisition (Draganski et al., 2004; Scholz, Klein, Behrens, & Johansen-Berg, 2009), attention (Rueda, Rothbart, McCandliss, Saccomanno, & Posner, 2005), processing speed (Green & Bavelier, 2003; Li, Polat, Makous, & Bavelier, 2009), working memory and cognitive control (Jaeggi, Buschkuehl, Jonides, & Perrig, 2008; Klingberg, 2010; Olesen, Westerberg, & Klingberg, 2004; Thorell, Lindqvist, Bergman Nutley, Bohlin, & Klingberg, 2009), long-term memory (Schmiedek, Lovden, & Lindenberger, 2010), and reasoning (Jaeggi et al., 2008; Mackey, Hill, Stone, & Bunge, 2011).

## THE POTENTIAL FOR BRAIN PLASTICITY VARIES OVER DEVELOPMENT AND ACROSS BRAIN REGIONS

The term "sensitive period" refers to the times in development during which a neural system is maximally sensitive to environmental influences. This window of maximal opportunity or vulnerability varies across neural systems (for reviews, see Nelson & Sheridan, in press; Rice & Barone, 2000). The development of each neural system depends on exposure to normal, expectable environmental input. For sensory systems in humans, the sensitive period corresponds roughly to the first year of life. For example, if normal visual input is not available during the first year, vision will not develop normally (Maurer, Mondloch, & Lewis, 2007; White & Fitzpatrick, 2007). Language systems are maximally plastic during the first 2 years of a child's life (Werker & Tees, 2005). Thus, if a child experiences an impoverished language environment during this time, his or her language development will be compromised. Nelson and Sheridan note that "As a rule, although different functional domains (including vision, hearing, language, and attachment) vary in precisely when their sensitive periods begin and end, most sensitive

periods run their course in the first few years of life . . . what happens in the first few years has a profound impact on the course of child development" (Nelson & Sheridan, in press). However, the sensitive period for higher cognitive functions that rely on PFC is thought to stretch late into childhood, since PFC follows a slow developmental trajectory (Casey et al., 2000; Fuster, 2002).

Although the sensitive period denotes the period during which a neural system is *maximally* sensitive to environmental input, it is not the case that inputs to the system after the end of this period can no longer influence development. Indeed, plasticity persists longer into childhood than was thought previously. With respect to sensory systems, recent studies by Pawan Sinha and colleagues have shown that children born blind whose vision is surgically restored, even as late as 13 years, can recover a considerable amount of visual function (Ostrovsky, Meyers, Ganesh, Mathur, & Sinha, 2009). With respect to language systems, there is now evidence of a high degree of plasticity even up to 8 years of age. Children who were born in Korea but adopted by French families do not show differential activity to Korean words than to words from other unknown languages, suggesting that early exposure to Korean was overwritten by later exposure to, and immersion in, French (Pallier et al., 2003).

In summary, although an infant's brain is certainly more plastic than an adult's, it is not the case that "the gate of plasticity" closes after early childhood. Instead, plasticity appears to become more tightly constrained with age, but the upper boundaries of plasticity at any age remain unknown. As discussed below, there is evidence that with intense training it is possible to "remove the brakes" on adult brain plasticity (Bavelier, Levi, Li, Dan, & Hensch, 2010).

## EXPERIENCE-EXPECTANT VERSUS EXPERIENCE-DEPENDENT PROCESSES

Development and learning have been described as existing on a continuum, with development being driven more strongly by "experience-expectant" processes and learning by "experience-dependent" processes (Figure 11–1; Galvan, 2010; Greenough, Black, & Wallace, 1987). Plasticity that emerges from typical development represents neural change that follows the norm for the species, whereas plasticity emerging from learning represents neural changes associated with experience that is specific to the individual (Galvan, 2010).

To develop normally, all members of a species require species-typical environmental input during the sensitive periods described above. These so-called experience-expectant mechanisms evolved to "expect" particular environmental cues; for example, the visual system expects contrast borders and the language system expects speech sounds. Brain plasticity during development can also give

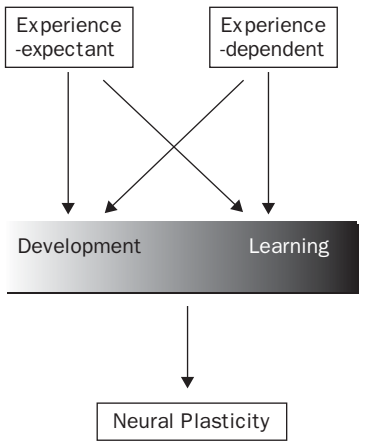


*Figure 11–1* This model shows the continuum between development and learning, which together and separately induce neural plasticity. Experience-expectant mechanisms shape development more strongly than experience-dependent mechanisms, but both do play a role. Similarly, experience-dependent mechanisms are more important for driving learning than experience-expectant mechanisms. Source: Reproduced, with permission, from Galvan © 2010.

rise to individual differences based on the unique experiences of an individual. These so-called experience-dependent mechanisms are more variable in their timing than experience-expectant ones, since unique experiences, such as learning opportunities, differ across children.

## GENETIC VERSUS ENVIRONMENTAL INFLUENCES ON BRAIN DEVELOPMENT? AN ILL-POSED QUESTION

The sequencing of the majority of the human genome by 2003 (Carroll, 2003; Collins, Morgan, & Patrinos, 2003) was hailed by many as the answer to all of our questions about the human body (including the brain). While this accomplishment was indeed significant, it marks an important milestone rather than the end of an era of exploration into the molecular underpinnings of the human brain. Borrowing a metaphor from Champagne and Mashoodh, unexpressed genes are like books sitting unread on the shelves of a library: only when a gene is expressed does it have any causal effects, just as a book must be lifted from a shelf and read before its contents can reach an audience (Champagne & Mashoodh, 2009). Indeed, "although genetics supply the basic blueprint for brain development, experience *adjusts* the genetic plan for the brain and shapes the architecture of its neural circuits, according to the needs and distinctive environment of the individual" (Nelson & Sheridan, in press).

Because gene expression is modulated by environmental inputs, we fail to do justice to the richly reciprocal causal interactions that play out over development if we describe the cognitive or behavioral (or physical) traits of an individual as being either predominantly genetically

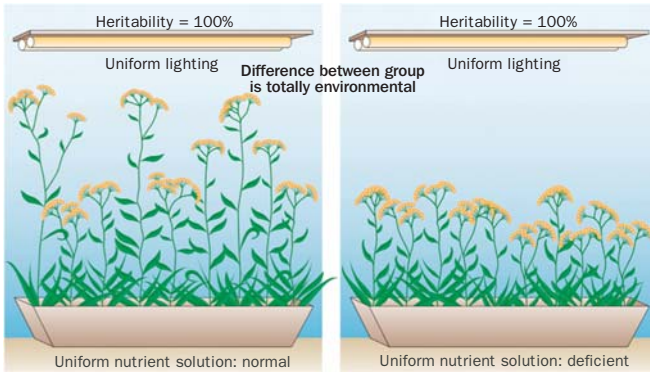


*Figure 11–2* Heritability in both cases is 100%, but the plants on the right are growing in nutrient-deficient solution, leading to less overall growth and fewer individual differences in height. This is an illustration of Lewontin's metaphor (Lewontin, 1970). Source: Reproduced, with permission, from Gray and Thompson © 2004, and Block, © 1995 Elsevier.

or environmentally mediated. In Figure 11–2, Gray and Thompson illustrate the point that even the seemingly simple characteristic of plant height involves a complex interplay of genetic and environmental factors. Genetic factors can make plants grow taller, but only when nutrient-rich soil is present. Within a uniform environment, height appears to depend entirely on genetic factors. However, when comparing across diverse environments, external conditions, such as the richness of soil nutrients, have a much bigger effect. Given this mix of factors, we may still wish to ask whether plant height is a result of nature or of nurture. But, as Figure 11–2 shows, that question is ill posed. The causal influences, both genetic and environmental, that act upon a developing child's brain are vastly more complex and much less understood than those that govern the height of plants. The seductively simple phrase "nature versus nurture" obscures many complexities and unknowns.

In addition to attempting to estimate the heritability of cognitive or behavioral traits with twin pair methodology (Posthuma et al., 2003; Tucker-Drob, Rhemtulla, Harden, Turkheimer, & Fask; Turkheimer, Haley, Waldron, D'Onofrio, & Gottesman, 2003), we can and should probe the mechanisms through which genetic and environmental factors *jointly influence* the functioning and development of the brain (Caspi & Moffitt, 2006; Meaney, 2010).

## GENE-ENVIRONMENT INTERACTIONS

The most commonly used sense of the term "gene-environment interactions" is the phenomenon whereby the environment can act to *gate* the manifestation of a genetic predisposition. For example, certain genes may make children more vulnerable to stress-induced anxiety (Caspi et al., 2002; Caspi & Moffitt, 2006; Kim-Cohen et al., 2006). This genetic vulnerability is revealed only if the child lives in a stressful environment. Although such gating by the environment is important and should not be ignored, the influence of environmental factors on genetics extends beyond this passive role. Environmental stimuli also actively turn genes on and off; this process is fundamental to learning and synaptic plasticity (Cohen & Greenberg, 2008). Changes in gene transcription can lead to the elaboration of axons, synapse elimination, and/or synapse consolidation (Figure 11–3; Knudsen, 2004). These structural changes, in turn, affect a neuron's function by altering its connectivity.

Changes can be short-lasting, on the scale of seconds, or long-lasting, enduring throughout an individual's lifetime. Environmental input can modify an individual's genome, permanently affecting which genes will and will not be transcribed. For example, experience can lead to the acetylation of histones, the protein structures around which DNA is wound. Increased histone acetylation causes DNA to be wound more tightly so that it cannot be transcribed easily (Figure 11–4). Environmental stimuli can also change methylation patterns of DNA. DNA methylation is a mechanism by which a methyl group is added to cytosine pyrimidine rings, in effect silencing regional gene transcription. It is important to note that the net effect of methylation could be increased transcription if the genes silenced by methylation code for repressor proteins (Levenson & Sweatt, 2005; Meaney, 2010).

## CHOICE OF ENVIRONMENT CAN MAGNIFY SMALL GENETIC DIFFERENCES

In addition to gene-environment interactions that are mediated at the molecular level, there are other possible forms of reciprocal causation between cognitive functioning and environment. Individuals with a slight genetic advantage over others in a given ability may (be encouraged to) seek out experiences that further hone this ability. As Dickens and Flynn (2001) explain, "People who are born with a genetic advantage are likely to enjoy an environmental advantage as a result.... The genetic advantage may itself be rather small. However, through the interplay between ability and environment, the advantage can evolve into something far more potent. So we have found something that acts as a multiplier:

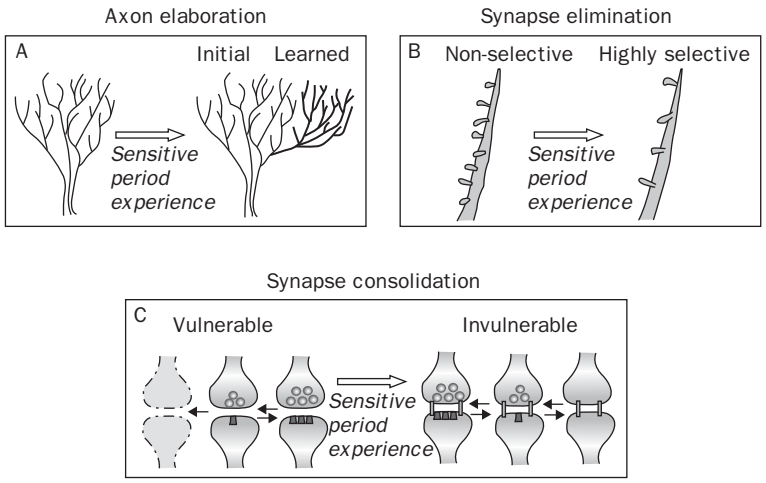


*Figure 11–3* (A) Elaboration of a new axonal projection field enables new connections to be formed. (B) Loss of dendritic spines leads to the elimination of unused synaptic inputs. (C) Invulnerable synapses are created by insertion of cross-linking proteins into the membrane (vertical bars). Even after this structural change occurs, the function of the synapse can be modified through up- or downregulation of vesicles containing neurotransmitters (spheres) or receptors (trapezoids). Source: Reproduced, with permission, from Knudsen © 2004.

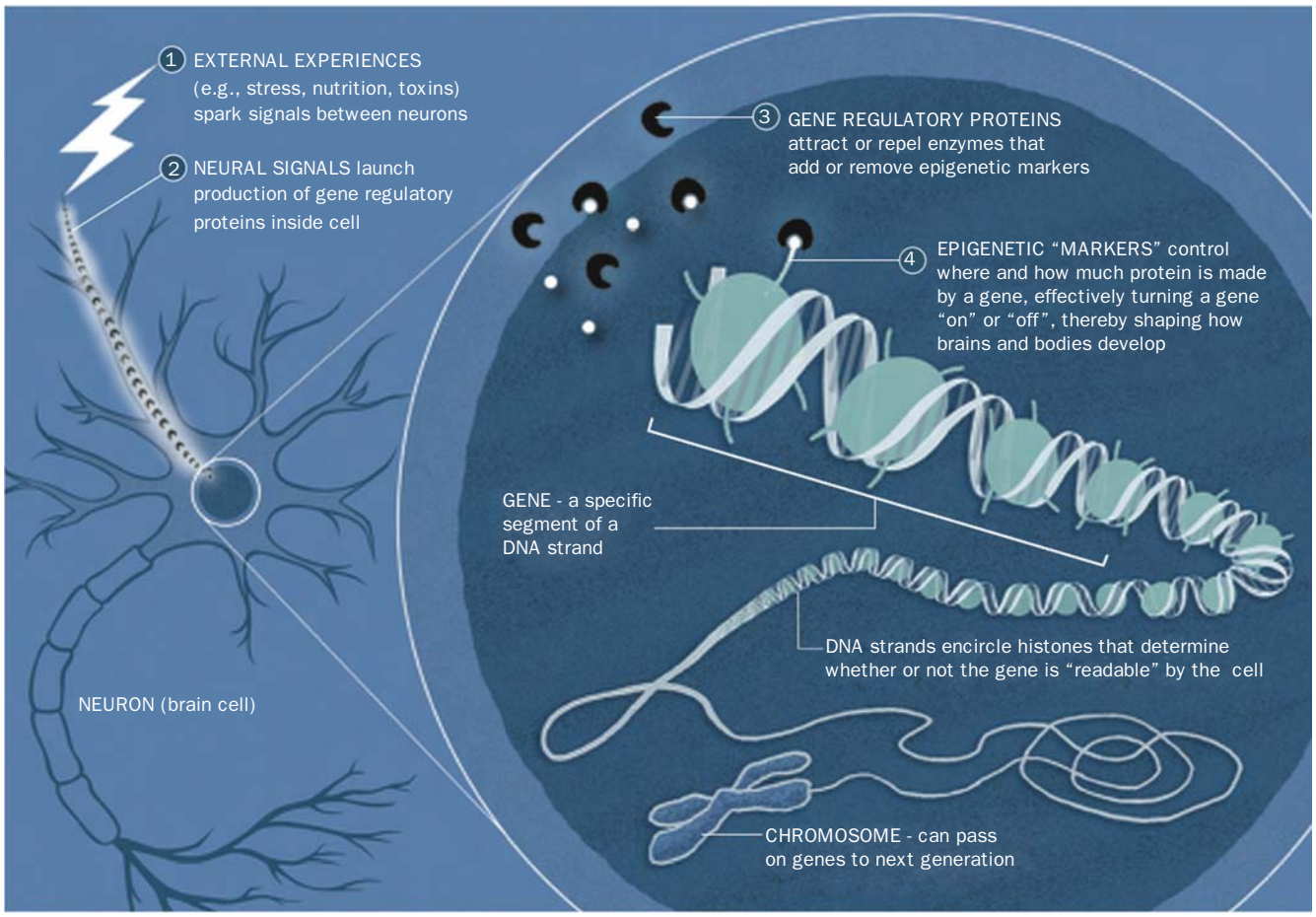


*Figure 11–4* Environmental input (1) drives neural activity (2) which activates gene regulatory proteins (3). These proteins act to turn "on" and "off" genetic markers such as histone acetylation and methylation, and these markers influence which genes are "read," that is, transcribed (4). Source: Reproduced, with permission, from the National Scientific Council on the Developing Child © 2010.

The process by which the ability of an individual and the environment of an individual are matched can increase the influence of any initial difference in ability—whether its source is genetic or environmental" (p. 350).

Such reciprocal interactions between cognitive ability and learning environment could account for the counterintuitive finding that the heritability of cognitive functions increases with age (Dickens & Flynn, 2001). That is, while one might expect that genetic influences on cognition should diminish over time as each of us is shaped by our idiosyncratic set of experiences, the opposite often occurs. For example, in a longitudinal twin study of children tested at age 5 and again at age 12, genetic factors accounted for a greater percentage of the variance in selective attention, working memory, and sustained attention at age 12 than at age 5 (Polderman et al., 2007). Similarly, longitudinal magnetic resonance imaging (MRI) research reveals that the heritability of cortical thickness patterns increases rather than diminishes with age (Lenroot et al., 2009). This effect may be related to the timing of expression of genes that influence cortical thickness and/or to the multiplier effect described by Dickens and Flynn.

## INTERIM SUMMARY

Given that one of the primary functions of the brain is to respond adaptively to changes in the environment, it makes perfect functional sense that the environment should be able to have a major impact on brain function. A brain that merely unfolded down a genetically predetermined path would be poorly adaptive to environmental change. Moreover, it is the PFC, perhaps more than any other region of the brain, that governs complex adaptive responses to changing environmental demands. Having outlined some general concepts relevant to brain plasticity, we now turn our attention to negative and positive environmental influences on the structure and function of the PFC.

## NEGATIVE ENVIRONMENTAL INFLUENCES ON PREFRONTAL DEVELOPMENT

Recall that the plants shown in Figure 11–2 contained the genetic material that could allow them to be tall, but the lack of sufficient soil nutrients prevented the plants from reaching this height. By a similar logic, children who experience detrimental or simply insufficient environments will thereby encounter obstacles to reaching their full potential. As we discuss in the section "Positive Environmental Influences on Prefrontal Development," two crucial questions are how these obstacles can be prevented beforehand and whether or how, once encountered, they can be overcome. Here, we consider in turn various negative influences on the development of PFC, including physical and psychosocial factors. The examples provided in the following three subsections illustrate the sensitivity of PFC to each of several specific environmental insults. In reality, however, these negative environmental influences tend to cluster together. As discussed in the section "Low SES,", children of lower socioeconomic status (SES) are at greater risk for many of these factors. Scientifically grounded programs designed to help lower-SES children overcome the challenges presented by these negative factors are therefore urgently needed.

### PHYSICAL FACTORS IN THE PRENATAL ENVIRONMENT

Research on the effects of prenatal exposure to teratogens (substances that increase the risk of birth defects, such as alcohol and other drugs) illustrates how the prenatal environment influences brain development (Langlois & Mayes, 2008). The specific patterns of deficits observed in children who were exposed to drugs and alcohol in utero shed light on the vulnerability of PFC to insult even before birth. Dopamine-rich cortical and subcortical fetal brain structures are particularly susceptible to damage from intrauterine drug exposure, given the large number of psychoactive substances that influence dopaminergic transmission.

We focus here on alcohol and cocaine because of the depth of the literature linking these substances to PFC dysfunction. However, there have also been studies suggesting that prefrontal development may be negatively impacted by prenatal exposure to other substances, including tobacco (Cornelius & Day, 2009) and marijuana (Campolongo, Trezza, Palmery, Trabace, & Cuomo, 2009). For an in-depth discussion of prenatal substance exposure, see Shankaran et al. (2007) and Derauf, Kekatpure, Neyzi, Lester, and Kosofsky (2009).

#### *Alcohol*

For at least 30 years, it has been known that alcohol exposure in utero can lead to negative developmental outcomes. In 1973, extreme symptoms associated with prenatal alcohol exposure, namely growth deficiency, facial malformation, and mental retardation, were grouped under the diagnosis of fetal alcohol syndrome (FAS). "Fetal alcohol spectrum disorder" (FASD) is a broader term that encompasses the full spectrum of negative outcomes associated with prenatal alcohol exposure (Norman, Crocker, Mattson, & Riley, 2009). Children with FASD have smaller brains than healthy children (Sowell et al., 2001) and an abnormal brain shape, specifically in frontal cortex and the left hemisphere (Sowell et al., 2002). Further, individuals with FASD show deficits in many PFC-dependent skills, including cognitive flexibility, working memory, planning, and reasoning (Mattson et al., 2010). Importantly, these deficits are found with and without facial dysmorphology, a hallmark symptom of FAS.

In a large study of executive function (EF) in 4-year- old children, Noland and colleagues found a negative correlation between severity of prenatal alcohol exposure and performance on a test of cognitive inhibition (Noland, Singer, Mehta, & Super, 2003). This relationship held when they controlled for verbal IQ, other prenatal drug exposure, and postnatal environmental factors. They also tested two other PFC-dependent cognitive measures, category fluency and motor planning, but did not find an effect of alcohol exposure on either of these tests. It is important to note that these tests were administered at an age—4 years—when the PFC is underdeveloped in all children.

Cognitive deficits resulting from prenatal alcohol exposure may be more evident later in development, when typically developing children begin to exhibit a variety of PFC-dependent skills. In fact, there is even some evidence that differences in cognition can be detected even in adulthood. Adults who were exposed to alcohol in utero perform well below average on consonant trigrams, a test of working memory that requires suppression of interference (Kerns, Don, Mateer, & Streissguth, 1997). To get an accurate picture of the long-term effects of prenatal alcohol exposure on the development of PFC-dependent skills in humans, it will be necessary to follow infants with FASD throughout childhood and adolescence.

Research in rats provides independent confirmation that prenatal alcohol exposure leads to deficits in PFC-dependent skills. For example, Mihalick and colleagues found that rats that had been exposed to alcohol in utero showed deficits in reversal learning, inhibition, and transfer of learning (Mihalick, Crandall, Langlois, Krienke, & Dube, 2001). The rats in this study had a significant decrease in the number of neurons in the medial PFC compared to rats whose mothers had been fed a standard diet during pregnancy. A number of factors have been shown to exacerbate the neurotoxicity of alcohol. For example, genetic susceptibility linked to polymorphisms in alcohol dehydrogenase and the serotonin transporter gene promoter (Warren & Li, 2005) can interact with alcohol to derail neurodevelopment.

### *Cocaine*

When cocaine use spiked in the 1980s, researchers expected the effects of intrauterine cocaine exposure to be disastrous (Lewis et al., 2009). Initial characterization of these effects, however, showed them to be remarkably subtle. More recently, though, long-term problems have been identified in children who were followed through the age of 15 years, including deficits in PFC-dependent functions.

In a large behavioral study involving a continuous performance test similar to a Go/No-Go task, Accornero and colleagues (2007) found that 7-year-old children who had been exposed to cocaine in utero were no more likely than nonexposed peers to correctly withhold responses to No-Go stimuli, but were slower and less accurate in responding to Go stimuli (Accornero et al., 2007). These results suggest that the drug-exposed group may have had to perform the task more cautiously than their peers to achieve the same level of response inhibition. Consistent with this interpretation, Sheinkopf and colleagues (2009) showed in a functional MRI (fMRI) study that cocaine-exposed children engaged the right inferior frontal gyrus and striatum more strongly than controls on No-Go trials despite similar levels of performance (Sheinkopf et al., 2009). These regions have been implicated in response control (Dodds, Morein-Zamir, & Robbins, 2011), suggesting that the cocaine-exposed children had to use greater control to achieve the same level of performance as typically developing children.

Animal research has pointed to three main mechanisms underlying the effects of prenatal cocaine exposure: (1) interactions with neurotransmitter systems, including monoamine systems (dopamine, serotonin, noradrenaline), gamma-aminobutyric acid (GABA), and glutamate, (2) vasoconstriction leading to intrauterine growth restriction, and (3) alterations in expression of genes important to placental function that cause dysregulation of stress responsivity (Derauf et al., 2009).

### *Interim Summary*

While both prenatal alcohol and cocaine have been shown to affect PFC development, alcohol seems to have more catastrophic consequences for PFC function than does cocaine. In other words, the severity of effects of substances on adults may not predict their effects on fetuses (Welch-Carre, 2005). This finding highlights the importance of this line of work: the impacts of prenatal factors may be counterintuitive. Understanding exactly how, and whether, substances that a fetus may be exposed to in utero affect brain development is critical for policymakers. Additionally, research on the neural and behavioral effects of prenatal substance exposure is critical because it may lead to the identification of biomarkers that can aid in the diagnosis and treatment of children who were exposed to drugs in utero.

## PHYSICAL FACTORS IN A CHILD'S ENVIRONMENT

Brain development during childhood can be negatively affected both by the absence of necessary nutrients (malnutrition) and by the presence of environmental toxins. The long developmental trajectory of PFC makes it vulnerable to environmental insult throughout childhood.

### *Malnutrition*

Adequate nutrition is critical for normative cognitive and brain development. One of the most glaring examples of this truism is research on the effects of iron deficiency in infancy.

Iron is important for neurological functioning and development, playing a role in neurotransmitter metabolism, myelin formation, and metabolism in the brain (Beard, 2003). Lukowski and colleagues have shown that chronic, severe iron deficiency in infancy leads to deficits in inhibitory control, set-shifting, and planning in adulthood (Lukowski et al., 2010). The researchers administered a series of neuropsychological tests designed to tap frontostriatal networks to young adults with and without iron deficiency as infants. Two tests showed particularly strong effects of lead exposure: Trails B and Stockings of Cambridge. Performance on both of these tasks is impaired in patients with frontal lobe lesions (Owen, Downes, Sahakian, Polkey, & Robbins, 1990; Stuss et al., 2001). On the Trails B task, which requires the test taker to draw a line to complete the pattern 1, A, 2, B, 3, C, and so on, young adults who had iron deficiency as infants made more switching errors relative to young adults with good early iron status. On the Stockings of Cambridge task, which requires participants to plan a series of moves to complete a problem, young adults with iron deficiency needed more time to plan for harder problems, and they needed more moves to complete these problems.

Animal research has shown that iron deficiency in early life impacts myelination, synaptogenesis, dendritogenesis, and neurotransmission, leading to long-term changes in abilities such as spatial learning and attention (Lozoff et al., 2006). Iron deficiency also leads to increased extracellular dopamine and reduced dopaminergic activity in the striatum, which affects frontostriatal networks. Given the widespread effects of iron on brain function, it is no surprise that iron deficiency negatively affects PFC function.

### *Lead Exposure*

Exposure to heavy metals in food, chemical waste, and synthetic materials is known to interfere with biochemical processes necessary for normal brain development. Lead exposure, in particular, is dangerous because it disrupts synapse formation and myelination and interferes with neurotransmitter systems. Exposure to lead during childhood, for example through contact with lead-based paints, has been shown to be devastating for the development of PFC-dependent cognitive functions. Canfield and colleagues tested 5.5-year-old lead-exposed children on a variety of PFC-dependent tasks. Even after controlling for factors such as SES, quality of caregiving, and maternal and child intelligence, blood lead level significantly predicted performance on tests of planning, working memory, and set-shifting (Canfield, Gendle, & Cory-Slechta, 2004). The structure of PFC is also affected by lead exposure: adults with childhood lead exposure have reduced gray matter in PFC (Cecil et al., 2008). Brubaker and colleagues investigated the effects of age at the time of lead exposure within the age range of 1 to 6 years. They showed that lead exposure *later* in this range leads to a greater decrease in PFC gray matter volume than earlier exposure (Brubaker, Dietrich, Lanphear, & Cecil, 2010).

Research in monkeys and rats has shown that PFC-dependent behaviors are compromised by even low levels of lead exposure. Monkeys exposed to lead were shown to be impaired in learning a delayed alternation task, and they failed to perform the task correctly when the delays were long (Rice & Karpinski, 1988). In rats, it has been shown that lead exposure disrupts neurodevelopmental processes such as neuron migration, synapse formation, and myelination, and also interferes with several neurotransmitter systems, including dopamine, glutamate, and acetylcholine (Costa, Aschner, Vitalone, Syversen, & Soldin, 2004).

## CHRONIC STRESS

A "stressor" can be defined as a real or perceived threat to homeostasis, and "stress" can be defines as the state of experiencing such stressors. Stressors can take many forms, including exposure to predators, physical restraint, and maternal separation. A neural pathway that includes the amygdala, hippocampus, and medial prefrontal cortex (mPFC) has been implicated in the physiological response to stress (de Kloet, Joels, & Holsboer, 2005; Krugers, Hoogenraad, & Groc, 2010). These brain structures exert influence over the hypothalamic-pituitary-adrenal axis. The hypothalamus releases corticotropin-releasing hormone, which regulates secretion of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. In turn, ACTH acts upon the adrenal glands, which regulate the secretion of cortisol. Hippocampus, amygdala, and PFC contain a large number of receptors for cortisol and glucocorticoid receptors, so it stands to reason that these regions are particularly sensitive to levels (de Kloet et al., 2005; Joels, Pu, Wiegert, Oitzl, & Krugers, 2006; Figure 11–5).

Cortisol release is adaptive when orchestrating an acute stress response: it leads to the release of energy from storage and puts long-term projects like reproduction and immune system maintenance on hold. However, chronically high levels of cortisol can wreak havoc on tissue systems throughout the body, including the brain (McEwen, 2004; Sapolsky, 2003). Chronic stress is a risk factor for many psychiatric illnesses (Brown, Varghese, & McEwen, 2004) but also takes a toll on cognition in healthy individuals. Here we will consider animal research on the effects of stress in utero and on postnatal development. This body of research provides a window into potential mechanisms underlying the neural effects of deprivation. We will discuss the effects of stress at the molecular and cellular levels and then widen our view to consider how stress affects PFC-dependent behavior in rodents. Animal models of chronic stress provide insights

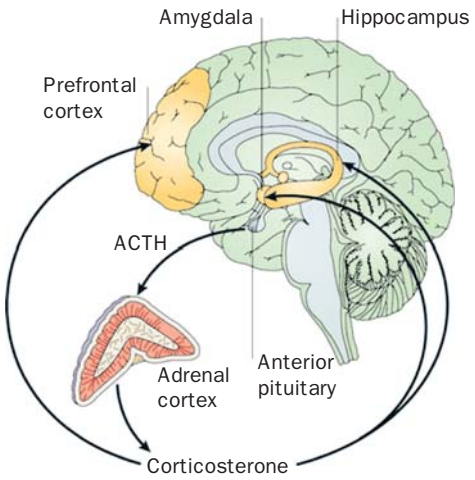


*Figure 11–5* The hypothalamic-pituitary-adrenal (HPA) axis regulates cortisol levels. The hypothalamus (not shown) triggers ACTH release from the anterior pituitary, which in turn activates cortisol release from the adrenal cortex. The amygdala, hippocampus, and PFC express receptors for cortisol, so structure and function in these regions are affected by its levels. These regions also play a role in controlling the HPA axis. Source: Reproduced, with permission, from Krugers et al. © 2010.

regarding children dealing with chronic stress, including children who experience early deprivation (the section "Psychosocial Deprivation") and children from low-SES homes (the section "Low SES").

Chronic stress can change gene expression. When glucocorticoid receptors bind cortisol, they dimerize and become activated transcription factors. In addition to acting directly as a transcription factor, cortisol can lead to histone acetylation and increased methylation (see the section "Gene-Environment Interactions"). An example of a direct link between environment and these epigenetic effects comes from work on the relationship between maternal behavior and stress reactivity (Weaver et al., 2004). High-quality maternal behavior, as measured by high levels of licking and grooming, alters the epigenomes of rat pups. This experience changes methylation patterns and histone acetylation to lead to reduced expression of glucocorticoid receptors (Szyf, Weaver, & Meaney, 2007). Rat pups that experience low-quality maternal behavior, in contrast, have higher glucocorticoid receptor expression and higher levels of stress reactivity. These pups have abnormal behaviors, including impaired novelty seeking, spatial learning (Liu, Diorio, Day, Francis, & Meaney, 2000), and working memory (Barha, Pawluski, & Galea, 2007), that persist into adulthood. This finding from the animal literature parallels the finding that deficient early caregiving in humans, as experienced in Romanian orphanages, could lead to long-lasting brain changes.

In part through its epigenetic effects, stress can alter cellular morphology. For example, exposure to stress hormones in utero leads to decreases in spine density and dendritic complexity in dorsal anterior cingulate cortex, a subregion of mPFC, and orbitofrontal cortex (Murmu et al., 2006). These changes mirror cellular morphology changes in hippocampus, in which cells also show dendritic hypotrophy. Stress actually reshapes neurons in the mPFC, hippocampus, and amygdala and, by changing their structure, affects network connectivity. Interestingly, mPFC seems to be more sensitive to the effects of stress than either the hippocampus or the amygdala. Dendrites in PFC begin to change after just 1 week of stress (Brown, Henning, & Wellman, 2005), but structural changes in these other regions take several weeks (McEwen, 2005).

The effects of this remodeling are evident in behavior. In addition to deficits in behaviors dependent on the hippocampus and the amygdala (Conrad, Galea, Kuroda, & McEwen, 1996; de Kloet, Oitzl, & Joels, 1999; Vyas, Pillai, & Chattarji, 2004), stress causes clear deficits in PFC-dependent behaviors such as working memory (Diamond, Park, Heman, & Rose, 1999; Mizoguchi et al., 2000) and attention. Liston and colleagues found that, in rodents, stress decreased apical dendrite length in PFC, and this was correlated with impairments in attention shifting (Liston et al., 2006). In summary, chronic stress leads to elevated cortisol levels, which in turn alter gene expression, neural structure and function, and PFC-dependent behaviors. In the next sections we discuss how environments associated with chronic stress, early deprivation, and low SES impact PFC structure and function in children.

## PSYCHOSOCIAL DEPRIVATION

Institutionalization in early childhood can drastically alter development. Institutional settings tend to be characterized by a low caregiver-to-child ratio, unresponsive caregiving, and impoverished sensory, cognitive, and linguistic stimulation (Nelson et al., 2007). As a result, children who spend time in these orphanages suffer cognitive impairments spanning a wide variety of abilities, including language, social-emotional development, and cognitive control. The literature on children who have experienced profound and prolonged deprivation is substantial (Gunnar, Bruce, & Grotevant, 2000; Gunnar & van Dulmen, 2007).

Here we summarize the extant literature on deficits in PFC-dependent cognitive function and PFC structure and function in children who have experienced early environmental deprivation. Behavioral research indicates that adolescents who were adopted because of early caregiver deprivation have impaired cognitive control relative to age-matched controls (Mueller et al., 2010). Adolescents who had experienced early deprivation were slowed to switch from a prepotent ("go") response to an alternative ("change") response. These adolescents also showed greater activity in inferior PFC in response during task-switching trials.

An early positron emission tomography (PET) study showed that children adopted from Romanian orphanages showed reduced orbitofrontal cortex (OFC) activity compared to adults and the nonepileptic hemispheres of childhood epilepsy controls (Chugani et al., 2001). These children also showed reduced activity in medial and lateral temporal lobes and brainstem. More recently, a diffusion tensor imaging (DTI) study provided evidence of reduced white matter integrity in children who had been institutionalized (Govindan, Behen, Helder, Makki, & Chugani, 2010). Reductions in fractional anisotropy (FA) were localized to the uncinate fasciculus, which connects the medial temporal lobe to OFC, and the superior longitudinal fasciculus, which connects frontal, parietal, and temporal cortices. In the right uncinate fasciculus, FA decreases were correlated with the duration of stay in an orphanage. Further, a structural MRI study revealed that OFC volumes were smaller in children who had suffered parental physical abuse (Hanson et al., 2010).

The deficits in PFC development associated with early institutional rearing have been attributed to the absence of "expectable" environmental inputs during sensitive periods, or periods of development during which certain neural systems are more plastic (Nelson & Sheridan, in press). This plasticity is adaptive in the sense that environmental input can shape the system to deal with the environment, but it leaves the system vulnerable in that the *absence* of positive environmental input can negatively impact development in a lasting way. The question of whether the effects of early deprivation can be remediated with an enriched environment will be addressed in the section "Positive Environmental Influences on Prefrontal Development."

## LOW SES

Leaving aside extreme environments, like the Romanian orphanages described above, children's schooling and home environments vary in ways that influence a child's acquisition of knowledge and skills. These differences between neighborhoods may influence the developmental trajectory of the PFC and other brain regions. Although the long-term consequences of low SES on brain development are still largely unknown, this topic has begun to receive attention over the last few years (Hackman & Farah, 2009; Hackman, Farah, & Meaney, 2010; Raizada & Kishiyama, 2010).

Low SES can be defined with reference to parental income, occupation, and/or education (objective SES) or by parents' assessment of where they stand within their community (subjective SES; Kopp, Skrabski, Szekely, Stauder, & Williams, 2007). Poverty, by contrast, is defined strictly with regard to parental income. The key aspects of the distinction between poverty and SES were well captured by Huston, McLoyd, and Coll (1994): "Poverty is not isomorphic with low SES. The term 'socioeconomic status' typically is used to signify an individual's, family's, or group's ranking on a hierarchy according to their access to or control over some combination of valued commodities such as wealth, power, and social status (Mueller & Parcel, 1981). It is not based on an absolute standard or threshold, and its indicators, such as occupational status, educational attainment, prestige, and power, are clearly related to, but distinct from, poverty status. Furthermore, poverty status is considerably more volatile than SES because income shifts markedly from one year to another more often than such SES indicators as educational attainment and occupational status (Duncan et al., 1984). These distinctions among categories of economic hardship are important because of their potential to affect children's development differentially" (p. 277).

### *Academic Achievement and Performance on Cognitive Measures*

It has been well documented that children from low-SES backgrounds are at higher risk of difficulties in school than their middle-class peers (Bradley & Corwyn, 2002). The list of possible reasons for this difference is extensive. Low SES tends to be associated with lower levels of parental education, as well as a higher incidence of many of the physical factors described above, such as exposure to environmental toxins like lead (Miranda, Edwards, Swamy, Paul, & Neelon, 2010). Additionally, the existence of socioeconomic disparities can lead to higher levels of chronic stress in lower-SES individuals. In animal models, as described below, chronic stress is correlated with changes in the structure and function of PFC. Regardless of the individual causal factors behind the deficits in PFC-dependent cognition in children from low-SES backgrounds, a better understanding of SES-related differences in brain and cognitive development is essential for designing effective brain-based interventions.

While there is a relationship between SES and performance on many tests of cognition (Bradley & Corwyn, 2002; Duncan, Brooks-Gunn, & Klebanov, 1994; Kiernan & Huerta, 2008; McLoyd, 1998), language and cognitive control appear to be influenced more strongly by childhood environment than other areas of cognition (Noble, McCandliss, & Farah, 2007). Here we will briefly discuss SES-related differences in language skills, with a focus on inferior frontal gyrus (IFG), then turn our attention to studies that have shown differences in prefrontal structure, function, and cognition between high- and low-SES children. A broader discussion of deficits across cognitive and emotional systems can be found elsewhere (Hackman & Farah, 2009; Hackman et al., 2010; Raizada & Kishiyama, 2010).

### *Effects of Childhood Language Exposure on the IFG*

Early language exposure is, on average, greatly diminished in children from low-SES backgrounds. Twenty years ago, it

was shown that the average number of hours of one-on-one picture book reading experienced by children prior to kindergarten entry was 25 for low-SES children and between 1000 and 1700 for middle-SES children (Adams, 1990). Subsequently, Hart and Risley showed that children from low-SES backgrounds have heard on average 30 million fewer words by the age of 3 than children from more privileged families (Hart & Risley, 2003). Exposure to child-directed speech strongly predicted vocabulary level at age 3 and academic outcomes through the third grade. It is also important to highlight—even though the consequences are not yet well understood—that by the age of 4, children from low-SES backgrounds have received on average 26,000 verbal encouragements and 57,000 discouragements, compared with 166,000 encouragements and 26,000 discouragements for children from higher-SES backgrounds.

Given these extreme differences in language exposure, it is perhaps not surprising that a critical brain region supporting language is influenced by SES. Raizada and colleagues found a correlation between SES and the degree of hemispheric specialization in left IFG during a rhyming task in 5-year-old children (Raizada, Richards, Meltzoff, & Kuhl, 2008; Figure 11–6). The higher the SES of the child, the greater the difference in level of fMRI activation in the left IFG (i.e., Broca's area) compared to the right IFG. In other words, higher SES correlated with higher left lateralization of language processing. The degree of left lateralization of language has been found in several studies to be an indicator of the maturation of language-processing areas of the brain (Amunts, Schleicher, Ditterich, & Zilles, 2003; Lu et al., 2007).

### *Attention and Working Memory*

There is behavioral evidence that children from low-SES backgrounds score lower than children from middle- and high-SES backgrounds on attentional tasks (Mezzacappa, 2004). This research has been conducted with Posner's Attention Network Test (ANT), which measures three forms of attention: alerting, orienting, and executive attention (Berger, Jones, Rothbart, & Posner, 2000). Children from lower-SES backgrounds performed worse than their peers on the alerting and executive attention components of the ANT.

This behavioral difference in attention has since been investigated with electroencephalography (EEG). D'Angiulli and colleagues found that children from a low-SES group did not show the same event-related potential (ERP) waveform difference between attended and unattended tones as a high-SES group (D'Angiulli, Herdman, Stapells, & Hertzman, 2008). In this task, children listened to two audio streams, one in each ear. These streams differed in frequency, and children were instructed to attend to only one of the streams, pressing a button each time they heard a tone that was longer in duration than other tones in that stream. The two groups showed differential patterns of theta activity related to target tones in the irrelevant stream. Interestingly, the groups did not differ either in accuracy or response times, suggesting that the neural measures were more sensitive than the behavioral measures. According to this interpretation, behavioral differences should be evident on a more challenging version of the task.

Orienting to novel stimuli is an important first step in learning. A novelty-orienting ERP response is characterized as a negative-going deflection over frontocentral electrode sites beginning around 200 ms after presentation of a novel stimulus (N2). Surprisingly, the results of a small study suggest that even this rapid orienting process may be affected by SES. Kishiyama, Knight, and colleagues investigated the prefrontal novelty response in children aged 7–12 from high- and low-SES backgrounds (Kishiyama, Boyce, Jimenez, Perry, & Knight, 2009). They found a reduced ERP response to novel pictures in children from the low-SES backgrounds. This finding mirrored the finding from a similar task in adult patients

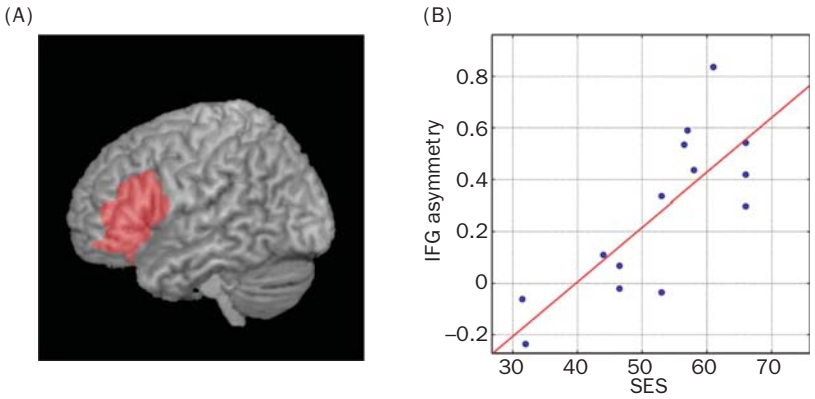


*Figure 11–6* (A) Anatomically defined IFG region of interest. (B) Correlation between SES and the left-minus-right rhyme-task activity in the IFG (termed "IFG asymmetry"). Each dot represents one child. Significance is $p < .05$ after FDR correction for multiple comparisons run in the study ($r = .78$, $p < .001$ uncorrected). Source: Reproduced, with permission, from Raizada et al. © 2008.

with PFC damage (Barcelo, Suwazono, & Knight, 2000; Knight, 1984; Yago, Duarte, Wong, Barcelo, & Knight, 2004). However, caution should be used in comparing adult patients with neurologically unimpaired children. Many of the most important questions will require multi-year longitudinal studies. What, if any, are the behavioral consequences of a blunted orienting response? Do the SES-related ERP differences observed in children persist into adulthood? Finally, can positive interventions counteract the early effects of socioeconomic disadvantage?

There is some evidence that when children grow up with a prolonged and unaddressed disadvantage, this can have long-lasting consequences for cognitive functioning. For example, Evans and Schamberg (2009) showed that spatial working memory performance in adults is correlated with duration of poverty during childhood. This relationship between childhood SES and later working memory performance appears to be mediated by stress levels during childhood (Evans & Schamberg, 2009).

### *Interim Summary*

The influence of SES on PFC development is a sensitive topic of research, and as such should be broached with care. However, it is only by directly investigating these issues that we can improve our understanding of the environmental factors that influence cognitive and brain development. New research is starting to indicate that positive interventions might be able to level the playing field of social disadvantage (see the section "Positive Environmental Influences on Prefrontal Development"). Currently, the vast majority of low-SES children never receive such assistance. Additional neuroscientific research on the effects of low SES and poverty could influence public policy for the better, for example through the work of such groups as the National Forum on Early Child Policy and Programs and the affiliated National Scientific Council on the Developing Child, both based in the United States.

## POSITIVE ENVIRONMENTAL INFLUENCES ON PREFRONTAL DEVELOPMENT

Intensive cognitive training studies in adults are beginning to reveal training-related prefrontal structure and function (Braver, Paxton, Locke, & Barch, 2009; Erickson et al., 2007; Klingberg, 2010; Miotto et al., 2006). Further, there is strong evidence that physical exercise confers beneficial effects on PFC-dependent cognitive function in both adults and children (Hillman, Erickson, & Kramer, 2008). For extensive discussion of the effects of cognitive training and exercise on prefrontal structure and function, please refer to Section IX of this book. Here we review extant intervention research involving children from deprived backgrounds and then turn to the animal literature on environmental enrichment to discuss potential neural mechanisms of training effects.

## INTERVENING AFTER SEVERE PSYCHOSOCIAL DEPRIVATION

In the section "Psychosocial Deprivation," we discussed the negative effects of early deprivation on PFC development. Here we will focus on research on interventions for these children and ask whether the impairments caused by institutionalization are reversible. Encouraging evidence has come from the Bucharest Early Intervention Program (BEIP), a study of a foster care intervention for institutionalized children in Bucharest, Romania. In this study, children were randomly assigned to either remain in the institution or were placed into a foster care intervention. Random assignment removed the confound present in other studies that children who are most physically or mentally fit are most likely to be adopted.

Behaviorally, the BEIP has shown that children who were raised in a foster home rather than the orphanage have greatly improved emotional function (Ghera et al., 2009), language (Windsor, Glaze, & Koga, 2007), general cognitive abilities (Nelson et al., 2007), and spatial working memory (Bos, Fox, Zeanah, & Nelson Iii, 2009). Importantly, improvements were greatest when children were removed from orphanages before the age of 2. While this seems to suggest that there may be a sensitive period in the first 2 years of life, the authors note that the younger children are when placed in foster care, the better they are able to recover from this adverse experience.

Neurally, the BEIP has shown that foster care normalized the abnormal pattern of EEG activity observed in institutionalized children, leading to an increase in alpha-band oscillatory activity and decreased short-distance EEG coherence (Marshall, Reeb, Fox, Nelson, & Zeanah, 2008), which likely reflect an increase in cross-talk between distant brain regions. Consistent with the behavioral results of the BEIP (e.g. Nelson et al., 2007), the effects of intervention on EEG activity were most pronounced in children who were placed in foster care before the age of 2. Future research with combined EEG/fMRI or magnetoencephalography is needed to localize definitively the source of the changes in the EEG signal.

Nelson and colleagues have attributed the improvements observed in the BEIP to activity-dependent mechanisms of plasticity engaged when children are placed in a cognitively stimulating environment (Nelson et al., 2007). They have emphasized that sensitive periods may be modifiable given the right circumstances, and that extending the window for intervention may improve the prognosis for children recovering from early deprivation. This line of research has wide-reaching policy implications for countries deciding how to best care for abandoned, orphaned, or maltreated children. The BEIP

has demonstrated that foster care leads to more positive developmental outcomes than institutionalization.

## PROGRAMS FOR CHILDREN FROM LOW-SES FAMILIES

The two best examples of randomized interventions with long-term longitudinal follow-up data are the Abecedarian Program (Barnett & Masse, 2007; Campbell, Pungello, Miller-Johnson, Burchinal, & Ramey, 2001) and the Perry Preschool Program (Belfield, Nores, Barnett, & Schweinhart, 2006; Muennig, Schweinhart, Montie, & Neidell, 2009; Weikart, 1998). Both programs concentrated on low-SES, predominantly ethnic minority children. The Perry program enrolled 64 children at ages 3 and 4 and consisted of intensive daily sessions lasting 2½ hours each, as well as a weekly 90-minute home visit to build parental involvement. These sessions lasted for 30 weeks each year for 4 years. Longitudinal follow-up is ongoing, with the most recent paper describing the participants 37 years later (Muennig, Schweinhart, Montie, & Neidell, 2009). The Abecedarian program was larger and was even more intensive, involving full-day care for 5 days per week, 50 weeks per year. The children started at an average age of 4.4 years and remained in the program until age 8. Longitudinal follow-up continued until age 21.

Even decades later, the combination of a rigorous randomized-control design, intensive intervention, and long-term follow-up provided by these two programs remains unique. All three of these factors are essential for increasing our understanding of the long-term causal role of early childhood intervention, but they are also the factors that are the most difficult to implement. At present, there are many open questions in this area that are ripe for empirical investigation (see the section "Future Directions").

The Perry and Abecedarian programs targeted a broad range of cognitive skills, so it is not possible to determine which components of these programs have been most effective or why. However, there also exist several low-SES-targeted interventions focused on strengthening PFC-dependent skills. One influential study showed that executive functions were enhanced by a program that taxed cognitive control throughout the preschool curriculum (Diamond, Barnett, Thomas, & Munro, 2007). Many of these children came from underprivileged backgrounds. This program consisted of instructional strategies that encouraged cognitive control throughout the day rather than expensive computer programs.

Recently, we conducted a study to determine whether fluid reasoning (FR) ability could be trained in children, using a set of commercially available games that require children to jointly consider several pieces of information to achieve a goal (Mackey et al., 2011). We compared the effects of FR training to those of a well-matched training program that also targeted a critical cognitive skill: processing speed (PS; Kail & Salthouse, 1994). Our study took place as part of an after-school program at a school in Oakland, California, with a history of low statewide test scores. Both training programs included a variety of commercially available computerized and noncomputerized games.

Children in the reasoning group showed a large improvement on a standard measure of FR. This improvement corresponded to an average increase of 10 Performance IQ points, with many individuals' normed scores going from well below average to average (Figure 11–7, "Matrix Reasoning"). The FR group did not improve significantly on a standard measure of PS. In contrast, children in the cognitive speed group improved on the PS measure but did not improve on the FR measure (Figure 11–7, "Cognitive Speed"). Thus, both groups

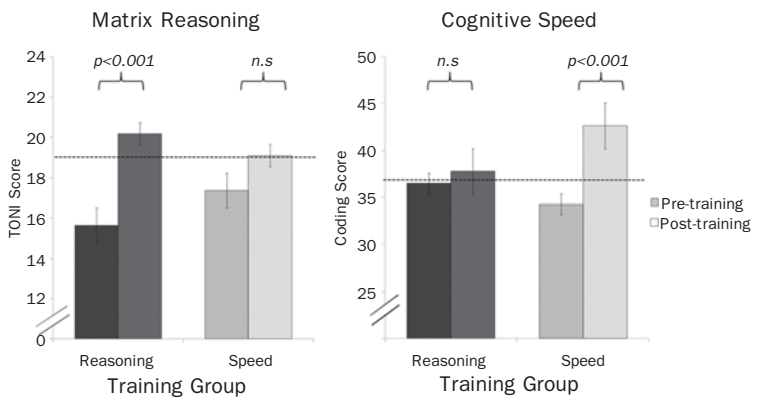


*Figure 11–7* Children aged 7 to 9 participated in one of two cognitive training programs for 60 minutes per day, 2 days per week, for a total of 8 weeks. Children in the reasoning group ($n = 17$) played games that targeted relational integration and planning. Children in the speed group ($n = 11$) played games that required rapid visual processing and motor responses. Children in the reasoning group improved selectively on a measure of matrix reasoning, the Test of Nonverbal Intelligence (TONI), while children in the speed group improved on a test of cognitive speed, Coding from the Wechsler Intelligence Scale for Children (WISC). The dotted lines represent the performance of an average 8.5-year-old child. Source: Reproduced, with permission, from Mackey et al. © 2011.

exhibited transfer of learning to tasks that were not included in the training programs.

These initial neuroscience-based cognitive training studies are encouraging, but there is much work to be done. Additional research is needed—both for this intervention and others—to determine how much training is needed, how often it must be repeated, and how these performance improvements relate to scholastic performance and other real-world outcome measures. There is also a need for additional neuroimaging research to uncover the changes in brain structure and/or function that underlie training-related behavioral improvements. Neuroimaging measures may also be able to predict long-term benefits from training programs, even when cognitive improvements are not detectable. However, these techniques can only help us understand changes at a gross level. At the cellular level, cognitive training could lead to synaptogenesis and myelination, but it is only possible to investigate changes at this level in animal models. Large-scale changes in myelination, however, can be detected with DTI. Recent DTI studies have indeed shown plastic changes in myelinated white matter tracts as a result of training in adults (Scholz et al., 2009) and in children (Hu et al., 2011).

## ANIMAL MODEL: ENVIRONMENTAL ENRICHMENT PARADIGM

Donald Hebb and his students showed more than 60 years ago that rats housed in a complex environment outperformed rats housed in a standard laboratory environment on several tests of rodent cognition (for review, see Markham & Greenough, 2004). Several groups, including those of Mark Rosenzweig and William Greenough, subsequently used this "environmental enrichment paradigm" to study how housing conditions could affect brain structure (Figure 11–8).

In these studies, rats were assigned to one of several housing conditions at weaning. In the standard condition (SC), three animals were kept in a standard laboratory cage and provided with food and water. In the enriched condition (EC), a group of 10–12 animals was kept in a large cage containing a variety of stimulus objects, which were changed daily. As Markham and Greenough (2004) note, the term "enriched" is a misnomer, because this condition was not enriched relative to a natural habitat, but rather relative to the standard laboratory environment or to an impoverished (or isolated) condition (IC), in which a single animal was housed in an SC-sized cage.

A landmark study by Mark Rosenzweig and colleagues showed that rats raised in the EC had heavier brains than those raised in the IC (Rosenzweig, Krech, Bennett, & Diamond, 1962). Up to that point, brain weight had been considered a very stable trait—not one that was subject to environmental influences. Subsequent neuroanatomical research revealed that these differences in brain weight were caused by differences in cortical thickness. Animals exposed to the EC environment developed slightly but significantly thicker cerebral cortices than their SC or IC littermates (Diamond, Krech, & Rosenzweig, 1964; Diamond, Lindner, & Raymond, 1967). More detailed neuroanatomical measurements of pyramidal neurons in the occipital cortex revealed changes in the size of cell bodies, number of dendritic spines, dendritic branching, and size of synaptic contacts (Rosenzweig et al., 1962; for review, see Rosenzweig, Breedlove, & Leiman, 2002). Subsequent research has provided evidence for environmental influences on the structure of PFC in addition to other cortical regions. These studies have found changes in spine density in medial PFC (Kolb, Gorny, Soderpalm, & Robinson, 2003) as well as in dendritic length in OFC (Bock, Murmu, Ferdman, Leshem, & Braun, 2008). Consistent with this research in animals, recent research in humans suggests that intensive training of attention, working memory, and other PFC-dependent cognitive functions may indeed lead to structural changes in the PFC.

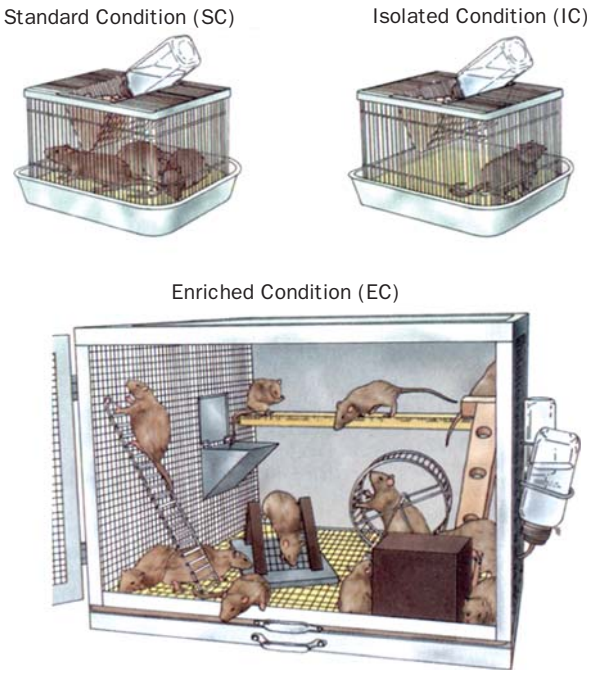


*Figure 11–8* Housing conditions used in animal enrichment experiments. In the standard condition (SC), animals are housed with littermates. In the isolated condition (IC), animals are housed alone. In the enriched condition (EC), animals are housed with toys and exercise wheels that are changed regularly. Source: Reproduced, with permission, from Rosenzweig et al. (2002), © 2002.

## SUMMARY

The key points of this chapter can be summarized as follows:

1. Extant research indicates that the development of PFC can be affected profoundly by environmental factors,

both physical and psychosocial. The biological and environmental factors that contribute to PFC-dependent behavior are summarized in Figure 11–9.

2. Because of its continued development throughout childhood and adolescence, PFC has a long sensitive period during which it can be strongly influenced by experience.
3. Research in nonhuman animals has begun to reveal multiple mechanisms through which experience can modulate gene expression and, in turn, PFC development.
4. Controlled experiments in nonhuman animals have characterized the detrimental effects of multiple environmental factors on brain development. Some of these factors, including drugs of abuse and exposure to lead, have a pronounced effect on PFC.
5. In humans, many negative environmental factors tend to co-occur, leading to cumulative risk. Further research is needed to better understand how this complex set of factors, taken as a whole, influences prefrontal development.
6. Environmental enrichment in rats is associated with increased numbers of dendrites and dendritic spines in PFC as well as elsewhere in the cortex.7. Intensive cognitive training studies in humans are beginning to reveal training-related changes in prefrontal structure and function; the cellular underpinnings of these changes in humans are currently unknown.

## FUTURE DIRECTIONS

There are still many unknowns regarding the role of environmental influences in the development and function of PFC. There is a need for additional research at all levels of neuroscience on the effects of negative and—even more so—positive experience on prefrontal development. This research will provide theoretical insights for our understanding of individual differences in PFC-dependent abilities. Additionally, it will provide practical insights improving our ability to prevent, limit, and potentially even reverse negative influences on the development of PFC. Because this research has important implications for policy, it must be carried out and reported with great care. Some important avenues of inquiry are the following:

1. What is the period of maximal sensitivity for PFC development in humans? Does it depend on the type of environmental influence in question, and does it vary widely across individuals? It will be necessary to follow individuals who were exposed to negative environmental influences early in life throughout childhood and adolescence to address these important but difficult questions. Because the PFC takes so long to mature, the impact of early negative environmental influences on prefrontal function may go unnoticed for years or may not be noticed at all. For example, a 3-year-old with compromised prefrontal function may not behave very differently from a healthy 3-year-old but may have a markedly different developmental trajectory later in childhood and in adolescence.
2. Do environmental factors influence the extent to which the PFC can be shaped by experience? The concept of "metaplasticity" refers to a change in the *potential* for change (Abraham & Tate, 1997). This term was coined to describe plasticity at the level of individual synapses, but metaplasticity may well take place at the level of larger neural systems. Does one's potential for plasticity in the PFC at a given age depend on factors

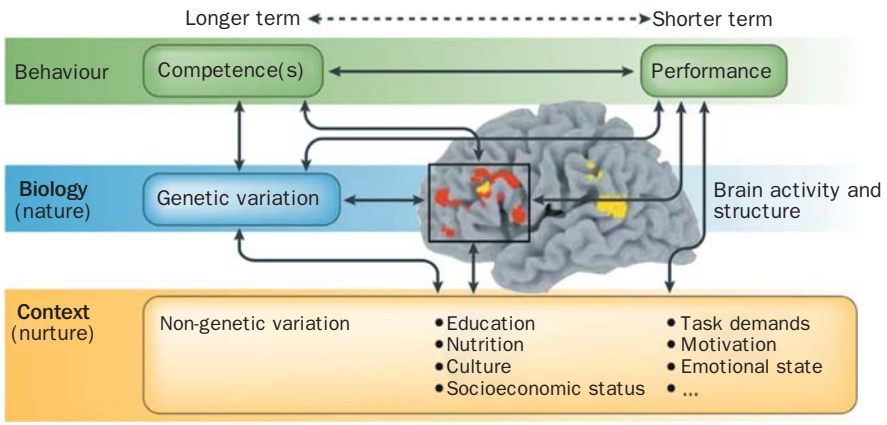


*Figure 11–9* This model from Gray and Thompson highlights the complex relationships between biology (nature) and context (nurture) in shaping prefrontal function. Factors such as genetic variation exert their influence on the time scale of generations, whereas factors like changes in brain electrical activity can act on the time scale of seconds. Contextual factors such as education, culture, nutrition, and SES shape cognition throughout an individual's lifetime, while more variable factors like motivation alter cognition from minute to minute. Source: Reproduced, with permission, from Gray and Thompson © 2004.

like educational attainment, physical exercise, and nutrition?

3. What is the role of hormones in the interplay between genetics, the environment, and brain development? And how are boys' and girls' brains affected by the process of going through puberty? Steroid hormones exert powerful influences on neural function because they cross the blood-brain barrier and diffuse into the extracellular space in the brain. These hormones can modulate the response parameters of neurons to neurotransmitters; this phenomenon is referred to as "metamodulation" (Mesce, 2002).

4. What are the cellular underpinnings of training-related changes in the PFC? In reviewing the animal research on environmental enrichment, Markham and Greenough (2004) note that "Initially, alterations in neuronal structure were the focus of investigation; however, more recently it has become clear that other components of the nervous system, such as macroglial cells and cerebrovasculature elements, also exhibit robust plasticity in response to experience" (p. 351). By and large, however, these findings are not based on investigations of changes in the PFC after training on PFC-dependent tasks. New research focused on cellular changes in the PFC will shed light on training-related changes in prefrontal structure and function observed in human imaging studies.

5. It is possible that training-related gains in PFC function fade quickly regardless of a child's age and level of functioning, necessitating regular maintenance. Such a finding would not invalidate the cognitive intervention; it is generally agreed that physical exercise is important for bodily health, even though one must exercise regularly to enjoy its benefits over the long term. Nonetheless, there are some learning experiences that put a child on a new trajectory. For example, teaching a child to read opens up a new world of opportunities because it provides her or him with a tool for lifelong learning. Evidence that short-term apparent fade-out can be followed many years later by meaningful gains comes from the Perry Preschool and Abecedarian programs mentioned above: children appeared to lose their gains within 1 or 2 years after the interventions ended, but decades later their rates of high school graduation, college enrollment, and related measures were markedly higher than those of the control group (Knudsen, Heckman, Cameron, & Shonkoff, 2006). Might particular cognitive training programs aimed at young children with poor PFC function similarly have the potential to alter the course of their development by boosting skills necessary for learning and problem solving (Blair & Diamond, 2008)? If so, in what ways might such programs alter brain development?

## ACKNOWLEDGMENTS

This chapter is dedicated to Mark Rosenzweig and Marian Diamond, professors at UC Berkeley, who contributed greatly to the field of brain plasticity. The authors are indebted to these and other researchers whose ideas and research are featured throughout this chapter, including Donald Hebb, William Greenough, Charles Nelson, Megan Gunnar, Nathan Fox, and many more. We thank Monique Porsandeh for assistance with manuscript preparation.

## DISCLOSURE STATEMENT

The authors were supported by an NSF predoctoral fellowship (A.P.M.) and a grant from the MacArthur Law and Neuroscience Project (S.A.B.). A.P.M., R.D.S.R., and S.A.B. have no conflicts of interest to disclose.

## REFERENCES

Abraham, W. C., & Tate, W. P. (1997). Metaplasticity: A new vista across the field of synaptic plasticity. *Progress in Neurobiology, 52*, 303–323.

Accornero, V. H., Amado, A. J., Morrow, C. E., Xue, L., Anthony, J. C., & Bandstra, E. S. (2007). Impact of prenatal cocaine exposure on attention and response inhibition as assessed by continuous performance tests. *Journal of Developmental Behavior and Pediatrics, 28*, 195–205.

Adams, M. J. (1990). *Learning to read: Thinking and learning about print*. Cambridge, MA: MIT Press.

Amunts, K., Schleicher, A., Ditterich, A., & Zilles, K. (2003). Broca's region: Cytoarchitectonic asymmetry and developmental changes. *Journal of Comparative Neurology, 465*, 72–89.

Andersen, S. L., & Teicher, M. H. (2008). Stress, sensitive periods and maturational events in adolescent depression. *Trends in Neurosciences, 31*, 183–191.

Barcelo, F., Suwazono, S., & Knight, R. T. (2000). Prefrontal modulation of visual processing in humans. *Nature Neuroscience, 3*, 399–403.

Barha, C. K., Pawluski, J. L., & Galea, L. A. (2007). Maternal care affects male and female offspring working memory and stress reactivity. *Physiology & Behavior, 92*, 939–950.

Barnett, W. S., & Masse, L. N. (2007). Comparative benefit-cost analysis of the Abecedarian program and its policy implications. *Economics of Education Review, 26*, 113–125.

Bavelier, D., Levi, D. M., Li, R. W., Dan, Y., & Hensch, T. K. (2010). Removing brakes on adult brain plasticity: From molecular to behavioral interventions. *Journal of Neuroscience, 30*, 14964–14971.

Beard, J. (2003). Iron deficiency alters brain development and functioning. *Journal of Nutrition, 133*, 1468S-1472S.

Belfield, C. R., Nores, M., Barnett, S., & Schweinhart, L. (2006). The High/Scope Perry

Preschool Program: Cost Benefit Analysis Using Data from the Age. *Journal of Human Resources*, *41*, 162.

Berger, A., Jones, L., Rothbart, M. K., & Posner, M. I. (2000). Computerized games to study the development of attention in childhood. *Behavioral Research Methods, Instruments, & Computers, 32*, 297–303.

Blair, C., & Diamond, A. (2008). Biological processes in prevention and intervention: The promotion of self-regulation as a means of preventing school failure. *Development and Psychopathology*, *20* 899–911.

Block, N. (1995). How heritability misleads about race. *Cognition, 56*, 99–128.

Bock, J., Murmu, R. P., Ferdman, N., Leshem, M., & Braun, K. (2008). Refinement of dendritic and synaptic networks in the rodent anterior cingulate and orbitofrontal cortex: Critical impact of early and late social experience. *Developmental neurobiology*, *68*, 685–695.

Bos, K. J., Fox, N., Zeanah, C. H., & Nelson III, C. A. (2009). Effects of early psychosocial deprivation on the development of memory and executive function. *Frontiers in Behavioral Neuroscience, 3*, 16.

Bradley, R. H., & Corwyn, R. F. (2002). Socioeconomic status and child development. *Annual Review of Psychology, 53*, 371–399.

Braver, T. S., Cole, M. W., & Yarkoni, T. (2010). Vive les differences! Individual variation in neural mechanisms of executive control. *Current Opinions in Neurobiology, 20*, 242–250.

Braver, T. S., Paxton, J. L., Locke, H. S., & Barch, D. M. (2009). Flexible neural mechanisms of cognitive control within human prefrontal cortex. *Proceedings of the National Academy of Sciences of the United States of America, 106*, 7351–7356.

Brown, E. S., Varghese, F. P., & McEwen, B. S. (2004). Association of depression with medical illness: Does cortisol play a role? *Biological Psychiatry, 55*, 1–9.

Brown, S. M., Henning, S., & Wellman, C. L. (2005). Mild, short-term stress alters dendritic morphology in rat medial prefrontal cortex. *Cerebral Cortex, 15*, 1714–1722.

Brubaker, C. J., Dietrich, K. N., Lanphear, B. P., & Cecil, K. M. (2010). The influence of age of lead exposure on adult gray matter volume. *Neurotoxicology, 31*, 259–266.

Campbell, F. A., Pungello, E. P., Miller-Johnson, S., Burchinal, M. R., & Ramey, C. T. (2001). The development of cognitive and academic abilities: Growth curves from an early childhood educational experiment. *Developmental Psychology, 37*, 231–242.

Campolongo, P., Trezza, V., Palmery, M., Trabace, L., & Cuomo, V. (2009). Developmental exposure to cannabinoids causes subtle and enduring neurofunctional alterations. *International Review of Neurobiology, 85*, 117–133.

Canfield, R. L., Gendle, M. H., & Cory-Slechta, D. A. (2004). Impaired neuropsychological functioning in lead-exposed children. *Developmental Neuropsychology, 26*, 513–540.

Carroll, S. B. (2003). Genetics and the making of *Homo sapiens*. *Nature, 422*, 849–857.

Casey, B. J., Giedd, J. N., & Thomas, K. M. (2000). Structural and functional brain development and its relation to cognitive development. *Biological Psychology, 54*, 241–257.

Caspi, A., McClay, J., Moffitt, T. E., Mill, J., Martin, J., Craig, I. W., et al. (2002). Role of genotype in the cycle of violence in maltreated children. *Science, 297*, 851–854.

Caspi, A., & Moffitt, T. E. (2006). Gene-environment interactions in psychiatry: Joining forces with neuroscience. *Nature Reviews Neuroscience, 7*, 583–590.

Cecil, K. M., Brubaker, C. J., Adler, C. M., Dietrich, K. N., Altaye, M., Egelhoff, J. C., et al. (2008). Decreased brain volume in adults with childhood lead exposure. *PLoS Med, 5*, e112.

Champagne, F. A., & Mashoodh, R. (2009). Genes in context: Gene-environment interplay and the origins of individual differences in behavior. *Current Directions in Psychological Science, 18*, 127–131.

Chugani, H. T., Behen, M. E., Muzik, O., Juhasz, C., Nagy, F., & Chugani, D. C. (2001). Local brain functional activity following early deprivation: A study of postinstitutionalized Romanian orphans. *Neuroimage, 14*, 1290–1301.

Cohen, S., & Greenberg, M. E. (2008). Communication between the synapse and the nucleus in neuronal development, plasticity, and disease. *Annual Review of Cell andl Developmental Biology, 24*, 183–209.

Collins, F. S., Morgan, M., & Patrinos, A. (2003). The Human Genome Project: Lessons from large-scale biology. *Science, 300*, 286–290.

Conrad, C. D., Galea, L. A., Kuroda, Y., & McEwen, B. S. (1996). Chronic stress impairs rat spatial memory on the Y maze, and this effect is blocked by tianeptine pretreatment. *Behavioral Neuroscience, 110*, 1321–1334.

Cornelius, M. D., & Day, N. L. (2009). Developmental consequences of prenatal tobacco exposure. *Current Opinions in Neurology, 22*, 121–125.

Costa, L. G., Aschner, M., Vitalone, A., Syversen, T., & Soldin, O. P. (2004). Developmental neuropathology of environmental agents. *Annual Review of Pharmacology and Toxicology, 44*, 87–110.

Crews, F., He, J., & Hodge, C. (2007). Adolescent cortical development: A critical period of vulnerability for addiction. *Pharmacology Biochemistry and Behavior, 86*, 189–199.

D'Angiulli, A., Herdman, A., Stapells, D., & Hertzman, C. (2008). Children's event-related potentials of auditory selective attention vary with their socioeconomic status. *Neuropsychology, 22*, 293–300.

de Kloet, E. R., Joels, M., & Holsboer, F. (2005). Stress and the brain: From adaptation to disease. *Nature Reviews Neuroscience, 6*, 463–475.

de Kloet, E. R., Oitzl, M. S., & Joels, M. (1999). Stress and cognition: Are corticosteroids good or bad guys? *Trends in Neurosciences, 22*, 422–426.

Derauf, C., Kekatpure, M., Neyzi, N., Lester, B., & Kosofsky, B. (2009). Neuroimaging of children following prenatal drug exposure. *Seminars in Cell and Developmental Biology, 20*, 441–454.

Diamond, A., Barnett, W. S., Thomas, J., & Munro, S. (2007). Preschool program improves cognitive control. *Science, 318*, 1387–1388.

Diamond, D. M., Park, C. R., Heman, K. L., & Rose, G. M. (1999). Exposing rats to a predator impairs spatial working memory in the radial arm water maze. *Hippocampus*, *9*, 542–552.

Diamond, M. C., Krech, D., and Rosenzweig, M. R. (1964). The effects of an enriched environment on the histology of the rat cerebral cortex. *The Journal of Comparative Neurology*, *123*, 111–120.

Diamond, M. C., Lindner, B., & Raymond, A. (1967). Extensive cortical depth measurements and neuron size increases in the cortex of environmentally enriched rats. *The Journal of Comparative Neurology, 131*, 357–364.

Dickens, W. T., & Flynn, J. R. (2001). Heritability estimates versus large environmental effects: The IQ paradox resolved. *Psychological Review, 108*, 346–369.

Dodds, C. M., Morein-Zamir, S., & Robbins, T. W. (2011). Dissociating inhibition, attention, and response control in the frontoparietal network using functional magnetic resonance imaging. *Cerebral Cortex, 21, 1155–1165*.

Draganski, B., Gaser, C., Busch, V., Schuierer, G., Bogdahn, U., & May, A. (2004). Neuroplasticity: Changes in grey matter induced by training. *Nature, 427*, 311–312.

Duncan, G.J. (1984). Years of poverty, years of plenty. Ann Arbor, MI: Institute for Social Research, University of Michigan.

Duncan, G. J., Brooks-Gunn, J., & Klebanov, P. K. (1994). Economic deprivation and early childhood development. *Child Development, 65*, 296–318.

Erickson, K. I., Colcombe, S. J., Wadhwa, R., Bherer, L., Peterson, M. S., Scalf, P. E., et al. (2007). Training-induced functional activation changes in dual-task processing: An FMRI study. *Cerebral Cortex, 17*, 192–204.

Evans, G. W., & Schamberg, M. A. (2009). Childhood poverty, chronic stress, and adult working memory. *Proceedings of the National Academy of Sciences of the United States of America, 106*, 6545–6549.

Fuster, J. M. (2002). Frontal lobe and cognitive development. *Journal of Neurocytology, 31*, 373–385.

Galvan, A. (2010). Neural plasticity of development and learning. *Human Brain Mapping, 31*, 879–890.

Ghera, M. M., Marshall, P. J., Fox, N. A., Zeanah, C. H., Nelson, C. A., Smyke, A. T., et al. (2009). The effects of foster care intervention on socially deprived institutionalized children's attention and positive affect: Results from the BEIP study. *Journal of Child Psychology and Psychiatry, 50*, 246–253.

Govindan, R. M., Behen, M. E., Helder, E., Makki, M. I., & Chugani, H. T. (2010). Altered water diffusivity in cortical association tracts in children with early deprivation identified with Tract-Based Spatial Statistics (TBSS). *Cerebral Cortex, 20*, 561–569.

Gray, J. R., & Thompson, P. M. (2004). Neurobiology of intelligence: Science and ethics. *Nature Reviews Neuroscience, 5*, 471–482.
Green, C. S., & Bavelier, D. (2003). Action video game modifies visual selective attention. *Nature, 423*, 534–537.
Greenough, W. T., Black, J. E., & Wallace, C. S. (1987). Experience and brain development. *Child Development, 58*, 539–559.
Gunnar, M. R., Bruce, J., & Grotevant, H. D. (2000). International adoption of institutionally reared children: Research and policy. *Developmental Psychopathology, 12*, 677–693.
Gunnar, M. R., & van Dulmen, M. H. (2007). Behavior problems in postinstitutionalized internationally adopted children. *Developmental Psychopathology, 19*, 129–148.
Hackman, D. A., & Farah, M. J. (2009). Socioeconomic status and the developing brain. *Trends in Cognitive Sciences, 13*, 65–73.
Hackman, D. A., Farah, M. J., & Meaney, M. J. (2010). Socioeconomic status and the brain: Mechanistic insights from human and animal research. *Nature Reviews Neuroscience, 11*, 651–659.
Hanson, J. L., Chung, M. K., Avants, B. B., Shirtcliff, E. A., Gee, J. C., Davidson, R. J., et al. (2010). Early stress is associated with alterations in the orbitofrontal cortex: A tensor-based morphometry investigation of brain structure and behavioral risk. *Journal of Neuroscience, 30*, 7466–7472.
Hart, B., & Risley, T. R. (2003). The early catastrophe: The 30 million word gap by age 3. *American Educator, 22*, 4–9.
Hillman, C. H., Erickson, K. I., & Kramer, A. F. (2008). Be smart, exercise your heart: Exercise effects on brain and cognition. *Nature Reviews Neuroscience, 9*, 58–65.
Hu, Y., Geng, F., Tao, L., Hu, N., Du, F., Fu, K., et al. (2011). Enhanced white matter tracts integrity in children with abacus training. *Human Brain Mapping, 32*, 10–21.
Huston, A. C., McLoyd, V. C., & Coll, C. G. (1994). Children and poverty: Issues in contemporary researc. *Child Development, 65*, 275–282.
Jaeggi, S. M., Buschkuehl, M., Jonides, J., & Perrig, W. J. (2008). Improving fluid intelligence with training on working memory. *Proceedings of the National Academy of Sciences of the United States of America, 105*, 6829–6833.
Joels, M., Pu, Z., Wiegert, O., Oitzl, M. S., & Krugers, H. J. (2006). Learning under stress: How does it work? *Trends in Cognitive Sciences, 10*, 152–158.
Kail, R., & Salthouse, T. A. (1994). Processing speed as a mental capacity. *Acta Psychologica* (*Amsterdan*)*, 86*, 199–225.
Kane, M. J., & Engle, R. W. (2002). The role of prefrontal cortex in working-memory capacity, executive attention, and general fluid intelligence: An individual-differences perspective. *Psychonomics Bulletin Review, 9*, 637–671.
Karni, A., & Bertini, G. (1997). Learning perceptual skills: Behavioral probes into adult cortical plasticity. *Current Opinions in Neurobiology, 7*, 530–535.
Kerns, K. A., Don, A., Mateer, C. A., & Streissguth, A. P. (1997). Cognitive deficits in nonretarded adults with fetal alcohol syndrome. *Journal of Learning Disabilities, 30*, 685–693.
Kiernan, K. E., & Huerta, M. C. (2008). Economic deprivation, maternal depression, parenting and children's cognitive and emotional development in early childhood. *British Journal of Sociology, 59*, 783–806.
Kim-Cohen, J., Caspi, A., Taylor, A., Williams, B., Newcombe, R., Craig, I. W., et al. (2006). MAOA, maltreatment, and gene-environment interaction predicting children's mental health: New evidence and a meta-analysis. *Molecular Psychiatry, 11*, 903–913.
Kishiyama, M. M., Boyce, W. T., Jimenez, A. M., Perry, L. M., & Knight, R. T. (2009). Socioeconomic disparities affect prefrontal function in children. *Journal of Cognitive Neuroscience, 21*, 1106–1115.
Klingberg, T. (2010). Training and plasticity of working memory. *Trends in Cognitive Sciences, 14*, 317–324.
Knight, R. T. (1984). Decreased response to novel stimuli after prefrontal lesions in man. *Electroencephalography and Clinical Neurophysiology, 59*, 9–20.
Knudsen, E. I. (2004). Sensitive periods in the development of the brain and behavior. *Journal of Cognitive Neuroscience, 16*, 1412–1425.
Knudsen, E. I., Heckman, J. J., Cameron, J. L., & Shonkoff, J. P. (2006). Economic, neurobiological, and behavioral perspectives on building America's future workforce. *Proceedings of the National Academy of Sciences of the United States of America, 103*, 10155–10162.
Kolb, B., Gorny, G., Soderpalm, A. H., & Robinson, T. E. (2003). Environmental complexity has different effects on the structure of neurons in the prefrontal cortex versus the parietal cortex or nucleus accumbens. *Synapse, 48*, 149–153.
Kopp, M. S., Skrabski, A., Szekely, A., Stauder, A., & Williams, R. (2007). Chronic stress and social changes: Socioeconomic determination of chronic stress. *Annals of the New York Academy of Sciences, 1113*, 325–338.
Krugers, H. J., Hoogenraad, C. C., & Groc, L. (2010). Stress hormones and AMPA receptor trafficking in synaptic plasticity and memory. *Nature Reviews Neuroscience, 11*, 675–681.
Langlois, E. M., & Mayes, L. C. (2008). Impact of prenatal cocaine exposure on the developing brain. In C. A. N. A. M. Luciana (Ed.), *Handbook of developmental cognitive neuroscience* (pp. 653–676). Cambridge, MA: MIT Press.
Lenroot, R. K., Schmitt, J. E., Ordaz, S. J., Wallace, G. L., Neale, M. C., Lerch, J. P., et al. (2009). Differences in genetic and environmental influences on the human cerebral cortex associated with development during childhood and adolescence. *Human Brain Mapping, 30*, 163–174.
Levenson, J. M., & Sweatt, J. D. (2005). Epigenetic mechanisms in memory formation. *Nature Reviews Neuroscience, 6*, 108–118.
Lewis, C., Koyasu, M., Oh, S., Ogawa, A., Short, B., & Huang, Z. (2009). Culture, executive function, and social understanding. *New Directions for Child and Adolescent Development, 2009*, 69–85.
Lewontin, R. (1970). Race and Intelligence. *Bulletin of Atomic Scientists*, 2–8. Reprinted in The IQ Controversy (eds Block, N. & Dworkin, G.) 78–92 (Pantheon, New York, 1976).
Li, R., Polat, U., Makous, W., & Bavelier, D. (2009). Enhancing the contrast sensitivity function through action video game training. *Nature Neuroscience, 12*, 549–551.
Liston, C., Miller, M. M., Goldwater, D. S., Radley, J. J., Rocher, A. B., Hof, P. R., et al. (2006). Stress-induced alterations in prefrontal cortical dendritic morphology predict selective impairments in perceptual attentional set-shifting. *Journal of Neuroscience, 26*, 7870–7874.
Liu, D., Diorio, J., Day, J. C., Francis, D. D., & Meaney, M. J. (2000). Maternal care, hippocampal synaptogenesis and cognitive development in rats. *Nature Neuroscience, 3*, 799–806.
Lozoff, B., Beard, J., Connor, J., Barbara, F., Georgieff, M., & Schallert, T. (2006). Long-lasting neural and behavioral effects of iron deficiency in infancy. *Nutrition Reviews, 64*, S34–S43; discussion S72–S91.
Lu, L., Leonard, C., Thompson, P., Kan, E., Jolley, J., Welcome, S., et al. (2007). Normal developmental changes in inferior frontal gray matter are associated with improvement in phonological processing: A longitudinal MRI analysis. *Cerebral Cortex, 17*, 1092–1099.
Lukowski, A. F., Koss, M., Burden, M. J., Jonides, J., Nelson, C. A., Kaciroti, N., et al. (2010). Iron deficiency in infancy and neurocognitive functioning at 19 years: Evidence of long-term deficits in executive function and recognition memory. *Nutrition Neuroscience, 13*, 54–70.
Mackey, A. P., Hill, S. S., Stone, S. I., & Bunge, S. A (2011). Differential effects of reasoning and speed training in children. *Developmental Science, 14,* 582–590.
Markham, J. A., & Greenough, W. T. (2004). Experience-driven brain plasticity: Beyond the synapse. *Neuron Glia Biology, 1*, 351–363.
Marshall, P. J., Reeb, B. C., Fox, N. A., Nelson, C. A., 3rd, & Zeanah, C. H. (2008). Effects of early intervention on EEG power and coherence in previously institutionalized children in Romania. *Developmental Psychopathology, 20*, 861–880.
Mattson, S. N., Roesch, S. C., Fagerlund, A., Autti-Ramo, I., Jones, K. L., May, P. A., et al. (2010). Toward a neurobehavioral profile of fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research, 34*, 1640–1650.

Maurer, D., Mondloch, C. J., & Lewis, T. L. (2007). Effects of early visual deprivation on perceptual and cognitive development. *Progress in Brain Research, 164*, 87–104.

McEwen, B. S. (2004). Protection and damage from acute and chronic stress: Allostasis and allostatic overload and relevance to the pathophysiology of psychiatric disorders. *Annals of the New York Academy of Sciences, 1032*, 1–7.

McEwen, B. S. (2005). Glucocorticoids, depression, and mood disorders: Structural remodeling in the brain. *Metabolism, 54*, 20–23.

McLoyd, V. C. (1998). Socioeconomic disadvantage and child development. *American Psychologist, 53*, 185–204.

Meaney, M. J. (2010). Epigenetics and the biological definition of gene x environment interactions. *Child Development, 81*, 41–79.

Mesce, K. A. (2002). Metamodulation of the biogenic amines: Second-order modulation by steroid hormones and amine cocktails. *Brain, Behavior and Evolution, 60*, 339–349.

Mezzacappa, E. (2004). Alerting, orienting, and executive attention: Developmental properties and sociodemographic correlates in an epidemiological sample of young, urban children. *Child Development, 75*, 1373–1386.

Mihalick, S. M., Crandall, J. E., Langlois, J. C., Krienke, J. D., & Dube, W. V. (2001). Prenatal ethanol exposure, generalized learning impairment, and medial prefrontal cortical deficits in rats. *Neurotoxicology and Teratology, 23*, 453–462.

Miotto, E. C., Savage, C. R., Evans, J. J., Wilson, B. A., Martins, M. G., Iaki, S., et al. (2006). Bilateral activation of the prefrontal cortex after strategic semantic cognitive training. *Human Brain Mapping, 27*, 288–295.

Miranda, M. L., Edwards, S. E., Swamy, G. K., Paul, C. J., & Neelon, B. (2010). Blood lead levels among pregnant women: Historical versus contemporaneous exposures. *International Journal of Environmental Research and Public Health, 7*, 1508–1519.

Mizoguchi, K., Yuzurihara, M., Ishige, A., Sasaki, H., Chui, D. H., & Tabira, T. (2000). Chronic stress induces impairment of spatial working memory because of prefrontal dopaminergic dysfunction. *Journal of Neuroscience*, *20*, 1568–157.Mueller, C. W., & Parcel, T. L. (1981). Measures of socioeconomic status : Alternatives and recommendations. *Child Development*, *52*, 13–30.

Mueller, S. C., Maheu, F. S., Dozier, M., Peloso, E., Mandell, D., Leibenluft, E., et al. (2010). Early-life stress is associated with impairment in cognitive control in adolescence: An fMRI study. *Neuropsychologia, 48*, 3037–3044.

Muennig, P., Schweinhart, L., Montie, J., & Neidell, M. (2009). Effects of a prekindergarten educational intervention on adult health: 37-year follow-up results of a randomized controlled trial. *American Journal of Public Health, 99*, 1431–1437.

Murmu, M. S., Salomon, S., Biala, Y., Weinstock, M., Braun, K., & Bock, J. (2006). Changes of spine density and dendritic complexity in the prefrontal cortex in offspring of mothers exposed to stress during pregnancy. *European Journal of Neuroscience, 24*, 1477–1487.

National Scientific Council on the Developing Child (2010). *Early Experiences Can Alter Gene Expression and Affect Long-Term Development: Working Paper No. 10*. http://www.developingchild.net

Nelson, C. A., 3rd, Zeanah, C. H., Fox, N. A., Marshall, P. J., Smyke, A. T., & Guthrie, D. (2007). Cognitive recovery in socially deprived young children: The Bucharest Early Intervention Project. *Science, 318*, 1937–1940.

Nelson, C. A., & Sheridan, M. A. (in press). Lessons from neuroscience research for understanding causal links between family and neighborhood characteristics and educational outcomes. In G. Duncan & R. Murnane (Eds.), *Social inequality and educational disadvantage project* (pp. ). New York: Russell Sage Foundation Press.

Noble, K. G., McCandliss, B. D., & Farah, M. J. (2007). Socioeconomic gradients predict individual differences in neurocognitive abilities. *Developmental Science, 10*, 464–480.

Noland, J. S., Singer, L. T., Mehta, S. K., & Super, D. M. (2003). Prenatal cocaine/polydrug exposure and infant performance on an executive functioning task. *Developmental Neuropsychology, 24*, 499–517.

Norman, A. L., Crocker, N., Mattson, S. N., & Riley, E. P. (2009). Neuroimaging and fetal alcohol spectrum disorders. *Developmnetal Disabilities Research Reviews, 15*, 209–217.

Olesen, P. J., Westerberg, H., & Klingberg, T. (2004). Increased prefrontal and parietal activity after training of working memory. *Nature Neuroscience, 7*, 75–79.

Ostrovsky, Y., Meyers, E., Ganesh, S., Mathur, U., & Sinha, P. (2009). Visual parsing after recovery from blindness. *Psychological Science, 20*, 1484–1491.

Owen, A. M., Downes, J. J., Sahakian, B. J., Polkey, C. E., & Robbins, T. W. (1990). Planning and spatial working memory following frontal lobe lesions in man. *Neuropsychologia, 28*, 1021–1034.

Pallier, C., Dehaene, S., Poline, J. B., LeBihan, D., Argenti, A. M., Dupoux, E., et al. (2003). Brain imaging of language plasticity in adopted adults: Can a second language replace the first? *Cerebral Cortex, 13*, 155–161.

Polderman, T. J., Posthuma, D., De Sonneville, L. M., Stins, J. F., Verhulst, F. C., & Boomsma, D. I. (2007). Genetic analyses of the stability of executive functioning during childhood. *Biological Psychology, 76*, 11–20.

Posthuma, D., Beem, A. L., de Geus, E. J., van Baal, G. C., von Hjelmborg, J. B., Iachine, I., et al. (2003). Theory and practice in quantitative genetics. *Twin Research, 6*, 361–376.

Raizada, R. D., & Kishiyama, M. M. (2010). Effects of socioeconomic status on brain development, and how cognitive neuroscience may contribute to levelling the playing field. *Frontiers in Human Neuroscience, 4*, 3.

Raizada, R. D., Richards, T. L., Meltzoff, A., & Kuhl, P. K. (2008). Socioeconomic status predicts hemispheric specialisation of the left inferior frontal gyrus in young children. *Neuroimage, 40*, 1392–1401.

Rice, D., & Barone, S., Jr. (2000). Critical periods of vulnerability for the developing nervous system: Evidence from humans and animal models. *Environmental Health Perspectives, 108*(Suppl 3), 511–533.

Rice, D. C., & Karpinski, K. F. (1988). Lifetime low-level lead exposure produces deficits in delayed alternation in adult monkeys. *Neurotoxicology and Teratology, 10*, 207–214.

Rosenzweig, M. R., Breedlove, S. M., & Leiman, A. L. (2002). *Biological psychology*. Sunderland, MA: Sinauer Associates.

Rosenzweig, M. R., Krech, D., Bennett, E. L., & Diamond, M. C. (1962). Effects of environmental complexity and training on brain chemistry and anatomy: A replication and extension. *Journal of Comparative Physiology and Psychology, 55*, 429–437.

Rueda, M. R., Rothbart, M. K., McCandliss, B. D., Saccomanno, L., & Posner, M. I. (2005). Training, maturation, and genetic influences on the development of executive attention. *Proceedings of the National Academy of Sciences of the United States of America, 102*, 14931–14936.

Sagi, D., & Tanne, D. (1994). Perceptual learning: Learning to see. *Current Opinions in Neurobiology, 4*, 195–199.

Sapolsky, R. M. (2003). Stress and plasticity in the limbic system. *Neurochemical Research, 28*, 1735–1742.

Schmiedek, F., Lovden, M., & Lindenberger, U. (2010). Hundred days of cognitive training enhance broad cognitive abilities in adulthood: Findings from the COGITO Study. *Frontiers in Aging Neuroscience, 2*.

Scholz, J., Klein, M. C., Behrens, T. E., & Johansen-Berg, H. (2009). Training induces changes in white-matter architecture. *Nature Neuroscience, 12*, 1370–1371.

Shankaran, S., Lester, B. M., Das, A., Bauer, C. R., Bada, H. S., Lagasse, L., et al. (2007). Impact of maternal substance use during pregnancy on childhood outcome. *Seminars in Fetal and Neonatal Medicine, 12*, 143–150.

Sheinkopf, S. J., Lester, B. M., Sanes, J. N., Eliassen, J. C., Hutchison, E. R., Seifer, R., et al. (2009). Functional MRI and response inhibition in children exposed to cocaine in utero. Preliminary findings. *Developmental Neuroscience, 31*, 159–166.

Sowell, E. R., Thompson, P. M., Mattson, S. N., Tessner, K. D., Jernigan, T. L., Riley, E. P., et al. (2001). Voxel-based morphometric analyses of

the brain in children and adolescents prenatally exposed to alcohol. *Neuroreport, 12*, 515–523.
Sowell, E. R., Thompson, P. M., Peterson, B. S., Mattson, S. N., Welcome, S. E., Henkenius, A. L., et al. (2002). Mapping cortical gray matter asymmetry patterns in adolescents with heavy prenatal alcohol exposure. *Neuroimage, 17*, 1807–1819.
Stuss, D. T., Bisschop, S. M., Alexander, M. P., Levine, B., Katz, D., & Izukawa, D. (2001). The Trail Making Test: A study in focal lesion patients. *Psychological Assessment, 13*, 230–239.
Szyf, M., Weaver, I., & Meaney, M. (2007). Maternal care, the epigenome and phenotypic differences in behavior. *Reproductive Toxicology, 24*, 9–19.
Thorell, L. B., Lindqvist, S., Bergman Nutley, S., Bohlin, G., & Klingberg, T. (2009). Training and transfer effects of executive functions in preschool children. *Developmental Science, 12*, 106–113.
Tucker-Drob, E. M., Rhemtulla, M., Harden, K. P., Turkheimer, E., & Fask, T. (2011). Emergence of a gene × socioeconomic status interaction on infant mental ability between 10 months and 2 years. *Psychological Science, 22,* 125–133.
Turkheimer, E., Haley, A., Waldron, M., D'Onofrio, B., & Gottesman, II. (2003). Socioeconomic status modifies heritability of IQ in young children. *Psychological Science, 14*, 623–628.
Vogel, E. K., & Machizawa, M. G. (2004). Neural activity predicts individual differences in visual working memory capacity. *Nature, 428*, 748–751.
Vogel, E. K., McCollough, A. W., & Machizawa, M. G. (2005). Neural measures reveal individual differences in controlling access to working memory. *Nature, 438*, 500–503.
Vyas, A., Pillai, A. G., & Chattarji, S. (2004). Recovery after chronic stress fails to reverse amygdaloid neuronal hypertrophy and enhanced anxiety-like behavior. *Neuroscience, 128*, 667–673.
Warren, K. R., & Li, T. K. (2005). Genetic polymorphisms: Impact on the risk of fetal alcohol spectrum disorders. *Birth Defects Research and Clinical Molecular Teratology, 73*, 195–203.
Weaver, I. C., Cervoni, N., Champagne, F. A., D'Alessio, A. C., Sharma, S., Seckl, J. R., et al. (2004). Epigenetic programming by maternal behavior. *Nature Neuroscience, 7*, 847–854.
Welch-Carre, E. (2005). The neurodevelopmental consequences of prenatal alcohol exposure. *Advanced Neonatal Care, 5*, 217–229.
Werker, J. F., & Tees, R. C. (2005). Speech perception as a window for understanding plasticity and commitment in language systems of the brain. *Developmental Psychobiology, 46*, 233–251.
White, L. E., & Fitzpatrick, D. (2007). Vision and cortical map development. *Neuron, 56*, 327–338.
Windsor, J., Glaze, L. E., & Koga, S. F. (2007). Language acquisition with limited input: Romanian institution and foster care. *Journal of Speech Language and Hearing Research, 50*, 1365–1381.
Yago, E., Duarte, A., Wong, T., Barcelo, F., & Knight, R. T. (2004). Temporal kinetics of prefrontal modulation of the extrastriate cortex during visual attention. *Cognitive, Affective, and Behavioral Neuroscience, 4*, 609–617.