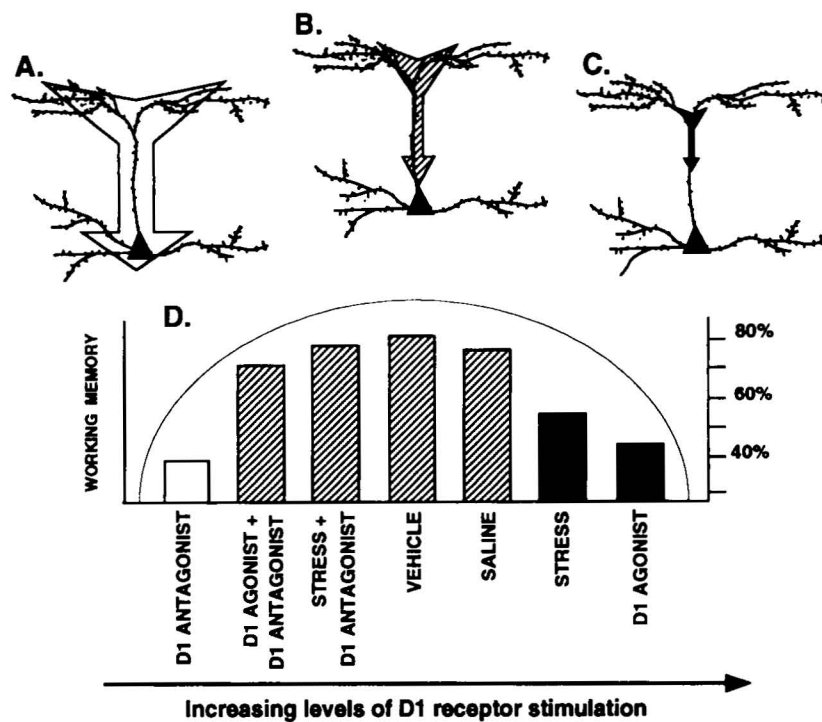


## Development of the Cerebral Cortex: XIV. Stress Impairs Prefrontal Cortical Function

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A 10-year-old boy has been referred to you at the school's insistence. For the past 6 months, he has had behavioral problems in class. He has difficulty paying attention, has been easily agitated, and fails to inhibit inappropriate and aggressive impulses. His parents report that he has always been active but he was never like this before. Does he suddenly

have attention-deficit/hyperactivity disorder (ADHD)? A little probing reveals that the parents' marriage is in trouble and that their child's problems in school coincide with problems at home. Recent advances in neurobiological research may help us understand reactive behavioral problems in children. Neurochemical changes in the prefrontal cortex (PFC)



**Fig. 1** Dopamine acting at D1 receptors in the prefrontal cortex (PFC) produces an inverted *U* dose response whereby either too little or too much D1 receptor stimulation impairs neuronal or cognitive function. A–C: Highly schematic representation of the work of Yang and Seamans (1996) of the electrophysiological effects of dopamine or D1 agonists on PFC pyramidal cell function. Intracellular recordings from PFC slices showed that D1 receptor stimulation diminishes the calcium currents that convey signals from the distal dendrites to the cell body. A: With insufficient D1 receptor stimulation, all signals are conveyed to the soma, resulting in diffuse, unfocused information. This is represented in A by the large arrow of incoming signals. The behavioral correlate is poor working memory and poor attention regulation. B: With optimal levels of D1 receptor stimulation, signal transfer is focused such that only the largest, coordinated signals are conveyed to the cell. This is represented in B by the normal-sized arrow. The behavioral correlate is optimal working memory and attention regulation. C: At very high levels of D1 receptor stimulation such as during stress, calcium currents are blocked and signal transfer is abolished. This is represented by the small arrow. The behavioral correlate is once again poor working memory and attention regulation. D: These electrophysiological results fit very well with cognitive studies, whereby an inverted *U* is observed with changing levels of D1 receptor stimulation. In this figure, working memory performance in rats was impaired by either insufficient or excessive D1 receptor stimulation in the PFC. Adapted from Zahrt et al. (1997), Supranormal stimulation of D1 dopamine receptors in the rodent cortex impairs spatial working memory performance. *J Neurosci* 17:8528–8535.

during periods of stress may take this brain region "off-line," making the child less able to govern his behavior.

The PFC is situated anterior to the motor cortices in the frontal lobe. It is much larger in primates than in other mammals. It continues to develop throughout adolescence. This region of our brains is critical for using "working memory," a form of memory that is required to appropriately guide behavior. Working memory has been called "scratch-pad" memory, because this type of memory must be constantly updated. Memories can be called up from long-term storage or from more recent buffers. The PFC uses these representations to effectively guide behavior, freeing us from responding only to our immediate environment, inhibiting inappropriate responses or distractions, and allowing us to plan and organize. Animals or humans with lesions to the PFC exhibit poor attention regulation, disorganized and impulsive behavior, and hyperactivity.

Recent research in animals indicates that exposure to stress can produce a functional "lesion" of the PFC. During stress exposure, catecholamines are released in both the peripheral and central nervous systems. In the periphery, the catecholamines norepinephrine and epinephrine are released from the sympathetic nervous system and adrenal gland, respectively. These catecholamine actions serve to "turn on" our heart and muscles and "turn off" the stomach to prepare for fight-or-flight responses during stress.

In the brain, high levels of the catecholamines dopamine and norepinephrine are released in the PFC during stress exposure, even during relatively mild psychological stress. As basal levels of dopamine and norepinephrine have essential beneficial influences on PFC function, it was originally presumed that high levels of catecholamine release during stress might facilitate PFC function. However, research in monkeys and rats demonstrated the contrary: exposure to stress impairs the working memory functions of the PFC. These findings in animals are consistent with older literature demonstrating that humans exposed to loud noise stress are less able to sustain attention or to inhibit inappropriate responses, functions now known to be carried out by the PFC. As in animal studies, these changes are most evident under conditions in which the subject feels no control over the stress.

A number of studies indicate that stress-induced working memory deficits result from high levels of catecholamine receptor stimulation on neurons in the PFC (Fig. 1). Working memory deficits during stress can be ameliorated by agents that prevent catecholamine release or block catecholamine receptors. For example, stress-induced cognitive deficits can be ameliorated by pretreatment with  $\alpha_2$ -adrenergic receptor agonists such as clonidine or guanfacine, which decrease stress-induced catecholamine release and enhance PFC function through actions at postsynaptic  $\alpha_2$ -receptors in the PFC.

Stress-induced cognitive deficits can also be prevented by treating with compounds that block either dopamine D1 or noradrenergic  $\alpha_1$ -receptors, suggesting that dopamine and norepinephrine have their detrimental effects in the PFC through actions at D1 and  $\alpha_1$ -receptors, respectively. Consistent with this interpretation, intra-PFC infusions of either D1 or  $\alpha_1$ -agonists impair working memory.

Electrophysiological recordings similarly indicate that high levels of D1 receptor stimulation can interfere with PFC neuronal function. Studies of  $\alpha_1$ -receptors have not been done. For example, large amounts of D1 agonist abolish the calcium currents that convey signals along dendrites, effectively "strangling" information transfer from dendrite to soma (Fig. 1). Conversely, low levels of D1 receptor antagonists can enhance memory-related neuronal responses in monkeys performing working memory tasks. Thus, high levels of D1 receptor stimulation erode the working memory responses that the PFC uses to effectively guide behavior.

Active neurochemical mechanisms to take the PFC "off-line" during stress may have had survival value in evolution, allowing faster, instinctual mechanisms regulated by subcortical and posterior cortical areas to regulate behavior during stress. However, these brain actions may often be maladaptive in human society when we are in need of PFC regulation to act appropriately, e.g., in the classroom when behavior must be highly controlled.

The reversal of stress-induced cognitive deficits with pharmacological treatments in animals suggests that medication may also be helpful in children with stress-related behavioral problems. The animal research showed that stress-induced PFC deficits could be prevented by pretreatment with very low doses of neuroleptics or with an  $\alpha_2$ -adrenergic agonist. However, drawing parallels between children and animals should be made with caution for several reasons. The laboratory studies were performed with acute stress exposure in adult animals; the effects of pharmacological interventions have not been tested under chronic stress conditions or in juvenile animals. Furthermore, even in animal studies the results with neuroleptics were problematic: there was a very narrow therapeutic dose window, and even low clinical doses were usually too high to restore PFC function. The danger of tardive dyskinesia and other neuroleptic-related disorders also cautions against the use of these compounds in children.

The usefulness of  $\alpha_2$ -adrenergic agonists in preventing stress-induced cognitive deficits in animals may have more clinical relevance, as clonidine and guanfacine are already in use for the treatment of ADHD. Animal studies indicate that guanfacine is more effective than clonidine in preventing stress-induced working memory deficits. It is important to note that  $\alpha_2$ -adrenergic agonists improve working memory performance in animals under conditions of either insuf-

ficient (e.g., catecholamine depletion) or excessive (e.g., stress) catecholamine receptor stimulation in the PFC. This quality may enhance the clinical utility of these compounds, but it does not help us distinguish between hypo- versus hypercatecholaminergic states when considering potential etiologies of PFC disorders in children. The animal data indicate that behavioral problems could arise from both states, as either too little or too much catecholamine receptor stimulation results in PFC dysfunction.

Our new neurobiological perspective suggests that behavioral problems in children can arise from PFC dysfunction due to either external factors, such as exposure to a stressful environment, or from inherent changes in PFC circuits, such as genetic changes in dopamine or norepinephrine transporters. It is possible that we assign the ADHD diagnosis to children with inherent changes, while those with visible causes for their behavioral problems are less likely to be given this diagnosis.

Current research suggests that common neurochemical changes in the PFC may underlie these problems irrespective of the cause. The similarity between ADHD symptoms and stress-induced PFC deficits may help to explain why ADHD is often not taken seriously as a true biological disorder. Our new understanding of stress effects on PFC function may also help to clarify why highly structured, low-stress environments can be especially helpful in treating children with ADHD and related problems. By understanding that behavioral problems may have a neurobiological basis, we may be able to deal with them more compassionately and intelligently.

## WEB SITES OF INTEREST

www.stress.org  
www.aacts.org

## ADDITIONAL READINGS

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Accepted August 13, 1998.

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## Erratum

In analyses of data that were published in the article "Validity of *DSM-IV* Attention-Deficit/Hyperactivity Disorder for Younger Children" by Benjamin B. Lahey et al. (Vol. 37, pp. 695-702), one symptom of inattention reported by teachers was incorrectly labeled in the SAS program. As a result, the number of inattention symptoms reported by teachers was underestimated for some children. After the error was corrected, one additional child met *DSM-IV* criteria for ADHD and some children's assignment to the subtypes of ADHD changed (2 more children met criteria for the combined type, 2 fewer children met criteria for the predominantly hyperactive-impulsive type, and 1 more child met criteria for the predominantly inattentive type). When all statistical analyses were repeated using the corrected variable, there were few changes in findings. Unlike in the published findings, however, children who met criteria for the combined type were significantly more likely to have had an unintentional injury than the comparison children, children who met criteria for the combined type were not rated by teachers as exhibiting more shy/withdrawn behavior than comparison children, children who met criteria for the combined type were not rated by teachers as ignored by more classmates than comparison children, and children who met criteria for the predominantly inattentive type were not given significantly lower ratings of adaptive functioning by interviewers than comparison children. When children who met criteria for oppositional defiant disorder or conduct disorder were dropped from the sample in follow-up analyses, children who met criteria for the predominantly hyperactive-impulsive type exhibited significantly greater underachievement in mathematics relative to intelligence than comparison children. Overall, the findings still strongly support the validity of all subtypes of the diagnosis of *DSM-IV* ADHD in terms of concurrent impairment. A corrected copy of the article may be obtained from Benjamin B. Lahey, Ph.D., Department of Psychiatry (MC 3077), University of Chicago, 5841 South Maryland Avenue, Chicago, IL 60637, or via e-mail at blahey@yoda.bsd.uchicago.edu. The author regrets the errors.