Genetics of Childhood Disorders: XVII. ADHD, Part 1: The Executive Functions and ADHD

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Attention-deficit/hyperactivity disorder (ADHD) is a developmental disorder with the cardinal features of difficulties with sustained attention, distractibility, hyperactivity, and impulse control. It arises early in childhood, typically between 3 and 7 years of age. The disorder is relatively stable over time and persists through adolescence and into adulthood in more than half the cases. A significant proportion of children will experience school failure and will develop conduct disorders, delinquent activities, and antisocial personalities. As a result, the burden of ADHD to affected individuals, to their families, and to society is considerable.

Over the next several months, this column will explore the underlying mechanisms that contribute to the disorder. The first columns will review the concept of executive functioning and the role the frontal cortex has in regulating mental skills that are required to sustain attention and inhibit impulsive behavior. Particular attention will be given to neurotransmitter systems that are thought to play a critical role in frontal cortical activity. The next 2 columns will be devoted to recent progress in the genetics of ADHD. Finally, we will review whether animal models of hyperactivity have been useful in furthering our understanding of the underlying etiology of the disorder.

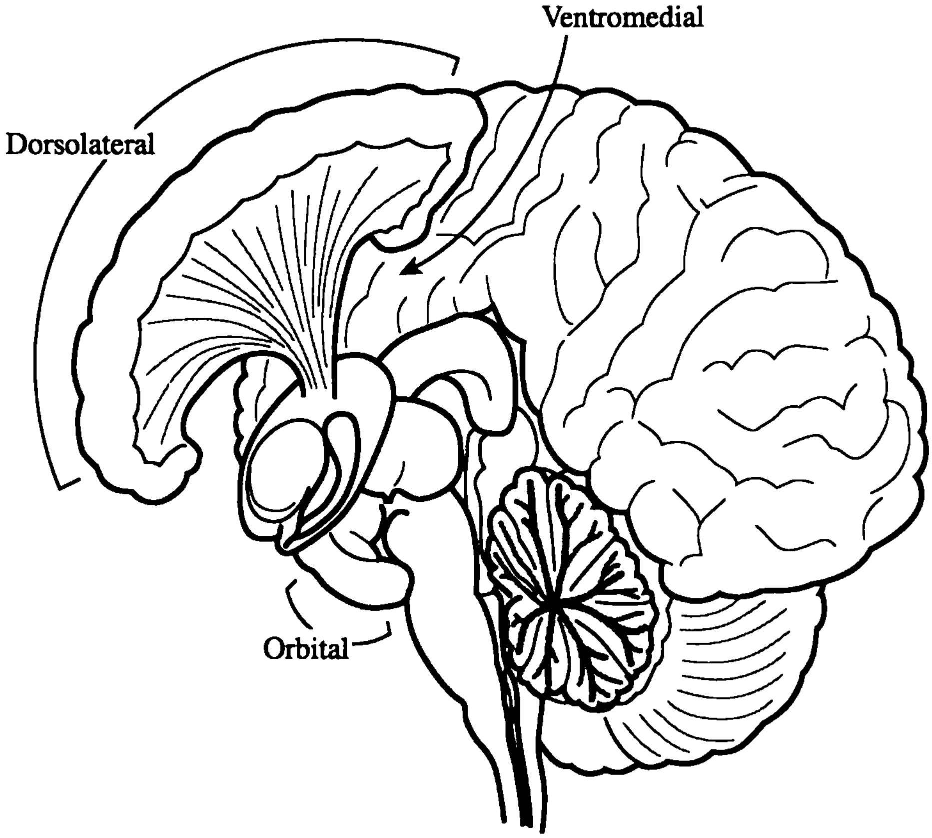

Fig. 1 The human brain with the left posterior cortical hemisphere removed to expose the right hemisphere, dorsolateral projections to the striatum of the basal ganglia, and orbital and medial aspects of the cortex. From Barkley RA (1997), *ADHD and the Nature of Self-Control.* New York: Guilford. Copyright Guilford Publications. Reprinted with permission.

It is important to note at the outset that ADHD is not a unitary illness. It is likely that a number of different pathways that include both genetic and environmental factors contribute to the expression of its symptoms.

The most prevalent clinical view of ADHD maintains that the central deficits of the disorder are the inability to sustain attention and symptoms of hyperactivity and impulsivity. However, this view of ADHD is only a description of the most commonly observed characteristics. It is not a theory that could serve as a useful scientific tool for researchers, nor does it point us to the underlying neural pathways that might be involved.

Over the past 2 decades, tremendous progress has been made in understanding the functions of the prefrontal cortex. This progress has led to an appreciation of how this region of the brain regulates specific mental activities that allow for self-control. These mental activities are unified under the term *executive functions*. This initial column will review recent theories of executive functioning and will review how deficits in executive functions occur with deficits in the development, structure, and function of the frontal cortex and its networks with other brain regions, such as the basal ganglia.

Karl Pribram may have been the first to describe the executive role of the prefrontal cortex when he concluded that it is "critically involved in implementing executive programs where these are necessary to maintain brain organization in the face of insufficient redundancy in input processing and in the outcomes of behavior" (Pribram, 1976, p. 509). Muriel Lezak defined executive function (EF) as "those capacities that enable a person to engage successfully in independent, purposive, self-serving behavior" (Lezak, 1995, p. 42). Actions are executive if they involve the "when" or "whether" aspects of behavior, whereas nonexecutive functions involve the "what" and "how." Left unclear in the vast neuropsychological literature on EF is any operational definition of what is encompassed by the term *executive*. The term *executive functions* seems to incorporate:

- Volition, planning, and purposive, goal-directed, or intentional action.
- Inhibition and resistance to distraction.
- Problem-solving and strategy development, selection, and monitoring.
- Flexible shifting of actions to meet task demands.
- Maintenance of persistence toward attaining a goal.
- Self-awareness across time.

Many authors have recognized the substantial overlap or interchangeability between EF and self-regulation. Maureen Dennis saw EF as partly social in nature (discourse and reciprocity). Stuart Dimond defined EF as entirely involving social intelligence (management of day-to-day social conduct). Others have simply lamented the lack of definition and declared EF to be what the frontal lobes do.

A leading candidate for one EF is working memory (WM). This is the capacity to hold a mental representation in mind to guide behavior. It is remembering in order to do. Often, the remembering must span a period of time so long that the remembered external events may no longer exist. The performance of the act must be linked to the arrival of some mentally conjectured future event. Time, timing, and timeliness in behavior are regulated in part by this EF, as Juaquim Fuster noted. Others, like Baddeley, suggested that WM had 3 components: (1) a visual-spatial sketchpad (nonverbal working memory), (2) verbal working memory and its associated phonological loop (private self-speech), and (3) a central executive. The central executive (3) enslaves (1) and (2) for its purposes (the overall goal to be achieved). Little is said about the nature of this central executive.

Another candidate EF is response inhibition. It is critical to WM in providing the initial delay in the response to an event during which WM is often activated; the protection to WM from interference by unrelated yet competing external and internal events; and the interruption of ongoing response patterns being guided by WM should they prove ineffective in attaining the goal.

A Theoretical Model of Executive Function

The history of the model below and its supporting research appear in my earlier textbook, *ADHD and the Nature of Self-Control*. It is drawn from the work of Jacob Bronowski, Juaquim Fuster, Patricia Goldman-Rakic, and Antonio Damasio. Its components appear in Table 1 along with those psychological and social abilities hypothesized to result from each EF.

Each EF contributes to the following developmental shifts in the control over human behavior:

- From external events to mental representations related to those events.
- From control by others to control by the self.
- From immediate reinforcement to delayed gratification.
- From the now to the conjectured social future.

Each EF probably arises by a common process:

- It originates in a general class of observable behavior toward others as a means of predicting and controlling the outside world.
- This class of behavior is then turned on the self as a means of controlling one's own behavior, yet such behavior may remain publicly observable for a period of development before becoming covert.
- It then becomes progressively private or covert (internalized) in form; that is, its associated musculoskeletal movements are suppressed while its execution within the brain continues.

Self-regulation (SR) can be defined as any self-directed action that serves to alter the probability of a subsequent response so as to alter the likelihood of a future consequence. Each EF is a type of self-directed action. Consequently, SR is an inherent part of EF, making EF inherently future-directed. The EFs are

TABLE 1
The Major Executive Functions, the Specific Component Processes in Each, the Psychological and Social Abilities They May Permit, and Their Probable Neuroanatomical Localization

Executive Function	Associated Component Processes	Psychological/Social Abilities	Probable Brain Localization (Fig. 1)
Response inhibition	Inhibiting prepotent responses Interrupting ongoing responses Interference (distraction) control	Impulse control/self-regulation Delay of gratification Regulation of activity level to setting/task demands	Orbital-prefrontal and striatum
Nonverbal working memory (sensing to the self)	Retrospective function Prospective function	Holding events in mind Imitation/vicarious learning Sense of past Sense of future Delayed reciprocal altruism Autonoetic awareness Sense of time Cross-temporal organization of behavior	Dorsolateral prefrontal (right > left)
Verbal working memory (internalization of language)	Covert receptive language Covert expressive language	Self-description, reflection, instruction, and questioning Rule-governed behavior Reading comprehension Moral control of conduct	Dorsolateral prefrontal (left > right)
Self-regulation of emotion and motivation (emoting to the self)	Covert affective expression Covert motivational states Covert regulation of arousal	Emotional self-control Intrinsic motivation/persistence Activation to task demands	Ventromedial prefrontal
Reconstitution (self-directed play)	Analysis Synthesis	Verbal/nonverbal fluency Goal-directed inventiveness Flexibility and ideational syntax	Anterior prefrontal poles

response inhibition and those 4 general classes of self-directed actions humans use to engage in SR toward conjectured social futures:

- Self-directed sensing (sensory-motor action) that creates nonverbal WM.
- Self-speech that creates verbal WM.
- Emotion/motivation to the self that creates intrinsic goal-directed motivation.
- Self-directed play that creates inventiveness, fluency, and flexibility in goal-directed behavior.

The developmental progression common to each EF is typified in the internalization of language. As the child matures, speech toward others becomes speech to the self yet, for a time, vocalized. It then progresses to subvocal self-speech and finally to fully covert or private speech that comprises verbal thought. The EFs act in concert to achieve the overarching goal of a net maximization of long-term social (economic) rather than more immediate outcomes for the individual. Thus, as Dimond, Vygotsky, and Luria all argued, the adaptive problems that the EF/SR system evolved to solve must be social in nature, making the EF/SR system the seat of social intelligence.

Response inhibition is the capacity to delay a response to an immediate environmental event. Delayed responding provides the foundation on which EF/SR develops. SR is impossible without a delay in that response directed toward immediate reinforcement. Response inhibition also permits the "internalization" or "privatization" of each EF. It does so by suppressing the observable musculoskeletal movements associated with the self-directed behavior that makes up each EF. Over the course of development, this makes that behavior become covert or "mental" in form. This is done so that the actions occurring during an EF cannot be directly observed by others. That privatization is likely necessitated by the selection pressures set up in a group-living species of self-interested imitators whose closest evolutionary competitors are their peers.

I. *Nonverbal Working Memory.* The first EF is nonverbal WM. Among the various senses, the most important to humans are vision and, to a lesser degree, hearing. It is not surprising, then, that this mental module is largely composed of visual imagery and private audition. Undoubtedly the other senses also contribute to this symphony of internalized resensing. It consists of 2 interrelated processes: (1) the ***retrospective function,*** which is resensing the past information and holding it online (in mind), making it largely a sensory activity; and (2) the preparation of motor action initiated by the resensing of the past, known as the ***prospective function.*** Together they provide for the progressive development of a cognitive window on oneself across time, or *autonoetic awareness,* and *the subjective sense of time* more generally. The past and future tenses in human languages likely derive their reference points from this WM. This EF grants humans the capacities for generalized imitation and vicarious learning, self-awareness, social exchange (delayed reciprocal altruism), and the more general capacity for the cross-temporal organization of behavior. The evolution of this EF likely permitted humans the capacity to engage in not only self-interested cooperation and coalition formation but also the "theft" of each other's behavior (vicarious learning) rather than acquiring it through the arduous process of trial-and-error learning. This would have set up a selection pressure that required that self-directed actions be made private so that one's peers could not appropriate the behavior prior to its more timely, opportunistic display. Given that mental representations are icons, this EF may have created the initial step needed toward the evolution of symbolization, from mental icons to indices, and then on to symbols.

II. *Verbal Working Memory.* This EF comprises the internalization of speech, as described above. It is covert (silent) receptive and expressive language. Individuals are afforded the same means of control over themselves that language serves in the control of others, such as self-description, reflection, instruction, and questioning. Rule discovery and rule-governed behavior more generally (the motor-controlling functions of language) arise here. And so, eventually, might hierarchically organized sets of rules about rules, or *meta-rules* (meta-cognition). In conjunction with nonverbal WM, this EF permits both reading comprehension and the moral guidance of behavior by internalized rules.

III. *Internalized Emotion/Motivation.* This function may well arise, at least initially, as a consequence of the first 2 EFs. By representing visual and verbal mental stimuli to oneself, emotional and motivation states ensue. These states are Damasio's somatic markers. Initially, they may be observable to others, as when a child laughs publicly in response to a privately reexperienced humorous event. Eventually these affective states become covert. Emotions are motivational states composed of level of arousal imposed on a reward/punishment gradient. Thus, this EF creates the SR of private motivational states in the service of future goals. It is the source of intrinsic motivation essential to driving future-directed behavior.

IV. *Reconstitution.* This EF likely arises from play. It consists of 2 interacting processes: *analysis* (taking apart) and *synthesis* (recombining). These are applied to the contents of the 2 WMs, thereby permitting the manipulation and dismemberment of old experiences to synthesize novel responses. It is a form of ideational darwinism in which the units of old experiences are recombined into novel behavior that is judged against the goal to be attained so as to select the most viable option. By so doing, as Karl Popper once noted, humans allow their erroneous ideas to die in their place. Here originates the flexibility, fluency, and inventiveness of human goal-directed actions.

In combination, the EFs provide a powerful set of tools for SR toward the social future that is unparalleled in any other species. The fields of science, art, and music, among others, are likely examples of this set of skills.

Research overwhelmingly demonstrates a deficit in response inhibition in persons with ADHD. Consequently, the EF model predicts that secondary deficits (e.g., greater errors and variability in performance) will arise in all other EFs. Deficits would then be detected in the psychosocial abilities of each (Table 1). These important predictions are an opportunity to test the model because those predictions are not drawn from the literature on ADHD but from the literature on EF. Consistent with these predictions, research on ADHD has found deficits in each EF. However, the support varies across the functions, largely due to the limited amount of research on some of them and the fact that much of that research did not set out to intentionally test this model.

This theory shows that ADHD impairs social intelligence through the cascading of deficits it creates throughout the EF/SR system. Delays occur in the 4 developmental shifts in the control of behavior. The attention deficits ascribed to ADHD can now be seen as *intention deficits* (attention toward the future). This would cause deficiencies in reciprocal altruism and vicarious learning in ADHD, among other deficits in universal social activities requiring EF (e.g., coalition formation, self-innovation, and social self-defense).

Suffice to say that there is much here in need of future research to establish its veracity. But as the time-limited tool that is any credible theory, its scientific and heuristic value for understanding EF and its evolution as well as ADHD should be evident.

WEB SITES OF INTEREST

http://www.sciam.com/askexpert/medicine/medicine9.html
http://www.sciam.com/1998/0998issue/0998barkley.html
http://www.chadd.org/fact6.htm
http://www.add.org/main/abc/hallowell.htm

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Uses and Abuses of Prescription Drug Information in Pharmacy Benefits Management Programs. Bernard Lo, MD, Ann Alpers, JD

A 1998 incident in which patients' prescription information was used to advertise a new drug exemplifies the importance of confidentiality in the era of managed care and computers. The ethical concerns voiced about this incident can also apply to pharmacy benefits management programs. The use of personal health information in pharmacy benefits management is particularly important because of increased pressures to control rising drug costs. Specific confidentiality concerns include whether the goal of benefiting patients will be achieved and whether the means are appropriate. The means may be problematic because of financial conflicts of interest, lack of patient authorization, inappropriate access to information by third parties, and inadequate safeguards for confidentiality. Policies should be crafted that protect confidentiality while allowing appropriate use of personal health information in pharmacy benefits management. Sound policies should require clear evidence of benefit to patients, an oversight committee, patient authorization, disclosure or prohibition of conflicts of interest, additional safeguards for sensitive medical conditions, strong confidentiality protections, and restrictions on advertising. JAMA 2000;283:801–806. Copyright 2000, American Medical Association.

Oral Androstenedione Administration and Serum Testosterone Concentrations in Young Men. Benjamin Z. Leder, MD, Christopher Longcope, MD, Don H. Catlin, MD, Brian Ahrens, David A. Schoenfeld, PhD, Joel S. Finkelstein, MD

Context: Androstenedione, a steroid hormone and the major precursor to testosterone, is available without prescription and is purported to increase strength and athletic performance. The hormonal effects of androstenedione, however, are unknown. *Objective:* To determine if oral administration of androstenedione increases serum testosterone levels in healthy men. *Design:* Open-label randomized controlled trial conducted between October 1998 and April 1999. *Setting:* General clinical research center of a tertiary-care, university-affiliated hospital. *Participants:* Forty-two healthy men aged 20 to 40 years. *Intervention:* Subjects were randomized to receive oral androstenedione (either 100 mg/d [n = 15] or 300 mg/d [n = 14]) or no androstenedione (n = 13) for 7 days. *Main Outcome Measures:* Changes in serum testosterone, androstenedione, estrone, and estradiol levels, measured by frequent blood sampling, compared among the 3 treatment groups. *Results:* Mean (SE) changes in the area under the curve (AUC) for serum testosterone concentrations were –2% (7%), –4% (4%), and 34% (14%) in the groups receiving 0, 100, and 300 mg/d of androstenedione, respectively. When compared with the control group, the change in testosterone AUC was significant for the 300-mg/d group ($P < .001$) but not for the 100-mg/d group ($P = .48$). Baseline testosterone levels, drawn 24 hours after androstenedione administration, did not change. Mean (SE) changes in the AUC for serum estradiol concentrations were 4% (6%), 42% (12%), and 128% (24%) in the groups receiving 0, 100, and 300 mg/d of androstenedione, respectively. When compared with the control group, the change in the estradiol AUC was significant for both the 300-mg/d ($P < .001$) and 100-mg/d ($P = .002$) groups. There was marked variability in individual responses for all measured sex steroids. *Conclusions:* Our data suggest that oral androstenedione, when given in dosages of 300 mg/d, increases serum testosterone and estradiol concentrations in some healthy men. JAMA 2000;283:779–782. Copyright 2000, American Medical Association.