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Kytja K.S. Voeller

J Child Neurol 1991 6: S2

DOI: 10.1177/0883073891006001011

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Toward a Neurobiologic Nosology of Attention Deficit Hyperactivity Disorder

Kytja K.S. Voeller, MD

This special supplement to the *Journal of Child Neurology* is devoted to attention deficit hyperactivity disorder (ADHD), as it is currently called. There is an enormous literature on this topic. Barkley¹ pointed out a decade ago that there were some 2000 articles on this subject, and the number has undoubtedly increased exponentially since that time. Hopefully, this special issue presents a fresh look at an old subject. The clinical section includes articles by Bennett and Sally Shaywitz, who discuss comorbidity and Weinberg and Emslie, who review the complex issues of differential diagnosis. Hynd and colleagues present information about the cognitive profile of children with attention deficit disorder with and without hyperactivity. Martha Denkla discusses the manifestations of ADHD in the adult. I have reviewed some of the issues of clinical management of ADHD for the clinician, and Eileen Ouellette reviews the forensic issues relating to psychostimulant use—an area of increasing importance for the clinician.

The research section deals with ADHD from the perspective of neuroscience and neuropsychology, interweaving the knowledge of behavioral neurologists and neuropsychologists who have studied frontal lobe and attentional deficits in adults with information from neuroscientists working with the visual attentional system and basal ganglia of primates. Frank Benson comments on the concept of frontal dysfunction as a component of ADHD. Heilman and colleagues present a model of ADHD that incorporates adult models of attentional and intentional dysfunction. Colby provides a detailed review of the neurophysiologic and anatomic substrates of attentional processes. Swanson et al describe the use

of the Posner paradigm in children. Trommer and coworkers apply an adult frontal lobe task to children, and describe the effect of methylphenidate on performance.

It has generally been accepted that ADHD involves some form of brain dysfunction, but a workable model has not been easy to come by. Over the last 20 years, there have been significant changes in the conceptualization of the syndrome by clinicians and in the way neuroscientists have thought about attentional and motor behaviors. At this time, it might be worth reviewing available information from both these areas as they pertain to a neurologic model of ADHD.

The shifts in clinical perspective had an important bearing on early concepts of brain dysfunction. For instance, hyperactivity was viewed as the salient symptom prior to 1970, and this was reflected in the terms "hyperkinesis" and "hyperkinetic impulse disorder," which was attributed to "minimal brain damage/dysfunction" in the 1960s.² It was known that children who had encephalitis,³ head injury,⁴ or prematurity^{5,6} were likely to develop a serious behavior disorder, of which hyperkinesis was a prominent symptom. The affected child was perceived as being both hyperactive and *hyperaroused*, being constantly bombarded by extraneous stimuli that were not properly modulated. The diencephalon was seen as the center that sorted, routed, and patterned impulses flowing through the reticular activating system from sensory receptors to higher brain areas.⁷ Amphetamines functioned to raise "synaptic resistance," thus decreasing this flood of impulses coming from the periphery. Laufer et al,^{8,9} studying the photo-pentylentetrazol threshold of children with hyperkinetic impulse disorder and the increase in the threshold with amphetamine, postulated that ". . . injury to or dysfunction of [the] diencephalon would alter resistance at synapses. This would allow incoming impulses to spread out of usual pathways and irradiate large cortical areas." This in turn would result in unusual sensitivity to ". . . stimuli

Received Oct 1, 1990. Accepted for publication Oct 5, 1990.

From the Department of Psychiatry and the Division of Pediatric Neurology, Department of Pediatrics, University of Florida School of Medicine, Gainesville, FL.

Address correspondence to Dr Kytja K.S. Voeller, Department of Psychiatry, Box J234, JHMHC, Gainesville, FL 32610-0234.

flooding in from both peripheral receptors and viscera."⁸ Anderson, writing in 1963, suggested that the ". . . entire syndrome is due to the lack of adequate integration of various types of perceptual modalities, as a result of minimal brain damage."¹⁰

In the late 1960s, research studies were reported that suggested that the children were, in fact, *under-aroused*. Satterfield et al¹¹ noted that the lower the arousal level (as measured by electroencephalogram, auditory-evoked cortical responses, and skin conductance), the greater the severity of clinical manifestations and the more effective methylphenidate in increasing arousal. They noted that "lack of inhibitory control over sensory function could be expected to result in easy distractibility, with the low aroused child responding to irrelevant stimuli. . . ."¹¹ This flood of stimuli resulted in an increased level of activity, which was attributed to dysfunction in the reticular formation.

A somewhat different approach was suggested by Wender¹² who viewed the basic pathology as involving decreased sensitivity to both pain and pleasure and diminished sensitivity to reinforcement. Based on the self-stimulation research of Olds and Milner,¹³ he postulated lesions involving the fornix/septal region. A model of "disinhibitory psychopathology" involving the septal region was also suggested by Gorenstein and Newman.¹⁴

The most prominent change in thinking about ADHD occurred in the early 1970s when Cohen and Douglas^{15,16} made a strong case that the most pervasive deficit was attentional, leading to the concept of attention deficit disorder with or without hyperactivity,¹⁷⁻²⁰ as put forth in the *Diagnostic and Statistical Manual of Mental Disorders*, 3rd ed (DSM III).²¹

In the mid 1970s, the frontal lobe emerged as one of the possible areas of dysfunction.* Zambelli et al²² suggested that frontal lobe dysfunction would explain the selective attention deficits observed in their subjects. Pontius²³ pointed out the resemblance of dysfunction in the caudate-frontal axis to the spectrum of behaviors seen in this syndrome. Mattes²⁴ reviewed the parallels between hyperkinesia and frontal lobe dysfunction. Gualtieri and Hicks,²⁵ focused on ". . . inconsistent levels of arousal and

reactivity . . ." and diminished capacity for self-regulation, suggesting that orbital surfaces of the frontal lobes were "essential to the coordination of somatomotor and visceromotor activities"²⁵ and emphasized the similarity between patients and experimental animals with frontal lobe dysfunction and hyperactive children. I am leaving the problem of how well frontal lobe deficits explain the spectrum of behaviors associated with ADHD to the expertise of Dr Frank Benson, who has contributed a Commentary article.

The locus ceruleus has also received some mention over the years. Mefford and Potter²⁶ hypothesized that the primary dysfunction in hyperactivity "is a low threshold for reactivity to sensory stimuli," consistent with "hypervigilance" and high arousal, decreased threshold for the orienting response, and increased exploratory behavior. On this basis, they postulated that the core deficit lies in an inhibition of locus ceruleus stimulation, via an imbalance in either adrenaline formation or α_2 -receptor numbers. The efficacy of clonidine in treating some children with ADHD²⁷ would provide some support for this concept.

In general, none of these proposed lesion sites have satisfactorily explained the entire spectrum of clinical facts and symptomatology seen in ADHD. Most children with ADHD do not have *brain lesions* in the usual sense of the word. Many have unremarkable pre-, peri-, and postnatal histories, providing little reason to suspect early encephalopathic events. The routine neurologic examination is often normal. It has not been possible to document classic brain lesions on computed tomographic scans.²⁸ On the other hand, cerebral blood flow studies have revealed hypometabolism in the caudate, particularly the right caudate²⁹; positron emission tomographic scan studies³⁰ have indicated a reduction in whole brain glucose utilization, particularly striking in the right frontal area, with a decrease in the posterior medial orbital areas; and asymmetry measurements on magnetic resonance imaging scans have revealed decreased right frontal width measurements compared to normal controls.³¹ In addition, a model of brain dysfunction in ADHD must include cases that have a genetic etiology.³²

A somewhat different approach involves localizing the neural basis for dysfunction in ADHD to the right hemisphere (see the article by Heilman et al in this issue). The right hemisphere is specialized for attentional processes in adults and for controlling various aspects of motor response, and a surprisingly high incidence of attentional deficits is ob-

*Some clinicians and researchers have implicated frontal lobe dysfunction in their descriptions of the associated behavior without identifying the neuroanatomical substrate. Sir George Frederic Still, in what was possibly the earliest description of the syndrome (Still GR: The Coulstonian lectures on some abnormal psychological condition, in children. *Lancet* 1902; 1:1008-1012, 1077-1082, 1163-1168.), attributed it to "morbid defects in moral control," and Barkley has described ADHD as consisting of *poor rule-governed behavior* (eg, sustained compliance, self-control, and problem solving).¹

served in children with documented right-hemisphere lesions.³³

From my perspective, the development of a neurologic model of ADHD is hampered by the current criteria for identifying affected children. The *DSM III* and the revised edition (*DSM III-R*)³⁴ address these issues by providing a list of symptoms that must be present for the diagnosis. These criteria consist of verbal descriptions of children's behaviors, with all the associated problems of precision. As Shaywitz and Shaywitz point out, "each clinician or investigator makes his own interpretation of how to operationalize *DSM III* criteria."³⁵ An additional problem is that the behavioral descriptions themselves cannot be mapped on to relevant neurologic behaviors. For instance, a neurologic model would distinguish between akathisia, locomotor hyperactivity, and stereotypy. Akathisia is characterized by restless and fidgety movements, coupled with an inner sense of restlessness, whereas exploratory locomotor hyperactivity is characterized by a high level of walking and running, typically in a novel environment. Both of these behaviors contrast to stereotypy, which involves repetitive movements. Akathisia and exploratory locomotor hyperactivity appear to be subserved by different neuronal circuits, which are in close proximity in certain brain areas, as lesions at various points in the dopaminergic mesocorticolimbic system can produce one or the other, with different patterns of response to stimulant drugs.³⁶⁻⁴⁰ Stereotypy is linked to the dopaminergic system, is induced by amphetamine, and is blocked by lesions of the caudate-putamen and globus pallidus.⁴¹ All of these behaviors would be labeled "hyperactive." The first two decrease with amphetamine administration, although there is some variation at different dose levels³⁹; the third increases with amphetamine. In *DSM III-R*, item 1, "often fidgets with hands or feet . . . ," can be linked to akathisia, but it is not clear whether item 2, "has difficulty remaining seated . . . ," relates to akathisia or locomotor activity. Item 14, "often engages in physically dangerous activities . . . eg, runs into street without looking," may indicate impulsivity, poor judgment, or locomotor hyperactivity. Similar confounds are seen in the hyperactivity factors of *DSM III*. Finally, although most clinicians would not label stereotypy as "hyperactivity," its presence may predict an unusual response to psychostimulant medication. Although this example is restricted to the motor system, it involves attentional and impulsive behaviors as well.

Another problem involves using a single label for all of these behaviors, without identifying sub-

types. In my opinion, one loses information regarding the diversity and heterogeneity of the disorder when subtyping is not considered. *DSM III*, by discriminating inattention from hyperactivity, improves on the situation, but does not consider other relevant behavioral subtypes. Although hyperactivity and inattention commonly occur together, they are dissociable. In our laboratory, we have tested children who have been in constant motion but are relatively unimpaired on attentional tasks. We have also seen children who are impulsive (in the sense of having major deficits in response inhibition) without being particularly hyperactive or inattentive.

Rather than viewing ADHD as one behavioral abnormality, with associated comorbidities, it may be more in line with neurologic thinking to view ADHD as a cluster of different behavioral deficits, each with a specific neural substrate, of varying severity, occurring in variable constellations, and sharing a common response to psychostimulants. The clinical manifestations would be modified by the age and sex of the patient in which they occur, and by the presence of comorbid conditions and associated cognitive deficits. Moreover, the behaviors would fluctuate—children with ADHD can behave relatively normally in certain situations.

At this point, it will be necessary to backtrack and review some of the pertinent developments in neuroscience and how this affects thinking about ADHD. In the 1960s, a great deal of research effort focused on the neurochemistry and anatomy of central catecholamine systems.⁴² Diminished levels of dopamine were identified in the substantia nigra of patients with Parkinson's disease,⁴³ and treatment with dopamine was developed.⁴⁴ In 1970, Kornetsky⁴⁵ stated the catecholamine hypothesis—drugs that were effective in treating these behaviors had marked effects on catecholamines—and proposed that further research should focus on comparisons of normal and affected children with a variety of metabolic studies relating to catecholamines. It is beyond the scope of this editorial to review the ensuing research, but this is summarized in a detailed recent review by Zametkin and Rapoport.⁴⁶

There is general acceptance that two catecholamines, dopamine and norepinephrine, are implicated in ADHD. Dopamine and norepinephrine are widely distributed in the central nervous system, but have an almost reciprocal pattern of distribution.⁴⁷⁻⁴⁹ In primates, dopaminergic innervation of associational cortex,⁵⁰ motor cortex, and subcortical structures is dense,⁵¹ and primary visual, somatosensory, and auditory cortices receive minimal dopaminergic in-

nerivation. Noradrenergic innervation has a contrasting pattern, with dense innervation of primary somatosensory and motor cortices, some innervation of visual cortex, and relatively little innervation of prefrontal and temporal cortical regions.⁵² At a neuronal level, these catecholamines serve to increase signal-to-noise ratio in different ways—"switching" and "tuning."⁵³ Dopamine may be involved in switching or selecting between different sources of information as well as controlling several aspects of motor behaviors⁵⁴—the timing, time-sharing, and the initiation of responses.⁵⁵ In contrast, norepinephrine is involved in a "tuning" or "neuromodulation" function—biasing the neuronal system so that it transmits information that is of high, rather than low, salience for the organism.⁵⁶ The effects of catecholamines on a wide variety of behaviors (attention, various aspects of inhibition and response in the motor system, and motivated behaviors, to name a few)^{57,58} are well known.

Another important set of discoveries concerned the relationship of the cortex to the basal ganglia and thalamus. Early silver impregnation methods could not demonstrate the nigrostriatal projection.^{59,60} The biochemical and fluorescent histochemical techniques developed in the 1960s provided the first convincing evidence of this pathway.⁶¹ Starting in the 1970s and continuing over the next two decades, modifications of silver impregnation methods,⁶² retrograde axonal transport of horseradish peroxidase,⁶³ anterograde transport of tritiated proteins,⁶⁴ and fluorescent dyes,⁶⁵ in conjunction with sophisticated neurophysiologic techniques, greatly expanded information about this region and its connectivity. It was previously believed that all afferents to the neocortex came from the thalamus⁶⁶ and that cortical information was funneled through the basal ganglia. By the mid-1970s, the technology existed to demonstrate discrete, parallel pathways between the precentral cortex and the putamen,^{67,68} and between the association cortex and the caudate.⁶⁹

The neuroanatomy of the caudate was essentially rewritten. Parietal, frontal, and limbic afferents from specific areas terminated in nonoverlapping, interdigitating areas in the caudate, arranged in mosaic patterns.⁷⁰ There is also a similarly organized, segregated, somatotopically organized outflow between the somatosensory and premotor cortices to the putamen.⁷⁰ Thus, there are multiple, parallel, segregated cortico-striato-nigro-thalamocortical loops that link the basal ganglia to the cortex, where convergence may occur at a corticocortical level.^{71,72} These loops appear to be segregated at all levels,

consisting of many subchannels, so that the system is composed of "thousands of 'miniloops,' emanating from and ending in a single cortical column or possibly a small set of columns."⁷³

What is remarkable is that even 10 years ago, this neural organization was not appreciated or widely known. As Goldman-Rakic and Selemon note, in the 1970s "every anatomical and medical textbook depicted the caudate and putamen as funnels for information of diverse origins: these neostriatal nuclei were considered important integrative centers. . . . Far from being a funnel, the neostriatum turns out to be a multilaned thoroughway for separate streams of influence over the thalamus and motor structures like the superior colliculus."⁷³

How does this information regarding catecholamines and these multiple loops linking cortex and subcortical structures relate to a neurologic model of ADHD? First, they provide a neuroanatomic base on which to construct a model for the complex array of behaviors seen in ADHD (see Heilman et al in this issue). They provide a way of thinking about brain dysfunction that is not limited to concepts of ablation or disconnection.⁷⁴ The cortico-striato-nigro-thalamocortical loops are systems that activate other regions and when disrupted, *inactivate* remote areas that are anatomically quite distant. Moreover, since the inactivated neurons are still capable of functioning, intense environmental stimuli or drugs that affect neurotransmitter levels may enable the systems to function, explaining situational variability.⁷⁵ Through complex gating mechanisms, this model provides an explanation for "top-down" arousal.⁷⁶

Secondly, interference of function at any level of a cortico-striato-nigro-thalamocortical loop may lead to a cluster of clinically similar signs. However, there may be considerable diversity depending on just which level of the loop is affected. Drug responses may vary with lesion location. Furthermore, one would expect that there would be a complex age-by-sex interaction in neuronal development that would be reflected in behavior and cognition.⁷⁷ Moreover, involvement of limbic areas coupled with frontal areas might result in behavior disorders that constitute comorbidities of ADHD.

Several articles in this special issue review specific aspects of these segregated loops. The anatomy and physiology of the segments related to the visual attentional system are discussed by Colby in a detailed review. An animal model of ADHD, using low-dose *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), is presented by Roeltgen and Schneider.

It is possible that ADHD will join the ranks of other neuropsychiatric syndromes in which behavioral disturbances are prominent and pathology implicates these cortical-basal ganglia loops (eg, Tourette's syndrome, Parkinson's disease, Huntington's disease, obsessive-compulsive disorder,⁷⁸ and possibly schizophrenia). This model would provide the conceptual framework for isolating specific behaviors associated with ADHD (attentional dysfunction, deficits in response inhibition, and motor impulsiveness). These behaviors can be measured using elemental, quantifiable tasks (such as deficits in response inhibition, or the attentional task described by Swanson et al in this issue), which can in turn be subjected to parametric statistical analysis. The measures are ideally suited to the comparison of behaviors in normal controls and children with ADHD and in comparisons of behaviors with and without psychostimulant treatment (for instance, see in this issue how Trommer et al used the go-no go test in the assessment of drug response). Recent neuroimaging techniques may provide support for this model. Hopefully this approach to ADHD will provide fruitful methods for investigating this intriguing and widespread disorder, certainly an appropriate subject for research in the Decade of the Brain.

Acknowledgments

The author is indebted to Mary Morris for her insightful commentary regarding the final manuscript, and to Kenneth M. Heilman for his helpful comments on an earlier version.

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