A Possible Pathophysiologic Substrate of Attention Deficit Hyperactivity Disorder

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Abstract

The attention deficit hyperactivity disorder (ADHD) is associated with defective attention and response inhibition and motor restlessness. Inattention, defective response inhibition, and impersistence are more commonly seen in adults with right than with left hemisphere dysfunction. In light of this fact and because children with ADHD not only appear to demonstrate these symptoms but also neglect the left side and have decreased activation of their right neostriatum, we propose that these children have a right hemisphere dysfunction. In addition, because both inattention and defective response inhibition can be seen in children with ADHD and in patients and animals who have frontal lobe and striatal dysfunction, we propose that children with ADHD have dysfunction in a right-sided frontal-striatal system. Motor restlessness may reflect frontal lobe dysfunction due to impairment of the mesocortical dopamine system. (*J Child Neurol* 1991;6(Suppl):S74–S79).

The attention deficit hyperactivity disorder (ADHD) is characterized by three cardinal symptoms: inattention, impulsiveness, and hyperactivity, including motor restlessness. Even though this disorder is both common and disabling, its pathophysiology has not been entirely elucidated.

Recently, several independent articles and abstracts have been published in the neurologic and neuropsychological literature that have enabled us to propose that dysfunction in a lateralized neuronal network may underlie many of the behavioral signs and symptoms associated with ADHD. Clues as to which anatomic areas this network comprises may be ascertained from investigations of behavioral aberrations that can be seen in both children with ADHD and adults with focal lesions. Animal studies may also provide us with important clues.

Evidence From Studies of Neglect

In regard to the attentional disorder seen with ADHD, one of the most profound disorders found in adult patients with focal hemispheric lesions is the neglect syndrome. In the absence of elemental sensory or motor defects, the patient with neglect often fails to recognize, respond to, or orient to stimuli presented on the side contralateral to his hemispheric lesion.[1] To a lesser degree, the patient with neglect may also fail to fully recognize stimuli even on the ipsilateral side.[2–4] This failure of recognition and response has been attributed to attentional and arousal deficits. Not only do patients with neglect fail to detect stimuli, but they also may have difficulty focusing their attention[5] and shifting their attention.[6] Although portions of the neglect syndrome can be seen after left hemisphere lesions, spatial neglect and sensory inattention-extinction appear to be more common and more severe with right hemisphere lesions.[7–9] Because many of the signs associated with neglect are seen more commonly after right hemisphere lesions, it has been posited that the right hemisphere may be dominant for mediating attention,[10] arousal,[11] and motor activation.[12] For example, in regard to attention, the right hemisphere has been posited to attend to both hemispatial fields, and the left hemisphere, primarily to the right hemispatial field. Because the right hemisphere can mediate attention in both fields, lesions of the left hemisphere will be associated with little or no inattention, but lesions of the right hemisphere will

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induce severe inattention. Electrophysiological and imaging studies in normal subjects appear to support the concept that the right hemisphere is dominant or superior in mediating attention.[10,13] Because children with ADHD have impaired attention, we posited that the right hemisphere in these children may be dysfunctional. To determine behaviorally if subjects with attention deficit disorder have right hemisphere dysfunction, Voeller and Heilman[14] tested attention deficit disorder with hyperactivity (ADDH) subjects with a cancellation task. In this task, stimuli such as letters or short line segments are distributed over a sheet of paper, and the subjects are instructed to cross out the target stimuli. Adult patients with left spatial neglect from right hemisphere lesions, even in the absence of hemianopia, more often fail to cancel lines on the side of the sheet contralateral to their lesions than on the side ipsilateral. To a lesser degree, patients with neglect may also fail to cancel lines even on the side ipsilateral to their lesion (in this case, right). Voeller and Heilman found that the performance of subjects with ADDH on this cancellation task is similar to patients with known right hemisphere lesions. Although there were cancellation failures distributed over the entire page, they were more frequent on the left side than on the right. This finding suggests these children have right hemisphere dysfunction and that right hemisphere dysfunction may induce their attentional disorder.

Several discrete anatomic areas appear to induce neglect when injured. These include the parietal lobe, the dorsolateral and medial frontal lobes (including the cingulate gyrus), the striatum, and portions of the reticular formation including the thalamus and mesencephalon. It has been postulated that these areas form a distributed system that mediates attention, intention (motor activation), and arousal.[1,15,16]

Motor Impersistence

Clues as to which of these areas are dysfunctional in patients with ADHD may be obtained from additional behavioral observations of both children with ADHD and adults with focal lesions. The inability to sustain a simple motor act has been termed motor impersistence. Motor impersistence is more frequently associated with right hemisphere damage than with left hemisphere damage.[17] Children with ADHD are more likely to have motor impersistence than controls,[18] providing additional evidence for the postulate that ADHD may be associated with right hemisphere dysfunction. Studies of adults who have motor impersistence suggest that not only does the right hemisphere play a critical role in motor impersistence but also that within the right hemisphere the frontal lobe may be the most important area.[17]

Failure of Response Inhibition: The Role of the Frontal Lobes

Impulsiveness and hyperactivity may be related in part to defective response inhibition such that children with ADHD respond to stimuli to which they should not respond. Using a go–no go paradigm, Trommer et al[19] demonstrated that children with ADHD had difficulty inhibiting a response. Animals with frontal lesions may also show defective response inhibition. For the most part, these frontal lesions in animals have been in orbital or inferior lateral regions;[20] however, dogs with lesions on the medial surface of the frontal lobes have been reported in a go–no go paradigm to have defective response inhibition.[21] Although response inhibition has not been extensively studied in patients with discrete lesions, Drewe[22] studied 25 patients with frontal lesions and found defective response inhibition on go–no go tasks. Drewe also found that medial lesions were "particularly important in giving rise to poor performance on this task."[22] Although Drewe did not find any systematic right-left differences, the details of the nature, extent, and specific location of injury were not published. Also using a go–no go paradigm, Leimkuhler and Mesulam[23] demonstrated defective response inhibition in a patient with a meningioma involving the medial aspects of both frontal lobes. After removal of the meningioma, the patient's defective response inhibition abated.

Verfaellie and Heilman[24] studied patients with right and left medial frontal lesions. Whereas the patient with a left-sided lesion was able to normally inhibit a response, the patient with a right-sided lesion had a defect in response inhibition. When asked to raise the hand opposite to that touched, the patient would make frequent errors and raise the hand that was touched instead of the opposite hand in spite of recalling the instructions and often making self-corrections. This patient also showed a defect in response preparation or motor set. That is, when given a choice reaction time test and provided with cues as to which hand to use, unlike controls or the patient with a left medial frontal lesion who re-

sponded more rapidly when provided with preparatory information, the patient with the right medial lesion did not have faster reaction times when provided with a cue than when no cue was provided. These results suggested that he was unable to develop a motor set.

The medial frontal lobes contain the supplementary motor area (SMA) and cingulate gyrus and, as discussed, lesions of the medial frontal lobe can be associated not only with impaired response inhibition but also with inattention and neglect. The medial frontal lobe receives heavy projections from the dorsolateral frontal lobes. Lesions of the dorsolateral frontal lobes in humans are also associated with inattention and defects of motor activation or set including motor impersistence, defective response initiation, and defective response inhibition. For example, Butter et al[25] studied a patient with an acute lesion of the right dorsolateral frontal lobe by asking him to either look toward or away from a lateralized visual stimulus. Initially, the patient demonstrated inattention such that when he was asked to respond to a contralateral (left) stimulus by moving his eyes rightward, he was impaired. He also showed a directional akinesia (a defect in response initiation) such that he failed to move his eyes contralaterally (leftward) in response to an ipsilateral (right-sided) stimulus. When the patient's contralateral (left) neglect improved he showed a defect in response *inhibition* such that when presented with a stimulus on the left side (contralateral to his lesioned hemisphere) he often inappropriately moved his eyes toward the left to view the stimulus rather than toward the right, as instructed.

The Striatum

Not only do the dorsolateral and medial frontal lobes have extensive reciprocal interconnections, but both also have projections to the striatum, which includes both the putamen and caudate. Whereas the prefrontal and frontal eye field portions of the frontal lobes project to the caudate, the premotor areas, including SMA, project mainly to the putamen.[26] Although striatal lesions in humans may cause neglect,[27,28] defects in response inhibition have not been systematically studied in patients with striatal lesions. Nadeau et al,[29] however, trained rats to turn to one side for a reward in response to touch to either side. Subsequently, the animals' striatum was unilaterally injected with a 6-hydroxydopamine, which destroys the dopaminergic input critical to striatal function. Following this injection, the animals responded correctly when touched contralateral to the lesion when they had to make a response contralateral to the lesion. However, if the stimulus was ipsilateral and the trained (correct) response was contralateral, then the rats erred. Instead of making the trained contralateral response, they made an ipsilateral response and turned toward the stimulus.

Although the rat paradigm of Nadeau et al[29] is not exactly the same as the hand movement paradigm of Verfaellie and Heilman (the rat was not trained to make ipsilateral movements to contralateral stimuli), in both the rat and the human paradigms there was a defect in response inhibition. Rather than performing the trained (desired) response, the organism responded with an untrained orienting response toward the eliciting stimulus.

Lou et al[30] studied children with ADHD with xenon 133 technique and noted that there was decreased regional cerebral blood flow and hence, decreased metabolic activity in the striatum. Whereas in their initial study, Lou et al[30] stated that the decrease in activation was symmetrical, in a second, more extensive study, they found that the regional cerebral blood flow was more diminished on the *right* than on the left.[31] Although Lou et al[31] did not comment on the significance of this right-left striatal asymmetry, it may have been predicted, given the hemispheric asymmetries we have discussed. The findings of Lou et al[31] not only support the postulate that children with ADHD have right hemispheric dysfunction but also provide evidence that dysfunction in a frontal-striatal system may underlie some of the signs and symptoms associated with this disorder.

Luria[32] posited that the frontal lobes are critical for transcoding volition into action. Sometimes volition calls for the inhibition of unwanted actions; the right frontal lobe, together with the right striatum, appears to be particularly important for inhibiting unwanted action in response to stimuli. The physiological role of the striatum in mediating this function is not clear. Both Lidsky et al[33] and Johnson et al[34] proposed that the function of the basal ganglia is to gate sensory inputs into motor systems. We propose that in ADHD there is a disorder in this gating system such that volition is not correctly transcoded into action. This defect leads both to a form of inattention where stimuli that should lead to action do not and to defective response inhibition where stimuli that should not lead to action do elicit a response.

Frontal-Striatal Gating of Behavior

It is not yet known precisely how frontal lobe-striatal systems perform this gating action but a number of important clues have emerged from anatomic and physiological studies. The prefrontal cortex (particularly the dorsolateral cortex and the frontal eye fields) projects to the caudate, which in turn projects to substantia nigra pars reticulata (SNpr).[26] The SNpr has extensive projections to the midbrain reticular formation[35] and the superior colliculus. The superior colliculus appears to be important in gating eye movements (saccades) in response to visual input and frontal eye field activity.[36] When there is a lesion in the frontal eye fields, a patient is still able to saccade because the superior colliculus is intact. However, in the absence of a functioning frontal lobe, as discussed, he cannot voluntarily inhibit a saccade to a visual stimulus. In a similar fashion the SNpr projections to the midbrain reticular formation may be important in gating orienting movements involving the head and trunk.

The SNpr also projects back to the ventral anterior nucleus of the thalamus, which projects back to the prefrontal cortex.[26] The prefrontal cortex, including the frontal eye field, projects to both the dorsolateral and medial premotor cortex (SMA)[37] and the anterior cingulate gyrus. The anterior cingulate gyrus also has extensive connections with other portions of the limbic system as well as the temporoparietal association cortex. The SMA not only receives projections from the dorsolateral premotor cortex and the ventral thalamus, but is also strongly connected with the anterior cingulate gyrus. The SMA, therefore, may be an intermediary between frontal-limbic motivational systems and motor systems.

Although the SMA has not been sufficiently studied to clearly define its function, we do know that lesions of the nondominant SMA produce deficits in response initiation and response inhibition.[24] Lesions of the dominant SMA produce apraxia.[38] We propose that the function of the SMA is to modify movements on the basis of the context in which they occur. For the nondominant hemisphere, the context is defined by exteroceptive input relevant to the movement to be produced, namely the correct timing and position in space as defined by external cues. Patients with nondominant SMA lesions have difficulty in using preparatory environmental cues to initiate an appropriate movement or to inhibit an inappropriate movement. For the dominant hemisphere, the context is defined by interoceptive input relevant to the movement to be produced, namely the timing, duration, and spatial position of the movement relative to other movements in the sequence being planned to accomplish a given task. Lesions of the dominant (left hemisphere) SMA therefore result in the temporal and spatial degradation of movement (apraxia) but do not affect the modification of movement according to preparatory set defined by external cues.

Our hypothesis is consistent with neurophysiological studies that indicate that SMA neuronal activity precedes activity in the motor cortex[39] and that some SMA neurons appear to inhibit activity in the motor cortex.[40] The proposal that a single SMA modifies movement in both limbs according to a single, hemispherically defined, contextual criterion is consistent with anatomic data that indicate that each SMA receives extensive input from both hemispheres and each SMA sends extensive projections to the motor strip of both hemispheres.[37] Our observations in humans of defective response initiation and inhibition with SMA lesions finds further support in animal studies in which rapid cooling of the SMA led to an inappropriate response to a signal in a go–no go task.[41]

Motor Restlessness

Motor restlessness in ADHD patients consists of an inability to remain still that does not appear to be related to external stimuli. Clinicians and parents liken this to "being driven by a motor." This restlessness resembles akathisia, which in adults is seen in some patients with Parkinson's disease[42] and as a side effect of neuroleptic use.[43] Experimental studies point to decreased dopamine in the prefrontal mesocortical dopamine system rather than in the striatum as the underlying cause of akathisia. In fact, Lang and Johnson[42] noted that when akathisia occurs in parkinsonian patients, it is unrelated to symptoms referable to the nigrostriatal system. Stewart[44] recently described an adult with akathisia associated with bilateral orbitofrontal lesions that improved dramatically with bromocriptine. In rats, lesions of the ventral tegmental area of the midbrain (the origin of the mesocortical and mesolimbic dopamine systems) produce marked motor restlessness in association with decreased attention and increased reactivity to stimuli.[45] The severity of the restlessness is inversely correlated with prefrontal cortical dopamine. The restlessness and inattention respond well to dopamine agonists.[46] Thus, a case can be made for linking the motor restlessness and, perhaps, the inattention and defective response inhibition of chil-

dren with ADHD to frontal lobe dysfunction due to hypofunction of the mesocortical dopamine system.

Possible Mechanisms of Drug Therapy

Drugs such as methylphenidate and dextroamphetamine, which potentiate the activity of dopaminergic and noradrenergic neurotransmitter systems, are known to improve the impulsiveness and hyperactivity of patients with ADHD. The means by which they do so are not known. As we have discussed, experimental studies of behavioral abnormalities in patients with ADHD and animals with selected focal lesions suggest functional impairment of a frontal-striatal system and further suggest that the right (nondominant) hemisphere may be preferentially involved. Xenon 133 blood flow studies in these patients also implicate the striatum and indicate greater involvement of the right side.[31] The behavioral abnormalities of ADHD patients may reflect frontal-striatal dysfunction, the pathologic asymmetry of function between the hemispheres, or both. Dopamine normally serves to regulate the signal to noise ratio in the striatum, and reduced dopamine levels, as in Parkinson's disease, result in a failure to initiate responses, presumably due to a failure to gate triggering sensory input into motor systems.[33,34,47] Because children with ADHD do not have parkinsonian features, the beneficial effect of methylphenidate cannot be mediated simply through augmentation of dopaminergic input to the striatum. It is conceivable, however, the methylphenidate improves behavior by ameliorating the hemispheric asymmetry in frontal-striatal function. Impulsiveness and hyperactivity may reflect a pathologically low threshold for gating behavior, defined largely by exteroceptive stimuli (attention and vigilance functions mediated preferentially by the right hemisphere). Methylphenidate may redress this imbalance in favor of behavior defined largely by interoceptive stimuli relevant to performance of the task at hand, mediated to a great extent by the dominant (left) hemisphere. Still other alternatives are conceivable. The locus ceruleus sends substantial noradrenergic projections to the striatum and its ventral extension, the nucleus accumbens, as well as brain areas known to be important in mediating attention, including the superior colliculus and the thalamus.[48,49] As we have noted, there are considerable data linking the motor restlessness of patients with ADHD to mesocortical dopaminergic hypofunction. There are also extensive dopaminergic and noradrenergic projections to the frontal lobes.[48,50] Methylphenidate may improve the impulsiveness and hyperactivity of ADHD patients by potentiating the activity of one or more of these catecholaminergic projections, with the net result that the pathologically low threshold for a behavioral response to exteroceptive stimuli is normalized.

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