Hypothesis For Prediction Of Stimulant Drug Effectiveness Utilizing Sensory Integrative Diagnostic Methods

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Despite extensive research, there has been no way to predict before drug administration which children with attention deficit hyperactivity disorder (ADHD) will respond to medication intended to calm them. A drug trial is the current method used. This paper discusses the action of stimulant medications and presents a hypothesis as to why they work on some children and not others. Sensory integration theory, particularly on vestibular system measures, that involves differential diagnosis of certain types of ADHD children, is used to explain why some children respond to stimulant medications.

D-amphetamine and methylphenidate (Ritalin) long have been used to control attention deficit disorder with hyperactivity (ADHD). Both of these drugs appear to increase attention, although some children respond to one and not the other. More recently, a third stimulant, pemoline (Cylert), has come into use. Its effects on attention are similar but not identical to the other two drugs.

This varying responsiveness suggests that these drugs do not work by identical mechanisms. There is presently no way to predict how a child will respond to drug therapy for the hyperactivity associated with attention deficit disorder.1-3

To date, no diagnostic test battery has been established as a valid predictor of stimulant response in treating ADHD children. Medical practitioners, therefore, have had to rely on the child’s response to the drug itself to establish its effectiveness. This procedure often leads to unnecessary problems for children and their parents. It also reflects our general lack of knowledge about drug effects on humans, especially ADHD children.

Reviewing literature on hyperactivity is a difficult task because of the many terms that have been used over the years to describe ADHD children. The terms minimal brain dysfunction or damage (MBD), hyperactive, and learning disabled (LD) all have been used in studies having subjects that presently would be described as ADHD. Although this paper focuses on ADHD children, the other terms will be used as they appear in the cited literature. Because hyperactivity was not differentiated from the LD and MBD labels, this is the only way to utilize the cited research.

The major question this paper attempts to investigate is: What could be different about the nervous system of the child who responds favorably to stimulant medication to control hyperactivity?

Current theories regarding hyperactivity mechanism in ADHD children

Porges4 states that research on hyperactivity can be categorized into three physiologic models: (1) hyperactivity affecting “an overaroused or highly aroused CNS;” (2) hyperactivity “as a compensatory behavior to raise the arousal of a suboptimally aroused individual via an increase in proprioceptive sensory input;” or (3) hyperactivity “as a correlate of defective cortical inhibitory mechanisms.”

Wender and associates5 developed a theory to explain the so-called paradoxical effect of stimulant drugs; that is, the drugs usually used to calm hyperactive children are stimulants. They explain the paradox in terms of a two-component model that includes an excitatory and inhibitory system in the lower brain. They believe that the typical hyperactive child has low cortical norepinephrine levels and, therefore, a deficient inhibitory system, which leads to a state of constant high arousal. Being chemically quite similar to the catecholamines epinephrine and norepinephrine (NE), amphetamines substitute for the NE acting on both the inhibitory and excitatory systems. The net effect for the high-arousal children is an increase in inhibitory capacity.

Laufer and colleagues6 also take the high-arousal position. They think that there is diencephalon dysfunction, specifically, that there is lowered synaptic resistance in the diencephalon, with the
consequence that incoming stimuli irradiate diffusely and flood the cortex. As a result, these children are overaroused and unable to inhibit or delay responses. Amphetamines increase synaptic resistance, thus reducing the abundance of impulses from the diencephalon.

The opposite conceptual position, low arousal, also has been studied. Satterfield and Dawson reported that hyperactive children have lower basal skin conductance and less nonspecific galvanic skin response (GSR), which indicates lower autonomic arousal. Overactivity is viewed as secondary to low arousal and serves as a stimulus-generating function. Amphetamines lower activity and calm hyperactive children by raising midbrain reticular activating system (RAS) excitability. Other investigators have found higher autonomic arousal in hyperactive children, and, in another study, Satterfield and coworkers found higher skin conduction levels in MBD children.

Satterfield and associates also found frequent slow dysrhythmias on EEGs of MBD children. They concluded that these children have delayed maturation of the CNS and that good drug responders are low in arousal before treatment. Kornetsky also believes that hyperactive children are CNS hypoaroused—that there is a dissociation between central and behavioral arousal.

As discussed by Ayres, differences in autonomic activity may be explained by the differential functioning of the tactile system in MBD and hyperactive children. The hypothesis of raising RAS excitability is demonstrated by her work on postrotary nystagmus.

According to de Quiros and Schragger, hyperkinesia is externalized by two different symptoms—hyperactivity and restlessness. Hyperactivity is connected more with brain dysfunction and depends on motor disinhibition elicited by external stimuli. In some of these children, administration of amphetamine or methylphenidate seems to produce a greatly excited state. Restlessness is connected with vestibular-proprioceptive disassociation and depends on postural disinhibition elicited by poor body information (internal stimuli).  

Obviously, there are contradictory theories and inconsistent experimental findings. One way out of the dilemma, according to Sroufe, is to assume that some hyperactive children are overaroused and some underaroused; that is, the variation in arousal level is greater among hyperactive children. He interprets this variation to be contrary to the notion of a syndrome, but, rather, to be indicative of heterogeneity. In order to establish that this variability is due to the existence of two or more types of hyperactive children rather than to sample heterogeneity, consistent predictors of drug response need to be identified.

Differences between good or poor responders to stimulant medication
Children taking stimulant drugs have long been divided into good and poor response categories by their behavioral manifestations while receiving the medication. More specific differentiation of children by response categories has been done at the Hospital for Sick Children, Toronto, where Swanson and Kinsbourne have used a paired associate learning procedure (PAL) to evaluate more than 400 children with symptoms of ADHD.

The drug-induced effect on the favorable responders was a rapid decrease in errors on the PAL, which reached its maximum at about two hours after medication. In contrast, the initial drug-induced effect on the adverse responders was a rapid increase in errors from baseline, and this deterioration of performance reached its maximum at three hours after medication.

Over many studies, Swanson and colleagues consistently found that 30 percent of their sample subjects were adverse responders to stimulant medication, even though they carefully selected patients on the basis of ADHD behavior. In their 1978 study, they stated that these adverse responders best fit the APA subgroup “over-anxious,” (DSM 308.2), because all children labeled as such were adverse responders. However, some adverse responders were found in other categories. Therefore, all hyperactive children are not the same, although the underlying reason for the differences is not clear.

Swanson and colleagues concluded that the same symptoms of hyperactivity occur in at least two quite distinct subpopulations, and that the children in each of the subpopulations respond in an opposite way (author’s emphasis added) to administration of stimulant medication (methylphenidate or amphetamine). In this connection, it is noteworthy that overdosed favorable responders yielded time-response curves similar to those of adverse responders. This supports a model that places adverse and favorable responders at opposite ends of a continuum with respect to the psychophysiological concept of CNS arousal or activation level. According to this model, stimulant drugs act to increase CNS arousal level, but this results in a normalizing effect on behavior only for those individuals who have an abnormal condition of underarousal in the unmedicated state (author’s emphasis added). Even in those cases, too much drug may push the patient to the other end of the continuum, resulting in “overarousal” and thus losing
its "normalizing" effect. This suggests quite distinct underlying disorders of brain dysfunction for the two groups of hyperactive children designated as favorable and adverse responders to stimulant medication.

According to Swanson, knowledge of a patient’s medical and behavioral history will not identify favorable responders to stimulants. He concludes that a method is needed to determine hyperactive children who are likely to benefit from stimulant therapy before any drug actually is administered.

**Sensory integration**

The research evidence suggests that there is no valid way to distinguish good and poor responders to stimulant drugs beforehand. Drugs are prescribed on the basis of symptoms and are designed to alleviate these symptoms rather than to correct the underlying disorder. No differentiating factors are seen in these children that are predictive of drug response after administration of medication. Swanson, for example, was unable to detect differences in the hyperactive behavior of good and poor responders. Although predictive distinctions previously have been elusive, there appear to be conceptual reasons for believing that it is possible to develop valid predictive indices.

A set of tests to delineate specific sensory integrative subgroups in children has been developed by Ayres. Her 1965 factor analytic study correlated 35 tests then commonly used for diagnosing hyperactive, LD, and brain-damaged children, with the results identifying five significant factors. Several of her other factor analytic studies confirmed the same set of factors: deficits in postural (vestibular) bilateral integration, praxis (motor planning), form and space perception, auditory language functions, and functions of the left side of the body. Ayre's work in this area led her to develop and use individual sensory integration therapy to ameliorate their vestibular-balance dysfunction.

The tests designed to delineate the five factors include the Southern California Sensory Integration Tests (SCSIT), the Southern California Postrotary Nystagmus Test (SCPNT), and related clinical observations of CNS reflex integration. (A new battery of tests, the Sensory Integration and Praxis Tests, currently are under development.)

Of these, the SCPNT is the best single indicator for differentiating between types of sensory integrative problems in LD (including hyperactive) children. Research on the SCPNT permits the conclusion that it is a measure unaffected by age or hyperactivity. Therefore, the SCPNT would appear to be a valid measure to use in differentiating types of hyperactive children.

What exactly does the SCPNT measure? Ayres has stated that lack of, or short duration of, postrotary nystagmus may be interpreted as overinhibition in the vestibular nuclei. The vestibular nuclei are relay stations for sensory input from the vestibular receptive apparatus in the inner ear. Another hypothesis is that an adequate amount of sensory excitation is not reaching the vestibular nuclei. The nystagmic rhythm is induced in the vestibular nuclei located in the brain stem and relayed to the eyes, thus producing the vestibulo-ocular reflex. Too much neuroinhibition acting on the vestibular nuclei involved in establishing this rhythm could reduce both the duration and excursion of nystagmus: The opposite case, too little neuroinhibition, could result in nystagmus of prolonged duration. Ayres has hypothesized that this prolonged nystagmus or hyperresponsivity may be due to an insufficient amount of inhibition acting on the vestibular nuclei. Other neuroprocesses also may be poorly inhibited.

Ayres documented the importance of deficits in vestibular functioning in LD (including hyperactive) children; 50% of a sample of LD children showed depressed vestibular functioning as measured by the SCPNT. Their depressed SCPNT scores improved significantly over matched controls on post-test measures of academic achievement when they were given individual sensory integration therapy to ameliorate their vestibular-balance dysfunction.

Vestibular system dysfunction has been shown to lead to form and space perception problems because of the strong basis the vestibular system gives right hemisphere functions. Vestibular system dysfunction and/or tactile system dysfunction also can lead to difficulties in motor planning (dyspraxia). Between 1958 and 1967, deQuiros performed caloric testing on more than 1,300 newborns in Buenos Aires. Numerous follow-up studies on this population revealed that vestibular disorders identified in newborn infants result in later learning problems, and that children with vestibular disorders and related postural disturbances constitute a large segment of the LD population.

In the early experiment, deQuiros found 68 infants in whom he could identify vestibular deficiency and proprioceptive disturbances at birth. He followed 77 vestibular disabled infants and 83 vestibularly normal infants until they reached the age of 3 years. Differences between the groups indicated the existence of a syndrome in the vestibular system.
lar disabled infant group. The characteristics of this syndrome were vestibular areflexia in response to caloric stimulation, delay of motor development, walking instability, and delayed speech. He then followed this group to age 11, and the differences still were apparent.30

In testing primary school children identified as having LD "without apparent justifiable cause," de Quiros29,30 found that 52 of 63 had abnormal vestibular responses. He characterized the problems of this group as caloric hyporeflexia, restlessness (hyperactivity), motor problems in reading and writing, and loss of interest in school learning. Also identified were equilibrium problems, low muscle tone, and overimposed emotional disturbance. Duration of nystagmus after rotation is not the only indication of vestibular functioning. Problems in the functioning of the vestibular system also may be reflected by decreased postural reactions, low muscle tone, poor cocontraction, poor one-foot standing balance with vision occluded, gravitational insecurity, or adverse responses to vestibular stimulation, or a combination of these.

The vestibular mechanism has several divisions. The semicircular canals generally are thought to be receptors that detect changes in position (linear movement). The SCPNT is thought to be tapping mainly the semicircular canal response to angular acceleration. Gravitational insecurity is thought to be a utricle-mediated response. If the otoliths of the utricle are displaced, a normal person perceives movement, but gravitationally insecure people feel a fear response as if they were unexpectedly falling. Keeping the utricle in a position of minimum discharge (30 degrees forward flexion) is the most comfortable position.31

Adverse reactions to the SCPNT may be due to an intravestibular conflict. That is, the semicircular canals and utricle-saccule may be sending conflicting messages concerning the body's position in space, which results in an autonomic nervous system response. A visual-vestibular conflict also is a possible cause.

Beside the vestibular system, the tactile system also is assessed in occupational therapy sensory integrative diagnosis. Some children, including many hyperactive ones, have been shown to have a disordered tactile system. In these children, the protective, excitatory sympathetic dimension of the two-part tactile system (protective-discriminative) stays predominant. The parasympathetic discriminative dimension does not function optimally in its usual inhibitory capacity. As a result, the child interprets tactile stimuli differently than the normal child; in fact, many react as if light-touch stimuli were painful or irritating (the tactile defensive child).

Certain types of tactile stimuli have been found to help to normalize this disordered system.9 The differences in autonomic arousal that were noted in several of the drug studies may be related to the tactile system irregularities seen in ADHD children.

Assessment of both the vestibular and tactile system functions is important for determining the type of sensory integrative problem experienced by an ADHD child. The SCSIT, SCPNT, and clinical observations of motor functioning can indicate whether the problem is more likely one of a cortical nature or based on lower center processing problems.

Hypothesis for stimulant drug effectiveness
The contradictory evidence about the effects of amphetamine, methylphenidate, and pemoline in hyperactive children might be due to the fact that children were not separated according to subgroups. It is now possible to identify subgroups through the use of the SCSIT, the SCPNT, and associated clinical observations. Perhaps the sensory integration differences seen in children are the crucial point in pre-establishing drug effectiveness. It would appear that the depressed-prolonged postrotary nystagmus dichotomy might provide a theoretic explanation for two types of hyperactivity (similar to the work of Porges4 [that is, hyperactivity as a compensatory behavior to raise the arousal of a suboptimally aroused system versus hyperactivity as a result of defective cortical inhibitory mechanisms], and de Quiros and Schrager14 [that is, restlessness versus hyperactivity]). It is possible that a child who has an overinhibition of the lower brain area (decreased nystagmus) becomes hyperactive in an attempt to compensate for this inhibition, thus allowing the brain to function more optimally. The effect that fast, excitatory vestibular stimulation has on the hyperactivity in these children is a clue.

Low nystagmus children are calmed by fast vestibular stimulation given during occupational therapy treatment sessions, while high nystagmus children often show increased activity levels. Conversely, perhaps the group of hyperactive children who have decreased cortical inhibition of the lower brain (increased nystagmus) become hyperactive because of this lowered inhibition.

Because methylphenidate and pemoline act primarily as lower brain stimulants, it is possible that
these drugs release the inhibition of the lower brain in the low nystagmus group, thus allowing them to function more optimally. These children should benefit from a drug therapy regime. The high nystagmus group (those who theoretically have poor cortical inhibition) would only receive more input to their already defective inhibitory system, flooding the cortex with additional signals that could not be properly inhibited, thus increasing hyperactive behavior. Children with this high duration postrotary nystagmus would be expected to be poor responders to stimulant medication.

I previously conducted two studies32,33 to investigate the relationship between sensory integrative functioning and response to stimulant medication. Methyphenidate and pemoline were studied (methylphenidate because it long has been the drug of choice for the treatment of hyperactive children, and pemoline because it is a relatively new drug in the field of hyperactivity). Good and poor responders to these two drugs were compared to delineate differences in their sensory integrative profiles; particular attention was paid to vestibular system functioning. In addition, the behaviors of good responders to Ritalin on and off the drug were compared.34 Results of the studies did show that good and poor responders to stimulant medication have differing sensory integrative profiles with the primary factor being vestibular system measures.

Conclusions

These findings confirm the hypothesis that there are at least two distinctly different subgroups in the ADHD population, and suggest that these subgroups need to be identified by researchers involved in studies as well as recognized by those involved in treatment programs. The differentiation of the two groups could lead to substantial differences in research and therapeutic outcomes.

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3. According to a written and phone correspondence with J. Swanson, PhD (1978).


33. Kimball JG: Prediction of pemoline (Cylert) responsiveness through the use of sensory integrative diagnostics, from a monograph to be published *Sensory integration and attention hyperactivity disorder*. Sensory Integration International, Torrance, Calif.

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