Relationship between Stimulant Effect, Electroencephalogram, and Clinical Neurological Findings in Hyperactive Children

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Claims have been made that hyperactive children respond better to stimulant treatment if they have clinical indicators of neurological dysfunction. However, studies report conflicting results. The present placebo-controlled study examined the relationship between neurological abnormalities and stimulant medication efficacy in 80 pervasively hyperactive children. Treatment outcome measures, which were adjusted for both age and initial severity of the disorder, included teacher and psychiatric ratings. No evidence was found to indicate that clinical neurological status, including encephalographic and neurological soft signs, was predictive of drug responsivity.


The usefulness of stimulant medication for the treatment of Attention Deficit Disorder with Hyperactivity (ADHD) in children is well established, with most investigators estimating that improvement occurs in about 70–80% of children (for reviews, see Barkley, 1977; Klein et al., 1980; and Taylor, 1983). Although some investigators have argued that a positive drug response confirms the diagnosis of ADHD (Swanson and Kinsbourne, 1976), it is not possible to predict accurately which children will be responders.

The identification of indicators prognostic of stimulant efficacy has clinical and theoretical importance. Whereas the clinical significance may not be substantial, since drug responsivity can be rapidly ascertained in any one child, and because such a large proportion of the children respond positively to stimulants (Klein et al., 1980), the theoretical significance would be great because prognostic indicators might shed light upon the relevant diagnostic correlates of the disorder.

The fact that ADHD is so responsive to pharmacological intervention has fostered the notion that it is a disorder of “organic” etiology. However, as pointed out by Taylor (1983), one would be on firmer ground using drug response as an indicator of biological antecedents if it could be demonstrated that those who are responsive to stimulant medication have additional signs of neurological dysfunction.

Several studies have examined the relationship between neurological abnormalities and stimulant efficacy in children with ADHD. The measures of neurological integrity have primarily been encephalographic (EEG), clinical neurological signs, and judgments of cerebral nervous system abnormalities based upon developmental and medical histories. This literature has been extensively reviewed elsewhere (Barkley, 1976; Cantwell, 1977; Klein et al., 1980).

Whereas several studies (Epstein et al., 1968; Satterfield et al., 1973; Shekim et al., 1979; Steinberg et al., 1971) report that ADHD children with neurological abnormalities are more likely to have a positive response to stimulant treatment than those without neurological signs, others (Knights and Hinton, 1969; Rapoport et al., 1974; Weiss et al., 1968) have not confirmed this relationship. Only one early study (Burks, 1964) reported that children without neurological dysfunction responded better than those with such evidence.

The reasons for these conflicting results are likely due to methodological inconsistencies. For example, the children in Epstein et al.’s (1968) “nonorganic” group, which was found to be less responsive to stimulant medication than those in the “organic” group, did not appear to be hyperactive until “later in life,” and in two of the five cases the behavioral disorder was believed to be due to “psychological harassment” or the child “coercing his parent to give him his way.” It seems unlikely that these children would meet cur-
rent criteria for ADDH, and, if so, it is not surprising that they were less responsive to the stimulant medication.

Similarly, Steinberg et al. (1971) studied a poorly defined group with “severe behavior and/or learning disorders” who were divided arbitrarily into those with two or more soft signs (or one hard sign) and those with less than two soft signs. Only 54% of the sample improved on medication, but the “organic” children comprised a significantly greater proportion of the positive responders (using one-tailed tests of significance). Furthermore, they reported that the “organic” children tended to be younger and rated as more hyperactive than the “nonorganic” ones. Finally, only a single dose of medication was used, which was determined by the child’s grade in school. Therefore, the low drug response rate was likely due to issues of diagnosis and dosage, and the relationship between responsivity and neurological dysfunction was confounded by age and severity of the disorder.

In a more rigorous investigation, Satterfield et al. (1973) examined the relationship of behavioral improvement with EEG abnormalities and neurological soft signs following methylphenidate treatment in a group of 57 well-defined hyperactive boys. They report that children with either an abnormal EEG or neurological soft signs in 4 or 5 functional categories showed better treatment response than those without indicators of neurological dysfunction. Furthermore, children with both an abnormal EEG and more than three abnormal neurological soft sign categories showed the greatest improvement with stimulant medication. Thus, they concluded that neurological and electrophysiological dysfunctions were predictive of treatment response, and should play an important role in the assessment of children with ADDH. Unfortunately, the relationships between age, severity of the behavioral disorder, neurological status and treatment response in the children are not reported. Since evidence exists indicating that younger children and those with more severe attentional disorders are likely to respond better to stimulant medication (Barkley, 1976), and that the presence of neurological soft signs is inversely related to age (Mikkelsen et al., 1982), it is difficult to determine whether the children who showed the greatest drug response did so because they were younger, had a more severe behavioral disorder, or because of their excessive neurological abnormalities. Another problem, but probably less important, is that no placebo control was utilized. Consequently it is not possible to remove the influence of nonspecific treatment variables that might affect the subgroups differentially.

Shekim et al. (1979) reported a positive relationship between neurological soft signs and teacher ratings of treatment response in children with ADDH. However, again, no placebo control was utilized, and although the presence of soft signs was highly age-dependent, there was no control for the effects of age.

Among studies finding no relationship between neurological abnormalities and responsivity to stimulant medication, similar methodological difficulties, and equivocal findings have still left the issue unresolved. Thus, more than half of Knights and Hinton’s (1969) sample had a chief complaint other than hyperactivity or poor attention span; essentially no information is given about Burks (1964) sample and the investigator was unaware of drug dose; Rapoport et al. (1974) gave no information regarding the nature of the neurological examination or the types of EEG or soft sign abnormalities; and Weiss et al. (1968), who used a well-defined group of children, with an adequate dosage range (5–20 mg of d-amphetamine) and well-defined neurological examinations, found a nonsignificant positive trend between suggestive brain damage and treatment response.

Because of the lack of clarity concerning the relationship between neurological dysfunction and response to stimulant medication in hyperactive children, the present study was undertaken, attempting to take into account previously mentioned methodological issues. Objective diagnostic criteria for hyperactivity were utilized along with a dosage regimen allowing for high doses to maximize efficacy. Both categorical and continuous measures of improvement were used, and a placebo-treated group allowed the control for effects of nonspecific treatment. Furthermore, the effect of age and initial severity of the behavioral disturbance were controlled for statistically.

Method

Subjects

The subjects comprised 80 pervasively (cross-situationally) hyperactive children who had been referred by schools because of behavior problems, and who had participated in a larger treatment study (Gittelman-Klein et al., 1976). This investigation includes all study children who received methylphenidate or a placebo.

All children were considered hyperactive by their teachers; in addition, they were either reported to be hyperactive by their parents or were observed to be hyperactive in the clinic. Furthermore, all children had to (1) be 6–12 years old, (2) be attending school, (3) be nonpsychotic, (4) have no diagnosed neurological disorder (neurological signs were not exclusionary), (5) be drug free, and (6) have a WISC Full Scale
IQ of at least 80, with a Verbal or Performance IQ of at least 85.

The children were randomly assigned to methylphenidate or a placebo in a double-blind fashion. The methylphenidate and placebo groups consisted of 39 and 41 children, respectively. As shown in Table 1, the two groups did not differ significantly in age, intelligence, or severity of hyperactivity.

Drug dosage was increased throughout the 4-week period such that all children received a maximum dose of methylphenidate hydrochloride of 60 mg/day, unless significant side effects occurred.

**Behavior Ratings**

Both prior to, and following 4 weeks of treatment, children were rated by teachers on the Conners Teacher Rating Scale (Conners, 1969). In addition, global improvement was rated by psychiatrists on a seven-point scale ranging from "Completely Well" to "Much Worse."

**Clinical EEG**

While mildly sedated with a low dose of chloral hydrate, clinical EEGs were recorded in 66 of the children prior to treatment. Each EEG recording was judged to be either normal, questionable, or abnormal. An EEG was considered abnormal if the recording showed evidence of diffuse slowing, focal slowing, 14- and 6-second spiking or other abnormal spiking. The judge of the EEG was aware that each child was a participant in a treatment study. However, he was unaware of the specific diagnosis, since not only hyperactive children were being evaluated at that time; of the group placement (i.e., drug or placebo) of the child; or of the child's neurological status.

**Clinical Neurological Examination**

Prior to treatment, 79 of the 80 children were given a physical and neurological examination which was adapted from that described by Clements and Peters (1962) and rated on a 130-item form (the scale is available from the authors upon request). For the present investigation, 56 items believed to assess neurological soft signs were selected and divided into seven neurological soft sign categories: (1) motor incoordination; (2) synkinesis or motor impersistence; (3) disorders of power, tone or reflexes; (4) choreiform or other abnormal movements; (5) abnormal plantar, Hoffman or clonus reflexes; (6) gait or balance disorder; and (7) sensory discrimination loss. The remaining 74 items, which were eliminated for the present investigation, consisted of ones examining the presence of minor physical anomalies (26 items); cranial nerve assessments (33 items), which were almost exclusively normal; and 15 items that were eliminated prior to the data analysis because of ambiguity as to how they should be categorized.

**Outcome Measures**

Three different measures of treatment efficacy were used: (1) the change in hyperactivity factor score on the Conners Teacher Rating Scale (Conners, 1969) adjusted for pretreatment scores, placebo effects, and age; (2) psychiatric global improvement ratings dichotomized into improved and not improved (ratings of slight improvement were considered as not improved); and (3) the presence or absence of persistent hyperactivity following 4 weeks of methylphenidate treatment. Persistence was defined by a hyperactivity factor score of 1.5 or greater on the Conners Teacher Rating Scale (Conners, 1969). This measure was used since it is widely applied as a criterion for the presence of clinical levels of hyperactivity.

**Data Analysis**

The change in hyperactivity factor score, adjusted for pretreatment scores, placebo effects, and age, was obtained using a three-step procedure: (1) a linear regression analysis was performed on the data from the placebo group to determine the relationship between baseline hyperactivity ratings and those following 4 weeks of placebo; (2) the resulting regression equation (post-treatment score = 0.632 pretreatment score + 0.8348) was applied to the methylphenidate group in order to estimate what each child's posttreatment score would have been, had he received 4 weeks of placebo rather than methylphenidate; and (3) the difference between the methylphenidate group's predicted and actual post-treatment scores were determined, which reflects the magnitude of the drug effect controlled for pretreatment score, and for time and placebo effects. The relationships between these difference scores in the methylphenidate-treated group and the neurological measures were evaluated using partial correlations controlling for age.

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**TABLE 1**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Methylphenidate (N = 39)</th>
<th>Placebo (N = 41)</th>
<th>t</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>104.2</td>
<td>103.7</td>
<td>1.7</td>
<td>0.18</td>
</tr>
<tr>
<td>S.E.</td>
<td>2.0</td>
<td>2.34</td>
<td>0.08</td>
<td>0.52</td>
</tr>
<tr>
<td>Age (in mo)</td>
<td>104.6</td>
<td>104.6</td>
<td>2.9</td>
<td>0.632</td>
</tr>
<tr>
<td>Full Scale IQ*</td>
<td>104.6</td>
<td>104.6</td>
<td>2.9</td>
<td>0.632</td>
</tr>
<tr>
<td>Hyperactivity Factor*</td>
<td>2.88</td>
<td>2.34</td>
<td>0.08</td>
<td>0.52</td>
</tr>
</tbody>
</table>

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*Wechsler Intelligence Scale for Children.

*Conners Teacher Rating Scale.
Results

Dosage

At the end of the 4-week period the treatment group was receiving a mean daily dosage of 50 mg (1.78 mg/kg) of methylphenidate hydrochloride. The dosage range was 20–60 mg (0.80–2.94 mg/kg).

Neurological Abnormalities

Table 2 shows the frequency of abnormalities in each of the seven soft sign categories. The most frequent abnormalities were in sensory discrimination, which resulted primarily from errors on tests of double simultaneous stimulation and graphesthesia. In addition, motor incoordination, synkinesis and mild movement disorders were frequent.

Table 3 shows the frequency of abnormal soft sign categories; 24% had no abnormal soft sign categories, and none of the children had abnormalities in more than five of the seven categories. The greatest number of children were deficient in only one category, and the frequency decreased thereafter. Across the group, the number of abnormal categories was significantly correlated with age \( (r = 0.38, p = 0.02) \); younger children had more abnormal soft sign categories. The number of abnormal soft sign categories was not related to the severity of the hyperactivity \( (r = 0.002, \text{NS}) \), however, there was very little variance on that behavioral measure.

Among the children who received clinical EEG evaluations, 32 (48.5%) were rated as normal, 2 (3.0%) were rated as questionable, and 32 (48.5%) were judged to be abnormal. The group receiving methylphenidate consisted of 14 children with EEG abnormalities. These were characterized primarily by 14- and 6-second spiking \( (N = 9) \), with a lower frequency of other abnormal spiking \( (N = 3) \), diffuse slowing \( (N = 1) \) and focal slowing \( (N = 1) \).

Table 4 shows the relationship between neurological abnormalities and the placebo-controlled measure of improvement among the children treated with methylphenidate. Neither the presence of EEG abnormalities or the number of abnormal soft sign categories was related to the magnitude of improvement. However, younger children demonstrated greater improvement. After controlling for age, the relationships between the neurological measures and improvement, which remained nonsignificant, were in the direction of greater drug efficacy for children without neurological abnormalities.

The relationship between psychiatric ratings of global improvement and the two neurological measures are shown in Tables 5 and 6. Approximately 78% of the children were judged to have improved in response to the medication, but the improvement was not related to either the number of abnormal soft sign categories or to the presence of EEG abnormalities. Other investigators have dichotomized children into groups based upon the number of neurological soft signs (usually the dividing point is between 2 and 4). Since this is somewhat arbitrary, we presented the data without combining categories (Table 5); however,

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**TABLE 2**

Types of Neurological Soft Signs in 79 Hyperactive Children

<table>
<thead>
<tr>
<th>Category</th>
<th>Abnormal</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensory discrimination</td>
<td>36</td>
<td>45.6</td>
</tr>
<tr>
<td>Motor incoordination</td>
<td>27</td>
<td>34.2</td>
</tr>
<tr>
<td>Synkinesis or motor incoherence</td>
<td>25</td>
<td>31.6</td>
</tr>
<tr>
<td>Chorea and other movements</td>
<td>22</td>
<td>27.8</td>
</tr>
<tr>
<td>Gait or balance</td>
<td>13</td>
<td>16.5</td>
</tr>
<tr>
<td>Power, tone or reflexes</td>
<td>1</td>
<td>1.3</td>
</tr>
<tr>
<td>Plantar, Hoffmann or clonus</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**TABLE 3**

Frequency Distribution of Abnormal Neurological Soft Sign Categories in 79 Hyperactive Children

<table>
<thead>
<tr>
<th>No.</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>19</td>
<td>24.1</td>
</tr>
<tr>
<td>1</td>
<td>28</td>
<td>35.4</td>
</tr>
<tr>
<td>2</td>
<td>11</td>
<td>13.9</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>15.2</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>8.9</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>2.5</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

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**TABLE 4**

Relationship between Improvement on the Teacher Hyperactivity Factor and Neurological Signs in Methylphenidate-Treated Hyperactive Children

<table>
<thead>
<tr>
<th>Soft Signs</th>
<th>EEG Abnormalities</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improvement(^a)</td>
<td>( r = 0.00 )</td>
<td>( p = 0.35 )</td>
</tr>
<tr>
<td>Improvement(^a)</td>
<td>( r = 0.15 )</td>
<td>( p = 0.31 )</td>
</tr>
</tbody>
</table>

\(^a\) Correlations uncontrolled for age.

**TABLE 5**

Relationship between Global Improvement Ratings and the Number of Abnormal Neurological Soft Sign Categories in Methylphenidate-Treated Hyperactive Children\(^a\)

<table>
<thead>
<tr>
<th>Number of Abnormal Soft Sign Categories</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>Unimproved</td>
</tr>
<tr>
<td>0</td>
</tr>
</tbody>
</table>

\(^a\) \( x^2 = 3.46, df = 5, \text{NS} \).
the results remain nonsignificant when the data are dichotomized.

Despite the fact that 78% of the children treated with methylphenidate were judged to show significant improvement, as measured by the psychiatric global improvement scale, and about 70% of them had greater than a 30% improvement according to teacher ratings, approximately half of them remained hyperactive as defined by a post-treatment teacher rating scale score of 1.5 or greater on the hyperactivity factor. There was no relationship between either neurological measure and the persistence of hyperactivity following treatment (Tables 7 and 8).

### Discussion

This study examined the relationship between minor neurological abnormalities and methylphenidate efficacy in a group of pervasively hyperactive children who received either methylphenidate or a placebo for a 4-week period. The data do not support the contention that the response of hyperactive children to methylphenidate is related to the presence of neurological soft signs or EEG abnormalities. These negative findings were consistent across several measures of improvement which included both psychiatric and teacher ratings. Age and initial ratings of severity of the behavioral disorder were controlled for, therefore eliminating those factors as possible confounds in the relationships investigated.

The reasons for the differences between our findings and those of other investigators are likely to be due to several methodological inconsistencies. Whereas some included poorly diagnosed children, those in the present study met relatively uniform criteria for hyperactivity across varied settings. The present investigation also utilized higher dosages of medication (up to 60 mg/day) than previous studies, as well as a placebo control, which may contribute to some of the differences. Perhaps more important, this is the only investigation that controlled for age and the initial severity of hyperactivity. Younger children showed greater behavioral improvement with methylphenidate treatment. Since some measures of minor neurological abnormalities are known to be highly age dependent (Mikkelsen et al., 1982), a finding that was replicated in the present investigation, the discrepancy between our findings and those of others may reflect the previous lack of control for age.

The study's findings cannot be interpreted as supportive of the notion that the behavioral symptomatology associated with ADDH is not due to a neurological dysfunction, only that these measures of neurological integrity are not predictive of treatment outcome. It is well known that neurological soft signs and EEG abnormalities are relatively crude measures of neurological condition; they may be present in children who have no other indications of neurological dysfunction, and absent in children with known brain damage.

In view of the findings that these neurological measures are not related to either treatment responsivity nor the severity of the behavioral disorder, the need for a determination of neurological status prior to the initiation of stimulant treatment in hyperactive children seems unwarranted, unless the presence of a specific neurological disorder is suspected. It appears unlikely that a direct association exists between either EEG abnormalities or neurological soft signs and the behavioral disturbance of ADDH. It is more likely that both the behavioral disturbance and these neurological abnormalities are part of a constellation of symptoms that are manifestations of other underlying neurophysiological disturbances.

### References


STIMULANT EFFECTS AND NEUROLOGICAL SIGNS IN ADDH


