

to the subjects and they were given four practice sequences (4).

The subjects were 76 right-handed and 53 left-handed university undergraduates (5). The average error rates for these two groups are shown in Table 1. The variance of the left-handed group was significantly higher than that of the right-handed group [$P < .05$ (6)]. Further, the left-handed subjects made significantly fewer errors than the right-handed (median test, $\chi^2 = 8.03$, d.f. = 1, $P < .01$) (7). Given the larger variance in the left-handed group, I hypothesized that those who were strongly left-handed might differ from those with a mixed preference, since individuals in the latter group would be expected to have more bilateral representation of function (8). Each population was therefore subdivided on the basis of strength of manual preference (Table 1) (9). There was an overall significant difference among these four subgroups (median test, $\chi^2 = 12.33$, d.f. = 3, $P < .01$). Further, the performance of the left-handers with a mixed preference (moderately left-handed) was significantly more accurate than that of any of the other three groups (Table 1). The other groups did not differ significantly from each other.

These findings suggest an explanation in terms of a duplication of storage of pitch information by the moderately left-handed. If the efficiency of storage and retrieval at one locus is identical for all populations, then the retrieval of this information from two separate loci should significantly increase the overall probability of correct judgment. We can further hypothesize that such duplication of representation occurs in parallel with the duplication of representation of speech functions in the two hemispheres. We cannot, of course, specify whether the pitch information is retained in the dominant or the nondominant hemisphere in the case of people for whom a more completely unilateral storage is hypothesized (10).

It remains to be determined to what extent the superiority of the moderately left-handed on this pitch memory task generalizes to other auditory or musical situations. However, other left-handed subjects selected for previous experiments on the basis of superior performance on such a task performed unusually well on a variety of tests of musical memory, including the transposition of melodic sequences (11).

The finding that the moderately left-handed differ significantly in performance from the moderately right-handed also demonstrates that the "ambi-

dextrous" should not be considered a single population, as is often assumed. Had the two groups been combined in this study, no significant differences would have been seen (12).

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13. Supported by PHS grant MH-21001. I thank S. Hickey for his assistance in data collection and J. Miller and W. Wickelgren for valuable discussions.

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Dextroamphetamine: Cognitive and Behavioral Effects in Normal Prepubertal Boys

Abstract. *The behavioral, cognitive, and electrophysiological effects of a single dose of dextroamphetamine (0.5 milligram per kilogram of body weight) or placebo was examined in 14 normal prepubertal boys (mean age, 10 years 11 months) in a double-blind study. When amphetamine was given, the group showed a marked decrease in motor activity and reaction time and improved performance on cognitive tests. The similarity of the response observed in normal children to that reported in children with "hyperactivity" or minimal brain dysfunction casts doubt on pathophysiological models of minimal brain dysfunction which assume that children with this syndrome have a clinically specific or "paradoxical" response to stimulants.*

Considerable clinical experience indicates that the behavioral response of increased alertness and focused activity of children with "hyperactivity" or minimal brain dysfunction (MBD) given stimulant drugs is nonparadoxical with regard to adult response, and nonspecific in comparison to other pediatric populations. Clinical nonspecificity is suggested by the fact that children selected for treatment on the basis of teacher recommendation alone (1), delinquent behavior without documented motor rest-

lessness or attentional deficit (2), or learning disorder without associated behavioral disturbance (3) all show approximately the same short-term improvement on cognitive test performance or show decrease in restless-impulsive behaviors when given stimulant medication. Moreover, the increased alertness and arousal, as measured by changes in reaction time and performance on cognitive tests, are similar to those reported for normal adults given comparable doses of stimulant drugs (4); in addition,

wide individual differences with both calming and alerting responses have been noted in adults and children (5).

However, animal studies have demonstrated that brain lesions (6) or chemical alteration of catecholamine metabolism in the central nervous system (7) can alter the amplitude or direction of the normal response (increased activity) of young rats to amphetamine. Primarily on the basis of these data, models have been proposed to account for the behavioral calming and cognitive test improvement of MBD children on stimulants; these models propose an underlying "brain dysfunction" or alteration in central nervous system chemistry in hyperkinetic-MBD populations (8). An incidental result of these models is that "brain damage" or "biochemical alteration" is often inferred by clinicians and educators on the basis of a child's behavioral calming response to stimulants.

To test the hypothesis that behavioral calming and increased attention in chil-

dren given stimulants indicate an underlying pathophysiology, a sample of normal prepubertal boys was studied after a single dose of amphetamine (0.5 mg/kg) or placebo in a double-blind, crossover design to see if their behavioral, cognitive, or psychophysiological responses to the drug would differ from those of hyperkinetic-MBD populations.

The subjects were 14 children of parents from the biomedical and mental health community. Boys between the ages of 6 and 12 were selected by these criteria: superior school performance, good coordination and good peer relations, no history of learning or behavior disorder in the child or his parents or siblings, and no family history of alcoholism, hysteria, or sociopathy. Informed consent was obtained from both parents and from children age 7 and over. Children and parents were told that this medicine helped some children with behavior and learning problems but that we did not know how it would affect them. The

mean age of the sample was 10 years 1 month (standard deviation, 2 years 1 month); mean IQ (Peabody), 131 ± 18 ; the mean item score on the hyperactivity factor of the Conners parent rating scale (9), 0.26 ± 0.28 ; and the mean item score on a standardized neurological exam, 0.34 ± 0.10 (10).

The study occupied three mornings: a baseline session (11) followed by drug or placebo sessions in a double-blind, crossover fashion. The mean dose of dextroamphetamine elixir was 15.8 ± 3.9 mg (range, 10 to 23 mg). The measures chosen have consistently been drug-sensitive with hyperactive child populations.

On all days (baseline, placebo, and drug) the following measures were obtained: motor activity, reaction time, continuous performance test, verbal learning and memory test, and linguistic analyses of language performance. Subjects completed a self-report mood scale, and behavior was rated during a ½-hour

Table 1. Significant behavioral and cognitive effects of dextroamphetamine (0.5 mg/kg, given orally) in normal prepubertal boys. Measures were made between 30 and 150 minutes after drug ingestion. Subjects completed a modification of a 28-item self-report mood scale (16), and behavior during a 20-minute psychiatric interview was rated by using 24 items from the children's psychiatric rating scale (16). The reaction time (RT) task consisted of 20 trials, ten with a fixed 4-second (short) preparatory interval (PI) and ten with a 10-second PI (data not shown). Galvanic skin response (GSR) was monitored continuously during a session in which the RT trials were preceded by a 3-minute rest period and a series of eight 75-db tones to which no response was required. Vigilance was assessed by using a modification of Rosvold's continuous performance task (17). A sequence of single numerals was presented to the subject on a digital display. The subject's task was to push a button if a 4 appeared, if and only if it was preceded by a 6. The failure to do so was an omission error; pressing the button at the wrong point was a commission error. The error rate was increased by reducing the interstimulus interval by 5 percent following each correct identification and increasing it by 5 percent following each error. Subjects were instructed to work to maximize stimulus presentation rate (18). A verbal learning and memory test was presented as a word game consisting of 20 different sets of three words each, in which the task was to "choose the word that does not belong on the basis of meaning (for example, orange, pear, house) or sound (for example, boy, toy, balloon)" (19). Immediately after completing this task, subjects were engaged for 10 minutes in a perceptual task, to prevent rehearsal, and this was followed by free recall of the previously presented words. After this, subjects were read one item from each set as a prompt for the recall of the related item (cued recall). Language performance was assessed from recordings of the children's speech while performing three structured tasks: picture description, storytelling, and instruction of a listener who could not see the child on how to construct block designs; S.D., standard deviation; d.f., degrees of freedom; N.S., not significant.

Measure	Placebo (mean $\pm$ S.D.)	Dextroamphetamine (mean $\pm$ S.D.)	Statistic	d.f.	P
Counts per 2 hours	421 $\pm$ 133	<i>Activity</i> 284 $\pm$ 88	16.92*	1, 10	<.002
Item 14: "Feel funny, not like myself."	0.50 $\pm$ 0.94	<i>Self-report mood scale</i> 1.64 $\pm$ 1.08	8.21*	1, 12	<.02
Hypoactivity	0.50 $\pm$ 0.65	<i>Psychiatric interview</i> 0.66 $\pm$ 0.97	7.00*	1, 12	<.02
Low voice	0.16 $\pm$ 0.37	0.86 $\pm$ 0.86	4.56*	1, 12	<.06
RT (msec), short PI	303.3 $\pm$ 77.07	<i>Psychophysiological</i> 270.9 $\pm$ 75.58	9.60*	1, 12	<.01
GSR (10^{-8} mho)	0.491 $\pm$ 0.31	0.309 $\pm$ 0.23	6.30*	1, 12	<.03
Free recall (total)	5.94 $\pm$ 1.55	<i>Learning and memory</i> 9.25 $\pm$ 1.60	6.59*	1, 12	.025
Cued recall (total)	5.63 $\pm$ 1.00	8.66 $\pm$ 1.41	5.74*	1, 12	.03
Omission errors	7.50 $\pm$ 4.9	<i>Continuous performance test</i> 5.86 $\pm$ 2.8	-2.22†	1, 12	<.05
Commission errors	6.79 $\pm$ 6.7	6.43 $\pm$ 6.0	0.61†	1, 12	N.S.
Task-directed phrases	58.83 $\pm$ 39.55	<i>Language performance</i> 78.83 $\pm$ 55.47	7.5‡		.05
Questions (not task-directed) per minute	0.43 $\pm$ 0.39	0.23 $\pm$ 0.25	5.5‡		.01

*F, two-tailed. †t, on log-transformed scores. ‡Wilcoxon T.

psychiatric interview. Other autonomic psychophysiological, and evoked potential measures will be reported elsewhere.

The children left the testing center 3 hours after medication or placebo had been administered; parents were asked to keep a diary record of behavior during the afternoon and evening.

Behavioral ratings showed both striking immediate and delayed effects which differed from each other. Behavioral and cognitive effects during the drug session are given in Fig. 1 and Table 1.

Amphetamine administration in comparison with placebo was associated with decreased motor activity (decreased actometer counts, low voice, and hypoactivity in the interview) combined with generally improved attentional performance (faster reaction time, superior memory, and improved vigilance) and decreased galvanic skin response amplitude. After drug administration, the children appeared unusually inactive, not simply less restless. There was an increase in task-related descriptive speech and a decrease in speech not task-related, such as questions (Table 1). These results are entirely consistent with those reported for hyperactive children on stimulant medication in previous studies (12).

In contrast to these effects on motor activity and performance, neither self-rated nor observer-rated mood effects were significant. This is despite the fact that 12 of the 14 subjects correctly identified the medication day, and the only self-report item differentiating drug and placebo days was, "I feel funny, not like myself" ($P < .01$).

Baseline scores of ages, activity, absolute drug dose, or neurological examination did not predict change with medication for any measure.

A marked behavioral rebound was observed by parents and teachers starting approximately 5 hours after medication had been given; this consisted of excitability, talkativeness, and, for three children, apparent euphoria. This behavioral overactivity was reported (by diary) for ten of the 14 subjects following amphetamine administration and for none of the group following placebo. Insomnia was the most common side effect (nine subjects), with stomach aches and mild nausea reported by three subjects.

The major finding is that children with no behavioral or learning difficulties, and in fact superior intellectual performance, showed behavioral and cognitive responses, that is, motor calming and improved performance, and some electrophysiological changes following am-

phetamine administration similar to those of hyperactive-MBD children.

These results indicate that models of MBD which assume that patients have an altered behavioral response to stimulants compared to normal children are not appropriate for the hyperactive child syndrome. Conversely, hypotheses of biological abnormalities in MBD, such as dopamine depletion or low arousal, are not necessary to explain the effects of stimulants in hyperkinetic children. It is important that no diagnostic significance be inferred from a beneficial drug effect: diagnostic labels in themselves, when incorrectly applied, may have deleterious effects upon children's behavior and achievement (13).

The decreased motor activity obtained in this study may be secondary to improved attention, because activity was

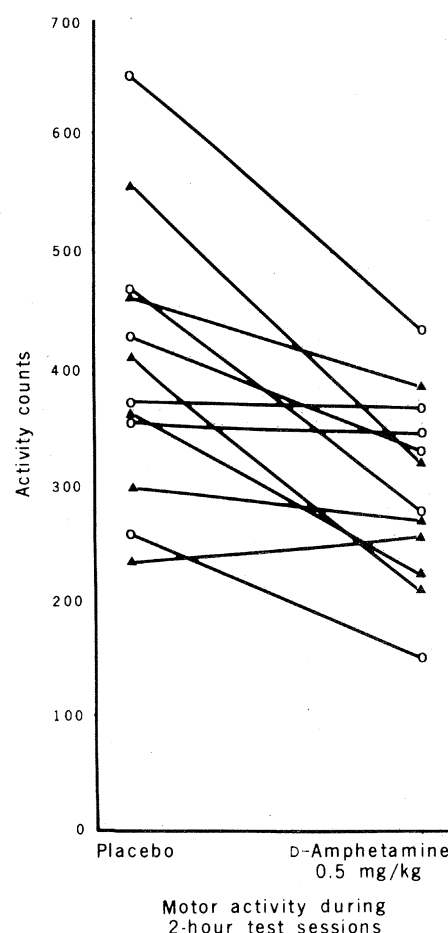


Fig. 1. Motor activity during 2-hour test period for placebo and amphetamine sessions. Motor activity was recorded during the session with a newly developed acceleration-sensitive device which recorded total activity counts each 7.5 minutes in a memory cell for the test period (15). The activity monitor was worn in a vest pocket over the thoracic dorsal area. Because of technical difficulties, activity recordings were not completed for two of the 14 subjects. Different symbols are used for clarity and do not denote different populations.

only monitored during cognitive testing. A direct motor effect of stimulants in "hyperkinetic" children has yet to be demonstrated.

This study does not address the empirical question of whether stimulant drugs are beneficial to the hyperactive-MBD syndrome. The lack of specificity of a treatment is no argument against its use; for example, diuretic agents are important in the treatment of congestive heart failure even though the drug's effect on the cardiac patient is nonspecific.

The clinical "rebound" effect seen in most of our subjects 5 hours after drug ingestion suggests that clinical complaints of late-afternoon behavior difficulties in medicated hyperactive children may be related to drug action and not simply to wearing off of therapeutic effect. The observed hyperactivity may be a consequence of some alterations in neurotransmitter interaction with receptors. Alterations in receptor sensitivity have been demonstrated over relatively short intervals (14). If such alterations in receptor sensitivity occur during the hours of drug action, the phase of overactive, excitable behavior seen in our sample may represent such alterations which outlast the drug. As the rebound behavior in our normal sample resembled clinical hyperactivity, the possibility of altered receptor sensitivity in hyperactive children should be investigated.

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 19. Words were chosen by using the Battig-Montague norms for frequency of association to a particular category.
 20. E. Silbergeld, I. Kopin, and W. E. Bunney, Jr. gave helpful discussion of this study. Technical assistance was provided by D. McGreer, C. King, G. Schechter, R. Coppola, and C. L. Thompson.
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Newborn Minor Physical Anomalies Predict Short Attention Span, Peer Aggression, and Impulsivity at Age 3

Abstract. From a 5- to 10-minute newborn examination, behaviors of males at age 3 could be predicted. The number of minor physical anomalies, assessed soon after birth, was significantly related to a cluster of behaviors that are frequently labeled hyperactivity.

Hyperactivity is a label used for children who have short attention spans, behave aggressively toward peers, and are impulsive and restless (1). This behavioral syndrome is a major concern for teachers, parents, researchers, and, above all, for the children themselves. In our use of the word "hyperactive" we are not speaking about clinical populations, but of the upper range of a behavioral dimension that is normally distributed in a general population of young children. The cluster of behaviors making up this dimension, however, does include the same behaviors that are included in what is known as the "hyperactivity syndrome" in the literature referring to children in clinical treatment programs (2). The behaviors of children referred to clinics probably represent the most extreme end of this dimension.

As a set, the 17 minor physical anomalies used in this and previous studies are best known for their occurrence in Down's syndrome (3). Individual anomalies, however, are present in the general population with an average of two to four per person. It has been argued that the minor physical anomalies are develop-

mental deviations that result from some form of genetic transmission, or from some insult in early pregnancy that mimics genetic transmission (4). The same factors producing deviation in the first weeks of pregnancy could influence the occurrence both of the anomalies and of some deviation in the development of that part of the central nervous system which is responsible for the hyperactive behaviors. The minor anomalies to which we refer are head circumference out of normal range, more than one hair whorl, fine electric hair, epicanthus, hypertelorism, malformed ears, low-set ears, asymmetrical ears, soft pliable ears, no ear lobes, high steeped palate, furrowed tongue, curved fifth finger, single palmar crease, wide gap between first and second toes, partial syndactylia of toes, and third toe longer than second (5).

In a sample of 74 normal preschool children attending a research nursery school, Waldrop *et al.* (6) found that hyperactive behaviors were related to the number of observed anomalies. Subsequent studies of boys, age 3 to 12, replicated this finding in another nursery school sample (7) and in three samples of

elementary school boys (8). Waldrop and Halverson (7) demonstrated the stability of the anomaly score and of hyperactivity from age 2.5 to age 7.5 and found that anomalies at 2.5 predicted hyperactivity at 7.5. Within a clinic population of 81 hyperactive boys, a subgroup with high anomaly scores, when compared with a subgroup with low anomaly scores, had greater plasma dopamine β -hydroxylase activity, earlier age of onset of hyperactivity, more fathers with histories of hyperactivity, and more mothers who reported bleeding during the first trimester (9).

As a part of the Bethesda Longitudinal Study, National Institute of Mental Health, 30 male newborns were examined for the presence of 16 minor physical anomalies (fine electric hair was omitted from the list). Twenty-three of the 30 were seen 3 years later when they attended a research nursery school. An additional 36 boys were in the nursery school sample but had not been assessed for anomalies as newborns, thus making a total of 59 boys in the nursery school sample. Females were included in the larger longitudinal study, but because hyperactivity is far more prevalent among males than females (10), data on female subjects were not a part of this study. The anomaly score for each child at each age was the total count of anomalies plus, for some anomalies, extra weight when the anomaly was judged to be extreme (5).

The anomaly score was found to be stable between the newborn period and age 3. For the 23 males in this study, the correlation was .86.

At age 3 (± 3 months) the subjects attended a research nursery school for 4 weeks in mixed sex groups of five children. Observations and ratings were made of behavior in a playroom where the children were free to play with a variety of toys and in a room where there were no toys but the children were free to run about and interact (11).

Data analyses of nursery school behaviors (measuring short attention span, peer aggression, and impulsivity) involved the use of two factor analyses to derive a small number of composite scores. One was a factor analysis of 23 free play observations in the playroom; the other was a factor analysis of the 25 measures that correlated significantly with activity level as measured by a mechanical activity recorder (12). Principal component factoring and varimax rotation was used throughout. Each factor analysis was replicated on two randomly selected samples of the data. Only those variables with consistent factor loadings