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Effects of Methylphenidate on Attention-Deficit Hyperactivity Disorder With and Without Aggressive/Noncompliant Features

Rafael Klorman, Joan T. Brumaghim, Leonard F. Salzman, Jaine Strauss, Agneta D. Borgstedt, Margaret C. McBride, and Stuart Loeb
University of Rochester

This study compared the impact of methylphenidate on patients with attention-deficit hyperactivity disorder (ADHD) with and without aggressive/noncompliant features. Methylphenidate (0.3 mg/Kg twice daily) and placebo were administered double-blind for 14 days each to 24 ADHD/nonaggressive, 19 ADHD/aggressive, and 20 borderline ADHD children. In general, the following benefits of methylphenidate were comparable for ADHD subgroups: (a) behavioral improvement observed by parents and teachers, (b) increases in accuracy and speed on two versions of the Continuous Performance Test (CPT), and (c) enlargement of the P3b wave of event-related potentials in the more difficult of the two CPTs. Thus, stimulant therapy had comparable benefits for ADHD patients with and without aggression/noncompliance.

The syndrome of attention-deficit hyperactivity disorder (ADHD) has attracted considerable research attention over the past two decades, at least in part because of the suitability of laboratory approaches to the study of two of its defining characteristics: attentional deficits and impulsivity (American Psychiatric Association, 1987). It is well established that these children have poorer accuracy and slower reaction time than their normal peers on several tests requiring persistence and rote performance (Conners & Werry, 1979; Douglas, 1983; Sroufe, 1975). Stimulants improve these performance deficits and decrease behavioral impulsivity and overactivity (Conners & Werry, 1979; Sroufe, 1975). Analogously, ADHD children display smaller amplitude of components of event-related potentials (ERP), such as the P3b wave, that are sensitive to cognitive processing. In turn, the amplitude of these ERP components is enlarged by stimulants (Coons, Klorman, & Borgstedt, 1987; Halliday, Rosenthal, Naylor, & Callaway, 1976; Klorman, Brumaghim, Borgstedt, & Salzman, in press; Klorman, Salzman, Pass, Borgstedt, & Dainer, 1979; Klorman et al., 1983; Loiselle, Stamm, Maitinsky, & Whipple, 1980; Michael, Klorman, Salzman, Borgstedt, & Dainer, 1981; Prichep, Sutton, & Hakerem, 1976; Zambelli, Stamm, Maitinsky, & Loiselle, 1977). Even though stimulants have similar effects on normal adults and normal children (Peloquin & Klorman, 1986; Rapoport et al., 1980), the foregoing findings indicate that these drugs reduce cognitive deficits in ADHD.

Despite the solid evidence for the preceding generalizations, there are several ambiguities in the literature concerning both the ADHD syndrome and the effects of stimulants. Several reviewers have noted the overlap of ADHD with aggression and noncompliance (e.g., Loney & Milich, 1982; Rutter, 1983). Thus, it is unclear to what extent findings of impaired performance by ADHD patients on tests such as the Continuous Performance Test (CPT) are due to noncompliance versus attentional deficits and impulsivity common to both disorders. Furthermore, stimulants achieve reductions of aggression/noncompliance as well as inattention/impulsivity in ADHD samples undifferentiated as to the overlap of these two disturbances (e.g., Amery, Minichiello, & Brown, 1984; Barkley & Cunningham, 1979; Conners, Taylor, Meo, Kurtz, & Fournier, 1972; Eisenberg et al., 1963; Maletzky, 1974; Pelham, Bender, Caddell, Booth, & Moorer, 1985; Winsberg, Bialer, & Kupietz, 1974). Thus, it is arguable that the improvements detected on tests presumably tapping cognitive functioning may be secondary or at least partly due to increased compliance. However, it is improbable that the benefits of stimulants are limited to noncompliant patients, because comparable effects have been found in highly cooperative and psychiatrically normal children and college students. Yet despite the diagnostic nonspecificity of these effects of stimulants, it is of considerable clinical and theoretical interest to examine the impact of stimulant therapy on ADHD children with and without aggressive/noncompliant features. This aim was pursued in the present research. In addition, we continued to evaluate the impact of methylphenidate on children with less well-defined ADHD. In our past work, we found comparable effects of methylphenidate on CPT performance and the P3b wave of the ERP for children with borderline and cross-situational ADHD (Klorman et al., 1983). It seemed instructive to continue the study of these children in view of the clinical nonspecificity of stimulant treatment (Peloquin & Klorman, 1986) and the relevance of stimulant treatment for relatively less disturbed patients (Halliday et al., 1976).

Two methodological improvements of our previous procedures were introduced. In our past research ADHD children received single doses of methylphenidate and placebo. Yet, clin-

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Correspondence concerning this article should be addressed to Rafael Klorman, Psychology Department, River Campus, University of Rochester, Rochester, New York 14627.

ical trials provide information on changes in clinically relevant behavior as well as cognitive processing. In addition, it was conceivable that the effects of single challenges might not be identical to those of longer treatment. Therefore, the present study involved a clinical trial in which the dosage (0.3 mg/Kg) used in our previous challenges was administered twice per day.

Another methodological refinement was that our present computation of ERPs excluded trials involving errors during vigilance tests, a constraint not observed in our previous studies of ADHD children. This improvement was introduced to rule out the possibility that our findings of larger ERPs under stimulants was secondary to the coincident increase in the number of correct detections, which are known to be associated with larger ERPs than are errors.

In summary, the present investigation evaluated the impact of a clinical trial of stimulants on cross-situational ADHD children with and without aggressive/noncompliant features as well as those without cross-situational disturbances. Besides the clinical outcome of the trial, performance and ERPs were assessed in CPTs. These tasks were designed to present two levels of difficulty in an effort to maximize their sensitivity to the impact of stimulants for children spanning a wide range of age and ability.

Method

Subjects

Subjects were 63 children 6–12 years old referred by a pediatrician, pediatric neurologist, or child psychiatrist for evaluation of their initial treatment with methylphenidate. The patients' parents provided informed consent after receiving explanations of the project from both the referring professional and the first author as well as a printed description of all procedures, potential side effects of medication, and the voluntary nature of the research.

Clinical workups by the referring physicians in combination with psychometric assessments ruled out mental retardation, psychosis, and organic brain disorder for all subjects. Before the clinical trial, all subjects were drug free, with the occasional exception of medication for allergies. All subjects obtained Verbal or Performance IQ scores exceeding 80 on the Wechsler Intelligence Scale for Children–Revised, which was administered within the year preceding testing, usually by the project staff. Except for one Puerto Rican child, all subjects were Caucasian.

The 63 children who met these exclusionary criteria included 33 with cross-situational ADHD. Specifically, they obtained ratings exceeding by at least 2 *SD*s the mean of normal children on (a) parent ratings on the Home Activity Scale (Werry & Sprague, 1970; 0 = *not at all;* 4 = *extremely*), that is, a cutoff score of 1.05 (see Michael et al., 1981); and (b) the Abbreviated Conners Teacher Questionnaire, that is, a cutoff score of 1.5 (Goyette, Conners, & Ulrich, 1978).

A further differentiation of the sample was made on the basis of two scales derived by Loney and Milich (1982) from the Conners Hyperactivity Teacher questionnaire (Goyette et al., 1978). The Inattention/Overactivity scale consists of items tapping ADHD and uncorrelated with aggression (e.g., "fidgeting" and "inattentive, easily distractible"). In turn, the Aggression scale contains items uncorrelated with core ADHD and reflecting noncompliance/aggression (e.g., "defiant," "quarrelsome," and "uncooperative"). All of the 33 cross-situational ADHD subjects placed at least 1.5 *SD*s above the mean of normal children of comparable age and gender (Pelham, Milich, & Murphy, 1986) for teacher ratings on the Inattention/Overactivity scale. In addition, 20 of these patients obtained teacher ratings on the Aggression scale within 1 *SD* about the mean of comparable normal children (Pelham et al., 1986), whereas 13 placed at least 1.5 *SD*s above the mean for their normal peers. These two subsamples were enlarged by the addition of 4 and 6 subjects, respectively, who essentially met the above criteria but fell slightly short on one measure (e.g., they earned a score of 1.4 vs. 1.5 on the Abbreviated Conners Teacher Questionnaire). In summary, the preceding classification yielded 24 ADHD/not aggressive and 19 ADHD/aggressive children.

The remaining 20 children did not meet criteria for cross-situational ADHD and are referred to as *not-criterion.* Eighteen of these patients met criteria for ADHD at home but obtained low or marginal teacher ratings. The other 2 patients fell short on ADHD criteria for both home and school. Four not-criterion patients exceeded the cutoff for the Inattention/Overactivity scale, whereas none did for the Aggression scale. Although these 20 children were not cross-situationally ADHD, they were scheduled by their referring physicians for a trial of stimulants, independently of the present research.

Demographic characteristics of the sample appear in Table 1. The three subgroups did not differ significantly on any of the tabulated demographic or psychometric variables, except for the teacher and parent ratings used to define the samples. In addition, the three ADHD subgroups were comparable in the male:female ratio—16:3 for ADHD/aggressives, 22:2 for ADHD/nonaggressives, and 19:1 for not-criterion, $\chi^2(2) = 1.38$, *ns.*

Procedure

After diagnostic procedures were completed, the subject entered a double-blind protocol consisting of two consecutive weeks of both placebo (lactose) and methylphenidate (0.3 mg/Kg dose to the nearest 1.25 mg), which were administered in two daily doses (morning and noon). The assignment of drug order was based on a random schedule. The ratio of subjects receiving placebo first versus second was 11:8 for ADHD/aggressives, 11:13 for ADHD/nonaggressives, and 10:10 for not-criterion, $\chi^2(2) < 1$, *ns.*

The trial was scheduled so as to maximize the time that the subject was in school, except for 13 subjects who were assessed during the summer. As a result of holidays or illness by the patient, sometimes an interval of 1–2 weeks intervened between phases of the trial. Also, occasionally a subject fell ill during the trial, and the phase affected was repeated while maintaining blindness.

Before each phase of the trial, the parent was given coded vials containing capsules for home and school as well as copies of the Abbreviated Conners, Inattention/Overactivity, and Aggression scales. At the end of each phase, parents and teachers independently rated the child's behavior for the preceding period, and the parent returned these questionnaires at the next appointment. At that time, the first author questioned the parent concerning each of the items of the Subjects' Treatment Emergent Symptom Scale (STESS; Guy, 1976) and rated each symptom as present or absent during the preceding phase. Finally, unused capsules were counted and used to establish that, for every subject, compliance had been satisfactory. At the conclusion of the last appointment, the code was broken.

Laboratory Sessions

Three procedurally identical laboratory sessions were held. The first was a baseline session without any medication, before the start of the trial, and was followed by additional testings on the 14th day of each phase. For each session, the parents were asked to give their child a snack around 10:30 a.m., and to ensure that he or she did not eat until after the appointment, which was always scheduled for noon. This request was intended to promote absorption of the medication administered at noon.

The three sessions were identical except that the second and third sessions began with administration of the patient's noon dose for the preceding phase of the trial. Next, the subject rested or chatted and

Table 1
Means and Standard Deviations of Demographic and Psychometric Measures

Measure	ADHD/aggressive		ADHD/not aggressive		Not-criterion		Combined groups	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age	8.35	1.60	8.27	1.56	8.58	1.47	8.39	1.52
Verbal IQ[a]	101.10	11.52	102.17	13.49	108.95	16.12	104.00	14.05
Performance IQ[a]	108.16	11.48	103.17	11.47	109.55	18.81	106.70	14.27
Full scale IQ[a]	104.53	9.72	102.62	11.37	109.75	18.09	105.46	13.60
WRAT Reading[b]	104.58	12.91	100.46	9.51	103.30	13.67	102.60	11.93
WRAT Math[b]	101.42	12.38	97.83	10.53	94.35	19.15	97.81	14.35
WRAT Spelling[b]	93.68	16.40	98.17	8.80	99.25	18.01	97.16	14.55
SES[c]	45.75	44.50	35.74	14.75	36.34	11.34	38.45	24.81
Weight (Kg)	27.42	6.58	27.99	7.07	30.62	9.20	28.65	7.68
Daily dose (mg)	16.44	4.19	16.56	4.02	17.88	4.75	16.94	4.30
Home activity	1.92	0.82	2.06	0.58	1.74	0.80	1.92	0.73
Parent Conners[d]	1.69	0.73	1.74	0.49	1.78	0.63	1.74	0.60
Parent I/O[e]	1.84	0.70	2.10	0.56	1.91	0.56	1.96	0.61
Parent Aggression	1.50	0.83	1.21	0.58	1.50	0.78	1.39	0.73
Teacher Conners[d]	2.18	0.43	1.82	0.33	0.89	0.35	1.63	0.64
Teacher I/O[e]	2.30	0.47	2.44	0.30	1.18	0.54	2.00	0.71
Teacher Aggression	1.96	0.56	0.58	0.38	0.28	0.37	0.90	0.84

Note. ADHD = attention-deficit hyperactivity disorder.
[a] Wechsler Intelligence Scale for Children–Revised.
[b] Wide Range Achievement Test standard scores (Guy, 1976, pp. 417–421).
[c] Hollingshead 4-factor score (socioeconomic status).
[d] Abbreviated Conners Hyperactivity Scale.
[e] Inattention/Overactivity Scale.

played with the experimenter for approximately 30 min, and electrodes were attached, as indicated later. There followed further informal interaction or rest until 60 min elapsed from ingestion of the appropriate capsule, or arrival on the baseline session. A 60-min interval was selected because plasma levels of methylphenidate peak around this point and remain relatively stable for the ensuing 2-3 hr (Gualtieri et al., 1982).

Chlorided silver Grass electroencephalogram (EEG) electrodes were glued with collodion to two midline scalp sites, Cz (vertex) and Pz (midparietal), at which the amplitude of the P3b wave of the ERP is maximal. Similar electrodes, clipped to the linked earlobes, served as reference for EEG leads. Beckman miniature electrodes were taped to (a) the middle of the forehead, which served as ground and (b) above and below the right eye, for detection of the electrooculogram (EOG). All sites were abraded so as to lower resistance below 3 Kohms. Grass Model 7P1 preamplifiers were used for EEG (nominal frequency band = 0.04–75 Hz) and for EOG (time constant = 10 s). All analog data and coding pulses were stored on magnetic tape by a Vetter Model A FM tape recorder.

Tasks

The experiment consisted of two versions of the CPT, administered in increasing order of difficulty. First, the X version of CPT was administered. Each of 8 letters (X, B, D, K, N, S, T, and W) was displayed with equal probability ($p = .125$) and unpredictable order in each of 3 blocks of 300 trials. Stimuli were presented by means of a Lehigh Valley projector positioned at eye level at a distance of 1 m from the subject. The letters were exposed for 50 ms to an image of 1.5 × 2.5 cm. The subject's task was to close a hand-held microswitch when the letter *X* was displayed. Intertrial intervals (onset to onset) were 1.5 s and each trial block took up 6.25 min.

The second CPT was patterned after Friedman, Vaughan, and Erlenmeyer-Kimling's (1981) Task B, which we have dubbed *CPT double,* because the target was defined as the occurrence of any letter that was identical to the preceding one. The double task was arranged identically to the X version with two exceptions. There were now 40, rather than 38, targets per trial block and 4, rather than 3, blocks of 300 trials. Different sequences of stimuli were used for each session and task, in order to rule out the possibility that recall of stimulus orders might affect subjects' performance.

The experimenter described each task to the subject and tested his or her understanding on a diagram of a hypothetical sequence of letters. Next, the child practiced the task, initially with coaching and prompting by the experimenter, until the patient independently made five consecutive correct detections. Before each trial block, the experimenter repeated the definition of the target as well as the importance of accuracy over speed.

Finally, there was a similar task involving discrimination of dim versus bright lights and loud versus soft tones, which lasted 11 min. The results of this task will be reported elsewhere.

Scoring

A composite measure of side effects for each phase of the trial was derived by counting the number of such symptoms rated as present for 12 STESS items deemed a priori to be relevant to methylphenidate (appetite loss, increased drinking, dry mouth, stomachaches, nausea, headaches, shakiness, sleep problems, anger, crying, unhappiness, and sadness).

For each of the CPTs, the following measures of performance were obtained: (a) mean reaction time (RT) for hits, that is, target trials that evoked a button press before the next trial at least 100 ms after stimulus onset; (b) percentage of misses, that is, target trials on which the subject failed to respond before the next trial; (c) percentage of false alarms, that is, nontarget trials on which the subject made a button press with a latency of at least 100 ms; and (d) d', an estimate of sensitivity of detection from signal detection theory (Davies & Parasuraman, 1982) and derived from Hochhaus's (1972) tables. Instances of zero misses or false alarms were scored as though one such error had occurred, an adjust-

ment resulting in a maximum d' of 4.65. Beta (i.e., response criterion) was not computed, because of problems in its estimation in vigilance tasks, which have a low probability of targets (Davies & Parasuraman, 1982).

The EEG and EOG data were passed through a Krohn-Hite filter with upper frequency cutoff of 40 Hz (24 dB/octave) before off-line digitization at a rate of 250 Hz by a Digital PDP-12 computer. The ERPs were derived from trials consisting of hits or correct rejections and free of ocular artifacts (EOG > 50 μv) or A/D converter overflow within a period of 50-ms prestimulus onset and 900-ms poststimulus onset. The ERPs were computed separately for leads, targets/nontargets, and tasks.

The ERPs depicted in Figure 1 illustrate parietally prominent P3b waves.[1] For each subject, a grand average of his three (one from each session) target-evoked ERPs at P_z was constructed, separately for each task. The P3b wave was identified visually from this grand average, and a window of ±36 ms was defined about its latency. Next, the most positive value within that window was scored for each of the subject's 12 ERPs (3 sessions × 2 stimuli × 2 leads) and defined as the P3b wave. A relatively similar procedure was described by Callaway, Halliday, and Herning (1983).

Results

Analyses of variance were performed with two between-subjects variables (ADHD subgroups and order) and several within-subjects measures (drug condition or laboratory sessions, EEG leads, and target/nontarget), as applicable. Probability levels were adjusted by the Greenhouse-Geisser correction. Because there were no effects of drug order that compromised the drug effects investigated, order will not be mentioned further. Differences between means were tested by using Tukey's honestly significant difference (HSD) procedure with two-tailed probability levels of .05, but almost all of the significant results exceeded .01 critical levels.

For measures of CPT performance and P3b, age was used as a covariate, and the HSD test was used to compare results for (a) placebo versus methylphenidate and (b) the baseline versus the placebo sessions. The second contrast evaluated our impression that performance declined after the baseline session.

Clinical Variables

As expected, analysis of STESS composite scores revealed that slightly, but significantly, more side effects were reported under methylphenidate (M = 3.98, SD = 2.09) than under placebo (M = 3.37, SD = 2.05), $F(1, 56) = 6.68$, $p < .02$. McNemar's chi-square test of change indicated that 4 of the 12 side effects assessed were appreciably higher under stimulant treatment: appetite loss (20.6 vs. 3.2%), $\chi^2(1) = 8.10$, $p < .005$; increased drinking (12.9 vs. 3.2%), $\chi^2(1) = 3.60$, $p < .06$; sleep problems (17.5 vs. 4.8%), $\chi^2(1) = 4.57$, $p < .04$; and crying (27.0 vs. 11.1%), $\chi^2(1) = 4.17$, $p < .05$.

Parents recorded significantly lower mean ratings under methylphenidate versus placebo on the Abbreviated Conners Scale (Ms = 1.23 vs. 1.48), $F(1, 57) = 9.18$, $p < .004$; Inattention/Overactivity scale (Ms = 1.20 vs. 1.54), $F(1, 57) = 16.25$, $p < .0002$; and Aggression scale (Ms = 1.02 vs. 1.25), $F(1, 57) = 8.73$, $p < .005$. None of the Drug × Subgroup interactions were significant.

Teachers also reported lower levels of disturbance for the stimulant versus placebo on the Abbreviated Conners Scale (Ms = 0.72 vs. 1.27), $F(1, 44) = 28.30$, $p < .0001$, and for the Inattention/Overactivity scale, (Ms = 0.90 vs. 1.58), drug $F(1, 44) = 37.81$, $p < .0001$. In contrast to the preceding two scales, teachers' aggression ratings indicated that the three subgroups derived different degrees of improvement from stimulant therapy, Drug × ADHD Subgroup $F(2, 44) = 4.58$, $p < .02$. The HSD test indicated that aggression ratings were lower under Ritalin versus placebo for ADHD/aggressive patients (Ms = 0.53 vs. 1.26), but not for ADHD/not aggressive (Ms = 0.25 vs. 0.58) or not-criterion subjects (Ms = 0.20 vs. 0.28).

A combined analysis of teachers' and parents' ratings, with the addition of raters as a within-subjects measure, revealed that teachers reported greater benefits from stimulant therapy than did parents on the Abbreviated Conners Scale, Drug × Rater $F(1, 44) = 6.92$, $p < .02$, and on the Inattention/Overactivity Scale, $F(1, 44) = 6.43$, $p < .02$.

Performance

Figure 2 displays results for performance measures for the X version of CPT. The analyses for errors were carried out on arcsine transforms in order to adjust for the binomial distribution of these scores (Myers, 1972). Reaction time data were not transformed, because their variances were homogeneous. The effect of sessions was significant for all performance measures in the X version of CPT, $F(2, 114) = 10.06$, $p < .0001$, for misses; $F(2, 114) = 5.16$, $p < .008$, for false alarms; $F(2, 114) = 8.83$, $p < .0005$ for d'; and $F(2, 114) = 31.68$, $p < .0001$, for RT. Tukey's test disclosed that the stimulant resulted in fewer missed targets, fewer false alarms, higher d', and faster RT. None of the Drug × ADHD Subgroup interactions were significant.

As also shown in Figure 2, performance in CPT-X worsened from the baseline testing to the placebo session, significantly so for misses and RT.

Similar analyses were applied to performance results from the double version of CPT, which are depicted in Figure 3. Once again, the effects of Sessions were significant for all accuracy measures: $F(2, 112) = 44.83$, $p < .0001$ for misses; $F(2, 112) = 25.66$, $p < .0001$ for false alarms, and $F(2, 112) = 60.33$, $p < .0001$ for d'. However, RT did not change over sessions, $F(2, 112) < 1$, *ns*. As depicted in Figure 3 and confirmed by Tukey's test, methylphenidate reduced misses and false alarms and increased d' in CPT double. These improvements were comparable for the three subgroups, that is, the Sessions × ADHD Subgroups interaction did not approach significance. In contrast, this interaction was significant for RT, $F(4, 112) = 2.78$, $p < .04$, but Tukey's test did not identify significant changes in speed under methylphenidate for any subgroup.

As also shown in Figure 3, accuracy tended to decrease from the baseline test to the placebo session, an effect that was significant for misses.

The high error rates for the double version of CPT might suggest that some subjects were not performing the task meaningfully, and that the increased accuracy under the stimulant might

[1] We also scored and analyzed findings for the two positive waves flanking P3b. These results were omitted to save space but can be obtained from the first author.

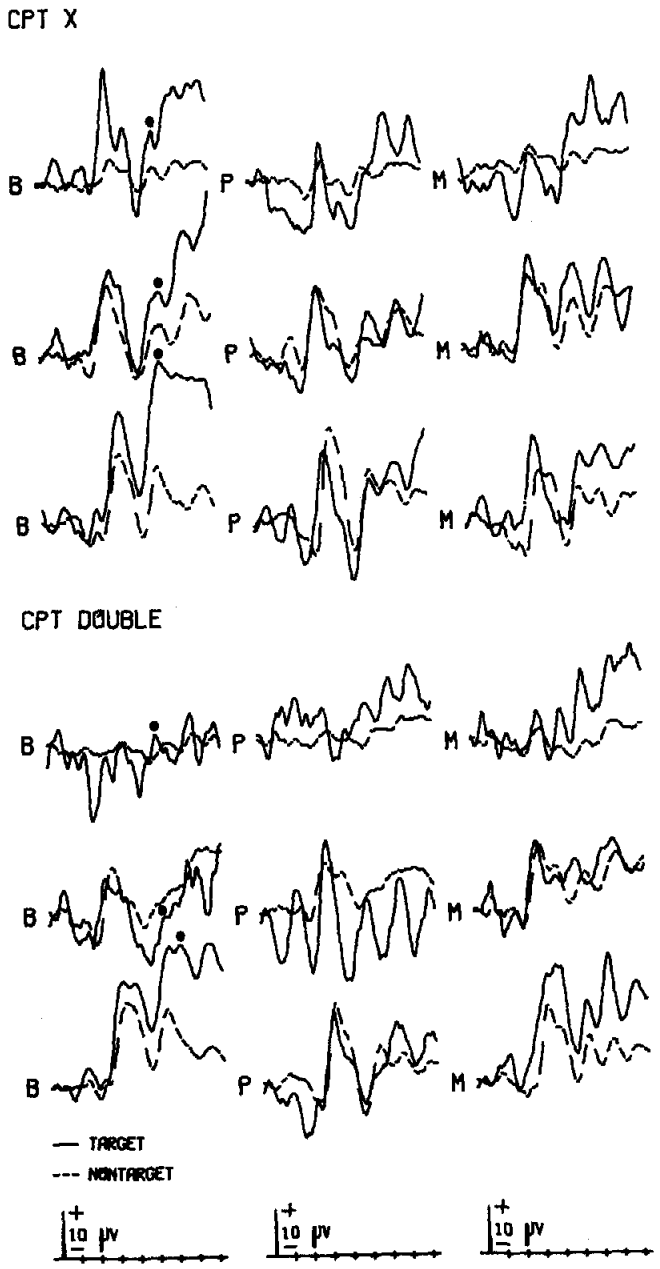

Figure 1. Illustrative event-related potential (ERP) waveforms for each task. (Each row displays P_z-derived ERPs for one of three individual patients across the baseline [B], placebo [P], and methylphenidate [M] sessions for the X and double versions of the Continuous Performance Test [CPT]. Patients' ERPs for each task are displayed in the same relative order. For each session, ERPs evoked by targets [solid lines] and nontargets [dashed lines] are superimposed at stimulus onset, which is indicated by the calibration mark. Positivity is displayed upward. The abscissa is demarcated in units of 100 ms. A filled circle marks the location of P3b for target-evoked ERPs obtained in the baseline session. The three patients whose waves are illustrated were selected from each of the three ADHD subgroups [not-criterion, ADHD/aggressive, ADHD/not aggressive, from the top down, respectively].)

have resulted from some subjects switching from random to meaningful performance. To address this issue, the sample was divided into three levels of accuracy based on the rate of misses in the placebo session (0–50%; 51–75%; > 75%). The results were reanalyzed with two between-subjects variables (accuracy level and order) and one within-subjects variable (methylphenidate vs. placebo). Age was not covaried out, because of its correlation with accuracy.

Methylphenidate enhanced accuracy comparably for all levels of accuracy, so that the Drug × Accuracy interaction was not significant for any measure. In contrast, RT data yielded a Drug × Accuracy interaction, $F(1, 56) = 4.38$, $p < .02$. As shown by the HSD test, low-accuracy subjects' *slowing* of RT under the stimulant versus placebo (*M*s = 881 vs. 844 ms) differed significantly from the *speeding* of RT under the drug versus placebo among medium-accuracy (*M*s = 912 vs. 946 ms) and high-accuracy patients (*M*s = 853 vs. 898 ms).

Event-Related Potentials' Amplitude Findings: CPT-X

Figure 4 illustrates results for P3b derived from the parietal lead for both tasks. In CPT-X, P3b had a mean latency of 559 ms and, as is characteristic for this wave, it was larger at the parietal ($M = 12.26\ \mu V$) than at the vertex electrode ($M = 7.23\ \mu V$), lead $F(1, 56) = 147.14$, $p < .0001$. As also expected, P559 was larger for targets than nontargets, target $F(1, 56) = 181.43$, $p < .0001$, and this relative difference was greater at the parietal electrode ($M = 13.33\ \mu V$) than at the vertex ($M = 6.45\ \mu V$), Lead × Target $F(1, 56) = 134.63$, $p < .0001$. Although the effects of sessions were significant, $F(2, 112) = 6.27$, $p < .003$, the amplitude of P3b did not differ under methylphenidate and placebo. Rather, as shown by Tukey's test, P3b amplitude decreased significantly from the baseline session to the placebo as well as the methylphenidate testings.

Event-Related Potentials' Amplitude Findings: CPT Double

The wave designated as P3b in the double version of CPT had a mean latency of 564 ms. In accord with previous findings, P3b was larger at the parietal electrode ($M = 11.42\ \mu V$) than at the vertex ($M = 6.29\ \mu V$), lead $F(1, 42) = 137.94$, $p < .0001$. In addition, P3b was larger for targets, target $F(1, 42) = 136.73$, $p < .0001$, and this difference was greater at P_z ($M = 10.32\ \mu V$) than at the vertex ($M = 5.80\ \mu V$), Lead × Target $F(1, 42) = 81.50$, $p < .0001$.

Analysis of P3b amplitude in CPT double yielded a significant effect of Sessions, $F(2, 84) = 9.35$, $p < .0004$, which was comparable for the three subgroups, Sessions × Groups $F(2, 84) < 1$, *ns*. As illustrated in Figure 4 and shown by Tukey's test, P3b was significantly larger for methylphenidate than placebo. In addition, the HSD test showed that, averaging over leads and stimuli, P3b amplitudes decreased from the baseline ($M = 9.74\ \mu V$) to the placebo ($M = 7.03\ \mu V$) session.

For the reasons outlined previously, the analyses of P3b amplitude were repeated as a function of accuracy in the placebo session. The nonsignificant Drug × Accuracy interaction, $F(2, 42) = 2.06$, *ns*, indicated that the drug effects on P3b were relatively homogeneous across levels of accuracy.

Event-Related Potentials' Latency Findings

The findings for P3b latency will not be detailed, because the differences obtained seldom exceeded two sampling intervals (i.e., 8 ms) and were not affected by the stimulant.

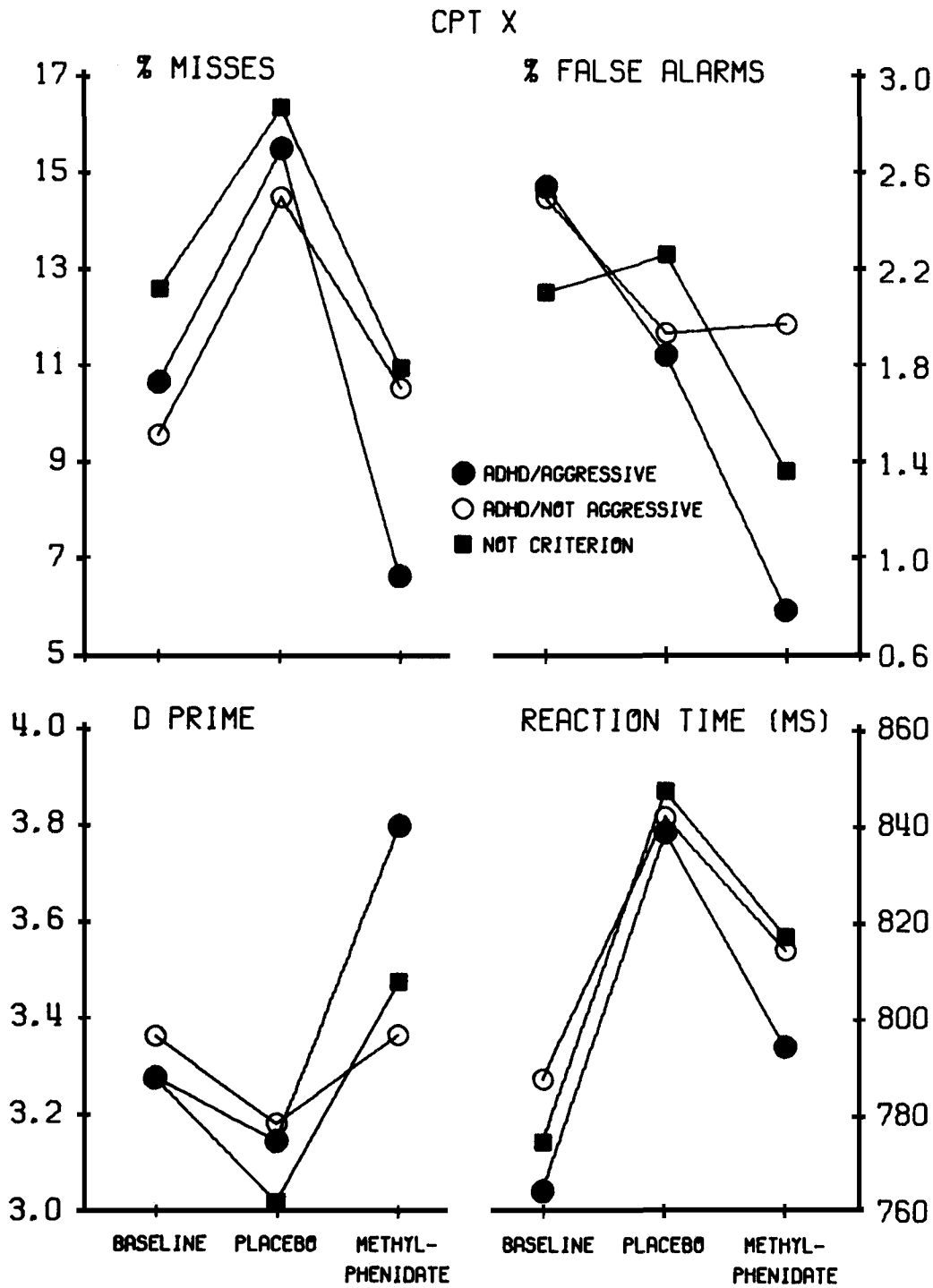

Figure 2. Results for four measures of performance in the X version of the Continuous Performance Test: percentage misses, percentage false alarms, *d'*, and reaction time (RT). (Means for each measure are graphed separately for each of the three subgroups [ADHD/aggressive, ADHD/nonaggressive, and not-criterion] for each of three sessions: baseline, placebo, and methylphenidate. These data were adjusted for their linear regression on chronological age.)

Discussion

Clinical Findings

A logical point of departure for a discussion of the results is an evaluation of the adequacy of the pharmacologic manipulation. The present choice of dosage is supported by the findings of (a) mild somatic effects, that is, evidence that the dosage approached the threshold of tolerance for several subjects, and (b) behavioral improvement on measures of clinical functioning. Conceivably, individual titration might have yielded optimal

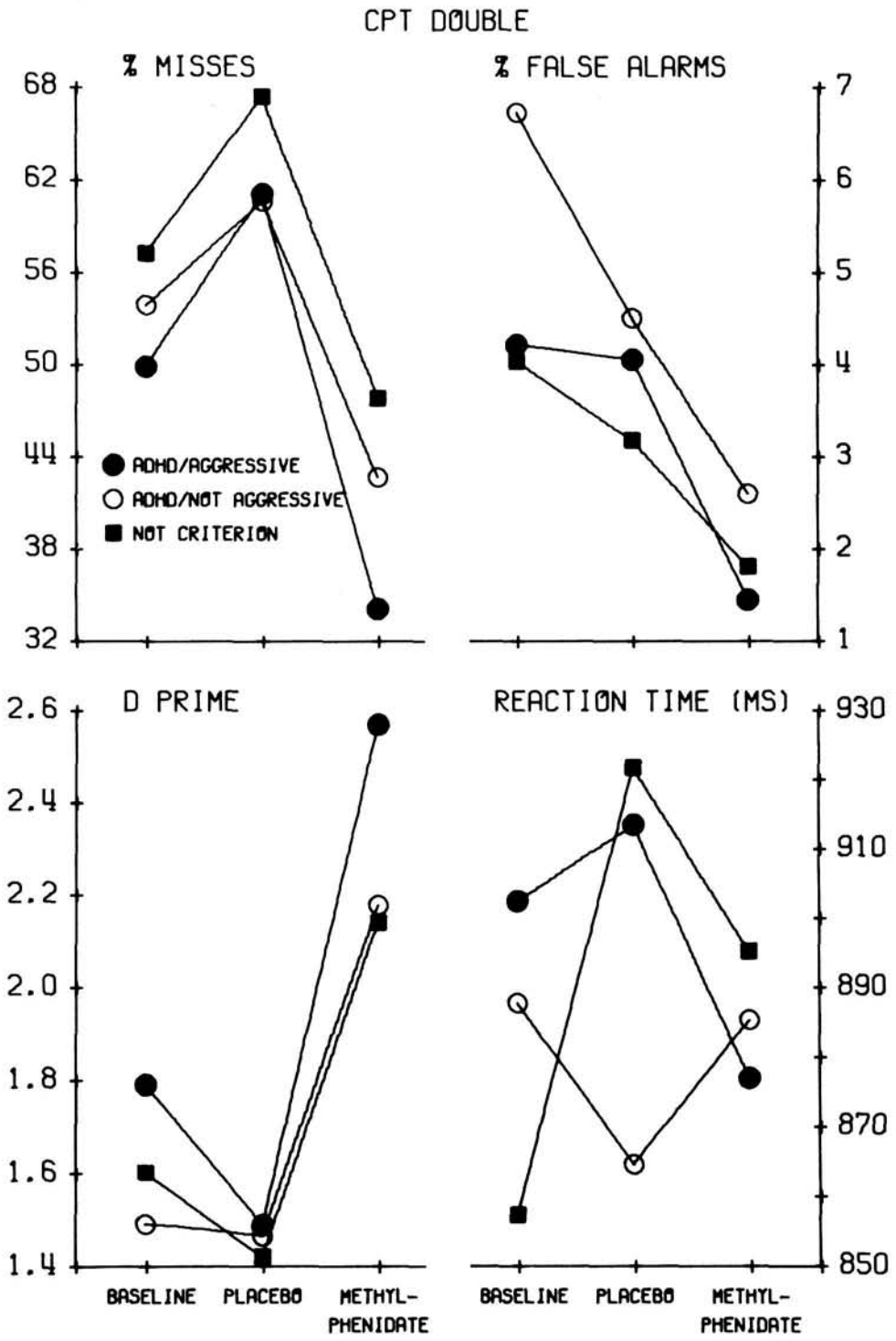

Figure 3. Results for four measures of performance in the double version of CPT. (These data were adjusted for their linear regression on chronological age. All conventions are as in Figure 2.)

dosages that avoided slightly under- or overmedicating some patients. However, that approach to dosing had the following disadvantages: possibly compromising the double-blind procedures, potentially undermining parents' and schools' cooperation by requiring a longer trial than seemed practicable in a crossover design, introducing some subjectivity in decisions concerning dosing, and increasing the difficulty of supervising the trial.

Several aspects of the findings on clinical change under methylphenidate deserve mention. First, as is common in this re-

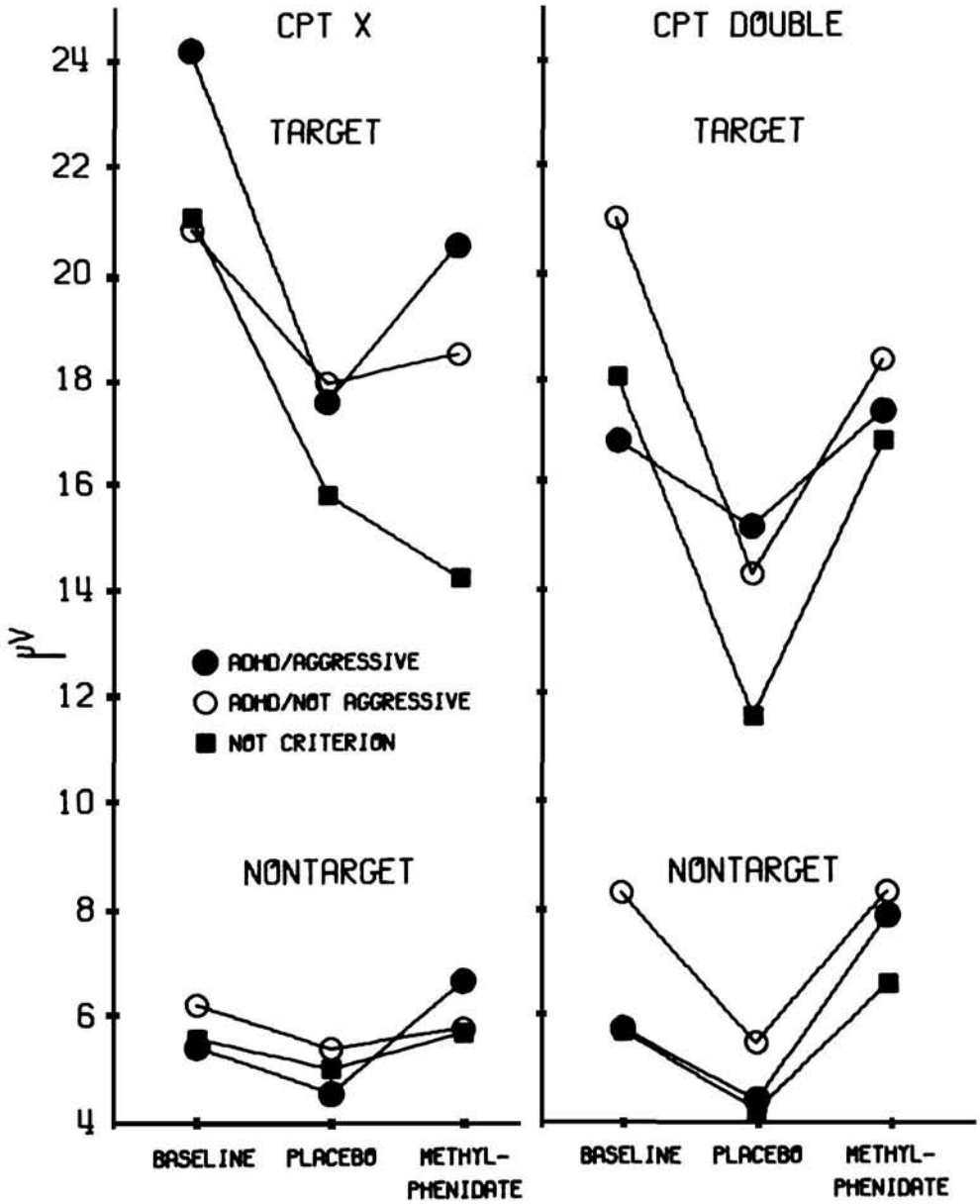

Figure 4. Mean amplitude of the P3b wave at the midline parietal electrode (P_z) for targets and nontargets for each version of CPT. (The results are graphed separately for each of the three ADHD subgroups and three testing sessions. The data were adjusted for their linear regression on chronological age.)

search (e.g., Conners et al., 1972; Werry & Sprague, 1974), teachers detected far greater improvement than did parents, even though significant amelioration was reported by both sources. Conceivably, teachers are more sensitive to the relevant behaviors by virtue of their experience or their access to structured settings, in which ADHD children's disturbances are most apparent (Jacob, O'Leary, & Rosenblad, 1978; Zentall, 1980). In addition, parents may have observed slighter benefits of treatment, because the drug had largely metabolized by the late afternoon and evening, the times of greatest contact between parents and children.

Another important clinical finding is that parents detected improvements, not only for items tapping disturbances classically associated with ADHD (e.g., the Inattention/Overactivity scale) but also for noncompliance/aggression. As noted earlier, several studies found improvement in disruptiveness and noncompliance with stimulant therapy (e.g., Conners et al., 1972; Taylor et al., 1987; Winsberg et al., 1974). Although the possibility of contamination of ratings by halo effects cannot be ruled out, these results suggest a relatively nonspecific range of behavioral changes.

In general, the three ADHD subgroups were judged as comparably responsive to treatment, except that teachers reported decreased aggression/noncompliance for only ADHD/aggressive patients. However, the ADHD/nonaggressive and not-criterion groups were defined on the basis of low scores on this scale,

so that a floor effect militated against the detection of change for them. In any event, the results indicate that aggressive/noncompliant ADHD patients are at least as likely to benefit from stimulant therapy as their nonaggressive ADHD peers. Of course, it is not possible to generalize the findings to aggressive children without ADHD. Similar conclusions were presented by Taylor and his colleagues (1987) in their study of clinical effects of methylphenidate on boys with disruptive behaviors.

Performance Results

On the whole, the results for performance confirm several aspects of previous reports. Accuracy was enhanced by methylphenidate treatment in both versions of CPT. As previously reported, the results for speed varied with the task (Klorman et al., 1983). Specifically, the stimulant improved speed only in CPT-X, which was easier, shorter, and administered earlier in the session (i.e., at a time of lesser fatigue). In the double version of CPT, low-accuracy subjects tended to slow down under methylphenidate, presumably in a trade-off of speed for accuracy. Thus, the effect of the stimulant was not merely a speeding one, as accuracy was enhanced preferentially over speed.

Another noteworthy result is the decline in accuracy from the baseline test to the placebo session. A probable reason for this negative practice effect is that as testing progressed, subjects may have found the laboratory testing increasingly tedious. Zahn, Rapoport, and Thompson (1980) drew similar conclusions from a study in which they evaluated ADHD and normal children in a no-medication baseline session followed by counterbalanced challenges with placebo and dextroamphetamine. Interestingly, motor restlessness and sympathetic arousal increased from the baseline session to a subsequent placebo test. However, RT, the only performance measure assessed, did not worsen in the placebo session, perhaps because the tests were relatively brief and did not induce inordinate fatigue. Zahn et al. concluded that the children's baseline quiescence reflected atypical, "Sunday-best" behavior that disappeared with repeated testing. These observations suggest that crossover designs lacking baseline evaluations may promote order effects. Counterbalancing of drug and placebo treatments may not eliminate the need for baseline sessions, because the "first-day" effects are confounded with pharmacologic manipulations, such that the magnitude of these treatments cannot be accurately estimated.

Finally, as was the case for clinical measures, performance in CPT was improved comparably for the three ADHD subsamples. These results parallel the findings for clinical ratings, except that laboratory measures of performance are immune to rating biases. Insofar as ADHD patients spanning a wide range of noncompliance/aggression improved comparably in performance on CPT, these benefits of stimulant therapy cannot be attributed primarily to increased compliance and, more likely, represent reductions in inattentiveness/impulsivity. On the other hand, if both noncompliance and inattentiveness promote poor performance in CPT, one might wonder why ADHD/aggressive patients did not exhibit worse performance than their nonaggressive peers when tested off medication. Although this finding may be puzzling, it is consistent with a recent report (Werry, Elkind, & Reeves, 1987) that found no differences between unmedicated ADHD patients with and without oppositional/conduct disorder on such tasks as CPT, Matching Familiar Figures test, and Sternberg's memory scanning test.

Event-Related Potentials

The wave identified as P3b conforms to this component's posterior topography and differentially greater amplitude for targets. Contrary to our hypothesis, P3b was not enlarged by methylphenidate in CPT-X. However, stimulants do not invariably increase P3b amplitude in this task (Coons et al., 1981; Michael et al., 1981), especially when few errors are elicited. In contrast, the expected enlargement of P3b amplitudes was obtained for all ADHD subgroups and accuracy levels in the more challenging CPT double. Finally, as was the case for performance, P3b amplitudes under placebo dropped below those present in the baseline session, perhaps also as a result of increased familiarity with the testing situation.

Together with results for performance, the ERP findings point to generally comparable enhancement by stimulant treatment of cognitive processing among ADHD children with and without aggression/noncompliance. As previously reported, similar improvements were obtained for the not-criterion patients, a result that encourages their continued consideration for this treatment as well as their inclusion in future research. A further extension of previous findings was that P3b was enlarged by methylphenidate even though error trials were excluded from ERPs. Thus, this finding cannot be attributed to merely fewer misdetections under methylphenidate, but rather to a direct effect of the stimulant on P3b and associated cognitive processes. Finally, the cognitive effects obtained after 2 weeks of stimulant therapy were comparable to those present after a single challenge. In combination, these observations suggest that the impact of stimulants is comparable for a range of ADHD subgroups as well as acute and chronic administrations.

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