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Methylphenidate Influences on Both Early and Late ERP Waves of ADHD Children in a Continuous Performance Test

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Although it has frequently been reported that hyperactive children have abnormally small P3 amplitudes of the event-related potential (ERP), which are normalized by the stimulant drug methylphenidate (MPH), the literature is inconsistent concerning earlier ERP waves. The aim of the present study was to investigate whether the normalizing effect of a 10-mg dose of MPH was also apparent on earlier waves, such as the N1, the P2, and the N2, besides the P3. Twelve attention deficit with hyperactivity disorder (ADHD) children performed a Continuous Performance Test involving a button-press response to the letter X (CPT-X) under the influence of MPH in a double-blind placebo controlled acute dosage design. ERPs were recorded at Oz, Pz, Cz, and Fz. The expected increase of the parietal P3, both to targets and nontargets, was apparent, as well as a significant increase in percentage of hits. There also was a significant increase of an earlier, negative going, wave, the N2, with a frontal maximum, under the influence of MPH. This wave was probably a manifestation of an increase in processing negativity for target stimuli only, after the intake of the stimulant drug. No effect of MPH was found on the N1 or the P2.

The present study investigated task performance and event-related potentials (ERPs) in children with diagnosed attention deficit hyperactivity disorder (ADHD) according to DSM-III-R criteria (American Psychiatric Association, 1987). These children show deficits in attention and are im-

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pulsive and hyperactive. Administration of stimulant drugs, in particular of methylphenidate (MPH), improves their behavior both in school and at home in 50-60% of the cases (Rapport & Kelly, 1991). In addition, stimulant drugs exert positive effects on cognitive tasks. One of the most widely used tasks for discriminating ADHDs from normal children which is also sensitive to stimulant drug effects is the Continuous Performance Test (CPT; Coons, Klorman, & Borgstedt, 1987; Garfinkel et al., 1986; Rapport et al., 1987). Although the effectiveness of stimulant therapy in ADHD children is well documented, it is still unclear how these effects are realized. The measurement of event-related potentials during attentional tasks such as the CPT offers a means to investigate how MPH affects the processing of information-containing stimuli in the central nervous system.

An advantage of the ERP method in comparison with other methods of noninvasive study of brain functioning [for example, positron emission tomography (PET)] is the high resolution in time, which is in the order of milliseconds. Early ERP waves, like the N1 and the N2 (Hillyard & Hansen, 1986) seem to reflect other aspects of stimulus processing than does the P3 (respectively, detection–attention, feature analysis, and stimulus evaluation). ERPs, therefore, offer a way to investigate on what aspects of stimulus processing and at which latencies after stimulus onset MPH exerts its effects. The P3 is sensitive to the delivery of task relevant information requiring a decision or response from the subject (Sutton, Braren, & Zubin, 1965). In a number of studies it has been reported that the P3 wave is smaller and that concurrent performance is worse in hyperactive children than in their normal peers (Klorman, Salzman, Pass, Borgstedt, & Dainer, 1979; Loiselle, Stamm, Maitinsky, & Whipple, 1980; Michael, Klorman, Salzman, Borgstedt, & Dainer, 1981; Prichep, Sutton, & Hakarem, 1976).

Methylphenidate increases the P3 amplitude in hyperactive children while simultaneously improving their performance (Halliday, Rosenthal, Naylor, & Callaway, 1983; Klorman et al., 1979; Michael et al., 1981; Prichep et al., 1976). Coons et al. (1981) did not find an enhancement of the P3 amplitude under methylphenidate in a CPT-X task (in this task six different letters were sequentially presented and subjects had to respond with a button-press to the letter X only), but their subject sample consisted of normal adult males, mean age 23.84 years. Michael et al. (1981) found an increase in P3 amplitude only for the younger hyperactive (mean age 9.31 years) and normal children (mean age 9.35 years). Klorman et al. (1979) also noted an enhancement of P3 amplitude for the hyperactive children (mean age 9.53 years). In a later study (Klorman, Salzman, & Borgstedt, 1988), with ADHD/aggressive, ADHD/nonaggressive, and borderline children (mean age 14.8 years), no increase in P3 amplitude as a result of MPH administration was noted. Although an effect of age may

thus play a role, there seems to be ample support for the P3-increasing effect of MPH, paralleled by an increase in attentional efficiency.

However, an important question is whether the P3b increase, found after ingestion of MPH, might be due to the fact that in some studies averaged ERPs were determined on the basis of the stimulus categories (signals and nonsignals) rather than on the basis of response categories (hits and correct rejections). The argument is that as MPH decreases the number of misses, and the corresponding P3b of misses is generally absent or very small, the inclusion of less miss-trials in the MPH average, relative to the placebo average, might "artificially" increase the P3b amplitude, the solution being to average over hits (i.e., a response category).

Elsewhere (Koelega et al., 1992; v. Leeuwen, Verbaten, Koelega, Kenemans, & Slangen, 1992) we have argued that an analysis of brain activity related to attentional performance should contain a within-factor signal/nonsignal (i.e., a stimulus category). When the brain does not detect a difference between a signal and a nonsignal (in the case of a miss) there is no P3 difference between these stimulus classes. If ERP waves concur with the detection of a signal, larger P3s to signals than to nonsignals have generally been found. If attention improves (e.g., the number of hits increases) under the influence of MPH, the question is which (signal/nonsignal) wave differences increase, because it is reasonable to assume that it is at these points in the time window that MPH has its effects. When ERPs are compared on the basis of hits (between placebo and MPH), we can only compare "successful" processes. Strauss et al. (1984) followed a similar line on reasoning, although pertaining to a different problem. They observed in a vigilance task that, although there was a significant decrease of hits over trials in a placebo condition, the concurrently measured P464 amplitude did not show a similar decline. The authors assumed that they had missed such a decrement by "deriving ERPs exclusively from errorfree trials (hits)" (Strauss et al., 1984, p. 618). In other words, in such cases there is an asymmetry between the measure of performance (a percent hit score lower than 100 includes both hits and misses) and the measure of concurrent brain activity (which includes only hits).

In a number of CPT-X studies reported by Klorman et al. (1990) both approaches have been followed and it turned out that in studies where averages were made on the basis of stimulus classes (Klorman et al., 1979; Klorman et al., 1983) MPH appeared to increase the P3b, while in studies where averages were made on the basis of response classes (hits), MPH did not increase the P3b (Klorman et al., 1987; Klorman, Salzman, & Borgstedt, 1988). Another matter is that hit-ERPs show an increase after MPH ingestion when the dose is increased. Our remarks pertain to the

CPT-X and "normal" doses of MPH. We have therefore used an averaging procedure based on stimulus classes.

Although in visual CPTs the effect of MPH on the P3 seems well documented (see above), the literature is unclear and inconsistent with respect to effects on earlier waves in such tasks. It is unclear because, in a number of studies in which positive effects of MPH on the P3 were found, data on earlier waves have not been reported (Klorman et al., 1979; Klorman et al., 1988; Michael et al., 1981). And where both earlier and late ERP waves were investigated, the results are inconsistent. With regard to the N1, no effects of MPH were reported by Hall, Griffin, Meyer, Hopkins, and Rappaport (1976); Halliday, Rosenthal, Naylor, and Callaway (1976); Klorman et al. (1983); Klorman et al. (1990); McIntyre, Firemark, Cho, Bodner, and Gomez (1981) (N1P1); and Swanson, Sandman, Deutsch, and Baren (1983). Increase of the N1 after MPH administration was reported by Halliday et al. (1983) and a decrease of the N1P2 has been reported by Dykman, Holcomb, Ackerman, and McCray (1983). An effect of MPH on visual processing negativity (PN) (a negative wave in the N2 latency range) has never been reported.

The aim of the present study was to carry out an acute dose study and to investigate the effects of MPH in ADHD children by means of ERPs including both early and late waves in order to improve our understanding of how MPH affects brain processing and how this may relate to improvements in attentional behavior.

METHOD

Subjects

Subjects were 12 hyperactive children (10 boys/2 girls, mean age 11.2 years, $SD = 2.1$, mean IQ 100.4, $SD = 7.3$, range 86 to 110) with a principal diagnosis of ADHD according to DSM-III-R criteria (APA, 1987). Mean body weight of the subjects was 42.1 kg (range 30 to 54 kg). The diagnosis was established independently by two child psychiatrists after extensive evaluations, including a developmental history, a psychiatric interview, and psychological investigations. Further, all subjects had scores in the clinical range on the hyperactivity factors of rating scales completed by the parents (Child Behavior Checklist, or CBCL; Achenbach & Edelbrock, 1983) and by the teachers (Connors, 1985). Five children had a comorbid conduct disorder; there were no other comorbid diagnoses. The children were outpatients of the Department of Child Psychiatry of the University of Utrecht. Although initially 19 children participated in the experiment, the data on only 12 children are reported in this study. There was a spontaneous drop out of five children, and two children

were excluded because of technical problems. The children were rewarded with presents for their participation in the experiment.

Apparatus: Electroencephalogram (EEG) and Electrooculogram (EOG)

Electroencephalographic activity was recorded from tin electrodes by means of an electrocap. Scalp locations were at Oz, Pz, Cz, and Fz, according to the 10-20 system. Linked ear lobes electrodes, connected with a 30-kΩ resistor, were used as reference. Horizontal EOG was recorded using tin electrodes in plastic cups attached to the outer canthus of each eye by means of adhesive rings. Infraorbital and supraorbital electrodes were placed in line with the pupil of the left eye for the vertical EOG, and also by means of adhesive rings. A ground electrode was attached to Fpz. Resistance of the EEG electrodes was never higher than 5 kΩ and the upper limit for the EOG electrodes was 3 kΩ. For both EOG and EEG, ECI (electrogel) EEG paste was used. All EOG and EEG signals were amplified and filtered by an Elema universal filter. A time constant of 5 s was employed in conjunction with a low-pass frequency filter of 30 Hz. To suppress mains frequency and harmonics, amplifier output was first sent through a 45-Hz passive low-pass network (roll-off 6dB/octave), followed by a 50-Hz notch filter with a bandwidth of 4 to 5 Hz. Subsequently, the signals were sent to the analog inputs of a PDP 11/23 (LSI) computer for on-line analog/digital (A/D) conversion. Sampling started 100 ms before stimulus onset and lasted 1024 ms, with a sampling rate of 250 Hz.

Task

The Continuous Performance Test (CPT-X version) consisted of the letters B, W, S, T, X, D of which the letter X was the target. Targets and nontargets appeared semirandomly with a probability of .17 at the center of the screen. The letters were 2.5 × 2.5 cm and the stimuli remained on the screen for 60 ms, with a fixed inter-stimulus-interval (ISI) of 1.6 s. The test consisted of 300 stimuli, five blocks of 60 stimuli, lasting 7.5 min.

After completion of the CPT, a further part of the experiment consisted of the random presentation of the symbol * (15 times) and the symbol o (21 times), which appeared at 2-s (fixed) intervals at random places on the TV screen. The children had to count the symbol *. The aim of this condition was to induce large sacccades in order to apply the regression technique for removing eye movements from the ERPs more powerfully (Woestenburg, Verbaten, & Slangen, 1983).

Experimental Conditions

During the experimental session, the child was seated in a dentist's chair in an acoustically and electrically shielded room. The chair was adjustable, permitting the subject's head to be placed to a position roughly parallel to a TV monitor (black–white, 26 in. screen), which was positioned above and in front of the subject at a distance of 60 cm from the eyes. A vacuum cushion was attached at the top of the dentist's chair for fixing the head in such a way that the center of the TV screen was in the center of the visual field. Eye movements from the center to any of the four corners of the TV screen were 28° of arc. There was always a person (mostly one of the parents) accompanying the child in the acoustically shielded room. EOGs and EEGs were displayed as ink records on an Elema (Mingograf EEG-10) polygraph.

Drug Conditions

Each child participated in two laboratory sessions, which were procedurally identical except for the pharmacological substance contained in a capsule and dispensed at the beginning of each session: placebo (containing lactose) or methylphenidate (10 mg) (mean of the individual MPH dose was 25 mg/kg). Before they participated in this study, all the children used daily doses of MPH, ranging from 15 mg to 25 mg. The children stopped their medication 3 days prior to participation in the experiment (washout period). After their first visit to the laboratory they could resume their usual medication, but 3 days prior to their second visit they were once more removed from medication. The time span between the first and second visits was approximately 1 week.

Procedure

Double-blind procedures and a random order of drug administration were followed. On arrival the child was familiarized with the procedure and put at ease regarding the methods employed and their part in the experiment. Then the child ingested the capsule with some water. The experimental session consisted of two different parts: the present study and a neuropsychological part, the data of which will be reported elsewhere. Order of presentation of the two experimental parts was balanced. The children were always tested during the same part of the day.

Testing began 45 min after drug ingestion. First the electrocap and the EOG electrodes were attached and their resistance was checked, and the subject sat down in the dentist's chair. The head was fixed in the desired position. Then the EEG and EOG were calibrated. The subject was instructed to press the button switch upon presentation of the letter X. The children received sufficient time to practice (1.5 to 3 min) in order to ensure comprehension of thee task. Accuracy and speed were encouraged. The children were motivated by telling them that by doing their best they would get a present afterward. After these instructions the experimenter left and closed the shielded room. Then presentation of the stimuli started. At the end of the stimulus presentation, the experimenter entered the shielded room and gave instructions for the following task. Because of memory-storage limits, for the CPT-X we only recorded the data sampled during the presentation of the targets and pretargets (the standard stimulus preceding a target stimulus). The 36 trials of the second visual condition (counting task) were all recorded.

ERP Analysis

Eye movements and eye blinks were measured by vertical and horizontal EOGs. EOG data were checked for clipping. There were no data outside the range of the A/D converter. Vertical and horizontal EOGs were subtracted from the ERPs by a regression method in the frequency domain (Woestenburg et al., 1983). ERPs were determined by averaging. Forty-eight trials for the pretargets and 48 trials for the targets were averaged. Eventually one averaged trial remained for the pretargets and one averaged trial for the targets for every child for both MPH and placebo. The N1 was scored, relative to a 100-ms prestimulus baseline, as the largest negative wave between 50 and 200 ms. The P2 was scored as the largest positive deflection after the N1 between 120 and 250 ms. The N2 was scored as the largest negative wave relative to the prestimulus baseline after the P2 and before 400 ms. Because inspection of the grand averages revealed that there were at least two different peaks in the P3 latency range, we scored an early P3, called the P3(1), as the largest peak occurring between 250 and 400 ms after stimulus onset and the P3(2), which is probably the classical "late" P3 or P3b, as the largest positive peak occurring between 400 and 700 ms (mean latencies for targets at Pz were 330 ms and 535 ms, respectively). Although mean peak latency times are reported in Table I, latency times were only used for peak identification and not included in the statistical analysis.

RESULTS

A univariate analysis of variance was performed with drug and stimuli as within-subjects factors. Drug consisted of two levels (MPH and placebo); stimuli also had two levels, pretargets (standards) and targets. The within-factor leads had four levels (Oz, Pz, Cz, Fz) and were analyzed by means of the program Multivariance (Finn, 1978). All reported p-values were two-tailed. For the ERP grand averages see Fig. 1.

ERP Data

N1. There was a significant leads effect [$mF(3, 9) = 7.05, p < 0.01$], with the largest N1 amplitudes at Cz (means were –3.01, –4.45, –5.78, and –4.74 μV, for Oz, Pz, Cz, and Fz, respectively). There were no further significant main effects or interactions.

P2. The leads main effect was significant [$mF(3, 9) = 5.63$], with the largest amplitudes at Pz, as well as a stimuli effect [$F(1, 11) = 46.37$] and a Stimuli × Leads interaction [$mF(3, 9) = 9.23$]. There appeared to be a significant target effect which was maximal at Pz, as early as the P2. There was, however, no effect of drug on the P2, nor any interaction which involved the factor drug.

N2. There was a significant leads effect [$mF(3, 9) = 21.83$], with the largest negativity relative to the prestimulus baseline at Fz (see Fig. 2). There also was a significant Drug × Stimuli interaction [$F(1, 11) = 8.34$). Further analysis revealed that the drug effect was significant for the targets [$F(1, 11) = 12.2$] but not for the standard stimuli [$F(1, 11) = 0.80$]. There was also a significant Drug × Leads interaction [$mF(3, 9) = 3.64$]; at Fz only the drug effect approached significance [$F(1, 11) = 3.68, p < .05$ one-tailed], while at the other leads the drug appeared to be not significant (see Table I for N2 amplitudes and latencies).

P3(1), P3(2). Although there was no main effect of drug on the P3(1) or the P3(2) (with leads pooled), and neither was there a significant Drug × Leads interaction for both dependent variables, a planned comparison based on earlier reported findings for the P3(2) at Pz revealed a significant effect of MPH [$F(1, 11) = 5.03$]. The mean P3(2) amplitude (standards and targets pooled) for MPH was 19.6 μV and for placebo 16.2 μV (see Fig. 3). No Drug × Stimuli interactions were found, but there was a stimuli main effect for the P3(2) at Pz [$F(1, 11) = 73.4$]. The pretargets at Pz had a mean amplitude of 9.4 μV, whereas the mean target amplitude was 26.5 μV (see Table I for means and latencies of the two P3 peaks). In addition there was a Stimuli × Leads interaction for both the P3(1) [$mF(3, 9) =$

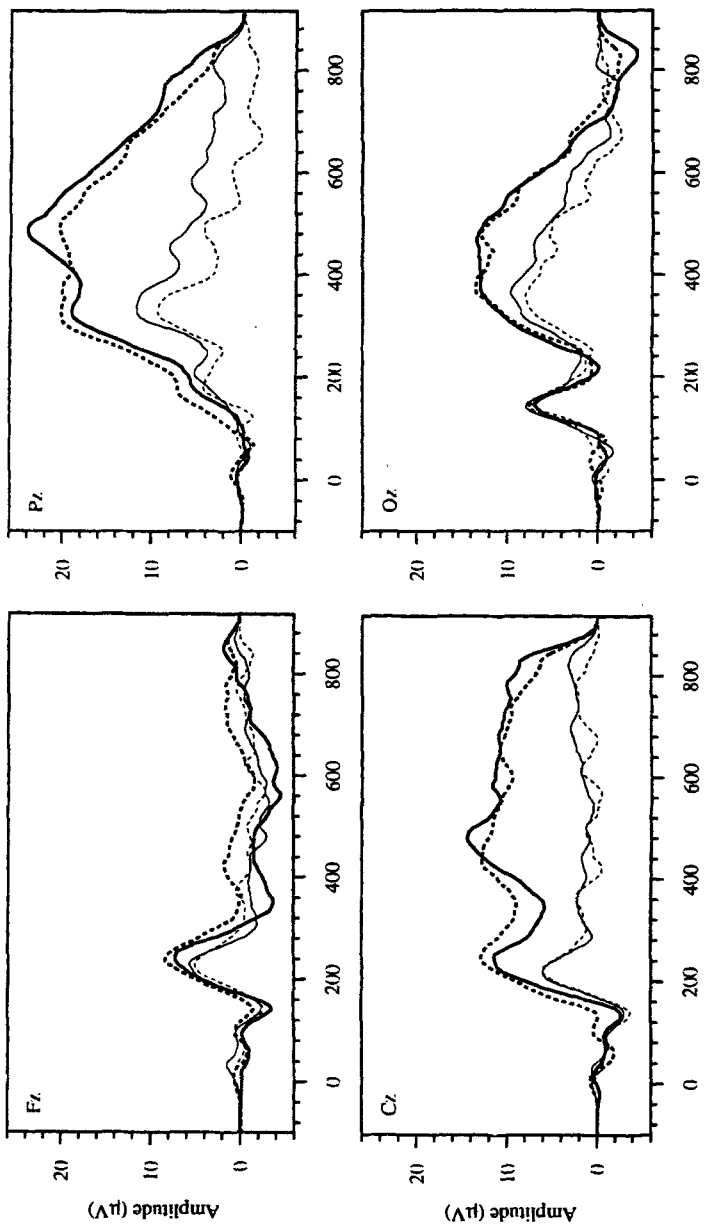

Fig. 1. Grand average event-related potentials of collapsed pretarget and target trials under methylphenidate and placebo at Oz, Pz, Cz, and Fz. PLPRE = placebo pretarget trials; PLTAR = placebo target trials; MPPRE = methylphenidate pretarget trials; MPTAR = methylphenidate target trials.

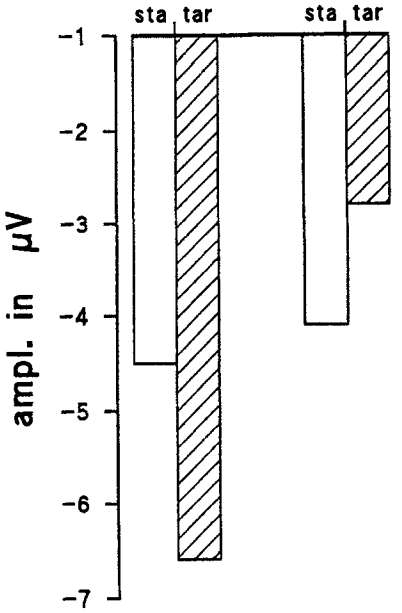

Fig. 2. Mean FzN2 amplitude for pretargets (standards) and targets under methylphenidate and placebo.

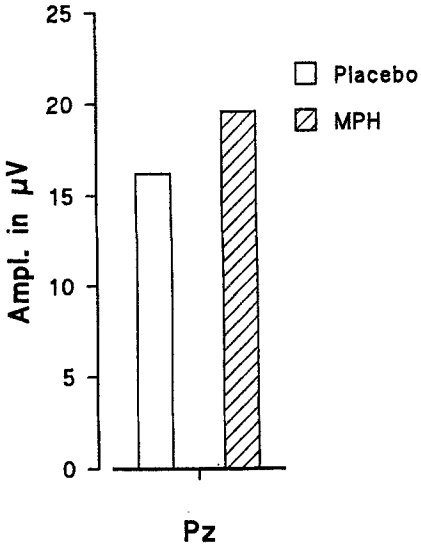

Fig. 3. P3(2) amplitude for placebo and methylphenidate pooled over pretargets and targets.

Table I. Mean N2, P3(1) and P3(2) Amplitudes (1a) and Peak Latencies (1b), Separately for Fz, Cz, Pz, and Oz; Peak Amplitudes Only Included in Table Ia When Significantly Different from Zero [$F(1, 11) > 4.84$]; When Peak Amplitudes Not Different from Zero (ns), the Latency Times Could Not be Determined (Indicated by – in Table Ib)

	Fz			Cz			Pz			Oz		
	N2	P3(1)	P3(2)	N2	P3(1)	P3(2)	N2	P3(1)	P3(2)	N2	P3(1)	P3(2)
						(a) Amplitudes in μV						
MPH[a]												
standard	–4.5	ns	ns	ns	5.2	6.0	ns	14.2	11.4	ns	11.0	9.5
target	–6.6	ns	ns	ns	7.4	19.7	ns	20.1	27.8	ns	13.3	13.6
PL[a]												
standard	–4.1	ns	ns	ns	5.0	5.0	ns	11.3	7.4	ns	9.4	7.4
target	–2.8	ns	ns	ns	13.1	16.5	ns	21.2	25.1	ns	12.9	14.5
						(b) Latency times in ms						
MPH												
standard	307	—	—	—	320	589	—	336	531	—	338	484
target	352	—	—	—	315	547	—	329	537	—	349	489
PL												
standard	346	—	—	—	293	560	—	323	508	—	352	494
target	372	—	—	—	325	519	—	332	534	—	356	491

[a]MPH = methylphenidate; PL = placebo.

3.81], and the P3(2) [$mF(3, 9) = 13.79$]. Further univariate analyses showed that the P3(2) difference between pretargets and targets was largest at Pz [$F(1, 11) = 73.42$], and was also significant at Oz and Cz [$F(1, 11) = 13.1$ and $F(1, 11) = 39.1$, respectively], but not at Fz [$F(1, 11) = 1.77$]. For the Pz P3(1), standard–target differences were significant at Pz [$F(1, 11) = 10.3$] and Cz [$F(1, 11) = 10.2$] only.

Performance Data

Hits. Children under the influence of MPH showed a percentage of hits (correct detection of the targets) of 96%. For placebo this percentage was significantly lower, i.e., 88% [$F(1, 11) = 6.09, p < .03$].

Reaction Time to Hits. The mean reaction time (RT) to hits was 539.45 ms under methylphenidate and 554.73 ms under placebo, but this difference was not significant. A *post hoc* analysis showed that the power in this study for detecting a significant RT effect was too low ($n = 24$, delta = 15.3 ms, *SD* 130.0 ms) (Winer, 1971).

Relationship Between Changes in Hits and Changes in ERP Waves [Pz P3(2) and Fz N2]

The reason for choosing the parietal P3(2) for a closer study of the relationship between hits and ERP waves is based on the fact that, both in the present study and in earlier ones, the P3 had a parietal maximum. The reason for choosing the Fz N2 derives from the fact that, although the Stimuli × Leads interaction was significant [$F(3, 9) = 3.68$], subsequent analysis revealed that the standard–target difference only approached significance at Fz [$F(1, 11) = 3.68, p < .05$, one-tailed] (see also the Fz grand averages in Fig. 1). The linear correlation (Edwards, 1967) between increase in hits from placebo to MPH and the concurrent P3(2) increase for targets was not significant [r pm ($df = 11$) = .16]. However, there might nevertheless be a nonlinear relationship between the two change scores. We therefore performed the McNemar test (McNemar, 1955, pp. 228-231) for a possible relationship between the two scores. The McNemar test showed a significant relationship between these variables ($\chi^2 = 4.0$, $df = 1, p < .05$); increases in P3(2) amplitude concurred with an increase in hits in a nonlinear way. The same picture emerged with regard to the N2: No significant linear correlation was found (r pm = .35, 0.01), but there was a significant nonlinear relationship ($\chi^2 = 4.0, p < .05$). Although increases in N2 and P3(2) thus both concurred with an increase in hits in a nonlinear way, only the linear correlation between the increases in N2 and P3(2) was

significant [r pm = .67, $p < .05$, two-tailed]. Thus an increase in N2 amplitude after MPH ingestion (relative to placebo) correlated with an increase in the amplitude of the parietal P3(2).

DISCUSSION

There are three reasons for assuming that what we have scored as the P3(2) is the classical P3b: First its latency was about 510 ms, second its maximal amplitude was at Pz, and third the largest standard–target difference was at Pz. The latency of the P3(1) was 325 ms, but the P3(1) also had its largest peak at Pz and also had the largest standard–target difference there. Our argument is thus based on latency. It turned out that in our study there were two peaks in the P3 window with maxima at Pz, with different latencies (see the averages in Fig. 1). Satterfield, Schell, Nicholas, and Backs (1988) reported a similar finding with one Pz P3 peaking at 340 ms and a second at 590 ms.

If the two peaks had been the result of averaging across two groups of subjects whose P3b amplitudes yielded a bimodal distribution, we would expect one group of subjects with a P3 around 340 ms and another group with a P3 around 510 ms. It appears however, that *all* subjects had *two* peaks at Pz in reaction to the target, showing a larger P3(2) in 83% of the cases. In order to clarify this point, we have included the mean latencies for the two P3 waves we have scored for all leads in Table I. The mean latency of the nontarget P3(2) was at Pz 520 ms and of the target P3(2) at Pz 535 ms (pooled over drug conditions).

Although there was no main effect of MPH on any of the ERP waves, a planned comparison of the late parietal P3 [called the P3(2) in the present study], showed a significant enhancing effect of MPH. This finding confirms results of earlier studies (Klorman et al., 1979; Michael et al., 1981). The results of the present experiment also confirm the earlier finding of Klorman et al. (1979) that MPH enhanced the late P3 amplitudes for targets and pretargets alike. We also replicated the well-known P3 difference between frequent (standard) and infrequent (target) stimuli at Pz (Duncan-Johnson & Donchin, 1977). With respect to performance, the earlier reported increase in hits as a result of MPH intake (Klorman et al., 1979) was also noted. But the mean reaction time to the targets under methylphenidate was not significantly shorter than under placebo, although the trend was in the expected direction.

All in all, earlier findings showing that administration of MPH to ADHD children (responders) not only improves their performance in the CPT-X but also increases the late parietal P3 wave under such circum-

stances have been replicated. In addition, it appears that there was a significant (nonlinear) relationship between the amount of improvement in hits and the increase in P3(2) amplitude.

The most important question of the present study, however, was whether there are effects of MPH on earlier ERP waves than the P3. With regard to the N1, this question must be answered negatively. Although there was a distinct N1 with the expected maximum at Cz, MPH did not influence this wave. This result is in agreement with the results of Halliday et al. (1976), Hall et al. (1976), Klorman et al. (1983), Swanson et al. (1983), and Klorman et al. (1990), but not with the results of Halliday et al. (1983) who reported an increase of the N1, and Dykman et al. (1983) who found a decrease of the N1P2 after MPH administration. The vertex N1 has been associated with "detection–attention" and has been dissociated from further identification and recognition of the stimulus, the latter activity being associated with the P3 (Parasuraman & Beatty, 1980). This first, crude, step in information processing was the same for targets and nontargets (there was no Cz N1 difference between the two stimulus classes in the present study) and was not influenced by MPH under the conditions of this experiment. Duncan and Kaye (1986) did not find an effect of the noradrenergic agonist clonidine on the vertex N1, so probably the role of the noradrenaline (NA) component of the action of MPH in producing the N1 is less important.

There was, however, an effect of MPH on a second wave preceding the P3, the N2. Target N2s increased under the influence of MPH, an effect that has not been reported before. A clue to the possible nature of this wave was given by its topographical properties and its direction: The effect had a Fz maximum and consisted of an increase in negativity. Two different kinds of negativities have been reported in the N2 latency window: the mismatch negativity (MMN) and the processing negativity (PN).

The first type of negativity, the MMN, has been described by Näätänen and Gaillard (1983) for the auditory modality. It occurs at about 200 ms and is associated with a mismatch process between the representation in memory of an auditory standard stimulus and a presented deviant stimulus. A comparable negativity although with a longer latency of about 320 ms, with a central (Cz) maximum in the visual modality has been reported by Kenemans, Verbaten, Roelofs, and Slangen (1989), and has been called the P2N2. Both the auditory MMN and the visual P2N2 seem to reflect an automatic (not under voluntary control) comparison of the deviant's physical stimulus properties with an existing neural model of the standard stimulus (Kenemans, Verbaten, Melis, & Slangen, 1992), but note that other authors failed to find a visual analog of the auditory MMN (Nyman et al., 1990), probably because the latter authors only measured up

till 300 ms after stimulus onset. However, in the present study the nontargets were not physically identical (five different letters). A target/nontarget (=mismatch) effect on the P2N2 appeared to be not significant [$F(1, 11) = 0.23$] and therefore was not further investigated (the P2N2 was determined as the amplitude between the P2 and N2).

The second type of negativity in the same latency range, with a frontocentral maximum, has been reported for the auditory modality by Näätänen and Michie (1979), and Hillyard and Hansen (1986), and for the visual modality by Harter and Guido (1980) and Wijers, Mulder, Okita, Mulder, and Scheffers (1989). Hillyard and Hansen (1986, p. 231) described this nonspecific negativity, also called processing negativity (PN), as "a sign of a post-selection processing that extracts additional information from attended-channel stimuli." These effects are not restricted to selective attention paradigms ("two-channel" experiments), but might be observed in studies in which task relevance is varied between conditions ("one-channel" experiments), albeit to a lesser extent (Courchesne, Hillyard, & Galambos, 1975; Näätänen & Gaillard, 1983). Both the topography of this effect (frontocentral maximum), the fact that MPH did not have an effect on the P2, and its restriction to targets seem to imply that in the present experiment MPH enhanced this aspect of stimulus processing. Satterfield et al. (1988) have reported that the PN in (younger) ADHD children is smaller than in normal controls, which could mean that in the present study MPH normalized the PN of the ADHD children.

ERP researchers seem to agree that the PN and the late P3 wave have a different psychological significance (respectively, information extraction, and information evaluation). In line with this view is that the MPH effect was related to the extraction of further information from target stimuli only. In that respect the effect of MPH on the target N2 differed from the effect of the drug on the P3(2), where both nontarget and target P3s were enhanced alike. MPH may therefore have two different effects on information processing: first, an effect on the P3—and there is evidence that NA is involved in its production (Pineda, Swick, & Foote, 1991); and second, an effect on the FzN2. It has to be noted, however, that there was a significant linear correlation between the increases of the two waves after MPH ingestion; more negativity at Fz at around 300 ms was correlated with an increase in positivity at Pz around 530 ms.

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