THE EFFECTS OF METHYLPHENIDATE DOSAGE ON THE VISUAL EVOKED POTENTIAL, HEART RATE AND REACTION TIME IN HYPERACTIVE CHILDREN

by

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ABSTRACT

The effects of methylphenidate (Ritalin) dosage on concurrent measures of heart rate (HR), the averaged visual evoked potential (VEP) and reaction time (RT) were investigated in 28 hyperactive children. Heart rate, VEPs and RTs were recorded in four different sessions 60 minutes following an oral dose of placebo, .16, .33 and .66 milligrams of methylphenidate per kilogram of body weight (mg/kg). Heart rate and VEPs were recorded under an active (ATT) and passive (PAS) attention condition. In the ATT tasks, subjects were instructed to press a microswitch whenever a dim flash was detected in a series of more frequently occurring brighter flashes. Reaction times to the target events were stored along with the psychophysiological data. In the PAS task the subject simply observed the bright flash and no dim flashes were presented. The two tasks were presented in an ATT-PAS-PAS-ATT order.

The data included an estimate of mean HR, changes in HR following the visual stimulus, the mean and standard deviation of RTs, the amplitude and latency of the N1 (N160) and P2 (P230) components of the VEP, and a normalized measure of VEP variability. These measures were analyzed by repeated measures analysis of variance with polynomial trends computed on the dosage factor.

The results showed that stimulant dosage produced several different dose-response curves. Reaction time measures and mean HR increased up to the .33 mg/kg dose and then showed no further changes with increasing dosage. The amplitude of N160 and correlations between RTs and the amplitude of the N160 component increased at the .16 and .33 dosages and then declined at higher dosages. The amplitude of P230 was larger in

older children while the latency of this component occurred earlier in the ATT task. These effects were, however, independent of dosage effects.

The results are discussed in terms of the similarities and differences between the present findings and those already in the literature. Specifically, it appears that stimulant dose-response curves can be classified into three groups. The theoretical, methodological and clinical implications of these findings are considered.

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INTRODUCTION: The Effects of Methylphenidate Dosage on the Visual Evoked Potential, Heart Rate and Reaction Time in Hyperactive Children

The hyperactive child syndrome is one of the most commonly diagnosed psychological conditions in childhood (Safer, 1971). Typically children with this diagnosis have deficits in attention, display inappropriate motor behavior and are easily excited (Werry, 1968a). Biologically oriented psychological investigators have been interested in this syndrome for a number of reasons. First, several of the behavioral characteristics shown by these children are associated with insults to the central nervous system. Secondly, many of the hyperactive child's problems markedly improve with the administration of sympathomimetic (stimulant) drugs. Finally, the nature of the hyperactive child's problems fits part of larger interest by psychophysiologists in the biological substrates of cognitive behavior.

This thesis is concerned with the effects of stimulant dosage on psychophysiological and behavioral measures of attention in the hyperactive child. The review of the literature provides an overview of the diagnostic and behavioral characteristics of these children and the current state of the psychophysiological research in this area. The emphasis is on the averaged evoked or event related potential and, to a lesser extent, heart rate and reaction time. Detailed reviews of the latter areas have already been published and thus, only the general results of these studies are presented.

The Hyperactive Child Syndrome

Diagnostic and Behavioral Characteristics

Descriptions of the hyperactive (HA) child have appeared in the clinical literature for over a hundred years (Cantwell, 1975a). However, it was not until Laufer and Denhoff (1957) published their classical account of what they termed "the hyperkinetic behavior syndrome" that these observations were integrated into a coherent diagnostic formulation. These investigators described a set of central or core behavioral deficits observed in otherwise normal children which were highly correlated and were often accompanied by secondary problems in academic and social adjustment. The core problems included inappropriate and poorly integrated motor activity, problems in attention and extreme variability in performance. Many, but not all, of these children were found to have difficulties in mastering basic academic skills, complying with classroom rules and showed extreme fluctuations in affect and mood. Standard pediatric examinations often revealed borderline neurological and EEG abnormalities and a lengthy history of irritability which frequently dated back to early infancy. The disorder was observed six times more frequently in boys than girls.

Research during the past twenty years has amply confirmed Laufer and Denhoff's observations. Both teacher ratings on standardized scales and direct classroom observations have shown that the HA child is less attentive, more fidgety and more demanding of the teacher's time as compared to normal asymptomatic age-matched controls (Sprague, Cohen and Werry, 1974; Gittelman-Klein, Abikoff, Pollack, Klein, Katz and Mattis, in press).

Laboratory measures of behavior have also revealed deficits in attention, impulse control and foresight in planning (Conners, Rothschild, Eisenberg, Schwartz and Robinson, 1969; Anderson, Halcomb and Doyle, 1973; Keogh and Margolis, 1976). These behavioral dysfunctions do not, however, appear in all situations. Attentional failures, for example, are more likely to be observed in vigilance tasks where the experimenter has control over the presentation of the stimuli and the child must continually monitor the display for events which are both unpredictable and infrequent. On tasks which presumably require more complex decisions, but at the same time allow the subject to initiate the stimulus sequence, HA children are less likely to differ from controls (Douglas, 1972).

In contrast to the attentional failures, the high level of motor activity - the supposed hallmark of the HA child - has been more difficult to document. Objective measures of gross motor activity have not consistently discriminated between HAs and controls. Although there are numerous technical problems in obtaining reliable and valid measures of activity level which may obscure whatever differences might exist, some investigators have suggested that it is the inappropriateness of the activity and not its sheer frequency which is the distinguishing characteristic of the disorder (Werry, 1968a).

Although there appears to be a good deal of consensus regarding the deficits shown by HA children as a group, there is no single discriminator which differentiates them from normals or other diagnostic groups. Likewise, the relationship between different assessment techniques, e.g. psychological test data and neurological findings, is generally poor (Werry, 1968b). At the same time diagnostic agreement between experi-

enced clinicians is often quite high (Loney, Langhorne and Paternite, 1978). Several explanations for this paradox have been suggested (Conners, 1972; Loney et al., 1978) but they all reflect one fundamental fact. Hyperactive children are extremely variable and do not present a unified set of symptoms.

In summary, clinical and objective data have consistently demonstrated that HA children have problems deploying attention and in controlling impulsive behavior. These deficits often appear in otherwise normal children and may be accompanied by poor school performance, equivocal neurological signs and an early history of irritability and restlessness. Attention deficits have been repeatedly reported in vigilance tasks although there is some indication that the ability to process information is not impaired in this group. While inter-rater diagnostic agreement is high there is little evidence that the disorder represents a single syndrome with a uniform etiology.

The Effects of Stimulants on Hyperactive Children

Sympathomimetic amines such as d-amphetamine, magnesium pemoline and methylphenidate (Ritalin) have been shown to markedly improve 50-70% of HAs treated with stimulants (Millichap and Fowler, 1967). Indeed, stimulant drug therapy is often viewed as the treatment of choice in these children. The clinical effects of these drugs have been known for at least forty years (Bradley, 1937-1938) and research using reliable assessment techniques and placebo controls have demonstrated the potency of stimulants on a wide variety of dependent variables (see Barkley, 1977 for a review of these findings). While there is no question of the

short-term gains induced by stimulants, the specific psychopharmacological mechanisms underlying these therapeutic effects have not been isolated. In part this is because HAs are not a homogeneous group and their response to stimulants is idiosyncratic and unpredictable (Halliday, Rosenthal, Naylor and Callaway, 1976).

Increases in performance on attention and short-term memory tasks have been reported by several investigators (Conners, 1970; Sprague, Barnes and Werry, 1970; Sykes, Douglas and Morgenstern, 1972; Zahn, Abate, Little and Wender, 1975; Elliott, Halliday and Callaway, 1978; Sprague and Sleator, 1977; Klorman, Salzman, Borgstedt and Dainer, 1979). These studies have shown that response accuracy increases and reaction time decreases with stimulant. While the results are consistent with the widely held view that stimulants improve "attention" it is difficult to determine whether this improvement represents an increase in general drive level (tonic arousal), an increase in inhibitory control, or improvements in the ability to select relevant information.

Since behavioral measures represent the output stage of a stimulus-response sequence, it is difficult to use such measures to determine where in the sequence drugs exert their influence. Psychophysiological responses, on the other hand, can be measured continuously between stimulus and response, and may provide additional information concerning the specific processes altered by stimulants. Thus, while the diagnoses of the hyperactive child and his clinical response to stimulant drugs are by definition behavioral problems, the application of psychophysiological measures may provide convergent data concerning the mediators of these drug responses.

Psychophysiological Studies of the Hyperactive Child

Historical and Theoretical Background

With the possible exception of mental retardation there have been more psychophysiological studies of the HA child than any other developmental-behavioral problem. Hyperactive children have been found to have significantly more slow wave EEG activity (Satterfield, 1973), more equivocal or soft neurological signs (Conners, 1967; Lerer and Lerer, 1976), more physical stigmata (Waldrop and Halverson, 1971) and a greater incidence of obstetrical complications at birth (Pasamanick and Knobloch, 1960). These data, along with the disproportionate number of boys given this diagnosis and studies indicating a genetic basis for the HA syndrome (Cantwell, 1975b), suggest that some underlying psychophysiological disturbance may be responsible for some of the observed deficits.

The possibility that many childhood behavior disorders might have a neural basis was suggested by many early pediatricians and neurologists. For example, there were several reports in the 1920s which proposed that hyperactivity and distractibility were often the sequela of eucephalitis (Werry, 1972). From a slightly different perspective, Bradley's discovery of the therapeutic value of stimulants in the 1930s is reputed to have begun as an attempt to alleviate headaches in behaviorally disturbed children whom he studied with the then new technique of pneumoencephalography - a procedure which he thought might reveal evidence of a central nervous system involvement in this and related disorders (Laufer, 1973). Somewhat later, Laufer and Denhoff (1957) extrapolating from an earlier suggestion made by Bradley and the work of Lindsley and Magoun (Magoun,

1958) on the functional organization of the reticular activating system, proposed that the hyperkinetic syndrome resulted from a dysfunction in the brain stem inhibitory pathways which mediated cortical arousal. Thus, the notion that some deficit in brain function was responsible for many of the HA child's symptoms had a good deal of historical precedent. There was, however, little empirical evidence to support such a claim. The neurological techniques of the day were simply not sophisticated enough to confirm or refute these hypotheses.

Prior to the 1960s, the range of techniques used to assess the integrity of brain function in the intact human was largely limited to the EEG and gross neurological examination. Rapid technological improvements in electronics and the introduction of small computers into the laboratory in the next two decades intensified the search for a neurological basis of hyperactivity and other developmental disorders. As a result, there is now a modest literature dealing with a wide range of central and autonomic nervous system correlates of the HA disorder. These investigations cover most of the customary psychophysiological techniques such as the electrodermal response, heart rate and respiration, event related potentials (ERPs) and pupillography.

A majority of these studies have focused on two broad issues. First, do HA children differ psychophysiologically from normals, and if so, what is the nature of this difference? Secondly, what are the psychophysiological changes which are induced by stimulants? Since this thesis concerns the effects of stimulants on the ERP and heart rate, only this psychophysiological literature will be reviewed. A comprehensive review of psychophysiological studies in the HA child can be found elsewhere (Hastings and Barkley, 1978).

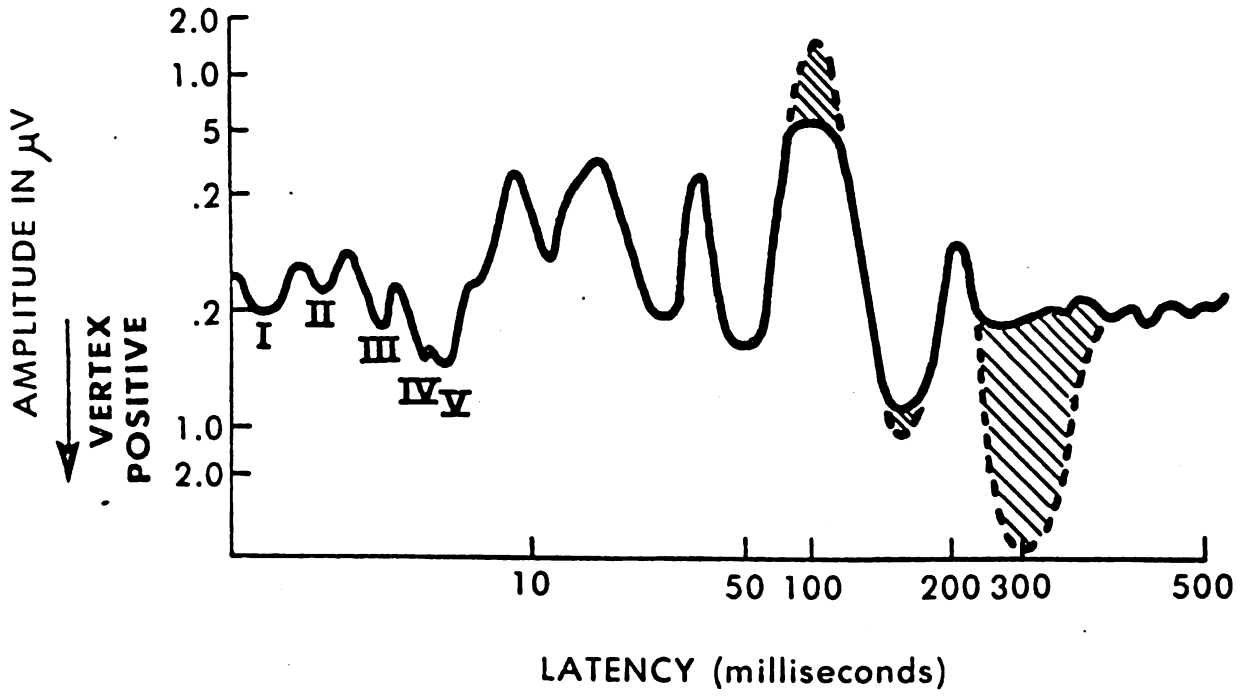
Overview of the Event Related Potential

The evoked potential or event related potential (ERP) consists of a family of brain electrical responses which are initiated by some stimulus event and generally recorded from scalp electrodes. Frequently, these responses are small and obscured by the larger amplitude activity of the background EEG. However, by taking advantage of the time locked nature of the ERP one can improve the signal to noise ratio by averaging or summing the EEG activity over several occurrences of the stimulus. This averaged ERP yields a series of voltage shifts or components which occur at reliable time points with respect to the stimulus. Current evidence suggests that the components of the ERP reflect the activation of different processes within the brain and therefore may be a useful means for tracking the transformations of information as it is modified by the nervous system (Goff, Allison and Vaughn, 1978).

Two different classes of ERPs have been identified (Hillyard, Picton and Regan, 1978; Donchin, Ritter and McCallum, 1978). The early components which extend from the onset of the stimulus to approximately 70-100 msec, are responsive to changes in the physical parameters of the stimulus and are termed exogenous components. Subsequent components are sensitive to drugs, attention, memory load, expectancy and other psychological factors. Some of these responses, e.g. the vertex potential, are jointly sensitive to variations in psychological and stimulus factors, while others like the late occurring positive potential, or P300 wave, are independent of the modality of the stimulus and under certain circumstances can be recorded in the absence of any sensory event. These latter potentials are termed "endogenous components". An idealized ERP is shown in Figure 1.

FIGURE 1. IDEALIZED (AUDITORY) EVENT RELATED POTENTIAL

THE SHADED AREAS INDICATE TYPICAL CHANGES IN THE WAVEFORMS WHICH ACCOMPANY INCREASES IN ATTENTION

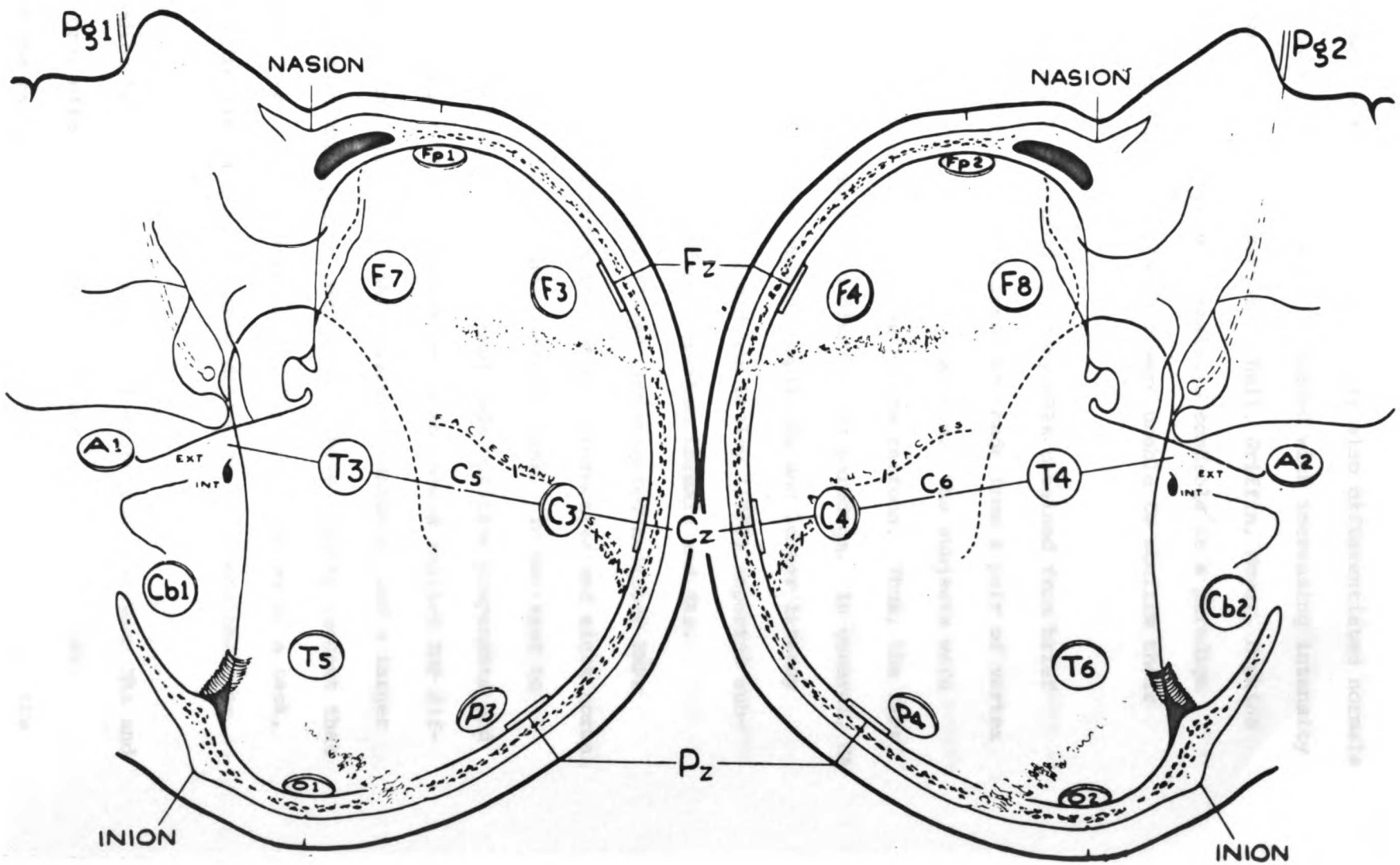


Several investigators have noted the sensitivity of endogenous components to drugs and attention and have examined these responses in HA children with the goal of isolating the psychophysiological components of this disorder and its response to stimulants. In this review, ERP components are designated by polarity and the approximate latency of occurrence. Thus, N150 refers to a negative component with a latency of approximately 150 msec post-stimulus. Unfortunately, polarity depends on the placement of the reference electrode and not all investigators have used the same reference. For example, a large negative component can usually be identified in the visual ERP when a noncephalic reference is used; however, this same component may appear as a positive component if an active reference is employed. Components may also change as a function of where the active lead is placed. Unless otherwise noted, the reference electrode is assumed to be noncephalic (e.g. the ear or mastoid). The active EEG electrode is designated by the international 10-20 system. A diagram of this system is shown in Figure 2.

ERP Comparisons of Hyperactive and Normal Controls

Buchsbaum and Wender (1973) compared visual ERPs to four different stimulus intensities in HA children and normal controls. Hyperactives showed a larger N140-P200 (recorded from Cz - see Figure 2) and a more rapid increase in the amplitude of this component with increasing stimulus intensity than did normals. Hyperactives also showed significantly shorter latency responses for all components, and the difference between groups was largest for the late, P200, component.

FIGURE 2. ELECTRODE LOCATION AND NOMENCLATURES FOR INTERNATIONAL 10-20 EEG SYSTEM



Changes in latency with increasing intensity also differentiated normals from HAs. In normals, P200 latency decreased with increasing intensity while HAs showed the opposite pattern. Hall, Griffin, Moyer, Hopkins and Rapport (1976) also compared normals to controls in a paradigm similar to Buchsbaum and Wender's, but were unable to confirm their results.

Satterfield (1973) compared auditory ERPs obtained from brief clicks in HAs and normals. Recordings were made from a pair of vertex electrodes while subjects watched a TV cartoon. The subjects were instructed to ignore the clicks and watch the cartoon. Thus, the ERPs were obtained in what amounts to a distraction paradigm. In general, HA children showed significantly smaller amplitude and longer latency responses. Subsequently, Satterfield and Braley (1977) reported substantial ERP maturational differences between normals and HAs.

Prichep, Sutton and Hakerem (1976) investigated auditory ERPs recorded from a vertex electrode in sixteen hyperactive and eight normal children during an attentional and a passive task. In contrast to normals, hyperactives showed smaller amplitude positive components and larger negative components. Hyperactives also showed smaller ERP differences between the attentional and passive conditions, and a larger P300 amplitude under the passive condition. These results suggest that hyperactive children not only have difficulty in attending to a task, but are also indiscriminate in how they deploy their attentional resources.

Most studies have not found consistent differences between HAs and normals, nor drug effects in the late portions (P300) of the ERP. However, with the exception of the work of Prichep et al. (1976), the

paradigms used do not generate late positive components (LPC). Klorman, Salzman, Pass, Borgstedt and Dainer (1979) investigated visual ERPs (Cz) in a task designed to generate LPCs. The results showed that the LPC, defined as the largest positive amplitude between 200 and 500 msec, was significantly smaller in placebo treated HAs than normals but these differences were only observed in the active task condition.

Zambelli, Stamm, Maitinsky and Loiselle (1977) investigated ERPs in teenagers who had been diagnosed hyperactive as children (ex-hyperactives) and age matched normals while they were involved in a selective listening task. In normals, the N100 amplitude at Cz was 26-30% smaller in the nonattended as compared to the attended channel. Ex-hyperactives showed only 1-12% differences. The overall amplitude of the ERPs between the two groups was not significantly different, thus ruling out the possibility that the attentional differences were secondary to a more fundamental deficit. The attentional explanation was further supported by the finding that the groups could not be discriminated on the basis of their ERPs obtained in the passive listening portions of the experiment. Accuracy data obtained from the counting or key press condition also revealed that HAs made significantly more errors of commission. Thus, both ERP and behavioral data showed a deficit in attention.

Stimulant Drug Effects on the ERP

Conners 1970) examined changes in the visual ERP in HA children before and after eight weeks of stimulant (d-amphetamine or magnesium pemoline) or placebo treatment. Event related potentials were collected once while the subject attended to an occasional dim flash

embedded in a series of brighter flashes and again while attending to an interposed auditory signal. Recordings were made using a P3, P4, T3, T4 montage referenced to vertex. Both stimulant groups showed an increase in the amplitude of a positive-negative component between 140 and 200 msec following treatment. Placebo treated HAs showed an amplitude decrease in these same components. These changes were specific to the visual attention condition.

Buchsbaum and Wender (1973) reported that amphetamine decreased the slope of the N140-P200 amplitude-stimulus intensity function in HAs who clinically improved on drug (Responders) but increased it for clinically nonresponsive children (Nonresponders). Amphetamine increased the latency of the P200 component in responders. Although Hall et al. (1976) were unable to confirm this drug effect they did observe an increase in the amplitude of the N150-P200 component following an acute dose of d-amphetamine.

Satterfield, Cantwell, Lesser and Podosin (1972), using the paradigm previously described (Satterfield, 1973) reported that methylphenidate increased ERP amplitude in nonresponders, but significantly decreased ERP amplitude in nonresponders. Attempts to replicate these findings have not been successful (Satterfield, Cantwell and Satterfield, 1974).

Prichep et al. (1976) reported that methylphenidate decreased the amplitude of N250 and increased the amplitude of P186 for ERPs obtained under task conditions. Thus, the drug abolished the differences between normals and HAs observed off medication. The HA subjects in this study were all drawn from a group of children who responded clinically to the medication and one cannot determine whether the normalizing effects of

stimulants on the ERP are related to improvements in behavior.

Halliday, Rosenthal, Naylor and Callaway (1976) found that both drug and attention are important in distinguishing the ERPs of clinically judged responders from nonresponders. Visual ERPs (Cz) were recorded from 43 HA children prior to a series of clinical trials. Responders to methylphenidate showed a significant increase in the amplitude of the N145-P190 component on the active drug day which returned to off drug levels when placebo was administered, but this effect was only found in the active attention condition. Nonresponders showed no significant changes in amplitude but exhibited a significant decrease in a measure of ERP variability when they went from an active to passive task. However, this effect was only observed when the nonresponders were given methylphenidate. They suggested that the drug related amplitude change represented a normalizing effect on responders and the variability shift an abnormalizing effect in nonresponders.

Conners (1976) studied the effects of methylphenidate on the vertex potential in HA children. Event related potentials were obtained to auditory and visual stimuli, and a simultaneous presentation of both stimuli presented in a random series. Stimulant increased the amplitude of P180 at Cz (reference electrode unspecified) for the ERP average to paired events, but had no significant effect on the ERPs to modality specific presentations.

Klorman et al. (1979) found that methylphenidate increased LPC amplitude in their paradigm. Reaction time and errors collected to the targets also differentiated the groups and showed significant improvement with drug. Changes in the behavioral measures, however, were not correlated with changes in the ERP. This is one of the few studies

which examined the effects of stimulants on concurrent measures of behavior and brain function.

In the ten experiments reviewed, only two used equivalent paradigms. Four studies examined auditory ERPs, five focused on visual ERPs, while one study used both stimuli. Despite differences in approaches the consistency of the results is remarkable. In terms of the effects of stimulants on the ERPs of HA children, the following generalizations can be made: 1) Stimulants have a significant effect on the latency or amplitude of the ERP irrespective of modality of the eliciting stimulus. Eight studies examined drug effects and all found some significant change in the ERP waveform; 2) Drug effects are observed largely to ERPs collected under task conditions. Six studies used an attentional task. Of these, five reported drug-attention effects. Only one study failed to find such an effect; 3) Drug effects are best seen in the 100-300 msec portions of the ERP. None of the studies reported stimulant effects on early, pre 100 msec, components and only one study reported effects later than 250 msec. Moreover, both signal and nonsignal stimuli appear to be sensitive to drug manipulations; 4) Stimulants appear to reduce the differences between HAs and normals observed off drug. This effect is short-term and no evidence was produced in any of the studies that psychoactive stimulants produce permanent changes in the ERP; 5) Clinical responders show slightly different ERP responses to stimulants, but there are probably no differences between these two groups off drug. Five studies examined this issue and all reported on drug differences. Only one study found off drug differences between clinical responders and nonresponders. An overview of these results is shown in Table I.

TABLE 1

An Overview of Ten Event Related Potential Studies of the Hyperactive Child.

HA = hyperactive. N = normal control. ME = methylphenidate. DA = d-amphetamine. MP = magnesium pemoline. R = responder. NR = nonresponder (classification based on the child's response to stimulant therapy). ON = on drug. OFF = off drug. LAT = latency. AMP = amplitude. Superscript T after result indicates that the findings were found only in an attentional task condition.

STUDY	SAMPLE	TYPE ERP	COMPARISON	RESULTS
Buchsbaum & Wender 1973	24 HAs 48 Ns	Visual	HA-N R-NR ON(DA)	HAs - larger N140-P200 AMP increased more rapidly with stimulus intensity (intensity function) HAs - shorter P100, P200 LAT NR - increased N140-P200 AMP intensity function R - decreased N140-P200 AMP intensity function
Conners 1970	33 HAs	Visual	ON-OFF (DA,MP)	Drug - both DA and MP increased P140-N200 AMP following eight weeks treatment^{T}
Conners 1976	18 HAs	Visual & Auditory	ON-OFF(ME)	Increased AMP of Vertex potential (180 msec) when stimuli presented jointly but not when presented individually
Hall et al 1976	26 HAs 19 Ns	Visual	N-HA R-NR ON-OFF (DA)	No consistent differences off drug R - had smaller AMP and longer LAT N150-P200 components OFF. ON increased P120-N150 AMP

Table 1 (contd.)

STUDY	SAMPLE	TYPE ERP	COMPARISON	RESULTS
Halliday et al 1976	42 HAs	Visual	R-NR R-NR:ON(ME)	No differences OFF R - N145-P190 AMP increased by drug^{T} NR - variability of ERP decreased in passive condition following drug^{T}
Klorman et al 1979	18 HAs 22 N	Visual	HA-N ON-OFF (ME)	HA - smaller AMP late positive component^{T} Drug - increased late positive component AMP
Prichep et al 1976	16 HAs 8 Ns	Auditory	HA-N ON-OFF (ME)	HA - smaller P186 AMP. Larger N250 AMP^{T} Drug - increased P186 AMP. Decreased N250 AMP^{T}
Satterfield et al 1972	22 HAs	Auditory	R-NR ON-OFF (ME)	R - OFF larger AMP P186-N280 Placebo treated HAs and NR showed an increase in AMP of P60-N120, N120-P180 and P180-N280. R showed a decrease in these components
Satterfield 1973	31 HAs 21 Ns	Auditory	HA-N	HA - smaller AMP N120, P180 Longer LAT N120 and P180 but shorter N280 LAT
Zambelli et al 1977	9 HAs 9 Ns	Auditory	HA-N	HA - smaller differences in N88 AMP between attended and nonattended stimuli^{T}

Cardiovascular Studies of the Hyperactive Child

Cardiovascular measures provide another psychophysiological approach to the study of attention and arousal. Although the cardiovascular system is mediated by the autonomic nervous system and brain stem nuclei, central factors have proported to play a role in its operation (Forsyth, 1974). Lacey (1967), in particular, has argued that phasic changes in heart rate reflect different modes of attention. Cardiovascular studies of the HA child have been primarily concerned with heart rate, and both tonic and phasic changes have been examined.

For the most part resting heart rate (HR) has not been found to be different in HAs (Hastings and Barkley, 1978), although a significant difference between normals and HAs in a multivariate test of several cardiorespiratory variables was reported in one carefully done study (Ballard, Boileau, Sleator, Massey and Sprague, 1976).

Stimulants have been shown to increase basal heart rate in a large proportion of the studies reported, typically raising heart rate by five to six beats per minute (BPM) (Hastings and Barkley, 1978). These increases have been shown to be dose related when dose is indexed in terms of milligrams drug/kilogram body weight (mg/kg) but not when dose is indexed in terms of absolute amount of drug (Ballard et al., 1976). These changes are based on group data. Some individuals evidence no changes in basal HR and a few show substantial decreases even at high mg/kg doses (Ballard et al., 1976). The conditions which lead to these discrepancies are not known.

There are few studies of HR deceleration in the HA population. Sroufe, Sonies, West and Wright (1973) compared HA and normals using a

5 second fixed foreperiod RT experiment and reported that HAs exhibited significantly smaller HR decelerations than normals. Zahn, Abate, Little and Wender (1975), on the other hand, found no significant differences in HR deceleration between a sample of normals and HAs in a 10 second fixed foreperiod RT paradigm.

These two studies, along with an additional report by Porges, Walter, Korb and Sprague (1975), also examined the effects of stimulants on HR indices of attention. Sroufe et al. (1973) reported significant increases in HR deceleration when HAs were given a large 1.0 mg/kg dose of methylphenidate. In contrast, Zahn et al. (1975) found that stimulants (d-amphetamine or methylphenidate) suppressed heart rate deceleration. However, this effect appeared to be substantially larger in one drug order condition and was also dependent on the off drug initial levels of HR.

Porges et al. (1975) studied the effects of methylphenidate on heart rate changes in a random foreperiod RT paradigm. They found that drug increased HR variability and overall heart rate in the interval preceding the warning signal. However, methylphenidate decreased these measures in the interval between the warning and imperative signals. Additional analysis showed that subjects with slow RTs exhibited heart rate accceleration on placebo which changed to a deceleration pattern with drug. This suggests that psychophysiological indices of drug responsivity are in some way tied to initial performance deficits such that drug specific changes in HR indices of attention are more likely to be observed for subjects with initially slow RTs. This idea has been suggested many times but never adequately examined in psychophysiological research. Finally, the authors found no significant drug

effects on the initial acceleratory response which often occurs in the initial interval following a warning signal.

In summary, mean heart rate appears to be increased by stimulants although there is very little evidence that HAs differ from normals off drug. Directional changes in heart rate which are believed to index sustained attention have not been found to consistently differentiate normals from HAs nor is it clear that stimulants increase cardiac deceleration. Dosage and drugs varied greatly in these studies and it is possible that changes in mean HR may indirectly affect the deceleratory pattern.

Stimulant Dosage Effects on Clinical, Behavioral and Psychophysiological Measures

Most drug studies in HA children have used only a single dose of stimulant. Single dose studies do not permit one to infer the underlying mechanisms of drug action because the effects observed at one dosage may be opposite to those obtained at another dosage. Theories based on data from single dose studies are limited for similar reasons.

Clinicians recognize the importance of dosage in the treatment of hyperactivity and typically increase the amount of drug until improvement is maximized or side effects appear. Double-blind clinical studies have also demonstrated that gross estimates of behavior improve with dosage (Werry and Sprague, 1974; Halliday, Gnauck, Rosenthal, McKibben and Callaway, in press). However, it now appears that dosage effects may not affect all behavioral and psychological measures in the same way. For example, Sprague and Sleator (1977) have reported that while

teachers' ratings improve with dosage, short-term memory performance may actually deteriorate at high dosages. This raises an important issue in the evaluation of drug responses in children and in the research strategies used to document drug effects. For example, if the clinician adjusts the dosage until behaviors at school and home show maximum improvement, he runs the risk of maintaining the child on a dosage which interferes with critical learning processes. Similarly, if a researcher investigates some process in the laboratory using a "clinically beneficial" dose, he may find no significant drug effect because the response measure is maximized at a smaller dose but depressed at higher doses.

Very few psychophysiological studies have examined the effects of dosage on their measures. Indeed, many have not even specified this variable in their report. Porges (1976) found that at low dosages, 0.5 mg/kg, methylphenidate increased coupling between heart rate and respiration indices of attention, while high doses, 1.0 mg/kg, degraded this relationship. Others have reported that dosage and age differentially affected the N150 and P220 components of the visual ERP (Elliott, et al., 1978; Halliday, Callaway, Rosenthal and Naylor, 1979). These results suggested dosage, attention and age interact in complex ways and therefore by manipulating dosage one might be able to dissect different electrophysiological components of arousal, attention and maturation.

The purpose of the present study is to determine what effects methylphenidate dosage has on concurrent measures of heart rate, reaction time and the visual ERPs (VEPs). In addition, the effects of attention on heart rate and ERP activity are examined to determine the specificity of any observed dosage effects.

METHODS OF PROCEDURE

Subjects

The subjects in this study were 28 hyperactive children who were referred to this project by the Learning Disabilities Clinic at Kaiser Permanente Medical Center, Oakland, California over a three year period (1976-1979). Ages ranged from 7.3 to 13 years ($\bar{x}$ = 122, SD = 21 months). Sixteen children were over ten years while twelve were less than ten years. There were 27 males and one female in the sample. The initial diagnosis of hyperactivity was made by the Director of the clinic, Joseph Rosenthal, M.D. on the basis of parental and teacher reports of hyperactivity, distractibility and school failure, as well as his own observations. Each child had a complete medical workup, which included seriological and amino acid screens, a neurological examination, tests of sensory functioning and a clinical EEG. Children considered for entrance into this study were all free from any medical problems, had no gross abnormal neurological disorders and were not mentally retarded. Clinical EEGs were considered within normal limits although some children showed some slow (4-7 Hz) wave activity.

Potential candidates for this study were then further screened on the basis of criteria proposed by the psychopharmacology branch of the National Institutes of Mental Health and a search of the literature. Specifically, entry into the study required a teacher rating on the Conners Teacher Rating Scale (Conners, 1969) which was at least two standard deviations above current norms on either the daydreaming, hyperactivity or abbreviated subscales of this instrument. This scale

has been found to differentiate hyperactive children from normals (Sprague et al., 1974) and is sensitive to the effects of methylphenidate, even at relatively low doses (Halliday et al., in press). The complete Conners Scale is reproduced in Appendix 1.

Additional acceptance criteria included agreement by the teacher and parents to complete ratings during the lengthy series of clinical trials and to participate in the laboratory sessions which are reported in this thesis. The mean score on the Conners Abbreviated Teacher Rating Scale (ATS) for the children accepted into the project was 1.88 with a standard deviation of 0.46. This score is comparable with other reports in the literature which have used the Conners Scale as a supplementary criterion in the diagnosis of hyperactivity. Twelve diagnosed hyperactive children who were contacted did not participate in the study either because the parents were unwilling or because they did not meet the inclusionary criteria. The mean ATS score for these children was 1.0 - well below the 1.5 cutoff criteria. Prior to final acceptance the pediatrician administered test doses of 5, 10 and 20 mg of methylphenidate to test for possible allergic or other deviant responses to the medication. Two children were eliminated because of atypical responses. In general, the diagnostic criteria used insured that the children studied met reasonably stringent criteria for the hyperactive child syndrome. In addition, they were free of any obvious medical or neurological problems.

Apparatus

The timing and presentation of stimuli and acquisition and storage

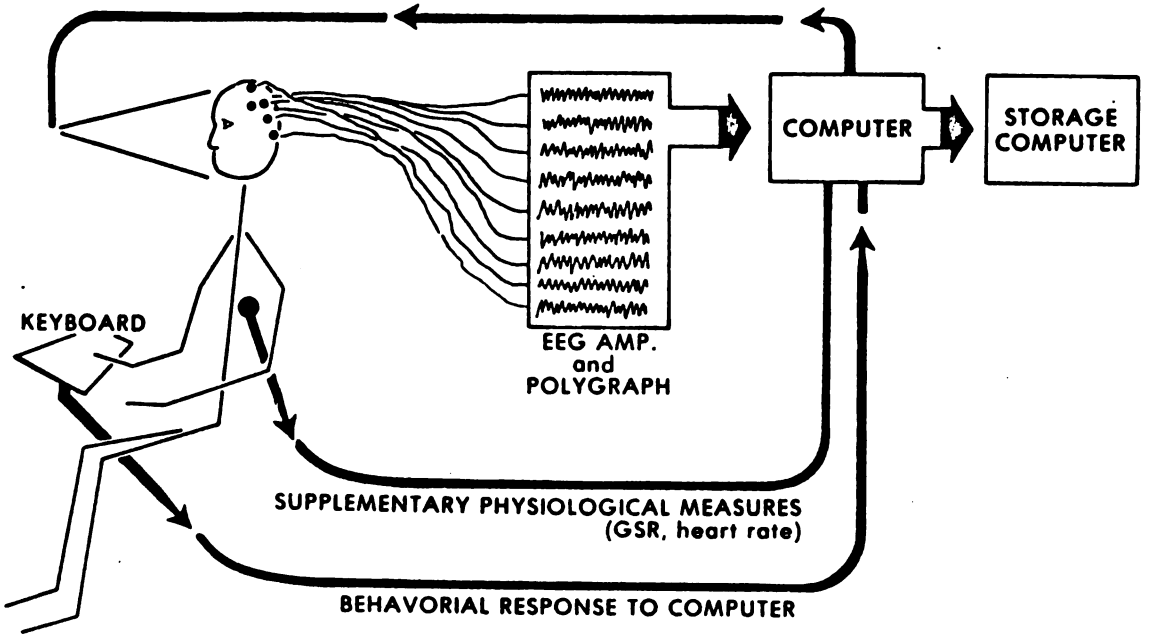
of physiological and behavioral data were controlled by a Data General NOVA 1220 computer. A schematic overview of the system is shown in Figure 3.

The visual stimulus for the nonsignal events was a 10 msec flash with an illumination level of 50 lux measured at the 4 cm opening of the source. Target flashes, i.e. those to which the subject responded with a button press, were considerably dimmer and easy to discriminate from the nonsignal flashes.

The EEG and eye movement (EOG) were amplified by a custom made amplifier in the first eight subjects, and a Grass model 8-10 Electro-encephalograph in the remaining twenty subjects. Changes in amplifiers were made to accommodate the recording of resting EEGs but the same recording parameters were used for all subjects. Filters were set at 1 and 35 Hz for the EEG channels and 0.1-35 Hz for the EOG channel. EEG and EOG channels were digitized over a one second period every 4 msec begining 50 msec prestimulus. In the first eight subjects the EEG was recorded from a single vertex (Cz) lead referenced to linked ears. In the next twenty subjects two additional recordings were made from frontal (Fz) and parietal (Pz) midline electrodes. Grass gold cup electrodes were used for the EEG recordings. Bentonite electrode paste was used for the active electrode and Beckman paste for the reference. A combination of acetone and EEG salt paste was used to clean and abrade the skin. Electrode impedance was kept below 5K ohms and was often less than 2K ohms. The EOG was recorded between the left superorbital ridge and the right canthus with a pair of minature Beckman electrodes.

Heart rate (HR) was recorded from a pair of Beckman skin potential electrodes attached to the lower left rib cage and right aortic area and

FIGURE 3. OVERVIEW OF SYSTEM FOR RECORDING VISUAL EVOKKED POTENTIALS, HEART RATE AND REACTION TIME



amplified by a Mousseau (Model SA-4) amplifier. A Tektronix oscilloscope equipped with a type T time base generator was then adjusted to trigger on the R wave of the cardiac cycle. This signal was then reconditioned by a waveform and pulse generator (Tektronix model 162 and 161) to deliver a 5 msec pulse to the computer. The time base on the oscilloscope was set so that body movements between R waves would not trigger the pulse.

Reaction time to the dim flashes was obtained by having the subject depress a microswitch mounted on the arm of the subject chair. The right hand was used for all subjects.

The presentation of the visual stimulus was initiated by the R wave of the cardiac cycle. Stimulus onset occurred 150 msec following the initializing pulse. This delay prevented the R wave from contaiminating the VEP. The initializing pulse for the next trial was randomly triggered on the R wave following the second, third or fourth post-stimulus R waves. Thus, the presentation of the stimulus was unpredictable.

Procedure

Once the child met the eligibility requirements the parents were mailed a packet containing information about the study and the informed consent papers. Four laboratory sessions were scheduled at least 48 hours apart. Sessions were run either in the morning or afternoon. However, individual children were run at the same time of day to control for any differences in diurnal cycles. Parents were informed that the child was to have a light breakfast or lunch and that no food was to be eaten two hours prior to the time the laboratory runs were scheduled to

start. This procedure was employed to reduce the variation in the metabolism of methylphenidate due to differences in food intake. During the first session, informed consent forms were checked and the procedure and equipment explained to parents and children.

The application of electrodes took 20-30 minutes. For the last twenty subjects, two minutes of resting EEG were recorded under eyes open and closed conditions. Following this the child took a gelatin capsule containing one of four different dosages of Ritalin. In the first session the dosage was always a placebo (lactose). In the remaining sessions a low (L), medium (M) or high (H) capsule was given. The dosages used were 0.16, 0.33 and 0.66 milligrams Ritalin/kilogram body weight (mg/kg). Thus, the M and H dosages were twice the amount of the next lowest dosage (log dose steps). For the L dose the calculated amount of drug varied from 3.52 to 7.84 mg ($\bar{x}$ = 5.29, SD = 1.17). For the M dose amount of drug varied from 7.26 to 16.17 mg ($\bar{x}$ = 10.92, SD = 2.45). For the H dose the amount of drug varied from 14.52 to 32.34 mg ($\bar{x}$ = 22.12, SD = 4.77). The session order in which the three active doses were administered was determined from a list of three possible orderings. These were, in order of session 2, 3 and 4: (1) L-H-M (N=9); (2) M-H-L (N=8); (3) H-L-M (N=6). Five children were assigned other sequences either because of experimenter error (N=2) or because scheduling problems dictated a revised sequence (N=3). Capsules were coded with a special number so that with the exception of the first session the experimenter was blind as to the particular dosage used. The capsules were prepared by the U.C.S.F. Pharmaceutical Technology Laboratory, and were within $\pm$ 1 mg of the calculated amount. The pharmacist also assigned each child to a particular order group.

The psychophysiological battery was then recorded 60-75 minutes post drug. Children in whom rating EEGs were obtained were retested just prior to this. For the VEPs and HR, the within-session conditions consisted of an active-attending task (ATT) and a passive-observing task (PAS). Whenever possible, one or both tasks were repeated. The number of replications was, however, unequal due to the fact that some children found it difficult to remain attentive during the latter portions of the experiment. This occurred mainly in the first session. For the ATT task the child was asked to press the microswitch whenever he detected a dim flash (signal) embedded in a series of brighter flashes (nonsignals). Signal events occurred on 10% of the trials and each correct detection earned a 10¢ reward. Heart rate and VEP data for approximately 100 nonsignals were collected in each attending run. Additionally, VEP, heart rate and response latency to the targets were also stored. In the PAS task the child was requested to simply observe the flashes. There were no dim flashes in the PAS run. A special eye movement algorithm continuously computed activity from the eye electrodes and tagged recordings that exceeded present levels. These records were excluded from the computation of the average VEP. The intertrial interval varied from two to four seconds. Each experimental condition took approximately six to eight minutes to complete so that the post drug portin of the experiment was completed 90-120 minutes following drug ingestion.

The child was seated in a comfortable chair in a sound attenuated, electrically shielded room. The visual stimulus was positioned in the central visual field 153 cm from the child. Before the start of each session the child was given sufficient practice to ensure that he understood the procedures. The child was encouraged to sit quietly during

the run and cautioned against irregular breathing or looking around the room. The EEG was monitored on line and the subject monitored through a closed circuit TV. In most instances children were extremely cooperative and required only an occasional reminder of the instructions.

(Quite contrary to the popular stereotype these children have an extraordinary need to please people and to perform well. Behaviorally, they are indistinguishable from normal children that I have observed in similar laboratory situations. At the conclusion of each ATT run the child was informed of the number of correct responses and the amount of money he or she had earned. They were given a choice of either being paid at the conclusion of each day's run or at the end of the four sessions. In most instances they chose the latter.)

At the conclusion of the laboratory sessions the children began a 12-13 week double-blind trial of the same drug to determine the effects of dosage on school and home behaviors. A majority of these children responded well to at least one of the dosages. Thus, the children studied here were, in general, stimulant responders.

Prior to any analysis, the VEP data for each child was examined trial by trial, and any records with muscle or eye movement artifacts were tagged and excluded from analysis. The edited records were then re-averaged and a laboratory assistant labelled each average file with a code number so that the VEP peaks and latencies could be identified without knowledge of any of the attention or dosage conditions.

The data reported here include the following measures. For the VEP, the latency and amplitude of the N160 and P230 components were visually identified. The amplitude measures were made with respect to a prestimulus baseline and the latencies with respect to the onset of the

stimulus. In addition, a normalized measure of VEP variability was computed over the first 500 msec of the average. This measure is computed by calculating the mean and standard deviation of the voltage values in each individual ERP trial. The individual voltage values are then "normalized" by subtracting the mean from each value and dividing it by the standard deviation. This computation is repeated for each of the ERP trials. Finally, the standard deviations of these normalized values are calculated for each time point and the averaged values of these deviations taken as the variability index. This measure, termed SD/NORM, provides an estimate of the trial by trial variability in individual ERP trials and has been found to be negatively correlated with some, but not all, amplitude measures. A detailed discussion of this measure and its relationship to other measures is found in Callaway and Halliday (1973).

For the heart rate data the measures include the mean interval between the post-stimulus R waves for the first, second, third and fourth heartbeats averaged over the bright flashes. The behavioral data consisted of the mean and standard deviation of reaction times within each ATT run. Accuracy data was not analyzed because very few errors occurred in any of the conditions.

The data were analyzed by Repeated Measures Analysis of Variance (ANOVA) using a program written by Bostrum (1978). The main effects of dosage were broken down into appropriate polynomials so that the form of the dose-response curve could be determined. The F values for repeated measures ANOVA assume that the correlations among repeated elements are equal (equality of the variance-covariance matrix), and the variance of the diagonal elements are drawn from the same population. These assumptions were routinely tested and an adjusted P value used if the assumptions

were not met. Choice of the adjusted P value was based on Bostrum's (1978) guidelines.

To reduce the number of missing observations, the heart rate and reacton time data were averaged over replications. Unless otherwise noted, an effect was considered significant at the $P < .05$ level. The abbreviation MSe stands for the mean square of the error term used to test a particular contrast.

RESULTS

The results are presented in four sections: 1) the effects of dosage and attention on the heart rate; 2) the effects of dosage on the reaction time; 3) the effects of dosage and attention on the amplitude, latency and variability of the VEP and, 4) the interrelationship between these measures.

The Effects of Attention and Dosage on Cardiac Measures

The effects of the experimental treatments on cardiac activity were examined in two ways. First, the average value over the first four heart beats was computed. This was done for each experimental unit, i.e. subject x dosage x attention condition. This value was taken as an estimate of the reciprocal of mean heart rate. Secondly, treatment effects on beat by beat variations were evaluated.

Mean Heart Rate

The effect of dosage on mean heart rate is shown in Figure 4. The data were analyzed by repeated measures ANOVA in which dosage and attention were within subject factors and age ($\pm$ 10 years) a between subject factor. This analysis revealed that dosage significantly increased mean heart rate [$F(3,57) = 12.283$, $MSe = 5895$]. This increase was largely linear with log dose [$F(1,19) = 18.558$, $MSe = 4424$]. While older children had slightly slower heart rates, as expected, this difference was not significant. Similarly, there was no significant interaction between age and dosage, nor did attention or any of its

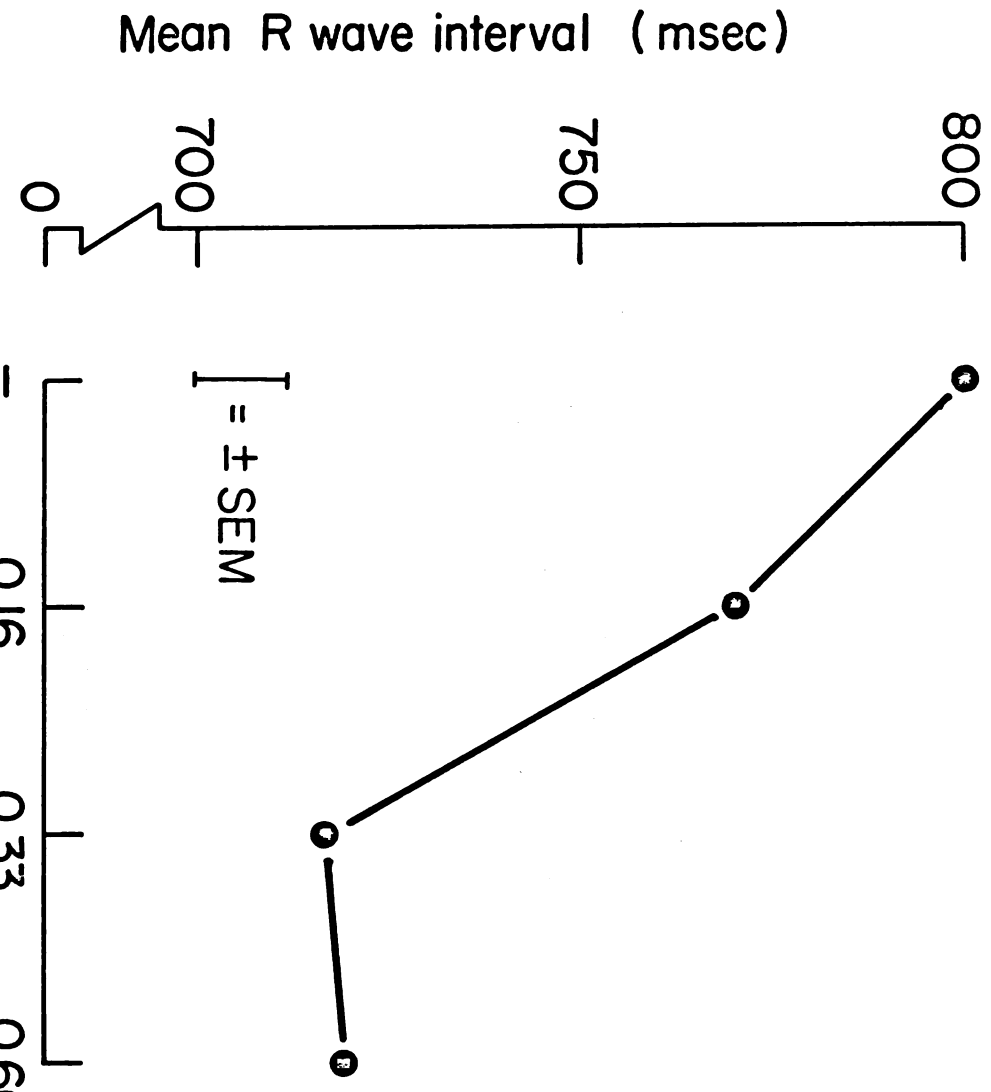


Figure 4. CHANGES IN MEAN HEART RATE WITH METHYLPHENIDATE DOSAGE

interactions have a significant impact on heart rate. The means and significant ANOVA components are provided in Appendix 2.

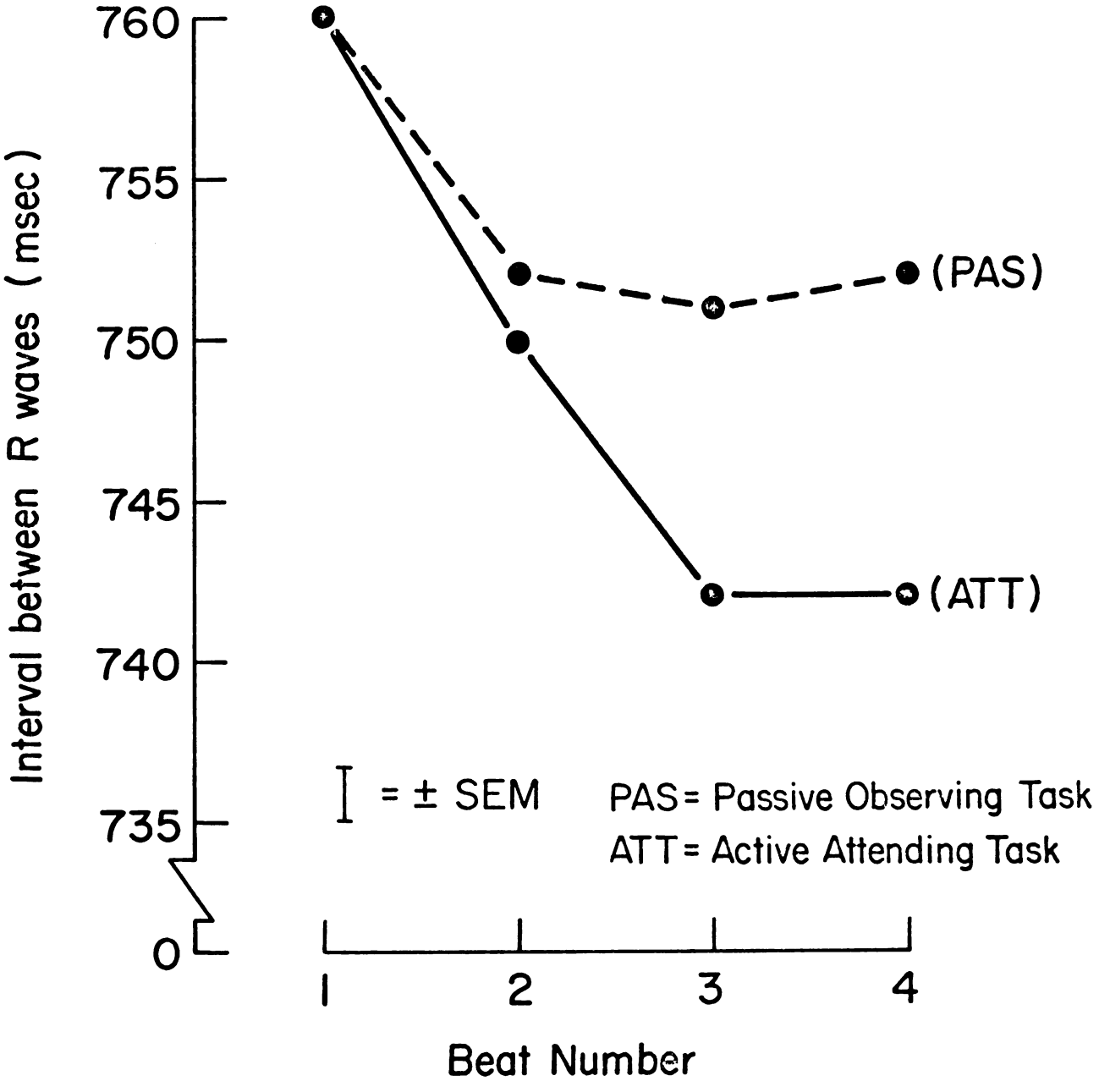
Comparisons between the dosage conditions by Newman-Keuls test (Winer, 1971) showed that both the medium and high dosages produced significantly faster heart rates than the placebo, but the low dose was not significantly different from placebo. The high and medium dosages were significantly faster than the low dose but were not significantly different from each other. The differences, while reliable, were modest in magnitude amounting to a 5.6 beat/minute difference between the low and medium dosages.

Beat by Beat Changes

Figure 5 shows that heart rate reliably increased following the flash [$F(3,60) = 16.135$, $MSe = 356$]. This phasic change was short and appeared to stabilize by the third beat. While dosage produced a significant main effect [$F(3,60) = 14.185$, $MSe = 23634$], this variable had no significant influence in the variations between beats. Attention, however, did have a significant impact on these phasic changes [$F(3,60) = 14.392$, $MSe = 81$]. As Figure 5 shows, the ATT condition produced a larger magnitude increase that stabilized later than the phasic changes recorded in the passive condition. The means and significant ANOVA components are listed in Appendix 3.

In summary, methylphenidate increased heart rate and this effect was linear with log dose. However, doubling the amount of drug past the medium dose did not result in further increases in heart rate. Heart rate reliably increased following the flash and showed a greater

Figure 5. CHANGE IN HEART RATE FOLLOWING VISUAL STIMULUS



acceleratory pattern in the ATT task condition. Methylphenidate had no significant effect on these phasic heart rate changes.

Dosage Effects on Reaction Time

The mean and standard deviation of the individual reaction time (RTs) to the dim (signal) flash were computed for each condition. Reaction times were measured to the nearest millisecond following flash onset. Repeated measures ANOVA were used to analyze the RT data. Age ($\pm$ 10 years) was a between subjects factor for some analysis while order of drug administration (sequence) was used in other analyses. Dosage was the within subjects factor. The means and ANOVA components for the two RT measures are given in Appendices 4 and 5.

Mean Reaction Time (RT)

The principal RT findings are summarized in Figure 6. Reaction time significantly decreased with dosage [$F(3,75) = 19.207$, MSe = 2977]. This effect contained significant linear and quadratic trends [$F(1,25) = 45.390$, MSe = 3029; $F(1,25) = 10.217$, MSe = 3266]. As the figure shows, RTs decreased linearly with log dose up to the medium dose and then appeared to stabilize at the high dose condition. Older children had significantly faster RTs than younger children [$F(1,25) = 9.607$, MSe = 21928]. However, the shape of the dose functions was not reliably different between the two age groups. Since the placebo was always given in the first session it is possible that some of the dosage variance is accounted for by differences between the first and second session. Therefore, a second ANOVA was computed on the RTs obtained for

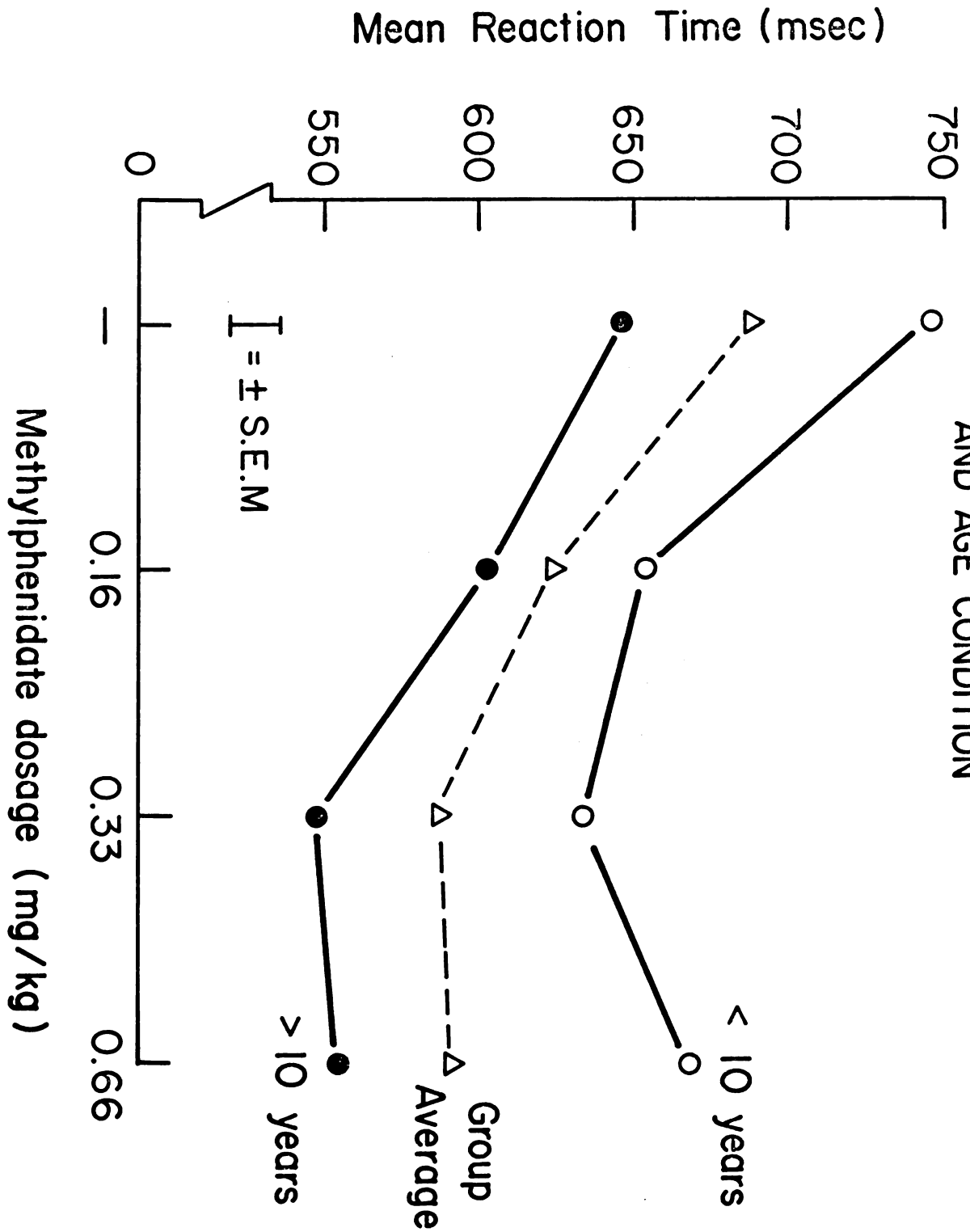


Figure 6. MEAN REACTION TIME FOR EACH DOSAGE AND AGE CONDITION

the active doses - excluding the placebo session. Although the overall F ratio for dosage decreased in this analysis it was nevertheless significant [$F(2,50) = 5.587$, $MSe = 2033$]. Both linear and quadratic components were significant [$F(1,25) = 7.275$, $MSe = 1779$; $F(1,25) = 4.273$, $MSE = 2286$]. Order of drug administration was also analyzed but neither the main effect nor the interaction of drug sequence with dosage were significant.

Newman-Keuls tests were computed between dosage to clarify the nature of the dosage effect on reaction time. Reaction times for the active doses were significantly faster than the placebo condition. The medium dose comparison was significantly faster than the low dose condition, but was not significantly different from the high dose condition. Finally, the low dose was not significantly different from the high dose comparison.

Standard Deviation of Reaction Time

Reaction time variability decreased with dosage [$F(3,75) = 6.482$, $MSe = 3567$]. This decrease was linear with log dose [$F(1,25) = 11.896$]. Younger children had more variable RTs than older children, but this factor was not significant nor did age interact with dosage.

To briefly summarize the behavioral data, methylphenidate decreased mean reaction time and RT variability. This decrease was maximal at the medium dose. The high dose produced no further improvement in performance.

The Effects of Dosage and Attention on the Visual Evoked Potential

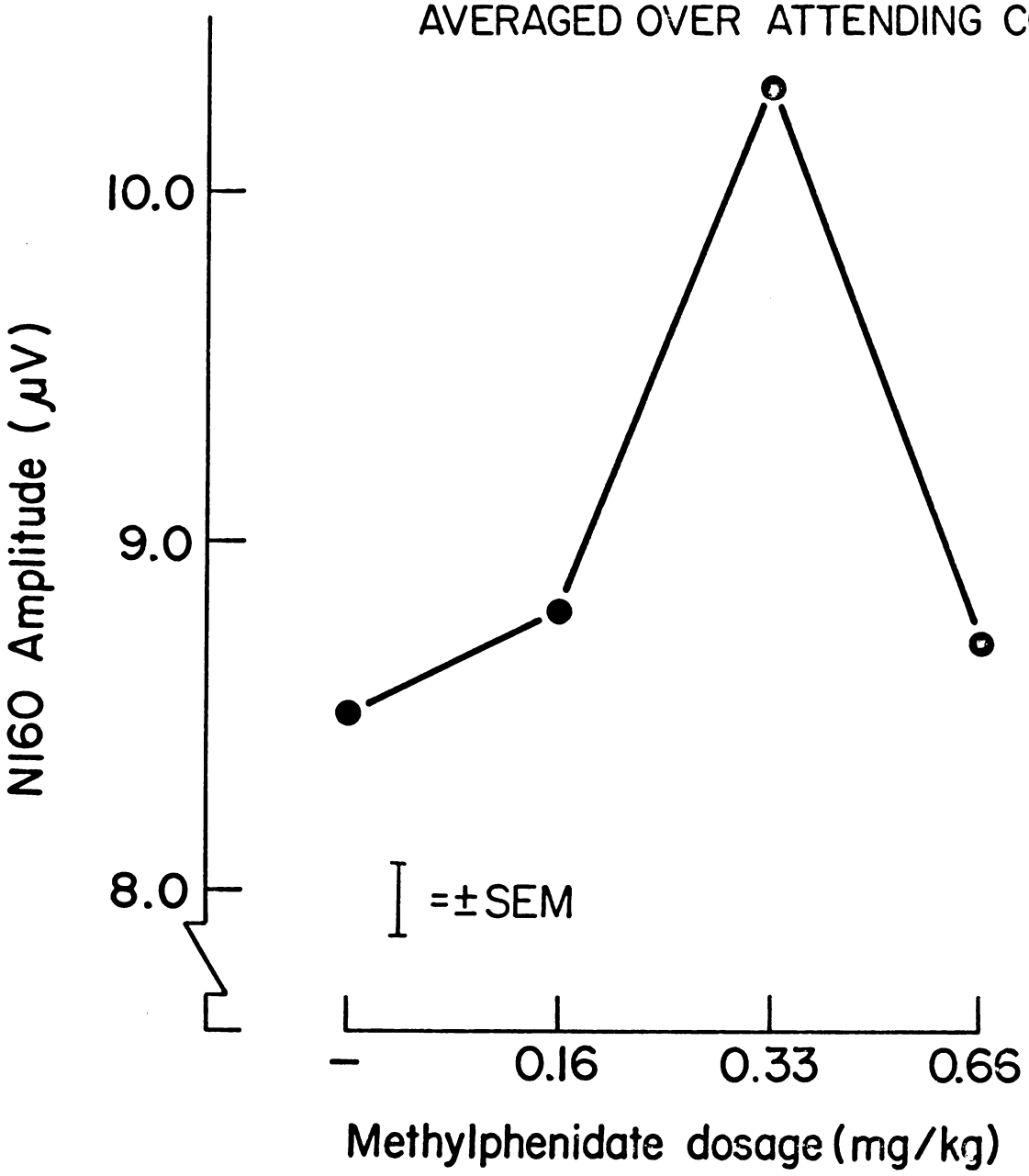
A preliminary analysis on a small set of subjects who had complete data revealed changes in some ERP measures over replications. Since only a few subjects had complete data on the within sessions replication factor, the data reported here are for the first ATT-PAS pair.

N160-P230 amplitude and latency data, and the normalized variance of the ERP (SD/NORM) were analyzed with repeated measures ANOVA in which age ($\pm$ ten years) was the between subjects factor and attention and dosage were the within subjects factors.

Figure 7 shows the principal findings of the N160 amplitude data. Appendix 6 lists the means and significant ANOVA components. As can be seen, the amplitude of the N160 component increased with dosage, maximizing at the medium dosage. Further increase in dosage, however, resulted in a dramatic amplitude decline to the placebo value. ANOVA showed a significant cubic component due to dosage [$F(3,20) = 4.503$, $MSe = 9.84$]. Although this effect was best observed in the ATT task, the interaction between dosage and attention was not significant. None of the other effects were significant. A second ANOVA computed for the active doses provided essentially the same results except that the quadratic component was significant [$F(1,20) = 5.272$, $MSe = 15.598$], thus indicating that the amplitude of the N160 component is related to dosage by a U-shape function.

Since amplitude and latency measures are often highly correlated (Callaway and Halliday, 1973), the latency of N160 was analyzed to determine the contribution of latency to the amplitude changes. No

Figure 7. AMPLITUDE OF THE N160 COMPONENT OF THE VISUAL EVOKED POTENTIAL AVERAGED OVER ATTENDING CONDITIONS



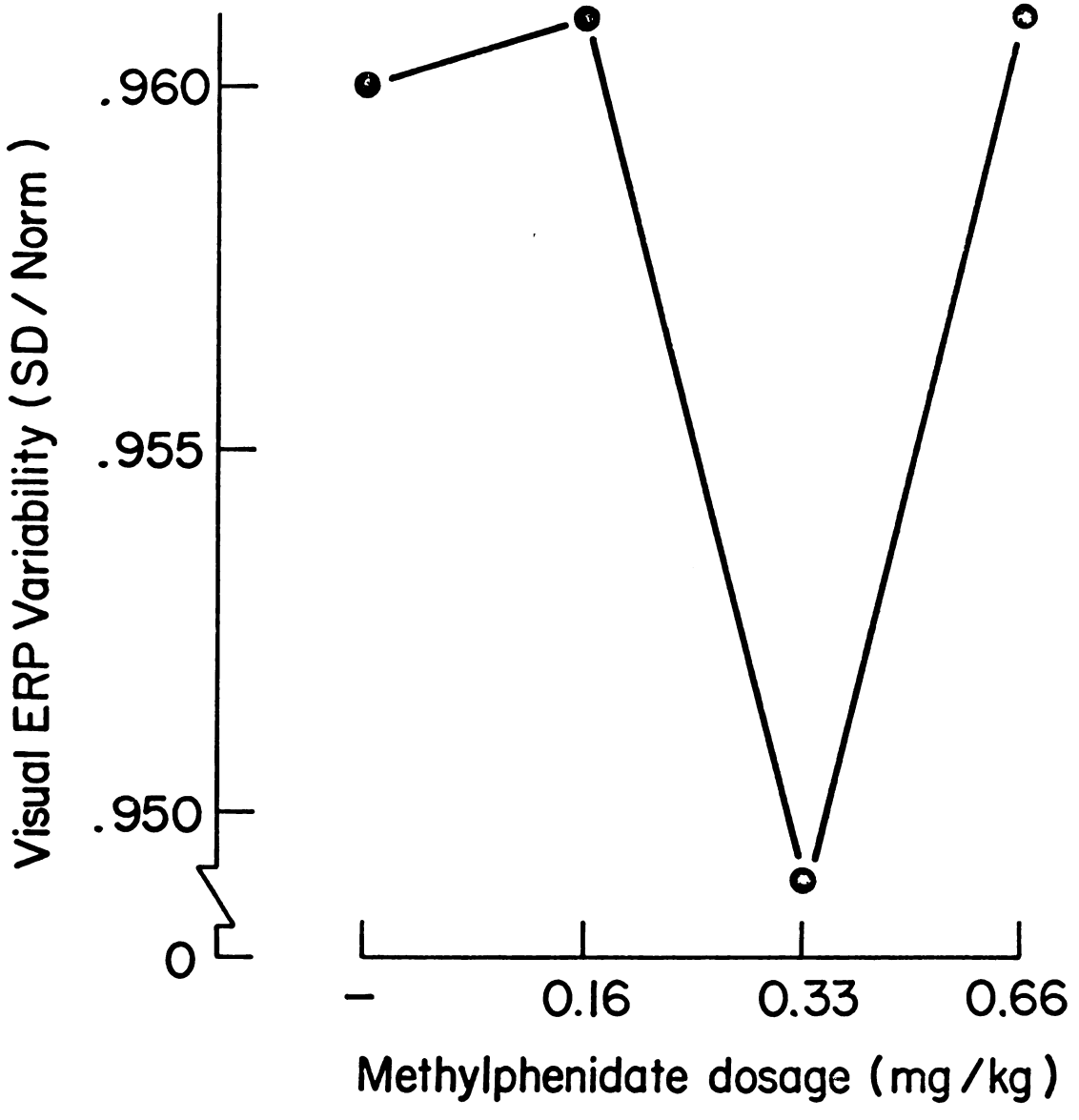
significant effects for any of the ANOVA components were observed in either the complete dosage analysis or the analysis restricted to the active dosages.

The analysis of the P230 data showed that children over ten years had larger amplitude responses than those under ten years [$F(1,21) = 4.763$, MSe = 162] but none of the other experimental factors were significant. The latency of P230 occurred significantly earlier in the ATT as compared to the PAS task [$F(1,20) = 7.084$, MSe = 232], but this measures was not affected by any of the other factors in the experiment. The means and significant ANOVA components for the P230 amplitude and latency data are provided in Appendices 7 and 8 respectively.

Figure 8 shows dosage related changes in the trial by trial estimate of VEP variability (SD/NORM). Appendix 9 shows the means and ANOVA components. SD/NORM decreased (became less variable) at the medium dosage and then increased at the high dose. The cubic component for dosage was significant [$F(1,23) = 6.504$, MSe = 288]. VEP variability was significantly lower in the ATT condition [$F(1,23) = 4.808$], but there was no significant interaction between dosage and task. Children under ten years had more variable VEPs that those over ten years but the differences were not significant.

Thus, for the visually identified N160-P230 component of the visual ERP, stimulant effects appear most prominently in the amplitude of the N160 component. This drug effect is characterized by a dosage related increase in N160 amplitude which is maximum at the medium dosage. Further increases in dosage reduced the amplitude of this component. This effect is best seen in the active attention (ATT) task, but the failure to find a significant dosage by attention interaction leaves the

Figure 8. NORMALIZED VARIABILITY (SD/NORM) OF THE VISUAL EVOKED POTENTIAL AVERAGED OVER ATTENDING CONDITIONS



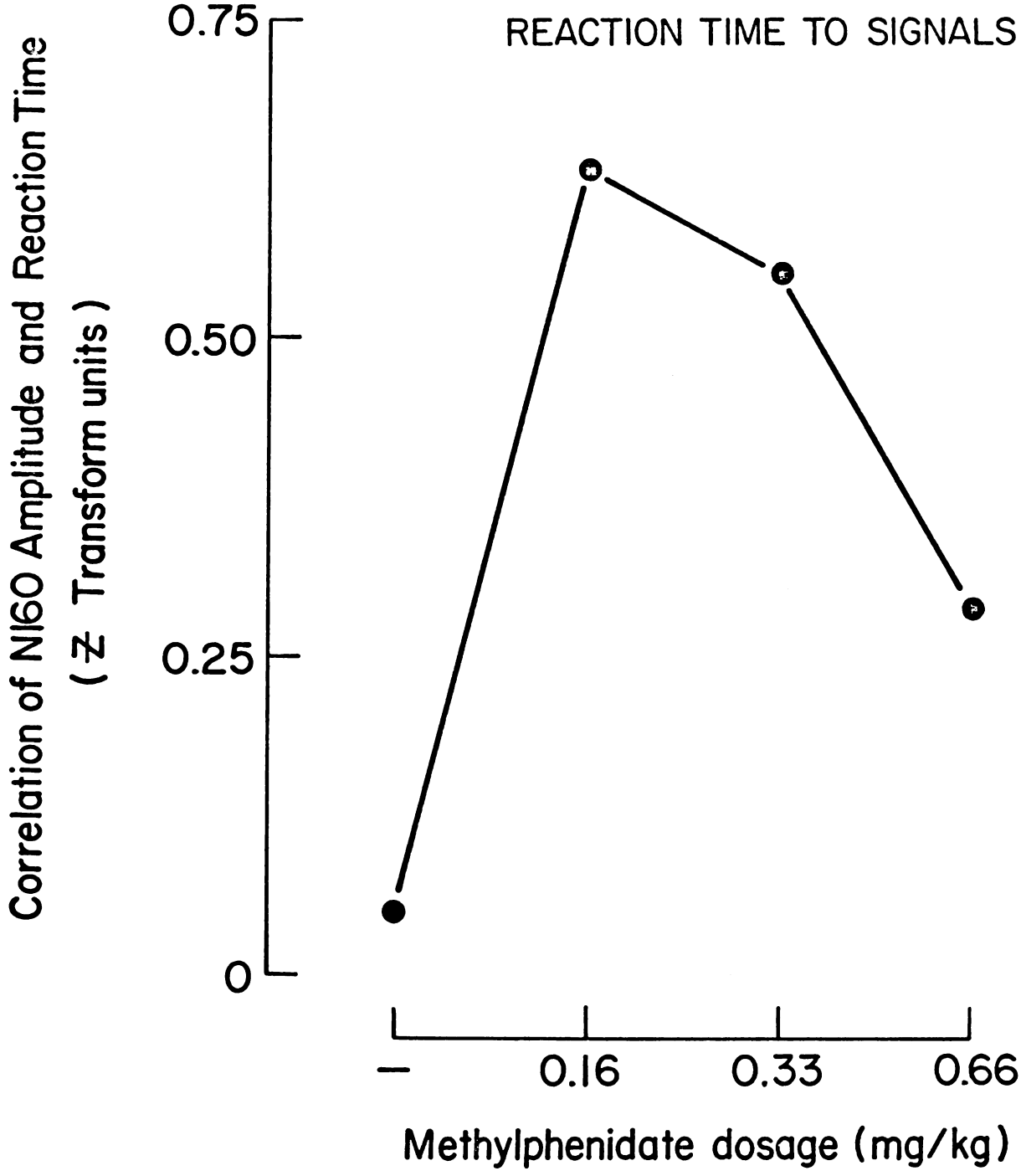
specific nature of the task contribution to the U-shape function equivocal. Estimates of trial by trial variability revealed a similar effect. Variability declined up to the medium dosage and then increased at the highest dosage condition.

The Interrelationship Between Heart Rate, Reaction Time and the Visual Event Related Potential

Mean heart rate, reaction time, the latency and amplitude of the N160 and P230 components and the index of VEP variability were inter-correlated within each dosage condition. In general, heart rate was not consistently related to either reaction time or the VEP. Slower heart rates were associated with larger N160 and P230 amplitudes ($r = .49$ and .45 respectively) but these were significant only in the low dosage condition. The correlations between heart rate and reaction time were all nonsignificant ranging between $r = -.33$ and $r = .10$.

Reaction time was, however, related to N160 amplitude and to a lesser extent the trial by trial variability index, SD/NORM. Figure 9 shows these correlations at each dosage level. In the placebo session the correlation was nonsignificant and near zero. Under the low and medium dosages the correlations jumped to $r = -.56$ ($p < .01$) and $r = -.50$ ($p < .01$) and then declined at the high dosage to $r = -.26$ ($p > .05$). These correlations indicate that faster RTs are associated with larger N160 amplitudes. The correlations between SD/NORM were $r = .39$ ($p < .05$), $r = .46$ ($p < .01$), $r = .35$ ($p > .05$ and $r = .43$ ($p < .05$) for the placebo, low, medium and high dosage conditions. Thus, less variable VEPs were in general predictive of faster RTs.

Figure 9. CORRELATION BETWEEN N160 AMPLITUDE TO NONSIGNALS AND REACTION TIME TO SIGNALS



Among the VEP variables the latency of N160 and P230 were found to be highly correlated with correlation coefficients ranging from .75 to .84. These correlations were all significant beyond the $p < .01$ level of confidence. The amplitudes of these two components were not significantly correlated in any of the dosage conditions and all the correlations were less than $r = .10$. Low and nonsignificant correlations were also obtained between the latency and amplitude of the N160 and P230 components. Finally, N160 and P230 amplitudes were correlated with SD/NORM. This was especially true in the low and medium dose conditions where both amplitude measures were correlated with VEP variability between $r = .51$ to $r = .54$ ($p < .01$). The correlations of SD/NORM and the N160 and P230 latencies were all low and nonsignificant. Thus, while reaction time and N160 amplitude were correlated in certain dosage conditions, these relationships were independent of changes in VEP latency and heart rate.

DISCUSSION

The principal findings of this study are summarized in Table 2.

Cardiovascular Effects of Dosage and Attention

Mean heart rate increased with methylphenidate dosage. This dose response curve was largely linear with log dose. However, the high dose produced no significant increase in heart rate when compared to the medium dose. There were no significant effects on this measure which were attributable to attention or age.

Increase in heart rate with stimulants has been consistently reported in the literature (Hastings and Barkley, 1978). The increase of 9.0 BPM observed for the high (.66mg/kg) dose in the present study is consistent with the literature, and is close to the 8.1 BPM increase reported by Ballard et al. (1976) using an average dose of .48 mg/kg and a different procedure for assessing heart rate.

A majority of the studies have been single dose studies, and consequently dosage effects on heart rate are not well documented. Ballard et al. (1976) reported that heart rate increases were significantly correlated with dosage expressed in mg/kg but not when absolute amount was used. Sprague and Sleator (1977) also reported that heart rate was dose related. However, they found that heart rate increased by 11.6 BPM from .3 to 1.0 mg/kg. In contrast, the results of this study showed that increasing the dose from .33 to .66 mg/kg produced, if anything, a small decrease in heart rate. This discrepancy cannot be currently resolved because of substantial methodological and procedural differ-

ences between the two studies. Thus, the evidence for dose related heart rate increases in the .33 to .66 mg/kg dosage range is equivocal.

Heart rate reliably increased following the flash and the magnitude of this effect was larger in the active (ATT) task condition. Methylphenidate had no effect on these phasic changes. Directional changes in heart rate have been reported by several investigators (e.g. Lacey, 1967) to accompany attentionally demanding tasks although the mechanisms underlying these findings are in dispute (Obrist, 1976). However, most studies have focused on decreases in heart rate which appear in the latter portions of a warned reaction time interval. Little attention has been paid to the initial rise in heart rate which often follows the warning signal. Graham and Clifton (1966), in their classic review of this area, equate cardiac deceleration with the orienting reflex and acceleration with a protective or defensive reflex which they felt was observed only for high intensity stimuli. It seems unlikely that the cardiac acceleration observed in this study represents a defensive reflex since the flash illumination levels were moderate, and the changes observed only in the active attending condition, i.e. when the child was being paid to be accurate. Moreover, these findings are compatible with a recent study by Simons, Öhman and Lang (1979) who reported a significant increase in initial cardiac acceleration to interesting slides (nudes) but not for boring stimuli (household items). The failure to find a stimulant dosage effect on phasic changes in heart rate is consistent with the study of Porges, et al. (1974) who also found that this cardiac component was not affected by methylphenidate.

Dosage Effect on Reaction Time

Mean reaction time and variability decreased with stimulant dosage. These decreases were linear with log dose up to the medium dosage, but further increases produced no significant changes in reaction time. These effects were not due to practice since drug order was not significant. This conclusion is restricted to the active drug comparisons since the fact that the placebo session was purposely confounded with the child's initial session does not permit one to rigorously disentangle dosage changes from practice effects.

The RT data are consistent with other studies in the literature (Barkley, 1977). Moreover, the dosage effects are very much like those reported by Sprague and Sleator (1977). They found that low doses of methylphenidate (.3 mg/kg) improved performance on a short-term recognition memory task, while high doses (1.0 mg/kg) decreased performance to placebo levels. This effect depended on the size of the memory set. Recognition responses for large memory sets declined at high dosages while those for small sets appeared to asymptote. These differences were observed for both percent correct and reaction time, although the statistical significance of these two measures differed according to which memory set size and performance index was compared. While the RTs in the present study appeared to increase at the .66 mg/kg dosage, the differences between the medium and high dosages were not statistically significant. However, since the processing load was low, the results are congruent with Sprague and Sleator's data.

One cannot specify, on the basis of present evidence, what specific cognitive processes are impaired by high dosages of stimulant. In

Sprague and Sleator's study high dosages could have interfered with memory storage or retrieval. In the present study the subjects may have reached their maximum level of performance, thus masking any further dosage changes. Thus, it appears that response decrements which emerge under high dosage conditions are more likely to be observed when the task is difficult. Moreover, it is likely that high dosages interfere with stimulus selection or organization (memory) rather than response selection since the response in Sprague and Sleator's study was a simple binary choice.

Future behavioral research should be directed towards testing specific hypotheses concerning the interrelationship between performance, task and dosage variables. The effects of stimulant dosage have been adequately demonstrated, but we have little in the way of a theoretical model which will predict these changes in other tasks and situations.

Dosage and Attention Effects on the Visual ERP

The amplitude of N160 increased with low dosages of stimulants but substantially decreased at the highest dosage. This effect was best seen in the active task but the interaction between attentional task and dosage was not statistically significant. The amplitude of N160 was larger for the ATT task but the differences were not statistically significant. Dosage effects on N160 amplitude were not related to changes in latency since none of the experimental effects had any significant impact on this variable. The enhancement of the 100-200 msec portion of the ERP has been observed in almost every study which has examined stimulant drug effects (see Table 1). Some recent data suggest

that the enhancement of this component is not specific to hyperactive children, but is also observed in normal children given stimulants (Buchsbaum and Rapoport, 1979).

The amplitude of P230 decreased with dosage but the differences were not significant. In a previous study, P230 showed a significant linear decline with dosage (Halliday et al., 1979). Apparently, the addition of a new sample of children introduced variance which obscured the significance of the P2 results. The difficulty of replicating results in this area has been pointed out elsewhere (Halliday et al., 1976; Hall et al., 1976). P230 latency significantly decreased in the ATT condition but did not interact with dosage. Thus, P2 latency behaved like the beat by beat heart rate in that it was sensitive to attention but not to dosage.

Finally, the trial by trial variability measure was also found to be significantly affected by dosage and attention but these two factors did not interact. The active attention condition reduced the variability of visual ERP. This finding replicates some previous work (Halliday et al., 1976). Dosage decreased ERP variability at the medium dose but increased it, relative to the other dosages, at the high dose. The significant correlations between amplitude measures and SD/NORM found in this study have been previously reported (Callaway and Halliday, 1973).

Theoretical, Methodological and Clinical Implications

The diversity of stimulant dose-response curves found in this and other studies presents an important challenge to theoretical attempts to explain the effects these drugs have on the HA child. In addition,

recent studies have reported that stimulants produce quite similar behavioral and electrophysiological effects in normal and hyperactive children (Buchsbaum and Rapoport, 1979; Rapoport, Buchsbaum, Zahn, Weingartner, Ludlow and Mikkelsen, 1978). Thus, drug responses in hyperactive children may be of broad scientific interest.

A comprehensive theory must eventually account for both the similarities and differences in the observed dose-response curves. Presently there appears to be three groups of such functions. The first group is characterized by a function which changes roughly with the logarithm of dosage. Teacher, parent and side effects ratings are examples of this function (Werry and Sprague, 1974; Halliday et al., in press). The second type of dose-response curve appears to peak at some optimal dosage and then shows few changes with further increments in dosage. The reaction time and heart rate data in the present experiment and some of the memory data in the Sprague and Sleator (1977) study, are examples of this dose-response function. The third dosage function increases up to some optimum dose and then declines at higher dosages. Changes in the N160 amplitude and correlations between N160 amplitude and reaction time found in the present study, recognition memory performance with large stimulus sets reported by Sprague and Sleator (1977) and changes in the coherence between heart rate and respiration reported by Porges (1976) are examples of this inverted U-shape function.

These basic functions may represent the action of stimulants on three different systems, or alternatively the activation of a basic mechanism which covaries with the choice of dependent variable. Current theories, however, do not account for these groupings. For example, Satterfield et al. (1972) proposed that stimulants increase alertness or

general arousal in stimulant responsive children. However, a general arousal theory does not predict the shape of the individual dose-response curves. Likewise, theories which propose that stimulants act directly on attentional mechanisms (e.g. Halliday et al., 1979; Conners, 1976) do not encompass the present results. Attentional task manipulations were found to decrease P230 latency and increase the phasic responsivity of heart rate, but these variables were not affected by stimulant dosage. Conversely, measures changed by methylphenidate dosage, e.g. N160 amplitude, were not affected by attention.

However, this evidence does not disconfirm either of these models. The task used in this study, while ideally suited to the problems of the hyperactive child, is not ideal from the standpoint of separating ERP changes associated with selective attention from those associated with general arousal. Briefly, the comparison between an active and passive task confounds changes in wakefulness or arousal with stimulus selection. Thus, changes between these tasks may represent changes in preparation and motivation, or the selective processing of information or both.

Event related potentials recorded in a passive task are particularly difficult to interpret because there is little control over what strategies the subject uses. For example, a few children volunteered that they had mentally counted the stimuli during the PAS run. Differences in approaches used by subjects might well have obscured subtle differences between tasks. Future research in this area should examine the nature of the ERP task in light of the specific hypothesis to be tested. A review of the major methodological problems inherent in separating arousal from selective attention effects in the ERP is available (Näätänen, 1975).

Although the issue of which specific cognitive components are changed by stimulants cannot be directly addressed, changes in the N160 amplitude of the VEP suggest that stimulants act early in processing of information. Furthermore, substantial changes in the correlation between N160 amplitude to the nonsignal (bright) flashes and RTs to the signal (dim) flashes with low and medium dosages, indicate that changes in processing extend to other signals in the task. These correlations suggest that N160 amplitude enhancement results in faster RTs. Changes in N1 amplitude have been found to correlate with RTs in other studies (Schwent, Snyder and Hillyard, 1976). However, a robust test of this hypothesis will require a detailed analysis of N1-RT changes based on single trial data.

The results of this study are also relevant to some general methodological issues in the field. Whalen, Henker, Collins, Finck and Dotemoto (1979) have pointed out that little is known about the specific behavioral deficits shown by HA children. This criticism is also relevant to the issue of how and what specific behavioral and electrophysiological responses are altered by stimulants. Improvement in the reliability and validity of measures is one important means for increasing experimental precision, but data obtained from the most exacting studies can lead to interpretive problems if one relies solely on single dosage comparisons. For example, had this study only compared the placebo to the .33 mg/kg dosage one would have concluded that all measures are uniformly increased by stimulants. On the other hand, a single comparison between placebo and the .66 mg/kg dosage would have led to a puzzling set of inconsistencies. Thus, variations in dosage provide an important method for characterizing the fine detail of drug

effects.

The present data is also of direct clinical relevance. For example, all measures showed maximal changes at the .33 mg/kg dose. Some measures decreased at the .66 mg/kg dose while others did not. What these measures index in terms of the HA child's adaptive abilities is not clear. However, assuming that they reflect some important processes, clinicians might proceed with caution in prescribing larger doses of stimulants solely on the basic of teacher and parent reports. At the same time one needs to be cautious in interpreting laboratory data as proving that high doses of stimulant do in fact impair processes associated with social and academic learning. A detailed dosage study using objective measures of the HA child's behavior in the classroom will be necessary before the specific nature of the laboratory effects are clear.

Finally, the method of concurrently sampling different behavioral and electrophysiological measures provides an important means for assessing drug effects on different functional systems. Conceivably, the use of multiple measures in conjunction with dosage and task manipulations may permit one to investigate the components of higher order cognitive processes which are relevant to more general psychological issues.

TABLE 2

Overview of Results for Cardiac, Behavioral and Event Related Potentials in the Present Experiment

TYPE OF VARIABLE	MEASURE	RESULTS
Mean heart rate	Averaged interval between successive R waves	Increasing dosage raised mean heart rate up to the medium dose. No difference between medium & high dose.
Beat x Beat variations in heart rate	Interval between R waves as a function of time after stimulation	Heart rate significantly increased following flash but only in active task. No drug effect.
Mean reaction time	Averaged response latency following dim flash for correct responses	Dosage decreased RTs up to medium dose. No difference between medium and high dosage. Children over 10 yrs. had faster RTs.
Reaction time variability	Standard deviation of correct RTs to dim flash	Reaction time variability decreased with dosage.
Amplitude of visual ERP	N160 amplitude	Increased up to medium dosage then decreased.

Table 2 (contd.)

TYPE OF VARIABLE	MEASURE	RESULTS
Latency of visual ERP	N160 latency	No effects
Amplitude of visual ERP	P230 amplitude	Children over 10 yrs. had larger amplitude responses.
Latency of visual ERP	P230 latency	Active task significantly faster than passive task.
Variability of visual ERP	SD/NORM. Normalized estimate of trial x trial variability over 500 msec interval.	Variability decreased up to medium dosage then increased. Curvilinear trend.
Correlation of reaction time and N160 amplitude	-	Negative correlations obtained in low and medium dosages
Correlations between reaction time and SD/NORM	-	Correlations in placebo, low and high dosage conditions.
Correlations between SD/NORM & N160, P230 amplitude	-	Correlations in low and medium dosage conditions.

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APPENDIX 1

Conners Teacher Rating Scale (Conners, 1969)

Observation	Degree of Activity			
	Not at all	Just a little	Pretty much	Very much
CLASSROOM BEHAVIOR				
1. Constantly fidgeting				
2. Hums and makes other odd noises				
3. Demands must be met immediately—easily frustrated				
4. Coordination poor				
5. Restless or overactive				
6. Excitable, impulsive				
7. Inattentive, easily distracted				
8. Fails to finish things he starts—short attention span				
9. Overly sensitive				
10. Overly serious or sad				
11. Daydreams				
12. Sullen or sulky				
13. Cries often and easily				
14. Disturbs other children				
15. Quarrelsome				
16. Mood changes quickly and drastically				
17. Acts "smart"				
18. Destructive				
19. Steals				
20. Lies				
21. Temper outbursts, explosive and unpredictable behavior				
GROUP PARTICIPATION				
22. Isolates himself from other children				
23. Appears to be unaccepted by group				
24. Appears to be easily led				
25. No sense of fair play				
26. Appears to lack leadership				
27. Does not get along with opposite sex				
28. Does not get along with same sex				
29. Teases other children or interferes with their activities				
ATTITUDE TOWARD AUTHORITY				
30. Submissive				
31. Defiant				
32. Impudent				
33. Shy				
34. Fearful				
35. Excessive demands for teacher's attention				
36. Stubborn				
37. Overly anxious to please				
38. Uncooperative				
39. Attendance problem				

APPENDIX 2

Means and Significant ANOVA Components for Mean Heart Rate

MEANS (msec)				
DOSAGE	P	L	M	H
	803	767	716	719

ANOVA Components

SOURCE	df	MEAN SQUARE	F	P
Dosage	3	72,402.00	12.283	.0023[1]
Error	57	5,894.58		
Linear Component	1	191,028.75	18.558	.0004
Error	19	10,293.87		

[1] Conservative F test

APPENDIX 3

Means and Significant ANOVA Components for Beat by Beat Changes in Heart Rate following Flash (msec)

MEANS (msec)

		Post Flash Beat Number 1	2	3	4
ATTENTION	ATT	760	750	742	743
	PAS	759	753	751	753

ANOVA Components

SOURCE	df	MEAN SQUARE	F	P
Dosage	3	335,238.56	14.185	.0012[1]
Error	60	23,633.68		
Dosage-Linear	1	858,376.00	21.614	.000
Error	20	39,714.15		
Dosage-Quadratic	1	81,482.75	4.547	.040
Error	20	17,919.73		
Dosage-Cubic	1	65,857.06	4.964	.030
Error	20	13,267.24		
Post Flash Beat No.	3	5,738.80	16.135	.001[1]
Error	60	355.68		
Beat-Linear	1	13,717.81	26.944	.000
Error	20	509.13		

SOURCE	df	MEAN SQUARE	F	P
Beat-Quadratic	1	3,456.43	7.600	.010
Error	20	454.82		
Attention by Beat No.	3	1,165.07	14.392	.001[1]
Error	60	80.95		

[1] Conservative F test

APPENDIX 4

Means and Significant ANOVA Components for Mean Reaction Time

		MEANS (msec)			
DOSAGE		P	L	M	H
AGE	Under 10 years	748	661	646	659
	Over 10 years	649	603	549	554

ANOVA Components

SOURCE	df	MEAN SQUARE	F	P
Age (± 10 yrs.)	1	210,660.38	9.607	.005
Error	25	21,927.98		
Dosage	3	57,199.39	19.207	.000
Error	75	2,977.97		
Dosage-Linear	1	137,520.06	45.390	.000
Error	25	3,029.71		
Dosage-Quadratic	1	33,372.55	10.217	.004
Error	25	2,637.94		

APPENDIX 5

Means and Significant ANOVA Components for the Standard Deviation of Reaction Times

MEANS (msec)				
DOSAGE	P	L	M	H
	141	107	79	80

ANOVA Components

SOURCE	df	MEAN SQUARE	F	P
Dosage	3	23,123.98	6.482	.020[1]
Error	75	3,567.44		
Dosage-Linear	1	60,345.96	11.896	.002
Error	25	5,072.59		

[1] Conservative F test

APPENDIX 6

Means and Significant ANOVA Components for the Amplitude of the N160 Component of the Visual Evoked Potential

MEANS (μv)				
DOSAGE	P	L	M	H
	8.5	8.8	10.3	8.7

ANOVA Components

SOURCE	df	MEAN SQUARE	F	P
Dosage-Cubic	1	44.32	4.503	.040
Error	20	9.84		

APPENDIX 7

Means and Significant ANOVA Components for the Amplitude of the P230 Component of the Visual Evoked Potential

MEANS (μv)	
AGE	
Under 10 years	Over 10 years
8.8	13.2

ANOVA Components

SOURCE	df	MEAN SQUARE	F	P
Age (± 10 yrs.)	1	773.56	4.763	.040
Error	20	162.41		

APPENDIX 8

Means and Significant ANOVA Components for the Latency of the P230 Component of the Visual Evoked Potential

MEANS (msec)	
ATTENTIONAL TASK	
ATT	PAS
226.4	232.5

ANOVA Components

SOURCE	df	MEAN SQUARE	F	P
Attentional Task	1	1,644.57	7.084	.02
Error	20	232.17		

APPENDIX 9

Means and Significant ANOVA Components for the Normalized Variance of the Visual Evoked Potential

		MEANS			
DOSAGE		P	L	M	H
ATTENTIONAL	ATT	.952	.952	.945	.953
TASK	PAS	.960	.963	.955	.969

ANOVA Components

SOURCE	df	MEAN SQUARE	F	P
Dosage-Cubic	1	1,875.40	6.504	.02
Error	23	288.34		
Attentional Task	1	6,452.44	4.808	.04
Error	23	1,341.95		