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ATTENTION AND THE AUDITORY EVOKED POTENTIAL IN HYPERKINETIC CHILDREN TREATED WITH METHYLPHENIDATE AND IN NORMAL CHILDREN

by

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A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, the City University of New York.

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To Patti,

who helped immeasurably in every stage of this endeavor.

Abstract

ATTENTION AND THE AUDITORY EVOKED POTENTIAL IN HYPERKINETIC CHILDREN TREATED WITH METHYLPHENIDATE AND IN NORMAL CHILDREN

by

LESLIE S. PRICHEP

Advisor: Dr. Gad Hakerem

Hyperkinesis is a behavior syndrome in children, the characteristics of which are most apparent under conditions requiring focusing of attention and inhibition of inappropriate responses. In the present study, differences between hyperkinetic children and non-hyperkinetic normal children and the effects of methylphenidate on hyperkinetic children, were investigated under conditions of differential attentional demands. Auditory average evoked potentials were recorded from vertex under conditions of certainty and uncertainty. In the certain condition the subject was told prior to each trial whether he would hear a single or double click. In the uncertain condition the subject was required to predict whether the next trial would consist of a single or a double click and received a monetary reward for correct guesses. The interval in the double click was 950 milliseconds.

Differences between the groups were largest in response to the second click under conditions of uncertainty, where attentional demands were maximal. Under these conditions, the late components in the response of the non-hyperkinetic normal children were more positive than those of the hyperkinetic children, i.e., positive components were larger in

amplitude and negative components were smaller in amplitude. However, these differences were statistically significant only in the $\overline{P200}$ and $\overline{N250}$ components. The late components of the evoked potential in hyperkinetic children treated with methylphenidate were also found to be positive in relation to those of the placebo treated hyperkinetic controls, again significant in the $\overline{P200}$ and $\overline{N250}$ components. Thus, under methylphenidate the evoked potentials of hyperkinetic children appeared more like those of non-hyperkinetic normal children.

Under conditions of certainty, when attentional demands were minimal, no significant group differences were found. Further, while across all groups the response to certainty was different from the response to uncertainty, the magnitude of this difference was larger in non-hyperkinetic normal children than in hyperkinetic children, reaching significance in the $\overline{P200}$ component. Such differences probably reflect the relative inability of hyperkinetic children to respond differentially to varied task demands. Similarly, the magnitude of difference between the response to certainty and uncertainty was larger under methylphenidate than placebo, significant for $\overline{P200}$. It appears again that drug "normalizes" the response of hyperkinetic children.

The absence of significant group differences in trial to trial variability measures for each component is evidence for the fact that the amplitude differences reported above were not a function of differences in intra-subject variability.

No differences between the hyperkinetic children and non-hyperkinetic normal children, and no changes under methylphenidate, were found in the emitted potential, i.e., the response to the non-occurrence of the second

click. In addition, there were no significant group differences in the contingent negative variation (CNV).

The $\overline{P200}$ component has been shown to be smaller under conditions of distracted attention (e.g., Wilkinson, Morlock, & Williams 1966), and smaller under conditions of certainty than uncertainty (e.g., Friedman, Hakerem, Sutton, & Fleiss, 1973; Tueting, 1968). In addition under conditions of decreased arousal the $\overline{N250}$ component has been found to increase in amplitude (e.g., Tueting, 1968; Wilkinson et al., 1966). In the present study, the fact that hyperkinetic children were found to have significantly smaller $\overline{P200}$s and larger $\overline{N250}$s under conditions of uncertainty than both non-hyperkinetic normal children and hyperkinetic children treated with methylphenidate: (1) reflects the defect in attention observed behaviorally in hyperkinetic children, (2) supports a model of hypoarousal in hyperkinetic children, and (3) reflects the behavioral "normalization" observed in hyperkinetic children treated with methylphenidate.

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Chapter I

Introduction

The diagnostic label hyperkinetic reaction of childhood has been used without precise definition and so globally that it conveys little clear meaning at present. Due to the lack of objective criteria the terms hyperkinesis, learning disability, and others are frequently included within the domain of the equally poorly defined minimal brain dysfunction syndrome (MBD) and the terms are used interchangeably (Clements, 1966; Clements & Peters, 1962; Omenn, 1973; Wender, 1971; Wolff & Hurwitz, 1973). Diagnosis of hyperkinesis is largely based on descriptive accounts of the child's behavior and, as such, is subjective in nature. The effectiveness of central nervous system stimulant drugs in treating hyperkinetic children (see Millichap, 1973; Wender, 1971) has served as a basis for a number of physiological models of the disorder (Wender, 1971). However, at this point etiology is unclear and remains hypothetical.

In the present investigation average evoked potentials were studied in an attempt to extend and clarify our understanding of the hyperkinetic syndrome. Such a physiological response measure could aid in diagnosis and in evaluating treatment response, as well as lending objective support to etiological models.

A selective review of the literature summarizes the findings in the fields of investigation which provide the framework for the present research. For this purpose, there follows a brief descriptive account of hyperkinesis, and a review of studies in the areas of average evoked potentials, average evoked potentials in hyperkinetic children, and other physiological response measures used in the study of hyperkinetic children.

Hyperkinetic Reaction of Childhood

Hyperkinesis is a behavioral syndrome estimated to affect between 5% and 20% of school age children, depending upon the stringency of the diagnostic criteria used (Wender, 1971). It is found to be more prevalent in males than females (Paine, Werry, & Quay, 1968; Werry, 1968). Although several subgroups are probably included in the hyperkinetic category, the symptoms described below are usually agreed upon as being characteristic of the hyperkinetic child (Laufer & Denhoff, 1957; Wender, 1971). It is generally accepted that all symptoms are not necessarily seen in each child and symptomatology within a child may appear to change with age and age-related demands on behavior.

Hyperactivity is the most prominent behavioral symptom. These children are typically described from infancy as being motorically overactive. Also outstanding is shortness of attention span and an inability to concentrate. Poor "impulse control," that is, an inability to inhibit response, is also typical. They appear unable to tolerate delay in gratification of needs and demands, exhibit low frustration tolerance levels and are irritable and explosive. They tend to be resistant to social controls and high levels of independence and aggressiveness influence their interpersonal relationships. Reactivity to both internal and external stimuli tends to be normal in kind but abnormal in degree (i.e., hyporeactive or hyperreactive). Anhedonia, an inability to experience pleasure, is also frequently reported. Impairment in perceptual-cognitive function is variably observed, e.g., difficulties in figure-ground perception and abstraction. Behavior is unpredictable and wide fluctuations in performance are seen.

Although these children are often of normal or above normal intelligence, learning disorders are prevalent (Frisk, Wegelius, Tenhunen, Widholm, & Hortling, 1967; Laufer, 1962). The previously described characteristics in themselves create a pattern which makes it difficult for the child to participate in the classroom. Many hyperkinetic children go undiagnosed until school age, at which time classroom demands accentuate their difficulties leading to diagnosis of the disorder. One of the most severe school problems is an inability to learn to read. Secondary to reading problems are other learning difficulties, and a pattern of decreased motivation and "underachievement" is frequently described.

Neurological "soft" signs, i.e., neurological signs that are not clearly associated with localized neuroanatomical lesions, are reportedly increased in prevalence in hyperkinetic children, while the occurrence of "hard" signs is approximately the same as in a non-hyperkinetic population (Prechtl & Stemmer, 1962; Stewart, Pitts, Craig, & Dieruf, 1966). For example, there may be impairment of fine motor or visual-motor coordination, synkinesis, speech disorder, motor impersistence, reflex asymmetry, motor weakness, or "clumsiness."

Interestingly, a number of studies show that the most effective means of treating these children is with central nervous system (CNS) stimulants, the drug of choice being methylphenidate (ritalin) or secondly, dextroamphetamine (Bradley, 1937; Burks, 1964; Conners & Eisenberg, 1963; Conners, Eisenberg, & Barcai, 1967; Denhoff, Davids, & Hawkins, 1971; Hoffman, Engelhardt, Margolis, Polizos, Waizer, & Rosenfeld, 1974; Knobel, 1962; Millichap, 1973; Millichap & Fowler, 1967; Satterfield, Cantwell, Lesser, & Podosin, 1972; Sprague, Barnes,

& Werry, 1970; Weiss, Minde, Douglas, Werry, & Sykes, 1971; Zrull, Westman, Arthur, & Rice, 1963). These CNS stimulants appear to suppress overactivity and impulsivity and lengthen attention span in many hyperkinetic children, an effect which appears "paradoxical" to that seen in normal adults. However, it is noted that a literature search revealed no relevant data on the response of normal children to stimulant drugs. Wender (1971) also reported a lack of data in this area. Adequate reviews of the literature dealing with drug therapy in hyperkinetic populations exist and therefore they will not be reviewed here (see Millichap, 1973; Wender, 1971).

The class of drugs which has been found to be effective in treatment, as indicated by several behavioral and psychological measures, is important in considering the etiology of the disorder. In general, the action of stimulants appears to be involved with central arousal level, probably by action on the reticular system (Bradley & Key, 1958). On a more specific operational level, evidence exists that amphetamines affect the biogenic amine metabolism and do so primarily through inhibition of the neuronal reuptake mechanism (Omenn, 1973). Wender (1971) suggests a physiological model of MBD, in which he hypothesizes that: (1) MBD children have an abnormality in the metabolism of monoamines (most probably dopamine) and (2) this biochemical abnormality affects behavior by impairment of both reward centers and activating systems of the brain. However, at this time, the relationship between the mechanism of action of CNS stimulants on hyperkinetic behavior remain hypothetical and require further study.

Objective criteria. Criteria differentiating hyperkinetic children from non-hyperkinetic normal children, as have been described above,

are behavioral in nature and appear vague and lacking in objectivity. An important issue, therefore, is whether physiological measures can be identified which might aid in clarifying the diagnosis of these children, and which might lend some insight into the etiology of the disorder.

A second related issue evolves in relation to the treatment of these children with CNS stimulant medication. "Improvement" is defined by the observation of the diminution of those behavioral characteristics which were used to define the syndrome, thus, once again relying on criteria which are subjective and behavioral in nature. The question of whether there are physiological response measures which can differentiate between a hyperkinetic child treated with a CNS stimulant medication as compared with a placebo treated hyperkinetic control, once again arises. The existence of such measures would help in establishing more objective criteria of treatment response.

Clearly, however, the two issues raised above are not independent of each other. Logically, the issue becomes a question of identifying physiological response measures which can distinguish between hyperkinetic children and non-hyperkinetic normal children and also reflect the "normalization" seen behaviorally in the hyperkinetic child under pharmacological treatment. A physiological measure meeting these requirements would be integral to the postulation, or evaluation, of a physiological model of the hyperkinetic behavior syndrome, as well as aiding in the clarification of diagnosis and treatment response.

Average Evoked Potential

A physiological response measure which appears to be particularly appropriate for the study of hyperkinesis is the average evoked potential as recorded from human scalp. This measure has been shown to be related to factors such as attention, arousal and motivation, all of which are important in descriptive accounts of hyperkinesis.

In Figure 1 an idealized vertex-recorded auditory evoked potential is shown. At a recent convention it was agreed to adopt polarity and latency as a common convention in the reporting of components (see Donchin, Callaway, Cooper, Desmedt, Goff, Hillyard, & Sutton, 1974). For example, P300 refers to a positive component with a peak latency at 300 msec. It was further agreed to distinguish theoretical or typical latencies from obtained latencies. Thus, P300 would mean that the actual average latency obtained in a given study for this particular component was 300 msec. On the other hand, $\overline{P300}$ refers to a theoretical component, identified not only by latency but by experimental operations and/or scalp distribution, whose actual latency in a given study may be 500 msec. This approach has been adopted in this dissertation, in reporting both the obtained data as well as the results of other investigators.

In normal adults, the amplitude of a particular component of the average evoked poetntial has been found to be related to the "salience" or "information value" of the stimulus. That is, stimuli which deliver more information, or are more task relevant, thereby commanding more attention on the part of the subject, are found to elicit larger amplitude for the $\overline{P300}$ component of the evoked potential than stimuli of no specific importance to the subject.

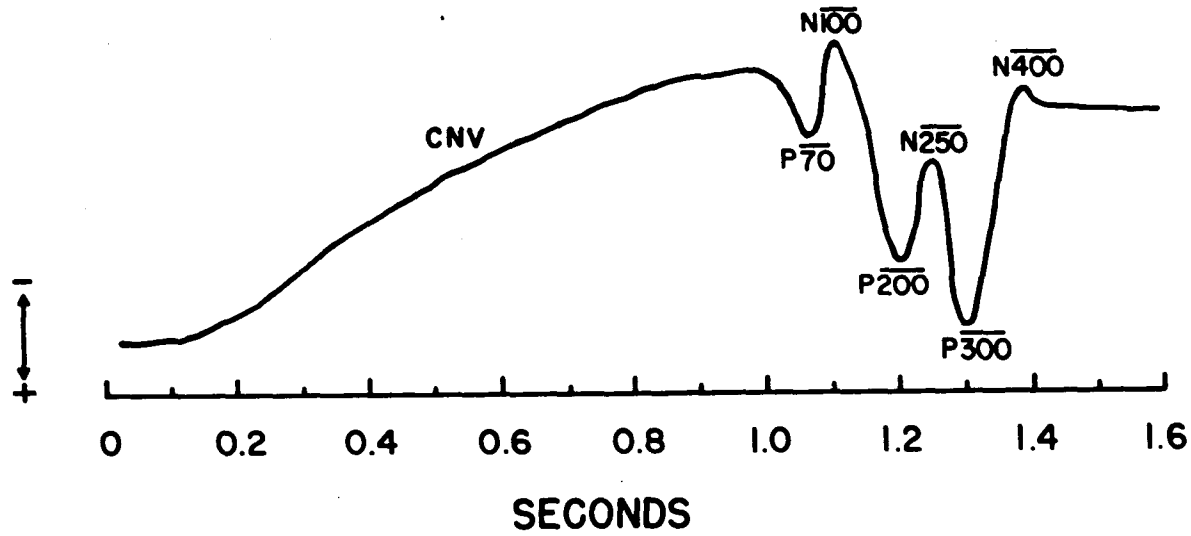

Figure 1. Idealized response representing a vertex-recorded auditory evoked potential in response to a stimulus which resolved uncertainty.

The amplitude of the $\overline{P300}$ component has been shown to be larger when a stimulus delivers information resolving uncertainty (confirming or disconfirming a prior guess) than when the identity of the stimulus is certain (Roth, 1973; Sutton, Braren, Zubin, & John, 1965; Sutton, Tueting, Zubin, & John, 1967; Tueting, 1968). Further, under conditions of uncertainty even the absence of a stimulus will elicit a $\overline{P300}$ component (Ruchkin & Sutton, 1973; Sutton et al., 1967). Similar findings of increased $\overline{P300}$ amplitudes have been reported when the stimulus:

(1) is task relevant (Donchin & Cohen, 1967),

(2) occurs unpredictably (Ritter, Vaughan, & Costa, 1968; Smith, Donchin, Cohen, & Starr, 1970),

(3) occurs with low stimulus probability (Tueting, Sutton, & Zubin, 1971),

(4) requires a difficult discrimination (Jenness, 1970),

(5) is associated with larger monetary payoffs (Sutton et al., 1965),

(6) is a detected signal stimulus (Ritter & Vaughan, 1969; Picton & Hillyard, 1974),

(7) delivers disconfirming feedback (Sutton et al., 1965; Squires, Hillyard, & Lindsay, 1973), and

(8) is an omitted stimulus in a regular train (Picton & Hillyard, 1974).

Directing attention toward a stimulus has consistently been shown to enhance the $\overline{N100}$ and $\overline{P200}$ components (Picton & Hillyard, 1974). The amplitudes of the $\overline{N100}$ and $\overline{P200}$ components have been shown to be related to vigilance and decision (Eason & Harter, 1969; Picton & Low, 1971; Satterfield, 1965; Spong, Haider, & Lindsley, 1965), uncertainty (Tueting, 1968; Tueting et al., 1971) and discrimination (Davis, 1964). Hillyard, Hink, Schwent, and Picton (1973) have shown that in a selective attention task the $\overline{N100}$ component was substantially larger for

attended tones than for ignored tones. Further, they propose that $\overline{N100}$ and $\overline{P300}$ are related to fundamentally different selective attention processes, with $\overline{N100}$ corresponding to "stimulus set" (selectively admitting sensory input to an attended channel and excluding irrelevant channels) and $\overline{P300}$ to "response set" (selectively recognizing task relevant stimuli).

The $\overline{N250}$ component, which has been shown to increase greatly in amplitude as the subject gets drowsy, is presumably inversely related to the arousal state of the individual (Fruhstorfer & Bergstrom, 1971; Picton, Hillyard, & Galambos, 1974; Weitzman & Kremen, 1965; Wilkinson, Morlock, & Williams, 1966; Williams, Tepas, & Morlock, 1962). $\overline{N250}$ has also been shown to decrease in amplitude with increased uncertainty (Tueting, 1968) and with increased vigilance (Wilkinson et al., 1966), both of which demand heightened attention.

A slow negative shift in the average baseline potential occurring prior to the occurrence of an expected "salient" stimulus, within a learned time period is referred to as the contingent negative variation (CNV), (Walter, Cooper, Aldridge, McCallum, & Winter, 1964). The amplitude of the CNV has been reported to increase with increased attentional demands and decrease with experimental manipulations inducing distraction (McCallum, 1969; Tecce & Scheff, 1969). Investigators have shown the CNV to be related to psychological events or states of mind such as:

(1) expectancy (Walter et al., 1964),

(2) decision (Walter, 1964),

(3) motivation (Cant & Bickford, 1967; Irwin, Rebert, McAdam, & Knott, 1966; Rebert, McAdam, Knott, & Irwin, 1967),

(4) volition (McAdam, Irwin, Rebert, & Knott, 1966),

(5) conation (Low et al., 1966), and

(6) arousal or the physiological state of excitability (McAdam, 1969; Tecce, 1971).

The fact that conditions associated with the appearance of the CNV are similar to conditions sometimes associated with an increase in P300 amplitude, has led several investigators to suggest the possibility of a relationship between the amplitude of the P300 component and the CNV (Donchin & Smith, 1970; Karlin, 1970; Näätänen, 1967, 1970; Weinberg, Walter, & Crow, 1970). A detailed discussion of the relationship between prestimulus negative shifts and poststimulus components of the averaged evoked potential is given by Tueting and Sutton (1973) and, therefore, will not be reviewed here.

In summary, evidence exists which relates the amplitude of different components of the evoked potential to factors such as the information value or task relevancy of the stimulus, attentional demands of the task, and arousal level of the subject.

Average Evoked Potentials in Hyperkinetic Children

Investigators have found distinguishing characteristics in the average evoked potentials of psychiatric populations (Buchsbaum, Goodwin, Murphy, & Borge, 1971; Buchsbaum & Silverman, 1968; Callaway, Jones, & Donchin, 1970; Callaway, Jones, & Layne, 1965; Jones, Blacker, Callaway, & Layne, 1965; Jones & Callaway, 1970; Levit, 1972; Levit, Sutton, & Zubin, 1973; Shagass, 1968a, 1968b; Shagass, Overton, & Bartolucci, 1969; Shagass & Straumanis, 1969; Speck, Dim, & Mercer, 1966). However, only those studies relating to hyperkinetic reaction of childhood will be reviewed here (for a review of the literature in adult psychiatric populations, see Levit, 1972).

Since, as has been pointed out, there exists a great deal of variability in the criteria for the diagnosis of hyperkinesis, it should be noted that, in most of the investigations to be reviewed, the investigators have narrowed their hyperkinetic populations by carefully defining criteria for inclusion. The following criteria are typical of those employed by most of the studies, and are meant only to be illustrative:

(1) male
(2) between the ages of 6 and 13
(3) attending school
(4) without gross neurological deficit
(5) IQ of 80 or above (full scale WISC)
(6) off medication at the time of testing
(7) without signs of psychosis
(8) diagnosed as suffering from hyperkinetic behavior syndrome based on definite evidence of hyperactivity and distractability and at least 6 characteristics of the syndrome.

By defining their populations in this way, they have attempted to exclude patient populations in which "hyperactivity" is a symptom of disorders other than hyperkinetic syndrome.

In reporting evoked potential findings the standard terminology used in the previous section is retained. However, since such a procedure involves some assumptions with respect to the identification of components, the probable relationship between the standard terminology and the nomenclature used by the individual investigators is presented in Table I.

Satterfield (1973) studied auditory evoked potentials in hyperkinetic and "normal" children during a passive task in which the children were instructed to ignore clicks presented in blocks at a slow

Table 1

Probable Equivalence Across Investigators

of Components Recorded from Vertex

Investigator[b]	Component: Theoretical Latency Nomenclature[a]						Stimulus
	$\overline{P70}$	$\overline{N100}$	$\overline{P200}$	$\overline{N250}$	$\overline{P300}$	$\overline{N400}$	
Buchsbaum & Wender (1973)	P100	N140	P200				visual
Satterfield (1973)		N_1	P_2	N_2			auditory
Satterfield, Cantwell Lesser, & Podosin (1972)	P_1	N_1	P_2	N_2			auditory
Pridhep (present study)	P63	N103	P186	N250	P295	N377	auditory

[a]Theoretical latencies are for auditory stimuli recorded from vertex.

[b]Not included in this Table are studies by Saletu, Saletu, & Itil (1973) and Saletu, Saletu, Simeon, Viamontes, & Itil (1974), in which visually evoked potentials were recorded from occipital scalp and would, therefore, not be expected to fit into the theoretical vertex nomenclature.

rate (one every 2.5 seconds), and at a fast rate (two per second). At both the slow and the fast rates the amplitude of the $\overline{N100}$-$\overline{P200}$ and $\overline{P200}$-$\overline{N250}$ components were found to be significantly smaller in the hyperkinetic children than in the normal children. Latency differences between the groups were dependent upon stimulus rate, but in general were longer in the hyperkinetic children. Age and IQ were not found to be correlated with either amplitude or latency of the evoked response.

The amplitude of the $\overline{P200}$ component was found to be the component which best differentiated between hyperkinetic and normal children, being of significantly smaller amplitude in the hyperkinetic population. In fact, 60% of the hyperkinetic children had smaller amplitude $\overline{P200}$s than did any of the normal controls. Since 60% of the hyperkinetic children could be identified solely on an averaged evoked response measure (i.e., amplitude of $\overline{P200}$), it appears that the evoked response may be a useful diagnostic tool.

In an earlier study Satterfield et al. (1972) took the hyperkinetic children who had the most extreme responses to methylphenidate and divided them into a "best response" group and a "worst response" group. Those children whose behavior was most improved by drug treatment (best response group) had significantly larger $\overline{P200}$-$\overline{N250}$ measures prior to drug treatment than those children whose behavior was least improved by drug treatment (worst response group). Also, prior to drug treatment the evoked potentials of the best response group showed less recovery, i.e., smaller amplitude at the fast stimulus rate as compared to the amplitude at the slow rate for the $\overline{P70}$-$\overline{N100}$ and $\overline{N100}$-$\overline{P200}$ measures than the worst response group, implying a low level of arousal in the best response group prior to drug. During drug treatment, the

worst response group showed an increase in amplitude of evoked response components while the best response group showed a decrease in amplitude; these group differences were only significant for the $\overline{P70}$-$\overline{N100}$ and $\overline{N100}$-$\overline{P200}$ components.

The meaning of these findings (Satterfield et al., 1972) with respect to those of the study reported above (Satterfield, 1973), is somewhat unclear. Satterfield (1973) does not mention these earlier findings, nor does he define the hyperkinetic subject group in the 1973 study in terms of drug response. It should be noted, however, that the more current study is based on a much larger subject group than was the earlier study. More importantly Satterfield et al. (1972) do not use a "normal" control group and, therefore, while differences between the best and worst response groups exist, how both these groups would compare with normal children is unknown. Thus, the findings of the two studies cannot be directly compared.

Buchsbaum and Wender (1973) recorded the average evoked response in hyperkinetic minimally brain damaged (MBD) children and "normal" controls, during a passive task in which subjects were instructed to watch the lights or listen to the tones. The MBD group tended to have larger amplitude (significant only for $\overline{N100}$-$\overline{P200}$) and shorter latencies (significant for $\overline{P70}$ and $\overline{P200}$) visual evoked responses than did normal children, results opposite to that reported above by Satterfield (1973) for auditory stimuli.

Buchsbaum and Wender found also that MBD children had a faster rate of increase in amplitude with increasing stimulus intensity than did the normal children (significant only for $\overline{N100}$-$\overline{P200}$). Dividing the hyperkinetic children into those who had a positive clinical response

to methylphenidate ("responders") and those who did not ("nonresponders"), they found group differences in the amplitudes of the evoked responses. In responders, methylphenidate was found to decrease the slope of the amplitude-intensity function (moving in the direction of the "normal" children), contrastingly, nonresponders showed an increase in the slope of the amplitude-intensity function (significant group differences for $\overline{N100}$ and $\overline{P200}$ components). No such differences between responders and nonresponders were evident in the off-drug condition. The results of Satterfield et al. (1972), under the drug condition, were similar to those of Buchsbaum and Wender, i.e., with intense stimulation (90 dB) the best response group showed decreased $\overline{N100}$-$\overline{P200}$ amplitude while the worst response group showed increased amplitude. However, Satterfield et al. also found differences in the off-drug condition, where Buchsbaum and Wender did not.

Studying the age-amplitude relationship in the hyperkinetic and normal children Buchsbaum and Wender found that with increasing age normal children show significantly smaller $\overline{P70}$-$\overline{N100}$ amplitudes, and significantly larger $\overline{N100}$-$\overline{P200}$ amplitudes. In contrast, the MBD children showed no significant differences in amplitude with increasing age. Additional age-related differences were found between the hyperkinetic and normal groups in the hemispheric response to sine wave stimulation for the first harmonic (recorded from occiput). Buchsbaum and Wender found that normal children's right hemispheric evoked responses are larger than left for younger children and this asymmetry decreases with age. In the MBD responder group, however, there was found to be increasing right hemispheric predominance with increasing age. In addition, for the normal children the amplitude

of the evoked response to sine wave stimulation decreased with increasing age, whereas the MBD responders show increased amplitude with increasing age. Results for the nonresponder group were not reported. In general, Buchsbaum and Wender interpret these results as showing relative immaturity in the MBD group. However, while the response of the hyperkinetic children may not be age appropriate, whether it is in fact "immature" is questionable.

In terms of variability of response the normal children were found to have significantly less variability in auditory averaged evoked responses than children with MBD, and further there was larger variability in the responders than in the nonresponders. Amphetamines were found to decrease, significantly, the variability in responders, thus "normalizing" them. Variability in the visual response was not measured.

In general, the results of Buchsbaum and Wender (1973) and Satterfield et al. (1972) both support the concept that associated with the differential clinical response to methylphenidate there is a differential neurophysiological response. Satterfield et al. go one step further in suggesting, based on their results, that physiological response differences exist prior to drug treatment as well. However, in several other aspects of their study Buchsbaum and Wender (1973) found results contradictory to those of Satterfield (1973). While Buchsbaum and Wender reported the amplitude of the $\overline{N100}$-$\overline{P200}$ component to be larger in normal than in hyperkinetic children, Satterfield found the amplitude of the $\overline{N100}$-$\overline{P200}$ and $\overline{P200}$-$\overline{N250}$ components to be smaller in hyperkinetic than in normal children. Also, Buchsbaum and Wender reported age-amplitude differences between the groups, and Satterfield did not.

Saletu, Saletu, Simeon, Viamontes, and Itil (1974) recorded visual evoked potentials from the occipital region in a group of hyperkinetic children during a passive task. The children were treated with a placebo, d-amphetamine, or thioridazine (a major tranquilizer). Only those results with d-amphetamine and placebo will be reported here. After four weeks of drug treatment, d-amphetamine was found to increase, generally, peak latencies and augment amplitudes. Studying the relationship between pre-treatment evoked response and clinical symptomatology it was found that the greater the degree of hyperactivity and conduct problems (as measured by teachers) the larger the amplitude of the evoked response for most peaks. Further, in general, the higher the pre-treatment amplitude the better the therapeutic outcome. While these results appear to be in general agreement with Satterfield et al. (1972) who reported that those who had the best drug response (responders) were those with larger pre-drug evoked potential amplitudes, caution must be observed in comparing the two studies as Saletu et al. recorded from occipital scalp, and Satterfield et al. from vertex.

Dividing the hyperkinetic children into drug therapy "responsive" and "resistant" subgroups, Saletu et al. (1974) found shorter latencies and higher amplitudes in the responsive than in the resistant children during the pre-drug period. These amplitude findings again appear consistent with those reported above by Satterfield et al. (1972). After four weeks of drug treatment, the resistant group showed smaller latency increases and larger amplitude increases than the responsive group (who showed almost no change in amplitude). Thus under drug treatment, Saletu et al. (1974), Buchsbaum and Wender (1973) and Satterfield et al. (1972) all report amplitude increases in hyper-

kinetic children who do not respond to drug treatment as compared with those who do respond to drug treatment.

In an earlier study Saletu, Saletu and Itil (1973) had measured visual evoked potentials recorded from the occipital region in a group of "behaviorally disturbed" children (those evidencing conduct problmes, impulsive-hyperactive behavior, and learning disturbances) while treated with dextroamphetamine and again when withdrawn from treatment. Stimuli were delivered to the relaxed subject and no response was required. Based upon the degree of clinical symptomatology which was observed after discontinuation of medication, the children were divided into two groups: (1) those who exhibited no change or improvement in symptomatology, called the "well group," and (2) those who exhibited a marked exacerbation of their clinical symptomatology, called the "deteriorating group."

While treated with dextroamphetamine, evoked potential amplitudes were smaller in the well group than in the deteriorating group, however, no latency differences were found. After discontinuation of drug treatment significant differences between the groups were observed for both latency and amplitude of the evoked response. In general the well group was characterized by marked latency decreases and amplitude increases, whereas the deteriorating group exhibited either a smaller latency decrease (or, in some cases, increases) and attentuation of amplitudes.

The results of this study are not directly comparable to any of those reported above. The temptation is to think of the "deteriorating" group as corresponding to drug "responders" and the "well" group to "nonresponders." However, several factors militate against such

parallels. For example, while the deteriorators show increased clinical symptomatology and the well group shows no change or fewer symptoms when taken off medication, only slight and insignificant changes in symptomatology were noted in any of the children when treated with dextroamphetamine. Thus, while the children could be divided into two groups based on differential responses following drug treatment, it appears that no such distinction could be made while on medication. In fact, based only on change in symptomatology when on drug, the entire group might be considered nonresponders. Due to such considerations comparisons of this study with others will not be made.

In the studies reported thus far, investigations have been limited to the response evoked by simple stimuli under constant conditions of passive attention. In contrast, in the studies reported below (Conners, 1971; Halliday, Rosenthal, Naylor, & Callaway, 1974) a dimension of task relevancy has been added and recordings are made under conditions of active and passive attention.

Conners (1971) studied both visual and auditory evoked potentials in a group of hyperkinetic children before and during drug therapy. Stimuli were presented in trains of dim flashes (or low intensity clicks) randomly interspersed with bright flashes (or high intensity clicks) to which the subject was instructed to respond. Evoked potentials to both relevant (requiring a response) and irrelevant (requiring no response) stimuli were recorded and compared. It should be noted, that in contrast to the other studies reported herein in which monopolar recordings were made, Conners' recordings were made bipolar relative to vertex. Before drug therapy there was found to be no

significant difference in the evoked potentials to relevant or irrelevant stimuli in the hyperkinetic group (for either visual or auditory stimuli). However, during drug therapy, and only in those children for whom the drug had a significant therapeutic effect, there was an increase in amplitude in the late components of the evoked potentials to the relevant stimuli, thus increasing the difference between the response to relevant and irrelevant stimuli. Since the late components of the evoked potential in normal subjects have been shown to be larger in task relevant than task irrelevant conditions (e.g., Donchin & Cohen, 1967; Sutton et al., 1965), Conners' findings may be interpreted as reflecting a "normalizing" effect of stimulant medication on hyperkinetic children.

Halliday, Rosenthal, Naylor and Callaway (1974) also manipulated attentional demands in their investigation of the evoked potential in hyperkinetic children in an active and passive task. However, in their study they compared variability of visual and auditory average evoked potentials rather than measuring amplitude as was done by Conners (1971). The children were divided into three groups based on clinical response to methylphenidate; "greatly improved," "slightly improved," and "not improved." In all conditions intra-individual variability in the visual evoked response was found to be largest in the greatly improved group, smaller in the slightly improved group, and smallest in the not improved group. However, these group differences were only significant in the passive visual task under methylphenidate. While Buchsbaum and Wender (1973) also reported higher variability in responders than in nonresponders they found differences for a passive task in the off-drug condition and further,

found variability to decrease in the responders when treated with amphetamines (a "normalizing" effect).

In contrast to the visual stimuli no significant differences in variability between the groups were found for the auditory stimuli. However, the mean variability for the three groups again tended to be largest in the greatly improved group, smaller in the slightly improved group, and smallest in the not improved group (with the exception of the passive task under placebo).

The relationship between attentional differences (in the visual response) and drug outcome was also studied by calculating the difference between variability for the two levels of attention for each drug condition in each outcome group. In the placebo condition there were no significant differences found between drug outcome and attentional changes as reflected in variability of the evoked response. However, under methylphenidate, significantly more children in the most improved group showed the normal pattern of more variability in the passive task than in the active task, as compared with those in the other two groups combined (who, in fact, showed the opposite relationship between variability and task demands). It is noted that these comparisons were only made for the visual response and they were not consistent with findings under auditory stimulation.

Thus, the attentional deficit described clinically in hyperkinetic children was also observed by Conners (1971) and Halliday et al. (1974) using two different evoked potential measures (amplitude and variability). Both these investigators found evidence that when not under drug hyperkinetic children were unable to match levels of attention with task demands. However, under drug treatment, both Conners and

Halliday and his colleagues reported that hyperkinetic children who behaviorally responded to drug treatment, showed differential responses to different task demands.

Habituation of the evoked potential. Habituation of the evoked potential upon repeated presentation of a stimulus is, according to Sokolov (1960), dependent upon the elaboration of an inhibitory conditioned reflex. Wender (1971) suggests that the excessive activity seen in hyperkinetic children is due to the manifestation of a hypoactive inhibitory system. Further, since an inability to inhibit a response to an irrelevant stimulus is a primary characteristic of hyperkinesis, it may be hypothesized that cortical habituation does not occur normally in these children.

Milstein, Stevens and Sachdez (1969) studied habituation of the alpha attentuation response (AAR) in children with psychiatric disorders. They measured the latency and duration of the AAR in response to successive redundant stimuli, which reportedly permits a quantitative investigation of central habituation. They found that children with hyperkinetic behavior disorders demonstrated longer duration of AAR (i.e., less habituation) compared with age-matched control children. Similarly, Tizard (1968) found no habituation of the evoked potential in "overactive" children. However, their population was subnormal in intelligence and thus, not really appropriate for comparison.

Contingent negative variation (CNV). Andreasen, Peters and Knott (1973) compared the CNVs of hyperkinetic children while on and off medication to a group of "normal" controls. A CNV paradigm was used in which subjects were instructed to respond to the second stimulus (S_2) when it followed one warning tone but not when it followed a dif-

ferent warning tone. While six of the seven normal subjects showed some CNVs, off medication only two of the seven hyperkinetic children did. On medication, six of the seven hyperkinetic children showed some CNV. Thus, Andreasen et al. concluded that hyperkinetic children who off medication rarely showed CNVs appear to be "normalized" by stimulants. However, Low and Stoiler (1973), in a similar study, found no significant relationship between CNV and clinical diagnosis in minimally brain damaged children.

Summary of evoked potential findings. The majority of the evoked potential studies done to date have attempted to correlate differential clinical drug responses in hyperkinetic children to differences in the cortical evoked potential recorded under conditions which required minimal attention. Results, while not entirely consistent, do show that associated with the differential drug response there appears to exist a differential neurophysiological response. That is, off drug those who have been shown to have a positive drug response appear to have larger amplitude, more variable evoked potentials than those who do not respond to drug treatment. When on medication, the evoked potentials of the hyperkinetic children who have a positive clinical response look more like those expected in normal children (i.e., the response is "normalized").

However, while investigators speak of "normalization," few studies have directly compared the evoked response of non-hyperkinetic normal children and drug free hyperkinetic children. Those studies which have made this comparison also used only passive tasks and report conflicting results. In attempting to predict clinical response to drug treatment through the use of an evoked response measure, the more

basic question of differences in evoked response between normal and hyperkinetic children has received relatively little attention.

In the few studies where evoked potentials were recorded under conditions which required varied degrees of attention, findings reflected the inability of hyperkinetic children to respond differentially to task demands. Under drug treatment, however, those hyperkinetic children who showed a positive clinical response appeared able to match levels of attention with task demands.

Other Physiological Response Measures in the Study of Hyperkinetic Children

While the focus of the present study is on average evoked potentials, it is important to consider findings in other areas. A review of the literature revealed that, aside from the average evoked potentials, the main physiological response measures that have been studied in hyperkinetic populations are: (1) electroencephalograms, (2) electrodermal responses, and (3) pupillary responses. Studies in these three areas are reviewed below in order to provide a broader understanding of physiological responses of hyperkinetic children, as well as to provide a framework for the present experiment.

Electroencephalographic findings. The electroencephalogram (EEG) represents a method of studying brain physiology which has been found to be useful in revealing focal lesions, brain tumors and disorders associated with distinctly abnormal waveforms. However, in the majority of psychiatric patients there are no pathognomonic EEG signs. The diagnostic usefulness of the EEG in childhood disorders has been found to be quite low (Ritvo, Ornitz, Walter, & Haley, 1970). There-

fore, the major contribution in EEG research has been to report statistical differences between "normal" and patient populations, rather than providing information about brain physiology other than in general terms of deviant cerebral excitability (Shagass, 1955).

Several studies of hyperkinetic or minimally brain dysfunctioned children report a higher incidence of EEG abnormalities (Capute, Neidermeyer, & Richardson, 1968; Ellingson, 1954; Klinkerfuss, 1965; Wikler, Dixon, & Parker, 1970). Capute and his associates (1968) studied children with minimal brain dysfunction, all of whom showed "soft" neurological signs and for whom hyperactivity was considered to be the most common symptom, and compared them with "normal" children. Significantly more of the minimal brain dysfunction group were found to have some EEG abnormality compared with the control group. Abnormalities were mainly non-focal in nature and the most common mild abnormality was excessive bilateral posterior slowing. Within the minimal brain dysfunction group, Capute found no significant correlation between clinical symptomatology and normal or abnormal EEGs. Thus, while the abnormal EEGs might be suggestive of cerebral disturbance (either morphological or on the basis of altered physiology) such disturbances are nonspecific and may occur in the absence of clinical or behavioral symptoms. Further, normal EEGs do not necessarily mean such disturbance is absent. Diagnosis, therefore, should not be based on EEG alone.

Wikler and his associates (1970) examined the electroencephalograms in children with "scholastic-behavior" problems, who showed no evidence of neurologic disease and whose outstanding characteristic was hyperactivity. They also found excessive non-age-dependent slow

activity and abnormal transient discharges.

Burks (1960, 1968) also found significantly more nonspecific EEG abnormalities in a group of children identified as having "behavior problems" in school than in "normal" controls. However, the subjects in Burks' studies are representative of a broad category of children classified as having "behavior problems" and showed more hyperactivity than normals. All would probably not be diagnosed as being hyperkinetic by more stringent criteria. Therefore, in terms of generalizing these results to a more homogeneous hyperkinetic population, the second part of Burks' study is of more specific interest. Comparing the "behavior problem" abnormal EEG group to the "behavior problem" normal EEG group on behavioral measures, Burks found that those qualities frequently observed in hyperkinetic children (hyperactivity, explosive and unpredictable behavior, and uncooperative behavior) were rated as significantly worse in the normal EEG group than in the abnormal EEG group. Therefore, behavior problem children rated high on those qualities which are considered to be more typical of hyperkinetic children tended to be those who had normal EEGs, a finding which is contrary with those reported above.

Studying the effects of amphetamine therapy in "behavior problem" children Burks (1964) found that medication had more dramatic effects on those children with normal EEGs than on those with abnormal EEGs. Others, however, have reported the opposite relationship between EEG abnormalities and prognosis (Masterson, 1958; Satterfield, 1973). Satterfield (1973) studied the correlation between electroencephalographic findings, neurological "soft" signs and response to methylphenidate treatment in hyperkinetic children. He found that those

with either an abnormal EEG or four or more "soft" neurological signs showed significantly more improvement to methylphenidate treatment than did those hyperkinetic children in whom these abnormalities did not exist.

Satterfield and his associates (1972) studied various characteristics of the EEGs, skin conductance levels and auditory evoked responses of hyperkinetic children and "normal" controls. Only the EEG results will be discussed here (the skin conductance and evoked potential results are discussed in the appropriate sections). Dividing the hyperkinetic group into "best" and "worst" responders to methylphenidate, he found that on pre-treatment measures, subjects who later showed the best response to drug treatment had significantly higher mean resting EEG amplitudes, higher mean resting EEG amplitude ranges, higher mean resting EEG power in the 9-8 hertz frequency range, and a greater number of EEG movement artifacts than did the worst response group. Further, both the best response and worst response groups tended to differ from the control group, but in different directions. That is, the mean resting EEG amplitude, the resting amplitude range, and the number of EEG movement artifacts were all higher than the controls in the best response group and lower than controls in the worst response group. When best and worst responders on medication were compared with placebo treated hyperkinetic subjects, both the placebo and worst response groups showed an increase in power in resting EEG (slow-wave activity) while the best response group showed little or no increase in power (slow-wave activity) in the resting EEG.

In conclusion, Satterfield et al. (1972) hypothesized that the results in the best response group are suggestive of low arousal and the

increase in movement artifacts may represent an attempt to compensate for this low arousal. The increase in slow-wave activity seen in the placebo and worst response group was taken to indicate a decrease in arousal often seen during the second testing session. However, methylphenidate would be expected to act in opposition to this effect. The lack of change in slow-wave activity in the best response group was interpreted as evidence that a greater central nervous system arousal from methylphenidate was operating in this group and thus counteracted the effects of the second session. Satterfield interprets these results in an arousal model, hypothesizing low arousal in the best response group.

Laufer, Denhoff and Solomons (1957) compared the photo-metrazol threshold [based on Gastaut's (1950) technique] in hyperkinetic children to that of children with no clinical evidence of hyperkinesis. Gastaut's photo-metrazol technique is one in which stroboscopic stimulation is provided while metrazol is slowly injected intravenously and a threshold is determined by the amount of metrazol necessary to produce a myoclonic jerk or photic driving of the EEG. Laufer and his colleagues found that hyperkinetic children had a photo-metrazol threshold that was significantly lower than that of controls. In addition, they reported that amphetamine significantly raised the mean photo-metrazol threshold in the hyperkinetic children to the level characteristic for non-hyperkinetic controls. These findings have implications about the location of a possible neurophysiological dysfunction in hyperkinesis. Based on human and animal experimental investigations, Gastaut (1950) and Gastaut and Hunter (1950), showed evidence that a photo-metrazol threshold which is lower than normal

indicates damage to or dysfunction of the diencephalon (especially the thalamus). Thus, this study implies a malfunction (or possibly a maturational lag) in the diencephalon of hyperkinetic children. It should be noted that while controls showed no evidence of hyperkinesis, all were selected from a population of emotionally disturbed children and presented a range of other diagnoses (e.g., psychosis, neurosis).

Neurophysiological differences between hyperkinetic and "normal" children were also suggested by Shetty (1971). Shetty studied the effects of intravenous stimulant drugs (dextroamphetamine or methylphenidate) on electroencephalographic responses to photic stimulation in hyperkinetic children. Hyperactive children who were found to show photic driving responses in the pre-injection phase showed suppression of this response upon injection of the stimulant drug. Further, hyperkinetic children who had shown the photomyoclonic response in the pre-injection period, showed the total absence of such response after the injection of methylphenidate. The remaining children who had no driving or photomyoclonic response in the pre-injection period showed no alteration in response when injected. As in the Laufer et al. (1957) study, a control population of normal children was not used. Controls consisted of normal adults all of whom exhibited photic driving response, and were found to show significantly less alteration in the response when injected with stimulants than did the hyperkinetic children with driving responses.

The results of the Shetty study concerning the drug effect on the photomyoclonic response supports the results of Laufer et al. (1957) reported above. Noting that EEG driving has been shown to be decreased by substances producing an adrenergic state (Floru, 1962), Shetty pro-

poses that stimulant drugs are able to enhance central adrenergic mechanisms in hyperkinetic children to a greater extent than in normals.

In general, studies by Capute et al. (1968), Wikler et al. (1970), and Satterfield et al. (1972) all present evidence of increased incidence of non-focal EEG abnormalities in hyperkinetic behavior disordered children. The abnormalities are frequently reported to be increased slow-wave activity. Since slow-wave activity has been correlated with low central nervous system arousal (Satterfield et al., 1972), these results suggest that hyperkinetic children are in a low state of arousal. Further, neurophysiological dysfunction in hyperkinetic children (possibly in the diencephalon) was also suggested in the studies of the photo-metrazol threshold and other related EEG measures (Laufer et al., 1957; Shetty, 1971).

Electrodermal responses. The clinical characteristics of hyperkinesis include attributes suggestive of behavioral excitation, leading some investigators to hypothesize an abnormal level of physiological excitation (arousal) in these children (as was noted in the summary of EEG results reported above, e.g., Satterfield et al., 1972). Electrodermal responses are one way of studying arousal level. Basal skin conductance level has been shown to be directly related to central nervous system arousal (Duffy, 1962; Silverman, Cohen, & Shmavonian, 1959). A second such index is frequency and magnitude of "spontaneous" non-specific galvanic skin response (GSR), which has been shown to be positively correlated with level of excitation (Burch & Greiner, 1960; Silverman et al., 1959). Thirdly, there reportedly exists a positive relationship between amplitude of specific

GSR (GSR elicited by a stimulus), and responsivity to novel stimuli (Johnson, 1963; Stern, Stewart, & Winokur, 1961).

Satterfield and Dawson (1971) studied electrodermal responses in hyperkinetic and "normal" children. Their findings showed that hyperkinetic children had lower basal skin conductance levels, fewer and smaller amplitude non-specific GSRs and smaller specific GSRs than those of normal children, all indicative of "hypoarousal." Citing studies in which electrodermal activity was shown to be related to stimulation of the mid-brain reticular activating system (Ismat, 1961), Satterfield and Dawson hypothesized that this hypoarousal may be due to lowered excitability in the mid-brain reticular activating system and that increased motor behavior in the hyperkinetic child may be an attempt to increase sensory input. In this context the beneficial response to amphetamines is not seen as "paradoxical" but rather as a "normalizing" arousal effect.

Satterfield and Dawson note, however, that there was a very high degree of intersubject variability in the electrodermal responses of the hyperkinetic children they studied. Therefore, in a later study, Satterfield et al. (1972) divided hyperkinetic children into two groups ("best response" and "worst response") based on clinical response to stimulant treatment and measured skin conductance levels comparing them to a group of "normal" controls. It was found that the skin conductance levels of the best response group were lower than those of normal controls which were in turn lower than those of the worst response group. Thus, those hyperkinetic children who had the best clinical response to methylphenidate were those with the lowest level of arousal before treatment, as measured by skin conductance

level. In Satterfield's formulation, this would imply that the best response group is hypoaroused, whereas the worst response group is hyperaroused.

In a similar study Spring, Greenberg, Scott and Hopwood (1974) compared the electrodermal responses of hyperkinetic children (all of whom were found to respond well to methylphenidate) both on-drug and off-drug to "normal" children. Subjects were not required to respond in any way throughout testing. Contrary to the findings of Satterfield and Dawson (1971), Spring and his associates found no differences between normal and hyperkinetic children on basal skin conductance level. However, the remaining results were quite similar to those of Satterfield and Dawson. Non-specific responses tended to be less frequent in hyperkinetic than normal children, and the frequency was significantly increased in hyperkinetic children under methylphenidate. Specific response amplitude was significantly larger for the normal children than hyperkinetic children, and this measure was not significantly affected by drug. Additionally, significantly more trials to habituation were needed in normal than in hyperkinetic children, and drug tended to increase the number of trials to habituation in hyperkinetic children. In general, these results led Spring and his colleagues to a conclusion similar to that reached by Satterfield and Dawson (1971), that is, as a group hyperkinetic children are less aroused than normal children and are normalized under methylphenidate.

Skin conductance level was also studied by Cohen and Douglas (1972) as a means of investigating the attentional deficit of the hyperkinetic child. Skin conductance, a component of the orienting response, has been considered by some to be the most sensitive indicant

of changes in the environment as well as an indication of habituation to these changes (Sokolov, 1963). Past studies have shown that deficiencies in characteristics of the orienting response and its habituation are sometimes found in patients who exhibit attentional deficiencies and difficulties with impulse control (Luria, 1963). Adding a dimension not used in the two studies reported above, Cohen and Douglas (1972) studied the skin conductance of hyperkinetic and "normal" children under passive conditions with nonsignal stimuli and active conditions requiring a response to signal stimuli.

Skin conductance level during relaxation and during blocks of nonsignal stimuli were found to be similar in hyperkinetic and normal children paralleling results of Spring et al. (1974), but contrary to the results reported above by Satterfield et al (1972). However, in the signal condition orienting responses (skin conductance) to the individual warning signals were significantly larger among the normal than among the hyperkinetic children. Further, skin conductance level in controls was found to increase significantly as a function of increase in task demands from the nonsignal to signal periods, whereas no such difference was seen in the hyperkinetic children. The hyperkinetic children tended to take fewer trials than the normals to habituate (three consecutive trials with no response) to the signal stimuli. Hyperkinetic children also showed significantly more intra-individual variability in their reaction times than did the normal controls.

The nonsignal and relaxation conditions demanded little attention on the part of the subject as compared with the signal condition, which demanded attention and readiness to respond. Normal children

showed greater differences in skin conductance level between these two conditions than did hyperkinetic children, and thus appear to be more responsive to task demands. The fact that group differences were only evident when task demands were manipulated is important in considering further study of hyperkinetic children.

In an earlier study, Cohen, Douglas and Morgenstern (1971) investigated the effects of methylphenidate on the electrodermal response in hyperkinetic children. While methylphenidate was found to increase, significantly, basal skin conductance level, its effects on skin conductance level under conditions of varied task demands were unclear.

In summary, while the results of the above studies of electrodermal responses in hyperkinetic children were not entirely consistent, all found differences between hyperkinetic and normal children in some aspect of the electrodermal response level indicating low arousal level in the hyperkinetic children. Further, stimulants were found to increase at least one measure of autonomic arousal.

Pupillary responses. Another physiological measure which has been shown to be correlated with arousal level is pupillary diameter. Pupillography studies have shown that pupil diameter increases with increased alertness (Lowenstein, Feinberg, & Lowenfeld, 1963; Yoss, Moyer, & Hollenhorst, 1970), increased task difficulty (Bradshaw, 1967; Elshtain & Schaefer, 1968; Payne, Parry, & Harasymiw, 1968) exposure to novel stimuli (Lieberman, 1965; Sokolov, 1963a, 1963b), increased task demands(Hakerem & Sutton, 1966), conditions of stimulus uncertainty (Friedman, Hakerem, Sutton, & Fleiss, 1973; Levine, 1969; Levine & Hakerem, 1969; Pratt, 1970), and low stimulus probability (Friedman et al., 1973). It appears from the results reported above

that pupil diameter and $\overline{P300}$ amplitude are related as they both show increases with conditions or tasks requiring increased attention on the part of the subject. Studies in which both have been simultaneously measured show this to be true (Friedman et al., 1973). Pupillary reflexes have been used in a series of experiments by Rubin (1960, 1962, 1964, 1970) as objective indices of autonomic dysfunction in psychiatric populations. Further, evidence exists of a relationship between pupillary dilation and stimulation of the reticular formation (Hodes & Magoun, 1942; Naquet, Fischer-Williams, & Fernandez-Guardiola, 1960).

Pupillography may be a meaningful tool for the study of hyperkinesis since pupillary diameter has been shown to be: (1) useful in measuring dysfunction in psychiatric populations, (2) related to alertness or attention, and (3) related to stimulation of the reticular formation. Using the electronic pupillogram, Yoss and Moyer (1971) found that 20%-25% of hyperkinetic children had a narcoleptic-like pupillogram, and, therefore, were considered to show signs of hypoarousal. This narcoleptic-like pattern was found to normalize under stimulant drug administration, as does the child's behavior. Yoss and Moyer's findings of hypoarousal, although only found in a portion of the hyperkinetic children they studied, agree with the general conclusion reached above in the studies of electrodermal measures and EEG findings.

Knopp, Arnold, Andres and Smeltzer (1973) also used the electronic pupillogram in their study of hyperkinetic children. Extent of pupillary contraction was measured before and following a test dose of d-amphetamine. It was found that based on the change in extent of

pupillary contraction, behavioral change could be predicted. That is, the further a child's extent of contraction deviated from the normal mean (in either direction) prior to medication, and the closer it approached the mean while on medication, the more probable it was that his behavior would improve with medication. Behavioral improvement was assessed by blind rating done by parents and clinicians. They noted, however, that while parent's ratings of behavioral improvement correlated significantly with pupillographic predictions of improvement, the correlation between the clinician's ratings of behavior improvement and predictions based on pupillograms did not reach significance. These results, while not entirely consistent with those reported above, lend further support to the contention that physiological differences exist between hyperkinetic children and "normal" children.

Studies of the main physiological response measures which have been investigated in hyperkinetic children were reviewed above. These studies were in three main areas: (1) electroencephalography, (2) electrodermal responsivity, and (3) pupillography. In summary, while the results reported were not without conflict, findings in all three of these areas generally lend support to a model of hyperkinesis based on hypoarousal.

The Current Problem

The literature reviewed shows that several physiological response measures have been studied in an attempt to describe differences between hyperkinetic children and non-hyperkinetic normal children, or to reflect differences between hyperkinetic children who respond to

drug treatment and those who do not. The fact that components of the average evoked potential have been shown to be related to attention and arousal, make it a particularly appropriate measure in studying hyperkinetic children since they have been described as showing dysfunction in these areas.

The majority of the previous investigations of evoked potentials in hyperkinetic children were designed to study the relationship between average evoked potential measures and differential clinical drug responses (e.g., Buchsbaum & Wender, 1973; Halliday et al., 1974; Saletu et al., 1973; Satterfield et al., 1972). The more general issue of differences in the evoked potential between non-hyperkinetic normal children and drug-free hyperkinetic children (Buchsbaum & Wender, 1973; Conners, 1971; Satterfield, 1973) has received comparatively little attention. While both types of studies report evoked potential differences between groups, results are inconsistent and are, therefore, inconclusive at this time.

Most of these prior studies have been limited to the study of the response evoked by simple stimuli under passive conditions which placed no attentional demands on the subjects. Since the behavioral characteristics symptomatic of hyperkinetic children are most clearly seen in situations which require focusing of attention and inhibition of inappropriate responses (Wender, 1971), it is under these conditions that hyperkinetic children would be expected to deviate most from normal children, both behaviorally and physiologically. Thus, studies conducted under conditions which placed no attentional demands on the hyperkinetic child may not be optimal for reflecting this disorder.

In the present study, in order to maximize the possibility of clarifying differences between non-hyperkinetic normal children, hyperkinetic children under placebo, and hyperkinetic children under drug (methylphenidate) evoked potentials were studied under conditions of varied attentional demands. A guessing paradigm was used in which either a single or a double click was presented in each trial. Under conditions of certainty, the child was told prior to each trial whtether a single or a double click would be presented. Under conditions of uncertainty the child had to predict prior to each trial whether a single or a double click would be presented. In this condition the occurrence of the single or double click informed the child whether his guess was correct or incorrect. Correct guesses were monetarily rewarded. In contrast with the certain condition where attentional demands are minimal, the task was attentionally demanding in the uncertain condition.

It was hypothesized that in the certain condition, where attentional demands were slight, differences between hyperkinetic children and non-hyperkinetic normal children would not be seen. However, in the uncertain condition where increased attentional demands were placed on the children, it was hypothesized that differences between groups would be seen. Such group differences were predicted to be seen in the components of the evoked potential which have been shown to be related to attention and arousal.

Further, the difference between the response to conditions of certainty and uncertainty were investigated. Studies in normal adults have shown differences in the late components of the evoked potential under conditions of certainty and uncertainty (e.g., Sutton

et al., 1965; Sutton et al., 1967; Tueting 1968). However, such differences were reduced in adult psychiatric populations (Levit, 1972; Levit et al., 1973). Since hyperkinetic children appear to be unable to focus attention (Wender, 1971) and have been shown experimentally to be incapable of responding to differential task demands (Cohen & Douglas, 1972; Conners, 1971; Halliday et al., 1974) it was hypothesized that they would show smaller differences between their response to certainty and uncertainty than non-hyperkinetic normal children.

CNS stimulants (especially methylphenidate) have been shown to be the most effective way of treating hyperkinetic children (see reviews by Millichap, 1973; Wender, 1971). These drugs appear to suppress overactivity and impulsivity and lengthen attention span in most hyperkinetic children. In the present study it was hypothesized that the evoked potentials of hyperkinetic children under methylphenidate would differ from the evoked potentials of hyperkinetic children under placebo. Further, it was predicted that the effects of the drug would be seen under those conditions in which differences were found between drug-free hyperkinetic children and non-hyperkinetic normal children. Since it was hypothesized that the largest differences between the drug-free hyperkinetic children and the non-hyperkinetic children normal children would be seen under conditions of uncertainty, it was expected that the drug effect would also be most clear under conditions of uncertainty, and further that the magnitude of the difference between the response to certainty and uncertainty would be increased under drug. Predictions of the response under drug are based largely on the assumption that evoked

potentials in hyperkinetic children when treated with methylphenidate would look like those of non-hyperkinetic normal children.

Chapter II

Method

The apparatus and general procedure were designed to obtain, store, and average scalp-recorded evoked potentials and baseline shifts to experimental contingencies in a guessing paradigm in hyperkinetic children and non-hyperkinetic normal children. Differences between non-hyperkinetic normal children and hyperkinetic children and the effects of methylphenidate treatment on hyperkinetic children were investigated with respect to conditions of uncertainty, certainty and certainty versus uncertainty. In conditions of uncertainty the subject's task was to guess on each trial if he would hear one or two auditory clicks. In the certain conditions he was told in advance if he would hear a single or double click. The evoked response to the first click and to the presence or absence of the second click were analyzed separately.

Subjects

Twenty-four male children, aged 8 to 11, served as subjects. Each subject was assigned to one of three groups according to the criteria described below. Group One consisted of eight children who were diagnosed as hyperkinetic and were tested under methylphenidate [hyperkinetic drug group, H(D)]. Group Two consisted also of eight children diagnosed as hyperkinetic, but these children were tested only under placebo [hyperkinetic control group, (H(C)]. Group Three consisted of eight non-hyperkinetic "normal" children tested under placebo [non-hyperkinetic normal control group, N(C)].

The hyperkinetic children were sampled from the Children's Clinic of the Psychopharmacology Research Unit of Downstate Medical Center.

All children in this group had been referred to the clinic from the New York City Elementary Schools, where they had come to the attention of the guidance counselor, school psychologist, social worker, or principal because of problem behavior in the classroom. In addition, the referral had to include spontaneous mention of motoric overactivity, which was documented by obtaining a mean score of 1.5 on the hyperactivity factor on the Conners Teacher Rating Scale[1](see Appendix 1). In addition, all children were seen by a child psychiatrist and diagnosed "hyperkinetic reaction of childhood."

The hyperactivity factor on the Teacher Rating Scale consisted of 8 items (or problems) related to hyperactivity (e.g., restless/overactive, excitable, fiddles). The child's teacher was asked to rate the degree to which the item was a problem for that child using a 4-point scale ranging from "not at all" 90) to "very much" (3). Teacher rating scales which quantify observations of the child's hyperactive behavior have been used as part of the diagnostic criteria or to measure the drug effect in many studies (Arnold, Wender, McCloskey, & Snyder, 1972; Buchsbaum & Wender, 1973; Hoffman et al., 1974; Satterfield, 1973; Winsberg, Press, Bailer, & Kupietz, 1973).

The children in the non-hyperkinetic normal group showed no behavioral signs of hyperactivity, did not exhibit behavioral problems in school, and had no history of psychiatric/psychological treatment. While this group is referred to as the normal control group, it is recognized that they are "normal" only within the limits of the criteria applied. All the children in this group were

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[1]Conners (1969) found the test-retest correlation on the hyperactivity factor of the Teacher Rating Scale to range between .70 and .84. Evidence for good construct validity was demonostrated in that highly significant changes in the hyperactivity scores were found with drug treatment as compared with changes in the placebo group scores.

volunteered by their parents (university and laboratory associates) for participation in the study.

Subjects in all groups were matched for sex and were equated for age. All subjects showed no clear evidence of neurological or physical disabilities and were of normal intelligence.

It is noted that two subjects (one from the hyperkinetic group and one from the normal group) left the New York area prior to completion of their participation in the study. Therefore, final analyses are based on data from 22 subjects.

Instrumentation

A schematic diagram of the apparatus is shown in Figure 2.

Experimental environment. The subject was seated in a modified dental chair in a dimly lighted sound attenuated experimental chamber which was electrostatically shielded with copper mesh. The height of the chair and headrest were adjustable in order to place the subject in the proper position. The electrode leads were attached (via shielded wires) to a small pre-amplifier unit which was located on the back of the chair (approximately 0.30 meters away). The subject's right arm rested comfortably on the armrest on which were located the choice keys. The choice keys were two Honeywell microswitches (Model 7AIHL) placed at the end of the plywood armrest. A very small amount of pressure and distance (approximately 28.3 grams moved through one centimeter) was necessary to close the switch, requiring no movement of the arm. The keys were an inch apart and raised ridges were placed on each key allowing them to be recognized by touch. A press on the right key (marked with two ridges), indicated a guess of "double" click, while a press on the left key (marked with a single ridge)

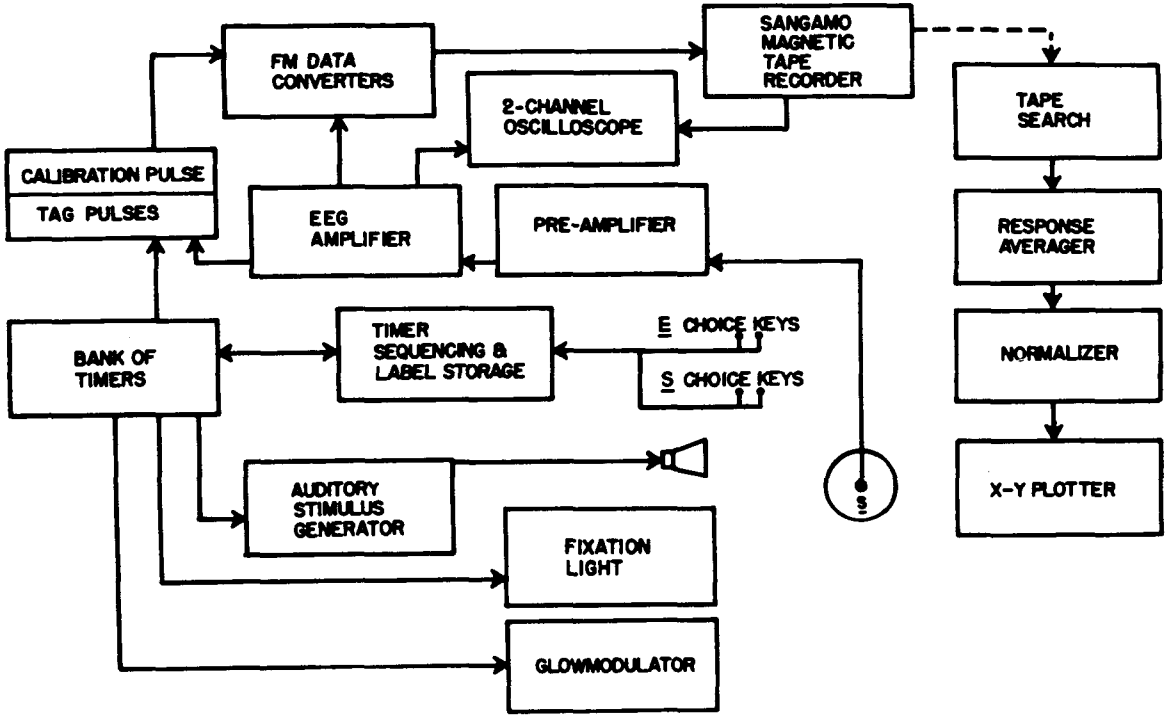

Figure 2. Simplified block diagram of the apparatus used in this study.

indicated a guess of "single" click.

Extraneous stimuli were masked by constant noise generated by an air conditioning unit and exhaust fans. Background noise, measured by a Bruel and Kjaer Precision Sound Level Meter (Type 2203), was 55 dB SPL.

Electrode placement. The electroencephalogram (EEG) was recorded from a vertex electrode, C_Z in the International 10-20 system (see Jasper, 1958). A reference electrode was placed on the right earlobe and a ground electrode was placed on the neck. A vertex electrode was used since the response to auditory stimuli has been shown to be maximal at this point (Goff, Matsumiya, Allison, & Goff, 1969; Vaughan, 1969; Vaughan & Ritter, 1970). Beckman standard biopotential skin electrodes (Model 650418 & 650414) were used. These electrodes contain a silver/silver chloride pellet within a plastic casing. They are non-polarizing and highly resistant to movement artifact.

C_Z was located on each subject, and the scalp in that area was cleaned with an ether acetone mixture in order to remove the outer layer of dead epidermal cells. The ear and neck were likewise cleaned in the area of electrode placement. The electrode reservoirs were filled with Beckman electrode paste in order to facilitate ion flow. The scalp electrode was secured in place by applying Mallinckrodt collodion around the edges of the electrode with a hypodermic syringe. The collodion was then dried with an air blower. The electrodes were secured on the neck and ear with the use of Beckman adhesive collars. Resistance between vertex-ear, vertex-neck, and ear-neck, were measured with a Simpson ohm meter. No resistances between vertex and ear exceeded 6000 ohms. The procedure was repeated when larger resistances

were encountered. Resistances were rechecked at the end of the experimental session. All values remained the same or were less at the end of the session.

Programming. The experimental sequence was controlled by a series of timers (of local design) interconnected through a matrix patch board through which the timer sequence was programmed by the experimenter, who was seated outside the subject booth. The E choice keys allowed the experimenter to present either the single or double auditory stimulus in each trial.

The experimenter's choice of single or double click in conjunction with the subject's guess (of single or double click) generated an electronic tag pulse representing one of the four experimental contingencies: single right, single wrong, double right, double wrong. In addition, two electronic tag pulses represented the contingencies in the certain condition in which no guess was made and the subject's key press was based on the experimenter having told him that the next stimulus would be single or double. These tags consist of positive or negative going pulses (approximately 4 msec in duration) deposited in the middle of the calibration pulse, on three channels of the tape, forming a binary code (positive = +1, and negative = 0). The decoding of this information allowed the separate analysis of trials in a given experimental contingency. This coding system was used only in on-line monitoring and for editing of the tape. In the computer analyses, trials were coded by hand.

Stimuli. The auditory stimulus was a single click of 1 msec duration, obtained by a capacitor discharge, which was then amplified and attenuated (Hewlett-Packard attenuator, Model 350 D) to approxi-

mately 55 dB above threshold. In the double click condition, a single click was repeated after an inter-click interval of 950 msec. The clicks were delivered through a loudspeaker approximately 0.91 meters above the subject's head. The single and double clicks were randomly presented in a 50/50 paradigm.

The visual warning stimulus was a single flash of a glow-modulator tube, 5 msec in duration. The glow-modulator tube was approximately 0.91 meters in front of the subject at eye level.

EEG amplification. EEG data was amplified by a Cyber amplifier (Model J1). The amplifier bandpass was set between 0.02 and 100 Hz, with a rolloff of 6 dB per octave. These bandpass characteristics allowed for the examination of both the relatively slow as well as fast components. The amplifier gain was calibrated by inputting a sine wave of known voltage and adjusting the output to produce a gain of 10,000. This calibration procedure was repeated at regular intervals throughout the data collection period.

Calibration of the evoked potential. A pulse of known amplitude was placed on the tape at the start of each trial. This pulse had an amplitude of 30 μV when referred to electrode input and served as a calibration pulse to which the average evoked potential was compared, thus, obtaining an absolute measure of response amplitude in μVs. In addition, since the calibration pulse is on each trial and was averaged in the same way as the data, any time jitter or other problems in the averaging process would result in distortion of the square wave calibration pulse. The pulse, therefore, served also as an indication of the proper functioning of the averaging process.

Monitoring and storage of data. The EEG and calibration pulse were converted from analog voltages into frequency code via FM data converters, and deposited on magnetic tape for storage. The tape speed during recording was 1-7/8 inches per second.

The data collection and storage procedures were monitored at several points to check on proper functioning of the equipment. Data was monitored on a Tektronix Type 561 dual-beam oscilloscope as it came out of the amplifier. This allowed the waveform to be seen by the experimenter trial by trial and thus any bad trial could be noted for later deletion, and further assured that the input to the tape was correct. Data was also monitored on the oscilloscope as it came off the tape and entered the Computer of Average Transients (Mnemetron Model CAT 400A) allowing "on -line" summing of the data which was then printed out on a Mosely X-Y plotter (Model 135M) assuring proper storage of data on the tape.

Another very important monitoring device was a closed circuit television on which the subject was monitored at all times. Head and eye movements (e.g., lateral and blinks) occurring during a trial could be detected and the trial noted for later deletion.

General Procedure

Each subject participated in four sessions, with approximately two weeks between sessions. During the first two sessions (Period I) subjects in the hyperkinetic drug group were tested while being treated with methylphenidate. During this period each child was being treated with the dosage level of methylphenidate prescribed at the Children's Clinic as achieving maximum treatment effect for that child. Mean

dosage level was 33.75 mg/day. During their second two sessions (Period II) the children in this group were treated with placebo, (placebo sessions occurred a minimum of one week after the subject was taken off methylphenidate). Psychopharmacological studies provide evidence that methylphenidate is a short-acting drug which is out of the child's system within 24 hours, (Andreasen, 1973; Dring, Smith, & Williams, 1970). This fact in conjunction with results from evoked potential studies in which drug and testing order were counterbalanced (i.e., half of the hyperkinetic children receive placebo first and the other half receive drug first) and no order effects were found to exist (Buchsbaum & Wender, 1973; Halliday et al., 1974), led to the conclusion that our placebo sessions could follow the drug sessions without fear of contamination. This was an important consideration since the drug/placebo schedule of the hyperkinetic children was determined at the Children's Clinic, and at the time this population was sampled, it was possible to maximize the number of subjects in the drug group by running drug sessions first.

Further, due to the fact that only a limited number of hyperkinetic children were available from the Children's Clinic, and since interest was in studying differences between hyperkinetic children on methylphenidate and placebo, as well as differences between hyperkinetic and normal children, it was important that one group serve as a control for both sets of comparisons. The hyperkinetic control group which received placebo during all four sessions, served this purpose. In the first set of comparisons any change in response between drug and placebo sessions in the drug group could be compared to the amount of change between repeated placebo sessions in the con-

trol group, and group differences attributed to the effect of drug. In the second set of comparisons, the hyperkinetic control group was compared to the normal control group, who also received placebo in all sessions, and group differences could be attributed to hyperkinesis. The drug protocol for each group is given in Table 2.

In order to keep motivation and attention at a high level, and frustration at a low level, and to minimize differences between the groups in respect to learning the experimental paradigm it was decided to use a monetary reward ($0.05) for each correct guess, and no penalty for an incorrect guess. Children were reminded at the end of each short block how much money they won in that block, and how much their total winnings were to that point. Such a reinforcement paradigm was decided upon in light of evidence that the type of reinforcement used largely determined how well hyperkinetic children learn (e.g., Freibergs & Douglas, 1969). In comparing concept learning in hyperkinetic and "normal" children Freibergs and Douglas (1969) found significant differences between the groups under partial reinforcement, but no differences under continuous reinforcement. They hypothesized that in hyperkinetic children continuous reinforcement served to reinforce task orientation (i.e., attention) and as such, acted to counter the distractability and restlessness observed under partial reinforcement where greater time intervals separated successive reinforced responses. Freibergs and Douglas also noted that hyperkinetic children were extremely sensitive to the frustration of non-reinforcement in the partial reinforcement paradigm.

Session procedure. There were two stimulus contingencies in the certain condition (single and double) and four stimulus contingencies

Table 2

Drug Protocol for Each Subject Group in Each Experimental Session

	Period I		Period II	
Subject Group	Session 1	Session 2	Session 3	Session 4
Hyperkinetic Drug	Methylphenidate	Methylphenidate	Placebo	Placebo
Hyperkinetic Control	Placebo	Placebo	Placebo	Placebo
Normal Control	Placebo	Placebo	Placebo	Placebo

in the uncertain conditions (correct or incorrect for single and double). The probability in the uncertain conditions was 50/50, and thus in order to have approximately the same number of trials to be averaged in each of the six experimental contingencies, there had to be twice as many uncertain trials as there were certain trials. Another consideration in determining the number of trials in a session was that prior reports of evoked potential studies in hyperkinetic children used very short sessions, reporting that this was an important consideration (Conners, 1971; Buchsbaum et al., 1973). It was decided that a session would consist of 12 blocks of 20 trials in each. This was divided into four blocks of certain trials and eight blocks of uncertain trials. Random numbers generated by computer were used to assign "single" or "double" to a trial. Randomization was done across all certain blocks and separately across all uncertain blocks in a session. The blocks were ordered such that the first block was certain followed by two blocks of uncertain trials. This sequence was then repeated three more times. Between each of the first three blocks there were short rest periods (1.5 minutes) followed by a longer rest period (3 minutes) before the sequence began again. Halfway through the session, between the sixth and seventh block, the rest period was 5 minutes. During each rest period the child was told how much money he won in the preceding block. One session (interspersed with 11 rest periods) lasted approximately 60 minutes and yielded 240 trials.

The four sessions in which each subject participated were divided into two periods. Period I represented the average of first and second sessions and Period II represented the average of the third

and fourth sessions. Therefore, the averaged evoked response for each of the six experimental contingencies, for both Period I and Period II, were based on approximately 80 trials each.

Instructions. The following instructions were read to the subject before the start of each session:

> We're going to play a guessing game and you'll have a chance to win some money. What you have to do is guess whether you will hear one click (demonstrate), or two clicks (demonstrate). Every time you guess correctly you will win a nickel. See the red light flashing in front of you? Watch the light at all times; when it stops flashing that's your signal to make a guess. Look straight ahead, keep your head on the head rest, keep your eyes open, try not to move or blink, and press one of these two buttons. Press this one if you think you are going to hear one click, and this one if you think it is going to be two clicks. When the light starts flashing again, you can relax, move around and talk to me if you want; but when it stops flashing again, remember to sit as still as possible, keep your eyes open and try not to blink. It is really important that you don't move, so if you think you won't be able to sit still, don't press the button.
>
> During part of the time, I am going to tell you over the loudspeaker what you will hear and you press the right button. If I say it is going to be one click, which button do you press? (Wait for appropriate press). That's good. If I say it is going to be two clicks, which button do you press? (Wait for appropriate response). That's good. During other parts, you will guess. If you want to guess one click, which button do you press? (Wait for appropriate response). That's good. If you want to guess two clicks, which button do you press? (Wait for appropriate response). That's good. Remember when you are guessing, that there is no way to tell if it's going to be one or two clicks, all you can do is guess.
>
> Do you have any questions?

Trial Procedure

The subject was told in advance if a block of trials would be "certain" (in which the experimenter tells him during the inter-

trial interval what stimulus he will receive in the following trial) or "uncertain" (in which the subject has no advance information about the stimulus and must guess). In both cases, in order to minimize movement artifact (e.g., position change, eye blink) the subject himself initiated the experimental sequence. That is, when the red light stopped flashing the subject was given three seconds within which he could make his key press, if, and only if, he was prepared. If he was not ready, for any reason, he simply did not respond, and the experimenter restarted the experimental sequence by externally triggering the fixation light.

It has been shown that the development of the contingent negative variation (CNV) is not dependent upon a motor response (Donchin, Gerbrandt,& Leifer, 1970) and, therefore, in order to avoid the possible confounding effects of a motor potential developing between the key press and the stimulus (Deecke, Scheid,& Kornhuber, 1969; Gilden, Vaughan,& Costa, 1966) and to simplify the subject task further, it was decided not to require a motor response to stimulus occurrence. It must be noted, however, that the CNV amplitude has been found to be somewhat lessened without a motor response (Low et al., 1966; Walter, 1966).

The trial procedure is represented diagrammatically in Figure 3. When the subject pressed one of the choice keys he initiated the experimental sequence and a calibration and tag pulse were placed on the tape. Following a 0.5 second delay (allowing for motor artifact from the key press) the EEG was sampled for 4 seconds. One second after sampling began, a 0.005 second light flash signaled the subject that verification of his guess would follow. Approximately 1 second later

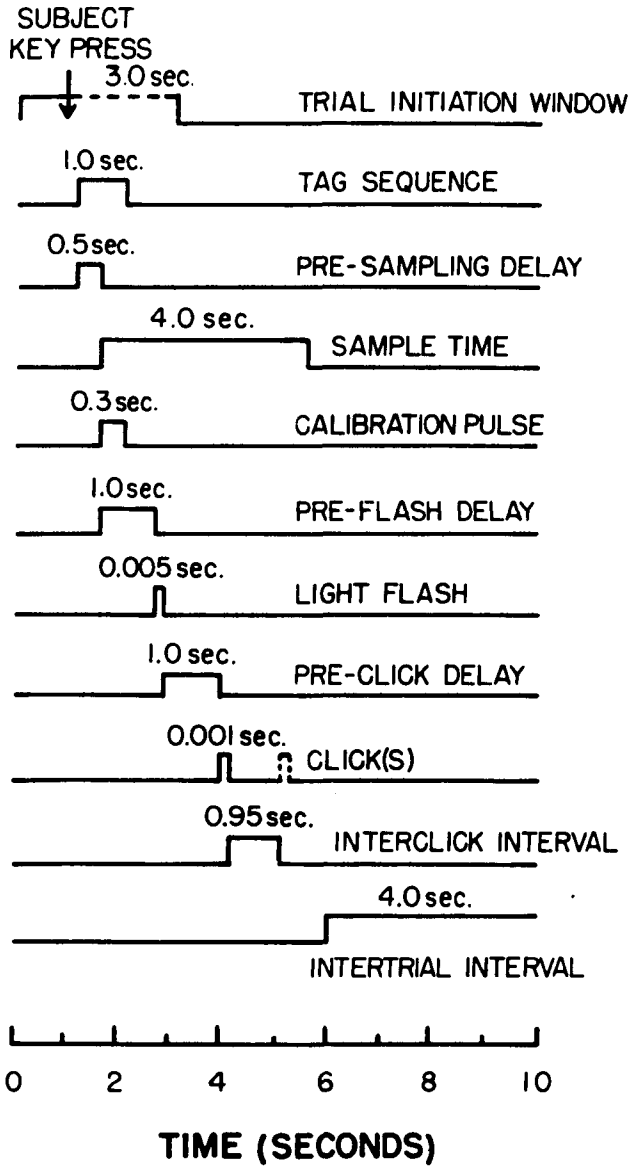

Figure 3. Representation of a trial sequence. Each trial was initiated by the subject's key press.

the first click occurred. This was followed by a 0.95 second inter-click interval after which the second click either did or did not occur. One second later sampling time ended and the red light began to flash again indicating to the subject that he could relax. There was a 4 second inter-trial interval before the next trial could be initiated.

Data Retrieval and Averaging

Analog to digital conversion. Data which was recorded and stored in analog form, on magnetic tape, had to be converted into digital form for computer analysis. For this purpose, the analog tapes were read from a tape deck (Honeywell, Model 3600) into a computer system (X.D.S. Sigma 7). To start the conversion process, the control channel of the analog tape was fed through a circuit designed to recognize the control envelope at the start of a trial. The recognition of this envelope triggered the sampling process which contined to sample at 10 msec intervals (real time). These samples were then taken from the data channel in the form of voltages and converted into digital numbers which were outputted on a digital tape. Four hundred samples were taken from each trial (two positions were used for time reference). The pulse from the recognition circuit and the analog data were monitored on a dual beam oscilloscope during this process. At the end of the digitalization process, the data output was in the form of a series of positive integers representing voltages.

Scaling of digital data. For each digitalized trial two points in the calibration pulse i and j were chosen to determine a scaling factor. Point i was chosen so that X_i (digitalized) corresponded to 0 μV and j so that X_j (digitalized) corresponded to -30 μV. All other

data points, X_k, were scaled proportionally to these two points, using the equation:

$$X_k \text{ (scaled)} = \frac{X_{k(\text{digitalized})} - X_{i \text{ (digitalized)}}}{X_{j(\text{digitalized})} - X_{i \text{ (digitalized)}}} \times -30.0 \ \mu V$$

Safety procedures were built into the program which tested for the presence of the calibration pulse in each trial and eliminated any trial in which a calibration pulse was absent. This assured that data and not noise had triggered the computer.

Coding of trials. Scaled trials were coded to indicate the experimental contingency for each trial. This code was then keypunched onto a card deck ordered in trial sequence. This deck was then reordered and repunched; grouping the trial numbers by experimental condition.

Data reduction. A series of programs computed the following statistics for the data of each point: mean, standard deviation, measures of change between points (explained more fully below). The output was then plotted separately for mean and standard deviation.

Identification and Measurement of the Response Components

Average evoked potential. Since sequential components may have different relationships to experimental variables (Wilkinson & Morlock, 1967; Morrell & Salamy, 1971), all components ($\overline{P100}$ through $\overline{N400}$) were measured relative to baseline rather than peak-to-peak. Baselines for the first and second click (whether present or absent) were established by averaging the 100 msec segment previous to the onset of each click. The amplitude of each component was then computed relative to the appropriate baseline. Components which were not in the appropri-

ate position relative to baseline, positive components which were above baseline, and negative components which were below baseline, were indicated with a negative sign. It should also be noted that the larger the number, the smaller the component. (Figure 4 exemplifies this point.)

As can be seen in the upper panel of Figure 4, $\overline{N100}$ is 5 units above baseline and, therefore, its amplitude relative to baseline is +5. $\overline{N250}$ is 4 units below baseline and, therefore, its amplitude relative to baseline is -4. In the bottom panel of Figure 4, $\overline{N100}$ is 2 units above baseline (+2) and $\overline{N250}$ is 1 unit below baseline (-1). Looking at both $\overline{N100}$ components (upper and lower panels) it is seen that the larger positive number (upper panel) is the larger component. On the other hand, considering both $\overline{N250}$ components (upper and lower panels), the smaller negative number (bottom panel) is the larger component.

In the most evoked potential work, components (peaks) are identified by eye, keeping in mind several criteria such as: average latency for the component, comparisons among experimental conditions -- particularly where the behavior of a particular component is known for some experimental condition, and distribrution of components on the scalp (Goff, Matsumiya, Allison, & Goff, 1969; Levit, 1972; Tueting, 1968). In some instances, however, if the curve is "noisy" and variability in latencies is high, identifying the component by eye becomes less than precise. In this study a method was developed for aiding in the identification of components and in separating a peak which is due to noise from a peak which is in fact a component of the evoked potential. It

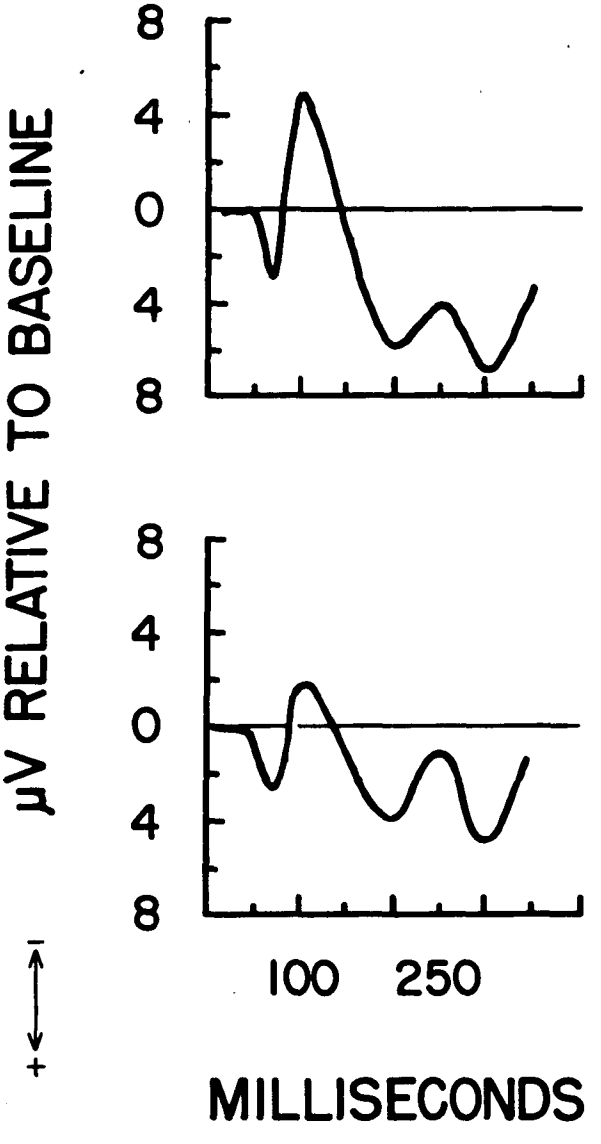

Figure 4. Schematic response illustrating the comparative magnitude of components measured relative to baseline. In both the upper and lower panels $\overline{N100}$ is in the expected position above baseline and therefore the larger component would be represented by a larger positive number. $\overline{N250}$, in both cases, is below baseline and therefore the larger component would be represented by a smaller negative number.

should be remembered that when one is averaging, a large voltage due to noise (such as can be produced by an unedited eye blink or other movement of the subject) will not "wash out" unless the number of trials in the average is very large. However, the experimenter is aided by the fact that such an artifact would have occurred by chance at the same point in time once or perhaps a few times. On the other hand, unless the time jitter (i.e., variability in latency) of the peak of components is large many individual trials would show a peak at the same point in time. We, therefore, took advantage of this difference in frequency between noise peaks and component peaks in discriminating the two.

The computer digitalization program sampled and transformed one point every 10 msec, thus a total of 400 points were sampled in the 4 second sampling time in each trial. In effect, we checked at each point in time, in what percentage of the trials a peak occurred. This was done using a subprogram which tested, for each trial, whether a criteria of change (0.2 μV) was met between every pair of successive points in time, and if so, the direction of change was noted. If X_i is smaller than X_{i+1} the curve was "rising," i.e., becoming more negative, and if X_i is larger than X_{i+1} the curve was "falling," i.e., becoming more positive. If the criterion for change was not met the curve was considered to be "flat" between the two points. This test was made for the same two points separately for each trial which enters the average curve. The percentage of time across all trials that there was a "rise," "fall," or "flat" between X_i and X_{i+1} was calculated and printed out for X_i. The difference between the rise and fall column is then taken. If the percentage of times a curve was rising was

larger than the number of times it was falling the difference would be positive and indicated that between the two points in time tested the curve was usually rising. If the difference had been negative it would have indicated that the curve was usually falling. A peak, therfore, can be identified in the difference column as a change from a relatively large negative number to a relatively large positive number (or vice versa).

Figure 5 shows a 450 msec segment of a response to the second click in the double right condition for one subject. All components can be easily identified by eye and will serve as a clear example of how the difference column substantiates the identification of a component. Table 3 gives the latency (from stimulus onset), mean amplitude, rise, flat, fall, and difference for each point in the 450 msec segment from Figure 5, as it appeared on the computer output.

Looking at the difference column starting at the point with a latency of 10 msec, it can be seen that the curve was falling, that is, between 10 and 20 msec the curve was falling more often than rising resulting in a negative number in the difference column. Negative numbers continue until 50 msec where there is a large positive number indicating that at 50 msec the curve changed from mostly falling to mostly rising, identifying this point as a positive peak. The numbers in the difference column then continue as positive numbers from 50 to 90 msec, but at 100 msec change to a large negative number. Thus, the curve which was rising between 90 and 100 msec began to fall between 100 and 110 msec, identifying the point with a latency of 100 msec as a negative peak. The next four change points, at latency 160, 210, 270 and 410 msec are also easily identified in this manner. Knowledge

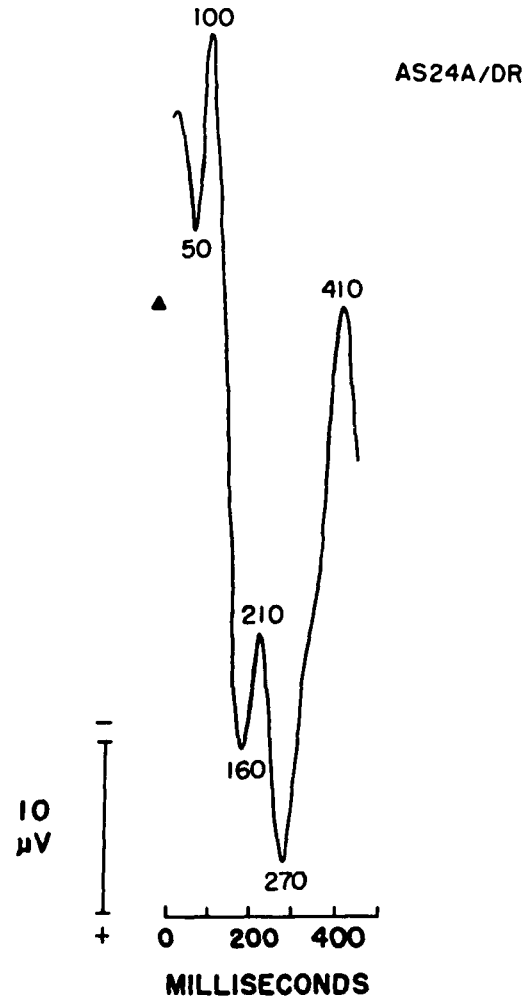

Figure 5. Averaged evoked potential of one subject in response to the second click in the double right condition. Latency, in msec from stimulus onset (▲), is given for each peak.

Table 3

Sample Computer Output Corresponding to the

Average Waveform Shown in Figure 5 for One Subject

AS 24A/DR

Latency (msec.)	Mean (μV)	Rise (%)	Flat (%)	Fall (%)	Difference (%)
10	20.77	44.55	1.98	53.47	- 8.91
20	19.39	48.51	0.99	50.50	- 1.98
30	19.12	39.60	0.99	59.41	- 19.80
40	17.31	40.59	0.00	59.41	- 18.81
50	13.46	55.45	0.99	43.56	11.88
60	14.23	51.49	0.99	47.52	3.96
70	16.26	56.44	0.99	42.57	13.86
80	19.32	69.31	0.00	30.69	38.61
90	25.00	57.50	0.00	42.50	15.00
100	25.17	31.68	0.99	67.33	- 35.64
110	19.51	22.77	1.98	75.25	- 52.48
120	11.90	25.74	1.98	72.28	- 46.53
130	3.50	26.73	0.00	73.27	- 46.53
140	- 4.49	34.65	0.00	65.35	- 30.69
150	-10.15	34.65	0.99	64.36	- 29.70
160	-14.44	50.50	0.00	49.50	0.99
170	-15.95	52.48	0.99	46.53	5.94
180	-15.11	62.38	1.98	35.64	26.73
190	-11.53	58.42	0.00	41.58	16.83
200	- 9.25	50.50	0.00	49.50	1.00
210	- 9.06	41.58	1.98	56.44	- 14.85
220	-10.26	41.58	0.00	58.42	- 16.83
230	-13.26	38.61	0.00	61.39	- 22.77
240	-16.92	35.64	1.98	62.38	- 26.73
250	-21.00	41.58	0.99	57.43	- 15.84
260	-22.25	49.50	0.00	50.50	- 0.99
270	-22.57	53.47	1.98	44.55	8.91
280	-22.31	58.42	0.00	41.58	16.83
290	-20.08	63.37	0.99	35.64	27.72
300	-16.50	62.38	0.99	36.63	25.74
310	-13.02	59.41	1.98	38.61	20.79
320	-11.29	58.42	0.00	41.58	16.83

(continued)

Table 3
(continued)

Sample Computer Output Corresponding to the

Average Waveform Shown in Figure 5 for One Subject

AS 24A/DR

Latency (msec.)	Mean (μV)	Rise (%)	Flat (%)	Fall (%)	Difference (%)
330	- 9.31	55.45	0.00	44.55	10.89
340	- 7.75	54.46	2.97	42.57	11.88
350	- 7.15	56.44	1.98	41.58	14.85
360	- 5.18	57.43	1.98	40.59	16.83
370	- 3.44	74.26	0.00	25.74	48.51
380	1.28	70.30	0.99	28.71	41.58
390	5.67	60.40	0.99	38.61	21.78
400	9.44	53.47	0.00	46.53	6.93
410	9.57	49.50	0.00	50.50	- 0.99
420	8.95	41.58	0.00	58.42	- 16.83
430	7.61	29.70	0.00	70.30	- 40.59
440	3.66	38.61	0.99	60.40	- 21.78
450	0.84	30.69	0.99	68.32	- 37.62
460	- 3.94	35.64	2.97	61.39	- 25.74

of the relation of the usual latencies to the various evoked potential components to clicks identifies their successive peaks as the components $\overline{P70}$, $\overline{N100}$, $\overline{P200}$, $\overline{N250}$, $\overline{P300}$, and $\overline{N400}$.

This waveform was so clear, with respect to the latencies and succession of components, that the above method of identifying peaks was unnecessary. In contrast, however, note Figure 6 in which it is not clear whether $\overline{P200}$ occurs at a latency of 160 or 210 msec, nor is it clear whether $\overline{N250}$ occurs at a latency of 290 or 320 msec. It is assumed here that in each case one of the extra peaks visible to the eye is noise and not an actual additional component, but it should be noted that this methodology would also be of help in deciding whether, in fact, an additional component is present.

Table 4 gives the latency, mean amplitude, rise, flat, fall and difference for each point in the 250 msec segment from Figure 6 as it appeared on the computer output. Looking at the difference column starting at the point with a latency of 140 msec, it can be seen that the curve is falling. That is, between 140 and 150 msec the curve was falling more often than rising, resulting in a negative number in the difference column. The curve continues to fall between 150 and 160 msec as is noted by the negative number in the difference column. Using the difference column it is seen that there is a large positive number at latency 160 msec, indicating that the curve which had been falling between 150 and 160 msec, is rising between 160 and 170 msec. Thus, it appears that the point at latency 160 msec may, in fact, be identified as a positive peak.

Returning to the difference column it is seen that positive numbers continued through 230 msec and thus with some assurance it may be

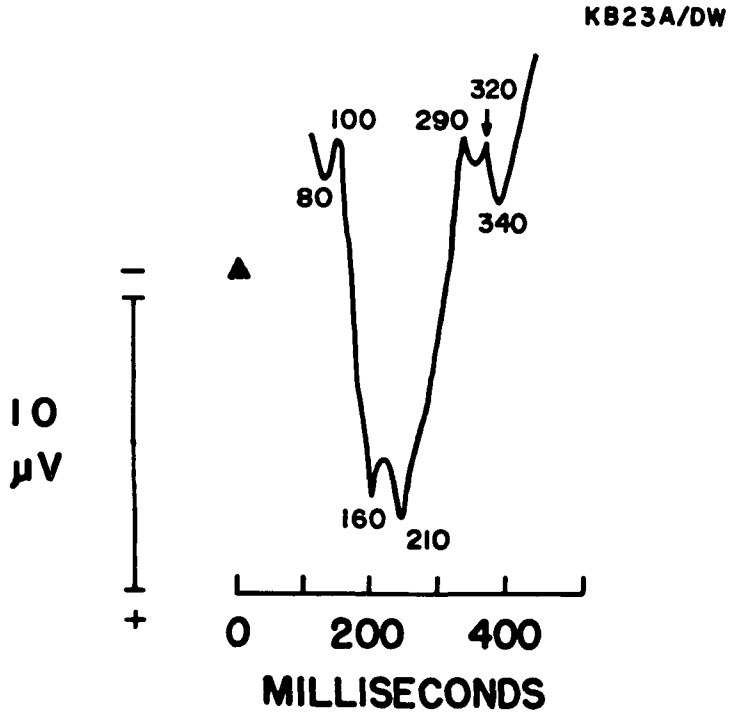

Figure 6. Averaged potential for one subject in response to the second click in the double wrong condition. Latency, in msec from stimulus onset (▲), is given for each peak.

Table 4

Sample Computer Output Corresponding to the Average Waveform Shown in Figure 6 for One Subject

KB 23A/DW

Latency (msec.)	Mean (μV)	Rise (%)	Flat (%)	Fall (%)	Difference (%)
140	- 2.06	37.31	0.00	62.69	- 25.37
150	- 4.48	40.30	0.00	59.70	- 19.40
160	- 6.38	55.22	1.49	43.28	11.94
170	- 5.02	50.79	0.00	49.25	1.49
180	- 5.07	50.75	0.00	49.25	1.49
190	- 5.30	56.72	0.00	43.28	13.43
200	- 5.72	52.24	0.00	47.76	4.48
210	- 6.88	53.73	0.00	46.27	7.46
220	- 5.35	52.24	1.49	46.27	5.97
230	- 4.38	44.78	0.00	55.22	- 10.45
240	- 3.68	56.72	0.00	43.28	13.43
250	- 2.33	58.21	0.00	41.79	16.42
260	- 0.50	49.25	0.00	50.75	- 1.50
270	1.19	62.69	0.00	37.31	25.37
280	3.42	61.19	1.49	37.31	23.88
290	5.88	49.25	0.00	50.75	- 1.49
300	4.98	49.25	0.00	50.75	- 1.49
310	5.45	48.25	1.00	50.75	- 2.49
320	5.97	47.76	1.49	50.75	- 2.99
330	4.71	46.27	1.49	52.24	- 5.97
340	3.78	49.25	2.99	47.76	1.49
350	4.34	56.72	0.00	43.28	13.43
360	6.08	55.22	0.00	44.78	10.45
370	7.31	55.22	1.49	43.28	11.94
380	9.39	64.18	0.00	35.82	28.36

assumed that the point at latency 210 msec was not a positive component. It is noted that had $\overline{P200}$ been identified by eye alone, the point at latency 210 msec which is the most positive going within the limits of the expected $\overline{P200}$ latency would have been incorrectly identified as $\overline{P200}$.

There is again uncertainty in identifying the $\overline{N250}$ component. Both the points at latency 290 and 320 msec would meet the criteria for a negative peak if it were to be identified by "eye." However, using the difference column it is seen that at 290 msec the difference column changes from a large positive number to a negative number, indicating that the curve which was rising began to fall at that point. No change in sign occurred at 320 msec. Thus, the point at 290 msec can be identified as the $\overline{N250}$ component. The curve was falling, and the difference scores remain negative, between 290 and 330 msec. The point at 340 msec can be identified as $\overline{P300}$ at which point the difference column becomes positive and the curve began to rise.

This method, while of great usefulness, was not infallible and, in fact, the final identification of components used several additional criteria. These were: (1) the usual latency for certain components as known from prior work, (2) the presence of a relatively clear peak at a given point in time in other average waveforms for the same subject, and (3) knowledge of the behavior of components as a function of experimental conditions, e.g., the well-established fact that $\overline{P300}$ becomes larger under uncertainty (Sutton et al., 1965; Sutton et al., 1967).

Contingent negative variation (CNV). Two CNVs were measured. The first was defined as the difference between baseline (the average of

the 100 msec period prior to the first auditory stimulus) and the average of the 100 msec period surrounding the most negative going point prior to the second auditory stimulus. The second was the resident CNV, defined as the difference between baseline (the average of the 100 msec period prior to the visual warning stimulus) and the average of the 100 msec period surrounding the most negative going point prior to the onset of the second auditory stimulus.

Emitted potentials. Two components of the emitted potential were measured: an early negative peak and a late positive peak. The negative component was identified as the most negative going peak following the point in time when the second auditory stimulus would have occurred. The positive component was identified as the most positive going peak following the point in time when the second auditory stimulus would have occurred.

Data Analysis

The $\overline{P70}$, $\overline{N100}$, $\overline{P200}$, $\overline{N250}$, $\overline{P300}$, and $\overline{N400}$ components of the evoked potential in response to the first and second click, and the CNV were identified for each experimental contingency and amplitudes were measured relative to baseline (according to the procedures described above). It is noted that for the absent second click only an early negative and late positive component and a CNV were identified. Each of these response components was analyzed separately and compared between groups under conditions of uncertainty, certainty, and certainty versus uncertainty. Statistical analyses were done in a series of 2 x 2 (group x condition) analyses of variance (with repeated measures). In two cases, where an analysis of variance was not appropriate, *t*

tests for significant differences between means were done (these cases are noted below).

Groups were compared in the following ways: (1) Hyperkinetic children who were receiving methylphenidate [H(D)] were compared with the hyperkinetic controls [H(C)] who received only placebo. These analyses tested the hypothesis that methylphenidate affected the evoked potential of hyperkinetic children. Period II amplitudes were subtracted from Period I and these difference scores were compared in analyses of variance (details of the ANOVARs are reported later). Any significant differences between difference scores in the two groups was taken to be a drug effect. However, statistically, difference scores do not completely remove "initial" level differences if they exist (initial here refers to placebo level). Therefore, before settling on difference scores to represent the drug effect, covariance analyses were done in several cases to see if difference scores were an appropriate measure. Using the amplitudes of responses in Period II (placebo) as the covariate, it was found that the slopes of the samples taken varied from 0.93 to 1.18. Being very close to 1.0, the covariance adjustment becomes almost identical to that made by taking the difference scores. More conclusively, no significant differences between the groups were found on the covariate (Period II i.e., placebo) and, therefore, difference scores can be used with no hesitation since this tells us that level effects do not, in fact, exist. In light of these findings and since it was considered easier to interpret the results of analyses based on difference scores, covariance techniques were not used in analyzing the results. The results to be reported herein are based on ANOVARs for difference scores. Additionally, in each case

the results of the ANOVARs for Period II alone are reported in order to reconfirm the findings of the samples reported above in which no differences existed between the groups when both were under placebo.

(2) The second set of group comparisons was between hyperkinetic controls [H(C)] and normal controls [N(C)]. These analyses tested the hypothesis that the evoked potentials of hyperkinetic and normal children were different. Before proceeding with these analyses, Period II amplitudes were subtracted from Period I and the difference scores were compared between groups so as to be assured that the hyperkinetic and normal children did not change in different ways over time (between Period I and Period II). This was done and no consistent differences were found, thus, Period I and Period II were collapsed and all further analyses were based on the average measures.

For both sets of group comparisons, conditions were compared according to the plan outlined below:

I. Hyperkinetic Drug versus Hyperkinetic Control

A. Uncertain condition comparisons:

1. First auditory stimulus -- response to a guess of single (average of the single right and double wrong contingencies) was compared with a guess of double (average of the single wrong and double right contingencies).

2. Second auditory stimulus -- right and wrong responses were compared (double right versus double wrong).

3. Absence of the second auditory stimulus -- emitted potentials for right and wrong responses were compared

(single right versus single wrong).

4. CNV (pre-stimulus response) -- a guess of single was compared with a guess of double.

B. Certain condition comparisons:

1. First auditory stimulus -- response to single certain was compared with the response to double certain.

2. Second auditory stimulus in the double certain condition. (t test)

3. Absence of the second auditory stimulus in the single certain condition. (t test)

4. CNV (pre-stimulus response) -- response to single certain was compared with double certain.

C. Certain versus uncertain condition comparisons:

1. First auditory stimulus:

a. Response to a guess of single was compared to single certain.

b. Response to a guess of double was compared to double certain.

2. Second auditory stimulus:

a. Response to double right was compared with double certain.

b. Response to double wrong was compared with double certain.

3. Absence of the second auditory stimulus:

a. Response to single right was compared with single certain.

b. Response to single wrong was compared with

single certain.

4. CNV (pre-stimulus response):

a. Response to a guess of single was compared with single certain.

b. Response to a guess of double was compared with double certain.

II. Hyperkinetic Control versus Normal Control

These analyses followed the same plan outlined above (for Section I above).

It should be noted that while comparisons between the hyperkinetic drug group and the normal control group were not appropriate for statistical analyses, inferences about the relationship between these two groups were made (based on the analyses outlined above) and are presented in the discussion.

Variability. Due to the fact that time locking of electrical events to a stimulus may, when poor, change the waveform, every analysis done for amplitude measures (as described above) was repeated using standard deviations. That is, all group x condition comparisons were made using the standard deviations for each peak in the same manner as had been done with amplitude. In addition, a baseline standard deviation for a 100 msec period prior to the presentation of the warning stimulus was computed for each condition for each child, and all group x condition comparisons were also made using this measure.

Latency. At the conclusion of this study it was learned that there had existed a systematic error (of approximately 5%) in the timers controlling the interval between the warning stimulus and the first click and the interval between the first and second click. Since it

could not be determined at what point the timers had drifted, latency data were not used for the purpose of group comparisons. Component latencies are reported as averages across all subjects in all experimental conditions over the course of the entire study. Although all timers were calibrated weekly on the oscilloscope in order to avoid such error, it was not learned until the conclusion of the study that the oscilloscope was out of calibration.

Chapter III

Results

This study was designed to investigate average evoked potential measures under various conditions of stimulation in hyperkinetic children treated with methylphenidate and placebo and in non-hyperkinetic normal children treated with placebo. A guessing paradigm was used in which there were single or double auditory clicks. Comparisons were made under conditions of uncertainty, certainty, and certainty versus uncertainty. The evoked potential measures studied were the amplitude and standard deviation of the P63, N103, P186, N250, P295 and N377 components[1] of the evoked response, and amplitude of the contingent negative variation.

The effects of methylphenidate were studied by comparing the hyperkinetic drug group, which received active drug in Period I and placebo in Period II, to the hyperkinetic control group, which received placebo in both Period I and Period II. As noted above, children in the hyperkinetic drug group were tested on active drug prior to placebo. A drug effect was defined as being any significant difference between the two groups in the amount of change from Period I to Period II (see Method Section). The use of the difference scores as a measure of the drug effect was confirmed by results of a series of analyses of covariance in which it was found that the covariance adjustment was almost identical to that made by taking difference scores (i.e., the

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[1]Component latencies are reported as averages computed across all subjects in all experimental conditions over all sessions (see Method Section).

regression coefficients were found to be very close to 1.0). More conclusively, since no significant differences were found between the groups when both were treated with placebo (Period II, i.e, the covariate), it could be assumed that no "initial" level differences (initial here refers to placebo level) existed and therefore, there was no reason to question the use of difference scores. In each of the analyses in which difference scores were used, Period II (placebo) was analyzed separately as a constant check for "level" differences.

The results of the analyses of variance for difference scores in the comparison of the hyperkinetic drug and control groups will be discussed in terms of: (1) group effects, i.e,, significant differences between the groups caused by drug, or more simply, significant drug effects, (2) condition effects, i.e., significant differences in the amount the response to different conditions change over time (from Period I to Period II), (3) Group x Condition interactions, i.e., significant drug effects dependent upon condition.

In order to study differences between hyperkinetic and normal children the evoked potential was compared in the hyperkinetic control group and non-hyperkinetic normal control group (both placebo treated). Since no differences between the groups were found in the amount of change in response across periods (in each analysis this was checked by using difference scores) responses averaged across periods were used in these analyses.

The results of the analyses of variance comparing the hyperkinetic control group and the non-hyperkinetic normal control group will be discussed in terms of: (1) group effects, i.e., significant differences between hyperkinetic children and non-hyperkinetic children,

(2) condition effects, i.e., significant differences between conditions regardless of whether hyperkinetic or non-hyperkinetic, (3) Group x Condition interactions, i.e., differences between hyperkinetic children and non-hyperkinetic normal children which are dependent upon condition.

The results presented below follow the outline described in the preceding section.

I. HYPERKINETIC DRUG [H(D)] versus HYPERKINETIC CONTROL [H(C)]

The results of the 2 x 2 (Group x Condition) analyses of variance reported below (Section I) are all based on the comparison of the hyperkinetic drug group and hyperkinetic control group. Comparisons were made under conditions of uncertainty, certainty and certainty versus uncertainty, and are reported separately for the first click, second click and absent second click.

A. Uncertain Condition Comparisons

1. First Click:

The hyperkinetic drug and hyperkinetic control groups were compared in the guess single and guess double conditions.

a. Group Effects (drug effects):

1.) In the response to the first **click**, considered across the guess single and guess double conditions, the amplitude of the P186 and P295 components were significantly smaller under drug than under placebo (P186, $p < .01$; P295, $p < .05$), whereas the amplitude of the N103 component was significantly larger under drug than under placebo ($p < .025$).

Figures 7, 8, 12, and 13 show the average amplitudes (in μV relative to baseline) for all components in the

various experimental contingencies. The hyperkinetic drug group, shown in the upper panels of these figures received methylphenidate in Period I (solid line) and placebo in Period II (dotted line). The hyperkinetic control group, shown in the middle panels, received placebo in both periods. Likewise, the non-hyperkinetic normal control group, shown in the lower panels, received placebo in both periods.

It can be seen in the upper panels of Figure 7 that the evoked potential under drug (solid line) is in fact different from that under placebo (dotted line). It appears that drug introduces and underlying "negativity" seen as a shifting upward of the curve, effecting all components (although only significant in P186, P295, and N103), thus decreasing the amplitude of positive components and increasing the amplitude of negative components. The two placebo curves for the H(C) group appear almost superimposable reflecting little consistent change.

2.) When both the hyperkinetic drug and hyperkinetic control groups were under placebo (Period II) there were no significant group differences, justifying our use of difference scores as a measure of the drug effect.

b. Condition Effects:

When both the hyperkinetic drug and hyperkinetic control groups were treated with placebo (Period II) there were significant differences between the guess single and guess double conditions seen in the P186 and N377 compon-

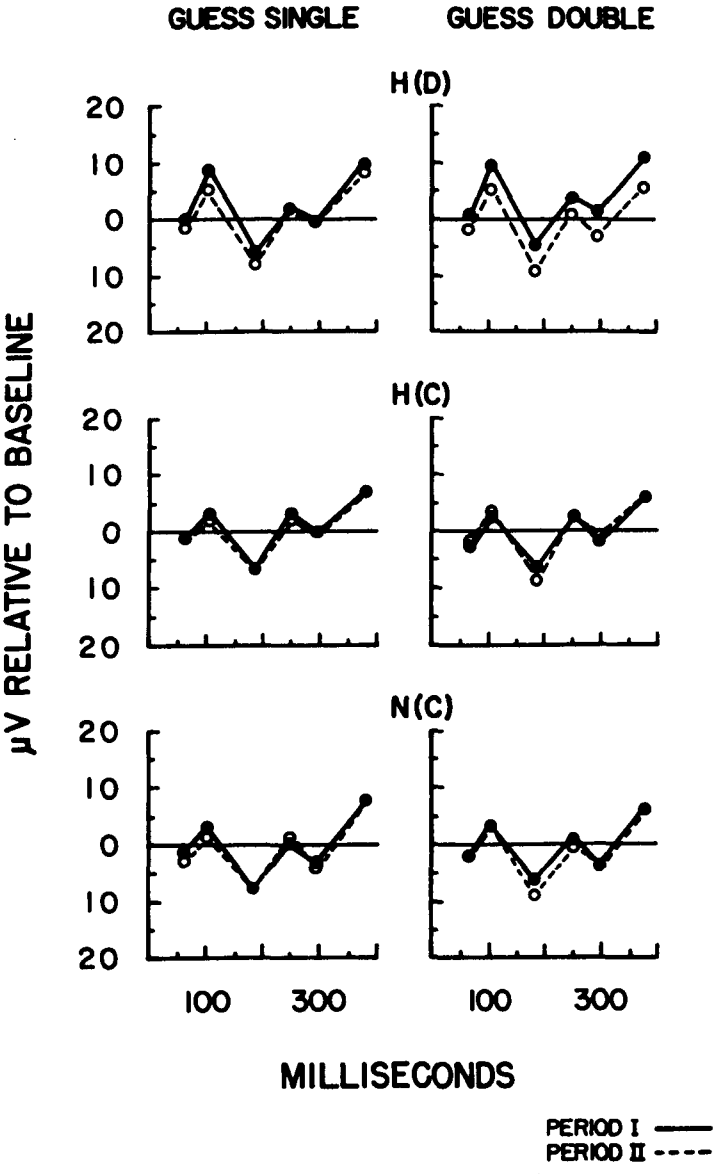

Figure 7. Response to the first click in the guess single (left panels) and guess double (right panels) conditions. Comparisons shown are between mean amplitudes (in μVs relative to baseline) for each component in Period I (solid line) and Period II (dotted line). The hyperkinetic drug group [H(D)], shown in the upper panels, received methylphenidate in Period I and placebo in Period II. The hyperkinetic control group [H(C)], shown in the middle panels, and the non-hyperkinetic normal control group [N(C)], shown in the lower panels, received placebo in both periods.

ents. The amplitude of P186 was significantly smaller in the guess single condition than in the guess double condition ($p < .01$). This effect was reversed for N377 in which the amplitude was significantly larger in the guess single condition than in the guess double condition ($p < .05$).

c. Group x Condition Interactions:

A significant Group x Condition interaction is present for difference scores (Period I minus Period II) in the P63 component ($p < .05$). The difference between the hyperkinetic drug [H(D)] and hyperkinetic control [H(C)] groups in the amount of change in amplitude across periods (i.e., drug effect) is larger in the guess double condition than in the guess single condition. The difference scores (in μVs) for the P63 component are given immediately below:

Group	Condition	
	Guess Single	Guess Double
H(D)	-1.46	-2.42
H(C)	-0.69	0.93

2. Second Click:

The hyperkinetic drug and hyperkinetic control groups were compared in the double right and double wrong conditions (i.e., right and wrong guesses).

a. Group Effects (drug effects):

1.) In the response to the second click, considered across the double right and double wrong conditions, the amplitude of the P186 component was significantly larger

under drug than under placebo ($p < .01$), whereas the amplitude of the N250 component was significantly smaller under drug than under placebo ($p < .01$).

It can be seen in the upper panels of Figure 8 that the evoked potential under drug (solid line) is in fact different from that under placebo (dotted line). It appears that in the response to the second click, drug produces a "positive" shift -- particularly in the later components P186 to N377. Thus, positive components increase in amplitude and negative components decrease. This is in contrast with the response to the first click in which drug appeared to produce a "negative" shift of the curve. The curves for the H(C) group show no large or consistent differences.

In Figures 9, 10 and 11 the evoked potentials in response to the second click in the double right condition are shown for Period I (solid line) and Period II (dotted line). Waveforms for both periods are superimposed and shown individually for each subject in the hyperkinetic drug group (Figure 9), hyperkinetic control group (Figure 10), and non-hyperkinetic normal control group (Figure 11). In Figure 9 it can be seen that drug (solid line) caused increased positivity in the late components of the evoked responses in 7 out of the 8 hyperkinetic children. By comparison it is seen in Figure 10 that the children in the hyperkinetic control group show no consistent relationship between Period I and

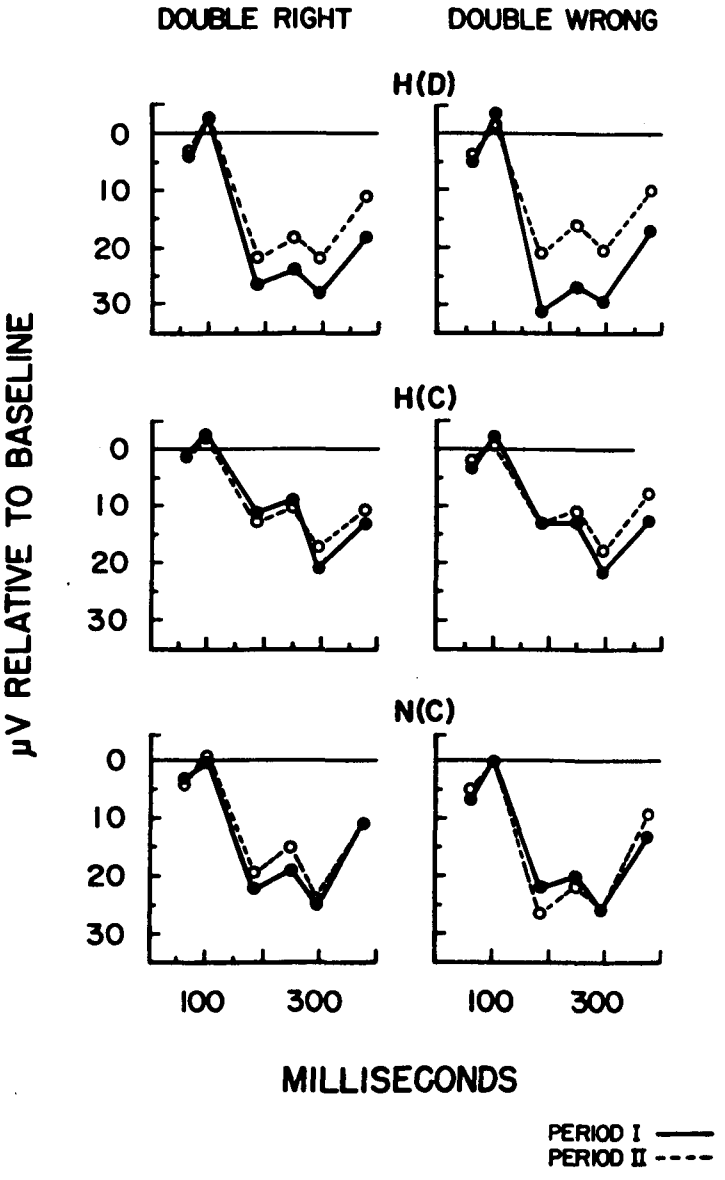

Figure 8. Response to the second click in the double right (left panels) and double wrong (right panels) conditions. Comparisons shown are between mean amplitudes (in μVs relative to baseline) for each component in Period I (solid line) and Period II (dotted line). The hyperkinetic drug group [H(D)], shown in the upper panels, received methylphenidate in Period I and placebo in Period II. The hyperkinetic control group [H(C)], shown in the middle panels, and the non-hyperkinetic normal control group [N(C)], shown in the lower panels, received placebo in both periods.

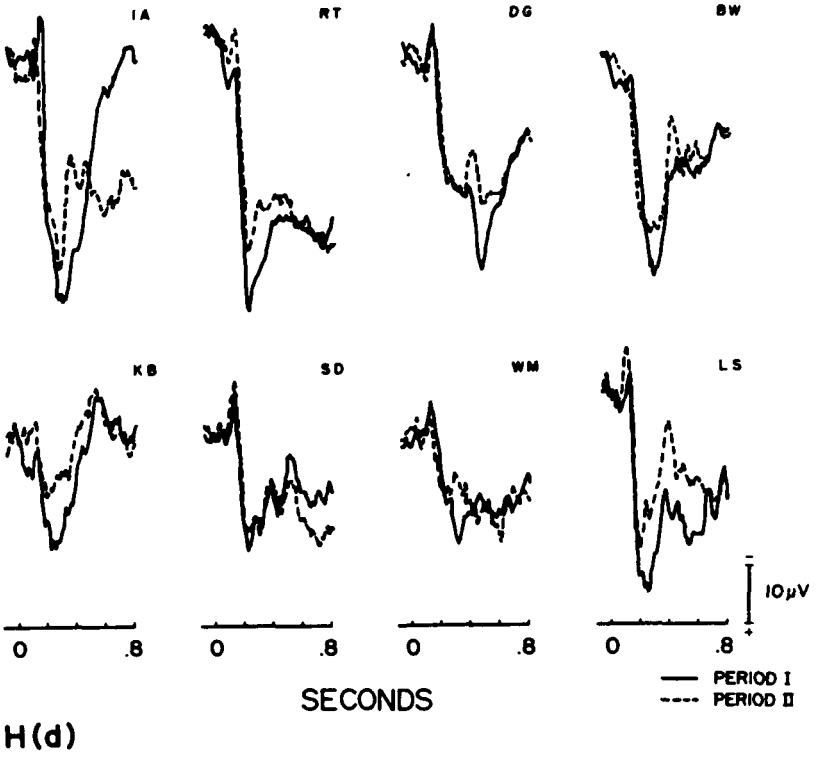

Figure 9. Comparison between the evoked potential under methylphenidate (Period I) and placebo (Period II), in response to the second click in the double right condition. Waveforms for both periods are superimposed and shown individually for each subject in the hyperkinetic drug group [H(D)].

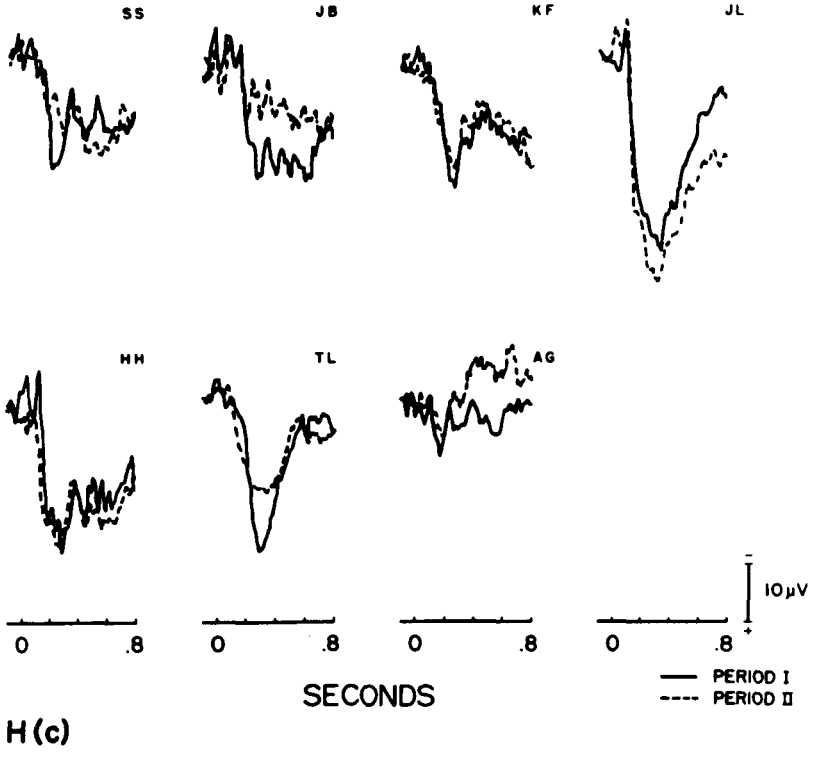

Figure 10. Comparison between the evoked potential in Period I (solid line) and Period II (dotted line), in response to the second click in the double right condition. Waveforms for both periods are superimposed and shown individually for each subject in the hyperkinetic control group [H(C)].

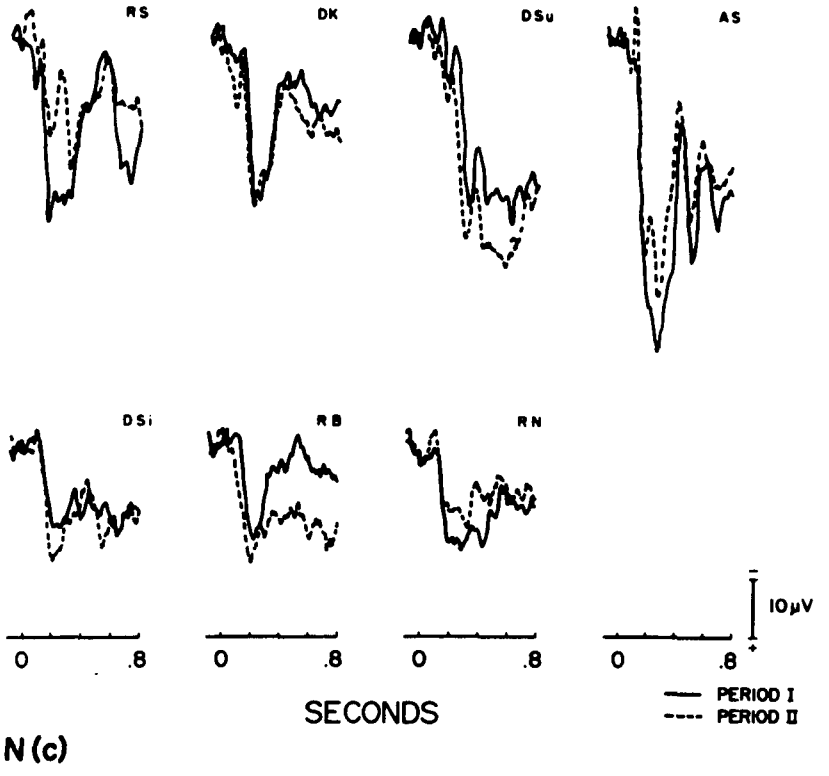

Figure 11. Comparison between the evoked potential in Period I (solid line) and Period II (dotted line), in response to the second click in the double right condition. Waveforms for both periods are superimposed and shown individually for each subject in the non-hyperkinetic normal control group [N(C)].

Period II responses (three show no change between periods, one shows more negativity in Period I and three show more positivity in Period I). This is also true of the non-hyperkinetic normal controls seen in Figure 11, who show no consistent relationship between Period I and Period II responses.

2.) When the hyperkinetic drug and hyperkinetic control groups were on placebo (Period II) there were no significant differences between them; again justifying our use of difference scores as a measure of the drug effect.

b. Condition Effects:

Considering both the hyperkinetic drug and hyperkinetic control groups together, the P186 component showed significantly more decrease in amplitude across periods in the double wrong than in the double right condition ($p < .05$).

3. Absent Second Click - Emitted Potentials:

The hyperkinetic drug and hyperkinetic control group were compared in the single right and single wrong condition (i.e., right and wrong guesses).

There were no significant drug effects found in the emitted potential.

B. Certain Condition Comparisons

1. First Click:

The hyperkinetic drug and hyperkinetic control groups were compared in the single and double certain conditions.

a. Group Effects:

There were no significant differences found between the hyperkinetic drug and hyperkinetic control groups in the response to the first click in the certain conditions. However, Figure 12 shows that, just as in the uncertain conditions, the drug tends to introduce a negative shift in the curve, such that positive components are smaller and negative components are larger.

b. Group x Condition Interactions:

A significant Group x Condition interaction was found in the P63 component ($p < .05$). In the hyperkinetic drug group [H(D)] there is a larger decrease in amplitude (Period I minus Period II) in the single certain condition as compared to the hyperkinetic control group [H(C)] where there is a larger decrease in amplitude in the double certain condition than in the single certain condition. The difference scores (in μVs) for the P63 component are given immediately below:

Group	Condition	
	Single Certain	Double Certain
H(D)	-4.23	-0.46
H(C)	-0.16	-2.22

2. Second Click:

The hyperkinetic drug and hyperkinetic control groups were compared in the single certain and double certain conditions.

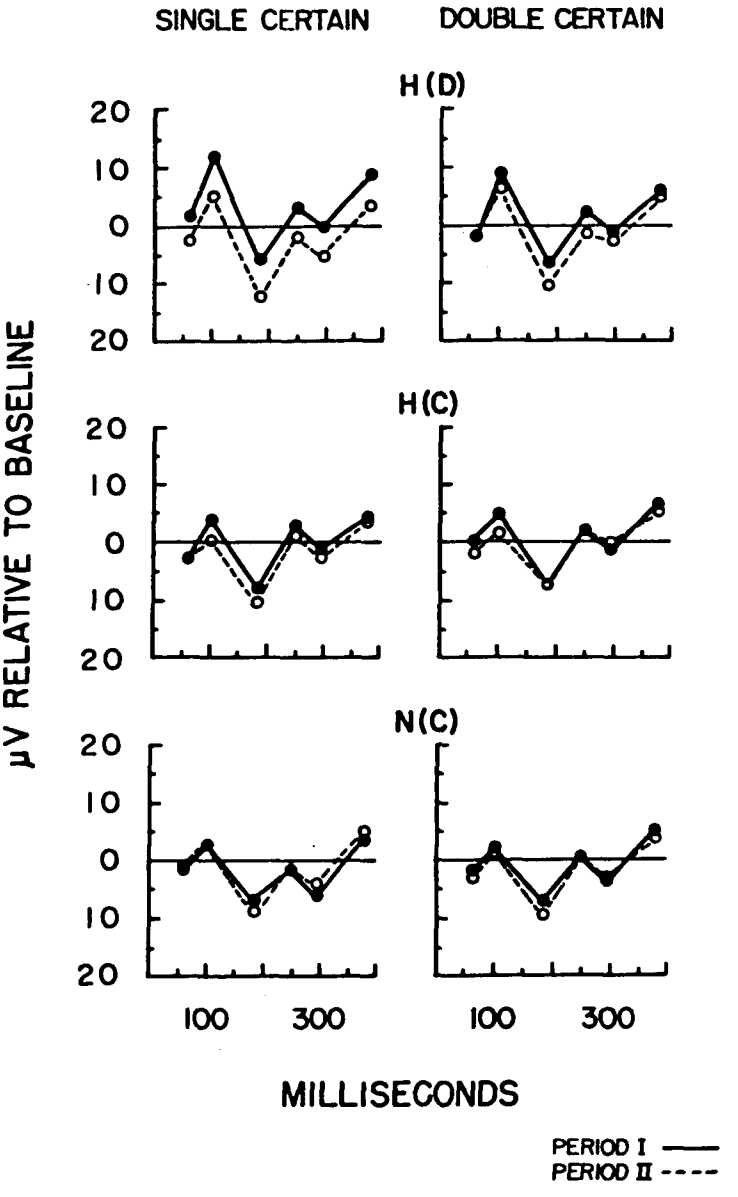

Figure 12. Response to the first click in the single certain (left panels) and double certain (right panels) conditions. Comparisons shown are between mean amplitudes (in μV relative to baseline) for each component in Period I (solid line) and Period II (dotted line). The hyperkinetic drug group [H(D)], shown in the upper panels, received methylphenidate in Period I and placebo in Period II. The hyperkinetic control group [H(C)], shown in the middle panels, and the non-hyperkinetic normal control group [N(C)], shown in the lower panels, received placebo in both periods.

Group differences in the response to the second click for the certain conditions were tested by t tests separately for single certain (emitted potential) and double certain. As in the case of the first stimulus there were no significant differences between the hyperkinetic drug [H(D)] and hyperkinetic control [H(C)] groups in the response to the second stimulus in the certain conditions. However, in Figure 13 it should be noted that, in the double certain condition as in the uncertain condition, the drug tended to produce a positive shift for the later components.

C. Certain versus Uncertain Condition Comparisons

In order to investigate whether the difference between the response to "certainty" and "uncertainty" was larger in the drug condition than in the placebo condition, a series of analyses of variance were performed. The main focus in these analyses was in the first order interaction. However, group and condition effects are also obtained and are presented.

1. First Click:

The hyperkinetic drug and hyperkinetic control groups were compared under conditions of certainty and uncertainty (for both right and wrong guesses), i.e., guess single versus single certain and guess double versus double certain.

a. Condition Effects:

For the first click, when both the hyperkinetic drug [H(D)] and hyperkinetic control [H(C)] groups were treated with placebo (Period II), there was a difference in the response to conditions of certainty as compared to uncertainty. In all the positive components the response

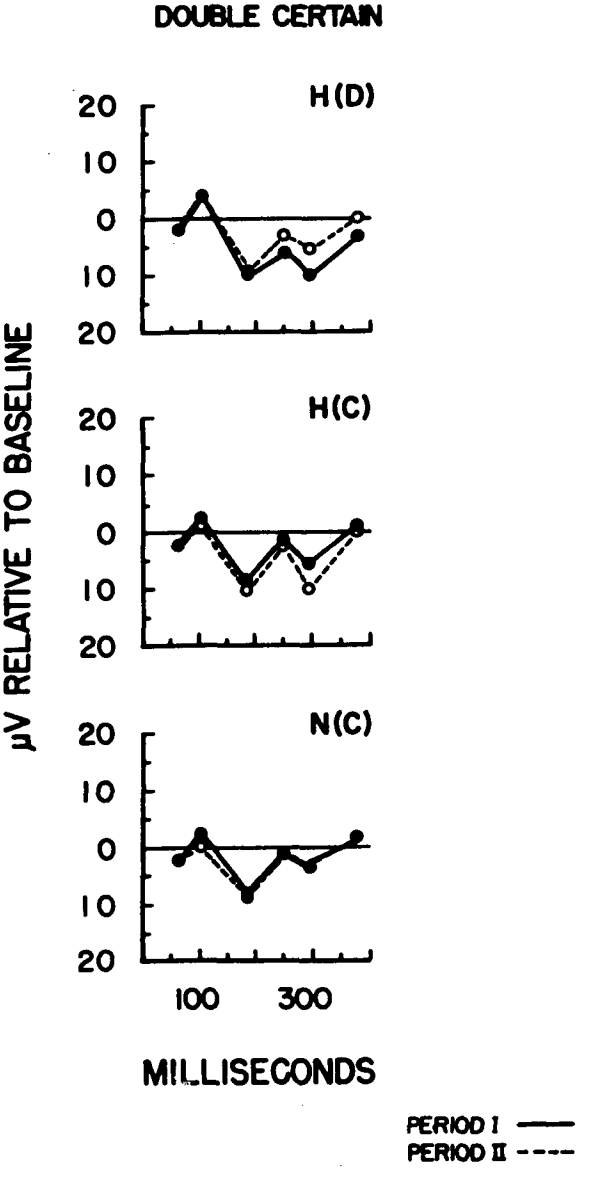

Figure 13. Response to the second click in the double certain condition. Comparisons shown are between mean amplitudes (in μV relative to baseline) for each component in Period I (solid line) and Period II (dotted line). The hyperkinetic drug group [H(D)], shown in the upper panel, received methylphenidate in Period I and placebo in Period II. The hyperkinetic control group [H(C)], shown in the middle panel, and the non-hyperkinetic normal control group [N(C)], shown in the lower panel, received placebo in both periods.

to the certain condition was larger than uncertain, although only significant for the P186 ($p < .01$) and P295 ($p < .025$) components. However, this was reversed in the negative components where the response to uncertainty was larger than to certainty, although only significant in the N377 component ($p < .05$).

The findings for the guess double/double certain comparison are not consistent with the above and none of the differences were significant.

The mean amplitudes (in μVs relative to baseline) for the components in which significant differences were found are given immediately below:

Component	Group	Condition			
		Guess Single	Single Certain	Guess Double	Double Certain
P186	H(D)	8.02	12.46	9.18	10.54
	H(C)	6.78	10.69	8.65	7.60
P295	H(D)	0.74	5.40	3.34	2.76
	H(C)	0.35	0.84	0.85	0.40
N377	H(D)	8.34	3.44	5.39	4.98
	H(C)	6.58	3.49	6.16	5.08

b. Group x Condition Interactions:

A significant Group x Condition interaction existed in the guess double versus double certain comparison for difference scores (Period I minus Period II), in the P63 component ($p < .025$). In the hyperkinetic drug group [H(D)] there is a larger decrease in amplitude (Period I minus Period II) in the guess double condition than in the double certain condition, as compared to the

hyperkinetic control group [H(C)] where there is a decrease in amplitude in the double certain and an increase in amplitude in the guess double condition. The difference scores (in μVs) for P63 are given below:

Group	Condition	
	Guess Double	Double Certain
H(D)	-2.29	-0.46
H(C)	1.16	-2.22

2. Second Click:

The hyperkinetic drug and hyperkinetic control groups were compared under conditions of certainty and uncertainty (for both right and wrong guesses), i.e., double right versus double certain and double wrong versus double certain.

a. Group Effects:

1.) Double Right versus Double Certain comparison:

Considering the double right and double certain conditions together the amplitude of P186 and P295 were larger under drug than under placebo (although only significant for the P186 component, $p < .025$) and the amplitude of N250 ($p < .025$) and N377 ($p < .05$) were significantly smaller under drug than under placebo. This appears to be the same positive shift brought about by drug described above when the uncertain and certain conditions were analyzed separately.

Difference scores (in μVs) for the P186, N250, P295 and N377 components are given immediately below:

Component	Group	Condition		
		Double Right	Double Certain	Double Wrong
P186	H(D)	4.65	0.72	10.19
	H(C)	-1.65	-2.07	0.05
N250	H(D)	-5.78	-3.02	-10.91
	H(C)	1.60	1.49	- 1.96
P295	H(D)	5.79	2.39	9.17
	H(C)	3.74	-3.91	3.51
N377	H(D)	-7.18	-3.50	- 7.18
	H(C)	-2.47	2.16	- 4.62

2). Double Wrong versus Double Certain comparisons: Considering the double wrong and double certain conditions together, similar group effects to those reported above in the double right versus double certain comparison were observed in the P186, N250, P295 and N377 components, however, the differences were only significant in the P186 and N250 components ($p < .025$). That is, P186 was found to be significantly larger and N250 significantly smaller under drug than under placebo.

3). There were no significant differences between the hyperkinetic drug and hyperkinetic control groups when both were treated with placebo (Period II) for either the double right versus double certain or double wrong versus double certain comparisons, justifying our use of difference scores as an indication of the drug effect.

b. Condition Effects:

1). When both the hyperkinetic drug and hyperkinetic control groups were treated with placebo (Period II) the amplitude of the positive components in the uncertain

conditions (in both the double right versus double certain and double wrong versus double certain comparisons) appear to be larger than those in the certain condition, these differences were found to be significant in the P186 and P295 components ($p < .01$). The amplitude of the negative components in the uncertain conditions (both right and wrong) appears to be smaller than those in the certain condition; these differences were found to be significant in the N250 and N377 components ($p < .01$).

The above findings of condition differences must be considered in view of the fact that the standard deviations for these components were significantly different for the certain and uncertain conditions. That is variability was found to be significantly larger in conditions of certainty than in conditions of uncertainty. In addition, these differences in variability were present at baseline, where no evoked potential components are present.

2). Differences in response to certainty and uncertainty were also found for both measures of the CNV. That is, during Period II, when both the hyperkinetic drug and hyperkinetic control groups were treated with placebo, the CNV was found to be significantly larger under conditions of uncertainty (guess single and guess double) than conditions of certainty (although only significant for the resident CNV in the guess double comparison, $p < .05$).

c. Group x Condition Interactions:

1.) A significant Group x Condition interaction existed for the double wrong versus double certain comparison in the P186 component ($p < .05$). It appears that the drug causes a larger increase in amplitude of P186 in the drug group relative to the control group for the uncertain (double wrong) than for the certain conditions. That is, the effect of drug in increasing the amplitude of the P186 component is significantly greater under conditions of uncertainty than certainty.

Figure 14 shows the amount of change between Period I and Period II for the double right versus double certain (left panel) and double wrong versus double certain (right panel) comparisons for the P186 component. It is noted that, while the significant interaction existed only for the double wrong versus double certain comparison, the double right versus double certain comparison shows a similar trend. Similar trends were also observed in the N250, P295, and N377 components.

2.) A Group x Condition interaction was also found for the P186 component in the double wrong versus double certain comparison for the placebo condition (Period II) when analyzed separately. That this occurs in the placebo condition suggests a residual effect of drug carrying over from Period I (drug). However, while the difference between the groups is larger in the uncertain condition

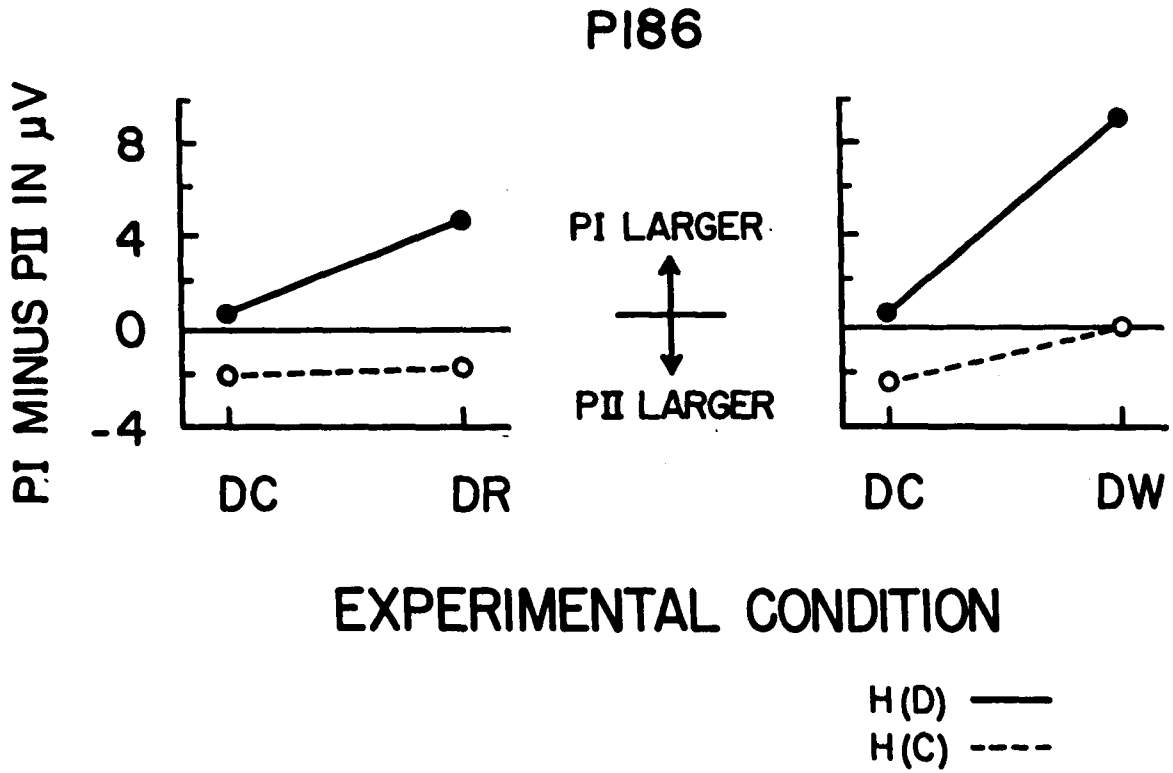

Figure 14. P186 component of the response to the second click. Mean change in amplitude (in μVs) of P186 from Period to Period II as a function of certainty [double certain (DC)] and uncertainty [double right (DR) in the left panel and double wrong (DW) in the right panel] for the hyperkinetic drug group [H(D), solid line] and hyperkinetic control group [H(C), dotted line]. It is noted that when P186 was larger in Period I than in Period II the difference appeared as a positive number, if it was larger in Period II the difference appeared as a negative number.

for both Period I and Period II, the magnitude of the difference is much greater in Period I (drug) than Period II (placebo).

3. Absent Second Click - Emitted Potentials:

The hyperkinetic drug and hyperkinetic control groups were compared in conditions of certainty and uncertainty (for both right and wrong guesses), i.e., single right versus single certain and single wrong versus single certain.

a. Group Effects:

There were no significant differences between the hyperkinetic drug and hyperkinetic control groups in the emitted potential. That is, it appears that drug did not make any significant difference in how hyperkinetic children respond to an absent stimulus, considering certain and uncertain (both right and wrong) conditions together.

b. Condition Effects:

When both the hyperkinetic drug and hyperkinetic control groups were treated with placebo (Period II) the amplitude of the late positive component in the emitted potential was significantly larger in the uncertain conditions (whether right or wrong) than in the certain condition ($p < .01$). The amplitude of the early negative component of the emitted potential, while not significant, tended to be larger in the certain than in the uncertain condition.

Thus, the effect of uncertainty in increasing the amplitude of the late positive components and decreasing the amplitude of negative components which was observed above in the response to the presence of the second click, was similarly noted here in the response to the absence of the second click.

II. HYPERKINETIC CONTROL [H(C)] versus NON-HYPERKINETIC NORMAL CONTROL [N(C)]

The results of the 2 x 2 (Group x Condition) analyses of variance reported below (Section II) are all based on the comparison of the hyperkinetic control group and the non-hyperkinetic normal control group. Comparisons were made in conditions of uncertainty, certainty, and certainty versus uncertainty, and are reported separately for the first click, second click and absent second click.

A. Uncertain Condition Comparisons

1. First Click:

The hyperkinetic control group and the non-hyperkinetic normal control group were compared in the guess single and guess double conditions.

There were no significant differences found between the hyperkinetic controls and the non-hyperkinetic normal controls in the response to the first click in conditions of uncertainty. Further, there were no significant differences between the response to a guess of single or double, considering the hyperkinetic controls and non-hyperkinetic normal controls together.

2. Second Click:

The hyperkinetic control group and the non-hyperkinetic normal control group were compared in the double right and double wrong conditions.

In the response to the second click, considered across the right and wrong conditions, the amplitude of the P186 component was significantly larger and the amplitude of the N250 component was significantly smaller in the non-hyperkinetic normal children than in the hyperkinetic children ($p < .025$).

Much like the difference between hyperkinetic children under drug in comparison with hyperkinetic children under placebo, it can be seen in Figure 15 that the non-hyperkinetic normal children (solid line) show more "positivity" in their curves than do the hyperkinetic control children (dotted line). That is, in the non-hyperkinetic normal children positive components are larger and negative components are smaller than those of the hyperkinetic control children (although only significant in the P186 and N250 components).

3. Absent Second Click - Emitted Potential:

The hyperkinetic control group and the non-hyperkinetic normal control group were compared in the single right and single wrong conditions (i.e., right and wrong guesses).

There were found to be no significant differences between the hyperkinetic controls and the non-hyperkinetic normal controls in the emitted response to the absent second click. Further, there were no significant differences between the emitted response to right or wrong guesses, considering the hyperkinetic controls and the non-hyperkinetic normal controls together.

B. Certain Condition Comparisons

1. First Click:

The hyperkinetic control group and the non-hyperkinetic normal control group were compared in the single certain and double certain conditions.

There were no significant differences found between the hyperkinetic controls and the non-hyperkinetic normal controls

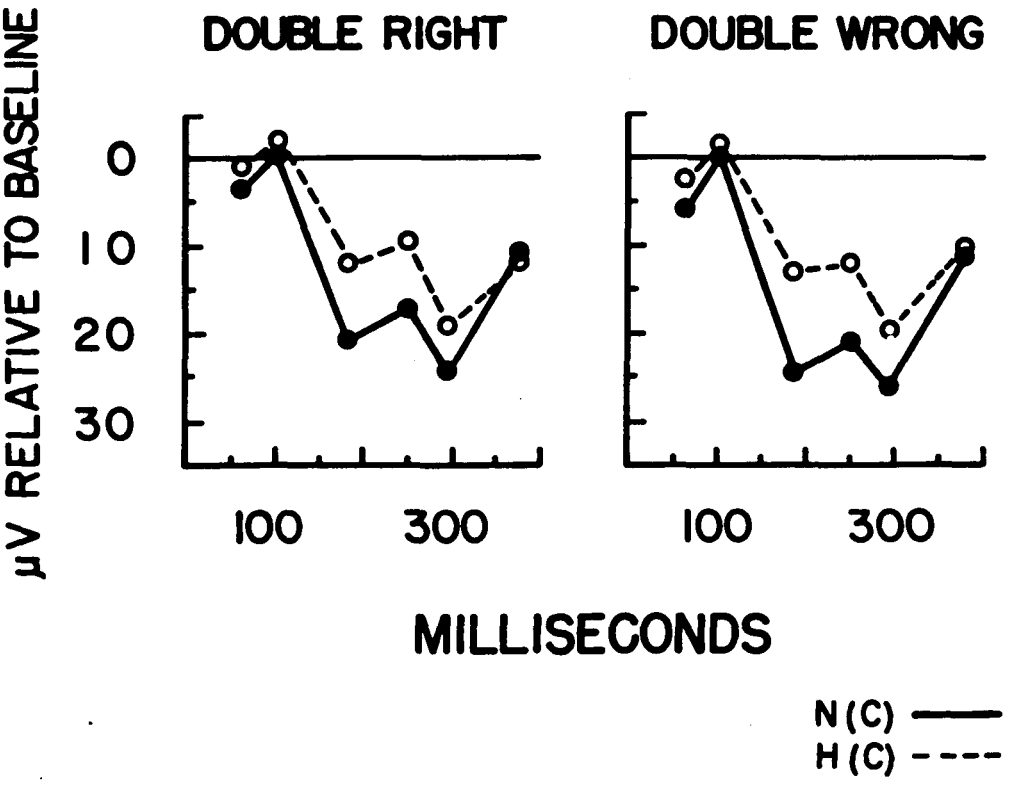

Figure 15. Response to the second click in the double right (left panel) and double wrong (right panel) conditions. Mean amplitudes (in μV relative to baseline) for each component are compared between the hyperkinetic control group [H(C), dotted line] and the non-hyperkinetic normal control group [N(C), solid line].

in the response to the first click in the certain conditions. Further, there were no significant differences between conditions, considering the hyperkinetic group and non-hyperkinetic normal group together.

Somewhat unclear is the finding of significant Group x Condition interactions in the certain conditions for the P63 and N103 components. While the differencesbetween means are small, the non-hyperkinetic normal children have a smaller P63 than the hyperkinetic children in the single certain condition, and larger than the hyperkinetic children in the double certain condition. For the N103 component, there is no difference between groups in the single certain condition, while the hyperkinetic children have a larger N103 than the non-hyperkinetic normal children in the double certain condition.

2. Second Click:

The hyperkinetic control group and the non-hyperkinetic normal control group were compared in the single certain and double certain conditions.

As in the comparisons between the hyperkinetic children under drug and hyperkinetic children under placebo, differences between the hyperkinetic controls and non-hyperkinetic normal controls in the response to the second click for the certain conditions were tested by _t_ tests separately for the single certain (emitted potential) and double certain conditions.

As can be seen in Figure 16 the relationship between the curves of the non-hyperkinetic normal and hyperkinetic children in the response to the double certain condition was oppo-

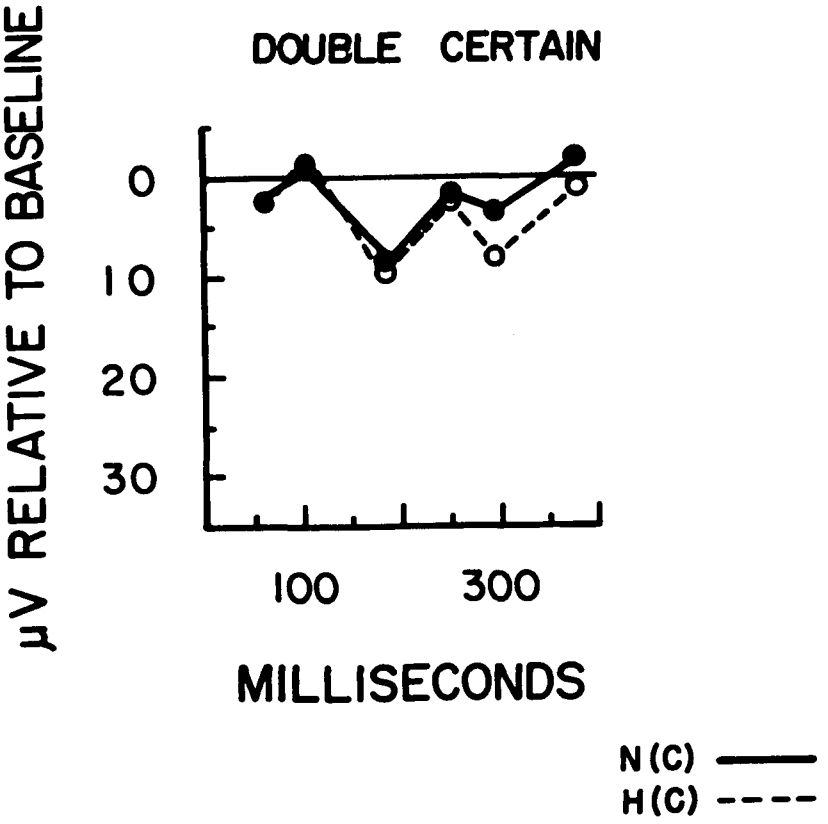

Figure 16. Response to the second click in the double certain condition. Comparisons shown are between mean amplitudes (in μV relative to baseline) for each component in the hyperkinetic control group [H(C), dotted line] and the non-hyperkinetic normal control group [N(C), solid line].

site to that seen in the uncertain condition comparisons (see Figure 15). That is, in the later components the curve of the non-hyperkinetic normal children is more negative than that of the hyperkinetic children (although only significant for the P295 component, $p < .05$).

C. Certain versus Uncertain Condition Comparisons

In order to investigate whether the difference between the response to "certainty" and "uncertainty" was different in hyperkinetic and non-hyperkinetic normal children, a series of analyses of variance were performed. As in the analyses of the effect of drug, the main interest in these analyses was in the first order interaction. However, group and condition effects were also obtained and are presented as well.

1. First Click:

The hyperkinetic control group and the non-hyperkinetic normal control group were compared under conditions of certainty and uncertainty (for both single and double guesses), i.e., guess single versus single certain and guess double versus double certain.

There were no significant group differences found between the hyperkinetic controls and non-hyperkinetic normal controls in the response to the first auditory stimulus, considered across certain and uncertain conditions.

However, just as was found in the drug analyses, in the present analyses when both groups (hyperkinetic and non-hyperkinetic) are considered together, the amplitude of the late positive components in the response to the certain condition appears to be larger than to the guess single condition, and this was reversed in the late negative compon-

ents where the response to uncertainty was larger than to certainty (although consistent, these differences were not statistically significant). Results for the guess double condition were less consistent and did not reach significance.

2. Second Click:

The hyperkinetic control group and the non-hyperkinetic normal control group were compared under conditions of certainty and uncertainty (for both right and wrong guesses) i.e., double right versus double certain and double wrong versus double certain.

a. Considered across the certain and uncertain conditions, the P186 component was found to be larger in the non-hyperkinetic normal children than the hyperkinetic controls (although only significant in the double wrong/double certain comparison, $p < .05$). Similar results were reported in the comparison of hyperkinetic drug and placebo groups reported above.

b. In figure 17 when one compares the curves for certain (dotted line) and uncertain (solid line) conditions, it is seen that for both the hyperkinetic controls and the non-hyperkinetic normal controls the curve for "uncertainty" is positive in relation to the curve for "certainty." That is, the amplitude of all positive components (with the exception of P63 in the right condition) are significantly larger in conditions of uncertainty (both right and wrong) than certainty [P186, P295, $p < .01$; P63 (double wrong) only, $p < .05$]. The amplitude of the negative components (with the exception of N103) are significantly smaller in conditions of uncertainty (both right and wrong) than certainty, ($p < .01$). These differences were also observed across

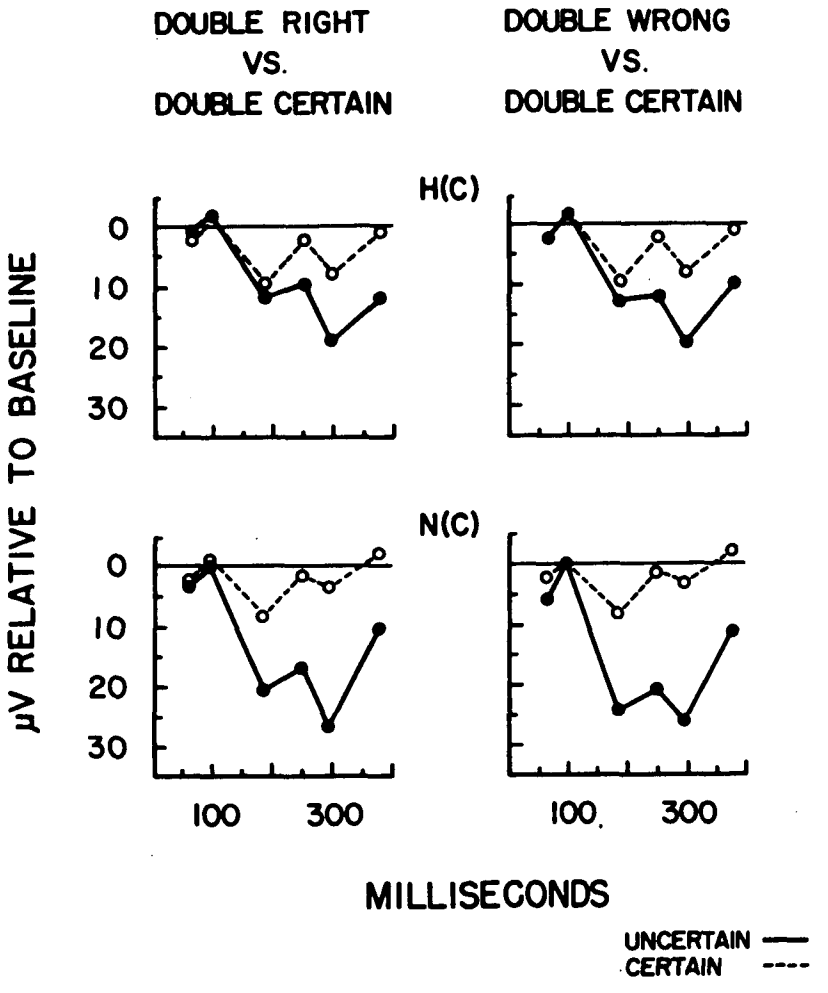

Figure 17. Response to the second click. Mean amplitudes (in μV relative to baseline) for each component are compared under conditions of certainty (dotted line) and uncertainty (solid line) for the hyperkinetic control group [H(C), upper panels] and the non-hyperkinetic normal control group [N(C), lower panels]. The certain condition is compared with correct guesses in the left panels and incorrect guesses in the right panels.

groups in the drug comparisons, and as was seen in those, these differences between the response to certain and uncertain are most clearly seen in the later components.

The above findings of condition differences must be considered in view of the fact that the standard deviations for these components were significantly different for certain and uncertain conditions. That is, variability was found to be significantly larger in conditions of certainty than in conditions of uncertainty. In addition, these differences in variability were present at baseline, where no evoked potential components are present. (This was also noted in the drug comparisons reported above.)

Differences in response to certainty and uncertainty were also found in both measures of the CNV. That is, considering the hyperkinetic control group and the non-hyperkinetic normal control group together, the CNV was found to be significantly larger under conditions of uncertainty than under conditions of certainty [guess double, $p < .05$; guess single (only for resident CNV), $p < .025$].

c. The main effects must be considered in light of the fact that significant Group x Condition interactions were found in these comparisons for the later components (P186 through N377). That is, the difference between the response to certainty and uncertainty was larger in the normal children than in the hyperkinetic children

(although only significant for the P186 component for both right, $p < .05$, and wrong guesses, $p < .01$). This can be observed in Figure 17, where it is noted that the magnitude of the difference between the response to certainty (dotted line) and uncertainty (solid line) is larger in the non-hyperkinetic normal controls (lower panels) than in the hyperkinetic controls (upper panels). Another way of summarizing these findings is that the normal children, as they should, show less positive later components in the condition of certainty than the hyperkinetic children. This interaction can be clearly seen in Figure 18.

3. Absent Second Click - Emitted Potential:

The hyperkinetic control group and the non-hyperkinetic normal control group were compared under conditions of certainty and uncertainty (for both right and wrong guesses), i.e., single right versus single certain and single wrong versus single certain.

In the response to the absence of the second click, considering the hyperkinetic controls and the non-hyperkinetic normal controls together, the same difference is found between certain and uncertain conditions that was found in the response to the presence of the second stimulus. The late positive component of the emitted potential was significantly larger in the uncertain conditions (both right and wrong) than in the certain condition ($p < .01$). The early negative component of the emitted potential was smaller in the uncertain than in the certain condition, however, this difference did not reach significance.

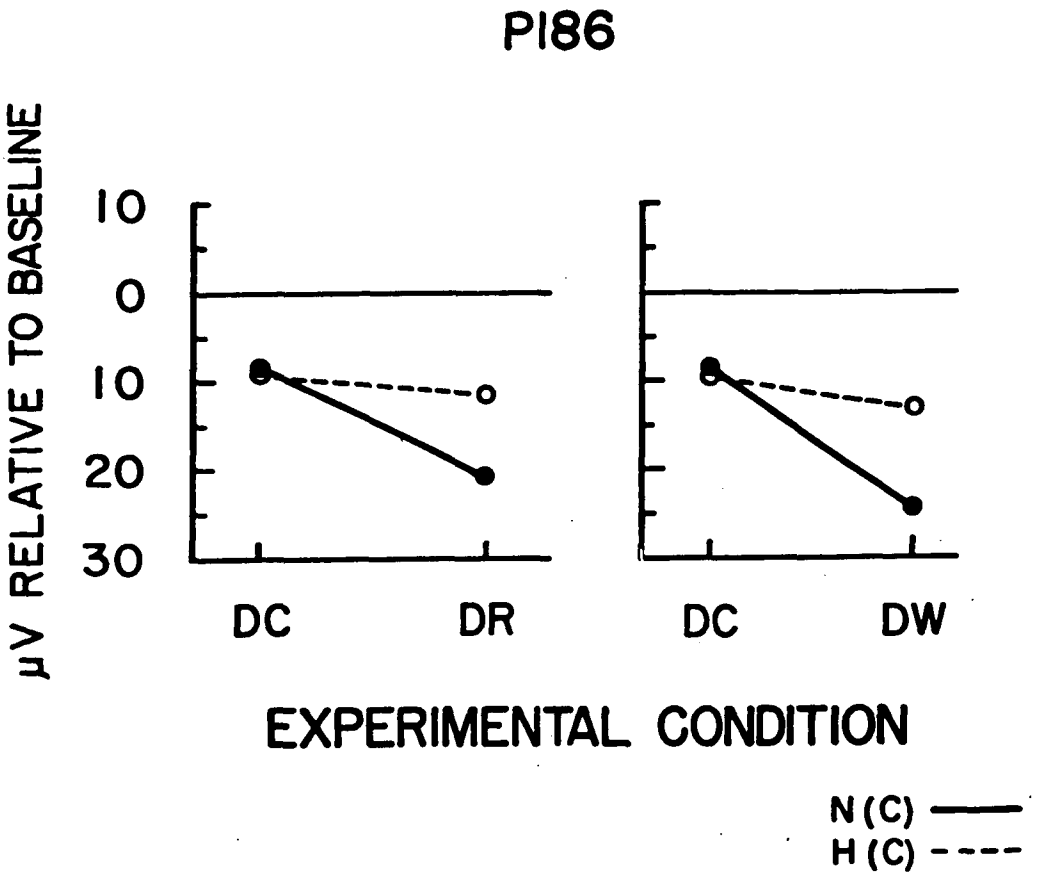

Figure 18. P186 component of the response to the second click. Mean amplitude (in μV relative to baseline) of the P186 component as a function of certainty [double certain (DC)] and uncertainty [double right (DR) in the left panel and double wrong (DW) in the right panel] for the hyperkinetic control group [H(C), dotted line] and non-hyperkinetic normal control group [N(C), solid line].

Summary of Major Findings

The effect of methylphenidate:

(1) a. In the response to the first click under conditions of uncertainty, drug appeared to shift the curve in the negative direction. Under drug, therefore, positive components decreased in amplitude (significant for P186 and P295) and negative components increased in amplitude (significant only for N103). While a similar trend was observed in the certain condition, the drug effect was much stronger, and only reached significance, under conditions of uncertainty.

b. Under conditions of certainty,uncertainty,and certainty versus uncertainty there was a significant Group x Condition interaction found in the P63 component.

(2) In response to the second click under conditions of uncertainty, drug appeared to shift the curve in the positive direction. Therefore, positive components increased in amplitude (significant only for P186) and negative components decreased in amplitude (significant only for N250). While a similar trend was observed in the certain condition, it did not reach significance. Further, the magnitude of the differences between the response to certainty and uncertainty was larger under drug than under placebo (significant only for P186).

(3) Drug did not effect the emitted potential in the response to the absence of the second click.

(4) There were no drug effects found in the contingent negative variation.

(5) None of the significant differences in amplitude found under drug were paralleled by significant differences in trial to trial variability.

Differences between hyperkinetic children and non-hyperkinetic normal children:

(1) In the response to the first click there were no significant differences seen between hyperkinetic children and non-hyperkinetic normal children under conditions of uncertainty, and certainty versus uncertainty. However, a significant Group x Condition interaction was found in the P63 component under conditions of certainty.

(2) a. In the response to the second click under conditions of uncertainty, the curve of the non-hyperkinetic normal children was positive in relation to the curve of the hyperkinetic children. That is, in non-hyperkinetic normal children the positive components were larger (significant only for P186) and negative components were smaller (significant only for N250) than those of the hyperkinetic children.

b. In the response to the second click in the certain condition, the later components (P295 and N377) in the response of the non-hyperkinetic normal children were negative in relation to those of the hyperkinetic children (significant only for P295). That is, P295 was significantly smaller in non-hyperkinetic normal children than in hyperkinetic children.

c. The magnitude of the difference between the response to

certainty and uncertainty was larger in non-hyperkinetic normal children than in hyperkinetic children (significant only for P186).

(3) In the response to the absence of the second click (emitted potential) there were no significant differences found between hyperkinetic children and non-hyperkinetic normal children.

(4) There were no differences between hyperkinetic children and non-hyperkinetic normal children in the contingent negative variation.

(5) None of the significant differences in amplitude found between hyperkinetic children and non-hyperkinetic normal children were paralleled by significant differences in trial to trial variability.

Condition effects (across groups):

(1) In the response to the first click, amplitudes of the late positive components tended to be larger (significant only for P186) and late negative components tended to be smaller (significant only for N377) in the certain condition than in the uncertain condition for a guess of single. This relationship was not consistent for a guess of double.

(2) In the response to the second click, the amplitude of the late positive components tended to be smaller (significant for P186 and P295) and late negative components tended to be larger (significant for N250 and N377) in the certain condition than in the uncertain condition (for both right and wrong guesses).

Further, trial to trial variability was found to be significantly larger under conditions of certainty than uncertainty both at baseline and peaks of specific components.

(3) In the absence of the second click, the relationship between the emitted potential to certain and uncertain conditions was similar to that seen in the presence of the second stimulus. That is, the late positive component of the emitted potential was significantly smaller in the certain than uncertain condition (for both right and wrong guesses), and the early negative component was larger in the certain than uncertain condition (for both right and wrong guesses).

Discussion

The major findings in the present study were seen, as was hypothesized, under conditions of uncertainty in the response to the second click. Significant differences between hyperkinetic children and non-hyperkinetic normal children were found in the P186 and N250 components. That is, the P186 component was smaller (less positive) and the N250 component was significantly larger (more negative) in the hyperkinetic children than in the non-hyperkinetic normal children. The effect of methylphenidate on hyperkinetic children was to increase the amplitude of the P186 component and decrease the amplitude of the N250 component moving both components in the direction of the non-hyperkinetic normal children. In accordance with hypothesis no differences between groups were found in the certain condition.

Another way in which differences between groups were considered was to compare the differences in amplitude between the condition of uncertainty and the condition of certainty. Here it was found that the increase in P186 amplitude which was brought about by uncertainty was significantly larger in non-hyperkinetic normal children than in hyperkinetic children; and in the hyperkinetic children was significantly greater under drug than under placebo. Differences between uncertainty and certainty in the N250 component were larger in non-hyperkinetic normal children than in hyperkinetic children; and in the hyperkinetic children larger under drug than under placebo. However, these interactions for the N250 component were not significant.

Nevertheless, it is useful to note that for both components the change in amplitude brought about by drug was in the "normalizing" direction.

A general overview of the findings can be obtained by consulting Figures 8 and 15. What these figures show is that all components from P186 to N377 are more negative in the hyperkinetic children than in the non-hyperkinetic normal children (see Figure 15). That is, positive components are smaller and negative components are larger, Further, the effect of methylphenidate is seen to shift all components beginning with P186 (N250, P295, and N377) in a more positive direction (see Figure 8). This positive shift may explain why it is that the amplitude of P186 was smaller in hyperkinetic children than in non-hyperkinetic normal children, while the amplitude of N250 was larger in hyperkinetic children than in non-hyperkinetic normal children. An increase in a positive component and a decrease in a negative component are both a shift of the curve in a positive direction. While the P295 and N377 components never achieve statistical significance, consultation of the result section shows that the effects were characteristically in the same direction. However, whether one focuses on the P186 and N250 components or on the positive shift of all the later components, the inescapable generalization which emerges is that the effect of methylphenidate is to alter the evoked potential of hyperkinetic children to make it more like that of the normal children.

Effects of Uncertainty

The P186 component. The amplitude of the $\overline{P300}$ component has been shown to increase with increased uncertainty and increased signal properties of the stimulus, conditions which have been shown to influ-

ence $\overline{P200}$ in the same manner (Tueting, 1968; Friedman et al., 1973). In the present study, the finding in hyperkinetic children of decreased P186 (probably identical to $\overline{P200}$) amplitude under the uncertain condition in which attentional demands are greater, may serve as physiological evidence of the attentional deficit observed behaviorally in hyperkinetic children. Further, the parallel finding of increased amplitude of P186 in hyperkinetic children under methylphenidate may reflect the increased attention span observed clinically in hyperkinetic children when treated with methylphenidate. However, the fact that in this study the $\overline{P300}$ findings, while in the same direction as the $\overline{P200}$ findings, did not reach statistical significance remains unexplained.

Satterfield (1973) reported that the component of the evoked potential which best differentiated hyperkinetic children from "normal" children was $\overline{P200}$, which was found to be significantly smaller in amplitude in hyperkinetic children. In the present study the P186 component (probably identical to Satterfield's $\overline{P200}$) was also found to be significantly smaller in amplitude in hyperkinetic children than in non-hyperkinetic normal children. Further, close to half of the hyperkinetic children had P186 amplitudes which were smaller than in any of the normal children.

In Figure 19 the cumulative frequency distributions of P186 amplitudes to the second click in the double wrong condition are plotted for the hyperkinetic drug group, hyperkinetic control group, and the non-hyperkinetic normal control group. It can clearly be seen that the distribution of the amplitudes of the hyperkinetic control group

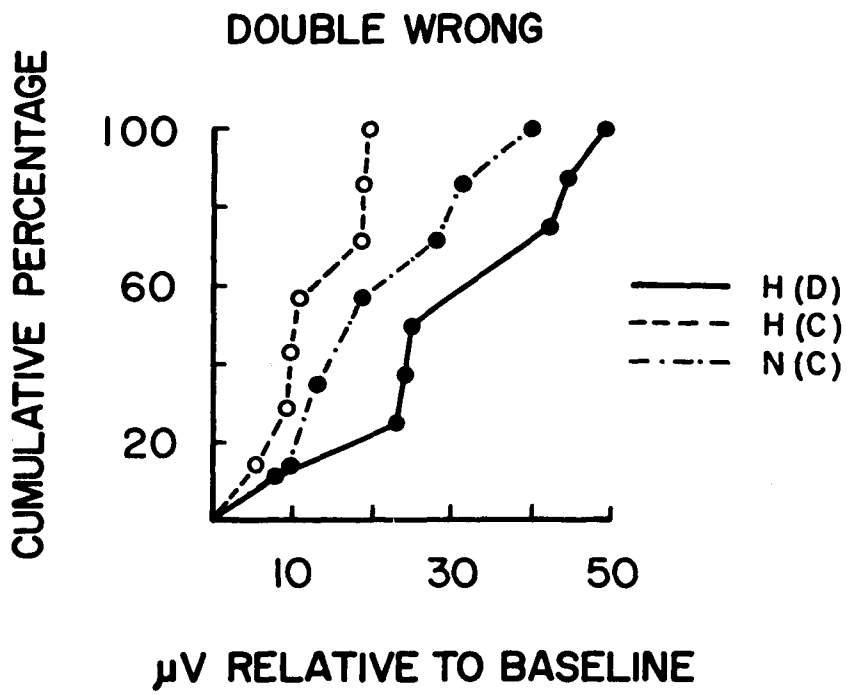

Figure 19. P186 component of the response to the second click in the double wrong condition in Period I. The frequency distributions of P186 amplitudes (in μVs relative to baseline), plotted as cumulative percentage curves, are compared between the hyperkinetic drug group [H(D), solid line], the hyperkinetic control group [H(C), dotted line], and the non-hyperkinetic normal control group [N(C), dash/dot line]. The hyperkinetic drug group received methylphenidate; the hyperkinetic control group and the non-hyperkinetic normal control group received placebo.

was quite different from those in the other two groups, and further that those of the hyperkinetic children under drug more closely resembled the non-hyperkinetic normal children than the hyperkinetic controls. Surprisingly, the curve which is farthest to the right, i.e., the group with the largest amplitude P186 components, is not the non-hyperkinetic normal controls but the hyperkinetic children under drug. Drug may tend to cause an overshoot, i.e., to result in a P186 component which is larger than that in the normal children. However, the difference between the hyperkinetic drug group and the non-hyperkinetic normal group was not significant.

The N250 component. Not reported in previous studies is the finding of significant differences in N250 amplitude found between hyperkinetic children and non-hyperkinetic normal children. The N250 component was found to be significantly larger in hyperkinetic children than in non-hyperkinetic children. As can be seen in Figure 8, methylphenidate decreased the amplitude of the N250 component in hyperkinetic children, once again appearing to "normalize" their response. Satterfield (1973) reported smaller $\overline{P200}$-$\overline{N250}$ components in hyperkinetic children. However, it is difficult to compare his results directly to those of this study since he did not report the $\overline{N250}$ component separately. He did report that $\overline{P200}$ was significantly smaller in hyperkinetic children, but this leaves open the question of whether $\overline{N250}$ was the same or larger. In the present study peak-to-peak measurement of the P186-N250 component did not yield significant differences between hyperkinetic and non-hyperkinetic normal children.

Studies in normal adults have shown $\overline{N250}$ to increase greatly in amplitude when the subject gets drowsy and thus its amplitude appears to be inversely related to arousal state (Fruhstorfer & Bergstrom, 1969; Picton et al., 1974; Tueting, 1968; Weitzman & Kremen, 1965; Wilkinson et al., 1966; Williams et al., 1962).

Wilkinson, Morlock and Williams (1966) reported that as accuracy decreased over time in a vigilance task the amplitude of $\overline{P200}$ declined while the amplitude of $\overline{N250}$ increased. They interpreted these findings to mean that the decline in amplitude for $\overline{P200}$ represented a distraction process and that the increase in $\overline{N250}$ was correlated with declining arousal. The amplitude of the $\overline{N250}$ component has further been shown to decrease with states demanding heightened attention, such as conditions of increased uncertainty (Tueting, 1968).

The fact that in the present study N250 was found to be significantly larger (and P186 significantly smaller as described above) in hyperkinetic children than in non-hyperkinetic normal children has several implications. In terms of attention, these findings are further physiological evidence of the attentional defect in hyperkinetic children which is reversed by drug treatment. Of even greater interest, however, is the implication for an arousal model of hyperkinesis. The finding of increased N250 amplitude suggests strongly that hyperkinetic children are in a state of <u>low</u> arousal. Methylphenidate decreased the amplitude of the N250 component, increasing the arousal state, and making the response of hyperkinetic children more like that of the normal children. Therefore, methylphenidate, a CNS stimulant drug, is not acting in a paradoxical fashion, but rather

has its normal stimulant effect on hyperkinetic children.

Supporting evidence for low arousal level in hyperkinetic children has been reported in several studies of electrodermal activity (Cohen & Douglas, 1972; Satterfield & Dawson, 1971; Spring et al., 1974). In addition, while results of the studies of electrodermal activity were not entirely consistent, all three found that stimulant drugs increased at least one measure of autonomic arousal. Also consonant with a low arousal model of hyperkinesis are the findings of increased slow wave activity in the electroencephalograms of hyperkinetic children (Capute et al., 1968; Satterfield et al., 1972; Wikler et al., 1970).

Positive shift in all late components. As can be seen in Figure 15 in response to the second click the curve of the hyperkinetic controls appears to be more "negative", i.e., the later positive components were smaller and the later negative components were larger than those of the normal children. Further, the effect of drugs, as seen in Figure 8, is to shift the curve in the positive direction, i.e., in the direction of the normal children. A positive shift is the most parsimonious explanation of an increase in amplitude of positive components and a decrease in amplitude of negative components; and the fact that no differences were found in peak-to-peak amplitudes is consistent with such an explanation. Since hyperkinetic children under drug, and placebo treated non-hyperkinetic normal children both have the same relationship to hyperkinetic controls, it is inferred that under drug the response of the hyperkinetic children is "normalized."

The meaning of such a shift in the response curve is unclear. One possible explanation is that the entire evoked potential is riding on some underlying process which may be thought of as summing with the response, moving the entire curve in one direction (i.e., toward positivity or negativity). For example, it might be hypothesized that in the present study this underlying process is related to arousal. Such a thought is consistent with Wilkinson et al. (1966) finding that with decreased vigilance $\overline{P200}$ decreased in amplitude and $\overline{N250}$ increased in amplitude.

The possibility of this apparent shift in the curve being attributed to differences in the return of the contingent negative variation (CNV) to baseline cannot be overlooked. However, the fact that no group differences were found in the amplitude of the CNV argues against this possibility.

Role of Task Demands

The behavioral characteristics of the hyperkinetic syndrome are most in evidence in a structured situation requiring focusing of attention and inhibition of inappropriate responses. It is, therefore, not surprising that most hyperkinetic children remain undiagnosed (and, therefore, untreated) until school age, when the first demands for conformance in behavior and focused attention are required. Our hypothesis that the maximum differences between hyperkinetic and normal children would be observed under conditions in which focusing of attention was required, followed in part from this observation.

In the present study attentional demands were manipulated by

comparing conditions of certainty and uncertainty. It is recalled that in the certain conditions the subject was told in advance whether he would hear a single or double click. Under these conditions the stimuli carry little information and require only minimal attention. In the uncertain condition, on the other hand, the subject must predict whether he will hear a single or a double click in each trial. Under these conditions the subject is required to maintain attention throughout the time interval in which the clicks may occur. The use of a monetary reward for each correct guess aids in requiring the maintenance of attention. Uncertainty is not resolved until the point in time when the second stimulus does or does not occur. Based on these facts, it was predicted that hyperkinetic children, described behaviorally as being less able to focus attention, would show smaller differences in amplitude between conditions of uncertainty and certainty.

The informational stimulus (second click). Findings of significant Group by Condition interaction for the P186 component support the above hypothesis. It is clearly seen in Figure 20 that little, if any, difference exists between the non-hyperkinetic normal children and hyperkinetic children in the certain condition, whereas large differences exist in the uncertain condition (for both right and wrong guesses). The magnitude of the difference between the certain and uncertain conditions was found to be considerably smaller in the hyperkinetic children as compared to the non-hyperkinetic normal children. It is suggested that the large difference in amplitude of the evoked response to uncertainty and certainty seen in normal child-

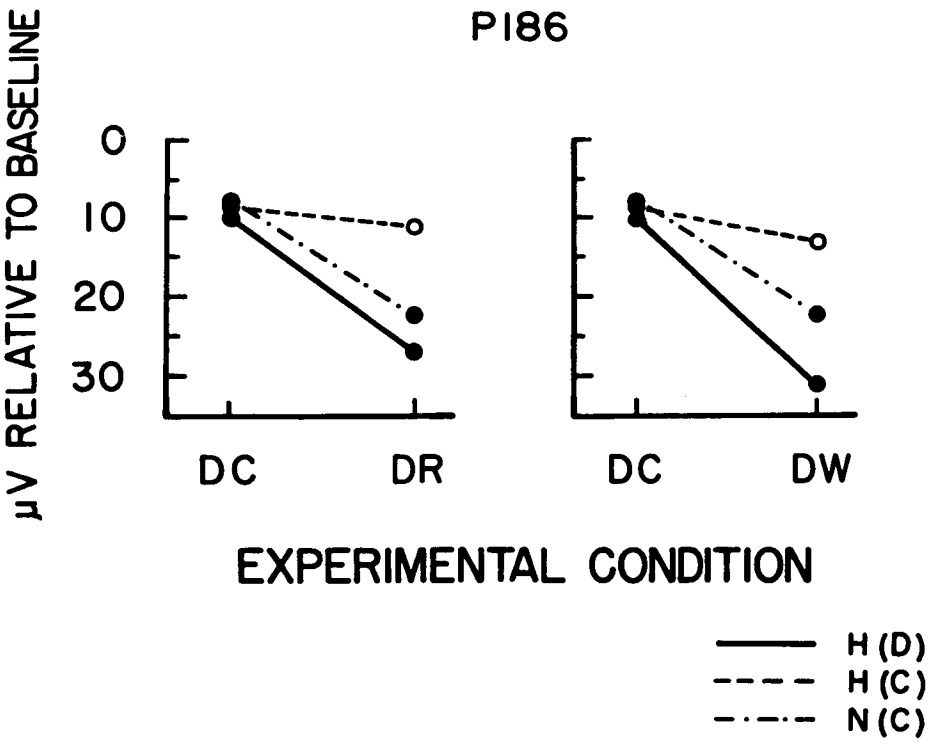

Figure 20. P186 component of the response to the second click in Period I. Mean amplitude (in μVs relative to baseline) of the P186 component as a function of certainty [double certain (DC)] and uncertainty [double right (DR) in the left panel and double wrong (DW) in the right panel] for the hyperkinetic drug group [H(D), solid line], hyperkinetic control group [H(C), dotted line], and non-hyperkinetic normal control group [N(C), dash/dot line]. The hyperkinetic drug group received methylphenidate; the hyperkinetic control group and the non-hyperkinetic normal control group received placebo.

ren reflects an ability to focus attention when the task demands are such. The smaller degree of differentiation in the evoked potentials of the hyperkinetic children appears to reflect their relative inability to focus attention in response to task demands.

Consistent with findings reported above of the "normalizing" effects of methylphenidate treatment, the magnitude of the difference between uncertainty and certainty in the P186 component was significantly increased in hyperkinetic children when treated with methylphenidate (see Figure 19). It can be seen that both the hyperkinetic drug group [H(D)] and the non-hyperkinetic normal group [N(C)], show large differences in the amplitude of the response to uncertainty and certainty, while no real differences are seen in the hyperkinetic control group [H(C)]. Similar findings were reported by Conners (1971) who found that differences between the response to relevant and irrelevant stimuli in the late components of the evoked potentials of hyperkinetic children were only seen when the children were under stimulant medication. Using electrodermal measures, the findings of Cohen and Douglas (1972) are also consistent with those of the present study. Skin conductance level in normal children was found to increase with increased task demands from nonsignal (passive attention) to signal (active attention) conditions, whereas no such differences were found in untreated hyperkinetic children. However, Cohen, Douglas and Morgenstern (1971) reported inconsistent findings with respect to the effect of methylphenidate on hyperkinetic children in response to varied task demands.

Differences in the magnitude of the effect of uncertainty on the

amplitude of the evoked potentials in normal and patient populations (schizophrenics and depressives) have also been reported by other investigators (Levit, 1972; Levit et al., 1973). Here too, smaller differences between uncertainty and certainty were found in the patient groups than in the "normal" group.

The non-informational stimulus (first click). The first click in a guessing paradigm carries no real information in the sense that it does not resolve uncertainty. As such, the amplitude of the late positive components, in the evoked potential in response to the first click under conditions of uncertainty, would be expected to be small. In this context it is interesting to consider the finding that the effect of methylphenidate under these conditions was to significantly decrease P186 and P295 amplitude in hyperkinetic children, making them more like the expected normal response. This would seem to imply that under placebo hyperkinetic children are overattending an irrelevant stimulus, and that under methylphenidate the mechanism of selective attention operates more appropriately. Such differences in the ability to respond to task demands were previously noted by Conners (1971) and Cohen and Douglas (1972). However, inconsistent with this interpretation is the fact that the early negative going component (N103, most probably identical to $\overline{N100}$) was increased under methylphenidate. Since evidence exists that $\overline{N100}$ amplitude is substantially larger for attended tones in a selective attention task (Hillyard et al., 1973) and under conditions of uncertainty (Tueting, 1968; Tueting et al., 1971), it would have been expected that methylphenidate would have decreased $\overline{N100}$ amplitude in the response to the first stimulus. How-

ever, insufficient evidence has accumulated in the literature on the role of $\overline{N100}$ in relation to attention to resolve this inconsistency at this time.

Additional Findings

In the comparison between the hyperkinetic drug and hyperkinetic control group, a significant Group x Condition interaction was seen in the P63 component of the response to the first click under conditions of uncertainty, certainty,and uncertainty versus certainty. In the certain versus uncertain comparisons, consistent with our hypothesis, group differences were larger under conditions of uncertainty than certainty. Somewhat unclear, however, were the interactions found in the other comparisons. In the uncertain condition the difference between the groups was larger in the guess double than in the guess single condition. Under conditions of certainty, the difference between the groups was larger in the single certain condition than in the double certain condition.

In the comparison between hyperkinetic controls and non-hyperkinetic normal controls, a significant Group x Condition interaction was also found for the P63 component in the response to the first click. That is, differences between the groups were larger in the double certain than in the single certain condition. Since the double condition was also the condition in which methylphenidate was seen to have the greatest effect under the conditions of certainty, this finding supports our hypothesis that the drug effect would be most clearly seen in those conditions in which differences were found between hyperkinetic con-

trols and non-hyperkinetic normal controls.

However, while the interaction in the P63 component was present for both sets of comparisons under conditions of certainty, it was only seen in the drug comparisons under conditions of uncertainty, and certainty versus uncertainty. In addition, a significant Group x Condition interaction was seen in the N103 component in response to the first click in the comparison of hyperkinetic controls and non-hyperkinetic normal controls. That is, differences between the groups were larger in the double certain condition than the single certain condition. Contrary to the hypothesis which would have predicted that a corresponding interaction would be seen in this component in the drug comparisons, none were found.

It is noted that no interactions were seen in either the P63 or N103 components under any conditions in the response to the second click for either set of comparisons. While the findings reported appear to be specific to the first click, and relatively consistent across conditions, not enough is known about P63 or N103 at this time to make any systematic interpretation of these findings. This suggests the need for further study of the $\overline{P70}$ and $\overline{N100}$ components.

Emitted Potentials

The fact that no group differences were found in the emitted potential was disappointing, since it was hoped that an estimate of differences in brain activity free of stimulus characteristics would be reflected in the emitted potential. In all groups, the amplitude of the late positive component of the emitted potential was signifi-

cantly larger under conditions of uncertainty (for both right and wrong guesses) than certainty,confirming that an emitted potential was indeed obtained. The early negative component, however, was not seen with any clarity in either condition, but this component is generally small and evanescent even in normal adults.

Presumably, the emitted potential reflects the point in time of the non-occurrence of a stimulus (Sutton et al., 1967). For example, in the present study, the inter-click interval (slightly less than one second) must carry over and be estimated in trials in which the second click does not occur. Further, the consistency with which the subject can estimate time is critical in determining the degree to which an emitted potential will be seen when one is using an averaging procedure. Investigators have proposed that variation in time estimation leads to a wide distribution in peak latencies of the components of the emitted potential and consequently to a broad duration, low amplitude waveform (Ruchkin & Sutton, 1974; Sutton et al., 1967; Sutton et al., 1974).

In the present study the late positive component ($\overline{P300}$) which is the major feature of the emitted potential was of extremely broad duration. Thus, it would suggest that children (both hyperkinetic and non-hyperkinetic normal) are poor time estimators. However, this statement requires qualification, since it was discovered at the completion of this study that the timer which controlled the inter-click interval had drifted over the course of the investigation. Therefore, the inter-click interval may not have been constant from the first to the second session in the same subject.

Techniques are now available which determine the peak latencies for single trials, align the $\overline{P300}$s around a common latency, and then compute the average waveform based on the aligned $\overline{P300}$s (Ruchkin & Sutton, 1974). Averages are thereby obtained which are free from the time estimation problem discussed above. It would be interesting to reanalyse the present data using such procedures.

Trial to Trial Variability

Due to the fact that poor time locking of electrical events to a stimulus may change the shape of a waveform, variability cannot be overlooked when comparing differences in evoked potential waveforms. This is particularly the case when one is comparing evoked potentials in two groups, one of which may be expected,a priori, to have greater trial to trial variability. For example, differences in the evoked potentials of schizophrenics and normal subjects reported by Callaway et al. (1965) and Jones et al. (1965), were later shown to be attributable to larger intra-individual variability in the evoked potentials of schizophrenics (Callaway et al., 1970; Jones & Callaway, 1970).

In the present study no significant group differences were found in intra-individual trial to trial variability. Thus, group differences in amplitude of the average evoked potential components could not be attributed to trial to trial variability.

Alternative Interpretations of the Findings

Maturational lag. A number of investigators have attempted to relate their evoked potential findings in hyperkinetic children to an

etiological model based on a maturational or neurodevelopmental lag (e.g., Buchsbaum & Wender, 1971; Satterfield, 1973). In reviewing the literature on the effects of maturation and aging on the waveform of the evoked potential a number of descriptive accounts of evoked potentials in adults and in infants were found, however relatively few studies describe evoked potential changes in relation to increasing years from infancy through adulthood (see review by Schenkenberg, 1970). For the purpose of comparison with evoked potential findings in hyperkinetic children, of specific interest are the results of studies of normal children from infancy to adolescence. Available data on evoked potential changes during these years are not entirely consistent (Dustman & Beck, 1966, 1969; Schenkenberg, 1970; Schenkenberg & Dustman, 1970).

Dustman and Beck (1966, 1969) found that the mean amplitude of components in the 126-250 msec portion of the visually evoked potential recorded from occipital scalp, increased markedly from infancy to ages 5-6 and then declined until age 13, at which time there was an abrupt increase to age 15. Dustman and Beck also recorded from central scalp. While they note that recordings from central scalp differed from those reported for occipital scalp, the results from central scalp were not reported.

Schenkenberg and Dustman (1970) reported that the components in the 100-200 msec segment of the visual, auditory, and somatosensory evoked potentials recorded from occipital, frontal and central scalp were found to increase in amplitude from childhood to adolescence. Unfortunately, both Dustman and Beck (1966, 1969) and Schenkenberg

and Dustman (1970) utilized a measure which was a composite of all components within a given segment of the evoked potential. Examination of the data for individual components from the studies of Dustman and Beck (1966, 1969) revealed a great deal of variability in the age-amplitude relationship. Likewise, a more detailed account of the data by Schenkenberg and Dustman (seen in Schenkenberg, 1970) suggest that the summary of results they reported were also somewhat simplified and that there was a great deal of variability in individual components, different recording sites, and for different modalities of stimulation.

Further complicating the age-amplitude relationship, is the fact that intra-individual variability of the evoked potential has been shown to be inversely correlated with age (e.g., Callaway & Halliday, 1973). In addition, variability is associated with decreased amplitude (e.g., Callaway & Halliday, 1973). Therefore, interacting with any results reporting a correlation between age and amplitude is the factor of variability.

In the present study, several factors militate against an explanation of the data based upon a maturational model. While the evidence presented above relating amplitude of the evoked potential to age is inconclusive, studies which reported changes (whether increases or decreases) found them to be in the same direction for positive and negative components, resulting in decreased or increased amplitude in peak-to-peak measurements. Findings of the present study indicate a shift in the response curve -- thus increases in the amplitude of one component (positive or negative) were accompanied by decreases in the adjacent components. Peak-to-peak measurements resulted in no signi-

ficant difference between groups. Further, group differences were not found in variability. Such group differences would have been expected if the results were based on a developmental or maturational difference between the groups. Thus, it appears that a model of hyperkinesis based on maturational lag is inconsistent with findings of the present study.

IQ. There is an extensive literature attempting to relate evoked potentials and IQ, however at this point the issue remains in controversy (see reviews by Callaway, 1973; Shagass, 1971). The majority of the studies relate latency of evoked potential components to intelligence, in general reporting decreased latency with increased intelligence. In some studies amplitude has also been related, but the evidence is contradictory.

Rhodes, Dustman and Beck (1969) found that the late components (positive and negative) of the evoked potential recorded from both occipital and central scalp were reliably larger in "bright" children (WISC IQs ranged from 120-140) than in "dull" children (WISC IQs ranged from 70-90). These results however, appear to be inconsistent with results obtained from the same laboratory in which mongoloid children were found to have larger amplitude evoked potentials than "normal" controls (Bigum, Dustman & Beck, 1970). Further, in a more recent study, Satterfield (1973) found no correlation between IQ and amplitude of the evoked potential recorded from vertex in hyperkinetic and "normal" children.

In the present study, all children were of normal intelligence. While the hyperkinetic children and the non-hyperkinetic normal children were not matched for IQ, there was a great deal of overlap in the

distribution of IQs in the two groups. It should be noted that in the studies reported above where evoked potentials were found to be related to intelligence, the IQs of the groups compared were quite disparate (Bigum et al., 1970; Rhodes et al., 1969).

The issue of the relationship between intelligence (as measured by IQ) and evoked potentials is further confused by the fact that the more intelligent a person, the more capable he would be expected to be of sustaining attention. Since there has clearly been shown to be a relationship between attention and the evoked potential (reviewed above, see Introduction), a finding of a correlation between IQ and evoked potential would be confounded by the relationship between IQ and attention. Therefore, all factors considered, it does not appear that the differences in IQs between groups would be a parsimonious explanation of the evoked potential differences reported in the present study.

Methylphenidate and the average evoked potential. A review of the literature revealed no studies investigating the influence of methylphenidate on the average evoked potential in normal (non-patient population) children, and only one study in normal (non-patient population) adults (Saletu, Saletu, Itil, & Coffin, 1972). Saletu and his colleagues (1972) studied the effects of stimulant drugs (methylphenidate and dextroamphetamine) on somatosensory evoked potentials in "normal" adults. Methylphenidate was found to decrease the amplitude of the early components and increase the amplitude of the late components. In contrast, no systematic changes in amplitude were seen under dextroamphetamine. Both methylphenidate and dextro-

amphetamine were found to decrease the latency of early and late components of the response. However, in general, studies which have been conducted using central nervous system stimulants other than methylphenidate (e.g., dextroamphetamine and methamphetamine) do not report consistent amplitude or latency findings (see review by Shagass, 1971).

The question arises whether the effect of methylphenidate on the evoked potential in this study was linked to the behavioral effects brought about by methylphenidate or represented the effect of methylphenidate on the evoked potential regardless of behavioral effects. Two lines of evidence suggest that the evoked potential changes brought about by methylphenidate in this study do indeed reflect the behavior changes. First, significant effects of methylphenidate occurred in the uncertain condition and not in the certain condition, i.e., in the condition in which attentional demands were high and not in the condition where attentional demands were low. Second, in other studies it has been shown that the evoked potential changes are larger in subjects in whom a greater clinical change was observed than in subjects in whom a smaller clinical change was observed (e.g., Buchsbaum & Wender, 1973; Halliday et al., 1974; Saletu et al., 1973; Satterfield et al., 1972).

Condition Effects

The most outstanding and consistent condition effects found in the present study were seen in the comparison of conditions of uncertainty and certainty in the response to the second click. In all subject groups P186 and P295 (including the emitted late positive)

were larger, and N250 and N377 were smaller under the uncertain condition than under the certain condition. The effect of uncertainty was also seen in the P63 component but only for wrong guesses and only in the comparison of hyperkinetic controls and non-hyperkinetic normal controls. In general, the finding of the effect of uncertainty is consistent with that reported by other investigators (Friedman et al., 1973; Levit, 1972; Levit et al., 1973; Sutton et al., 1965; Sutton et al., 1967; Tueting et al., 1971; Zubin & Sutton, 1970), who reported that $\overline{P300}$, and to a lesser extent $\overline{P200}$ (Friedman et al., 1973; Tueting, 1968; Tueting et al., 1971), were larger when uncertainty was resolved than when uncertainty was not resolved.

In the present study the significant condition effect as seen in the P186 component must be considered in light of the fact that the Group x Condition interaction was significant. That is, differences between the response to certainty and uncertainty were larger in the non-hyperkinetic normal controls than in the hyperkinetic controls; and in the hyperkinetic children, larger under drug than placebo. Similarly, Levit (1972) and Levit et al. (1973) reported that the effect of uncertainty was larger in "normal" than in patient populations.

Not reported in previous studies was the finding of the effect of uncertainty seen in the response to the first click. Results were opposite to those reported above; the amplitude of the late positive components were smaller in the response to uncertainty than certainty. This finding leads to some interesting interpretations.

While the condition findings in the response to the second click were consistent with an explanation based on the resolution of uncertainty, condition effects with respect to the first click cannot be understood in these terms. That is, the resolution of uncertainty occurs only with respect to the second click. The amplitude of the late positive components (P186 and P295) in the response to the first click were larger, and the late negative was smaller in the certain (single certain) than in the uncertain (guess single) conditions.

One might propose that the amplitude of the late positive components would be larger when information was "complete" than when it was not. Thus, in the single certain condition, when the first click occurs, the trial may be thought of by the subject as being "over" and, therefore, the amplitude of the late positive components would be larger than in the guess single condition where the information is not complete since it is as yet unknown whether a second click will occur. The fact that no significant differences were found in the guess double versus double certain comparison is also consistent with this explanation, since in both these conditions "completeness" is dependent upon the occurrence (or non-occurrence) of the second click. Inconsistent with this proposed explanation, however, is the finding of significantly smaller P186 amplitude in the response to the guess single as compared with the guess double conditions. Since in both the guess single and the guess double conditions "completeness" is dependent upon the occurrence of the second click, no difference would have been anticipated in the response to the first click. The finding of a smaller N377 component in the guess single condition than in

the single certain condition is neither consistent nor inconsistent with this explanation since not enough is known at this time about the behavior of this component. It must be noted that while these findings tended to occur in all children, results were only significant for hyperkinetic children.

All of these condition effects must be reconsidered in view of the fact that there were also significant differences in the trial to trial variability, i.e., variability was greater in the certain condition than in the uncertain condition. The reason for this caution arises from the fact that greater time jitter will be reflected in larger variability and smaller average amplitude. Therefore, a finding of a significant amplitude difference under the condition where the standard deviation is larger for the smaller amplitude, could be due not to a true amplitude difference, but to a difference in time jitter in the two conditions. This reasoning brings the findings for the positive components into question as they fulfill the above pattern, i.e., larger amplitude and smaller standard deviation; smaller amplitude and larger standard deviation.

However, for the present data this reasoning which leads to a questioning of the reality of the differences for the positive components is not compelling. This is due to the fact that the significant larger variability in the certain condition is also true at baseline where no evoked potential components are present. This suggests that the source of the greater variability in the certain condition is a higher noise level in that condition and not due to greater time jitter of components. This argument is further supported by the fact

that the negative components have greater variability but larger amplitude in the certain condition than in the uncertain condition. This provides further support for the contention that, in this experiment, the greater variability in the certain condition was due to higher noise level rather than increased time jitter in the individual components.

Right and wrong guesses. Across all groups, amplitudes tended to be larger for wrong guesses than for right guesses, although only significant for the P186 component in the hyperkinetic children. These findings are in line with those reported by Sutton et al. (1965), who found that wrong guesses yielded larger average evoked potential amplitudes than right guesses in "normal" subjects, and Squires et al. (1973) who found that in a discrimination task, disconfirming feedback yielded larger amplitude late positive components compared with confirming feedback. However, Friedman (1972) found no significant right/wrong differences in his study of "normal" subjects.

Contrary results were reported by Levit (1972) and Levit et al. (1973) who found that in both patient and "normal" populations the amplitude of the response to right guesses was larger than wrong guesses, and by Haider, Spong and Lindsley (1964) who found that evoked potentials are larger for correct discriminations than for incorrect discriminations. Further, the findings of Tueting et al. (1971) which showed an inverse relationship between average evoked potential amplitude and obtained probabilities of outcome, suggest that the relationship between evoked potential amplitude and correctness of guess may not be a simple one. A systematic understanding of the differences

between right and wrong guesses, and why it is that different studies yield different results, continues to elude investigators in this field.

General Overview

As was hypothesized, differences between hyperkinetic children and non-hyperkinetic normal children were seen under conditions of uncertainty in which attentional demands were placed on the children, but not under conditions of certainty where demands on attention were minimal. The late positive components of the evoked potential have been shown in normal adults to increase with increased uncertainty. These late components were found to be smaller in hyperkinetic children than in non-hyperkinetic normal children, most likely reflecting the deficit in attention described clinically in these children. If one were to use the amplitude of the P186 component (most probably identical to $\overline{P200}$) approximately half of the hyperkinetic children could be differentiated from the non-hyperkinetic normal children. This suggests the possible usefulness of the evoked potential as an additional diagnostic tool.

Further, the N250 component, which has been shown to be inversely related to arousal level in normal adults, was found to be significantly larger in hyperkinetic children than in non-hyperkinetic normal children. Based on this finding, it appears hyperkinetic children are in a state of low arousal. This hypothesis is consistent with the findings using other physiological measures (e.g., electrodermal response and electroencephalography). An underarousal model is also consistent with the fact that CNS stimulants are therapeutically effective. Such a model may appear to be in conflict with clinical reports of motoric overactivity. However, attempts to document a gross increase in motor activity in hyperkinetic children using objective measuring devices have been largely unsuccessful (see review by Wender, 1971). While gross motor activity may not be excessive, increases were documented in activities such as fidgeting and restlessness; and time spent in any single activity was found to be

greatly decreased. Studies in sensory deprivation report that under states of decreased stimulation there is an increase in restlessness, fidgeting, random movements and irritability (see review by Brownfield, 1965) -- very much the same type of activity which has been shown to be increased in hyperkinetic children. Satterfield and Dawson (1971) pointed to this similarity and suggested that the activity observed in hyperkinetic children, as in sensory deprivation, constitute an attempt to increase proprioceptive and exteroceptive sensory input through self-stimulation.

The effect of methylphenidate was to decrease the amplitude of the N250 component, consistent with a hypothesis that methylphenidate achieves its therapeutic effect by increasing arousal level, since it has been shown that arousal is inversely related to the amplitude of the N250 component (e.g., Picton et al., 1973; Wilkinson et al., 1966). Also consistent with this formulation is the fact that, as hypothesized, methylphenidate altered those components of the evoked potential (P186 and N250) which were significantly different in hyperkinetic children. Furthermore, also as hypothesized, the effect of methylphenidate was to alter these components in a "normalizing" direction, i.e., to make them more like the non-hyperkinetic normal children. Specifically, under drug the P186 component increased in amplitude and the N250 component decreased in amplitude.

Another approach to understanding the differences between hyperkinetic children and non-hyperkinetic normal children, as well as the effect of drugs on hyperkinetic children, is to consider the magnitude of the difference between the response to uncertainty and certainty. Studies in normal adults have shown that the late positive components of the evoked potential are larger under conditions of uncertainty than certainty.

Differences in the late positive components of the response to uncertainty and certainty were found to be significantly smaller in hyperkinetic children than in non-hyperkinetic normal children. It is believed that this is reflective of the inability of hyperkinetic children to focus attention in response to task demands. Methylphenidate was once again seen to "normalize" the response of hyperkinetic children, increasing the magnitude of the difference in the response between uncertainty and certainty.

The question of the relationship between the average evoked potential and differential clinical response to drug was not studied in this investigation. The comparison between responders and nonresponders is usually done prior to drug sessions. In the present study, the drug sessions always preceded the placebo sessions and an evaluation prior to drug treatment was not possible. While the responders and nonresponders could have been compared under the placebo condition, this is not completely satisfactory since one could not rule out the possibility of some subtle carry over effect from the preceding drug sessions. However, since the present study has shown that evoked potential measures are useful in differentiating hyperkinetic children from non-hyperkinetic normal children, and in reflecting the effect of medication on hyperkinetic children, further studies investigating differences in hyperkinetic children who are clinically described as drug responders and nonresponders in relation to the present findings would be of interest.

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Appendix 1

Conners Teacher Rating Scale

Conners Teacher Rating Scale (As adapted by Psychopharmacology Research Unit – Downstate Medical Center.)

Listed below are descriptive terms of behavior. Place a check mark in the column which best describes this child. ANSWER ALL ITEMS.

Observation	Degree of Activity			
	Not at all	Just a little	Pretty much	Very much
1. Restless or overactive				
2. Excessive demands for teacher's attention				
3. Disturbs other children				
4. Hums and makes other odd noises				
5. Exciteable				
6. Teases other children or interferes with their activities				
7. Sits fiddling with small objects				
8. Overly anxious to please				
9. Defiant				
10. Selfish				
11. Impudent				
12. Quarrelsome				
13. Acts "smart"				
14. Lies				
15. Temper outbursts				
16. Stubborn				
17. Uncooperative				
18. Sullen or sulky				
19. Destructive				
20. No sense of fair play				
21. "Tattling"				
22. Steals				
23. Daydreams				
24. Difficulty in concentrating				
25. Appears to lack leadership				
26. Inattentive				
27. Appears to be easily lead				
28. Coordination poor				
29. Submissive				
30. Oversensitive				
31. Fearful				
32. Overly serious or sad				
33. Shy				
34. Falls apart under stress or examination				
35. Attendance problem				
36. Does not get along with same sex				
37. Appears to be unaccepted by group				
38. Does not get along with opposite sex				
39. Isolates himself from other children				
40. Drowsiness				
41. Personal hygiene neglected				

Appendix 2

Mean Amplitude For Each Component In Each Condition For Each Subject Group

Table A

Mean Amplitude[a] (in μV relative to baseline) for Each Component of the Average Evoked Potential in Response to the First Click in the Guess Single and Guess Double Conditions

Group	Condition	Component[b]					
		P63	N103	P186	N250	P295	N377
Period I:							
Hyperkinetic Drug	Guess Single	0.23	8.63	5.93	1.85	0.50	9.74
	Guess Double	-0.72	9.45	4.56	3.69	-1.39	10.87
Hyperkinetic Control	Guess Single	1.82	2.95	6.76	3.00	0.49	6.89
	Guess Double	2.95	2.63	6.38	2.39	1.93	5.96
Normal Control	Guess Single	1.38	3.27	7.54	-0.22	3.07	7.67
	Guess Double	2.07	3.55	6.35	0.58	3.73	6.03

(continued)

Table A
(continued)

Group	Condition	Component[b]					
		P63	N103	P186	N250	P295	N377
Period II:							
Hyperkinetic Drug	Guess Single	1.69	5.19	8.02	1.79	0.74	8.34
	Guess Double	1.70	5.18	9.18	0.82	3.34	5.39
Hyperkinetic Control	Guess Single	2.51	2.33	6.78	2.21	0.35	6.58
	Guess Double	2.02	3.42	8.65	2.20	0.85	6.16
Normal Control	Guess Single	2.85	1.57	7.86	1.41	4.34	7.88
	Guess Double	2.23	3.03	9.11	-0.56	4.37	5.76

[a]Amplitudes are averaged across subjects separately for each group.

[b]Components which are not in the appropriate position relative to baseline (i.e., negative components which are below baseline or positive components which are above baseline) are indicated by a negative sign. In these cases, the smaller the negative number the larger the component.

Table B

Mean Amplitude[a] (in μV relative to baseline) for Each Component of the Average Evoked Potential in Response to the Second Click in the Double Right and Double Wrong Conditions

Group	Condition	Component[b]					
		P63	N103	P186	N250	P295	N377
Period I:							
Hyperkinetic Drug	Double Right	4.09	2.48	26.40	-23.88	27.61	-18.11
	Double Wrong	5.09	3.47	31.21	-26.84	29.46	-17.22
Hyperkinetic Control	Double Right	0.09	2.56	11.13	- 8.80	20.72	-12.91
	Double Wrong	3.40	2.22	13.15	-13.11	21.45	-12.44
Normal Control	Double Right	2.95	-0.29	22.23	-19.06	25.13	-10.54
	Double Wrong	6.58	0.09	22.04	-20.00	25.83	-13.15

(continued)

Table B
(continued)

Group	Condition	Component[b]					
		P63	N103	P186	N250	P295	N377
Period II:							
Hyperkinetic Drug	Double Right	3.22	2.93	21.75	-18.10	21.80	-10.83
	Double Wrong	3.79	1.63	21.02	-15.93	20.29	- 9.91
Hyperkinetic Control	Double Right	1.63	1.82	12.78	-10.40	16.97	-10.45
	Double Wrong	1.99	0.75	13.01	-11.15	17.93	- 7.82
Normal Control	Double Right	4.12	0.94	19.59	-15.01	23.75	-10.93
	Double Wrong	4.81	-0.37	26.45	-21.82	26.10	- 9.04

[a]Amplitudes are averaged across subjects separately for each group.

[b]Components which are not in the appropriate position relative to baseline (i.e., negative components which are below baseline or positive components which are above baseline) are indicated by a negative sign. In these cases, the smaller the negative number the larger the component.

Table C

Mean Amplitude[a] (in μV relative to baseline) for Each Component of the Average Evoked Potential in Response to the First Click in the Single Certain and Double Certain Conditions

Group	Condition	Component[b]					
		P63	N103	P186	N250	P295	N377
Period I:							
Hyperkinetic Drug	Single Certain	-1.63	11.84	5.89	2.89	0.45	8.93
	Double Certain	1.76	9.18	6.73	2.31	1.26	6.19
Hyperkinetic Control	Single Certain	3.11	3.82	8.09	2.67	1.36	4.37
	Double Certain	-0.17	4.76	7.25	1.97	1.40	6.51
Normal Control	Single Certain	1.68	2.28	6.86	-1.98	6.30	3.79
	Double Certain	1.84	2.12	7.21	0.36	3.73	5.04

(continued)

Table C
(continued)

Group	Condition	Component[b]					
		P63	N103	P186	N250	P295	N377
Period II:							
Hyperkinetic Drug	Single Certain	2.59	5.00	12.46	-2.11	5.40	3.44
	Double Certain	2.22	6.31	10.54	-1.58	2.76	4.98
Hyperkinetic Control	Single Certain	3.29	- 0.13	10.69	0.91	2.84	3.49
	Double Certain	2.05	1.44	7.60	2.00	0.40	5.08
Normal Control	Single Certain	0.99	2.96	8.87	-1.41	4.30	4.93
	Double Certain	3.59	0.96	9.60	0.00	2.90	3.73

[a]Amplitudes are averaged across subjects separately for each group.

[b]Components which are not in the appropriate position relative to baseline (i.e., negative components which are below baseline or positive components which are above baseline) are indicated by a negative sign. In these cases, the smaller the negative number the larger the component.

Table D

Mean Amplitude[a] (in μV relative to baseline) for Each Component of the Average Evoked Potential in Response to the Second Click in the Double Certain Condition

Group	Condition	Component[b]					
		P63	N103	P186	N250	P295	N377
Period I:							
Hyperkinetic Drug	Double Certain	2.28	3.91	10.06	-6.02	10.09	-3.18
Hyperkinetic Control	Double Certain	2.27	2.55	8.38	-1.54	5.71	1.15
Normal Control	Double Certain	2.56	2.23	8.10	-1.30	3.53	2.19
Period II:							
Hyperkinetic Drug	Double Certain	1.79	3.98	9.35	-3.00	7.70	0.32
Hyperkinetic Control	Double Certain	2.47	0.85	10.45	-2.75	10.11	0.06
Normal Control	Double Certain	2.07	-0.17	8.71	-0.91	3.32	2.11

[a] Amplitudes are averaged across subjects separately for each group.

[b] Components which are not in the appropriate position relative to baseline (i.e., negative components which are below baseline or positive components which are above baseline) are indicated by a negative sign. In these cases, the smaller the negative number the larger the component.

Table E

Mean Amplitude[a] (in μV relative to baseline) of the Early Negative and Late Positive Components of the Average Evoked Potential in Response to the Absence of the Second Auditory Stimulus in the Single Right, Single Wrong and Single Certain Conditions

		Component[b]	
Group	Condition	Early Negative	Late Positive
Period I:			
Hyperkinetic Drug	Single Right	-1.09	28.71
	Single Wrong	0.11	25.90
	Single Certain	1.35	17.28
Hyperkinetic Control	Single Right	0.41	17.74
	Single Wrong	1.08	17.80
	Single Certain	2.40	12.83
Normal Control	Single Right	1.65	22.57
	Single Wrong	1.44	23.32
	Single Certain	2.14	9.87

(continued)

Table E
(continued)

Group	Condition	Component[b] Early Negative	Late Positive
Period II:			
Hyperkinetic Drug	Single Right	0.87	25.69
	Single Wrong	0.75	22.68
	Single Certain	2.95	13.95
Hyperkinetic Control	Single Right	2.29	17.26
	Single Wrong	2.65	15.04
	Single Certain	2.61	9.56
Normal Control	Single Right	0.87	23.84
	Single Wrong	1.84	23.50
	Single Certain	2.58	9.60

[a]Amplitudes are averaged across subjects separately for each group.

[b]Components which are not in the appropriate position relative to baseline (i.e., negative components which are below baseline or positive components which are above baseline) are indicated by a negative sign. In these cases, the smaller the negative number the larger the component.

Table F

Mean Amplitude[a] (in μV relative to baseline) of the Contingent Negative Variation (CNV) in the Guess Single, Guess Double, Single Certain, and Double Certain Conditions

Group	Condition			
	Guess Single	Guess Double	Single Certain	Double Certain
Period I:				
Hyperkinetic Drug	13.00	13.60	13.18	10.34
Hyperkinetic Control	12.25	10.69	8.78	8.06
Normal Control	10.03	9.71	7.48	5.04
Period II:				
Hyperkinetic Drug	11.56	9.47	6.86	5.37
Hyperkinetic Control	10.81	9.57	9.24	7.63
Normal Control	10.26	7.59	5.81	3.41

Table G

Mean Amplitude[a] (in μV relative to baseline) of the Resident Contingent Negative Variation (CNV) in the Guess Single, Guess Double, Single Certain, and Double Certain Conditions

Group	Condition			
	Guess Single	Guess Double	Single Certain	Double Certain
Period I:				
Hyperkinetic Drug	13.04	11.75	8.24	7.43
Hyperkinetic Control	13.43	10.41	10.42	10.13
Normal Control	9.10	9.68	1.58	3.93
Period II;				
Hyperkinetic Drug	10.63	8.54	7.04	2.64
Hyperkinetic Control	10.37	9.98	6.21	6.43
Normal Control	12.96	9.84	5.35	3.18