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Recovery of auditory event-related potentials in normal and Down's syndrome individuals

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RECOVERY OF AUDITORY EVENT-RELATED POTENTIALS IN NORMAL AND DOWN'S SYNDROME INDIVIDUALS

by

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ABSTRACT

Recovery of Auditory Event-Related Potential Amplitudes
in Normal and Down's Syndrome Individuals

Alexander Amochaev

The amplitude of auditory event-related potentials (ERPs) increases in equal increments as the interval between stimuli is doubled. This recovery function provides an index of the extent to which the central nervous system has recovered or released from inhibition its capacity to respond to the following stimulus. The decay of a number of inhibitory processes has been postulated to underlie amplitude recovery; these include neural refractoriness, temporal certainty of stimulus arrival and slow and fast habituation. The purpose of the present study is to determine which of these is the primary inhibitory process. Previous research has revealed that individuals with Down's syndrome do not habituate the amplitude of ERPs to repetitive stimuli. If these individuals exhibit a recovery function with increasing inter-stimulus intervals (ISIs), then habituation can be eliminated as a primary attenuating process.

Auditory stimuli at ISIs from .5 to 32 seconds were presented in groups with equal intervals and in randomized order to 14

normal individuals and 9 with Down's syndrome. Stimuli with randomized ISIs in a third condition were preceded by 1 second with the onset of a light-emitting diode (LED). ERPs at each ISI were averaged from 10 post-stimulus epochs.

Individuals with Down's syndrome exhibited a recovery function similar to that of normals when stimuli were presented in groups with equal intervals. Randomizing the order in which ISIs are presented should minimize the development of habituation and prevent temporal certainty of stimulus arrival. The recovery function obtained with this schedule differed significantly from that obtained with regularly presented ISIs. Maximum ERP amplitudes were reached at a much shorter interval, thus also eliminating neural refractoriness as a significant factor. Stimuli preceded by a fixed period warning signal evoked ERPs with amplitudes that were equal at all ISIs.

These results show that loss of temporal certainty is the major process underlying the recovery of ERP amplitudes. A decrease in habituation, historically advanced as the primary process, was determined not to be a contributing factor. It was also demonstrated that peak P200 of the auditory ERP indexes an expectancy process distinct from temporal certainty of stimulus arrival. These two processes can be viewed as changes in subjective probability of absolute and estimated time of stimulus occurrence.

INTRODUCTION

A. Event-Related Potentials

The electrical activity detectable from the human scalp following a brief sensory stimulus, is recorded as a waveform containing a series of positive-negative potentials representing the brain's response to the stimulus. In order to extract these event-related potentials (ERPs) from ongoing activity, stimuli are repeated and the ensuing bioelectric activity is averaged over a specified time epoch. One of the assumptions underlying this form of averaging is that the signals of interest (the ERPs) are relatively constant following each stimulus whereas the ongoing (spontaneous) activity is considered to be random in nature. The ERPs following an auditory stimulus, for example, may persist over 500 milliseconds and include evidence of excitation from the sensory end organ to the cortex. Event-related potentials consist of the summated activity of both action potentials and graded post-synaptic potentials involving many neurons (Wood, et al., 1981).

The averaged waveform evoked by auditory stimuli may consist of as many as twenty five positive-negative peaks over 500 msec.; it is not possible to assign each peak solely to one neuronal pool or nucleus. At best an estimate of each peak's origin is suggested as a caudal to rostral progression through different levels of the acoustic sensory pathways. The earlier peaks (1-25 msec.), therefore, are presumed to originate in auditory brain stem and diencephalic structures (Buchwald, 1983). The longer latency peaks

(25-500 msec) most likely originate in or near the primary and associative auditory cortex in the temporal-parietal region, although activity in other cortical and sub-cortical areas may also contribute to the waveform (Squires and Hecox, 1983). The scalp site of the active recording electrode determines to a large extent the number of peaks present later in the waveform.

Individual potentials or peaks are identified by their polarity and usual or expected peak latency (e.g. P300 is a positive peak with a post-stimulus latency of 300 msec.) (Donchin, et al., 1977). The late potentials can also be classified as having exogenous or endogenous properties. The former term is related to sensory processing while the latter is thought to be related to cognitive processing (Donchin, et al., 1978). The amplitudes and latencies of exogenous peaks (50-250 msec) are influenced by and generally considered to primarily reflect stimulus parameters such as intensity, duration, frequency and interval. The endogenous peaks (250-500 msec) on the other hand are thought to reflect primarily psychological processes such as subjective probability of specific stimulus occurrence or stimulus evaluation. They are also employed in studying brain correlates of such hypothetical constructs as stimulus and response set in information processing. In reality this distinction is somewhat arbitrary, since all of the components can respond to both exogenous and endogenous factors. For example, the late P300 peak can reflect stimulus intensity (Roth et al., 1982), while the earlier peaks (50-250 msec) are dependent on a subject's state of

consciousness, degree of attention paid to stimuli, habituation and certainty of stimulus arrival (Hillyard, et al., 1978).

B. Recovery Function of Auditory ERPs

Lengthening or decreasing the interstimulus interval (ISI) is one of the major determinants of the amplitude of the ERPs (Hillyard, et al., 1978). As the ISI between two stimuli is prolonged, the ERPs evoked by the second stimulus increase in amplitude. A recovery cycle can be determined by presenting paired stimuli at successively greater intervals and plotting the amplitudes of the ERPs to the second stimulus as a function of ISI. This recovery function, or cycle, provides an index of the degree to which the central nervous system has recovered or released from inhibition it's capacity to respond to a new stimulus. A number of mechanisms have been postulated to underly the progressive diminution of ERPs amplitudes with decreasing ISIs. These include neural refractoriness (Ritter, et al., 1968; Rothman, et al., 1970) implying fatigue or depletion of metabolic neural processes, adaptation (Nelson and Lassman, 1973), fast habituation (Callaway, 1973), sensory gating (Rothman, et al., 1970), habituation (Fruhstorfer, et al., 1970) and temporal certainty (Wastell, 1980; Schafer, et al., 1981). Recent studies demonstrate that the recovery of auditory ERPs' amplitudes are mediated by a number of neural substrates. Knight et al. (1980) demonstrated that in the presence of unilateral temporal-parietal lesions the N100 component did not increase in amplitude with lengthening ISIs. Woods et al. (1980) found that the P300 component could recover completely after

900 msec. while the earlier components did not recover with ISIs of less than 7 sec. They suggest that the generators of P300 differ from those of other long-latency components. Hari et al. (1982) recorded ERPs from multiple scalp locations as well as averaged magnetoencephalographic (MEG) responses. They found that as ISIs were prolonged from 1 to 16 seconds, the amplitude maximum of component N100 moved posteriorly to the vertex, indicating that different neural sources are activated by frequent and infrequent stimuli.

Recovery functions are similar in response to auditory, tactile and somatosensory stimuli. Visual stimuli, it has been found, evoke a less steep recovery function at 1 and 2 sec. intervals than do stimuli in the other modalities (Gjerdingen and Tomsic, 1970). The auditory modality has been employed most extensively and will be the focus of this research.

C. Recovery Cycles - Previous Research

Davis and his colleagues (1966) were among the first to systematically investigate the effects of varying interstimulus intervals on the auditory vertex ERPs. They reported that the amplitude of the ERPs to the second stimulus of a pair separated by 0.5 sec. increased as the interval between pairs was prolonged. When the inter-pair ISIs were progressively lengthened from 2 to 20 seconds, the relative amplitudes of the second ERPs to the first maintained a ratio in the range of .33 to .50, even as the absolute amplitudes of both ERPs increased. They also reported

that when a 1 sec. interval is maintained between pairs of stimuli, the ERPs, to the second stimulus are larger if the interval between pairs is widely spaced rather than a regular series at 1 sec. per stimulus. They concluded that the recovery of ERPs is dependent not only on the first but also on the second prior interval between stimuli, and that maximum amplitude recovery occurs with an ISI of at least 10 sec. Their method of separating stimuli was not adopted by later investigators. Nelson and Lassman (1968) examined the recovery function of auditory ERPs using regular blocks of ISIs of 0.25 to 6 sec. They reported that the amplitudes of component N100-P200 increased an equal amount with each doubling of ISI; the magnitude of this component increases as a linear function of the logarithm of the recovery period. They also reported a positive correlation between subjects' absolute peak amplitudes and the steepness of their recovery function. These investigators also examined the effect of the order in which different blocks of ISIs up to 6 sec. were presented, either as regularly ascending or descending blocks or randomized, and found that this manipulation produced no unique effect on recovery. Gjerdingen and Tomsic (1970) also reported a monotonic increase in ERPs amplitudes with increases in ISIs from 0.5 to 5 sec, with no further increase at 10 sec.

1. Stimulus Schedule

The effect of presenting stimuli with randomly varying ISIs in contrast to regularly occurring ISIs has been explored by Nelson, Lassman and Hoel (1969); Rothman, Davis and Hay (1970); Ohman

McLean and Lader (1975) and Nelson and Lassman (1977). Typically the random ISIs used had a rectangular mean distribution around an ISI equal to the regularly presented stimuli. Ohman et al. (1975) stated that a refractoriness hypothesis for the ERPs recovery function would predict a larger amplitude decrement with irregular ISIs since there would be shorter intervals present than with regularly presented ISIs. However, since there would also be longer than average ISIs, and the recovery function is exponential, the net averaged ERPs should have larger amplitudes. One group (Nelson, et al., 1969, 1977) employed a geometric distribution which better approximates the ERPs recovery function; they found that aperiodicity tended to increase ERP amplitudes, but not significantly so. In summary, the general finding has been that little or no amplitude advantage is gained by using randomly presented ISIs. However, no direct comparison of the same ISIs, presented in blocks and randomly distributed, has been made.

2. Habituation and Refractoriness

Habituation of ERPs has often been proposed as the mechanism responsible for amplitude diminution. Callaway (1975) argues that habituation and recovery cycle studies should be considered together, since "most forms of habituation involve some sort of recovery cycle (p. 80)." Roemer et al. (1984) argue that while "habituation may be a particular subset of the more general physiological property of recovery or relative refractory periods, habituation requires meeting a different set of criteria" (p. 336). Many studies investigating habituation employ experimental designs

that allow for analysis of stimulus by stimulus response decrements. When blocks of regularly occurring stimuli at a 2 sec ISI were presented in such a manner that ERPs could be averaged by stimulus position in a block, it was revealed that the amplitude of component P200 declines by 50% after the second or third stimulus (Ritter, et al., 1968); Callaway (1975) termed this fast habituation. The same sort of amplitude decrement was not observed when an ISI of 10 sec within blocks was employed. These researchers failed to dishabituate the ERPs to the 2 sec ISIs (using their own criteria of habituation) and concluded that the amplitude decrements were due to relative refractoriness within the generators of the auditory ERPs. Roth and Kopell (1969) using a similar experimental design and recording vertex ERPs, found similar amplitude attenuation to the second and subsequent stimuli. These researchers declined to speculate on the neurophysiological mechanisms underlying this amplitude decrement, but indicated that neural refractoriness was an unlikely one, given the relatively long ISIs employed.

Bess and Rhum (1972) presented pairs of click stimuli to opposite ears in intervals from 1 to 5000 msec. while recording ERPs from electrodes placed over the ipsilateral lobe. They found that the ERPs to the second click showed a 50% recovery after as little as 3 msec. This is comparable to the interpair recovery ratio reported by Davis et al. (1966) with ISIs up to 20 sec between pairs of stimuli presented binaurally. The conclusion reached by Bess and Rhum was that monaural stimuli activated neural

units comprising the population representing the ipsilateral ear and minimally activating contralateral neurons. These would then not be refractory and could respond to the second stimulus. Butler (1973) demonstrated that with ISIs of less than 300-400 msec, ERP amplitudes may increase rather than diminish. Sutton et al. (1967) demonstrated that when the second of two stimuli separated by 580 msec, carried information relevant to subjects, ERPs did not show diminished amplitudes. Salamy et al. (1984) have found while recording auditory brain stem evoked potentials (BEP), that stimuli could be separated by as little as 6 msec. without affecting the amplitude of P5 of the second BEP. Since each peak of the BEP represents activity in multiple generators, simple neural refractoriness does not appear to explain diminished amplitudes at longer ISIs. Callaway (1973) suggests that periods of unresponsiveness in aggregates of cells reflect an active inhibitory process rather than temporary exhaustion of physiochemical systems.

Habituation, however, also cannot be invoked as the sole mechanism or process by which ERP amplitudes are diminished at ISI greater than .5 sec. In a recent review (Roemer, et al., 1984), studies claiming ERP habituation were examined using the nine criteria of Thompson and Spencer (1966) in an attempt to separate habituation processes from refractory ones. They conclude that the available literature on human ERPs fails to establish a clear differentiation between these processes and that, "In the absence of convincing evidence that habituation accounts for EP response decrements, simplicity requires that these decrements be attributed

to refractory periods".

3. Adaptation

"Recovery cycles", according to Roemer et al. (1984) "predict response decrements independent of stimulus intensity, habituation does not." They further state: "For ISIs greater than .5 sec, a recovery or refractory model predicts EP response decrements at all intensities of stimulation. Conversly the dual process model predicts response decrement at low intensities and increment at higher intensities independent of ISI" (p. 340). Nelson and Lassman (1973) examined vertex ERP recovery from ISIs of .5 to 6 sec at six intensities, from 15 to 90 dB SL. They found that higher stimulus intensity evoked larger absolute amplitudes and steeper recovery functions. Intensity had more of an effect on peak amplitudes (N1-P2) at long than at short ISIs. This result indicates an interaction between habituation and recovery processes. It is not at all clear that they can be separated as to which is predominantly operating at a given ISI. Nelson (1970) posits that this interaction is similar to adaptation, which he states follows two fundamental rules: "1) more adaptation should occur as the time since previous stimulation is shortened, and 2) more adaptation should occur at intense than at low stimulation levels".

4. Attention

The effect of focusing attention on stimuli evoking ERPs has been widely investigated (see Hillyard et al., 1983). The general finding has been that increased attention enhances ERP peak amplitudes. Nelson and Lassman (1977) observed an increased

amplitude of component N2-P3 when subjects counted stimuli compared to when they were reading. This was observed with both regularly and randomly presented stimuli, however, all stimuli in each condition were averaged together and a recovery function was not determined. A study by Roth et al. (1976) in which subjects' attention was directed towards all stimuli by having subjects perform a reaction time response to target stimuli failed to find any amplitude increases in N100 and P200 compared to a condition in which subjects were reading. In this study three ISIs of 0.75, 1.5 and 3 sec. were presented randomly to determine how stimulus intensity, stimulus sequence and subjects' direction of attention affected the recovery function. While it was confirmed that each doubling of ISI produced equal increments in ERPs amplitudes, as in previous studies, no effect of the second prior interval was observed. This is in contrast to the conclusion reached by Davis, et al. (1966). These earlier researchers however, had contrasted a regular series of 1 sec. ISI with stimulus pairs that were separated by 1 sec., but with longer interpair intervals. As was noted earlier, consecutive stimuli presented at short ISIs decrease amplitudes much more rapidly than those with longer ISIs.

5. Temporal Certainty

A number of studies have demonstrated that temporal certainty of stimulus arrival can attenuate ERP amplitudes. Schafer and Marcus (1973) demonstrated that peak N100-P200 amplitudes were smaller in response to stimuli that subjects delivered to themselves than when the same sequence of stimuli arrived via tape playback. A

later study (Schafer et al., 1981) demonstrated a similar effect could be obtained if the arrival of auditory stimuli was cued visually. Wastell (1980) conducted a similar experiment using two ISIs of 3 and 9 sec. While cued stimuli evoked ERPs with smaller peak amplitudes, he also reported that in the cued condition there were no differences in N100-P200 amplitude between 3 and 9 sec. ISIs. Wastell argues that amplitude recovery reflects an increase in temporal uncertainty of stimulus arrival. Indeed, Roth and Ford (1981) demonstrated that when stimuli arrive earlier than expected by subjects, even at an ISI of 300 msec., amplitudes of ERPs were increased. They concluded, however, that the ERP components they recorded may reflect a stimulus mismatch and are not stimulus determined in the same manner as the normally recorded N100-P200 components. Ornitz et al. (1972) recorded ERPs to stimuli separated by 0.5 sec. within pairs and 2 and 6.5 sec. between pairs from very young children during sleep. The second of the pair of stimuli evoked ERPs with smaller amplitudes than the first stimulus in general, although the stage of sleep did interact with the interpair ISI amplitude ratios and absolute amplitudes. These results present some problems to Wastell's hypothesis, since it is unlikely that much conscious stimulus anticipation occurs during sleep.

D. Down's Syndrome

A number of studies over the past fifteen years have reported that individuals with Down's Syndrome exhibit ERPs with enhanced amplitudes compared to normal subjects (Bignum, et al., 1970;

Callner, et al., 1978; Straumanis, et al., 1973). This finding has been attributed to a lack of response decrement, often described as a failure to habituate, to both regularly and randomly presented trains of stimuli at ISI from 2 to 8 sec. (Barnet, et al., 1971; Lichy, et al., 1975; Schafer and Peeke, 1982). This deficiency has been observed in both fast habituation occurring over just several stimuli, and slow habituation over longer periods of stimulation. It has been proposed that the failure to decrement ERP amplitude results from either a general dysfunction of afferent inhibitory mechanisms (Callner, et al., 1978) or from an inability to form temporal expectancy of stimulus arrival which would invoke specific inhibition (Barnet, et al., 1971; Schafer and Peeke, 1982).

If habituation or temporal expectancy are primary mediating factors in recovery, then Down's individuals would not be expected to exhibit a recovery cycle since they do not decrement the amplitudes of ERPs as readily as normals. However, if a recovery function can be obtained then some other process of response inhibition, separate from the two generally proposed, must be operating. A study by Yellin (1980) employing four Down's subjects reports an increase in N100-P200 amplitudes between clocks of stimuli presented at 1 and 4 sec. with no further increase at 8 sec. ISIs. This result points to a possibility that Down's individuals may be able to inhibit ERP amplitudes.

RESEARCH OBJECTIVES

There is no clear agreement as to why ERP amplitudes continue to increment when the ISI is lengthened beyond .5 sec. A reversal of neural refractory states is not a likely mechanism since peak amplitudes do not necessarily decrease even at short ISIs (app. 600 msec.) if stimuli carry information relevant to the subject (Sutton, et al., 1967). A slower rate of habituation, in terms of it's strictest definition, also has not been fully accepted as a major process underlying this ERP recovery. Lack of temporal certainty or temporal conditioning, that results when responses are made to stimuli that are anticipated by virtue of their regular occurrence, is consistent with previous data and the most likely explanatory concept.

If temporal uncertainty is a major determinant in recovery of ERPs in normal subjects, then it follows that amplitudes should no longer increase after some ISI that exceeds a psychological timekeeping ability or when all succeeding ISIs become similarly unpredictable. This should apply equally to randomly and regularly presented stimuli. At short ISIs, those arriving randomly would be both less expected and less certain and thus should evoke larger amplitudes than identical ISIs presented regularly. Callaway (1975) has demonstrated that any temporal advantages gained by self-delivering stimuli is lost if more than a 3 sec. delay is introduced before the stimulus. Longer ISIs in either schedule should engender more expectancy as time passes, but less certainty as to the moment of occurrence. The first two experiments in this

thesis are designed to test these propositions.

The affect of temporal certainty can be tested directly by cuing stimulus arrival. If this is the primary decremental process, then when randomly presented stimuli are preceded by a fixed warning period, ERP amplitudes should be independent of ISI. This proposition is tested by the third experiment.

It has been proposed that Down's individuals do not form a temporal expectancy to regularly occurring stimuli, since they do not exhibit fast or slow habituation. It is hypothesized that if a recovery function of the amplitude of auditory ERPs can be obtained with Down's individuals, then an inhibitory process distinct from habituation, as strictly defined or as described in previous studies, underlies their response decrement. Furthermore, if a similar recovery cycle can also be obtained with randomly occurring stimuli, then this would eliminate temporal conditioning as the primary mediating factor, particularly at short ISIs.

A recent experiment (Adler, et al., 1982) demonstrated that acutely psychotic schizophrenics fail to show substantial decrements of P50 amplitude. This enhanced response to the second stimulus in a pair, having an intra-pair ISI of .5 sec. and an inter-pair ISI of 10 sec., suggests "a defect in an inhibitory pathway for gating auditory evoked activity...". Although there are no other parallels in ERPs between this group and the Down's group, it is instructive to test the latter group with an equivalent procedure to determine if they display the same degree of dysfunction of inhibitory processes. The normal subjects will also be tested to determine the expected amount of recovery obtainable with the present procedure.

METHODS-NORMAL SUBJECTS

The present set of experiments used auditory stimuli at varying inter-stimulus intervals to produce recovery functions of event-related potential amplitudes. Random and regular stimulus schedules were employed. In a third condition stimuli were preceeded by the onset of a light emitting diode (LED) to cue their arrival. An inhibitory process, in response to the second of two stimuli separated by .5 sec. with a 10 sec. inter-pair recovery period, was also assessed.

Subjects

Fourteen normal adult subjects (7 men, 7 women) were recruited from the staff of Sonoma State Hospital. Participation was voluntary and required informed consent. They had a negative history of hearing loss or neurological disorders by self report. Their mean age was 34 years and ranged from 28 to 47.

Procedures

Subjects were given a brief explanation of the experimental protocol and were given a Human Subject's consent form to read and sign. Throughout the one and a half hour session subjects were seated in a comfortable reclining chair in a small room and asked to sit quietly with their eyes open. They were visible to the experimenter, at all times, through a one way mirror. Specific instructions concerning deployment of attention to stimuli were given before each experiment.

Recording

During all experiments ERPs were recorded from Grass gold cup electrodes. The skin underlying the electrodes was first cleaned with alcohol then gently rubbed with a mildly abrasive gel, they were held in place with a conductive cream. The active electrode was placed at Cz (vertex of the scalp) and referred to linked ear lobe electrodes; an electrode placed on the forehead served as the common. Since eye movements or blinks can introduce an artifact into the EEG, vertical electro-oculogram (EOG) activity was also recorded. A silver-silver chloride electrode was placed (with an adhesive collar) approximately 1/2 inch above the left supraorbital ridge and 1/2 inch below the infraorbital ridge in line with the subject's pupil.

EEG activity was amplified with a gain of 25,000 by Grass p-511 preamplifiers, and conditioned by Krohn-Hite active filters set at a bandpass of 1Hz to 40Hz with a 24dB per octave rolloff. EOG activity was similarly conditioned, but each subject's gain was set at a level that did not exceed the limits of the computer's analog to digital converter. Both EEG and EOG activity were sampled every 2 msec. by the computer (Data General Nova 2 minicomputer) over 600 msec. for each stimulus, including a 100 msec. prestimulus baseline. In all of the experiments save one, both the ERPs and EOG were averaged from 10 post-stimulus epochs of activity. A pilot study indicated that well formed ERP waveforms could be reliably obtained from this small number of stimuli. This procedure permitted averaging seven waveforms during a single

condition, reducing subject fatigue and long term ERP decrements.

Stimuli were 50 msec. bursts of white noise delivered binaurally through headphones at an intensity level of 60 dBnHL. The stimulus delivery schedule in all experiments was under control of the computer.

Stimulus Schedules

Experiment 1

Eleven stimuli with equal ISIs were presented within 7 blocks. Each block contained one of the following ISI: .5, 1, 2, 4, 8, 16, or 32 seconds. The order of blocks was randomized, with the same order presented to all subjects. The response to the first stimulus in a block was not included in the averaged ERPs. There was a random 25 to 40 sec. interval between blocks. Subjects were informed as to how many stimuli would occur in each block and were asked to count the total number of blocks.

Experiment 2

The same seven ISIs were presented in a randomized order, the only restriction was that the same ISI was not presented more than three times consecutively. Each of the seven ERPs were again averaged from 10 stimuli, which were segregated by the computer. Subjects were asked to keep a mental count of the total number of stimuli.

Experiment 3

Five different ISIs of 2, 4, 8, 16 and 32 sec. were presented in a randomized order with 10 stimuli at each ISI as above. Each

auditory stimulus in this experiment was preceded by 1 sec. with the onset of a dimly lit LED. The LED was mounted at eye level and 5 feet in front of the subject; it was turned off with the noise burst. A randomized block of 10 LED onsets was presented without auditory stimuli to three subjects to insure that LED onset did not evoke ERPs. Subjects were again asked to keep a count of all stimuli.

Experiment 4

Thirty two stimulus pairs were delivered with an intra-pair ISI of .5 sec. and an intra-pair interval of 10 sec. Two averaged ERPs were recorded, from the first and second stimulus in a pair. No instructions were given to keep track of the stimuli.

All of the four procedures listed above were randomized in their order of presentation across subjects.

RESULTS

The independent measures in these experiments were interstimulus intervals, presented in a regular and random order. The dependent measures used to assess their effect were ERP amplitudes and peak latencies. The average amplitude and latency recovery functions were contrasted for differences between stimulus schedules.

Event Related Potentials

ERPs were recorded from Cz and were scored visually on a CRT display to identify four peaks having approximate latencies of P50, N100, P200 and N250 msec. post-stimulus. Peak amplitudes were measured in microvolts from a pre-stimulus baseline by the computer. When double peaks were encountered in a designated post-stimulus time range, the deflection nearest the group averaged ERPs was used in the analyses. An automatic peak picking program was evaluated and found to be too sensitive, identifying a confusing multiplicity of peaks. Average ERP amplitudes and their standard deviations, by ISI for all conditions, for four peak to baseline measures are listed in Tables 1 to 4.

Eye-movement Potentials

The averaged EOG activity was analysed in the same manner as the EEG. No deflections greater than 3uv were found in the latency ranges for the four ERP peaks. This activity was regarded as having minimal influence on the amplitudes recorded at Cz, and was not further analysed.

Statistical Analyses

Amplitudes

Experiments 1 and 2.

A two way repeated measures analysis of variance (ANOVA) was performed on peaks N100, P200 and N250 with two levels of the Condition factor (random and regular) and seven levels on ISI (see Methods). A significant Condition by ISI interaction was obtained for N100, $F(6,78)=4.65$, $p<.05$, and P200, $F(6,78)=9:55$, $p<.01$. Significant main effects and specific contrasts are presented for each peak below. All significant t-tests reported have an associated probability level of $p<.01$.

Peak N100

A significant main effect was obtained for Condition, $F(1,13)=5:68$, $p<.03$, a significant main effect for ISI was also obtained, $F(6,78)=15.24$, $p<.002$.

T-tests of differences between pairs of ISI in each condition revealed that there was no significant increase in N100 amplitudes across ISIs in the random condition. In the regular condition there was no change in amplitude between .5 and 1 sec. ISIs, after that there was an average increase of 2.5 uv at each doubling of ISI to 32 sec. Significant differences were obtained between every other ISI rather than between consecutive ones.

T-tests of differences of equal ISIs between conditions revealed significantly larger amplitudes at .5 and 2 sec. during random stimulation. These recovery functions are graphed in Figure 1.

Peak P200

A significant main effect for Condition was obtained, $F(1,13)=28.37$, $p<.001$ and also for ISI, $F(6,78)=9.59$, $p<.001$.

T-tests of differences between pairs of ISIs with random stimulation revealed a significant increase in amplitudes between each ISI from .5 to 2 sec. There was also a significant 3uv increase in amplitude at 32 sec. contrasted with that at 2 sec. In the regular condition there was an increase in amplitude between .5 and 1 sec of 2.5uv, no change between 1 and 2 sec. and then a steady increase of approximately 5 uv to 32 sec, however, there was no increase between 8 and 16 sec.

T-tests of differences in equal ISIs between experiments revealed that there were no differences in amplitude at .5 sec. The amplitudes during random stimulation were significantly greater at ISIs of 1, 2, 4, and 16 sec. These functions are graphed in Figure 2.

Peak N250

A significant main effect was obtained for Condition, $F(1,13)=5.23$, $p<.05$ and ISI, $F(6,78)=7.6$, $p<.01$.

Post-hoc contrasts revealed no significant changes in amplitude across ISIs during random stimulation. There was an increase in amplitude by a mean of 2uv between ISIs after 1 sec. These functions are graphed in Figure 3.

Experiment 3.

A one way repeated measures ANOVA was calculated for each peak with one factor, ISI, at 5 levels. A significant main effect

for ISI was obtained with peak P200, $F(4,52)=3.58$, $p<.05$. Post-hoc analysis revealed that the amplitude of this peak at 2 sec. was smaller on the average by 3uv from those at all other ISIs ($p<.01$), which did not differ from each other.

Experiment 4.

A one way repeated measures ANOVA on peak P50 revealed a significant difference in amplitudes in response to the first and second stimulus in a pair, $F(1,13)=16.29$, $p<.002$. The amplitude of P50 in response to the second stimulus was on the average 60% smaller than the first.

Latencies

A two way repeated measures ANOVA was performed individually on the latencies of each of the four peaks. The two factors were Condition, with two levels (see Methods, Exp. 1, 2) and seven levels of ISI. A significant main effect was obtained with Condition, $F(1,13)=5.52$, $p<.05$ and ISI, $F(6,78)=10.9$, $p<.005$ for peak N100. Post-hoc t-tests revealed that the latency was increasingly prolonged with a lengthening in ISI during the regular condition. The first change occurred between 1 and 2 sec then again at 4 sec. and then at 16 sec. There were no other significant latency shifts.

DISCUSSION-NORMAL SUBJECTS

The main hypothesis under consideration in this thesis is whether temporal certainty constitutes the sole decrementing process responsible for reduced ERP amplitudes with decreasing inter-stimulus intervals. The alternative proposition, that loss of subjective temporal certainty of stimulus occurrence with lengthening ISIs underlies amplitude augmentation, is also tested. A secondary hypothesis posits that at ISIs exceeding a psychological time keeping ability of approximately 4 seconds, there should be no difference between peak amplitudes irrespective of the stimulus schedule. These propositions were examined by presenting stimuli on random and regular ISI schedules as well as by cuing stimulus arrival in a different sensory modality.

The results obtained in Experiments 1 and 2 clearly demonstrate that the recovery function of auditory ERP amplitudes is differentially affected by the stimulus delivery schedule. Temporal certainty or conditioning was not found to be the only process by which peak amplitudes are reduced at short ISIs, since stimuli presented with randomly occurring short ISIs also evoked potentials with diminished amplitudes. The ISI at which ERP peaks approach maximum amplitude is also different between the two stimulus delivery schedules, it is longer when regularly presented. Response decrements and increments are governed by at least two separate processes, reflecting changes in both the probability of absolute and expected times of stimulus occurrence. These effects

are observed at peaks N100, P200 and N250. However, as will be described below, not all peaks respond in the same manner within a given stimulus condition. These results support existing evidence that different ERP peaks can index diverse psychological processes.

The analyses of the amplitudes of these peaks across ISIs and between stimulus schedules revealed a significant Condition (random vs. regular) by ISI interaction for peaks N100 and P200 (see Table 1). This indicates that the pattern of amplitude changes across ISIs is different in each experiment. Significant main effects for Condition indicate that the amplitudes of the peaks were not similar between experiments, while a significant main effect for ISI indicates that there are differences in peak amplitudes between ISI.

An analysis of the amplitude differences between successive pairs of ISIs revealed that with a random schedule, N100 and N250 did not increase significantly as ISI was lengthened. Peak P200 amplitude increased significantly by an average of 10uv between .5 and 1 sec. (200% increase) and then increased by a mean of 1uv between each succeeding ISI (see Figure 2). These results for P200 are similar to those of Roth, et al. (1976), who also obtained a recovery function with randomly presented stimuli. The minimum ISI they employed was .75 sec. and the maximum was 3 sec. A recovery function similar to theirs can be extrapolated from the present data between those time intervals. However, they also observed a similar increase in N100 amplitude, which was not observed in the present data.

When stimuli were presented in blocks of equal ISIs, a different pattern of ERP amplitude effects emerged. Peak N100 increased by an average of 2.5uv with each increment in ISI after 1 sec (see Figure 1). Peak P200 amplitude increased by a mean of 2uv between .5-1 sec. and 1-2 sec. ISIs. It increased further by a mean of 7uv at 4 sec. and then by about 4uv at 8 and 32 sec. ISIs (see Figure 2). A least squares linear regression predicted an increase of 3.5uv in P200 amplitude with each doubling of ISI. An increase of 1.5uv per doubling of ISI after an ISI of 1 sec was predicted for peak N250. The present regression data on peak P200 are similar to the incremental increases in amplitude of peaks N1-P2 with each doubling of ISI reported by Nelson and Lassman (1973).

Specific contrasts at identical ISIs of peak amplitude differences revealed that peaks N100, P200 and N250 reached a maximum amplitude at different ISIs between conditions. The amplitudes of peaks N100 and N250 were significantly smaller with regular stimuli at ISIs of .5 to 4 sec. compared to randomly presented stimuli (see Figures 1 and 3). P200 was significantly smaller with regular stimuli at ISIs of 1, 2, 4, 8, and 16 sec. but not at .5 and 32 sec. (see Figure 2).

When temporal certainty is eliminated by randomizing time of stimulus arrival as in experiment 1, P200 approached maximum amplitude after an interval of approximately 2 to 4 sec. The hypothesis that amplitudes would no longer show enhancement after all succeeding ISIs become equally unpredictable, seems to be

partially supported by this result. However, as the time from the previous stimulus is prolonged, the subjective probability of the next stimulus occurrence could continue to increase. The small 1uv increase in P200 amplitude between ISIs longer than 4 sec. may be a reflection of such a development in moment-to-moment expectancy. Conversly, the smaller amplitudes at shorter ISIs may reflect the lack of time to develop that expectancy. This will be labeled "expectancy refractoriness" to distinguish this process from temporal certainty. The probability of stimulus occurrence at short ISIs is lower, since the distribution of ISIs in the present experiment is weighted towards longer intervals. This is especially evident with an ISI of .5 sec., where the P200 amplitude was smaller by 10uv compared to the one at the next longer interval. Peaks N100 and N250 do not reflect this process, they did not show changes in amplitude with increasing ISI during random stimulation.

When stimuli are presented regularly, so that temporal certainty or conditioning can develop, the maximum amplitude of P200 is not evoked until an ISI of 32 sec. It could be concluded that all shorter intervals above approximately 4 sec. are not equally unpredictable, as hypothesized. Previous research (Callaway, 1975; Schafer and Marcus, 1973) indicates that temporal certainty does not appear to extend beyond approximately 3 or 4 sec. The steeper slope of amplitude growth observed in this experiment (2), approximately 3.5uv for P200 between ISI longer than 2 sec., most probably represents the interaction of a continuous increase in both temporal uncertainty and expectancy of

stimulus occurrence, as in the random condition. The negative peaks, N100 and N250 approach a maximum amplitude at or shortly after an ISI of 4 sec. These peaks support the hypothesis that amplitudes should no longer increase after an accurate time keeping ability is exceeded. Peaks N100 and N250 may solely reflect the degree of stimulus certainty, since they did not increase in amplitude in response to lengthening ISIs whose order was randomized.

Research in a related field in which subjects are required to respond with a button press as soon as possible after a stimulus in a fixed interval sequence, has demonstrated that response latency varies directly with interval duration. This was true when intervals ranged from 10 to 320 sec. (Bevan, et al., 1965) as well as from 1 to 5 sec. (Naatanen, 1970). When subjects had to estimate the time of arrival of a stimulus in a regular sequence, the error of the estimate grew as the intervals were increased (Naatanen, et al., 1974). If ERP amplitudes are inversly related to stimulus certainty as proposed, then the gradual increment in amplitudes observed in response to a lengthening in the ISI of regularly presented stimuli may also reflect an increasing error in the estimate of the time of stimulus occurrence. The latency of N100 also increased progressively with lengthening ISIs when stimuli were presented in blocks of fixed intervals. This peak's latency did not change with randomly delivered ISI.

It appears that there are two processes responsible for amplitude suppression at ISIs under 4 sec. If stimuli arrive randomly, in a series with long and short intervals, then an

"expectancy refractoriness", induced by a low probability of stimulus occurrence, may be operating with short stimuli as seen with peak P200. On the other hand, if stimuli are presented at fixed intervals, then temporal certainty serves to decrement ERP amplitudes. The differences in the magnitudes of all the peaks measured in the present experiments, and contrasted between random and regular stimulus conditions, indicate that these processes are not equal; temporal certainty has a stronger suppressive effect. It is hypothesized that with regular ISIs the effect of temporal certainty gradually wanes as the probability of ascertaining the moment of stimulus occurrence decreases. With lengthening intervals the moment-to-moment expectancy simultaneously increases as the probability of stimulus occurrence at the next moment in time decreases.

There was no difference in the amplitude of P200 at the .5 sec. interval between experiments. This result may point to an interval at which there is no development of expectancy, and thus there is a negligible incrementing effect when ISIs are presented randomly. However, since temporal certainty was not present with random ISIs, it cannot be invoked as a decrementing process. This leaves the possibility that an absence of expectancy in an ongoing stimulus situation can induce a suppressive state similar to that of temporal certainty. This result may be related to the much researched "psychological refractory period". This phenomenon occurs when a short interval (usually less than 1 sec.) is maintained between stimuli, reaction times (RT) to the second stimulus are then

prolonged (Smith, 1967; Boddy, 1972). As the inter-pair interval is lengthened, RTs decline until some ISI at which no further delays are evinced. A number of explanatory hypothesis have been put forward to explain this phenomenon. Among them are refractoriness of response systems, lack of preparatory states and low expectancy or probability of stimulus occurrence (Smith, 1967; Naatanen, 1970).

In experiment 3, a light emitting diode was illuminated 1 sec. prior to the delivery of an auditory stimulus, thereby cuing its time of arrival. The five different ISIs were presented pseudo-randomly and ranged from 2 to 32 sec. A significant difference was obtained in the analysis of the amplitude of P200 across ISIs. The amplitude of this peak was significantly smaller at the 2 sec. interval than at all the others. The absolute amplitudes of P200 across ISIs from 4 to 32 sec were of a magnitude equal to that of an extrapolated interval of approximately 3 sec in experiment 2 (regular stimuli). It was predicted that temporal certainty would have an equal inhibitory effect across all ISI. However, the smaller amplitude of P200 observed at an ISI of 2 sec., may indicate that additional operation of an "expectancy refractoriness" as discussed above. Peaks N100 and P250 did not increase in amplitude at any ISI in this condition. This result is not surprising since temporal certainty did not diminish in this condition and their amplitudes appear to be disinhibited only by a decrease in certainty as discussed earlier. The latency of peaks N100 and P200 did not change between ISIs in this condition. They

were significantly shorter than during randomly delivered ISIs. This result is similar to previous data showing decreased peak amplitudes and latencies with temporal certainty (Schafer and Marcus, 1973; Schafer, et al., 1981).

In summary, the present results suggest that two processes act to diminish or enhance ERP amplitudes with changes in inter-stimulus intervals (ISI). With short ISIs, under 4 sec., both temporal certainty and a relative lack of stimulus expectancy act to inhibit amplitudes. After an ISI of approximately 4 sec. the inhibitory effect of certainty gradually decreases while the effect of expectancy gradually enhances selected ERP peak amplitudes.

METHODS-DOWNS'S SUBJECTS

The present set of experiments employed auditory stimuli at varying ISIs to produce recovery functions of ERP amplitudes. Random and regular stimulus delivery schedules were presented. An inhibitory process to the second of two stimuli separated by .5 sec. with a 10 sec. inter-pair recovery period was also assessed.

Nine adult subjects with Down's syndrome (5 men, 4 women) were recruited from the client population of Sonoma State Hospital. Their mean age was 34 years and ranged from 28 to 47. Their mean IQ score was 50 and ranged from 40 to 70. They had normal hearing, established by audiometric testing in the Audiology clinic. Participation was voluntary and required informed consent from the subject's conservator, who signed a Human Subjects consent form.

Procedures

An explanation of the general nature of the experimental procedures was given to the subjects at their living units prior to the test session. They were informed that they did not have to participate if they were at all apprehensive. The subjects were all verbal and seemed to understand the explanation. Throughout the half hour test session the subjects were seated in a comfortable reclining chair in a small room and asked to sit quietly with their eyes open. They were visible to the experimenter through a one-way mirror. An associate sat in the room with the Down's subjects at all times to reassure them if necessary and to help control extraneous behavior. No problems of any kind were encountered with these subjects.

Recording

The ERPs for the present experiments were recorded from Grass gold cup electrodes. The skin underlying the electrodes was first cleaned with alcohol then gently rubbed with a mildly abrasive gel. They were held in place with a conductive cream. The active electrode was placed at Cz (vertex of the scalp) and referred to linked ear-lobe electrodes; an electrode placed on the forehead just below the hairline served as the common. The EEG activity was amplified and conditioned as in the procedures with normal subjects. The stimuli were given 50 msec. bursts of white noise delivered at 60dBnHL. The longest ISI employed with these subjects was 16 sec. to minimize the length of the test session; it is a sufficiently long duration to establish a recovery function.

Stimulus Schedules

Experiment 1

Eleven stimuli at equal ISIswere presented in 6 blocks. Each block consisted of one of the following ISI: .5, 1, 2, 4, 8, or 16 seconds. The order in which the blocks were presented was randomized, same order for all subjects, with a 25 to 40 sec. inter-block interval. The response to the first stimulus in each block was not included in each of the six averaged ERPs since the ISI preceding it was longer than that within the block.

Experiment 2

The same six ISIswere presented in a randomized order, the only restriction was that the same ISI was not presented more than

three times consecutively. Each of the six ERPs were again averaged from 10 stimuli, which were segregated by the computer.

Experiment 3

Thirty two stimulus pairs were delivered with an intra-pair ISI of .5 sec. and an inter-pair ISI of 10 sec. Two averaged ERPs were recorded, from the first and second stimulus in a pair.

The associate who sat with the Down's subjects prompted them to sit still and to keep their eyes open. No other instructions were given. The order in which experiments were run was randomized across subjects.

RESULTS

The independent measures in these experiments were inter-stimulus intervals presented in a regular and random order. The dependent measures used to assess their affect were ERP amplitudes and latencies. The average amplitude and latency recovery functions were contrasted for differences between stimulus schedules. The amount of recovery obtained to the second of a regularly presented stimulus pair was also determined.

Event Related Potentials

ERPs were recorded from Cz and were identified and scored as described with normal subjects. Average ERP amplitudes and their standard deviations, by ISI for all conditions for four peak to baseline measures are listed in Tables 6 to 8. The average latencies and standard deviations of peak N100 are listed in Table 9.

Statistical Analyses

Amplitudes

Separate two way (Exp. 1 and 2) repeated measures analysis of variance (ANOVA) were performed on the amplitudes of ERP peaks P50, N100, P200 and N250. Two within subjects factors with two levels on Condition and six levels on ISIs were employed. A one way repeated ANOVA was performed on the amplitudes of peak P50 in Experiment 3 with two levels of ISI. The most conservative levels of significance were used to compensate for performing multiple ANOVAs. Post-hoc comparisons between pairs of measures were made using an adjusted t-test procedure with significance accepted at a

probability of $p < .01$.

Experiment 1 and 2.

Significant main effects on ISI were obtained with the two factor repeated measures ANOVA with peaks P200, $F(5,40)=5.01$, $p < .05$ and N250, $F(5.40)=5.33$, $p < .05$. Repeated measures t-tests between pairs of ISI revealed that for P200 with random stimuli there were significant increases in amplitude up to 16 sec. A significant change occurred between .5-1 sec. then at 4 sec. and finally at 16 sec. With random ISIs there was a significant increase between .5-1 and 1-2 sec. and a final increase at 4 sec. There was no change in amplitude between 1 and 2 sec. nor between 4 and 8 sec. There was no significant increase in N250 amplitude during randomized stimulation. With regular stimuli the amplitude at .5 sec. was smaller than at all other ISIs.

A least squares linear regression was performed on the P200 amplitudes in both conditions. With a random ISI schedule the predicted amplitude increase was 1.3uv for each doubling of ISI; the correlation was not significant with $r=.60$, $p < .13$. With regular intervals the predicted increase was 2.1uv with a significant correlation of $r=.95$, $p < .004$.

Experiment 3.

A significant main effect for ISI was obtained in experiment 3 for P50, $F(1,16)=5.54$, $p < .05$. The amplitude in response to the second stimulus of a pair was smaller on the average by 35%.

Latencies

Experiment 1 and 2.

A two way repeated measures ANOVA was performed on the

latencies of each of the four peaks with two levels on the Condition factor and six on ISI. A significant Condition by ISI interaction was obtained for N100, $F(5,40)=5.29$, $p<.05$, P200, $F(5,40)=5.71$, $P<.05$ and N250, $F(5,40)=5.77$, $p<.05$. Post-hoc t-tests of specific contrasts revealed that the latencies of these peaks were significantly shorter at the .5 sec. than all other ISIs during regular stimulation. Peak N100 was faster by 45 msec., P200 by 70 msec. and N250 by 120 msec. Peak P50 was also faster under similar conditions, but this difference did not achieve statistical significance.

Down's Contrasted with Normal Subjects

The amplitude of P200 recorded during similar experimental conditions was compared between Down's and normal subjects. The amplitudes recorded at the 32 sec. ISI with normal subjects were removed from these analyses.

Experiment 1.

An ANOVA with one between subjects factor revealed a significant difference between groups during randomly presented ISIs, $F(1,21)=16.61$, $p<.001$. Specific contrast t-tests revealed that normals had a larger amplitude at all ISIs except at .5 sec., where there was no difference.

Experiment 2.

A one way between subjects ANOVA on the amplitude of P200 during blocks of regular ISIs also revealed significant differences, $F(1,21)=4.80$, $p<.05$. Post-hoc contrasts showed that the only difference between groups was at an ISI of 8 sec., with normals having a larger amplitude.

DISCUSSION-DOWN'S SUBJECTS

The purpose of these experiments was to determine if individuals with Down's syndrome exhibit a recovery of event-related potential (ERP) amplitudes with increasing inter-stimulus intervals (ISI). Both randomly and regularly presented ISIs were employed to assess whether recovery was related to temporal certainty as in normal subjects.

Previous researchers have hypothesized that these individuals do not or cannot form a temporal expectancy or be temporally conditioned. When presented with stimuli at constant intervals of 1 or 2 sec., Down's subjects do not display a decrement in ERP amplitudes. This is true for both what has been labeled "fast habituation", a large drop in amplitude after the first few stimuli in a series, and long term habituation, which is a decrease in amplitude after many stimuli (Schafer and Peeke, 1983; Barnet, et al., 1971). It has been proposed on the basis of these past results, that they have a dysfunction of inhibitory mechanisms in afferent sensory pathways (Callner, et al., 1978).

The results of the present experiments reveal that Down's subjects' ERPs do exhibit a recovery function. However, this was observed only with peak P200, and not with N100 or N250. With regularly spaced ISIs this function is very similar to that displayed by normal subjects. When stimulus intervals were randomly presented the differences between subject groups were more pronounced. Down's individuals had significantly smaller amplitudes at all but the shortest ISI. In the present experiments Down's

did not display ERP amplitudes larger than those of normals as previously reported.

No significant Condition by ISI interactions were obtained in the analyses of peak amplitudes. A significant main effect for ISI was obtained with peak P200, indicating a difference in amplitude between ISIs. Analysis of the amplitude differences between successive ISIs revealed that with peak P200 during random stimulation there was a significant increase between .5-1 sec. and 1-2 sec., there was another significant increase at 4 sec. There was no increment in amplitude after this ISI (see Figure 4). During regular stimulus interval delivery there was a significant increase between .5-1 sec., no change between 1-2 sec., an increase at 4 sec. and again at 16 sec. (see Figure 4). This result is similar to the recovery observed by Yellin (1980) in that there was an increase between 1-4 sec. ISIs but not from 4-8 sec. The present study shows continued P200 amplitude augmentation with an ISI of 16 sec. The slopes of P200 recovery were different in each condition. With regular ISIs a highly significant positive correlation between an increase in interval and amplitude was observed. The correlation observed with random ISIs and amplitude was not significant. However, a significant difference was not obtained among identical ISIs between the two conditions when specific contrasts were performed. In both conditions the minimum amplitude of P200 was 7uv and the maximum was 17 uv. When stimulus intervals were randomized this maximum was reached at an ISI of 4 sec. With regular ISIs P200 reached maximum amplitude at 16 sec.

Down's subjects display a recovery cycle very similar to that exhibited by normals with regularly presented stimuli. An analysis of the difference between amplitudes at identical ISIs of P200 in normal and Down's subjects with regular stimulation revealed that the only significant difference obtained was at 8 sec., when normals had a larger mean amplitude. The same arguments presented in the discussion of the previous experiments with normals can be applied to this group to support temporal certainty as a decremental process at short ISIs. Increasing temporal uncertainty and moment-to-moment expectancy can similarly be argued to underlie amplitude augmentation at longer ISIs. The presence of recovery argues against the assertion that these individuals possess a generalized deficiency in inhibitory processes (Callner, et al., 1978) or that they "manifest an aberration in the memory processes responsible for temporal expectancy" as proposed by Schafer and Peeke (1982). The presence of a recovery cycle in these individuals does provide evidence that fast habituation and temporal certainty are distinctly separate inhibitory processes.

When ISIs were delivered randomly, the correspondence in the recovery slopes between groups was less similar. The major difference in the Down's group was a smaller than normal P200 amplitude at ISIs longer than .5 sec., followed by an absence of a substantial amplitude difference between .5 and 1 sec. ISIs. The similarity is discerned in the result that in both groups P200 amplitude was approximately maximum at an ISI of 4 sec. This result can be used to invoke the operation of an "expectancy

refractoriness" as an amplitude decrementing process when short ISIs are presented randomly, as it was with normal subjects. The magnitude difference in P200 amplitudes between the groups can be explained as a function of differential attention. An experiment conducted with the normal group that was not reported in this thesis, employed random intervals between stimuli while subjects watched a television program. The recovery slope observed was very similar to the one reported above with Down's subjects. P200 amplitudes were significantly attenuated at all ISIs and the difference in amplitude between ISIs of .5 and 1 sec. was no larger than ones between succeeding ISIs. The Down's subjects in the present experiments were not directed to attend to stimuli. In the absence of evidence to the contrary, it must be assumed that their attention was not focused on the stimuli. The effectiveness of attention directed to stimuli in augmenting ERP amplitudes has been well documented (Picton, et al., 1978).

The third experiment conducted with the Down's subjects employed a "conditioning-testing" procedure aimed at examining the recovery of peak P50. Stimulus pairs were presented with an intra-pair ISI held constant at .5 sec. while the inter-pair interval was 10 sec. This procedure is widely used in neurophysiological studies to demonstrate inhibitory pathways (Adler, et al., 1982). The ratio of the amplitude of P50 between the first and second stimulus in a pair is expressed as a percentage of recovery. The Downs' subjects showed a mean recovery of 65% with a range of 20% to 125%. The normal subjects had a mean

recovery of 40% with a range of 20% to 100%. The mean amplitude of P50 in the Down's group to the first stimulus was not significantly smaller than in normal subjects. These results differ from those reported by Adler et al., (1982) comparing schizophrenic and normal subjects. The schizophrenics in that study had smaller P50 amplitudes to the first stimulus in a pair and the range of percentage of recovery did not overlap between groups. Several normal subjects in the present study showed recovery greater than 40%, which was the maximum observed with normals by Adler et al. Despite the discrepancies in findings between normal subjects, which may be attributed to procedural differences, the Down's subjects as a group do show a significantly greater recovery of P50 amplitude than normals. This is indicative of an inhibitory dysfunction in these individuals that is distinct from previously reported failures to habituate ERP amplitudes.

SUMMARY

The recovery function of the amplitude of event-related potentials (ERPs) has been historically examined from a number of perspectives. The increase in amplitudes with lengthening ISIs is presumed to reflect disinhibitory processes. The nature of the process hass been described variously as reflecting an aspect of habituation, cortical excitability, psychological refractoriness, orienting, memory processes, intelligence, attention and information processing. Among psychologists and neurophysiologists the predominant explanation for the phenomenon has been in terms of a slower development of habituation. The exponential increase in amplitude observed when ISIs are successively doubled is a mirror image of the theoretical decrease in responsivity predicted by habituation with repetitive stimuli. As the interval between stimuli is increased, habituation occurs at a slower rate. If response magnitudes are averaged over an equal number of trials, then they must be larger at longer ISIs since habituation would not have progressed as rapidly. The major stumbling block in interpreting recovery in terms of habituation is the difficulty in demonstrating dishabituation in ERP research. This is one of the defining parameters of habituation which to date has not been successfully demonstrated (Roemer, et al., 1984).

The present thesis argues that recovery of ERP amplitudes, when stimuli are presented in blocks with equal intervals, is largely a function of a loss of temporal certainty. It is demonstrated that when stimulus arrival is priorly cued by 1 sec.,

amplitudes at all but the shortest interval are not enhanced by the passage of time; this extends and affirms previous research (Wastell, 1980; Schafer, et al., 1981). On the basis of results obtained when stimulus intervals are randomized, it is hypothesized that a second process which has a decrementing and augmenting influence on ERP amplitudes and is related to an increase of expectancy of stimulus occurrence, is also operating. This process is indexed by the positive ERP peak P200 but not by negative peaks N100 and N250. The changes in peak amplitudes with varying ISIs can also be described as reflecting changes in the temporal probability of stimulus occurrence.

That habituation is not a process underlying recovery is demonstrated directly by the results obtained with subjects afflicted with Down's syndrome, a congenital genetic abnormality. A number of studies have demonstrated that these individuals do not display decrements in ERP amplitudes that are attributed to habituation in normals. They do, however, exhibit recovery functions similar to those obtained with normal subjects. It is hypothesized that loss of temporal certainty and an increase in expectancy that the stimulus will arrive at the next moment in time are the processes operating in these individuals, as well as in normals. The present results also point to the probability that active attention towards stimuli may interact with, but is not a necessary condition for recovery.

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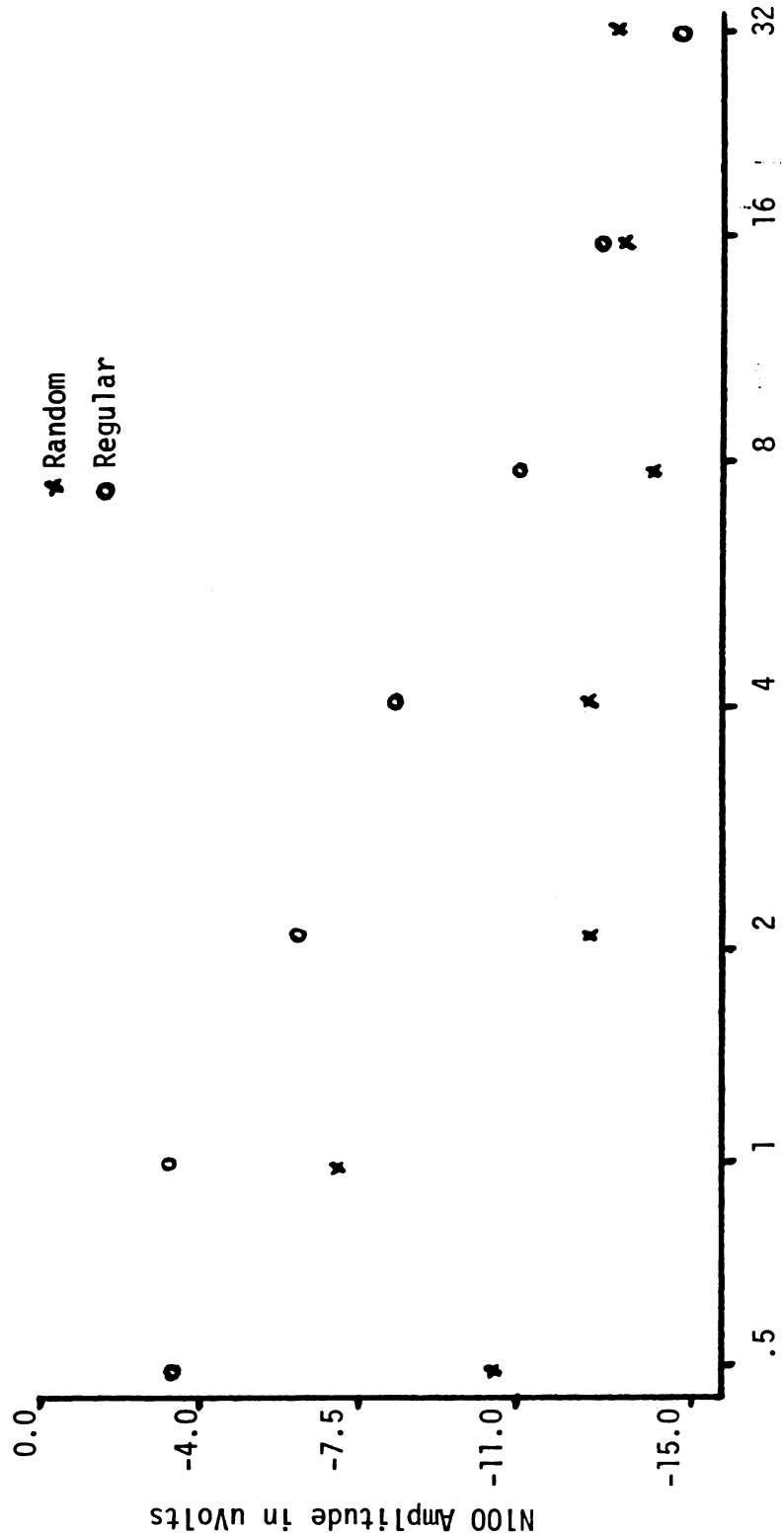

Figure 1. Recovery slopes of peak N100 to Random and Regular Inter-stimulus Intervals in Normal Subjects

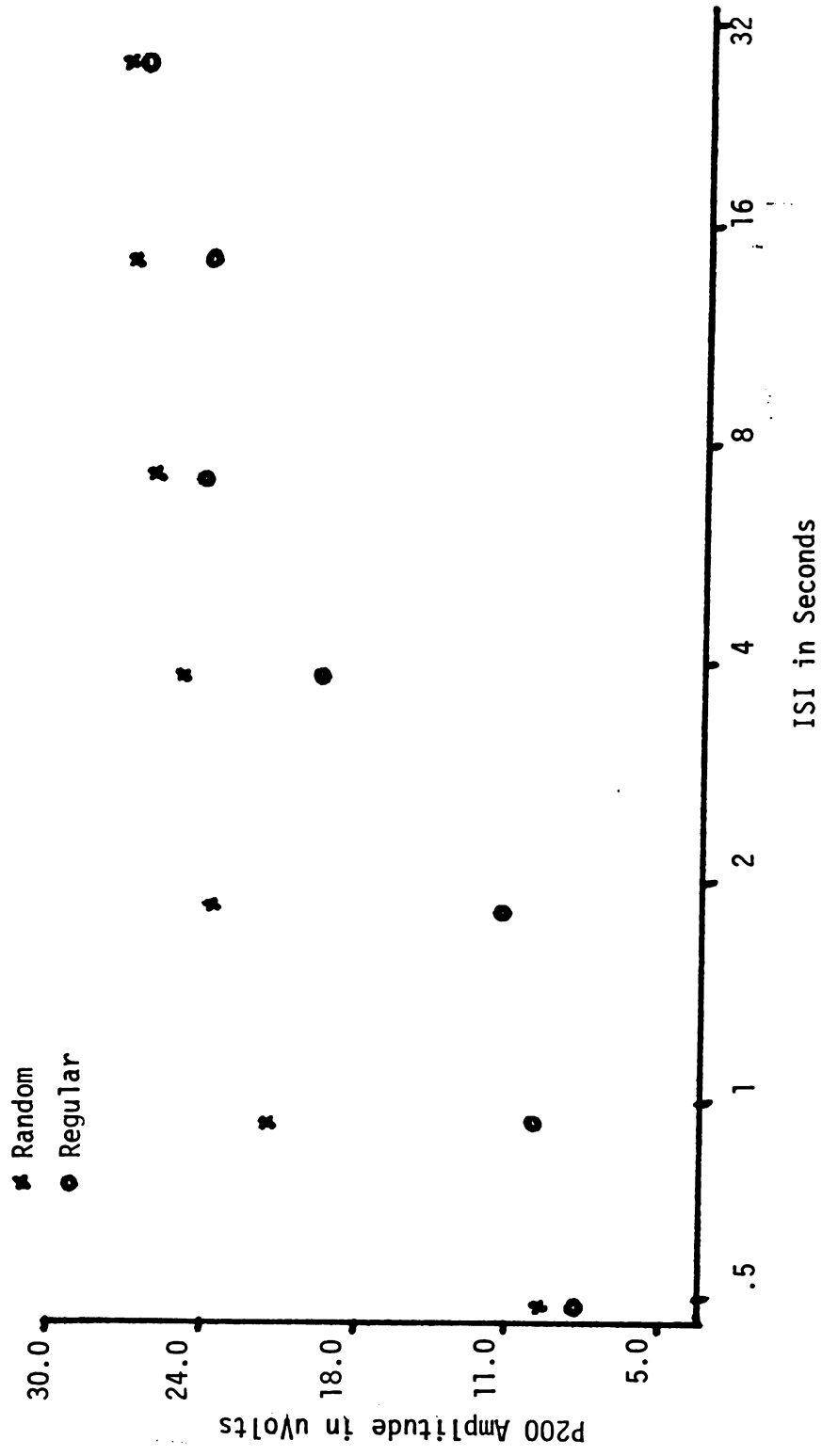

Figure 2. Recovery slopes of peak P200 to Random and Regular Inter-stimulus Intervals in Normal Subjects

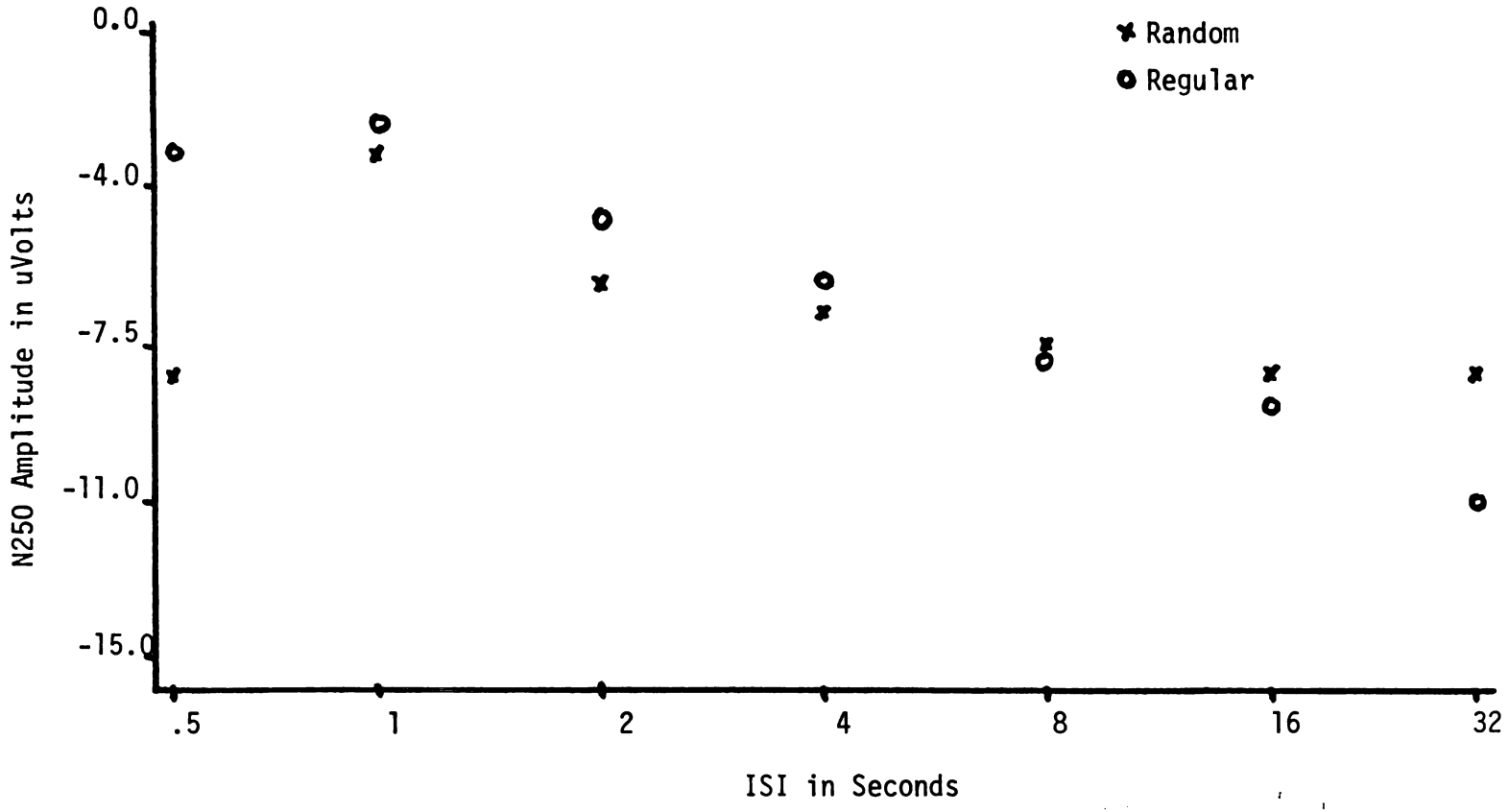

Figure 3. Recovery slopes of peak N250 to Random and Regular Inter-stimulus Intervals in Normal Subjects

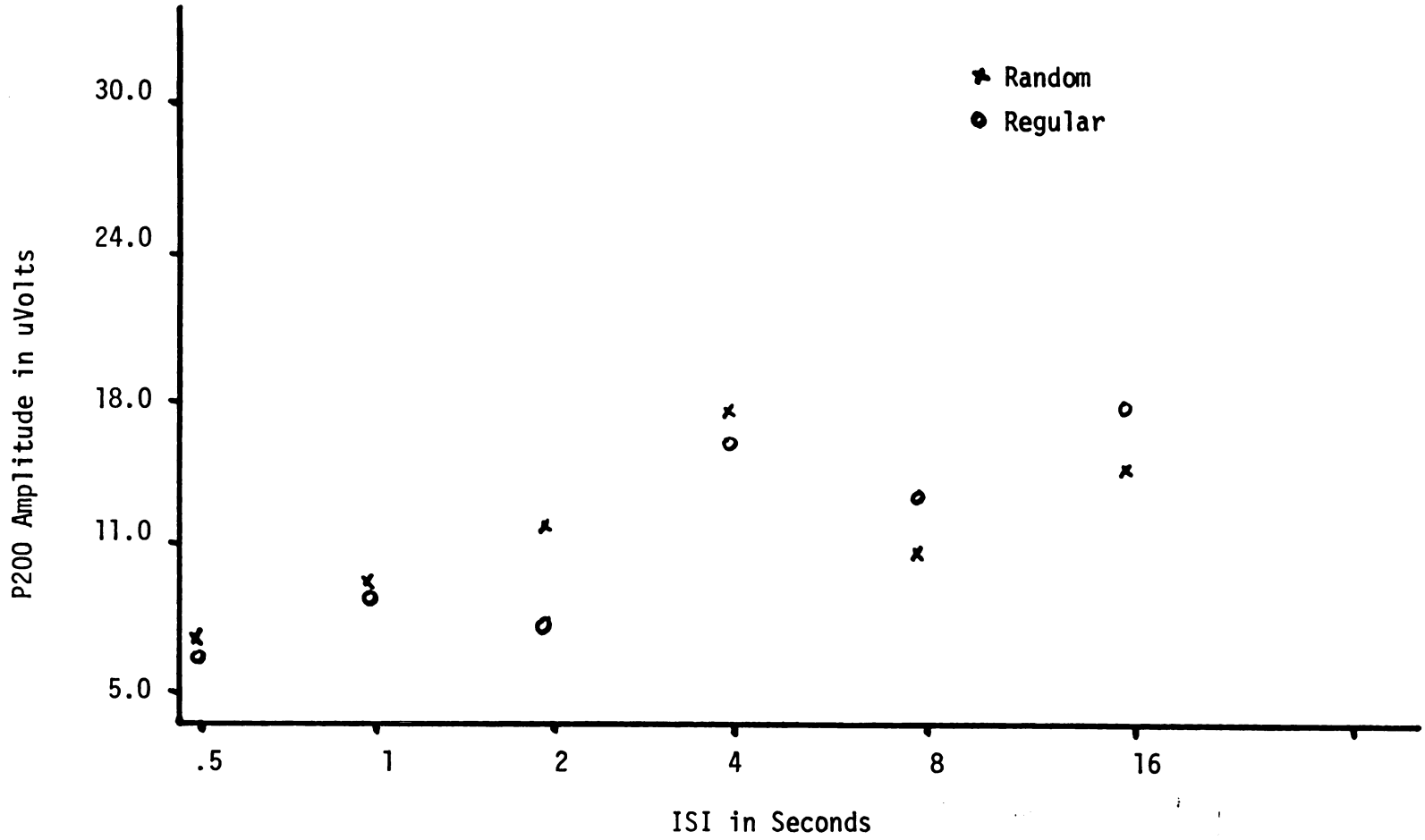

Figure 4. Recovery slopes of peak P200 to Random and Regular Inter-stimulus Intervals in Down's Subjects

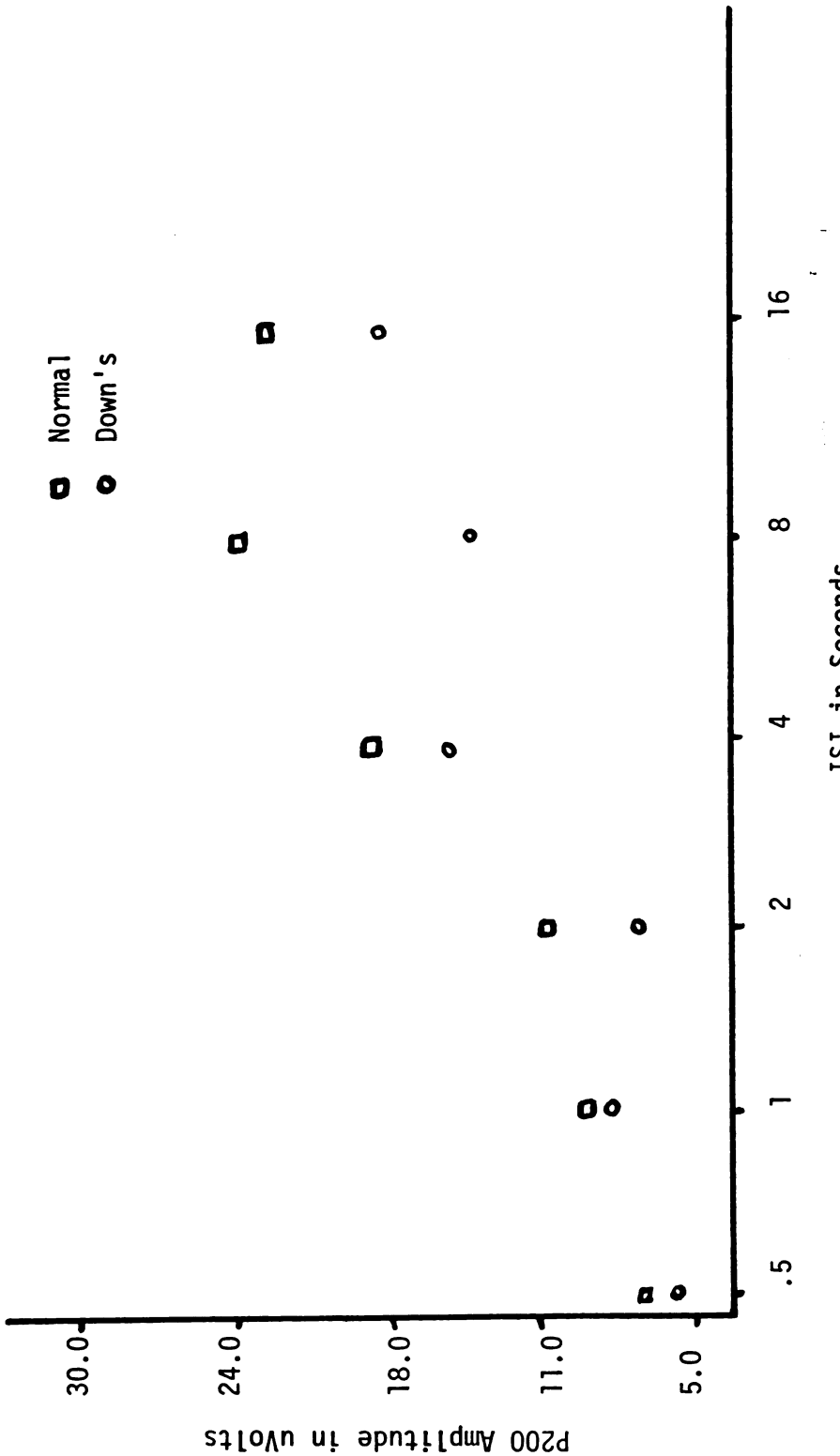

Figure 5. Recovery slopes of peak P200 to Regular Inter-stimulus Intervals in Normal and Down's Subjects

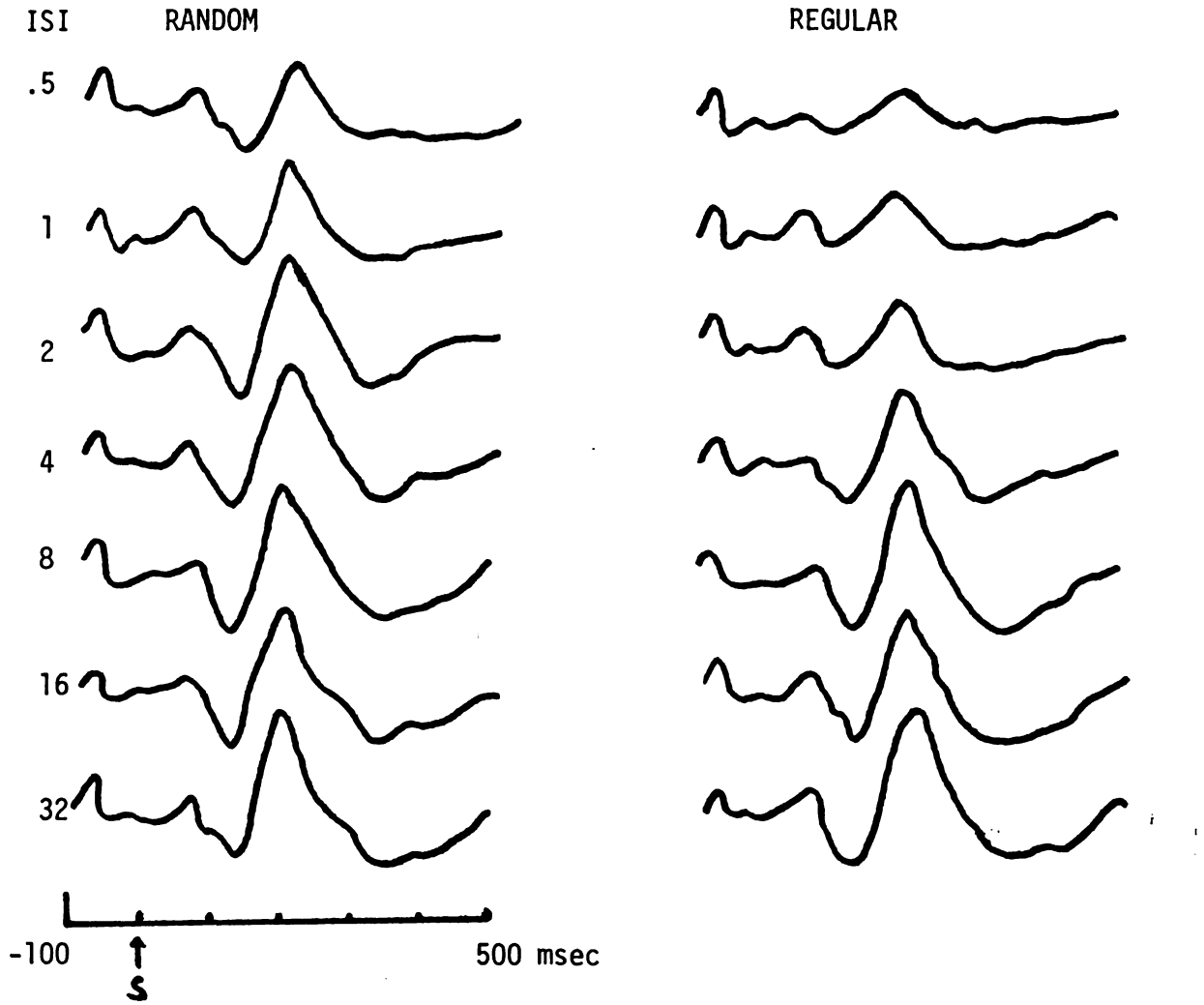

Figure 6. Grand Average ERPs Across Normal Subjects
Stimulus delivered at arrow marked S.

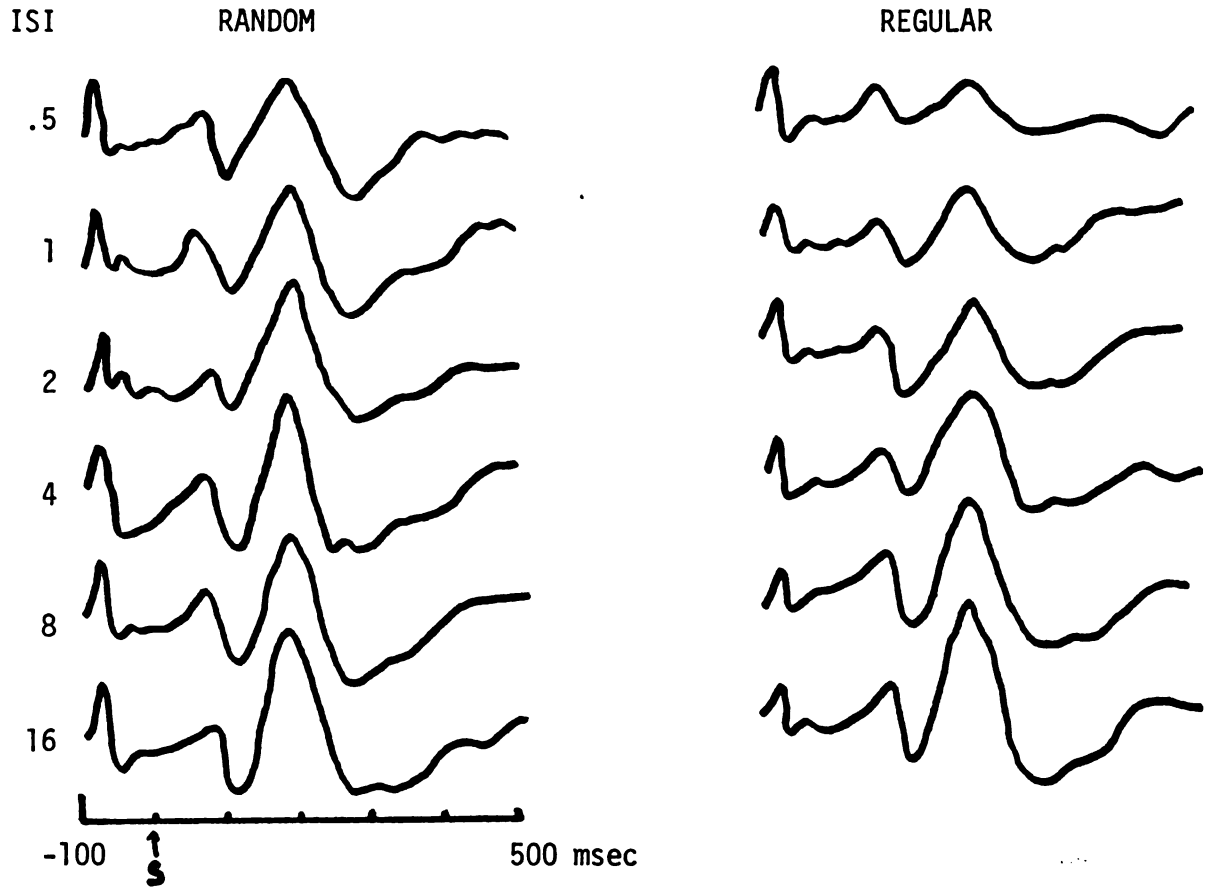

Figure 7. Grand Average ERPs Across Down's Subjects
Stimulus delivered at arrow marked S.

TABLE 1

Normal Subjects

Repeated Measures Analysis of Variance for Peak Amplitudes

	N100				P200			
Source	MS	(df)	F	P	MS	df	F	P
Within Subjects								
Condition	774.10	1	5.68	.032	1532.16	1	28.37	.0002
ISI	2417.95	6	15.24	.002	1089.75	6	43.24	.0000
Condition x ISI	630.65	6	4.65	.05	141.51	6	9.55	.01
Residual	3507.62	78			14.75	78		

TABLE 2

Normal Subjects

Event-Related Potential Amplitudes and Standard Deviations
For Four Peaks During Regular ISI

	ISI in seconds						
	.5	1	2	4	8	16	32
	2.57	4.71	3.71	3.14	4.57	6.07	5.07
P50	(2.62)	(3.83)	(2.49)	(4.90)	(4.59)	(4.25)	(3.61)
	-3.57	-3.51	-6.07	-8.21	-11.00	-13.57	-14.71
N100	(2.93)	(3.63)	(5.28)	(4.95)	(7.85)	(6.12)	(7.39)
	8.1	10.43	11.36	18.64	24.43	22.43	27.07
P200	(2.30)	(4.53)	(3.71)	(5.66)	(8.07)	(6.89)	(8.44)
	-3.71	-2.21	-4.43	-6.43	-7.64	-9.29	-10.86
N250	(4.89)	(4.15)	(4.26)	(6.38)	(6.70)	(6.14)	(7.88)

TABLE 3

Normal Subjects

Event-Related Potential Amplitudes and Standard Deviations
For Four Peaks During Random ISI

	ISI in seconds						
	.5	1	2	4	8	16	32
	3.36	6.64	6.50	7.86	5.00	7.36	6.00
P50	(2.98)	(3.75)	(5.23)	(4.29)	(5.13)	(4.83)	(4.59)
	-10.43	-7.00	-12.86	-12.71	14.07	13.00	13.21
N100	(7.76)	(7.54)	(6.36)	(7.82)	(7.59)	(7.91)	(8.45)
	10.79	21.00	23.93	24.71	26.21	26.71	27.21
P200	(6.50)	(7.00)	(8.90)	(8.10)	(6.74)	(8.10)	(7.22)
	-8.57	-2.86	-6.29	-6.71	-7.79	-8.43	-7.93
N250	(7.53)	(5.53)	(5.90)	(8.02)	(7.13)	(7.25)	(6.15)

TABLE 4

Down's Subjects

Event-Related Potential Amplitudes and Standard Deviations
For Four Peaks During Regular ISI

	ISI in seconds					
	.5	1	2	4	8	16
P50	4.33 (1.80)	4.28 (3.03)	4.00 (3.87)	8.56 (4.13)	4.33 (3.04)	4.78 (3.31)
N100	-4.78 (4.12)	5.33 (5.94)	4.00 (3.71)	3.78 (2.91)	5.67 (3.64)	7.00 (5.59)
P200	7.78 (2.99)	10.11 (5.23)	13.00 (7.40)	17.56 (8.16)	11.33 (4.98)	15.22 (5.74)
N250	-9.22 (10.40)	-7.67 (5.24)	-6.89 (4.43)	-5.56 (5.45)	-6.67 (4.30)	-7.11 (5.67)

TABLE 5

Down's Subjects

Event-Related Potential Amplitudes and Standard Deviations

For Four Peaks During Regular ISI

	ISI in seconds					
	.5	1	2	4	8	16
P50	4.67 (5.03)	4.89 (6.51)	3.00 (5.50)	5.89 (4.40)	6.22 (3.11)	6.67 (3.87)
N100	-1.11 (4.19)	-2.11 (6.74)	-7.56 (7.57)	-2.78 (5.31)	-6.78 (6.14)	-6.56 (4.53)
P200	7.00 (6.02)	8.78 (8.33)	8.56 (3.05)	14.67 (6.76)	14.33 (6.58)	17.22 (9.82)
N250	-1.00 (4.82)	-4.11 (3.79)	-6.56 (4.39)	-4.78 (5.07)	-7.22 (5.19)	-8.89 (6.05)

TABLE 6

Normal Subjects

Event Related Potential Latencies and Standard Deviations

For Four Peaks During Regular ISI

	ISI in Seconds						
	.5	1	2	4	8	16	32
P50	51 (18)	57 (11)	61 (11)	60 (10)	61 (9)	60 (14)	64 (8)
N100	104 (18)	103 (18)	107 (15)	118 (13)	119 (12)	128 (9)	126 (10)
P200	183 (13)	184 (17)	185 (12)	188 (7)	192 (8)	194 (10)	196 (15)
N250	273 (25)	268 (22)	285 (24)	294 (24)	289 (22)	297 (18)	317 (26)

TABLE 7

Normal Subjects

Event Related Potential Latencies and Standard Deviations

For Four Peaks During Random ISI

	.5	1	2	4	8	16	32
	57	62	64	63	69	64	61
P50	(12)	(11)	(10)	(8)	(9)	(12)	(12)
	119	122	126	126	127	127	129
N100	(18)	(12)	(6)	(12)	(9)	(6)	(7)
	199	195	193	194	194	195	198
P200	(10)	(6)	(9)	(11)	(9)	(11)	(11)
	283	291	292	289	290	299	298
N250	(14)	(17)	(16)	(22)	(25)	(28)	(23)

TABLE 8

Down's Subjects

Event Related Potential Latencies and Standard Deviations

For Four Peaks During Regular ISI

	.5	1	2	4	8	16
	40	62	63	67	64	72
P50	(31)	(29)	(26)	(33)	(10)	(14)
	68	106	126	114	113	115
N100	(54)	(45)	(28)	(19)	(8)	(9)
	109	153	192	178	181	186
P200	(84)	(59)	(20)	(19)	(18)	(17)
	152	231	263	256	260	265
N250	(119)	(89)	(23)	(14)	(21)	(26)

TABLE 9

Down's Subjects

Event Related Potential Latencies and Standard Deviations

For Four Peaks During Random ISI

	.5	1	2	4	8	16
P50	72 (13)	68 (14)	65 (26)	64 (11)	70 (10)	74 (16)
N100	114 (10)	118 (12)	117 (17)	119 (14)	116 (10)	115 (12)
P200	180 (13)	185 (22)	182 (21)	181 (20)	180 (18)	178 (18)
N250	271 (14)	278 (22)	263 (27)	259 (22)	266 (8)	270 (22)