EYE MOVEMENTS AND ELECTRODERMAL RESPONSIVITY AS POSSIBLE GENETIC MARKERS OF HUNTINGTON'S CHOREA

by

Diane Lacoste

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Department of PSYCHOLOGY

The University of British Columbia
1956 Main Mall
Vancouver, Canada
V6T 1Y3

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Abstract

This study examined two possible genetic markers of Huntington's chorea: eye movements and electrodermal responsivity. Seven subjects in the early stages of Huntington's disease were compared to twenty-nine subjects in each of two other groups, a group of subjects at-risk for Huntington's chorea and a group of controls. Subjects completed a series of smooth pursuit and saccadic eye tracking tasks as well as listened to soft tones, loud tones, and sounds while electrodermal activity was recorded.

Visual inspection of the eye movement data revealed that the Huntington's chorea group performed the poorest, across all the eye tracking tasks. Data analyses showed that the at-risk subjects, when compared with control subjects, tracked with a greater lag when the target moved at the greatest speed. There were no differences between the two groups on similar eye tracking tasks at the target's slower speeds. The at-risk and the control groups performed the vertical smooth pursuit, horizontal saccadic, and vertical saccadic tracking tasks equally well, at all target speeds. No differences between the at-risk and the control group emerged when direction of eye movement (right, left, up or down) was analyzed. Subjects in both groups tracked more poorly when they moved their eyes to the right in the horizontal tasks.

The electrodermal data yielded uniformly negative results

indicating that there were no differences between the three groups in their responsiveness to soft tones, to loud tones or to the sounds of a barking dog and a newsroom teletype. The positioning of the three groups on the dependent measures were as described in previous research in that the Huntington group was the least responsive and the control group the most responsive. However, mean responsivity, as measured by amplitude, latency to response, the number of spontaneous skin conductance responses emitted, and the number of subjects who failed to respond did not significantly differentiate the groups. An examination of habituation did not support the hypothesis that the Huntington subjects would be fast habituators or that they would not habituate at all.

This study supports previous research which found differences in the smooth pursuit eye tracking of at-risk and Huntington subjects when compared with normal controls. The overlap among the three groups suggests, however, that individual differences are too large to use smooth pursuit eye tracking as a genetic marker of Huntington's chorea. In contrast with previous research, there is no support for the contention that electrodermal indices of responsiveness can be used as markers.

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Cette thèse est dédié à mon cousin Lucien, qui était si bien aimé par sa famille.

Introduction

Huntington's chorea (HC) is an inherited chronic degenerative disorder characterized by gradual mental deterioration and choreiform movements. Overt manifestations of the disease appear relatively late in the affected individual's life, often after they have completed their families (Bruyn, 1968), thus ensuring that the disease will be passed from generation to generation. A reliable means for early detection of the gene carriers among the offspring of a parent with HC is actively being sought (Paulson, 1976). Until recently (Gusella et al., 1983), no predictive test of any type for these asymptomatic carriers was available (Klawans, Goetz, & Perlik, 1980). The present research evaluates psychophysiological measures that could distinguish carriers from non-carriers among those at-risk for HC.

The clinical diagnosis of Huntington's chorea currently rests on the presence of a confirmed family history and/or the results of a brain autopsy of an affected parent. These data can only be brought to bear once the at-risk individual begins himself to manifest symptoms of the disorder. With the advent of the G8 DNA marker discovered this year (Gusella et al., 1983), presymptomatic diagnosis of Huntington's may eventually be possible in approximately half of the families with Huntington's provided a blood sample from an affected parent is available. The new test faces the same kinds of problems that confront the traditional clinical diagnostician. A

degree of unreliability exists in cases where the parent with HC died before manifesting symptoms. A diagnosis of HC is also difficult to reach in individuals whose family history is not obviously one of Huntington's disease per se. One of the problems associated historically with Huntington's chorea is the frequency with which it is mistaken for other disorders, notably schizophrenia, Alzheimer's disease, multiple sclerosis, Parkinson's disease, and a gamut of other cerebrospinal degenerative disorders involving ataxias. Such diagnoses may be scattered in a pedigree making a clinical diagnosis of HC that much less certain. A predictive test for Huntington's disease that could overcome these difficulties ie. be applicable in suspected cases of HC where little definitive family information was available would be welcome.

Two types of detection studies have been performed. The first approach focuses on developing sensitive detection devices to diagnose the disease at its true inception. For example, Petajan, Jarcho, and Thurman (1979) recorded the firing rates of single motor neurons in an attempt to measure microchorea during the voluntary movements of 17 subjects with 'HC'. All but two of the 'HC' subjects showed excessive recruitement of motor units, i.e. poor motor control. The purpose and advantage of this approach lies in the rapidity with which a suspected case of Huntington's could be diagnosed were this test to prove predictive of chorea. As it is, a diagnosis of Huntington's is often reached some two to seven

years after the first subtle signs of the disease's actual beginnings (Hayden, 1981). The Petajan et al. (1979) study further subdivided their 17 'choreic' subjects into three groups: 3 subjects with a likely diagnosis of HC, 4 with a possible diagnosis of HC and 10 with a definitive diagnosis of HC as shown by pneumoencephalogram, by brain autopsy, by computerized axial tomography scans or by clinical signs. If this type of electromyographical measure was predictive, the three likely and four possible choreics could be diagnosed definitively.

The second approach to the early detection of gene carriers focuses on the issue of presymptomatic diagnosis and may attempt to identify biochemical, physiological or neuropsychological abnormalities which precede any signs of the disease in the population at-risk. These studies have covered neurological measures (e.g., Baro, 1973; abnormal muscle tone), neurophysiological measures (e.g., Patterson, Bagchi, & Test, 1948; slow, low voltage EEG), neuroendocrinological measures (e.g., Hayden, Vinik, Paul, & Beighton, 1977; disturbed prolactin release), psychological measures (e.g., Goodman, Hall, Terango, Perrine, & Roberts, 1966; personality change, dementia), and neurochemical measures (e.g., Manyan, Hare, Katz, & Glaeser, 1977; decreased cerebrospinal fluid GABA). So far, none of these areas of investigation has been successful in differentiating carriers from non-carriers. Common research strategies involve

comparing confirmed HC patients or their progeny on the variable(s) under investigation for quantitative or qualitative differences with a group of normal controls or brain-damaged patient samples (Klawans, Goetz, & Perlik, 1980). The major assumption underlying this latter approach is that the gene for HC is activated and its effects detectable long before the appearance of overt symptoms.

The purpose of the present study was to investigate the utility of two genetically influenced psychophysiological measures--eye movements and electrodermal activity--as possible markers of Huntington's chorea. A genetic marker for HC can be defined as a biological or psychological characteristic which when observable, identifies the presence of the HC genotype. This marker is assumed to be present both before and during the disease. The marker reflects a measurable alteration in the structure or functioning of the carrier which is temporally stable. Ideally, the genetic marker should appear in all individuals who will develop Huntington's chorea and in none of those who do not possess the gene. While this ideal may be possible with some types of biochemical characteristics, it is not likely to be achieved using psychophysiological techniques. That some persons not at-risk will show the psychophysiological characteristic is likely because the range of individual differences in psychophysiological responding in normals is great enough that overlap with clinically deviant groups will occur. In

addition, that some persons with the gene will not have the marker must also be expected because a wide variety of factors in addition to the presence of the gene may affect the expression of the psychophysiological characteristic. Moreover, although HC is determined by a single dominant gene, its physical and clinical correlates are known to vary considerably across individuals. That psychophysiological characteristics may show similar variability is perhaps to be expected. This variation has led some researchers to speculate that there may be more than one HC genotype to account for the data (Myers, Madden, Teague, & Falek, 1982). It would however, seem more likely that there were environmental events or other genes altering or masking the expression of the HC gene. Just as such factors alter or mask the expression of the gene itself, they may also be expected to colour the genetic marker such that perfect identification in those truly at-risk will not be possible (Iacono, 1982b).

A variety of benefits follow from utilizing eye movements and electrodermal responsivity as possible genetic markers of HC:

(1) Such measures are at least partially under genetic control. There is a literature examining the effect of heredity on psychophysiological responses. This research indicates that oculomotor control is determined in part by genetic factors (Iacono & Lykken, 1979a, 1979b; Holzman, Kringlen, Levy, & Haberman, 1980; Iacono & Lykken, 1981;

Iacono, 1982a) and reflects a temporally stable trait. Iacono & Lykken (1979b, 1981) studied a sample of 32 pairs of normal monozygotic twins on smooth pursuit, saccadic and eye-hand coordination tracking tasks and found intraclass correlation coefficient values ranging from .54 to .83. Holzman et al., (1980) determined that two groups of 21 monozygotic (MZ) and 30 dizygotic (DZ) twin pairs who were discordant for schizophrenia were nonetheless concordant for bad eye tracking. 81% of the MZ twins were bad trackers as compared to 67% to the DZ twins on smooth pursuit tasks. Iacono (1982a), in an extension of earlier research, reported two-year retest reliability coefficients of .60 or greater for various measures of eye tracking. There were significantly different intraclass correlations--.68 as compared to .35--on a measure of smooth pursuit eye tracking performance in 34 normal MZ and 24 normal DZ twin pairs. There was less evidence that a measure of phase lag--which reflected the degree to which the subject's eyes lagged the target to be followed--was genetically influenced. Concordance rates for saccadic eye movement latencies were not significantly different in the two sets of twin pairs.

The hereditary influences on electrodermal activity have not been as well investigated but the major twin studies that exist suggest that various aspects of electrodermal arousal are partially determined by genetic factors. Earlier studies of the genetics of electrodermal responsivity were not

included in this review because they are not strictly comparable with the newer research since they were fraught with numerous methodological difficulties.

Lader and Wing (1966) in a study of 11 monozygotic and 11 dizygotic twin pairs reported significantly higher correlations for the MZ twins for rate of habituation as well as for the number of spontaneous skin conductance responses they emitted. Hume (1973) examined 44 pairs of monozygotic twins and 51 pairs of dizygotic twins on measures of skin potential response to tones as well as to a cold pressor; measures of spontaneous skin potential responses during rest; a measure of habituation rate; and a measure of the number of spontaneous responses during the habituation task. He reported that monozygotic twins were more alike (homogeneous) than the dizygotic twins in their responsivity, and concluded that genetic factors exerted a significant effect. The intraclass correlation coefficients on the other measures ranged between .11 and .37 providing only weak support for the hypothesis that there is some genetic determination of these other responses. Iacono & Lykken (1979c), measuring habituation rate in 35 pairs of MZ twins reported a significant intra-class correlation coefficent of .60 when data gathered over three sessions held at two month intervals were collapsed over sessions. Test-retest correlations ranged from .50 to .68 indicating that there was some stability of the skin conductance response over time. The habituation

criterion adopted in this research was defined as the number of trials to two consecutive zero (amplitude) skin conductance responses.

(2) Psychophysiological responses tap global capacities i.e. they depend on the proper functioning of all areas of the brain as a whole. If any one function is disturbed, this may show up as a response deficit. These global (molar) types of measures can be held in contrast to the specific (molecular) measurement approaches popular in most research on Huntington's chorea. Investigations based on a single enzyme or a specific type of cell membrane, while valid, necessarily ignore other variables which may play a role in the development of HC. However, the complex and global nature of these psychophysiological measures will in itself make it difficult to isolate a particular area of the brain as responsible for the obtained results. A series of studies would be required to delineate the origins of any observed deficits. This study simply proposed to determine if oculomotor function and electrodermal activity are disturbed in individuals with Huntington's disease or in the progeny at-risk to develop chorea. To this end, a group of choreics in the early stages of HC were added to the study.

(3) Psychophysiological techniques are advantageous in that they are a noninvasive means of examining brain function.

(4) These techniques make possible the use of extremely sensitive electronic equipment and powerful computer analyses.

The proposed search for genetic markers of chorea is also part of an effort towards understanding the etiology of abnormal electrodermal activity (Gruzelier & Venables, 1972; Iacono, 1979d) and of smooth pursuit eye tracking deficits (Holzman, Proctor, Yasillo, Meltzer, & Hurt, 1974; Shagass, Amadeo, & Overton, 1974; Iacono, Tuason, & Johnson, 1981) which are repeatedly found in schizophrenia (See Iacono, 1982b, for an in depth review of genetic markers for schizophrenia). The possibility exists that there are similarities between the psychophysiological responses produced by some schizophrenics and those of choreics. The advantage in such a comparison lies in the fact that, unlike the situation for schizophrenia, HC is a disorder of definite genetic origin and of known neurologic and biochemical features (eg. the basal ganglia are shrunken, GABA levels are reduced etc.). If as a result of this investigation, similarities on these variables between schizophrenics and choreics are revealed, more specific hypotheses concerning the structural or biochemical defects of schizophrenia could be advanced. The use of neurological populations with known areas of structural damage can also contribute to the 'mapping' of which behavioural deficits are resulting from which particular CNS processing abnormality. The restricted neuropathology of Huntington's chorea makes it possible to ascertain a correlation between a neuronal deficit and mental or psychological symptoms (Coyle, Schwarz, Bennett, &

Compochiaro, 1977; Oscar-Berman, 1978). By working 'backward' in this manner, it would be possible to apply the results obtained with HC patients to schizophrenic patients who showed similar behaviour deficits.

Types of Eye Movements

There are two forms of conjugate eye movements of interest to the present research: saccadic and smooth pursuit eye movements. A saccade serves to shift the eyes from one stationary point in the visual field to the next, at velocities up to 550 degrees/second (Fuchs, 1976). The saccadic system brings visual targets onto the fovea and is the most frequently used eye movement. Smooth pursuit movements are slow (1 to 40 degrees/second), sweeping rotations of the eyes generated in response to a moving target. Eyeball velocity is matched to the target's velocity. A stable image is thus maintained on the fovea. The two systems normally interact when target velocity exceeds 40 degrees/second. The saccadic system produces step-like jumps in eye position so that retinal slippage (eyes lagging excessively behind the target) caused by the limited speed of the smooth pursuit system is corrected. Smooth pursuit eye movements are generally considered to be involuntary since the presence of an external moving object is usually required for the system to function. Saccades, while highly automatic once initiated, can be produced at will and are deemed 'voluntary'.

Oculomotor Disturbances Associated with Huntington's chorea

Disturbances in blinking and staring have long been described in choreics (Huntington, 1872) although the identification of impaired ocular motility per se as a feature of HC is more recent (André-Thomas, Abély, Ajuriaguerra, & Eulier, 1945; Dereux, 1945). Impaired eye movements are present "in more than 50% of the cases with well-established chorea" (Petit & Milbled, 1973, p.287). This figure may reach 80% when more precise techniques for recording eye motion are applied (Hayden, 1981). The incidence of the most serious defect, a reduction in vertical saccadic velocity may affect two-thirds (Petit, Tilloy, Dhedin, & Milbled, 1971) to virtually all HC subjects examined (Avanzini, Girotti, Caraceni, & Spreafico, 1979). Since the more advanced cases of chorea are usually excluded from research on the basis of frank dementia or inability to control head movements well enough to track a target, these studies may be biased toward finding a lower incidence of oculomotor abnormalities than actually exists. The motor manifestations (including eye movement dysfunction) of some choreics are known to change for the worse over the course of the disease (Starr, 1967) so that studies in which the bulk of the subjects are in the earlier stages of chorea are likely to underestimate the prevalence of oculomotor abnormalities.

The most conspicuous disturbance of ocular motility in choreics occurs with vertical saccades directed in an upward

gaze. These saccades may be entirely absent ("paralyzed") or seriously impaired. The earliest reports of patients literally unable to lift their eyes to a point above them (Dereux, 1945; Schilder, cited in in Bruyn, 1968) have been recently confirmed (Petit et al., 1971; Starr, 1967; Petit & Milbled, 1973). When present, saccades are characterized by significant reductions in velocity, as well as increased latency and smaller amplitudes (Avanzini et al., 1979; Oepen, Clarenbach, & Thoden, 1981). Petit and Milbled (1973, p. 287) have stated that "the velocity was so decreased that the eyes appeared to move in an oil bath". These deficits are present to a lesser degree in horizontal saccades and vertical saccades in a downward direction. Impaired saccades are often accompanied by compensatory blinking and head movements. The larger saccades tend to be performed even more slowly or they disintegrate into smaller corrective saccades. Starr (1967, p. 562) speculates that "a disturbance of rapid movements is a general feature of Huntington's chorea and not merely a peculiarity of the extraocular muscles."

The slower, smooth pursuit eye movements are also altered in HC. Following movements are performed more rapidly and easily but are irregular in amplitude and often jerky in appearance (Avanzini et al., 1979; Oepen, Clarenbach, & Thoden, 1981). This jerkiness is attributed to the presence of corrective saccades and it occurs predominantly at higher target velocities (ie. 30°/second or more). Oepen and his

associates reported that jerkiness was especially noticeable in patients with 'manifest' chorea, presumably implying the more advanced cases.

The inclusion of Huntington subjects in the present research is also a reflection of the state of the art as concerns HC research with eye movement measures. It is no exaggeration to say that the apparent consistency in the types of abnormalities reported in the eye movement literature on Huntington's disease are only matched by the consistently flawed designs, analyses and so forth encountered in these reports. Comparisons between studies can only be made tentatively since the recording techniques are all different (e.g. eye movements can be recorded with electronystagmography, infrared recordings, cinematography, photoelectric corneal lenses etc.) or the measures taken are vague and imprecise (e.g. no standard eye tracking task is used). A few of the studies have no control groups; others mix choreic patients with rigid, akinetic patients. Some of the subjects included are so advanced in the disease that anterograde lesions secondary to the ones basic to HC may have been involved. Sample sizes are often small; a few studies are based on single cases.

Oculomotor Disturbances in Other Disorders

Deviant pursuit eye tracking patterns have been observed in a variety of clinical disorders, including Parkinson's disease (Shibasaki, Tsuji, & Kuroiwa, 1979), multiple sclerosis, myotonic dystrophy, spinocerebellar dysfunction (von Noorden & Preziosi, 1965), and schizophrenia (Holzman et al., 1974). As such, deviant tracking may be used as an index of central nervous system pathology. Thus if a structural or biochemical defect is present in the HC gene carrier, it may be revealed as a subtle impairment of saccadic or smooth pursuit eye tracking. What makes the oculomotor system particularly useful in this respect is its physical complexity and its sensitivity. Practically every level and part of the brain is involved in some shape or form in the operation and control of the eyes (Bach-y-Rita, 1973; Henn & Cohen, 1973). Because the visual system is so extensive it is liable to be subjected to any neuronal damage that the abnormal gene may bring about. Damage in one area may well affect the output of the rest of the system. Pirozzolo and Hansch (1981) suggest that there is a strong relationship between degree of cortical structural integrity and simple oculomotor reaction time in demented patients. Also the small size of the motor units regulating the extraocular muscles may make these units particularly susceptible to the effects of breakdowns at higher levels of control (Holzman et al., 1974).

Types of Electrodermal Phenomena

A skin conductance response (SCR; also called a skin conductance orienting response) is recorded as a phasic, waveform pattern produced when there is an increase in eccrine sweat gland secretion. This increased secretion takes place when the organism is presented with novel stimulation or with stimuli that have acquired signal value (Raskin, 1973). It is theorized that SCRs precede cognitive processing of such stimuli and subserve a selective attention mechanism (Kahneman, 1973). The organism's attention is thus focused and maintained on those stimuli relevant to its survival. The sweat glands are innervated by the sympathetic branch of the autonomic nervous system.

Electrodermal habituation can be defined as a decrease in--followed by a disappearance of--the skin conductance response as a result of repeated exposure to a stimulus (Lynn, 1966). Typically, electrodermal habituation is seen as a rapid diminution of SCR amplitude in the first and second repetitions of the stimulus. Response amplitude continues to decrease and the SCR disappears entirely somewhere between the third and twentieth stimulus presentation. The actual number (eg. 3, 10 or 20) of the stimulus presentations occurring before the SCR finally disappears varies across individuals. Stimulus properties have been shown to affect habituation. For example, low intensity stimuli near the threshold for perception and high intensity stimuli produce abnormally large

skin conductance (orienting) responses and startle reactions, respectively. The individual consequently habituates slowly to repeated presentations or does not habituate at all. In general, habituation is inversely proportional to stimulus intensity (Thompson, Berry, Rinaldi, & Berger, 1978). Arousal also affects habituation, with high levels of arousal associated with delayed SCR habituation (Bohlin, 1976).

Habituation is seen as a centrally determined form of information processing which has survival value for the organism since it leaves the organism free to attend to more significant stimuli in its environment. Electrodermal habituation reflects autonomic nervous system arousal but cannot be explained as a 'fatiguing' of the neurons (Sokolov, 1960) as any change in the stimulus will elicit a new response. Habituation depends on changes in activity occuring at two levels: (i) in the peripheral system--in this study, an increase or decrease in sweat gland activity (ii) centrally--as an increase or decrease in the firing rates of excitatory and inhibitory neurons.

Electrodermal Activity in Huntington's chorea

Studies of electrodermal activity in patients with Huntington's chorea are practically non-existent, perhaps because habituation is not directly observable, as are eye movements. Lawson (1981), in a pilot study, examined skin conductance responses in a sample of 25 HC patients. Twenty of the twenty-five choreics were found to be nonresponders to

a series of auditory stimuli. That is, they emitted no SCR to a variety of tones, to phonemes and to white noise that they heard. Of the remaining five subjects, three showed an occasional small amplitude response and two were normal responders. Of potential significance is Lawson's observation that "the few responding subjects (invariably to the phonemes) who gave only 1 or 2 SCRs may point to fast habituation as a distinct category among the responders". (Lawson, 1981, p. 34). Oscar-Berman and Gade (1978) measured a variety of electrodermal indices of arousal in 7 choreics. The group of choreics was one of 4 brain-damaged groups included in a study of Korsakoff's syndrome patients. The investigation revealed that the choreic subjects gave significantly reduced orienting responses to the first two auditory stimulus presentations as compared to the aphasic, the Parkinson and the normal subjects. They were still significantly less responsive than the former two groups even after 12 stimulus presentations. From the information given in the article, it was impossible to determine the number of stimulus presentations it took before the normals and the HC group showed the same level of responsiveness. The choreic patients also exhibited a significantly lower rate of habituation. While no definition of habituation was given in the Lawson study, these two studies seem to support each other in their conclusions.

The reduced SCR and relatively rapid habituation that has been reported in connection with HC patients may suggest that

Huntington's chorea involves a reduction of arousal to incoming stimulation (Oscar-Berman & Zola-Morgan, 1978). The central neural mechanisms by which this may come about are unknown although the hippocampus and the reticular activating system have been implied (Sokolov, 1960). Arousal is believed to facilitate memory and learning processes by sensitizing the organism to significant stimuli (Routtenberg, 1968). Oscar-Berman and Gade (1978) speculate that the hyporeactive arousal exhibited by their group of HC subjects may underlie their diffuse intellectual impairment. In addition, normal orienting responsivity (and therefore habituation) has been linked to the integrity of the thalamic reticular system and its projections to and from the frontal cortex (Rozin, 1976) as well as to frontal cortex integrity (Pribram & McGuiness, 1975). The frontal cortex is known to be one of the earliest and most affected structures in the choreic brain (Barbeau, Chase, & Paulson, 1973).

One of the difficulties in evaluating the literature on electrodermal responding in Huntington's disease is that there are such large discrepancies in the methods, in the subject samples, in the types of stimuli subjects were required to respond to, and in the ways of scoring the skin conductance response amplitudes, the habituation rates, the latencies to onset, the number of spontaneous skin conductance responses etc. that are typically measured. Many studies give vague details or no information at all on crucial aspects of their

research. For example, habituation rate is left undefined or simply plotted in charts with no explanations.

Eye Movements and Electrodermal Activity as Markers of Huntington's chorea

Over the past ten years, a small number of studies have dealt with either deviant eye tracking or electrodermal responsiveness as possible markers of Huntington's chorea. These studies generally attempted to demonstrate that impaired eye movements or decreased responsiveness occur at a higher frequency in progeny at-risk for Huntington's chorea than in normals. Since each offspring of a choreic parent has a 50% chance of inheriting the gene, it is expected, theoretically, that about 50% of the individuals in a progeny sample (i.e. the carriers) would exhibit abnormal SCRs or deviant eye tracking. The other half of the sample would be expected to give normal responses.

In a study of eye movement, twenty-eight progeny were examined by Petit et al. (1971), 18 of whom showed no eye tracking deficit. The remaining 10 presented a variety of abnormalities including: increased ocular latency, small amplitude responses, overly large saccades, especially in a vertical direction. Oepen, Clarenbach, and Thoden (1981) found that eight of their ten progeny displayed some form of oculomotor abnormality. These subjects had difficulties with pendular pursuit movements and slowed vertical voluntary saccades. There is unfortunately no indication of the exact nature of the deficiencies involved.

To date, only one early detection study of the electrodermal characteristics of progeny at-risk exists. Lawson (1981) reported that of 52 at-risk subjects, 17 (35%) emitted no skin conductance response to a series of twenty-four auditory stimuli. This rate of nonresponding is well above the 7% base rate in the normal population reported by Venables (1977). For example, 7.7% of Lawson's normal control group were nonresponders. There is no mention in the article of whether or not the rate of habituation of the progeny was measured.

Present Study

The goal of the present research was to contribute to the literature by comparing electrodermal responsivity in a sample of HC progeny to the responsivity of a group of normal controls. It also served as an attempt to replicate the findings of oculomotor abnormalities in the eye tracking performance of individuals at-risk for Huntington's disease as reported by earlier researchers. The specific hypotheses are outlined below.

Hypotheses

The purpose of the proposed study was to investigate the potential value of electrodermal characteristics and abnormal eye movement as genetic markers for Huntington's chorea. More specifically, the major hypotheses concerning these measures were:

1) that more of the progeny at-risk than the normal control

subjects would either (i) show fast habituation or (ii) give no or smaller amplitude skin conductance responses when presented with the auditory stimuli.

2) that the choreic subjects would (i) be electrodermal 'nonresponders' (ii) or be fast habituators (of those choreics who did give an electrodermal response).
3) that more of the progeny at-risk than the normal controls would have some deficiency in visual tracking and that these deficiencies would show up most frequently when they tracked upwardly moving targets.
4) that the choreic group would be poor eye trackers i.e. show more deficiencies than any other group being investigated.

Method

Subjects

Huntington and At-Risk Subjects

Subjects were recruited from at least three different sources via presentations and/or a detailed information sheet (Appendix A) describing the proposed research project. The experimenter attended monthly meetings of the British Columbia chapter of the Huntington Society and continued to recruit subjects through brief presentations and the information sheet. Through this network, it was also possible to tap into a pool of subjects who did not attend the meetings or who attended irregularly. Two separate groups of individuals were sought. The first consisted of choreics in the early stages of the disease. A functional definition of early was applied. Subjects had to be currently working, or able to cook and do household work or still be able to drive their cars. Seven male subjects in the early stages of Huntington's chorea took part. The age span for this group was 31 to 67. The mean number of years since the choreic subjects had been diagnosed as having Huntington's disease was 3.38 years, with a range of 8 months to 7 years. Two of the seven choreic subjects were taking isoniazid--an experimental drug treatment for Huntington's chorea--one was taking a hypnotic, and the other four were not taking any drugs. The second and largest group consisted of at-risk individuals who were symptom-free. Eight male and twenty-one female at-risk subjects whose ages ranged

Table 1

Demographic and Questionnaire Scores

	Demographics				Questionnaire Scores		
Group	Age	Sex M	Sex F	Education[a]	BDI	STAIT	STAIG
Huntington N=7	41.0 (12.1)	7	0	12.6 (2.2)	11.6 (8.9)	38.9 (11.2)	43.4 (11.3)
At-Risk N=29	31.6 (10.2)	8	21	12.7 (2.2)	3.5 (4.1)	33.4 (9.5)	35.3 (9.6)
Control N=29	28.8 (11.9)	11	18	13.9 (1.9)	1.9 (2.2)	31.5 (8.5)	32.8 (6.3)

Note. Standard deviations are given in parentheses.

Note. The values given are for the Beck Depression Inventory (BDI), the State-Trait Anxiety Inventory, Form X-1, (STAIT), and the State-Trait Anxiety Inventory, Form X-2, (STAIG).

a Number of years subjects engaged in a full-time course of education.

from 15 to 50 years participated. One at-risk subject was taking an analgesic, another, antihistamines, and a third subject, a hypnotic. At-risk subjects were otherwise drug-free. A family and personal history given to the experimenter served as the basis for establishing at-risk or early Huntington status. Table 1 provides information regarding the mean age and education of the at-risk and the Huntington group.

Control Subjects

Control subjects were recruited and screened in interviews completed by the personnel of the M.A.P. (Markers and Predictors) Research Project, and then tested in the laboratory by the experimenter or a laboratory technician on the eye movement and electrodermal measures. The M.A.P. Project is an extension of the World Health Organization International Pilot Study on Schizophrenia and is currently investigating schizophrenia in the Lower Mainland. Subjects were recruited by participating professionals attached to the Fairmount Family Practice Clinic of the Vancouver General Hospital, to the REACH Community Health Clinic, and to the Broadway Employment Center (Please consult Appendix B). In addition, control subjects were also recruited through two poster sessions on Huntington's disease given during the annual UBC Open House in March 1981 and in March 1982. Subjects were paid twenty dollars for their participation. Selection criteria included: absence of neurological disease,

no history of psychiatric treatment, and absence of other debilitating physical conditions. Subjects were also screened for drug or alcohol abuse. In addition, there was no family history of psychiatric illness. Subjects were excluded if they had any problems with their eyes or vision that could not be corrected by glasses or if their age fell outside the range of 15 to 54 years. (Appendix C contains the intake questionnaire). Participants under sixteen years of age were required to fill in a consent form signed by their legal guardian or parent. Eleven male and eighteen females whose ages ranged from 16 to 60 took part in the research as normal subjects. Table 1 contains further information regarding the mean age and education of the control group.

Setting and Apparatus

All sessions took place in a laboratory in the Health Sciences Centre Hospital on UBC campus. A six channel Beckman R612 Dynograph was used to record electrodermal activity, and the vertical and horizontal electrooculogram (abbreviated VEOG and HEOG, respectively). Calibration was verified prior to each recording. All eye tracking signals and a record of target movement were simultaneously recorded onto magnetic tape with a Vetter Model A FM recorder for later analysis. A Digital PDP 11/23 computer (Digital Equipment Corporation) was used to digitize and quantify the psychophysiological measures.

All electrodes used to gather eye tracking data were

filled with Redux electrode paste (Hewlett-Packard). Electrode sites for the eye tracking tasks were massaged with the Redux paste to decrease skin resistance. The area of skin in contact with the electrolyte was .95 cm^2. Whenever possible, electrodes were soaked--prior to recording--in an electrolyte solution of a similar concentration as the electrode paste. This helped to ensure stability of recording.

During the eye movement recordings, subjects' heads were held in place by an adjustable head rest (with a chin and forehead rest bar) mounted onto a Tektronix RM15 oscilloscope. This ensured that all subjects tracked the target from an equal distance (29 cm). The head rest also reduced the likelihood of artefacts in the eye tracking data due to small head movements. The oscilloscope control panel was covered with black felt to minimize distraction. A black, Plexiglass tunnel extending from the oscilloscope screen to the head rest was also used for this purpose.

Horizontal eye movements were recorded through a modified Type 9806A A-C coupler using time constants of 3 seconds (for smooth pursuit tracking) and 10 seconds (for saccadic eye tracking). Eye blinks during the horizontal tracking tasks were recorded through a similar coupler using a time constant of 0.1 seconds. Vertical eye movements during both smooth pursuit and saccadic eye tracking were also recorded with a Type 9806A A-C coupler, using a time constant of 3 seconds.

One cm Ag/AgCl Beckman biopotential electrodes were placed near the outer canthi of the right and left eyes for horizontal recordings. Electrodes were also placed above the eyebrow and below the lower lid of the dominant eye for the vertical EOG. These electrodes also recorded eyeblinks in the EOG.

For the smooth pursuit tasks, subjects watched a spot of light driven by a sine wave generator (Wavetek Digital VCG model 113) or a rectangular wave generator (used in Iacono & Lykken, 1979a, 1979b). The dot traversed the screen of the cathode ray oscilloscope both vertically and horizontally. To test saccadic eye tracking, the target spot moved abruptly from side to side as well as up and down at irregular intervals varying from 1.5 to 4 seconds. For the saccadic tracking tasks, the target was driven as a rectangular wave by the rectangular wave generator. The target was a 5 mm circle with a 1 mm dot in the middle. The dot traversed 20 degrees of visual arc during the horizontal eye tracking tasks, and it traversed 10 degrees of visual arc during the vertical tracking tasks.

Poor eye tracking performance has been noted in subjects who are less attentive to the task demands. These individuals produce smooth pursuit movements interrupted by saccades without being aware of doing so (Iacono & Lykken, 1979a). To reduce the confounding effects of inter-subject variability in attentiveness, a monitor task was included that required

subjects to monitor aperiodic changes in the stimulus being tracked. During this task, the dot in the center of the circle appeared and disappeared unpredictably. Subjects signaled the presence or absence of the dot by pressing or releasing a hand-held pushbutton switch. The use of this monitor task has been shown to improve smooth pursuit tracking (Iacono & Lykken, 1979a, 1979b).

Skin conductance was recorded on two channels using two Type 9844 skin conductance couplers. One cm Beckman biopotential Ag/AgCl electrodes were attached to the medial phalanges of the first and second fingers of each hand, using a standard double adhesive collar system. This system involved first applying an adhesive collar with a center hole .95 cm^2 in diameter on the appropriate phalanges. A second adhesive collar was then applied to the electrode cap. The electrode was next filled with electrolyte paste, and the two collar centers were aligned, and pressed firmly together. This ensured that the skin surface area in contact with the electrolyte was .95 cm^2. A standard electrolyte medium (physiological saline mixed with commercially available Unibase neutral ointment) was employed. A one cm Ag/AgCl Beckman biopotential electrode was affixed to the shin of the right leg and served as the ground electrode. During the electrodermal activity tasks, subjects were presented with tones binaurally through AKG K240 headphones. The tones were generated by an audio oscillater that was triggered to produce

the tone sequence by signals recorded on a tape. This tape was played on a Sanyo stereo cassette deck.

Procedure

Each subject had some knowledge of the research rationale and of the measures that would be taken prior to the actual testing session. Participants were assigned a code number to ensure anonymity and confidentiality. Once subjects had arrived, they were asked to complete consent forms (Appendix D presents the MAP consent forms). Parental consent was required for minors (Appendix E contains the parental consent form). Subjects were informed that they could withdraw at any time without prejudice. No subjects withdrew. Volunteers who wore contact lenses were required to use their eyeglasses since the contact lenses introduce blink artefacts in the eye movement recordings. Subjects were told that for ethical reasons, no individual results would be given out. Subjects were required to complete the Beck Depression Inventory as well as the State-Trait Anxiety Inventory (Forms X-1 and X-2). The BDI, the STAI today and the STAI general questionnaires were included to control for the effects of depression and anxiety on the electrodermal measures. Anxiety is associated with higher skin conductance levels, smaller skin conductance responses, (Neary & Zuckerman, 1976; Katkin, 1975), and slower rates of habituation (Maltzman, Smith, Kantor & Mandel, 1971). Depression has been linked to decreased electrodermal responsivity (Iacono, Lykken, Peloquin, Lumry, Valentine, &

Tuason, 1983). It was, in addition, important to take into account the fact that there were items on each of these questionnaires that related to the symptomatology of Huntington's chorea. On the BDI for example, the HC subject is liable to choose 3, on item 'S', since Huntington's chorea is associated with a major weight loss (Appendix F). Items 'B', 'I', 'L', 'M', 'N', and 'U' may also be measuring symptoms of HC. In the STAI general questionnaire, items 22 and 28 may be tapping into the symptoms of Huntington's chorea as well (Appendix G contains the State-Trait Anxiety Inventory). It could be argued that these items magnify rather than change the direction of the HC scores. It may be the case that an individual with HC is more likely to be depressed or to be more anxious than an individual who does not have to deal with a disease.

Subjects were also required to give information relative to their age, education, and drug use (Appendix H contains the medication information sheet). Age is known to affect eye tracking performance in a positive, linear fashion ie. the greater the age, the poorer the eye tracking (Kuechenmeister, Linton, Mueller, & White, 1977; Sharpe & Sylvester, 1978). Various drugs have been shown to affect eye tracking (Wilkinson, Kime & Purnell, 1974; Holzman, Levy, Uhlenhuth, Proctor & Freedman, 1975). Most of the commonly used antipsychotics such as the phenothiazines do not affect eye tracking performance, since studies investigating the tracking

of schizophrenic or manic-depressive populations have shown that such subjects, when they are taken off medication, track as well as they do when they are taking medication (Iacono & Koenig, 1983). Sex was not analyzed as there is no relation between gender and eye tracking performance (Pivik, 1979; Shagass, Amadeo & Overton, 1974; Holzman et al., 1974). Similarly, gender is not a significant factor in electrodermal responsivity (Castleman, Brennan & Kimmel, 1978).

The general procedure of electrode placement and the presentation of the visual and auditory tasks was explained to each subject as the subject was seated in front of the oscilloscope. Electrodes were filled, attached to the subjects, and secured with surgical tape. Earrings, bracelets and sweaters that would interfere with electrode placement were removed.

A taped, standardized, verbal description of the purpose of the study was then played and subjects were asked to take deep breaths, to cough, to move their head and to blink so that these artefacts could be recognized should they occur later on in the session. Task instructions were provided from the same pre-taped cassette for each subject. Throughout the eye tracking tasks, subjects were reminded to relax their facial muscles, to refrain from blinking, to hold their heads still, and to follow the target closely. In addition, during the saccadic tracking tasks, subjects were instructed to avoid moving their eyes before the target actually moved. Subjects

then visually tracked a .4 Hz sinusoidal target while the EOG channels were calibrated. This ensured that subjects were familiarized with the task and could follow instructions correctly.

Both vertical and horizontal smooth pursuit eye movements (SPEMs) were recorded. The subjects tracked sinusoidal targets horizontally for 20 cycles at three different frequencies: .4 Hz, .8 Hz and 1.2 Hz. The tracking tasks were repeated a second time while subjects engaged in the monitor task. A sinusoidal vertical SPEM test at .4 Hz concluded the smooth pursuit tracking tasks.

Vertical and horizontal saccadic EOG tasks were presented next. The subject horizontally tracked a rectangular wave target which had an average frequency of .2 Hz for 20 cycles each. A similar vertical saccadic task ended the saccadic eye tracking tasks.

In the second half of the session, skin conductance electrodes were attached to the subject who was requested to hold the arms and fingers still so as to reduce contamination of the data by movement artefacts. A 5 minute resting period commenced and ensured that the SCR readings were stabilized. The subject was asked to wilfully cough to determine what a typical response might look like. This gave the experimenter the time to calibrate the skin conductance channel. The subject was then given headphones to wear, through which a series of soft and loud tones were heard. Eight 85 db tones

were presented, followed by ten 105 db tones at 1,000 Hz. Tones lasted 1 second each. The intertone intervals were 20-40 seconds long, of 30 seconds duration on average. A relaxation inducing set of instructions was delivered prior to the commencement of the tone presentation and subjects were informed that the task was a measure of their ability to ignore the distracting tones while they concentrated on becoming completely relaxed (See Appendix I). These instructions were included to reduce intersubject variability with respect to the significance the subjects attached to the tones by focusing their attention on the task of becoming relaxed (Iacono & Lykken, 1979c). After the tone presentation, subjects were then instructed to focus their attention on two familiar sounds and requested to try to identify them. They were then presented with a dog barking and a teletype (taped from a sound effects record). These sounds were included in an attempt to contrast subjects' electrodermal responsivity to (meaningless) tones with their response to (meaningful) sounds.

At the end of the two hour session, the electrodes were removed and the subjects' questions answered. Subjects were then asked if they wanted a brief summary of the overall results of the study sent to them once the data were analyzed.

Quantification of Measures

Eye Tracking Tasks

Data from each SPEM task as well as from the target

channel associated with the task were recorded on magnetic tapes. These tapes were then digitized by the computer and the data stored on floppy disks. The computer stored the first twenty cycles of both the eye tracking and the target channel, aligning the two channels so that cycles 1, 2, etc. of the target and the tracking data could be compared for phase lag differences. The phase lag score essentially measures the degree to which the eyes move ahead or fall behind the target as the eyes attempt to track it. A large lag indicates poor tracking; a lag value close to zero indicates near perfect synchrony of the eyes' and the target's movements. A positive lag indicates that the eyes are lagging behind the target.

The best sixteen cycles from each eye tracking task were then selected for analysis. This usually resulted in the first sixteen cycles of attempted tracking being selected as the sixteen best cycles. Criteria for rejecting cycles were established as follows:

(1) The first cycle of "tracking" was rejected if the subject did not track the entire first cycle.

(2) Cycles associated with an extreme EOG signal that was out-of-bounds on the FM tape were rejected.

(3) Cycles were deleted if the subject was obviously not attending to the task e.g. the subject talked during the task.

Once the best sixteen cycles were chosen, the program divided each cycle of tracking (as well as dividing the

corresponding cycle from the target channel) into 500 amplitude data points. Each cycle of tracking was standardized to have a mean of zero and a standard deviation of one and centered about a horizontal axis set equal to the mean. This ensured that the two sets of cycles were expressed in the same units of measurement and hence were comparable. The second measure of smooth pursuit eye tracking performance--the RMS(root mean square) error deviation score--was then calculated from the two channels and multiplied by 1,000. An RMS error score was computed individually for each of the sixteen cycles. The median RMS score was utilized in subsequent data analyses because the median is less sensitive to inflation by momentary inattention that could grossly distort one or two cycles. The median RMS score is also unaffected by blinks in the eye tracking record (Iacono et al., 1982). A low RMS score indicated that the subject tracked well (ie. the eye tracking channel data showed little deviation from the target channel data) and that the shape of the eye tracking data closely approximated the shape of the cycles in the target channel. A high RMS score represented a poor tracking performance.

The saccadic eye tracking tasks were similarly digitized on FM tapes and stored on floppy disks. The computer then identified saccadic eye movements in the best sixteen cycles of tracking. The best cycles were chosen in the same way as the cycles for the smooth pursuit eye tracking tasks. A

minimum velocity (40 degrees/second) and a minimum duration (40 msecs) criterion were used to identify a saccade. Its velocity, duration and amplitude were measured. The amplitude was calculated as the difference between the peak of the saccadic eye tracking movement and the trough at the eye movement onset.

Skin Conductance Measures

The scoring protocol for the electrodermal measures is presented in Appendix J. Tonic or resting skin conductance level was calculated in the left and right hands at the start of each tone or sound. This established a baseline of responsivity to the soft tones, to the loud tones, and to the two sounds--the dog bark and the teletype. A skin conductance response was defined as any response occurring one to four seconds after tone onset. A spontaneous skin conductance response was counted if it occurred ten seconds after stimulus onset and before the onset of the next tone. The modifier 'spontaneous' restricts this response to those SCRs that occured without the the presentation of any stimuli. To establish whether a subject was a responder or a nonresponder, responses were counted if they were greater than .05 micromhos in amplitude. This minimum size was adopted to help control for movement artefacts in the data. Electrodermal habituation was deemed to have taken place when subjects gave three consecutive responses of less than .05 micromhos in amplitude. The three zero responses criterion was adopted to ensure

comparability with other research dealing with electrodermal habituation in Huntington's chorea. The time that elapsed between the tone initiation and the beginning of the skin conductance response was adopted as the measure of response latency. The amplitude of the first response, as well as the amplitude of the biggest response (calculated as the largest skin conductance value reached during the stimulus minus the prestimulus tonic level) to the dog and teletype stimuli were calculated in addition to the resting skin conductance for the data analyses of the sounds.

Results

In all analyses, the degrees of freedom utilized were adjusted to take account of possible dependencies created in the scores by the inclusion of members from the same family. One degree of freedom was assigned per nuclear family. Eighteen at-risk families and twenty-two control families participated. The adjustment involved computing F tests utilizing the appropriately reduced number of degrees of freedom in the formula (See Winer, 1971).

Demographic Variables and Questionnaire Analyses

The means for the demographic variable scores, as well as the means for the questionnaire scores are contained in Table 1. A one-way ANOVA with group as the only factor examined the interrelationships between the groups (ie. Huntington, at-risk, and control) on these variables and on the questionnaire scores. There was no significant difference between the groups in terms of age, $F(2,44)=2.64$, $p<.08$. The groups differed on the BDI scores, $F(2,42)=13.71$, $p<.05$. The Huntington subjects had higher scores on the BDI than either of the other two groups of subjects. There was a difference between the groups in education, $F(2,44)=4.03$, $p<.02$. A Newman-Keuls multiple range test indicated that the control subjects had more years of education than the at-risk but not the choreic subjects. The groups did not differ on their STAI general scores, $F(2,41)=3.00$, $p<.06$. Scores for the STAI today were comparable across all groups, $F(2,39)=1.24$, $p<.30$.

Eye Tracking Data Analyses

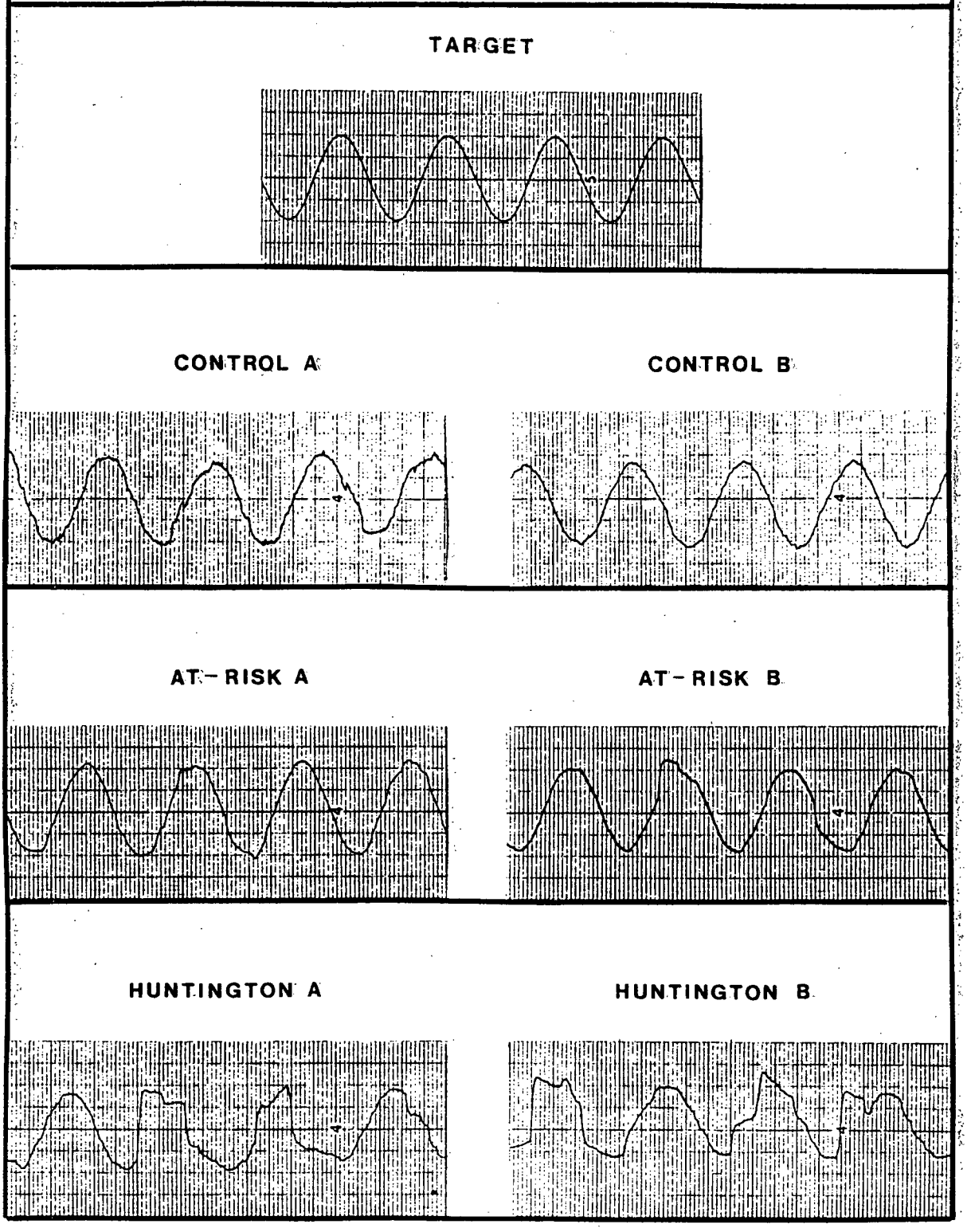
Preliminary Analyses

As a result of several ANOVAs designed to test for significant differences between the groups, it was revealed that the variances of the groups on the smooth pursuit eye tracking tasks were considerably heterogeneous, and Bartlett chi-square tests of homogeneity of variance with $p<.0001$ were typical. Inspection of the group variances indicated that the variances for the Huntington group were often three to ten times that of the other two groups; and in the eye tracking tasks involving tracking a target at a high frequency, the variance from the Huntington's group could be as much as fifty times larger than the variances of the at-risk and the control groups. Variances on some saccadic eye tracking tasks were similarly much larger in the Huntington group, or for some tasks much smaller than the variances in the at-risk or the control group scores. Visual inspection of the data clearly showed that the Huntington group was tracking in a highly deviant fashion from what would be expected on such tasks. Examples of normal, at-risk, and Huntington eye tracking records are contained in Figure 1. The computerized eye tracking analyses were therefore restricted to a comparison of the eye tracking performance of the normal controls and the at-risk subjects.

Highly unequal variances are known to limit the validity of the probability statements generated by the ANOVA *F* tests.

FIG. 1

EYE TRACKING RECORDS OF TWO SUBJECTS FROM EACH GROUP ON HORIZONTAL SMOOTH PURSUIT AT .4 HZ.



The problem of dubious validity is compounded in the present research by the large discrepancy in sample size ie. the early Huntington subjects numbered only seven, that is, the Huntington group was one quarter the size of the other two groups. Highly unequal sample sizes combined with heterogeneity of variance greatly limits the validity of the conclusions that can be drawn from the analysis of variance (Glass, Peckham, & Sanders, 1972; Box, 1954; Kramer, 1956). The robustness of F tests to violations does not hold up with highly unequal Ns. The frequency of Type I errors under such conditions as are present in the eye tracking data could easily be tripled, leading one to conclude that many more significant differences exist between the groups when the null hypothesis is actually true. In general, if the sample with the smallest N is also the sample with the largest variance, the actual significance level, p greatly exceeds the nominal significance level (usually $p<.05$). The eye tracking tasks would have been subjected to highly inappropriate analyses, had the Huntington group been included. There is no consensus in the statistical literature as to tests that could be valid given such circumstances (Miller, 1981).

The discrepancy in sample size and variance existed as well in the saccadic eye tracking data. The problem of exceptionally large variances existed in some measures (e.g. in the latency measures of horizontal saccadic tracking, but only for leftward eye movements) but in other measures,

the Huntington group contributed exceptionally small variances when compared to the other two groups. (e.g. in the amplitude measure of both up and down vertical eye tracking). The latter situation greatly increases the frequency of Type II errors. Other studies with brain-damaged populations have encountered similar problems (Holloway & Parsons, 1971; Davidoff & McDonald, 1964) on measures of electrodermal responsivity.

It was clear from visual inspection alone that the tracking of the Huntington group was highly deviant in many respects. The tracking of the Huntington subjects was also much worse than that of schizophrenic patients who had completed the same tracking tasks (Iacono, personal communication, December 1983). A blind rating of tracking performance utilizing photocopied eye tracking records found the Huntington group to be the worst group overall when their tracking was compared to psychotic subjects with either affective or schizophrenic disorders on the .4 Hz horizontal smooth pursuit tracking task. Using the mean performance score of the three diagnostic groups (Huntington, schizophrenic and affective disorder) as a cutoff point, subjects were classified as good or poor trackers. A chi square with one degree of freedom (subjects were classified as Huntington or non-Huntington) was significant, $\chi^2=4.31$, $p<.05$, confirming that membership in the Huntington group was significantly related to poor tracking performance.

The important point in these analyses was in any case to focus on the comparison of the at-risk with the normal control group to determine if (a) there were significant differences between the groups and (b), if the at-risk were found to be poor trackers, were there similarities in the deficiencies produced by the at-risk group and the deficiencies produced by the choreic group. A .05 level of confidence was adopted for all tests of significance. The Greenhouse-Geisser epsilon (ϵ) correction procedure (Greenhouse & Geisser, 1959) was utilized in the repeated measures analyses to adjust the degrees of freedom in the F-tests. The procedure effectively reduces the number of false positives which would otherwise be generated (See Winer, 1971, p. 523, for a discussion of this procedure). The Greenhouse-Geisser probabilities and epsilon factors for degrees of freedom adjustment are reported where applicable. The epsilon factor was applied to degrees of freedom that had already been adjusted to account for familial interdependencies in the eye tracking scores. One at-risk subject did not do the eye tracking tasks because of a vision problem (strabismus). The data from two normal controls were withdrawn from the eye tracking analyses, again because of problems with strabismus. These normals were originally screened for eye problems but were found, during the actual testing session, to be tracking as strabismic individuals would. On close questioning, both of these normal control subjects described a childhood history of eye problems.

Smooth Pursuit Tracking Analyses

Horizontal Smooth Pursuit Eye Movement (SPEM) Analyses

For two subjects, missing data for one task was estimated by interpolating data points from the similar tasks they had already completed at different frequencies.

The group means for the phase lag and the median RMS error measures of SPEM tracking are shown in Table 2. The data from the at-risk and normal control subjects were subjected to a three-way analysis of variance (using Dixon, 1981, BMDP:2V) with repeated measures on two factors. The two repeated measures factors were target frequency (.4 Hz, .8 Hz, 1.2 Hz); and task (monitor, nonmonitor). The between factor was group (at-risk, control). The phase lag analysis revealed significant differences between the groups $F(1,40)=6.75$, $p<.02$. At-risk subjects tracked with greater phase lag (ie. with their eyes lagging behind the target) than did the normal control subjects. There was a significant task effect, $F(1,38)=18.44$, $p<.01$, indicating that phase lag was greater in the monitor than in the nonmonitor task condition. That is, the eyes lagged further behind the target in the nonmonitor condition. The frequency at which the target moved across the screen was significantly related to phase lag performance, $F(1.22,46.4)=101.02$, $p<.01$, $\epsilon=.61$, in that subjects' eyes lagged further behind the target at the higher frequencies. There were no significant interaction effects. Figure 2 shows phase lag scores for the three groups in the monitor and

Table 2

Means for Horizontal Smooth Pursuit Eye Movements

Group	Frequency	Phase Lag[a]		Median RMS[b]	
		Non-Monitor	Monitor	Non-Monitor	Monitor
Huntington	.4 Hz	-10.00 (6.4)	-2.14 (5.9)	411 (254)	260 (285)
	.8 Hz	1.29 (31.3)	10.29 (6.7)	424 (351)	238 (230)
	1.2 Hz	23.71 (26.1)	44.14 (55.2)	619 (371)	355 (331)
At-Risk	.4 Hz	-4.37 (10.3)	0.04 (2.3)	122 (94)	91 (42)
	.8 Hz	-0.64 (13.2)	9.32 (6.0)	202 (123)	113 (42)
	1.2 Hz	15.54 (21.4)	27.93 (8.8)	273 (116)	168 (56)
Control	.4 Hz	-7.37 (12.8)	-1.63 (2.2)	139 (112)	107 (41)
	.8 Hz	-5.78 (10.1)	4.37 (5.0)	186 (121)	122 (32)
	1.2 Hz	10.67 (14.9)	19.85 (11.4)	230 (103)	165 (38)

Note. Standard deviations are given in parentheses.

a Values are in number of sampling points. One sampling point equals .04 degrees of visual arc.

b The means and standard deviations for the RMS error score were averaged over right and left eye movements. Values are in arbitrary units.

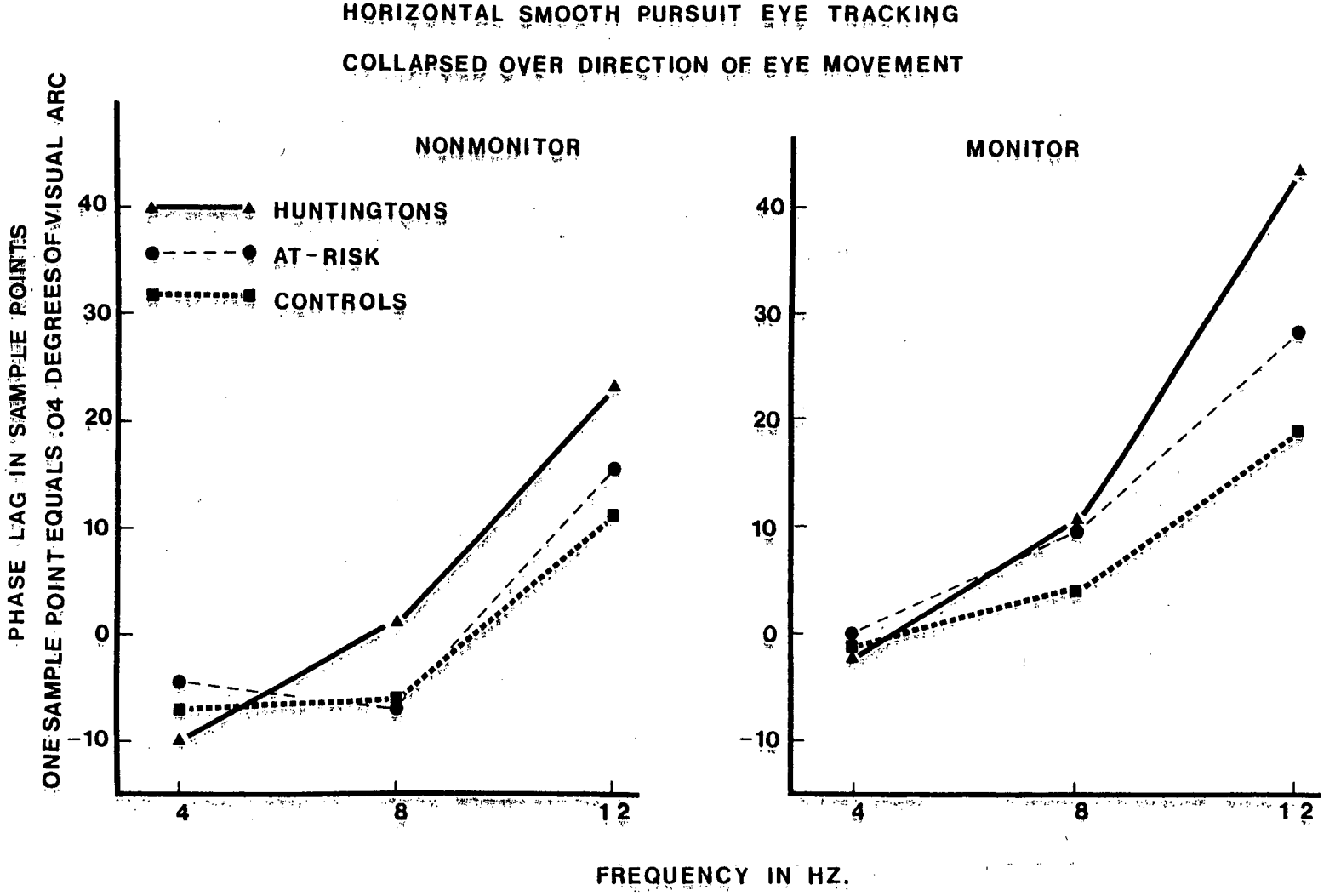

HORIZONTAL SMOOTH PURSUIT EYE TRACKING
COLLAPSED OVER DIRECTION OF EYE MOVEMENT
NONMONITOR
MONITOR
HUNTINGTONS
AT-RISK
CONTROLS
PHASE LAG IN SAMPLE POINTS
ONE SAMPLE POINT EQUALS .04 DEGREES OF VISUAL ARC
40
30
20
10
0
-10
4
8
12
FREQUENCY IN HZ.

FIG. 2

FIG. 3

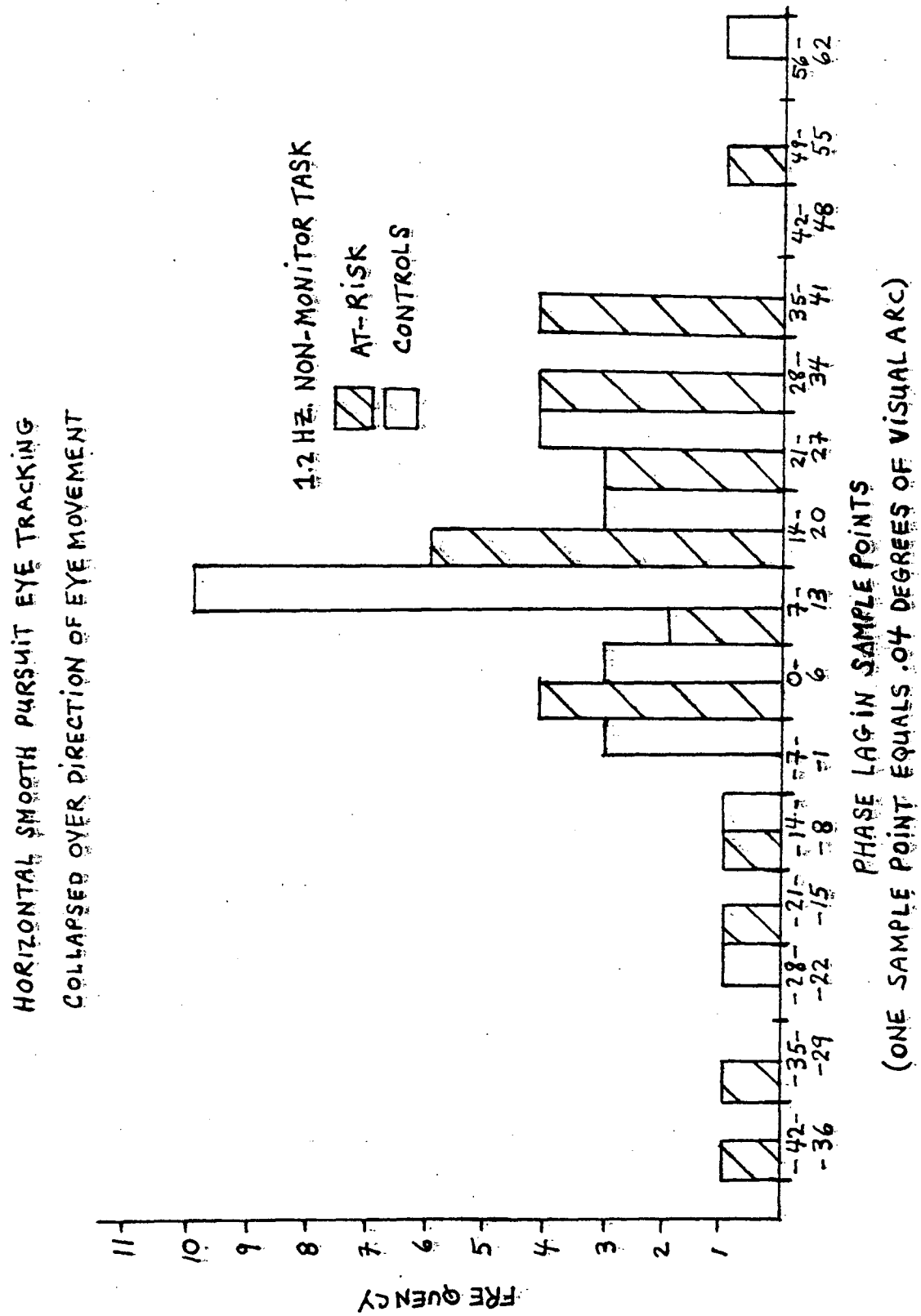
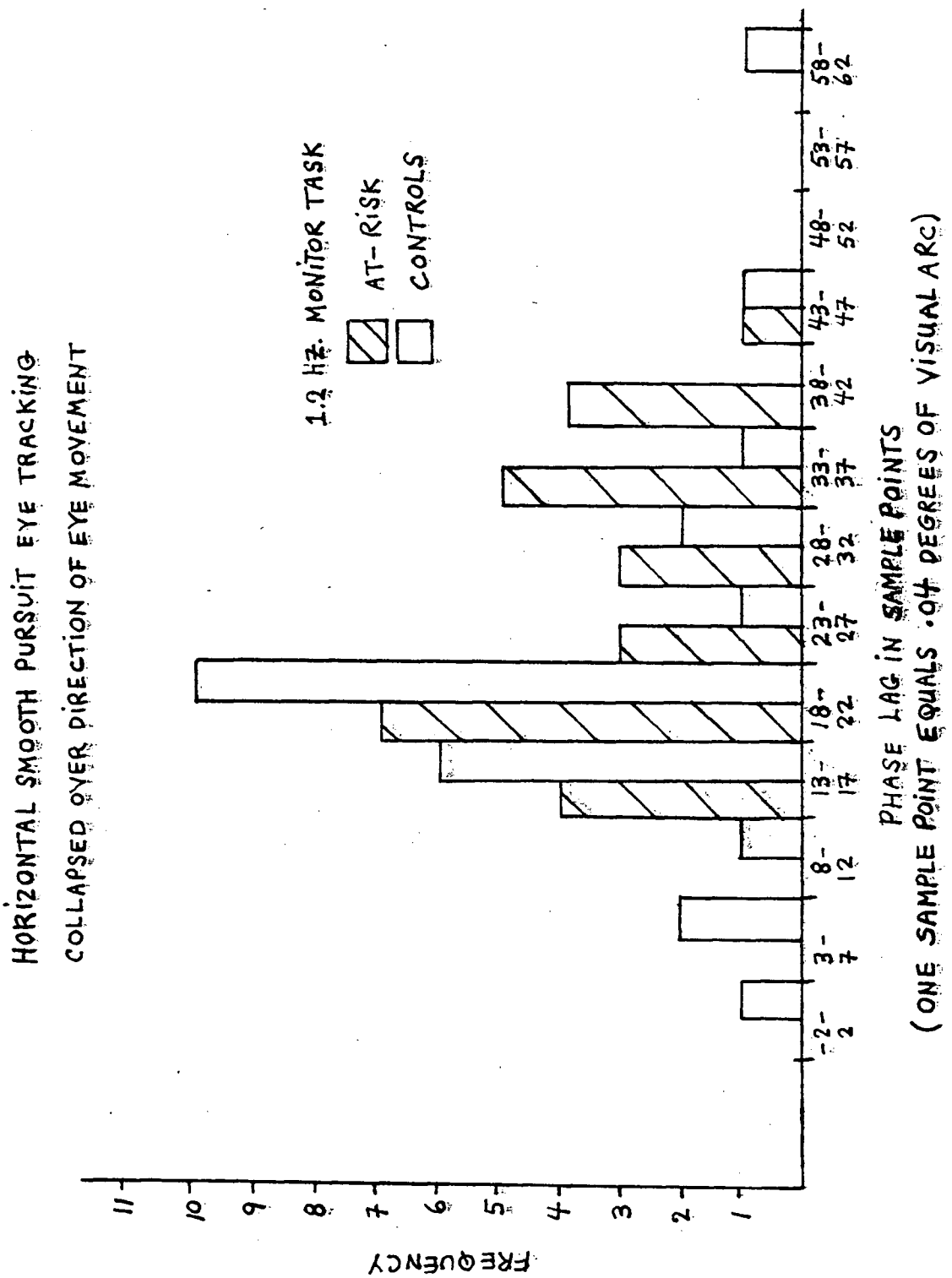

HORIZONTAL SMOOTH PURSUIT EYE TRACKING
COLLAPSED OVER DIRECTION OF EYE MOVEMENT
1.2 HZ. NON-MONITOR TASK
AT-RISK
CONTROLS
FREQUENCY
PHASE LAG IN SAMPLE POINTS
(ONE SAMPLE POINT EQUALS .04 DEGREES OF VISUAL ARC)

FIG. 4


HORIZONTAL SMOOTH PURSUIT EYE TRACKING
COLLAPSED OVER DIRECTION OF EYE MOVEMENT
1.2 Hz. MONITOR TASK
AT-RISK
CONTROLS
FREQUENCY
PHASE LAG IN SAMPLE POINTS
(ONE SAMPLE POINT EQUALS .04 DEGREES OF VISUAL ARC)

nonmonitor conditions.

Contrasting group means may not be a sensitive test of group differences if a small number of at-risk subjects consistently score outside the range of normal scores. Figures 3 and 4 show the distribution of scores for the at-risk and control subjects. 1.2 Hz was chosen for these figures, since the ANOVA had found the greatest difference in the distribution of the scores for this target speed. A post-hoc examination of the proportion of the higher phase lag scores across subjects in the at-risk and control groups found that there were nine subjects at-risk who tracked with more than thirty sampling points of lag as compared to one normal control. Yates' corrected chi-square with one degree of freedom was significant, $\chi^2=6.19$, $p<.01$.

For the analyses of the median RMS performance scores, a four-way ANOVA with repeated measures on three factors (frequency, task, direction of eye movement) was computed. No significant group effect, $F(1,40)=0.03$, $p<.85$, was revealed. Direction effects were present, whereby eye movements to the right were linked to higher RMS scores, $F(1,40)=36.72$, $p<.01$, indicating that subjects in both groups tracked more poorly when tracking in the rightward direction. Task, $F(1,40)=23.39$, $p<.01$, and frequency, $F(1.62,61.6)=79.29$, $p<.01$, $\epsilon=.81$, effects were significant. As expected, the nonmonitor tasks were more poorly tracked than were the monitor tasks. The higher frequencies were associated with a

greater median RMS value, indicating that tracking deteriorated as the target frequency increased. A significant interaction of frequency and group, $F(1.62,61.6)=3.41$, $p<.05$, $\epsilon=.81$, was uncovered. The median RMS measure similarly unveiled that some of the at-risk subjects were poor at reproducing the target pattern at the 1.2 Hz frequency. That is, while the performance of both groups deteriorated as the target moved at greater speeds, more of the at-risk subjects produced impaired eye tracking at the highest frequency. A post-hoc examination of these data revealed that there were seven at-risk and three control subjects who gave median RMS scores indicative of poor tracking. An analysis resulted in a Yates' corrected chi-square with one degree of freedom, $\chi^2=1.21$, $p<.27$, which was not significant. There were no other significant interaction effects. Refer to Figure 5.

Vertical SPEM analysis

The phase lag data were analyzed via two-way ANOVAs with repeated measures on direction of eye tracking. Group (at-risk, control) was the between factor. Table 3 presents the means for the vertical smooth pursuit tracking task. The at-risk and control groups were not significantly different in the extent to which their eyes lagged the target, $F(1,38)=.01$, $p<.92$. There was no significant difference between the groups in their RMS scores, $F(1,40)=0.00$, $p<.98$. There was an effect due to direction, $F(1,40)=5.30$, $p<.03$ whereby subjects in both groups had greater RMS scores when they tracked the dot as it

HORIZONTAL SMOOTH PURSUIT EYE TRACKING
COLLAPSED OVER DIRECTION OF EYE MOVEMENT.

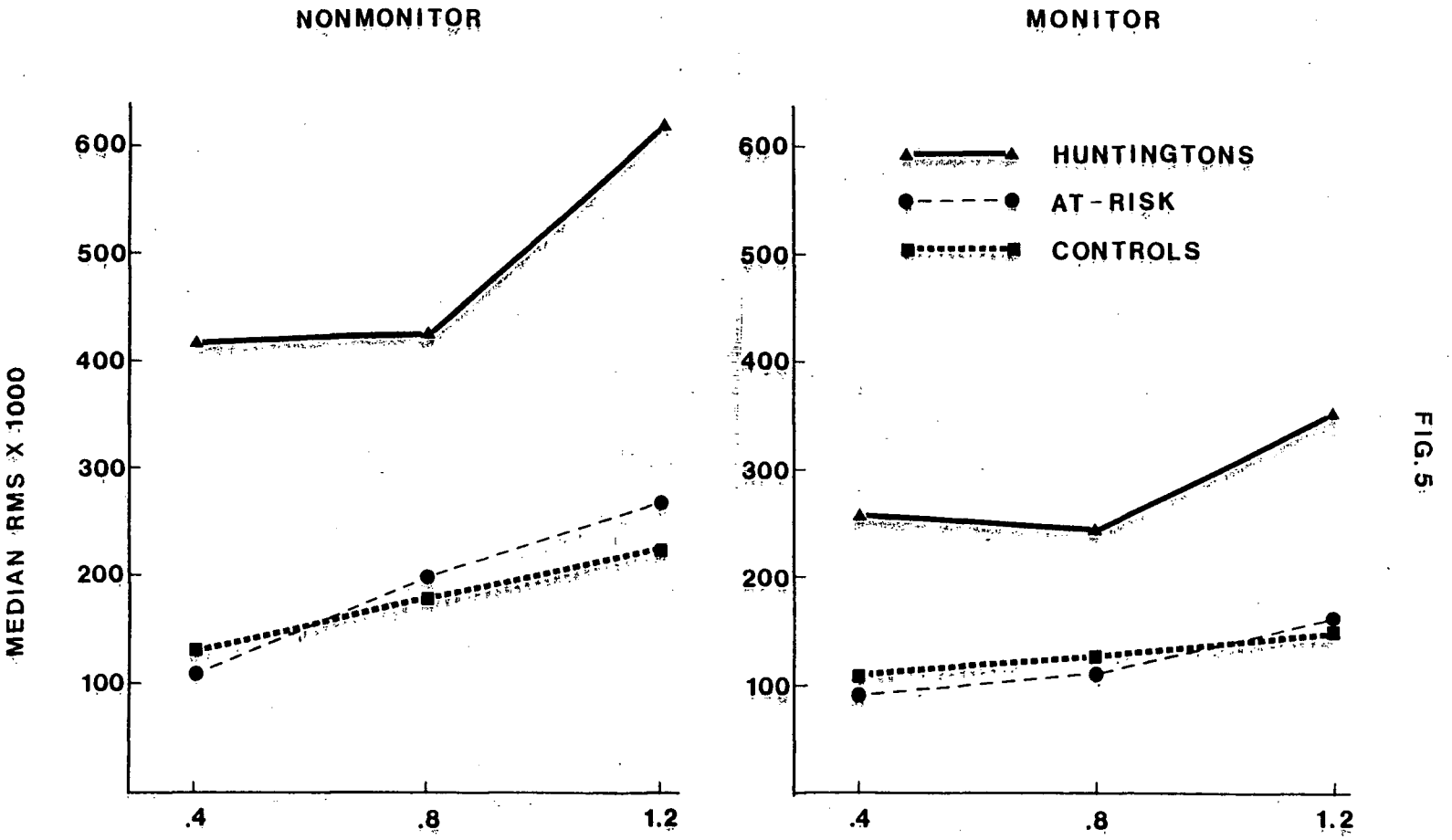


FIG. 5

Table 3

Means for Vertical Smooth Pursuit Eye Movements

Group	Phase Lag[a]	Median RMS[b]	
		Up	Down
Huntington	15.43 (61.5)	899 (245)	892 (214)
At-Risk	-6.88 (25.1)	470 (186)	411 (172)
Control	-11.15 (29.6)	451 (270)	433 (252)

Note. Standard deviations are given in parentheses.

a Values are in number of sampling points. One sampling point equals .04 degrees of visual arc.

b Values are in arbitrary units.

moved up the screen. No significant interaction effects were uncovered.

Saccadic Eye Tracking Analyses

A value of $p<.05$ was utilized as the criterion for the attainment of significance in all analyses. The data from one at-risk subject were not available due to a mechanical failure during the laboratory test session.

Horizontal Saccadic Eye Tracking Analyses

The median latencies to initial movement are presented in Table 4. Several two-way analyses of variance with repeated measures on direction were performed. Group (at-risk, control) was the only other factor. The groups exhibited similar latencies, $F(1,40)=.53$, $p<.47$. The range of oculomotor saccadic reaction times for the groups was 209-223 milliseconds ie. highly uniform reaction times were apparent. Rightward saccadic eye movements, $F(1,40)=5.03$, $p<.03$ were linked to increased latencies.

The median amplitudes associated with the horizontal eye tracking task are contained in Table 4. Two-way ANOVAs with repeated measures on direction were performed. There were no differences in the size of the movements produced by the two groups, $F(1,40)=0.00$, $p<.97$. Rightward eye movements were of greater amplitude, $F(1,40)=8.74$, $p<.01$.

Similar ANOVAs for the median response duration measure yielded no main effect for group, $F(1,40)=.68$, $p<.44$. There were no differences found between the at-risk and the normal

Table 4

Means for Horizontal Saccadic Eye Tracking; Right(R) or Left(L) Eye Movements

Group	Latency[a]		Amplitude[b]		Duration[a]	
	R	L	R	L	R	L
Huntington	227 (32)	236 (53)	20.45 (2.4)	-20.72 (4.1)	113 (7)	111 (11)
At-Risk	223 (35)	209 (31)	19.70 (1.7)	-19.18 (1.6)	96 (6)	97 (5)
Control	221 (27)	212 (24)	19.61 (1.5)	-19.21 (1.3)	92 (14)	92 (13)

Note. Standard deviations are given in parentheses.

a Values are in milliseconds.

b Values are in degrees of visual arc.

control groups, in the duration of their saccadic eye movements. Median duration scores were not affected by the direction the eyes were tracking the target, $F(1,40)=.15$, $p<.70$. There were no significant interaction effects in any of the median latency, median amplitude, or median response duration analyses.

Vertical Saccadic Eye Tracking Analyses

Two-way analyses of variance with group (at-risk, control) and direction of eye movement (upward, downward) as the two factors were computed. Table 5 contains the mean latency and duration of vertical saccadic eye tracking. Examining the median latency to onset, no main effect by group was uncovered, $F(1,40)=.62$, $p<.44$. There was no significant effect for direction of eye movements, $F(1,40)=2.90$, $p<.10$.

The analysis of the median duration of the saccadic eye movements showed that the at-risk and control groups produced movements of equal duration, $F(1,40)=1.89$, $p<.18$. Eye movements in the upward direction were of longer duration, $F(1,40)=41.24$, $p<.01$.

Electrodermal Data Analyses

Data from twenty-nine at-risk, twenty-nine controls and seven Huntington chorea subjects were examined. There were no variance problems associated with the electrodermal data that would preclude including the early Huntington group in the electrodermal analyses.

Table 5

Means for Vertical Saccadic Eye Tracking; Up(U) and Down(D) Movements

Group	Latency[a]		Duration[a]	
	U	D	U	D
Huntington	269 (22)	239 (38)	90 (36)	91 (15)
At-Risk	226 (38)	220 (48)	95 (18)	73 (13)
Control	235 (31)	198 (48)	89 (18)	69 (14)

Note. Standard deviations are given in parentheses.

a Values are in milliseconds.

Tonic Skin Conductance Level Analyses

Electrodermal data collected from at-risk, control and early Huntington chorea subjects were analyzed. A three way ANOVA with repeated measures on hand and tone trials as factors was undertaken to examine skin conductance level to the soft tones. Table 6 contains the means for the skin conductance levels to the soft tones. There was no significant effect of group, $F(2,47)=1.23$, $p<.30$. As expected, there was an order effect on the tones, $F(1.53,88.8)=12.28$, $p<.01$, $\epsilon=.27$, with skin conductance level dropping progressively as subjects listened to all eight soft tones. There were no laterality differences, $F(1,47)=2.78$, $p<.11$; skin conductance levels were similar across the left and right hands.

The resting or tonic skin conductance level to loud tones was examined using a similar three-way repeated measures analysis of variance, including group, hand and tone trials as factors. The three groups were found to be strictly comparable, $F(2,45)=.74$, $p<.48$. Laterality differences again did not reach significance, $F(1,47)=2.31$, $p<.14$. An order effect for tones was found, $F(3.3,155.1)=4.69$, $p<.01$, $\epsilon=.30$, indicating that subjects responded most to the earlier tones in the sequence. There were no significant interaction effects in any of the resting skin conductance data. Table 7 contains the means for resting skin conductance to the loud tones.

Table 6

Means for Skin Conductance Levels to Soft Tones; Right(R) and Left(L) Hands

	Huntington		At-Risk		Control	
Tones	R	L	R	L	R	L
1	4.73 (3.72)	3.85 (2.62)	3.10 (2.54)	2.95 (2.53)	4.14 (3.02)	4.06 (2.66)
2	4.64 (3.61)	3.72 (2.56)	3.06 (2.51)	2.85 (2.50)	4.16 (3.07)	4.12 (2.71)
3	4.63 (3.48)	3.65 (2.43)	2.92 (2.46)	2.67 (2.49)	4.10 (3.00)	4.12 (2.79)
4	4.86 (3.25)	3.56 (2.31)	2.87 (2.48)	2.60 (2.45)	3.89 (2.79)	3.93 (2.61)
5	4.42 (3.13)	3.62 (2.41)	2.79 (2.47)	2.51 (2.37)	3.74 (2.70)	3.81 (2.57)
6	4.36 (3.02)	3.56 (2.29)	2.76 (2.49)	2.56 (2.34)	3.63 (2.64)	3.69 (2.52)
7	4.30 (2.93)	3.52 (2.22)	2.70 (2.46)	2.49 (2.31)	3.51 (2.57)	3.57 (2.48)
8	4.24 (2.96)	3.43 (2.17)	2.68 (2.49)	2.45 (2.27)	3.43 (2.52)	3.49 (2.43)
Mean	4.52	3.61	2.86	2.64	3.83	3.85

Note. Standard deviations are given in parentheses.

a Values reported are in micromhos.

Table 7

Means for Skin Conductance Level[a] to Loud Tones; Right(R) and Left(L) Hands

Tones	Huntington		At-Risk		Control	
	R	L	R	L	R	L
1	4.50 (3.46)	3.65 (2.44)	3.07 (2.56)	2.78 (2.33)	3.80 (3.08)	3.82 (2.83)
2	4.55 (3.51)	3.70 (2.45)	3.47 (2.65)	3.15 (2.38)	4.21 (3.44)	4.21 (3.22)
3	4.54 (3.48)	3.66 (2.46)	3.47 (2.74)	3.19 (2.49)	4.45 (3.58)	4.28 (3.25)
4	4.38 (3.33)	3.62 (2.40)	3.52 (2.80)	3.19 (2.52)	4.42 (3.57)	4.28 (3.29)
5	4.20 (3.04)	3.47 (2.20)	3.33 (2.62)	3.06 (2.40)	4.26 (3.50)	4.20 (3.29)
6	4.17 (2.93)	3.45 (2.16)	3.31 (2.58)	3.03 (2.34)	4.24 (3.47)	4.18 (3.31)
7	4.10 (2.85)	3.42 (2.15)	3.21 (2.53)	2.93 (2.28)	4.15 (3.56)	4.20 (3.36)
8	4.06 (2.78)	3.36 (2.09)	3.11 (2.53)	2.82 (2.24)	4.04 (3.42)	4.11 (3.30)
9	4.04 (2.72)	3.36 (2.10)	3.10 (2.55)	2.81 (2.24)	3.97 (3.38)	4.05 (3.29)
10	4.04 (2.79)	3.40 (2.15)	2.96 (2.39)	2.73 (2.21)	3.87 (3.30)	3.97 (3.25)
11	4.17 (2.72)	3.50 (2.22)	2.94 (2.30)	2.71 (2.21)	3.87 (3.32)	3.99 (3.27)
12	4.12 (2.71)	3.46 (2.20)	3.02 (2.56)	2.77 (2.30)	3.80 (3.22)	3.93 (3.22)
Mean	4.52	3.61	2.86	2.64	3.83	3.85

Note. Standard deviations are given in parentheses.

a Values reported are in micromhos.

Skin Conductance Response (SCR) Analyses

A three-way ANOVA with repeated measures on hand (right and left) and soft tone trials (1 to 8) was performed with SCR as the dependent variable. The means are presented in Table 8. Results indicated that all three groups responded similarly to the series of soft tones they heard, $F(2,47)=.49$, $p<.53$. There was an order effect on the tones, $F(2.52,118.4)=6.03$, $p<.01$, $\epsilon=.36$, in that subjects in all groups tended to respond less to the later tones than to the earlier tones. There were no differences between the hands in terms of degree of responsivity, $F(1,47)=.59$, $p<.45$. See Figure 6.

A second three-way repeated measures analysis of variance, with the same factors as in the previous analysis, revealed no significant differences between the groups in their responsivity to loud tones, $F(2,47)=.56$, $p<.58$. These means are presented in Table 9. There was no difference in responsivity across the hands, $F(1,47)=.01$, $p<.91$. Tones again evidenced an order effect, $F(2.31,108.6)=7.41$, $p<.01$, $\epsilon=.21$, with subjects responding most to the earlier tones. There were no significant interaction effects present in the SCR data. Please refer to Figure 7.

Table 8

Means for Skin Conductance Response to Soft Tones; Right(R) and Left(L) Hands[a]

Tones	Huntington		At-Risk		Control	
	R	L	R	L	R	L
1	0.19 (0.38)	0.13 (0.23)	0.26 (0.45)	0.21 (0.36)	0.35 (0.44)	0.37 (0.38)
2	0.03 (0.05)	0.02 (0.04)	0.14 (0.27)	0.09 (0.16)	0.19 (0.31)	0.22 (0.32)
3	0.02 (0.04)	0.02 (0.04)	0.06 (0.15)	0.07 (0.19)	0.10 (0.17)	0.14 (0.27)
4	0.10 (0.23)	0.05 (0.12)	0.05 (0.13)	0.04 (0.09)	0.09 (0.22)	0.10 (0.23)
5	0.05 (0.11)	0.05 (0.11)	0.03 (0.09)	0.02 (0.06)	0.04 (0.11)	0.05 (0.13)
6	0.04 (0.12)	0.03 (0.08)	0.04 (0.15)	0.03 (0.09)	0.03 (0.09)	0.03 (0.09)
7	0.07 (0.18)	0.04 (0.10)	0.04 (0.09)	0.04 (0.11)	0.03 (0.11)	0.05 (0.13)
8	0.24 (0.58)	0.14 (0.34)	0.02 (0.09)	0.02 (0.12)	0.00 (0.02)	0.01 (0.04)
Mean	0.09	0.06	0.08	0.07	0.10	0.12

Note. Standard deviations are given in parentheses.

a Values reported are in micromhos.

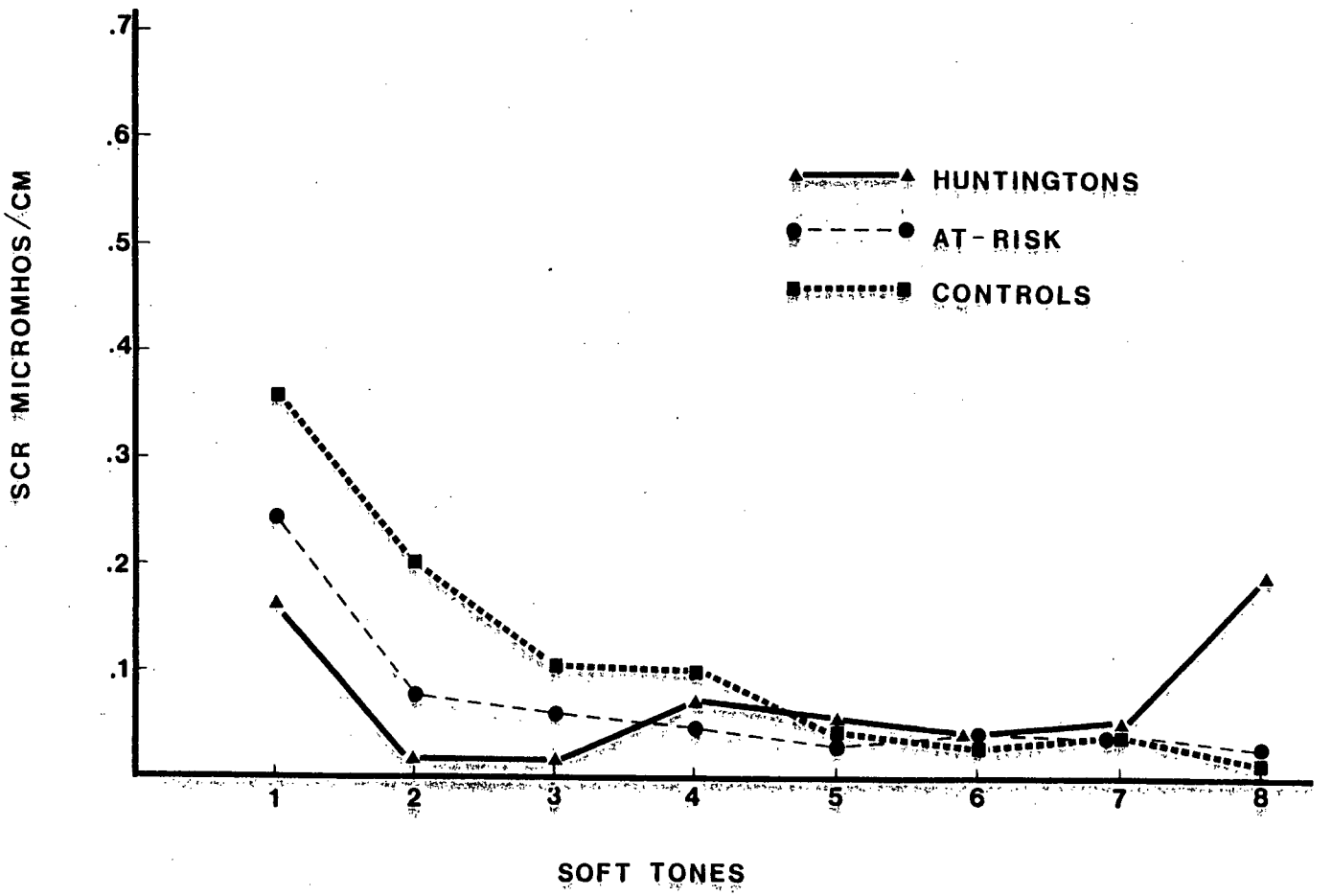

MAGNITUDE OF SKIN CONDUCTANCE RESPONSES
ELICITED BY SOFT TONES, COLLAPSED OVER HANDS
SCR MICROMHOS/CM
.7
.6
.5
.4
.3
.2
.1
HUNTINGTONS
AT-RISK
CONTROLS
1
2
3
4
5
6
7
8
SOFT TONES

FIG. 6

Table 9

Means for Skin Conductance Response to Loud Tones; Right(R) and Left(L) Hands[a]

Tones	Huntington		At-Risk		Control	
	R	L	R	L	R	L
1	0.65 (1.02)	0.49 (0.64)	0.75 (1.15)	0.70 (0.98)	0.87 (0.42)	0.79 (1.14)
2	0.37 (0.62)	0.27 (0.33)	0.50 (0.70)	0.50 (0.57)	0.50 (0.69)	0.57 (0.63)
3	0.32 (0.38)	0.28 (0.30)	0.39 (0.65)	0.45 (0.64)	0.43 (0.57)	0.48 (0.59)
4	0.15 (0.14)	0.14 (0.14)	0.29 (0.55)	0.41 (0.62)	0.25 (0.43)	0.27 (0.38)
5	0.30 (0.44)	0.24 (0.33)	0.30 (0.53)	0.39 (0.66)	0.26 (0.36)	0.26 (0.32)
6	0.18 (0.18)	0.15 (0.15)	0.17 (0.52)	0.23 (0.56)	0.18 (0.21)	0.21 (0.21)
7	0.07 (0.04)	0.07 (0.04)	0.17 (0.43)	0.27 (0.53)	0.15 (0.16)	0.16 (0.18)
8	0.12 (0.10)	0.12 (0.12)	0.17 (0.45)	0.20 (0.46)	0.18 (0.24)	0.21 (0.30)
9	0.10 (0.06)	0.08 (0.03)	0.09 (0.35)	0.10 (0.30)	0.19 (0.29)	0.18 (0.27)
10	0.31 (0.53)	0.30 (0.52)	0.14 (0.48)	0.18 (0.52)	0.15 (0.18)	0.15 (0.18)
11	0.22 (0.41)	0.23 (0.41)	0.01 (0.20)	0.07 (0.35)	0.11 (0.13)	0.10 (0.12)
12	0.11 (0.15)	0.10 (0.11)	0.05 (0.25)	0.07 (0.25)	0.12 (0.14)	0.14 (0.15)
Mean	0.24	0.21	0.25	0.30	0.28	0.29

Note. Standard deviations are given in parentheses.

a Values reported are in micromhos.

MAGNITUDE OF SKIN CONDUCTANCE RESPONSES ELICITED BY LOUD TONES, COLLAPSED OVER HANDS.

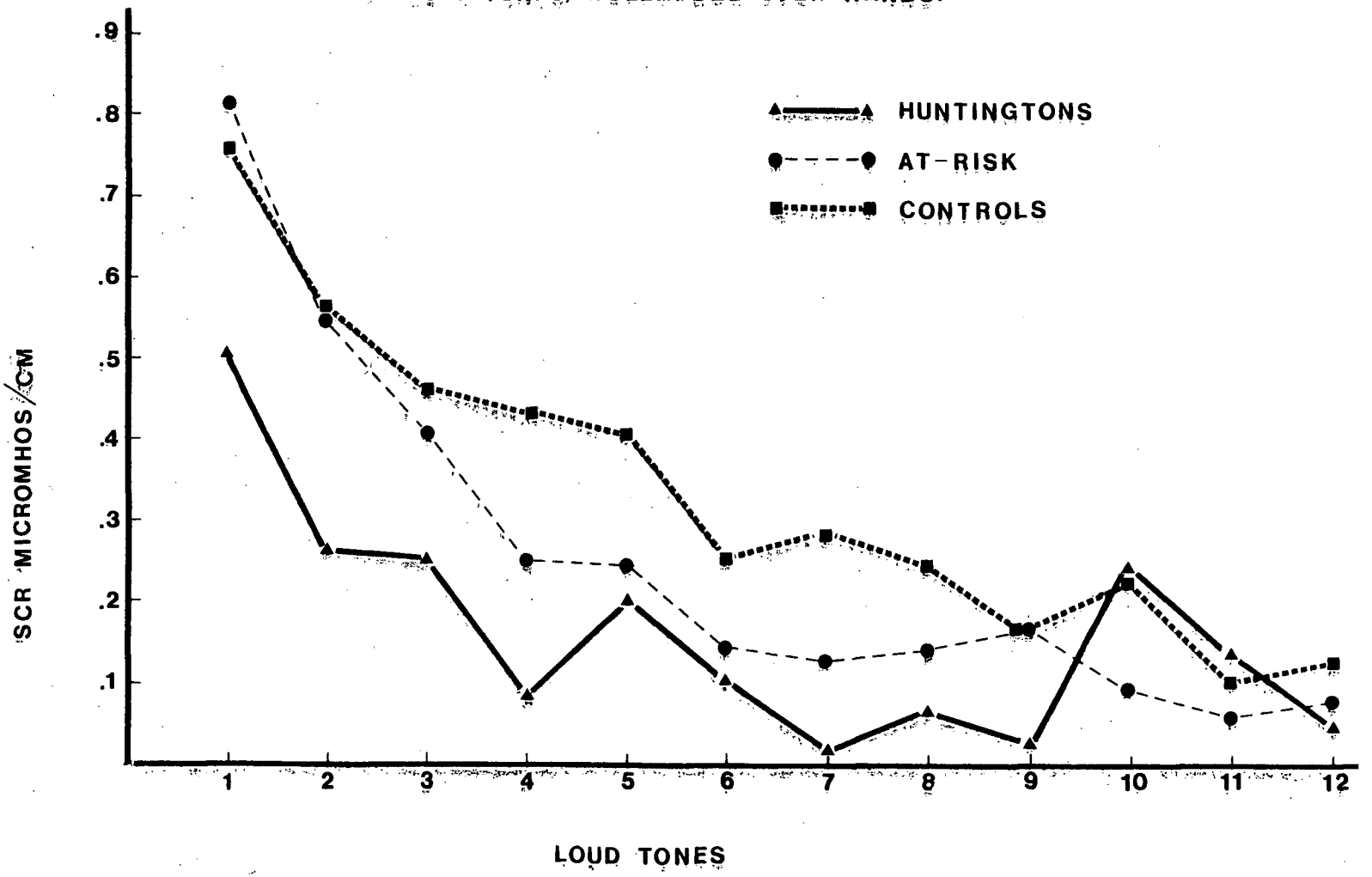


FIG. 7

Table 10

Number of Nonresponders to Soft(S) and Loud(L) Tones

	Group					
	Huntington		At-risk		Control	
	S	L	S	L	S	L
Non-Responders	0 (0)	2 (28.6)	1 (3.4)	3 (10.3)	0 (0)	8 (27.6)
Responders	7 (100)	5 (71.4)	28 (96.6)	26 (89.7)	29 (100)	21 (72.4)

Note. The values in parentheses describe the percentage of responders or nonresponders within each group.

Nonresponders

The number of non-responders to soft and loud tones is presented in Table 10. Combining the data for the left and right hands, it can be seen that only one individual (an at-risk subject) was a nonresponder to the eight soft tones. There were more nonresponders to the twelve loud tones: three at-risk, eight normal control and two Huntington subjects. Nearly one-third of both the Huntington and the normal control subjects did not respond to the loud tones. The SCR data for the loud tones were subjected to a Pearson chi square analysis with two degrees of freedom, $\chi^2=3.05$, $p<.22$, indicating that group membership could not be predicted from whether an individual subject was a responder or a nonresponder.

Habituation Analyses

The analyses of the habituation rate revealed that there were no differences between the three groups in the number of trials subjects required to reach habituation ie. to stop responding. The data were subjected to a three-way analysis of variance (group x hands x tone loudness). The group effect was nonsignificant, $F(2,44)=.10$, $p<.90$. None of the main or interaction effects was significant except the tone loudness effect which was significant $F(1,44)=18.98$, $p<.01$. The mean number of trials before habituation was reached are given in Table 11 for each group.

Table 11

Mean Number of Trials to Habituation to Soft and Loud Tones; Right(R) and Left(L) Hands

	Group					
	Huntington		At-Risk		Control	
Tones	R	L	R	L	R	L
Soft	3.14	2.86	2.28	2.03	2.37	2.50
Loud	3.43	5.00	6.66	6.31	5.73	5.87

Spontaneous Skin Conductance Responses (SSCR) Analyses

The mean number of SSCRs per tone during the presentation of the soft and loud tones was calculated and is given in Table 12. A three-way (group x hand x tone loudness) analysis of variance was computed. There were no significant effects of group, $F(2,44)=2.20$, $p<.12$, of hand, $F(1,44)=1.41$, $p<.24$, or of tone loudness, $F(1,44)=.60$, $p<.44$. None of the interaction effects was significant.

Latency of Response Analyses

Latency of response was analysed by a three way analysis of variance with group, hand, and tone loudness as factors. None of the main or interaction effects was significant. The group effect was $F(2,44)=.40$, $p<.67$. The hand effect was $F(1,44)=.48$, $p<.50$. The tone loudness effect was $F(1,44)=3.91$, $p<.06$.

Data Analyses Relating to the Sound Stimuli: Dog & Teletype

Table 13 contains the means for skin conductance level and the means for skin conductance responses to the sound stimuli. Tonic skin conductance level (SCL) was assessed through a three way analysis of variance with group, hand, and stimulus as factors. The stimulus factor had two levels corresponding to the dog and teletype stimuli. SCL was equivalent across the groups; $F(2,44)=.45$, $p<.64$. The hand effect was also nonsignificant; $F(1,44)=2.02$, $p<.16$. The stimulus factor, however, did result in a significant effect; $F(1,44)=9.87$, $p<.01$, indicating that subjects in all groups

Table 12

Mean Number of Spontaneous Skin Conductance Responses to Soft and Loud Tones in the Right(R) and Left(L) Hands

	Group					
	Huntington		At-Risk		Control	
Tones	R	L	R	L	R	L
Soft	.554	.518	.233	.224	.175	.171
Loud	.667	.631	.284	.256	.186	.206

Note. All values are measured in micromhos.

Table 13

Means for Resting Skin Conductance(SCL) and First Skin Conductance Response(SCR) to the Dog and Teletype Stimuli; Right(R) and Left(L) Hands

	SCL[a]				SCR[a]			
	Dog		Teletype		Dog		Teletype	
Group	R	L	R	L	R	L	R	L
Huntington	5.24 (3.67)	4.35 (2.74)	5.02 (3.73)	4.02 (2.50)	0.21 (.28)	0.13 (.15)	0.11 (.17)	0.08 (.11)
At-Risk	4.10 (3.08)	3.70 (2.77)	3.89 (3.00)	3.46 (2.62)	0.29 (.41)	0.31 (.46)	0.35 (.41)	0.37 (.55)
Controls	5.31 (4.01)	5.32 (3.54)	4.85 (3.71)	5.04 (3.47)	0.35 (.36)	0.47 (.47)	0.40 (.48)	0.45 (.55)

Note. Standard deviations are given in parentheses.

a Values are in micromhos.

had higher resting skin conductances when they were presented with the dog stimulus, that is, the first of the two sound stimuli. None of the interaction effects was significant.

A similar three-way analysis of variance was performed with respect to the amplitude of the first response to the stimuli. No group differences were found, $F(2,44)=1.34$, $p<.27$. No other main or interaction effects were found to be significant. Another three-way analysis of variance revealed that the at-risk, control and early Huntington chorea groups were also comparable in the size of their biggest response to the stimuli, $F(2,44)=.67$, $p<.52$. There were no significant main or interaction effects associated with the data pertaining to the biggest SCRs to the sounds.

Discussion

The purpose of the present study was to conduct an investigation of the eye tracking capabilities and the electrodermal responsivity of at-risk and control populations to determine whether these psychophysiological measures could function as markers for Huntington's chorea. In the analyses relating to the horizontal smooth pursuit eye tracking performance of the at-risk and control subjects, a significant difference between the groups was found in the phase lag measure whereby at-risk subjects pursued the dot with their eyes lagging further behind the target than did the control subjects. The eyes typically lag behind the target in normal tracking. Good trackers can follow a target with their eyes lagging only a little behind the target and without the need to use catch-up saccades to correct the position of the image on the retina. A large phase lag was produced by some of the at-risk subjects when the target moved at its' greatest frequency, indicating that their eye tracking performance was different. The monitor task was associated with greater phase lag, as in previous reports (see Iacono & Koenig, 1983).

There were no differences in eye tracking performance on any of the horizontal or vertical saccadic tasks between the groups. A review of the literature indicated that choreic subjects have shown the greatest impairment in tracking vertically moving targets. This finding combined with the fact that saccadic tracking is generally considered the most

stringent test of eye tracking ability should have produced the greatest differences between the groups. This was not the case. One possibility is that a difference between the groups on the latency to onset measure may have been obscured by the large variability in saccadic reaction time that has been reported in other research with control subjects (Baloh & Honrubia, 1976). While the consistency of saccadic reaction time within any particular subject has been established, a large variability between subjects could confound the data.

There was no direction effect related to the saccadic eye tracking performances. The literature on eye tracking in Huntington's disease suggests that choreic subjects experience difficulties with targets moving upward. The deficiencies in tracking upward vertical saccades reported in the literature may reflect a qualitative difference between control or at-risk subjects and Huntington subjects' eye tracking performance.

There were consistent effects of direction of tracking in the horizontal eye movement tasks. The at-risk and the control groups both tracked more poorly in the rightward direction on the SPEM tasks. The rightward saccadic tasks were associated with increased latency and greater amplitudes. These greater latencies and amplitudes may reflect a habitual pattern of viewing (for example, reading texts from left to right) in the subjects included in this study. Horizontal direction of eye movement did not differentiate the groups in

any way.

The eye movement data quantification techniques used in the present study may have worked against finding greater abnormalities in the eye tracking performance records of the at-risk group as only the best 16 cycles of tracking were used in the data analysis. It is possible that the at-risk group would have produced a higher frequency of eye tracking errors had the first 16 cycles been analyzed. However, this is mitigated by the fact that the cycles were only rejected when some obvious extraneous factor was operating on the subject's performance, and during these cycles the subject could not be said to be actually tracking.

While the present research does not purport to explain such differences, it is consistent with previous literature pointing to impoverished eye tracking performance in brain damaged subjects when compared to other psychiatric samples (Oscar-Berman, 1978; Oscar-Berman & Zola-Morgan, 1978). That the HC subjects tracked poorly across the board makes any conclusions reached concerning the link between the degeneration of the basal ganglia and the production of impaired eye movements less precise than if a single type of eye tracking deficit had been uncovered. Visual inspection of the data indicated that the performance of the Huntington subjects was very different from what would normally be produced on such tasks.

It was clear from visual inspection and from blind

ratings that the tracking of the Huntington group was highly deviant in many respects and that the Huntington subjects were worse at eye tracking tasks than psychotic patients with affective and schizophrenic disorders.

The fact that Huntington subjects were poorer trackers on both smooth pursuit and saccadic eye tracking tasks certainly accords with previous research. The discovery of severe eye tracking deficiencies in this group is perhaps all the more important given that the group was composed of high functioning choreic subjects. Research to date has focused on hospitalized, or heavily sedated subject populations who are in the middle or late stages of the disease. While two of the subjects in this sample were using isoniazid, none were ingesting drugs which are known to adversely affect eye tracking. There has been to date no investigation of the possible long or short term effects of isoniazid on eye tracking performance. What is most noticeable about the eye tracking performance of the Huntington subjects is that no aspect of eye tracking was unaffected ie. the group as a whole tracked consistently poorly on all the tasks, even the easiest ones. While it is true that the mean age for the Huntington group was higher than the mean age for the control group, age per se could not account for the frequency and severity of eye tracking deficits encountered in the Huntington eye tracking records since a visual comparison with the older control subjects clearly showed that the choreic subjects were much

poorer trackers. The Huntington's group was, however, significantly more depressed than both the at-risk and the control groups; and tended to be more anxious (as measured by the STAI general form) than the control group. It could be argued that the extraneous effects of anxiety or depression may have accounted for the Huntington subjects' eye tracking performance. This is unlikely since none of the questionnaire scores reached clinical cut off points ie. while the Huntington group may experience more state anxiety or be slightly more depressed, the effects of these factors per se are not strong enough to produce such highly deviant eye tracking patterns. It is likely too that the scores for the Huntington group were inflated on these particular questionnaires since as mentioned previously, there are items on the questionnaires that tap into the symptomatology of Huntington's chorea.

A possible alternate explanation is that the eye tracking deficits encountered in this population are not related to the presence of the HC gene so much as they are secondary to Huntington's disease. That is, the poor eye tracking could be a result of temporary lapses in attention, or difficulty remembering instructions pertinent to the task, since short term memory problems and attentional deficits are common to many individuals with Huntington's (Wexler, 1979; Wilson & Garron, 1973; Oscar-Berman, 1978). The present research attempted to control for attentional deficits by providing

subjects with precise instructions and giving them monitor eye tracking tasks that required paying close attention to the target. In addition, only subjects in the early stages of Huntington's disease were tested, minimizing the effect of cognitive impairments. Simple momentary inattention does not, moreover, lead to highly impaired or deficient smooth pursuit tracking movements (Pass, Salzman, Klorman, Kaskey & Klun, 1978). The poor tracking cannot be traced to poor motivation or disinterest in the tasks as these individuals as a group gave effortful responses to tasks they were presented with. It is likely that the eye tracking deficiencies relate specifically to the premature neuronal degeneration occurring in the basal ganglia of the choreic subjects.

This study compared 29 at-risk and 29 control subjects on eye tracking performance measured across various tasks, at different frequencies. The performances of the at-risk group in the study was generally similar to that of the control group in both the vertical smooth pursuit and the horizontal and vertical saccadic eye tracking tasks that were completed. There were two statistically significant differences between the groups which indicated that some at-risk subjects tracked differently from the controls. These were related to horizontal SPEM at high target frequencies. The findings of this study thus depart radically from what may have been theoretically expected if eye tracking deficiencies were functioning as a marker for Huntington's chorea except in the

horizontal SPEM tracking at high target frequencies. The findings of this study are also contrary to what may have been expected from previous reports in the literature regarding saccadic eye tracking tasks and subjects at-risk for HC. The different results of the current study could stem from many sources including sampling variations, diagnostic unreliability, and differences in the techniques utilized to record the eye movements. The recording techniques of the present study certainly differs from that used in Petit et al. (1971) who used corneal lenses. This study, however, overcame many of the problems associated with previous reports in measuring eye tracking deficiences by using standardized recording procedures and analyses that have been shown to be reliable and valid indicators of tracking ability; as well as by testing a larger group of subjects at-risk on a variety of tracking tasks. It is possible that subject variability exerted an effect on the saccadic duration and amplitude measures, as the saccadic eye tracking tasks were the most difficult for the subjects to perform. An alternate explanation could be that SPEM deficits are the first to appear in the eye tracking performance of choreic subjects. One argument against this is that the saccadic eye tracking system requires greater precision and accuracy to function than the smooth pursuit tracking system because the former involves high velocities. Further study would be required to determine the validity of this statement.

As concerns the electrodermal measures, it is apparent that the data do not support the hypotheses generated by a review of the literature on Huntington's disease and skin conductance responsivity.

The at-risk and the Huntington groups gave as many responses as did the normal control group when presented with an array of auditory stimuli which included eight soft (85 db) tones, twelve loud (105 db) tones, a dog barking and a teletype. In addition, when response amplitude was examined, no differences in the size of the skin conductance response was evident between the three groups. Although there were no significant differences between the groups in SCR amplitude, the Huntington group gave smaller responses to the two sets of tones as well as to the dog and the teletype sounds. The mean responsivity of the at-risk group fell between the mean scores for the controls and the Huntington groups. While there were no significant differences between the groups, the pattern of interrelationships between the groups was as expected. The comparability of these SCR measures rested in part on the subjects' tonic skin conductance levels, since high SCLs are linked to larger SCRs and to a slower habituation rate. The analyses of SCL indicated that all groups exhibited similar tonic levels.

The rate of habituation was comparable in the three groups. There was no support for the hypothesis that the at-risk group would contain a greater percentage of fast

habituators than the control group. The Huntington subjects were not fast habituators, as would have been expected from earlier research findings. The Huntington subjects in fact were the slowest to habituate to the loud tones, although their rate of habituation was not significantly different from the rates of the two other groups. A greater number of trials to habituation has been linked to brain-damaged populations in some studies but not in others (Stern & Janes, 1973).

The slow habituation of the subjects to the loud tones may have ensued because the loud tones were loud enough to provoke startle reactions or larger response amplitudes than what would normally be expected. An examination of the habituation rates of the groups revealed that the subjects took on average 3.43 to 6.66 tone trials, to habituate to the loud tones. This is longer, for example, than the HC subjects in the Oscar-Berman & Gade (1980) study. The Huntington subjects who took part in the present research are however not truly comparable to the subjects seen by Lawson or by Oscar-Berman & Gade. The latter two studies both examined hospitalized HC patients. In addition, the Lawson research subjects were taking medication to control for choreic movements.

The results of the present study depart as well from that reported by Lawson (1981) in terms of the results obtained with the at-risk subjects. The methodological procedures employed in the Lawson study were not strictly comparable to

those procedures used in the present study as Lawson tested subjects on portable polygraph equipment in their homes. Such field studies cannot control for extraneous variables such as room temperature and humidity which are known to affect both SCL and SCR measures.

There were fewer at-risk subjects who never responded to the tones than there were control subjects who were nonresponders. A third of both the Huntington and the control subjects did not respond to the loud tones; this is unusual in that louder tones are more likely to elicit a response than softer tones. This figure is also much higher than the 7% base rate of nonresponders that has been found in control populations. Iacono et al., (1983) have however found that 24% of their control subjects were nonresponders to a series of seventeen tones.

A plausible explanation for such a result is that there was an effect of the instructions given to the subjects on their responsivity. Subjects were told to ignore the tones and given brief relaxation instructions before the tones were presented to them. This attempt to control for intersubject variability in the significance subjects assign to essentially meaningless tones may have dampened responsivity as subjects possibly did indeed relax and ignore the tones. Iacono & Lykken (1983), in a recent study on the role of instructions on electrodermal habituation report subjects required to ignore tones as they heard a taped story gave fewer tone-

elicited responses and that these were of smaller magnitude than those responses given by subjects with neutral instructions or subjects required to attend carefully to the story. Thus the need to control for the significance subjects assigned to the tones may have led to more attenuated responses. This does not explain why there were more nonresponders to the loud tones in particular. Nor does it explain why more at-risk subjects were responding. This curious finding was limited in interest in the sense that there were after all no significant differences between the groups in either responsivity or in terms of actual numbers of nonresponders.

While laterality was not a focus of this research, it was interesting to note that there were no significant differences between the hands. The groups were equally responsive in both hands. Research with control and other psychiatric or brain-damaged populations have occasionally found that electrodermal activity is greater in the right hand (Bell, Mednick, Gottesman, & Sergeant, 1976). This study gave no support for greater electrodermal activity in the right hand. Subjects gave SCRs of similar amplitude to the dog and the teletype. Group differences were not significant even though the instructions immediately prior to the onset of the two sounds required subjects to pay close attention as they would be required to identify the sounds once they were terminated. The sounds were included in the study so that a comparison of

subjects' electrodermal responsivity could be made as they responded first to a set of meaningless stimuli (tones) and then to a set of meaningful stimuli (familiar sounds). No elucidation of the relation between meaning and attention--as measured by electrodermal indices--can be made from the results of the present study. This seems unfortunate since attentional deficits have been found in choreic subjects in the past. The present research does not contribute additional information as to the role of attentional processes as measured by the skin conductance orienting response since the groups were not different. If anything this study gives little support for the notion that choreic subjects are hypoaroused, even though the mean responsivity for the HC subjects was the lowest of the three groups. This finding is perhaps a result of the inclusion of choreic subjects in an earlier rather than in a more advanced stage of Huntington's chorea.

A limitation of the present study was the small sample size of choreic subjects. A larger sample size would have had greater power to discriminate the groups on the electrodermal measures. A follow-up study could include as well, a greater variety of stimuli to present to subjects. An interesting addition would have been the use of meaningful words, or phonemes as were used in the Lawson (1977) research. Lawson's conclusions regarding the fast habituation of her Huntington subjects were derived from the responses these subjects gave

to verbal stimuli (phonemes) and not to neutral tone or sound stimuli.

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Reference List

William G. Iacono, Personal Communication, December 1983.

APPENDIX A

Huntington's Disease Family Research Project at the
University of British Columbia

At the University of British Columbia, we are conducting a study that will aid in predicting who will develop Huntington's Disease. We are taking this opportunity to inform you and your family members of this project and encourage your participation.

For nearly the past 10 years in research currently funded by the Medical Research Council of Canada, we have been striving to identify biological signs that can be used to predict who will succumb to severe psychiatric and neurological disorders. Our goal is to develop techniques that will aid in the diagnosis, treatment, and prevention of these diseases. We know that heredity plays an important role in illnesses which affect the brain and nervous system. We are combining this knowledge with recent findings that certain biological responses, which broadly tap brain functioning, are also genetically influenced. In other words, with regard to Huntington's Disease, we know HD is a genetically-determined neurological illness. We also know that certain biological responses which give a global picture of how the brain works are genetically influenced. Our plan is to put these pieces of information together to determine if we can use the genetically-determined brain responses to predict who has the HD gene.

As you probably know, previous attempts to identify the HD gene prior to the onset of symptoms have been unsuccessful. You may wonder what we are doing differently that leads us to be optimistic. Most of this unsuccessful research has focused on a few chemicals found in specific areas of the brain that are believed to play a role in HD. However, the brain is very complex and involves the interaction of many chemicals, nerves, and groups of cells. Investigations based on a single brain chemical cannot begin to tap these intricacies and could easily overlook factors important in the development of HD. Our measures, on the other hand, tap the general functioning of the brain and depend on all the parts of the brain working together in a normal way. If any one function of the brain is impaired, this impairment might show up in the general type of readings we take. Not much research has been done with the measures we will be using; what little has been done has produced some encouraging findings, which require further study.

In this project, we will be monitoring your brain waves, eye movements, and the amount of sweating in your fingertips while you watch flashing lights, listen to sounds, and follow moving lights with your eyes. To make these measurements, we will attach sensing devices (electrodes) to your skin. Our procedures do not involve pain or discomfort; most people who volunteer find participation in our tests interesting. This project has been approved by the UBC committees that monitor research with human subjects and has been reviewed by the Huntington's Society of Canada and its B.C. chapter. Strict confidentiality of all information collected will, of course, be maintained.

We are looking for two separate groups of individuals who come from families in which there is HD. The first consists of persons who are in the early stages of the disease. That is, people who are a) currently working or b) able to cook and do other household work or c) drive their cars.

The second and largest group consists of individuals who are the children or descendants of a parent with HD and who are themselves totally symptom-free. From this group, we are forming two subgroups: At-risk persons aged 25 and over and at-risk individuals under age 24. Parental consent will be required for participants under age 16.

APPENDIX B

M.A.P. Project

U.B.C./G.V.M.H.S./W.H.O.

Why do some people develop physical and mental disorders while others do not? Even in a single family, where people share common heredity and life stresses, it is difficult to understand why only certain family members seem vulnerable to such illnesses. Only through research can we learn more about these disorders and the role genetic and social factors play in their development.

With the help of grants from the Medical Research Council and Health and Welfare Canada, the Family Practice Unit is cooperating with scientists at the University of British Columbia who are studying these problems in depth. This project is part of a major international collaborative effort sponsored by the World Health Organization.

In order to successfully complete our project, we need information from normal volunteers because it enables us to compare findings from families with ill members to normal families such as yours. Only in this way can we hope to discover the causes and best ways of treating severe medical disorders.

Who is eligible? Anyone in good health, between the ages of 15 and 54, who has never been treated and whose close relatives (parents, brothers, sisters, children) have never been treated for a severe psychiatric disorder or for alcohol or drug abuse. The ordinary stress, depression, or anxiety which almost all of us experience from time to time is not considered a severe psychiatric disorder and would not make you ineligible to participate. In addition, a participant should not be suffering from a long-term physical illness or have vision problems that cannot be corrected by glasses. Since we are studying families, for purposes of comparison, we would like members of your family over age 15 to participate as well.

What would you do as a volunteer for our study? Arrangements would be made for you to visit with us at UBC during your free time to provide some interview information and take some simple perceptual tests in our laboratory. Most people find our procedures interesting; there is nothing about our tasks that is stressful, embarassing or painful. You need not be concerned about how well you perform because there is no such thing as doing badly on these tasks. We are merely collecting information. All aspects of your participation will be kept strictly confidential.

What do you get out of it? The main thing is simply the satisfaction of knowing you have contributed to a very important research project. In addition, we will provide every volunteer with $20 once all the tests are completed. This means we will also pay $20 to every member of your family who decides to participate. Finally, we will be happy to share the results of this project with you should you be interested.

If you are interested, please complete the attached forms and leave them with the clinic receptionist. By completing this form, you are under no obligation to participate; you are merely expressing your interest. A member of the M.A.P. project will be contacting you to discuss the project and provide an opportunity to answer any questions that you might have. Please feel free to take this information sheet with you; just leave the attached forms.

For further information, please contact Dr. Verite Livingstone or Ms. Rosemary Grant, R.N. of the Fairmount Family Practice Clinic or Dr. Neil Kyle of the M.A.P. project

Thank you for considering our request.

APPENDIX C
INTAKE QUESTIONNAIRE

1. Have you ever received treatment for an emotional or psychiatric illness?

☐ No

☐ Yes Nature of problem _____

What kind of treatment (including medication, hospitalization)

_____

2. Have your mother, father, brothers, sisters, or children ever received treatment for an emotional or psychiatric illness?

☐ No

☐ Yes Nature of relative's problem _____

Relative _____

Treatment _____

3. Have you ever had a drinking problem or has anyone ever suggested that you had a drinking problem?

☐ No

☐ Yes Treatment _____

4. Have your mother, father, brothers, sisters, or children ever had a drinking problem?

☐ No

☐ Yes Who _____

Extent _____

Treatment _____

5. Do you have any disorder affecting your brain or spinal cord, long-term pain disorder. or long-term physical disorder (e.g. epilepsy, chronic back pain, arthritis, diabetes. hypertension, multiple sclerosis, stroke, etc.)

☐ No

☐ Yes Specify _____

6. Do you have any problems with your eyes or vision?

☐ No

☐ Yes Specify _____

Corrected by glasses? ☐ No

☐ Yes

APPENDIX D

MAP PROJECT CONSENT FORM

I have been asked to participate in a study in which my body's responses will be recorded while I perform several simple tasks. These tasks include comfortably relaxing while listening to brief tones, watching brief flashes of light, and watching a spot of light move back and forth on a screen and attempting to produce similar movements by turning a knob back and forth. The responses of my body that will be recorded include my eye movements, heart beat, brain waves, and the activity of my sweat glands. To make these recordings, sensors will be attached to my arms, legs, and head, but no discomfort or danger to myself is involved. In another part of this study, a drop of oil similar to cooking oil will be placed on my skin near each of my fingernails and a photograph of my skin will be made. I understand that these tests will not influence my medical care or treatment, and that all the information obtained in this project will be kept confidential and used only for the purposes of this study. By signing this form, I agree to participate, although I realize I am free to withdraw from this study at any time, without prejudice to current and future care and treatment.

_____ witness

_____ signature

_____ print name

_____ date

_____ I.D. number

APPENDIX E

Parental Consent Form

I, _____, parent/guardian of
NAME

_____, agree to let my son/daughter
NAME OF VOLUNTEER UNDER 16

participate in the Huntington's disease family research project at UBC.

APPENDIX F

NAME: DATE:

Please pick out the statement in the groups below which best describes the way you feel today, that is, right now. Indicate your answer by circling your choice.

A. 0 I do not feel sad.
1 I feel blue or sad.
2a I am blue or sad all the time and I can't snap out of it.
2b I am so sad or unhappy that it is quite painful.
3 I am so sad or unhappy that I can't stand it.

B. 0 I am not particularly pessimistic or discouraged about the future.
1a I feel discouraged about the future.
2a I feel I have nothing to look forward to.
2b I feel that I won't ever get over my troubles.
3 I feel that the future is hopeless and that things cannot improve.

C. 0 I do not feel like a failure.
1 I feel that I have failed more than the average person.
2a I feel I have accomplished very little that is worthwhile or that means anything.
2b As I look back on my life, all I can see is a lot of failure.
3 I feel I am a complete failure as a person (parent, husband, wife).

D. 0 I am not particularly dissatisfied.
1a I feel bored most of the time.
1b I don't enjoy things the way I used to.
2 I don't get satisfaction out of anything anymore.

E. 0 I don't feel particularly guilty.
1 I feel bad or unworthy a good part of the time.
2a I feel quite guilty.
2b I feel bad or unworthy practically all the time now.
3 I feel as though I am very bad or worthless.

F. 0 I don't feel that I am being punished.
1 I have a feeling that something bad may happen to me.
2 I feel I am being punished or will be punished.
3a I feel I deserve to be punished.
3b I want to be punished.

G. 0 I don't feel disappointed in myself.
1a I am disappointed in myself.
1b I don't like myself.
2 I am disgusted with myself.
3 I hate myself.

H. 0 I don't feel I am any worse than anybody else.
2 I am critical of myself for my weaknesses or mistakes.
2 I blame myself for my faults.
3 I blame myself for everything bad that happens.

I. 0 I don't have any thoughts of harming myself.
1 I have thoughts of harming myself but I would not carry them out.
2a I feel I would be better off dead.
2b I feel my family would be better off if I were dead.
3a I have definite plans about committing suicide.
3b I would kill myself if I could.

APPENDIX F

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J. 0 I don't cry any more than usual.
1 I cry more now than I used to.
2 I cry all the time now; I can't stop it.
3 I used to be able to cry but now I can't cry at all even though I want to.

K. 0 I am no more irritated now than I ever am.
1 I feel annoyed or irritated more easily than I used to.
2 I feel irritated all the time.
3 I don't get irritated at all at the things that used to irritate me.

L. 0 I have not lost interest in other people.
1 I am less interested in other people now than I used to be.
2 I have lost most of my interest in other people and have little feeling for them.
3 I have lost all my interest in other people and don't care about them at all.

M. 0 I make decisions about as well as ever.
1 I try to put off making decisions.
2 I have great difficulty in making decisions.
3 I can't make any decisions at all any more.

N. 0 I don't feel I look any worse than I used to.
1 I am worried that I am looking old or unattractive.
2 I feel that there are permanent changes in my appearance and they make me look unattractive.
3 I feel that I am ugly or repulsive looking.

O. 0 I can work about as well as before.
1a It takes extra effort to get started at doing something.
1b I don't work as well as I used to.
2 I have to push myself very hard to do anything.
3 I can't do any work at all.

P. 0 I can sleep as well as usual.
1 I wake up more tired than I used to in the morning.
2 I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3 I wake up early every day and can't get more than 5 hours sleep.

Q. 0 I don't get any more tired than usual.
1 I get tired more easily than I used to.
2 I get tired from doing anything.
3 I get too tired to do anything.

R. 0 My appetite is no worse than usual.
1 My appetite is not as good as it used to be.
2 My appetite is much worse now.
3 I have no appetite at all now.

S. 0 I haven't lost much weight, if any, lately.
1 I have lost more than 5 pounds.
2 I have lost more than 10 pounds.
3 I have lost more than 15 pounds.

APPENDIX F

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T. 0 I am no more concerned about my health than usual.
1 I am concerned about aches and pains or upset stomach or constipation.
2 I am so concerned with how I feel or what I feel that it's hard to think or much else.
3 I am completely absorbed in what I feel.

U. 0 I have not noticed any recent change in my interest in sex.
1 I am less interested in sex than I used to be.
2 I am much less interested in sex now.
3 I have lost interest in sex completely.

APPENDIX G

SELF-EVALUATION QUESTIONNAIRE

Developed by C. D. Spielberger, R. L. Gorsuch and R. Lushene

STAI FORM X-1

NAME _____ DATE _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you *feel* right now, that is, *at this moment*. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe your present feelings best.

	NOT AT ALL	SOMEWHAT	MODERATELY SO	VERY MUCH SO
1. I feel calm	①	②	③	④
2. I feel secure	①	②	③	④
3. I am tense	①	②	③	④
4. I am regretful	①	②	③	④
5. I feel at ease	①	②	③	④
6. I feel upset	①	②	③	④
7. I am presently worrying over possible misfortunes	①	②	③	④
8. I feel rested	①	②	③	④
9. I feel anxious	①	②	③	④
10. I feel comfortable	①	②	③	④
11. I feel self-confident	①	②	③	④
12. I feel nervous	①	②	③	④
13. I am jittery	①	②	③	④
14. I feel "high strung"	①	②	③	④
15. I am relaxed	①	②	③	④
16. I feel content	①	②	③	④
17. I am worried	①	②	③	④
18. I feel over-excited and "rattled"	①	②	③	④
19. I feel joyful	①	②	③	④
20. I feel pleasant	①	②	③	④

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APPENDIX G

SELF-EVALUATION QUESTIONNAIRE

STAI FORM X-2

NAME _____ DATE _____

DIRECTIONS: A number of statements which people have used to describe themselves are given below. Read each statement and then blacken in the appropriate circle to the right of the statement to indicate how you *generally* feel. There are no right or wrong answers. Do not spend too much time on any one statement but give the answer which seems to describe how you generally feel.

	ALMOST NEVER	SOMETIMES	OFTEN	ALMOST ALWAYS
21. I feel pleasant	①	②	③	④
22. I tire quickly	①	②	③	④
23. I feel like crying	①	②	③	④
24. I wish I could be as happy as others seem to be	①	②	③	④
25. I am losing out on things because I can't make up my mind soon enough	①	②	③	④
26. I feel rested	①	②	③	④
27. I am "calm, cool, and collected"	①	②	③	④
28. I feel that difficulties are piling up so that I cannot overcome them	①	②	③	④
29. I worry too much over something that really doesn't matter	①	②	③	④
30. I am happy	①	②	③	④
31. I am inclined to take things hard	①	②	③	④
32. I lack self-confidence	①	②	③	④
33. I feel secure	①	②	③	④
34. I try to avoid facing a crisis or difficulty	①	②	③	④
35. I feel blue	①	②	③	④
36. I am content	①	②	③	④
37. Some unimportant thought runs through my mind and bothers me	①	②	③	④
38. I take disappointments so keenly that I can't put them out of my mind	①	②	③	④
39. I am a steady person	①	②	③	④
40. I get in a state of tension or turmoil as I think over my recent concerns and interests	①	②	③	④

APPENDIX H

SUBJECT ID _____

DATE _____

MEDICATION

1. Prescription Drugs

   A. Current medication

Name	Amount/frequency	Date use began

   B. Most recent time subject was not taking any prescription drug

   _____

   Medication history since date entered above

Name	Amount/frequency	Date use began	Duration of use

2. Nonprescription Drugs

Name	Amount/frequency	Last time used

APPENDIX I

Electrodermal Habituation

To begin this next part of our session the first thing we want to do is check the recording equipment to make sure it is working correctly. We would like to see how your body reacts when you cough, just an ordinary cough like this (cough). Please cough once now ... cough again ... and one more time. Alright. Now take a deep breath and hold it. Take a deep breath now. Hold it, don't let any air out... OK, you can breathe normally now.

OK. That's the most excitement you're going to get. During the next part of our session, we'll ask you to sit perfectly still for about 10 minutes, so take a few moments now to get comfortable in your chair. Next, we want to measure your ability to ignore distracting sounds while you concentrate on becoming completely relaxed. Every so often you will hear a short tone; the tones will come at unpredictable times. All the tones will sound exactly alike. Our equipment will record your body's reactions to these tones. At first you'll probably respond to them. As they are repeated you'll get used to them and soon you won't react to them at all. We want to see how quickly you can stop responding to these sounds. Some people can stop responding to a meaningless, distracting sound very quickly. For others, it takes longer. We want to see how quickly you can stop responding.

It's easier to ignore something that's distracting and unimportant if you have something else to focus your attention on. We want you to focus your attention on becoming completely relaxed. This will require some concentration. One way to concentrate on relaxing, to become deeply relaxed, is to repeat over and over to your self sentences like "I feel deeply relaxed. My whole body is completely relaxed." This is what we want you to do while listening to the tones. Keep repeating these sentences over and over in your mind. The more you do, the more relaxed you will become, and the easier it will be to ignore the tones.

APPENDIX I

Take a moment now to get comfortable. Close your eyes now and let your whole body start to relax. Let the day's tensions just drain out of your body. Breathe easily, in a steady, regular way. Swallow if you have to but try not to move any other muscles. I'm going to give you some instructions now to help you become deeply relaxed. Since I want you to concentrate on relaxing by saying things to yourself in your mind, the instructions you will hear next are spoken as though you were saying them to your self. After I say each sentence, repeat it to yourself in your thoughts. Here we go.

"My whole body is becoming limp and relaxed. My feet feel heavy and relaxed. My legs feel heavy and relaxed. My ankles, knees and hips feel heavy, relaxed, and comfortable. My hands feel heavy and relaxed. My arms feel heavy and relaxed. My wrists, elbows, and shoulders feel heavy and relaxed. My stomach and chest feel deeply relaxed. The muscles in my face and neck feel heavy and relaxed. My neck, my jaw, and my forehead feel comfortable and deeply relaxed. My whole body feels completely relaxed."

In a few moments we will turn on a soft, rustling noise that sounds like wind in the trees or running water. Remember, the more you concentrate on relaxing the easier it will be to ignore the tones. Keep saying to yourself over and over "I feel deeply relaxed. My whole body feels heavy and relaxed." If you feel tension anywhere in your body, for example, in your jaw, keep saying to yourself "My jaw feels heavy and relaxed" until you can feel the tension melt away. Then continue to repeat to your self "I feel deeply relaxed. My whole body feels heavy and relaxed." Start saying that now. You'll know when this part of the session is over because I'll speak to you again. Here we go.

(8 85 db tones)

Continue to relax deeply. If you need to move about you can do so now, but try to stay comfortable and relaxed. We are going to to listen to some

more tones, only this time the tones will be much louder than before. Once again we will ask you to relax and ignore the tones. Now you've had some practice so even though the tones will be louder than before, you should still be able to relax and ignore them. Remember, the more you focus your attention on becoming completely relaxed, the easier it will be to ignore the tones.

Just concentrate on relaxing, keep your muscles free of tension, repeat to yourself "I feel deeply relaxed. My whole body feels heavy and relaxed". Keep repeating that to yourself. Once again, you will know when this part of the session is over because I will speak to you again. Here we go...

(12 105 db tones)

OK. We are finished with this type of task. Take a moment now to stretch and wake up... Move your arms and legs and your body. We have one more task for you, but before I explain it to you, we'll help you sit up in your chair.

Next, we want you to listen to some different types of sounds. These sounds are recordings of things that you might hear from time to time in your everyday life, like a fire engine siren or the sound of a jet plane. While none of the interesting sounds you will hear are frightening or scarey, some are a little unusual and you may have difficulty identifying them. In the last part of our session, we were measuring your ability to ignore sounds. Now, however, we want you to do the opposite. We want you to pay close attention to these sounds. See if you can figure out what each one is. Listen carefully so you can decide if all the sounds are different or if some of them are the same. After we have finished with this part of our session, we will ask you some questions about the sounds to see how many you were able to identify. Get comfortable now and try not to move during the rest of our session. Pay close attention to the sounds. We'll turn on the rustling noise again. Here we go.

(sounds played here)

Okay. We're finished with this part of the session.

APPENDIX J

Scoring Skin Conductance

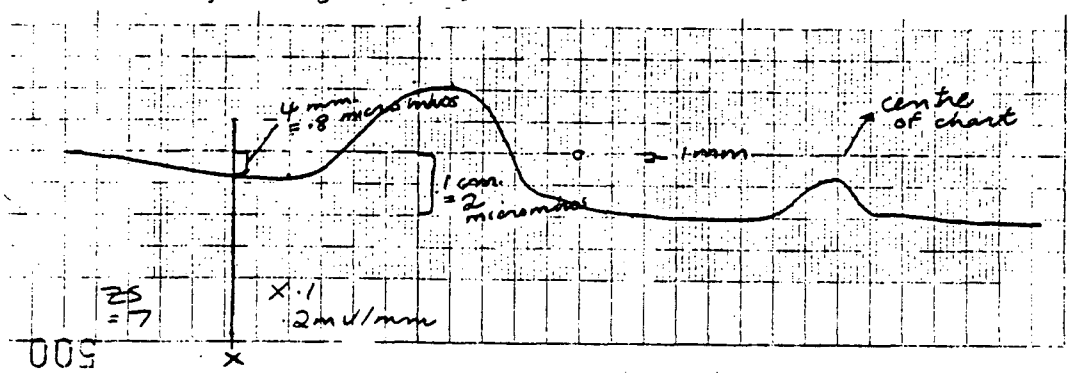
Skin conductance level (SCL) and skin conductance response (SCR) are each measured in micromhos (μmhos). A micromho is one millionth of a mho. A mho is the inverse or reciprocal of an ohm, which is a measure of resistance.

Tonic level of skin conductance is the amount of skin conductance when a subject is not exposed to a stimulus. Tonic level of skin conductance, or skin conductance level (SCL) is calculated using 2 pieces of information:

1) zero suppression (zs). This is usually a whole number and indicates, in micromhos, what the conductance level would be if the pen were in the center of the chart.

   If the pen is in the center of the chart, this is the only piece of information necessary to know the level of skin conductance.

   To calculate skin conductance level at any point on the chart, take the zero suppression and add/subtract micromhos according to the sensitivity settings.



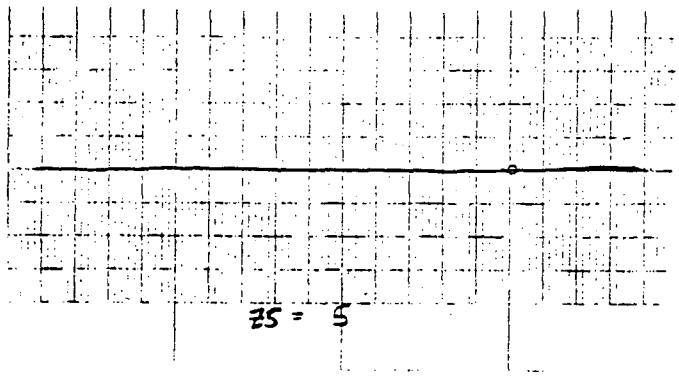
   To calculate SCL at point X, draw a line upward at point X until it crosses the skin conductance record.

   Since zs = 7, the center of the chart represents 7 micromhos of conductance.

   Since sensitivity = .2 mv/mm, a .5 cm deflection represents 1 micromho of conductance (1 cm = 2 micromhos).

APPENDIX J

At point X, the recording is .4 cm or 4 mm below the center of the chart. Therefore, the SCL at this point is 7-0.8 = 6.2 micromhos. In the example below, SCL = 5 micromhos.

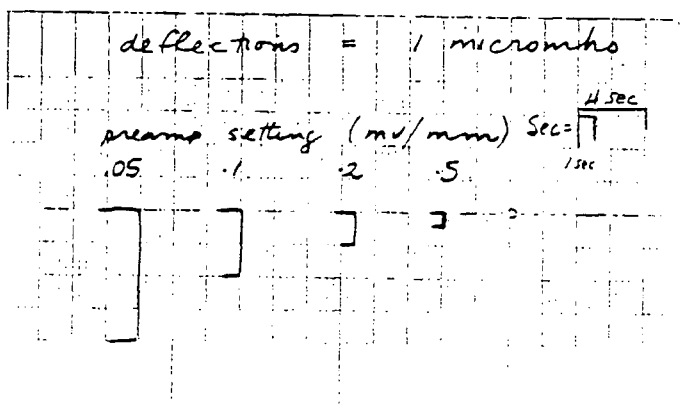


2) sensitivity. This equals the setting on the preamplifier (which ranges from .05 mv/mm to .5 mv/mm) multiplied by the setting on the preamp multiplier (always = x.1).

The equipment is constructed such that when the preamp multiplier is set at x.1, the premp setting (which is in millivolts per mm) can be read as micromhos per mm.

The preamp settings that are normally used are .05, .1, .2, and .5. A setting of .05 means that one (vertical) mm represents .05 micromhos. Thus, a deflection of 1 cm = .5 micromhos. A deflection of 2 cm = 1 micromho.

The chart on the next page indicates the distances, or pen deflections, that represent 1 micromho if the preamp is set at the 4 commonly used settings.



APPENDIX J

Scoring Skin Conductance on Charts

1. SCL

   1) Draw vertical line through left side of each tone.

   2) Calculate tonic level for each hand at intersection of line (micromhos).

   3) Write tonic level on chart.

2. SCOR - ANY RESPONSE AFTER 1 SECOND NOT AFTER 4 SECONDS

   1) Measure the amplitude (in mm) of each response on each hand (i.e. distance from highest point within 4 secs following treatment to lowest point within 1 sec following tone onset).

   2) Convert mm to micromhos.

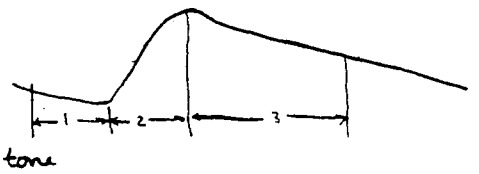
3. For the first tone of each series, calculate:

   1) latency: distance (in mm) from tone initiation to beginning of response

   2) rise time: distance (in mm) from the beginning of the response to the time it takes to reach peak amplitude

   3) recovery half-time: measure the number of mm from the peak of a response to half the response amplitude

   (If this can't be calculated, use distance from peak to next tone.)



4. Spontaneous Responses

   1) Count 10 sec from onset of each tone and draw another line.

   2) Count spontaneous responses from this line to the onset of the next tone. Circle all SR's on chart.

   3) 2 categories of SR: (1) $\geq$ .05 micromhos

      (2) < .05 micromhos

When a Known Artifact occurs e.g. cough, movements, sneezes, disregard SSCOR

APPENDIX J

5. Sounds

Draw a line at the beginning and end of each sound.

Calculate: 1) SCL at beginning.

2) amplitude of first response to the sound.

3) amplitude of the maximum response to the sound; i.e., maximum SC value reached during the sound minus SCL at beginning.

4) number of discrete responses during the sound.

(Remember: response latency is 1 sec = 2.5 mm. Responses that occur within this time after the sound ends count as responses to the sound.)

6. Calculate highest and lowest SCL's during the session (independent of a response).