PUPILLARY AND DIGITAL VASCULAR RESPONSES TO STRESS IN MIGRAINOUS AND NON-MIGRAINOUS SUBJECTS

by

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Acknowledgments

It is with great pleasure that I place pen to paper to write the final and least aversive section of this dissertation. It is also with a sense of a certain loss, somewhat like the loss of a friend. Not the loss of a good friend but certainly an old one.

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Abstract

The vasoconstriction phase of the migraine sequence is presumed to be the result of aberrant sympathetic responsiveness to stress. The present study examined migraine and control group responses to two stressful conditions, word-naming and cold pressor. Twenty-seven migraineurs and 27 controls matched on relevant variables were recruited through advertisements. Digital blood volume and pupil size were the dependent variables. Stress recovery was monitored following each stress condition. Group digferences in stress inhibition of the pupillary light-reflex were examined by presenting light stimulation to the pupil contiguously with the two stress stimuli. Migraineurs overall blood volume reduction was greater than controls during word-naming and cold pressor. Post stress recovery differences on blood volume were not found. Migraine and control pupil size responses were not different during either stressor or during either stress recovery period. No differences in pupillary light-reflex inhibition were found. These data were interpreted as suggesting that migraineurs are "vulnerable" to exaggerated vascular responsiveness to stress and possibilities for further research in this area were discussed.
An ancilliary analysis showed a positive relationship between group differences in diastolic blood pressure and differences in blood volume responses to stress. These data were viewed as suggestive of a possible link between migraine and hypertension and avenues for further research were discussed. A significant relationship between group differences on trait anxiety, state anxiety, and neuroticism and group differences in blood volume responses to stress was not found. It was concluded that psychopathology was neither characteristic of the migraineur nor instrumental in the initiation of migraine. Issues for migraine treatment were discussed.

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CHAPTER I

Introduction

History

Migraine headache has appeared in literature for at least 2,000 years and it is probable that man has been afflicted with this disorder since the beginning of recorded time. Pearce (1969) has noted that the earliest recognisable descriptions are found in the writings of Aretaeus of Cappadocia at the end of the first century A.D., and Galen (Pearce, 1969) introduced the term "hemicrania" (half-head) in the second century. The symptoms of migraine were first elaborated by Tissot in 1790 (Pearce, 1969) and systematic accounts of the disorder were initially given by Liveing and Gowers in the nineteenth century (Pearce, 1969). Laboratory investigation of the mechanisms involved in migraine is relatively recent. H.G. Wolff and his colleagues (1963) initiated this work some 40 years ago, and although much progress has been made in elucidating the physiological and biochemical aberrations involved, to date neither an adequate pathophysiological mechanism nor a generally effective treatment have been found.

Definition

Headache is a common affliction. In a series of careful epidemiological studies Waters (1970) found headache occurring in the previous year in up to 92 percent of the population. Ziegler's (1975) survey of 1,809 non-clinic subjects found 48 percent of males and 50 percent of females reporting that they had experienced severe, incapacitating headache at some point in their lives.

Many complex classificatory systems for distinguishing types of headache have been presented. Diamond and Dalessio (Diamond and Medina,

1976) listed a total of 22 headache subgroups, nine of vascular origin, four due to psychogenic factors and nine due to traction and inflamation. This great variety makes classification a complex diagnostic problem. Migraine must be distinguished from other vascular and psychogenic headaches which may mimic it to a large extent.

Severe intermittent headache is the most consistent descriptive element of migraine. Beyond that, the disorder is relatively ideopathic and a vast array of additional diagnostic criteria have been cited. Wolff (1963) emphasized the paroxysmal nature of the headache, its unilateral onset, and its association with nausea, vomiting, photophobia, constipation and/or diarrhea. Scintillating scotoma, hemianopia, unilateral paraesthesia, and aphasia were noted by Wolff as common preheadache symptoms. Friedman and Von Storch (1951) listed seven criteria: (1) recurrent, throbbing unilateral headache; (2) nausea, vomiting and irritability with attacks; (3) preheadache visual disorders; (4) positive family history; (5) paresis, plegia, and/or vasomotor dysfunction during attacks; (6) relief by ergotamine tartrate; (7) specific personality characteristics of perfectionism and rigidity.

An attempt to introduce order into headache classification was made by the Ad Hoc Committee on Classification of Headache (Friedman, Finley, Graham, Kunkle, Ostfeld, and Wolff, 1962). Vascular headache of the migraine type was described by this group as follows:

> Recurrent attacks of headache, widely varied in intensity, frequency and duration. The attacks are commonly unilateral in onset; are usually associated with anorexia and sometimes with

> nausea and vomiting; in some are preceded by, or associated with conspicuous sensory, motor, and mood disturbances, and are often familial. (p. 127)

Two forms of migraine have been described by Grapham (1955). The classic variety is preceded by neurological phenomena such as scotoma. Ordinary migraine is not preceded by neurological features and is thought to occur in approximately 90 percent of sufferers. Graham's distinction remains in use to date, although the term "ordinary" has been rejected in favour of "common" (Friedman et al., 1962). Classic and common migraine are not mutually exclusive and individuals are often subject to both types. Furthermore, classic migraine may be more prevalent than is usually reported. The present author's clinical experience indicates that many sufferers do not spontaneously report preheadache symptoms, either because they are unaware that these disturbances are a part of the headache syndrome, or because they are reticent to report phenomena that may be considered by others as characteristic of mental disorder (hallucinations, mood changes, etc.). A cursory diagnostic interview may thus lead to the conclusion that common migraine is present when in fact classic symptoms are simply not being reported.

Two additional migraine variants have been described (Friedman et al., 1962). Hemiplegic and opthalmoplegic migraine are rare and involve paresis or plegia of general motor and oculomotor function respectively. These attacks are usually severe and they may or may not be associated with preheadache phenomena. Opthalmoplegic migraine is rare. Confusion regarding appropriate diagnostic criteria has resulted in many mistaken diagnoses of opthalmoplegic migraine when other pathological processes

were operative. Vijayan (1980) reviewed 200 case descriptions of apparent opthalmoplegic migraine. He concluded that only 17 of these cases were correctly diagnosed. Vijayan appeals for the use of careful differential diagnostic procedures in order to prevent potentially dangerous misdiagnosis.

Despite the establishment of fairly specific diagnostic criteria several definitional problems remain. Because the sites of migraine and tension headache pain often overlap (Bakal & Kaganov, 1977), and because migraine is frequently initiated by stressful circumstances, milder migraine episodes and psychogenic or tension headache are often difficult to distinguish from one another. Frequently, people are subject to more than one kind of headache and care must be taken to ascertain how many different kinds of headaches any individual experiences. Equally problematic is the great inter and intra-individual variability in the severity, frequency, and characteristics of head pain. An individual who experiences 50 severe (i.e. nausea-plus) migrainous attacks per year and an individual who experiences two mild attacks per year are not equally representative of a supposedly homogeneous population.

Empirical approaches to the classification of headache have attempted to provide an alternative to the more subjective clinical classificatory schemes. Ziegler, Hassanein, and Hassanein (1972) administered a symptom questionaire, composed of 27 criteria used to define migraine, to 289 subjects attending a headache clinic. When the responses were subjected to a principal component factor analysis, no single factor contained more than three of the 27 migraine descrip-

tors. The migraine variables were distributed among three factors. Nausea during headache did not occur in the factor with unilaterality of pain, and neither nausea nor unilaterality occurred together with preheadache visual and motor disturbances. In a similar study, Waters (1975) extracted the same three descriptive factors but found that the association among them was not significantly greater than would be expected under the null hypothesis of no association.

In sum, neither descriptive nor statistical approaches to the classification and diagnosis of migraine have proven productive in elucidating a single migraine syndrome. Migraine may in fact consist of several heterogeneous disorders, both within and across individuals, and the precise nature of the relationships among these disorders remains unclear.

Prevalence

Statistical evidence regarding the prevalence of migraine varies greatly, the primary factor contributing to this diversity of estimated incidence being the lack of consensus regarding the definition of the disorder. Epidemiologists using various degrees of stringency as to their defining criteria thus reach different conclusions. Estimates have ranged from two to 19 percent of the total population of women and five to 20 percent of men (Waters, 1975), numerous studies reporting figures between these extremes (Ziegler, 1976).

Virtually all studies of migraine incidence report that women are more frequently affected than are men. Wilson (1940) reported that 71 percent of patients attending a migraine clinic were female. Dalsgaard-Nielsen (1947) recorded 79 percent of patients to be women,

and 60 percent of Selby and Lance's (1960) patients were female. Ostfeld (1962) suggested that simply calculating percentages of people actually attending a migraine clinic may be misleading. He maintained that women are more willing to attend a physician and report physical disorders than men, partly because men are not prepared to lose a day's work, and partly because men are generally expected to be "silent sufferers". Nevertheless, studies of migraineurs in the general population show higher migraine incidence among women (Waters & O'Connor, 1971; Waters, 1975). The question of whether these data are confounded by a "silent sufferers" effect remains open.

Inheritance

The assumption that migraine has a strong family tendency has been so widely endorsed that many classificatory systems use familial occurrence as a diagnostic criterion. Early efforts to show the importance of heredity in migraine reported its incidence in the family of the identified sufferer. Allan (1928) found a history of migraine in one or both parents in 91 percent of 382 migrainous patients. Goodell, Lewontin, and Wolff (1954) collected data on the relatives of 119 migraine patients. About 84 percent of this sample had at least one relative with migraine. Twenty-eight percent of children without migrainous parents had migraine, 44 percent of those with one migrainous parent had migraine, and 69 percent of those with both parents affected had migraine. The authors concluded that a recessive gene, with approximately 70 percent penetrance, was implicated.

Waters (1971) questioned the conclusions based on the foregoing familial incidence data. Few studies utilized control groups from the same population. Reports of familial incidence are informative only

if examined in the light of population base rates. Secondly, unbiased assessments of the headaches of the relatives of migrainous patients were seldom made, the patients themselves often providing all diagnostic information. Waters' epidemiological study (1971a), which met both these criteria, found that although first-degree relatives of the probands of migraine had slightly more migraine (10 percent incidence versus 6 percent in the non-headache group), this difference was not statistically significant.

Twin studies have been few, and careful determination of zygosity has often been neglected (eg. Havald & Hauge, 1956). Ziegler, Hassanein, Harris, and Stewart (1975) determined zygosity by extensive blood grouping and evaluation of height, weight, and appearance, in 106 twin pairs. Two of 41 monozygotic pairs were concordant for migraine, seven pairs being discordant. The concordance rate in dizygotic same-sex pairs was even lower, two of 10 being concordant. Lucas (1977) presented data for 161 twin pairs, 86 monozygotic and 75 dizygotic. No significant difference between migraine concordance rates for monozygotic and same-sex dizygotic twin pairs was found. The characteristics and precipitants of attacks were studied in detail in nine monozygotic and five dizygotic concordant pairs. Lucas reasoned that if a strong genetic factor was operating, some sharing of headache characteristics would be evident. No common pattern was found for severity, laterality, time of onset, duration of attack or precipitants.

It seems, then, poor methodology, rather than systematic investigation, has founded the conclusion that genetics are strongly implicated in migraine. The data available to date do not permit the

formulation of a simplistic statement on the genetics of the migraine syndrome. It has been argued that what is inherited may be abnormal physiological reactions to environmental influences (Bille, 1962; Dalsgaard-Nielsen, 1965). This suggests that the determination of whether or not the migraine event occurs may involve complex ideopathic interactions between some inherited physiological diathesis and various biochemical and environmental factors.

Pathophysiology

Migraine is generally acknowledged to be a biphasic process, initial cranial and cerebral vasoconstriction being followed by a painful rebound dilation of the same vessels (Dalessio, 1972). The full and throbbing appearance of facial arteries during the attacks has been noted in clinical literature since before the turn of the century (DuBois-Reymond, 1860; in Dalessio, 1972). Similarily, the temporary ameliorative effect of the application of pressure to the external common carotid artery, thus reducing the amplitude of arterial pulsations, has long been noted (Mollendorf, 1867; in Dalessio, 1972). Graham and Wolff's (1938) observations on the calibre and amplitude of pulsations of the temporal artery were the first systematic investigations of the causes of migraine pain. Fifty-two attacks in 22 patients were treated by intraveneous injections of ergotamine tartrate, a potent vasoconstrictor. Pulse amplitude was reduced an average of 50 percent within 30 to 40 minutes of drug administration. Although correlational statistics were not gathered, a large number of subjects reported reductions in pain proportional to the degree of arterial constriction. This observation, together

with subsequent research by Wolff and his colleagues (1963), have led to the view that dilation and stretching of cranial arteries is the cause of migraine pain, the intensity of which is augmented by the local release of pain-threshold-lowering substances.

Pre-headache disturbances in classic migraine were examined by Ostfeld and Wolff (1957). Two observations linked the prodrome to intracranial vasoconstriction. First, preheadache visual disturbances were reduced or eliminated by inhalation of vasodilators such as amyl nitrate and carbon dioxide. Second, preheadache visual defects were induced by the administration of levarterenol, a potent vasoconstrictor.

Wolff (1963) incorporated his observations on pre and during headache phenomena with the formulation of the neurogenic theory of migraine.

> ...any noxious factor within the brain that threatens survival of the cerebrum may induce cerebral vasodilation. If this be sufficiently great, the cranial arteries on the outside of the head dilate. With the liberation of chemical factors such as proteases and polypeptides, edema and a lowering of the pain threshold are engendered. Tenderness and headache ensue. Thus almost simultaneously the changes would be occurring inside and outside the cranial cavity. It is conceivable that the initial event within the head is vasoconstriction, resulting in ischemia. (Dalessio, 1972; p. 346)

Although Wolff's conclusions regarding the role of cerebral vasoconstriction in the initiation of migraine were somewhat inferen-

tial in nature, based largely on the observation of extracranial structures, more recent cerebral blood flow studies have supported his views (Obrien, 1967, 1971; Hachinski, Norris, & Cooper, 1977). The observations of Sakai and Meyer (1977, 1978) are particularly informative. Using the radioactive xenon-133 inhalation method, cerebral blood flow was observed during the prodromal and headache phases of so-called classic, complicated, and common migraine. Pre-headache reduction of blood flow was found to be maximal in those brain regions responsible for the neurological deficit. During the headache phase, cerebral blood flow was significantly higher compared to a control group measured in the non-headache state. Subjective reports of increased pain correlated with increased hyperfusion, and correspondence between the site of pain and the area of greatest hyperfusion was noted. No differences were found between classic and common migraine with regard to the pattern and time course of cerebral vasodilation during or after headache, indicating that cerebral tissues seem to be being repaid their oxygen deficit to the same extent in both classic and common migraine. These data support the notion that common migraine may also be preceded by cerebral vasoconstriction even though prodromal phenomena are not experienced or reported by these sufferers.

Migraine Initiation

The physiology of the actual migraine sequence seems fairly well documented. Vasoconstriction induced local cerebral ischemia threatens cortical survival and is followed by a protective but painful rebound hyperemia. A host of factors that may be involved in the initiation of the vasoconstriction phase have appeared in the literature. No

single factor adequately accounts for all migraines, in all migraineurs, across all situations, and the interaction of several precipitants seems more heavily implicated than a single cause. Three classes of possible precipitants will be discussed; ingested vasoactive substances, abnormal vasomotor reflexes, and the interactive effect of personality, stress, and emotion.

Ingested Substances

Some migraineurs report that ingestion of cheese, chocolate, or alcohol precipitates severe headaches (Selby & Lance, 1960; Pearce, 1971). Tyramine, which causes the release of serotonin and norepinephrine, both vasoconstrictors, is contained in these substances, and an impairment in the migraineur's ability to metabolize tyramine normally has been postulated (Youdim, Carter, & Sandler, 1971). Clinical tests of the role of tyramine in migraine initiation have yielded equivocal results. Hanington and Harper (1968) reported that tyramine induced headache more frequently than did a placebo, but Ziegler and Stewart (1977) failed to replicate these findings in their double-blind study of 80 patients. Headache was precipitated by ingestion of 100 milligrams of tyramine and not by a placebo in eight subjects. Retesting seven of these subjects, however, did not produce the same result. Placebo and tyramine produced equally severe headaches. The authors concluded that tyramine alone is rarely, if ever, the major precipitant of a migraine attack, and causally, the possible interplay of multiple factors should be considered. Dalessio (1979) similarly concluded that diet may be a factor in migraine initiation but not necessarily the most important factor.

Vasomotor Abnormalities

Other searchers for a constitutional predisposition to migraine have focused on possible deficiences of central vasomotor control as relevant to migraine initiation (Dalessio, 1972; Appenzeller, Davison, & Marshall, 1963). Before considering the evidence, basic mechanisms of autonomic vasomotor control will be discussed.

Vasomotor tone is governed, in part, by the activity of the medulary vasomotor centre (Abramson & Ferris, 1940; Guyton, 1976). Impulses descend via vasomotor neurons to the spinal gray matter where they synapse with preganglionic sympathetic neurons. The axons of these cells form the white communicating rami through which they reach the paravertebral ganglia where pre and postganglionic fibres synapse. The postganglionic efferents subsequently innervate their respective vascular smooth muscles. The upper-lateral part of the vasomotor centre is tonically active and maintains a state of partial contraction in the blood vessels whereas the lower-medial portions of the centre may inhibit the upper-lateral area, thereby inducing vasodilation. Hypothalamic stimulation has been shown to have powerful excitatory and inhibitory effects on the vasomotor centre, posteriolateral hypothalamic stimulation causing vasoconstriction and anterior stimulation causing vasodilation (Hess, 1954).

Both extracranial (Dalessio, 1972) and intracranial (Sakai & Meyer, 1977) arteries have been implicated in the migraine sequence. The importance of sympathetic vasomotor innervation of extracranial vessels is shown most dramatically in Horner's Syndrome. The postganglionic supply to extracranial arteries arises in the superior

cervical ganglion. Interruption of these sympathetics results in chronic dilation of the blood vessels of the face and head ipsilateral to the lesion. Although the importance of sympathetic innervation of the cerebral circulation has been minimized (Lassen, 1974), there is now abundant evidence that cerebral arteries and arterioles, especially the pial vessels on the surface of the brain, are as richly supplied by sympathetic nerves as are other vascular structures. As with extracranial innervation, the cerebral sympathetics also arise from the superior cervical ganglion and are vasoconstrictor-adregenergic (Hernandez-Perez & Stone, 1974; Nielsen & Owman, 1967).

Stavraky (1936) was the first researcher to demonstrate the relationship of the hypothalamic-medulary vasomotor system to cerebral vessel calibre. He found that stimulation of the posterior region of the hypothalamus, an area known to have excitatory effects on the vasomotor centre, caused an array of sympathetic effects, including a bilateral constriction of pial vessels. Response latency was short and independent of respiration-induced blood-gas tension changes. Cervical sympathectomy reduced or abolished the response as did transection above the level of the vasomotor centre.

More recent investigations have continued to show the importance of neurogenic innervation of cerebral vessels (Vasquez & Purves, 1977). Although cerebral vascular behavior is determined by delicate balances of many factors, including blood-gas tensions, circulating monoamines, and metabolic requirements, the small changes in pial vessel diameter induced by increased sympathetic activity can have large effects on deeper cerebral circulation (Rosenblum & Commonwalth, 1977). It is

anatomically feasible, then, that abnormalities of sympathetically mediated vascular behavior may be involved in the initiation of the migraine sequence. Tonically or phasically high levels of extracranial and/or intracranial activation may lead to vasoconstriction and local or regional cerebral ischemia, thus launching the rebound dilation which results in the pain of migraine.

Exaggerated cranial artery responsiveness and variability has been noted in migraineurs. Tunis and Wolff (1952) compared temporal artery pulse-wave contours in migrainous and headache-free subjects. In headache-free periods, migraineurs showed significantly higher contours than controls. When cranial artery pulse-waves were recorded two to five times per week for up to 30 weeks, a greater range of pulse-wave amplitudes was recorded for the migraine group as compared to controls. Periods of greatest variability were accompanied by mood alterations, feelings of tension, sustained effort, and restlessness, leading Wolff (Dalessio, 1972) to speculate that these vascular changes were the sequel of exaggerated autonomic (sympathetic) responsiveness to environmental stressors.

Recent studies of the relationship between volitional control of peripheral vasomotor behavior and cerebral blood flow changes have provided additional support for the notion that migraineurs show differences from non-migraineurs in cerebral vasomotor responses (Mathew, Largen, Dobbins, Meyer, Sakai & Claghorn, 1980; Claghorn, Mathew, Largen & Meyer, 1981). Migraine and control subjects were assigned to either hand-warming or hand-cooling biofeedback training groups. Cerebral blood flow was monitored by the 133 Xenon inhalation method.

Marked differences in the pattern and magnitude of cerebral blood flow changes were observed between migraine and control subjects. While normals showed slight right hemisphere cerebral blood flow reductions in both hand-warming and hand-cooling conditions, migraineurs in the hand-warming group showed increases in left and right hemisphere regional cerebral blood flow. The authors concluded that excessive cerebral vasomotor responsiveness was demonstrated in the migraine group. Whether active vasodilation or inhibition of vasoconstriction mediated the observed changes remains undetermined, however; Mathew et al. speculated that excessive sympathetic tonus of the cerebral vasculature may be operative in the initiation of migraine.

Other researchers have reasoned that if abnormal autonomic function is relevant to the initiation of migraine, abnormalities should be observable not only in cranial but also in peripheral vascular structures. Some tests of this hypothesis have been based on Kerslake and Cooper's (1950) observation that heating the trunk or either leg caused two to three-fold increases in hand blood flow. Because of the short latency of the response, (10-15 seconds), and because arterial occlusion of the heated leg did not interfere with dilation of the hand, the circulation of heated blood did not seem implicated. Lumbar sympathectomy abolished the effect, and in persons with unilateral sympathectomy, only the normal leg exhibited the dilation response. These observations indicate that a sympathetic vasomotor reflex mediates the dilation of the hand in response to heating the body elsewhere. Consequently, this paradigm has been used extensively in the investigation of reflex vasomotor abnormalities in migrainous subjects.

Appenzeller et al. (1963), Downey and Frewin (1972), and Elliot, Frewin, and Downey (1973) presented data confirming a reflex vasomotor abnormality in migraineurs while French, Lassers, and Desai (1967), and Hockaday, Macmillan, and Whitty (1967) found no confirming evidence. These studies have been critically reviewed by Morley (1977) and the following discussion is largely taken from his article.

The study of Downey and Frewin (1972) is inadequate in two areas, the first of which is subject selection. Control and experimental groups were not matched for age or sex, both factors known to affect cardiovascular variables (Geigy, 1970). In addition, females were overrepresented in the migraine group. In a disorder which is thought to be affected by menstrual cycle changes (Pearce, 1969), it is of paramount importance to control for the sex factor. A second deficiency in this study involves the interpretation of results. Subjects were initially warmed, then cooled. Regression analysis of blood flow change scores against the final temperature of the water revealed no differences between groups. The regression intercepts (i.e. flow at 0°C) did show a difference and the authors concluded that vasomotor abnormalities were demonstrated. However, the minimum temperature of the water used to cool the subjects was 14°C and inferred blood flow differences below this point go beyond the actual observations. Only if blood flow changes between 14°C and 0°C were perfectly linear would comparison of regression intercepts be valid and data supporting this notion are not presented by Downey and Frewin. It is possible, then, that the vasomotor abnormalities reported by Elliot and Frewin reflect nothing more than inadequate subject selection and statistical misinter-

pretation.

Appenzeller et al. (1963) and French et al. (1967) conducted identical experiments but, not surprisingly, reached opposite conclusions. Both studies involved heating the body trunk with light bulbs and measuring blood flow through the hand using venous occlusion plethysmography. Appenzeller et al., who purported to find reflex abnormalities, failed to equate sex distribution; six of 10 migrainous subjects were female whereas only one of 10 controls was female. The conclusions of French et al. are questionable on similar grounds. Sex and age distribution were not reported for the migraine group and control group composition was somewhat suspect. This group consisted of eleven subjects. Five were convalescing from illnesses which were neither cardiovascular nor neurological, one was epileptic, and five were healthy. One wonders whether this group can be considered representative of the population of "normal" subjects.

Elliot et al. (1973) matched subjects for age and sex and found no difference between migraine and control groups in mean resting hand heat elimination, mean oral temperature, and heat dilation responses after 15 minutes of warming the contralateral arm in water at 44 C. However, lower heat elimination responses were observed in the migraine group after 25 minutes of heat application. As pointed out by Elliot et al., the result may have been confounded by age in that the older migraineurs showed the reduced response. Although an interaction between age and vascular responsiveness may be indicated, the results do not provide strong evidence of a vasomotor abnormality among migrainous subjects in general. A second possible confound involves body temperature.

Eight of 12 migraineurs and four of nine control subjects had oral temperatures below 36.8°C. Hockaday et al. (1967) have shown that the heat dilation reflex may not occur below this critical core temperature. Because Elliot et al. did not exclude subjects with core temperatures below the critical value, their conclusion of vasomotor abnormalities in migraineurs must remain tentative. Only one heat dilation study met adequate criteria of design and execution. Hockaday et al. (1967) controlled for age, sex, duration of migraine, medication, menstrual cycle and body temperature. Procedures in this study replicated those of Appenzeller et al. (1963) and the results showed no significant difference between migraine and control groups.

Thus, experimental shortcomings in the heat dilation studies make it difficult to draw a firm conclusion regarding the role of peripheral vasomotor dysfunction in the initiation of migraine. Findings of differences between migraineurs and controls (Appenzeller et al., 1963; Downey & Frewin, 1972; Elliot et al. 1973) await methodologically adequate replication.

A different methodological strategy was used by Price and Clarke (1979). These researchers used classical conditioning to investigate possible peripheral vasomotor deficit in migrainous subjects. Twenty-two female migraine sufferers and normal controls were carefully matched for each of Morley's (1977) possible confounds and were given a differential digital pulse volume classical conditioning paradigm. The CS- (a neutral tone) was followed by silence and the CS+ was followed by a 90 db white noise. Control subjects learned to make the appropriate

vasomotor responses (vasoconstriction following the CS+ and vasodilation following the CS-) while migraineurs showed vasoconstriction to both the CS+ and CS-. Because migraineurs tended to constrict digital blood vessels in response to all stimuli, Price and Clarke concluded that disordered autonomic functioning in migraineurs was demonstrated. In addition, migraineurs failed to moderate their responses with additional practice. Price and Clarke postulated that excessive and indiscriminant sympathetic activation was responsible for the observed conditioning differences.

Werbach and Sandweiss (1978) presented additional data suggesting vasomotor dysfunction in migraine. Migraine patients entering a program of biofeedback-assisted relaxation training showed significantly lower baseline finger temperatures than patients with either non-migrainous headaches, tinnitus or hypertension. In addition, while the other three patient groups showed finger temperature increases during the first biofeedback-assisted relaxation training session, the migraineurs showed a slightly decreased finger temperature during the first session.

In sum, although the heat dilation paradigm has not proved fruitful in demonstrating consistent reflex vasomotor abnormalities in migraineurs, more recent investigations have provided data supporting the notion that the peripheral vasomotor behavior of migraineurs is different from that of control subjects. The vasomotor behavior of migraineurs appears to be characterized by excessive sympathetic tonus in the resting state (Werbach & Sandweiss, 1978) and by response stereotypy whereby they react with excessive sympathetic activation regardless of

whether increased sympathetic activity is called for in the situation (Price & Clarke, 1979). Moreover, these vasomotor abnormalities have also been observed in cerebral vascular structures.

Personality

Wolff's (1937) subjective impressions of a sample of 46 migrainous subjects as tense, driving, obsessional, perfectionistic, inflexible people with unexpressed and unresolved hostilities and resentments laid the groundwork for the inclusion of psychological factors in the initiation of the migraine sequence. These characteristics are presumed to make the sufferer unable to adapt appropriately, and prone to react with excessive sympathetic nervous system activation to environmental and interpersonal stressors (Stroebel, 1975). The subjective certainty of this viewpoint is exemplified by the following theoretical rationale presented by Mitchell and Mitchell (1971).

> The general therapeutic position taken from the combined desensitigation treatment programme... was that migraine is a symptom representing the interactive effect of constricted overt emotional expression and chronic covert emotional over-reactivity with its somatic concomitant, excessive sympathetic nervous system activity, manifested via hypersensitive cranial arteries which are presumed to be an inherited physiological reactivity pattern. (p. 151)

We have noted that anatomically and physiologically, excessive sympathetic outflow may cause cerebral ischemia. The evidence for the mediating effects of psychopathology will be reviewed.

Wolff's (1937) views have been widely endorsed. Alvarez (1947) found hypersensitivity, dislike of change, perfectionism, and a tend-

ency to worry and become tense to be characteristic of his clinical sample of 500 cases. Friedman and his colleagues (Friedman, VonStorch, & Merritt, 1954; Friedman & Hoch, 1955; Friedman, 1964) found no objective evidence for a "migraine personality" in a series of studies of 5,000 cases but they remain of the opinion (italics this author) that migraine sufferers are likely to be sensitive, intelligent, perfectionistic, and abnormally strong reactors to stress. Unconscious conflicts over hostility, guilt, dependency needs, identifications, and sexual adjustment are postulated by Friedman (1964) to be the mediators of these emotional responses. Similar personality constellations have been reported by other case studies of clinical samples (Dalsgaard-Nielsen, 1965; Selby & Lance, 1960; Klee, 1973), by psychoanalytic assessments of sufferers seeking aid (Fromm-Riechmann, 1959; Sperling, 1964) and by a recent study which used the Minnesota Multiphasic Personality Inventory (MMPI) to examine psychopathology in migraineurs involved in biofeedback and drug therapies (Sovak, Kunzel, Sternbach & Dalessio, 1980). In contrast, Cuypers, Altenkirch and Bunge (1980), using the Freiburg Personality Inventory (FPI), found only one slightly elevated scale score (nervousness) in groups of cluster and migraine headache patients. For both groups, the nervousness scale score remained within the normal range.

Although clinical case studies have been extensive, relatively few researchers have used objective psychological assessment devices and control groups. Ross and McNaughton (1945) compared 50 migraineurs to an equal number of controls matched for age and sex. Using standardized Rorschach scoring procedures, they found an excess of perfectionism, inflexibility, conventionality, intolerance, persistance towards

success, and sexual adjustment difficulties in the migraine group. (It should be noted that the Rorschach test has been shown to be less than "objective". See Mischel, 1968.) Using the Maudsley Personality Inventory, Maxwell (1966) compared 32 migraineurs with 32 control subjects. Although no difference in extraversion was found, migraineurs were significantly higher in neuroticism.

While the use of control group comparisons represents an improvement over the clinical case study method, a stumbling block still remains. The subjects who comprised the migraine groups in the above studies were those sufferers who actually sought help from physicians. Waters and O'Connor (1970) presented evidence showing that only 46 percent of migraine sufferers seek medical advice. People who complain to their doctors regarding any ailment have been found to be more extraverted and neurotic than those who complain a little, or not at all (Bond & Pilowsky, 1966), consequently the psychopathological features found in migraineurs may be more a function of self-selection of subjects than of true population differences. Data presented by Henryk-Gutt and Rees (1973) support this contention. Migraineurs actually attending physicians with headache complaints scored significantly higher in neuroticism, anxiety, and somatization than did a sample of migraineurs not seeking aid. Phillips (1976) also found that sufferers selected on the basis of the severity of their headaches, and their desire for treatment, showed significant elevation of neuroticism scores.

Studies utilizing objective personality assessment devices and random samples of headache sufferers have usually failed to find substantial differences between migrainous and non-migrainous subjects. Waters

and O'Connor (1971) randomly selected female migraine and control subjects from a community. Using nine items from the Cornell Medical Index, no difference in degree of neurosis was found. In a further epidemiological study, Waters (1971b) found no differences in intelligence, social class, visual acuity, or incidence of hypertension between migrainous and non-migrainous subjects. Phillips (1977) presented data indicating that headache sufferers (39 migraine, 24 tension, five mixed), selected from a community sample, were indistinguishable from each other in terms of personality features. Moreover, all groups scored within appropriate age norms on the four personality dimensions (Extraversion/Introversion, Neuroticism, Psychoticism, Lie) of the Eysenck Personality Inventory (EPI) (Eysenck & Eysenck, 1964). Lucas's (1977) twin study presents the strongest evidence against the notion that psychopathology is relevant to migraine initiation. Twins discordant for migraine were compared using the Eysenck test. No differences were found between the twin with migraine and the twin without migraine.

Henryk-Gutt and Rees (1973) also used objective personality assessment devices and a random sample of headache sufferers. They distributed headache questionaires to the entire staff of two government departments in London, England. Common and classic migraineurs were matched on age, sex, marital status and civil service grade with sufferers of non-migraine headache, asthma sufferers and no-headache controls. Scores on the EPI showed migraineurs to be significantly higher in neuroticism than the combined no-headache and non-migraine headache groups. On the basis of this finding and semi-standardized personal interviews of all subjects the authors concluded that migraineurs "experience sig-

nificantly more subjective symptoms of emotional distress than do controls. However, the life stresses to which the groups have been exposed do not differ in so far as they can be assessed objectively". (p. 153). Henryk-Gutt and Rees cite Eysenck's (1967) evidence that neuroticism scores are directly related to the degree of activation of hypothalamic centres and thus autonomic nervous system responses, and they conclude that migraineurs are overreactors to stress.

Several considerations indicate that Henryk-Gutt and Rees may have made interpretations beyond their data. First, although neuroticism scores were higher for migraineurs than for controls, their scores were not significantly higher than Eysenck and Eysenck's (1964) norms for the general population. Pronounced differences in autonomic reactivity cannot be inferred from these data. Secondly, objective indicies of the amount of life stress to which migraine and control subjects have been exposed were not used. Since the first author conducted all interviews, no reliability estimates are possible. In addition, non-blind interview procedures were used. Such techniques are well known to be less than objective (Mischel, 1968). Furthermore, the composition of the control group used for statistical comparison can be questioned. The authors combined data from classic and common migraine groups and tested for mean differences against a combined non-migraine headache and no-headache group. This statistic provided the basis for the conclusion of higher neuroticism among migraine sufferers. Comparisons of migraine sufferers versus sufferers of non-migraine headache were not made. My calculations show no significant neuroticism differences between these groups. Firm conclusions regarding differences in personality be-

tween migrainous and non-migrainous headache sufferers cannot be drawn from these data.

Only one study meeting adequate methodological criteria has found personality differences between migrainous and non-migrainous subjects. Price and Blackwell (1980) found that migraineurs scored higher on the Taylor Manifest Anxiety Scale (TMAS) and on the Trait scale of the State-Trait Anxiety Inventory (STAI) than did a group of matched controls. Migraineurs also had higher Lie scale scores on the EPI. The researchers also compared verbal responses to a stressful anthropological film which depicted a primitive subincision ceremony. Migrainuers rated the film significantly less unpleasant than controls. Some support for the contention that migraineurs are more anxious than controls is provided by these data. The observation that migraineurs minimized the severity of a situation that controls found stressful supports the specualation of Mitchell and Mitchell (1971) that migraineurs may respond to stressful stimuli physiologically but not verbally.

We see, then, that the evidence for the existence of a "migraine personality" is inconclusive. Many medical and psychological practitioners have formed subjective impressions based on biased samples of sufferers who actually seek their help. Similarily biased objective assessments have reinforced their views. Methodologically adequate studies showing psychopathology in migraineurs are rare.

Stress and the Sympathetic Overshoot Hypothesis

Regardless of whether psychopathological factors act as mediators, responses to situational stressors are often implicated in the initiation of the migraine sequence. Dalessio (1972) recounted an incident

in which a physician's overt hostility toward a migrainous patient precipitated an attack. I have observed similar phenomena. Many migraineurs being screened for inclusion in a biofeedback treatment program have reported that the stress of the interview, (upon which their participation in the program is largely dependent), precipitated an attack. More objective evidence concerning the role of stress is provided by Henryk-Gutt and Rees (1973). Migrainous subjects recorded precipitatants over a two month period. Fifty-four percent of all migraine attacks coincided with emotional stress.

The mechanism by which stressors are thought to initiate migraine was first elaborated by Sargent, Walters and Green (1973). Further elaborations of their hypothesis have been made by Stroebel and Glueck (1976). Their view is not dissimilar to those proposed by others (Stroebel, 1975; Mitchell & Mitchell, 1971; Dalessio, 1972). Psychopathology is not considered by them to be necessary predisposing factor. Sargent et al. have based their formulation on the work of Papez (1937) and subsequent elaborations of Papez's work by Brady (1958). The limbic system, the "visceral" or "emotional" brain, is thought to be the major responder to psychological stress. The hypothalamus receives and integrates limbic impulses, redistributing them to appropriate autonomic centres. In the case of migraine, Tunis and Wolff's (1952) observation of exaggerated cranial artery responsiveness, together with the observation that migraine is often preceded by vasoconstriction induced coldness in the hands and feet, are taken as evidence that a disorder of hypothalamic-autonomic (sympathetic) function is implicated. In times of stress, this dysfunction is thought to predispose the migraineur to

react with excessive sympathetic outflow, specifically neurogenic constriction of cranial blood vessels. Cerebral ischemia is induced and is followed by the rebound vasodilation that results in migraine pain. This ischemia may be acute or of relatively long duration.

The "sympathetic overshoot" hypothesis of Sargent el al. has received widespread acceptance and a plethora of psychological and behavioral approaches to the treatment of migraine have adopted the notion as their theoretical base. Extensive reviews of the treatment literature have been presented by Baldwin (1978) and Blanchard and Epstein (1978). Treatments usually involve subjects' learning voluntary control of sympathetic activation through the control of peripheral vasomotor behavior. Warming of the hands, structures rich in sympathetic vasomotor innervation, is the normally targetted response. All other factors held constant (ambient temperature, body movement, cardiac output), an increase in skin temperature is a function of vascular dilation and increased blood flow. Dilation of skin blood vessels is in turn a function of reduced sympathetic vasomotor tone. Peripheral skin temperature is thus considered a one variable indicator of general sympathetic nervous system activity. Subsequent to the learning of the warming response, subjects are instructed to initiate hand warming at the first sign of a migraine (if there is a prodrome), or whenever they experience stressful situations. They do this by utilizing the various strategies that proved successful during biofeedback sessions (autogenic phrases, relaxation, imagery). The reduction in sympathetic activation that results in increased hand blood flow is thought to generalize to the cranial and cerebral vasculature and interrupt the vasoconstriction

phase of the migraine sequence, thus aborting the attack itself. Recent studies of changes in regional cerebral blood flow accompanying biofeedback-aided volitional hand warming in migrainous subjects by Mathew et al. (1980) and Claghorn et al. (1981) have supported the notion that dilation of peripheral vascular structures is associated with increases in regional cerebral blood flow.

Reports of positive treatment outcomes are common (Blanchard & Epstein, 1978) but although these outcomes are encouraging, they do not necessarily attest to the validity of their theoretical base. Adequate research designs, control groups, complete experimental documentation, long-term follow-ups, and appropriate statistical analyses are rare in the treatment liberature (Adams, Feuerstein & Fowler, 1980). Studies showing the effectiveness of hand warming (Turin & Johnson, 1976) are contradicted by other data showing false skin temperature feedback to be as effective as true feedback in reducing migraine activity (Mulinex, Norton, Hack & Fishman, 1978). Clinical improvement has been shown in migraineurs who were not successful at significantly increasing finger temperature (Werbach & Sandweiss, 1978) and overall, approximately 70 to 80 percent of migraineurs show significant clinical improvement along various criteria regardless of the degree of skin temperature change achieved during biofeedback therapy (Diamone & Medina, 1976). A recent report by Largen, Mathew, Dobbins and Claghorn (1981) showed clinical improvement in <u>both</u> hand warming and hand cooling groups. The learning of control of vasodilation in the hands may thus be a factor contributing to successful intervention; it is not necessarily the only factor.

Stress Responses-Experimental Evidence

To review briefly, we have seen that the evidence concerning the importance of metabolic deficiencies, reflex vasomotor abnormalities, and psychopathology in the initiation of migraine is inconclusive. We have also noted that the notion of migraine as a stress-related sympathetic nervous system dysfunction (Sargent et al., 1973) has received wide acceptance and has led to the establishment of a large number of temperature-biofeedback treatment programs.

This review should now progress to a discussion of the experimental evidence concerning the physiological responses of migraineurs to stress, however lack of evidence limits such a discussion. One essentially serendipitous finding has provided some data. In a study of responses to self-control procedures, Price and Tursky (1976) assigned 40 migraineurs and 40 controls to one of four treatments: (1) binary and analog feedback, (2) yoked (False) feedback, (3) relaxation-tape induction, and (4) neutral-tape control. Digital and extracranial blood volume were the dependent measures. Of most interest was the observed difference in responses to the "neutral" condition. Subjects were told that they would listen to a relaxing tape recording which would help them to increase the temperature of their hand. This tape consisted of 32 minutes of instructions on how to grow an avocado plant. Controls showed temporal artery and digital vasodilation while migraineurs showed marked vasoconstriction at both sites. Although not designed as such, the "neutral" condition may in fact have been a stressor. As pointed out in a critique of the Price and Tursky study by Sovak, Fornek, Sternbach, Dalessio, and Kunzel (1977), subjects who volunteered their services to a scien-

tific study of migraine and were subsequently given a half-hour tape on avocado growing may have considered or experienced the condition as an irritant. Subjects' subjective reactions to the avacado tape were not systematically documented, consequently, it is not known whether differential responsiveness to stress between migraineurs and controls was evident. It is clear, however, that systematic investigation of differences between migrainous and non-migrainous subjects' reactivity to stress is in order. The following will propose such an investigation.

Autonomic Tuning and Migraine Initiation

Gelhorn's (1970) notion of autonomic tuning provides a framework within which abnormal physiological functioning in migraine may be conceptualized. According to Gelhorn, stimuli which excite the sympathetic division of the autonomic nervous system will have the peripheral effects of increased heart rate, vasoconstriction, increased blood pressure, pupillary dilation, increased skin conductance, and increased somatic activity. Parasympathetic activation would result in the opposite changes in most of these response systems. Sympathetic activation is referred to as ergotropic and parasympathetic as trophotropic. In the normal individual, ergotropic and trophotropic tendencies are balanced or tuned, and appropriate autonomic responses occur to a given stimulus, however when the balance of tuning is constitutionally shifted, the individual is more likely to respond according to his state of tuning.

Gelhorn's system must be considered generally descriptive rather than physiologically accurate. Lacey and his colleagues have shown large individual differences among patterns of autonomic responses

(Lacey, 1950, 1956; Lacey & Lacey, 1958; Lacey & VanLehn, 1952). Neither sympathetic nor parasympathetic nervous systems discharge en masse and few organ systems are exclusively sympathetically or parasympathetically innervated. Autonomic indices may thus disagree in terms of whether ergotropic or trophotropic tuning is being expressed.

Nonetheless, ergotropic tuning and its concomitant, sympathetic overresponsiveness, is predicted by the sympathetic overshoot hypothesis of migraine initiation. In order to investigate this concept, it is initially necessary to identify autonomic indices which will lend themselves to clear interpretations of whether ergotropic tuning is evident. Structures with exclusive sympathetic innervation would provide this clarity in that any changes would be attributable to increases or decreases in the activity of only one branch of the autonomic nervous system. Where dual innervation is involved, the index must permit interpretations of whether activation of one autonomic branch or inhibition of the other is responsible for any observed changes. A second consideration is whether the autonomic indices chosen provide evidence concerning the behavior of cerebral blood vessels. Digital blood flow and pupillary dynamics are proposed as indicies meeting these requirements.

Digital Blood Flow and Stress

Transient reductions in hand or finger blood flow have been shown in response to a wide range or stimuli, including immersion of another part of the body in cold water (Pickering, 1933), pinching, and posing a question in mental arithmetic (Abramson & Ferris, 1940), electric shock (Hovland & Riesen, 1940), white noise (Uno & Grings, 1965), and

loud tone presentations (Cook, 1970; Hogan, 1970). The physiology of this response is as follows: the skin of the extremities is densly supplied with arteriovenous anastomoses and capillary loops (Clark, 1938). The anastomoses have thick muscular walls and are under tonic sympathetic vasoconstrictor control (Adson & Brown, 1925, 1929). Because the fingers are composed largely of skin, the increase in sympathetic outflow which occurs under stress has a powerful vasoconstricting effect in these structures. According to contemporary psychophysiological theory, peripheral vasoconstriction helps increase blood flow in those parts of the body (e.g. the muscles) which will help the organism to cope with the stressor (Mathews & Lader, 1971; Pace, McCashland, & Landolt, 1965). Because changes in finger blood flow are directly attributable to variations in sympathetic activity, this response measure is well suited to the detection of possible excesses of this activity in migraine. In addition, abnormal vascular responsiveness in the fingers may provide evidence concerning the more generalized vasomotor dysfunction that has been suggested as relevant to cerebral vasospasm and consequently, migraine initiation.

The cold pressor test was first used by Hines and Brown (1932) as a means of experimentally increasing blood pressure in hypertension studies. Many researches have subsequently adopted the cold pressor as a relatively benign method of experimentally inducing stress and a variety of psychophysiological concepts have been explored through its use. The procedure consists of the immersion of a part of the body in ice water. Generalized ergotropic activation is the initial response, and increased heart rate, increased arterial pressure, and muscular

vasodilation and cutaneous vasoconstriction are reliably observed (Appenzeller, 1970). These responses depend upon intact peripheral innervation and involve the action of cortical, subcortical, and probably limic structures via the reticular formation and the tectum (Lovallo, 1975).

Individual differences in vascular responses to the cold pressor have been studied in efforts to elucidate the autonomic concomitants of psychosomatic and psychological disorders. Hines and Brown (1932) found that subjects could be classified as normal, hyperreactive, or hypertensive on the basis of their responses to the cold pressor. Hypertensives showed the highest blood pressure increases, normals the lowest, and hyperreactors were between the extremes. Subsequent studies have used this trichotomy as a tool for identifying various psychosomatic subjects. For example, Hines (1937) found that children of hypertensives showed hyperreactive blood pressure responses and Eyster, Roth, and Kierland (1952) found peripheral vasoconstriction in the hyperreactive range in patients with atopic dermatitis, a kind of vascular allergic response.

These studies have focused, in part, on the concept of symptom stereotypy (Lacey, Kagan, Lacey, & Moss, 1963) which states that psychosomatic patients will show a maximum reaction in the autonomic response consistent with their somatic disorder. In the case of migraine, the hypothesized somatic disorder is excessive sympathetic outflow in response to stress. Since the cold pressor is know to elicit peripheral vascular constriction, a sympathetically mediated response, cold pressor responses in the hypertensive range would be expected in migrainous subjects.

Another approach to the induction of stress in the laboratory has involved the use of cognitive tasks. Abramson and Ferris (1940) measured hand and forearm blood flow in response to a mental arithmetic task. During the task, reduced hand blood flow and increased forearm blood flow were observed. Flows returned to baseline following the solving of the problem. The findings of Abramson and Ferris have been replicated (e.g. Cook, 1974) and the effect of cognitive stimuli on blood flow has been shown to be greater than the effect of shocks (Rosenberg, 1970) or of imagining a stressful scene (Gelder & Mathews, 1968). Autonomic responses to various stimuli were examined by Wenger and Cullen (1972). Several responses, including hand blood flow, to mental arithmetic, word fluency tasks, the cold pressor, and 11 other stimuli were studied. It was found that the pattern of response was nearly identical for both cognitive tasks, similar for the cold pressor, and different for the remaining stimuli. These data indicate that cognitive tasks reliably elicit peripheral vascular responses similar to those elicited by the cold pressor. It was predicted earlier that migrainous subjects should show inordinately high levels of hand vasoconstriction in response to the cold pressor. Given the similarity of response patterns elicited by the cold pressor and cognitive tasks, correspondingly marked vascular responses should be observed in migraineurs during cognitive activity.

The Pupillary Response-Physiology

As noted by Janisse (1977), a relationship between pupillary and other autonomic responses have been noted for more than a century. Before examining the literature on the pupillary response as a measure of

stress reactions, the physiology of the pupil and the relationship between pupillary and vascular physiology will be discussed.

It is generally acknowledged that control of the size of the pupil is the result of the action of two physiologically antagonistic systems. Parasympathetic (cholinergic) nerves innervate the pupillary sphincter muscles of the iris and are responsible for contraction, while sympathetic (adrenergic) nerves innervate the dilator muscles. Preganglionic fibres of the parasympathetic supply to the pupil arise in the Edinger-Westphal nucleus in the tectum. They travel in the third nerve trunk to the ciliary ganglion where they synapse with post-ganglionic fibres that innervate the sphincter muscles. The first sympathetic efferent neurons originate in the posterior part of the hypothalamus and descend to the cilliospinal Centre of Budge where they synapse. Preganglionic fibres leave the cord through the ventral roots of the first and second thoracic segment, join the sympathetic chain, and continue uninterrupted until they synapse in the superior cervical ganglion. Post-ganglionic fibres, which leave the superior cervical ganglion and accompany the internal carotid artery and its branches, run through the Gasserian ganglion and along the opthalamic division of the fifth cranial nerve to the long ciliary nerves which innervate the dilator muscles (Loewenfeld, 1958). There is some evidence that additional sympathetic fibres travel to the eye by way of sympathetic plexi associated with the vertebral and basilar arteries (Duke-Elder & Wybar, 1961).

The mechanism of reflex pupillary constriction and dilation have been summarized by Rubin (1974). Constriction is produced in two ways: (1) contraction of the sphincter muscle, in response to light, through

the action of parasympathetic nerve fibres; (2) reduction in parasympathetic tone through diminished inhibition of the Edinger-Westphal nucleus as in sleep, fatigue, narcosis, or organic injury. Reflex pupillary dilation results from: (1) active sympathetically mediated contraction of the dilator muscle; (2) increased inhibition of the Edinger-Westphal nucleus by cortical, thalamic, hypothalamic, or peripheral sensory pathways.

In response to strong stimuli, the arrival at the eye of blood-borne adrenal epinephrine intensifies and prolongs pupillary dilation (Lowenstein & Loewenfeld, 1962). An additional humoral mechanism of dilation has been suggested by Lowenstein and Loewenfeld (1962). Under moderate stress, adrenergic substances are thought to discharge into the circulation from the heart and the arteries, thus effecting a shorter latency dilation than does adrenal epinephrine.

Of the four mechanisms influencing dialtion, inhibition of the Edinger-Westphal nucleus appears to add least to the total response. Loewenfeld (1958) and Lowenstein and Loewenfeld (1950) have shown that active sympathetic-adrenergic influences account for from four-fifths to nine-tenths of the total extent of reflex dilation. Close anatomical parallels can be drawn between extracranial and intracranial sympathetic vasomotor innervation and the innervation of pupillary dilation. Paralysis of both types of efferents, as seen in Horner's syndrome, results in pupillary constriction and extracranial vascular dilation.

Given that cranial vasomotor and pupillary sympathetic efferents share common origins and pathways, the question of whether preganglionic influences generalize to both types of fibres arises. Two lines of

histological evidence support the notion that pupillary changes may have vasomotor concomitants. Ebbeson (1963, 1968) has shown that in humans, the ratio of preganglionic to postganglionic neurons varies between 1:63 and 1:196. Preganglionic impulses are thus multiplied by virtue of their convergence upon many postganglionic cells. Secondly, preganglionic fibres to the neurons innervating the pupils and vascular smooth muscles are similar in terms of their low stimulation threshold (Folkow, Johansson, & Oberg, 1958). These findings suggest that some generality of response to a stressor is possible. Pupillary and vascular preganglionics are likely to respond simultaneously, and the influence of each type of preganglionic may generalize to both types of postganglionics.

Physiological studies extend the notion of anatomical and functional similarities between pupillary and vasomotor innervation to higher nervous centres. Hess (1954) found that electrode stimulation of the posterior hypothalamus elicited an array of sympathetic visceral reactions, including pupillary dilation, rise in respiration and pulse rates, and peripheral vasoconstriction. Stimulation of the more anterior parts of the hypothalamus elicited the discharge of parasympathetic responses, most notably pupillary constriction and peripheral vasodilation. Stavraky (1936) also showed that posterior hypothalamic stimulation resulted in pupillary dilation, piloerection, peripheral vasoconstriction, and constriction of pial vessels.

In sum, anatomical and physiological data indicate that pupillary dynamics may have vascular concomitants, both in peripheral and cranial vascular systems. The pupil response thus provides data at two levels of investigation: (1) because sympathetic activity accounts for the

majority of the dilation response, interpretations of possible excesses of ergotropic tuning in the migrainous autonomic system are possible; (2) pupillary dilation in response to a stressor may provide an analogue measure of the behavior of cerebral vascular structures, which are thought to be relevant to migraine initiation.

The Pupillary Response to Stress

Although pupillary dilation has been observed to a wide range of cognitive, emotional, and physical stimuli (Janisse, 1976, 1977; Goldwater, 1972), relatively few studies have examined the pupillary response to the cold pressor. This is mostly attributable to researchers' preferences of other autonomic measures, such as heart rate or peripheral vascular responses, over the pupil response, largely because of methodological and technological difficulties that have been associated with pupilometric investigations. However, recent advances in measurement techniques and the elucidation of appropriate experimental control procedures have established the pupillary response as an autonomic index with properties similar to those more frequently used, and in a sense superior to others in that it is open to unaided observation, at least with respect to large diameter changes.

Pupillary responses to the cold pressor have been examined extensively by Rubin (1974) in efforts to elucidate possible neurohumoral dysfunctions in neurotic and psychotic subjects. He assumed that if central adrenergic-cholinergic imbalances are characteristic of these disorders, abnormal pupillary responses should be manifested. Rubin first recorded constriction and dilation to light and dark stimuli. Subsequently, a cold pressor, usually immersion of a hand, was applied

contiguously with the light and dark stimuli. In a normal individual, the increase in sympathetic activation resulting from cold press application augmented the normal darkness-reflex, primarily through the action of superior cervical adrenergic fibres, and attenuated the light-reflex, largely through the inhibition of the Edinger-Westphal nucleus by higher brain centres (Lowenstein & Loewenfeld, 1962). Excessive augmentation and/or attenuation are interpreted by Rubin as indicative of generalized sympathetic overresponsiveness and hence an ergotropically tuned autonomic system. Deficient augmentation and/or attenuation is considered a sign of parasympathetic overresponsiveness and trophotropic tuning.

Rubin's pardigm has found some success in distinguishing between normal and neurotic or psychotic subjects. Abberrations of stressed and non-stressed light and dark reflexes have been found to be indicative of schizophrenia while normal light and dark-reflexes, coupled with abnormally long recovery periods following termination of stress are usually observed in neurosis.

Apart from Rubin's investigations, one study has presented additional data on the behavior of the pupil in response to the cold pressor. Janisse and Dumoff (Note 1) exposed college students to a one minute cold pressor, a cognitive task, and a combination of the two stimuli. All subjects showed dilation to the pressor. Peak dilation was reached within approximately 10 seconds, following which constriction to baseline was observed.

Returning to the question of autonomic dysfunction in migraine, portions of the methodologies of Rubin (1974) and of Janisse and Dumoff

(1977) may prove useful for detecting the presumed excesses of ergotropic tuning that are thought to be relevant to migraine initiation. Excessive dilation in response to the cold pressor and excessive inhibition of the light-reflex by the contiguous presentation of the cold pressor should be observed in the migrainous subject.

It has been repeatedly demonstrated that the pupil dilates when subjects are engaged in a cognitive task (Polt, 1970; Arima & Wilson, 1972; Kuc & Janisse, Note 2; Janisse & Dumoff, Note 1). In the Kuc and Janisse study, an eight-item digit-span task was administered to college subjects under high and low stress conditions. Both conditions elicited dilation during the input of digits and constriction during recall. The high stress condition yielded greater dilation throughout. Janisse and Dumoff observed pupillary responses during a word-naming task. Subjects were required to produce a word beginning with a given letter of the alphabet when they heard a tone. Tones were presented every five seconds for a total of one minute and subjects were instructed to produce a new word for each tone presentation. The task thus became more difficult, and consequently more stressful, as time progressed. Marked pupillary dilation was observed during the task. Peak dilation was reached between production of the third and fourth words, and this peak level was maintained throughout the remainder of the task.

Two interpretations of the cause of pupillary dilation during stressful cognition have been forwarded. Hess and Polt (1964) were the first researchers to break from the traditional arousal interpretation of pupillary dilation. They observed that the difficulty of multiplication problems was positively correlated with the extent of dilation

and that completion of the problem was followed by constriction to baseline. A similar relationship between task difficulty and dilation has been found using continous processing tasks (Bradshaw, 1968a), reaction time (Bradshaw, 1968b), recall tasks (Elshtain & Schaefer, 1968), and psychophysical judgments (Kahneman, Beatty, & Pollack, 1967). These findings are the basis for the view that pupillary dilation during a cognitive task is not due to arousal alone, but to the power of mental effort to produce arousal (Kahneman, 1973).

The more traditional interpretation of the pupillary response during cognition is forwarded by Paivio (1973). He maintains that the stress of the decision-making situation and the resultant autonomic (sympathetic) arousal is the primary factor contributing to dilation. The issue is by no means resolved, and the researchers have continued to explore whether mental effort or arousal cause pupillary dilation (e.g. Coulter, 1977).

What may be of most interest regarding this controversy is why the pupil has been singled out as the autonomic measure upon which interpretations of cognitive mediation have been founded. Contrary to what the term "autonomic" suggests, the responses of autonomically innervated organs rarely occur autonomously from the activity of cerebral structures. Blood pressure changes, inhibition of respiration, vasoconstriction and vasodilation, gastrointestinal hypermotility, salivation, abnormalities of sweating, and pupillary dilation have all been produced by electrical stimulation of various cortical areas. The influence of cognitive activity on other autonomically innervated organs is well known. For example, close inspection of figures presented by Albramson and Ferris (1940) reveals that finger blood flow was markedly reduced during the solving of

a problem in mental arithmetic, and that vasodilation occurred promptly upon resolution of the problem. The profile is similar to those upon which the mental effort interpretation of pupillary dilation have been based. Should vasoconstriction in the fingers consequently be attributed to the effects of either mental effort or autonomic arousal? Neither interpretation considers the interaction of cortical and autonomic functions. It is known that blood flow responses to cognitive activity are abolished by sympathetic paralysis (Sturup, Bolton, Williams, & Carmichael, 1935) and there is little doubt that decortication would erase any responses to a problem in mental arithmetic. The only tenable interpretation is an interactive one and all autonomic responses, including pupillary dilation, must be viewed as the result of intimate functional relationships between central and peripheral nervous systems.

For the purposes of this investigation, pupillary responses to the introduction of a cognitive task will be viewed in the context of an autonomic response to a stressor. It is expected that the excessive ergotropic tuning thought to be characteristic of migrainous subjects will be manifested by exaggerated pupillary dilation in response to a word-naming task and by marked attenuation of the light-reflex when word-naming and light stimuli are contiguously presented.

Problem and Hypotheses

Migraine headache is generally recognized as a biphasic process (Dalessio, 1972). Initial vasoconstriction of extracranial (Wolff, 1963) and intracranial (Sakai & Meyer, 1977) arteries leads to cerebral ischemia, a threat to the survival of the brain. A rebound vasodilation in these structures seeks to protect the brain and repay the oxygen deficit resulting from the initial vasoconstriction phase. The ensuing

dilation causes painful stretching of intracranial and extracranial arteries and this pain is intensified by the local release of pain-threshold lowering substances.

It has been suggested that the vasoconstriction phase of the migraine sequence is the result of aberrant autonomic nervous system responsiveness to stressful stimulation (Sargent, Walters, & Green, 1973; Mitchell & Mitchell, 1971, Dalessio, 1972, Stroebel, 1975). The migrainous subject is thought to respond to stress with excessive sympathetic outflow. This outflow presumably causes constriction of cerebral arteries, thus inducing ischemia and painful rebound vasodilation.

Although it is fairly well established that stress can induce migraine (Dalessio, 1972; Henryk-Gutt & Rees, 1973), to date, no experimental evidence has been presented indicating that the migraineur's stress response is in any way different than that of the non-migraineur. The study proposed here addresses itself to this issue. Two stimuli known to induce stress, the cold pressor and a word-naming task, will be administered to a group of migrainous subjects and a group of non-migrainous subjects matched on relevant variables. Pupillary and digital blood volume responses will be used as measures of stress reactions, i.e. as the dependent variables.

Experimental Hypotheses

Two groups of hypotheses will be investigated. The first group considers the basic question of whether aberrant autonomic responsiveness to stress is characteristic of migrainous subjects. It is predicted that:

(1) Migraineurs will show greater digital blood volume reduction and pupillary dilation than non-migraineurs in response to the cold pressor.

Excessive responsiveness will be manifested by:

a. greater overall blood volume reduction throughout the pressor period;

b. greater overall pupillary dilation throughout the cold pressor period;

c. greater rate of blood volume reduction and pupillary dilation over time as reflected by the interaction of Group and Time effects;

d. slower post stress recovery on both blood volume change and pupil size change.

(2) Migraineurs will show greater digital blood volume reduction and pupillary dilation than non-migraineurs in response to a word-naming task. Excessive responsiveness will be manifested by:

a. greater overall blood volume reduction throughout the word-naming period;

b. greater overall pupillary dilation throughout the word-naming period;

c. greater rate of blood volume reduction and pupillary dilation over time as reflected by the interaction of Group and Time effects;

d. slower post stress recovery on both blood volume change and pupil size change.

(3) Stress inhibition of the pupillary light reflex will be greater in migraineurs than in non-migraineurs when a word-naming task and a light stimulus are presented contiguously.

(4) Stress inhibition of the pupillary light-reflex will be greater in migraineurs than in non-migraineurs when a cold pressor and a light

stimulus are presented contiguously.

The second group of hypotheses considers the proposition that personality factors mediate excessive autonomic responsiveness in migraineurs. It has been suggested that chronically or phasically high levels of anxiety and/or neuroticism predispose the migrainous subject to pernicious physiological arousal under stressful circumstances. If this is the case, two predictions would follow:

(5) Migraineurs and non-migraineurs will show differences on a multivariate package of personality variables including state anxiety, trait anxiety, and neuroticism, migraineurs scoring in the direction of more pathology.

(6) The mediating effects of anxiety and neuroticism will account for observed differences in autonomic responses to stress between migraineurs and non-migraineurs.

CHAPTER II

Method

Subjects

a) Recruitment and Screening

Sixty-two women replied to advertisements in the local newspapers, local newspaper articles, and local radio station announcements requesting volunteers for an experiment studying the nature of migraine headache (see Appendicies A, B & C). Subjects responded by telephone at which time they were asked to reply to a standard set of questions designed to determine their appropriateness for inclusion in the study (see Appendix D). Criteria for inclusions were:

1) a minimum of two migraine headaches per month (averaged over 6 months prior to experimentation);
2) headaches diagnosed as migraine by a medical doctor;
3) at least two of the following headache characteristics:
    a. unilateral throbbing headaches;
    b. headaches accompanied by nausea and/or vomiting;
    c. positive family history of migraine;
    d. positive response to ergotamine preparations (i.e. reduced headache frequency and/or intensity).

Medical contraindications to participation in the study included pregnancy, hypertension, a history of seizures, or past or current systemic illness. Migraineurs using vasoactive substances on a daily basis were excluded as were any post-menopausal women.

Of the 62 women who responded, 25 were immediately excluded. Six had fewer than two migraines per month, six were post-menopausal, four

used vasoactive medications daily, three were not available when the study was to be run, one was hearing impaired, and one had extremely vague symptomatology even though a medical diagnosis of migraine had been made. Four women refused to participate because the researcher did not promise a cure for their headaches.

Thirty-seven migraine subjects were given experimental appointments. Each subject completed a Headache Questionaire (devised by the author - see Appendix E) in order to ensure that they met all criteria for inclusion in the study. The questionaire also documented the nature of their headaches and determined whether any subjects had ingested any medications that might affect vascular responses within the past 48 hours. Four subjects were excluded on the basis of information gained from the Headache Questionaire; three had taken ergotamine medications during the previous 48 hours and one subject had started daily treatment with a vasoactive medication. Three subjects did not arrive for experimental appointments. One migraine subject's data were not usable due to experimenter error and two subjects' pupil responses could not be reliably recorded due to ptosis (drooping eyelids). Final migraine group size was 27.

As in the procedure of Price and Tursky (1976), the volunteer migraineurs were asked to recruit a woman not diagnosed as having migraine, matched for age ($\pm$ 5 years), who would be willing to participate in the experiment. Relatives of migraineurs were not allowed as controls to eliminate possible genetic confounds. The migraineurs and their control partners attended the experimental appointments together.

Twenty-nine control subjects arrived for experimental appointments.

Each control completed a Headache Questionaire (devised by the author - see Appendix E) which was designed to screen for medical contraindications to experimental participation and to ensure that no controls suffered from migraine but had never been diagnosed as such by a medical doctor. Six prospective controls indicated having unilateral, throbbing headaches which were sometimes accompanied by nausea or vomiting. These subjects were excluded because their headaches were probably of the migraine type. One control was excluded because of a history of hypertension. At this stage there were 22 controls.

Sitting blood pressure was taken for all subjects prior to their participation in the experiment. This was to ensure that individuals showing blood pressures in the hypertensive range (above 160/100 mm Hg.; Julius, 1977) were not submitted to the stress of the procedures. Two control subjects showed blood pressures in the hypertensive range and were consequently excluded. One control subject was excluded because of ptosis. This left 19 control subjects. Eight additional non-migraine females were recruited from Introductory Psychology classes at the University of Manitoba. These students participated voluntarily and no financial reward or course credit was given. Resultant control group size was 27.

b) Control and experimental group characteristics

Mean ages of migraine and control groups were 29.25 (s.d.=7.03) and 30.81 (s.d.=7.57) respectively. This difference was not significant. Headache characteristics of control and experimental groups are shown in Table 1. Migraineurs experienced an average of 4.03 (s.d.=2.56) migraine headaches per month. Their headaches lasted an average of 23.11 (s.d.= 17.90) hours. Twenty-five migraineurs experienced unilateral headaches

accompanied by nausea and/or vomiting and 23 had throbbing pain. Twenty-one had a close relative who also experiences migraine. All had been diagnosed as having migraine by a medical doctor and 23 indicated experiencing more than one kind of headache. Subsequent questioning revealed that these migraineurs distinguished migraine headaches from sinus or muscle tension headaches.

Twenty-four migraineurs reported being aware of warning signs before the onset of a migraine. These warning signs included blurry vision, numbness in the extremities, dizziness, muscle tension in the neck and/or back, nausea, increased sensitivity to light, a general feeling of detachment and classic scintillating scotoma. These migraineurs were indistinguishible from the three who did not report being aware of pre-headache phenomena in terms of migraine frequency, intensity or duration. Consequently no distinction was made between classic and common migraine for data analysis purposes.

Control subjects experienced an average of 2.48 (s.d.=1.59) headaches per month. Mean duration of control headaches was 2.96 (s.d.= 1.80) hours. One control described having unilateral headaches, four described having throbbing pain and none experienced nausea and/or vomiting during headaches. One control had a close relative who had been diagnosed as having migraine and six controls reported experiencing more than one kind of headache. Subsequent questioning indicated that these six controls distinguished between tension and sinus headaches. No control subjects' headaches fulfilled more than one criterion for the diagnosis of migraine.

Although all subjects were asked to remain drug free for 48 hours

TABLE 1

Migraine and Control Group
Headache Characteristics

Characteristic	Migraine(n=27)	Control(n=27)
Mean frequency per month	4.03	2.48
Mean duration (hours)	23.11	2.96
Unilateral	25	1
Throbbing	23	4
Nausea/vomiting	25	0
Family history of migraine	21	1
M.D. diagnosis of migraine	27	0
Experience more than one kind of headache	23	6

prior to experimental participation, 12 migraineurs and eight controls had taken some form of drug during that period. The drugs taken by the migraineurs included Tylenol, Aspirin, antihistamines, ASA/codeine combinations and muscle relaxants. The controls had taken Aspirin, ASA/codeine combinations, muscle relaxants, antihistamines and alcohol. Three migraineurs and five controls used birth control pills. Migraine and control groups did not differ in terms of the stage of their menstrual cycle at which they participated in the experiment. Migraineurs participated an average of 20.04 (s.d.=9.96) days after the start of their last menstrual period while controls participated an average of 19.57 (s.d.=10.78) days after the start of their last period. Migraineurs showed significantly higher diastolic blood pressure than controls ($\bar{X}$ migraine = 73.37 mm Hg, s.d. = 8.45; $\bar{X}$ control = 67.19 mm Hg, s.d.= 7.69; $t_{52}=2.81$, $p<.009$. Systolic blood pressure was not significantly different between groups ($\bar{X}$ migraine=112.96 mm Hg, s.d.=12.45; $\bar{X}$ control= 109.21 mm Hg, s.d.=10.46.

Apparatus

Pupil responses were measured by a Whittaker Space Sciences Eye-view Monitor and Television Pupillometer System, Model 1992S. The left eye was monitored. Both the pupillary light-reflex and dilation in response to stress are bilateral (Loewenfeld, 1958), consequently, measurements of one eye represented the behavior of both. Blood volume at the distal phalange of the middle finger of the right hand was measured by the photoplethysmographic transducer of a Whittaker Space Sciences Division Pulse-Watch (Model 420). This instrument was modi-

fied such that raw photocell output was routed directly to a D.C. backing off circuit and into a Harvard Apparatus Bioamplifier (Model 355). The signal was amplified in D.C. mode in order to extract the blood volume component and routed to an MFE chart recorder (Model M22). Pupillometer output was recorded on a second channel of the same MFE chart recorder. Chart speed was set to 1 mm per second. Gain on the Harvard and MFE amplifiers was set such that 1mm of pupil size change and 1 mm of blood volume shift produced 10 mm of pen deflection. Eye movement and eye blink artifact was eliminated by assuming a linear slope between the valid recordings at the beginning and end of the artifact period.

Pupillometer calibration and pupil diameter analogue output were checked against a standard 4 mm model pupil before each subjects' responses were recorded.

All experimental procedures were performed in a 4.5 by 9 meter sound attenuated room which housed both the subject and the apparatus. Ambient light was provided by five adjustable incandescent lights powered by a constant voltage transformer. The lights were equipped with reflectors and provided uniform illumination on the focusing target.

The stimulus for the pupillary light-reflex was provided by a trachiascope equipped with a battery powered sub-miniature light bulb. This instrument was modified so that it could be attached to the pupillometer camera bracket. The light was thus directed into

the subject's right eye. Light intensity was controlled by a mechanical rheostat. The cold pressor consisted of immersion of the left hand in a bucket of ice water which was maintained at 5°C ($\pm$2°C). All experimental instructions were presented by tape recorder. (See Appendix G for full transcript of instructions.)

Control Considerations

To control for the near-vision reflex, that is, the tendency for the pupil to constrict when focusing on a point near the subject (Lowenstein & Loewenfeld, 1964), subjects viewed a neutral target located approximately 3 meters away during all experimental conditions. To achieve median pupil sizes of 4 to 4.5 millimeters, a brightness of approximately 64 lumens per square meter of light was maintained at the target (Peavler, 1974). All pupillary baselines were taken with subjects viewing this target. Room temperature was maintained at approximately 25°C. The hand from which blood volume measures were taken was supported on a pillow at approximately heart level.

Procedure

All subjects received identical treatments. Subjects were seated in a chair in the laboratory but away from the apparatus. The experimenter explained the purpose of the various experimental devices and answered any questions. Subjects then completed three paper and pencil measures. Anxiety was assessed by means of the State-Trait Anxiety Inventory (Spielberger, Gorsuch & Lushene, 1970). This scale distinguishes between anxiety as a state, or the amount of anxiety experi-

enced by an individual in a particular situation, and anxiety as a trait, or the level of anxiety experienced in general. Since both chronic and situational factors may be implicated in migraine, both state and trait anxiety were measured. The Eysenck Personality Inventory (Eysenck & Eysenck, 1964) was used to assess neuroticism.

Following subjects' completion of the personality inventories, sitting blood pressure was taken by the experimenter. Subjects were then seated at the pupillometer and the plethysmograph was applied. Blood volume was monitored until each subject reached a relatively stable baseline. The above procedures required approximately 20 to 30 minutes which allowed time for accommodation to the experimental situation. Five procedures were carried out in the following order.

1) Word-naming

Subjects heard a series of five orienting tones (1 per second), after which a letter and a word were presented (e.g. "b" as in "boy"). Following presentation of the letter, tones, each 5 seconds apart, were presented. Their task was to name a new word, beginning with the letter previously named, after each tone. A practice trial was given in order to ensure that the task was understood. The subject was then positioned at the pupillometer and blood volume and pupil baselines were determined. Word-naming began and continued for 60 seconds, after which the subject stopped naming but remained quietly in place. Post-stress recovery was monitored for 1 minute. A 5 minute rest period followed.

Difficulty of letters has been rated by Janisse and Lee (Note 3) on the basis of a count of the number of words in the dictionary that begin with each letter. A relatively easy letter ("b") was used to help ensure that all subjects continued naming for the full 60 seconds. This procedure followed those of Janisse and Lee, Janisse and Dumoff (Note 1) and Dumoff (Note 4).

2) Cold Pressor

Before the cold pressor was applied, subjects were told that during the immersion period, tones, each 5 seconds apart, would be presented. Their task was to recite one letter of the alphabet after hearing each tone. This procedure equated the dilatory effect of verbalization on the pupil (Simpson, 1969) across the cold pressor and the word-naming tasks and permitted comparisons of the response curves for both stressors. Baseline pupil size and blood volume were then determined, following which the cold pressor was applied. After 30 seconds the hand was removed from the water by the experimenter and wrapped in a towel. The subject remained at the pupillometer quietly for an additional 1 minute and post-stress recovery was monitored. A 5 minute rest period followed. This procedure was similar to that of Janisse and Dumoff (1977).

3) Non-stressed Pupillary Light-reflex

To control for any differences in subjects' sensitivity to light, the amount of light necessary to produce approximately 1 mm of pupillary constriction was determined in the following manner. After the subject was positioned at the pupillometer, the experimenter presented varying light stimulus intensities until the brightness necessary to produce approximately 1 mm of pupillary constriction within 3 seconds on two out

of three trials was determined. This light level was then used as the stimulus for that subject. [1] Following a short rest period, the stimulus was presented for 6 seconds (the pupillary light-reflex is known to peak at about 3 seconds (Rubin, 1974), and the non-stressed pupillary light-reflex was recorded.

4) Light-reflex - Word-Naming

This task proceeded in the same manner as the first word naming task, however the light stimulus was presented 13 seconds following the beginning of the task. This specific time was chosen on the basis of Janisse and Dumoff's (1977) finding that maximum pupillary dilation in response to word-naming peaks at approximately 13 seconds. The light stimulus remained on for 6 seconds, during which time word-naming continued. The task was then terminated and subjects rested for 5 minutes.

5) Light-reflex - Cold Pressor

After the subjects were positioned at the pupillometer and baseline was determined, the subject's left hand was placed in the ice water. Ten seconds later, when peak dilation should have been reached (Janisse & Dumoff, 1977), the light stimulus was presented for 6 seconds. The subjects hand was then removed from the water and the experiment was terminated.

Subjects were briefed and the experimenter answered any questions about the experiment or about migraine in general.

Scoring

The experimenter scored all subjects' data. Four migraine and four control subjects' chart records were randomly selected for calculation

of scorer reliability estimates. During and post-stress data were combined for each variable and over both word-naming and cold pressor experiments, resulting in 42 pairs of observations on each variable for each subject. Interscorer correlations were .86 and .89 for pupil size change and blood volume change respectively. The interscorer correlation on the 18 pairs of pupillary light reflex scores for the same four subjects was .92.

CHAPTER III

Results

Pupillary responses were quantified in terms of mm of change from pre-stimulus baseline as reflected in mm of pen deflection on the pupil channel of the chart recorder. Blood volume responses were quantified in terms of mv of D.C.blood volume shift over prestimulus baseline as reflected by mm of pen deflection on the blood volume channel of the chart recorder. Pupil size and blood volume values were averaged over 5 second time blocks during both word-naming and cold pressor procedures. Twelve during stress and 12 post-stress data points on each variable resulted for both word-naming and cold pressor procedures.

Time block main effects and Group X Time block interactions were explored using orthogonal polynomial trend analysis. Step-down univariate F statistics and standardized discriminant function coefficients[2] were examined for post-hoc evaluation of the omnibus multivariate tests. The computer program used for all multivariate and univariate analyses was "Multivariance: Univariate and multivariate analysis of variance, covariance, and regression. Version V, Release 3" (Finn, 1976). Each dependent variable was examined separately for both word-naming and cold pressor experiments. During and post-stress periods were analysed separately. Pupil size initial values were not significantly different for either word-naming ($\overline{X}$ migraine=4.32, s.d.=.64; $\overline{X}$ control=4.37, s.d.=.80) or cold pressor ($\overline{X}$ migraine=4.15, s.d.=1.26; $\overline{X}$ control=4.37, s.d.=.85) experiments. The Group main effects and the Group X Time blocks interactions were the migraine versus control comparisons of predictive concern for the word-naming, cold pressor, and light-reflex

experiments. Time main effects were examined only as a reflection of the dependent variable responses at both groups taken together. A posteriori pairwise comparisons among means were performed using Tukey's (1953) HSD (honestly significant difference) procedure.

Experiment 1 - Word-naming

During Stress

Migraine and control group means and standard deviations on pupil size change and blood volume change during word-naming are shown in Tables 2 and 3 respectively. Bivariate correlations of pupil size change with blood volume change are shown in Table 4. Correlations were consistently low with only Time blocks 7 and 8 showing significant correlations within the control group only. These two correlations, although significant, failed to show an important degree of association between pupil size change and blood volume change and relatively little of the variance in one variable was accounted for by variance in the other (r^2 at T_7=.1222; r^2 at T_8=.1151).

Blood Volume Change. Migraine and control group blood volume change responses during word-naming are presented graphically in Figure 1. The results of the multivariate analysis of repeated measures on these data are shown in Table 5. Over the 12 time block during word-naming period, migraineurs showed greater overall digital vasoconstriction as shown by the significant Group main effect ($F(1,52)=4.1456$, $p< .0469$. Controls did not show significant vasoconstriction at any time during word-naming and in fact showed dilation above baseline from time block 6 through time block 12. Post hoc comparisons of migraine-control differences at each time block indicated that the

groups differed significantly from time block 2 through time block 7 (HSD=.82, $p<.05$). The test of the Group X Time block interaction yielded a multivariate F (11,42) of 1.8564 ($p < .0744$) and was considered worthy of further univariate analysis. Step-down F statistics and standardized discriminant function coefficients for the interaction orthogonal polynomials are shown in Table 6. The largest step-down F and the largest standardized discriminant function coefficient was associated with the Groups X Quadratic interaction term. The Group and Interaction effects thus showed that migraineurs vasoconstricted more than controls early in the stress period and approached the level of the controls approximately half way through the stress period. Groups did not differ significantly following time block 7.

The Time main effect showed a significant multivariate F (11,42) of 2.9813 with $p < .0052$. Step-down univariates were significant on linear ($F(1,52)=19.29$, $p < .0001$) and quadratic ($F(1,52)=8.285$, $p < .0059$) trends. Linear and quadratic respectively were the most highly weighted standardized discriminant function coefficients. The combined migraine and control groups, then, showed initial vasoconstriction followed by gradual, linear vasodilation to approximately baseline levels by the end of the word-naming period. The significant Group main effect suggests that migraineurs' greater initial vasoconstriction accounted for the significant linear and quadratic trends within the Time main effect.

Pupil size change. Figure 2 shows migraine and control group pupil size change profiles during word-naming. Multi-

Table 2

Group Means on Pupil Size Change and Blood Volume Change During Word-Naming

	Control		Migraine	
Time blocks	Pupil size	Blood volume	Pupil size	Blood volume
T_1	.3315	-.2611	.3959	-.9407
T_2	.2704	-.1704	.3681	-1.0704
T_3	.2959	-.1148	.3051	-1.1926
T_4	.3000	-.1370	.2552	-1.2741
T_5	.2526	.0166	.2626	-1.0704
T_6	.3167	.2259	.2252	-1.0593
T_7	.3593	.1500	.2737	-.7481
T_8	.2870	.2852	.3015	-.4852
T_9	.3141	.3390	.2644	-.2296
T_{10}	.3333	.4889	.2441	-.2000
T_{11}	.3241	.6741	.2348	.0148
T_{12}	.2519	.5500	.1496	.3185

Table 3

Group Standard Deviations on Pupil Size Change and Blood Volume Change During Word-Naming

	Control		Migraine	
Time blocks	Pupil size	Blood volume	Pupil size	Blood volume
T_1	.2897	1.3204	.3282	1.5300
T_2	.2605	1.4368	.3680	1.7411
T_3	.2871	1.3788	.2984	1.8047
T_4	.2797	1.5788	.3322	1.7419
T_5	.2577	1.7335	.3622	1.9205
T_6	.2967	1.7282	.3389	1.9205
T_7	.3267	1.8257	.4061	1.6778
T_8	.3705	1.6419	.4690	1.7340
T_9	.4549	1.7050	.5235	1.8759
T_{10}	.4538	1.6779	.5466	1.6569
T_{11}	.4944	1.6215	.5204	1.9036
T_{12}	.5216	1.7889	.4870	1.9850

Table 4

Bivariate Correlations of Pupil Size Change with Blood Volume Change During Word-Naming

Time blocks	Control	Migraine
T_1	-.0014	-.0475
T_2	-.1820	-.0823
T_3	-.0796	-.2623
T_4	-.2922	-.1390
T_5	-.1640	-.1577
T_6	-.2523	-.1441
T_7	-.3495*	-.0635
T_8	-.3393**	.1815
T_9	-.2600	.0689
T_{10}	-.2126	-.0863
T_{11}	-.1482	-.0076
T_{12}	-.3118	-.0790

*p=.037, r^2=.122

**p=.042, r^2=.1151

Figure 1

Blood Volume Change

During Word-naming

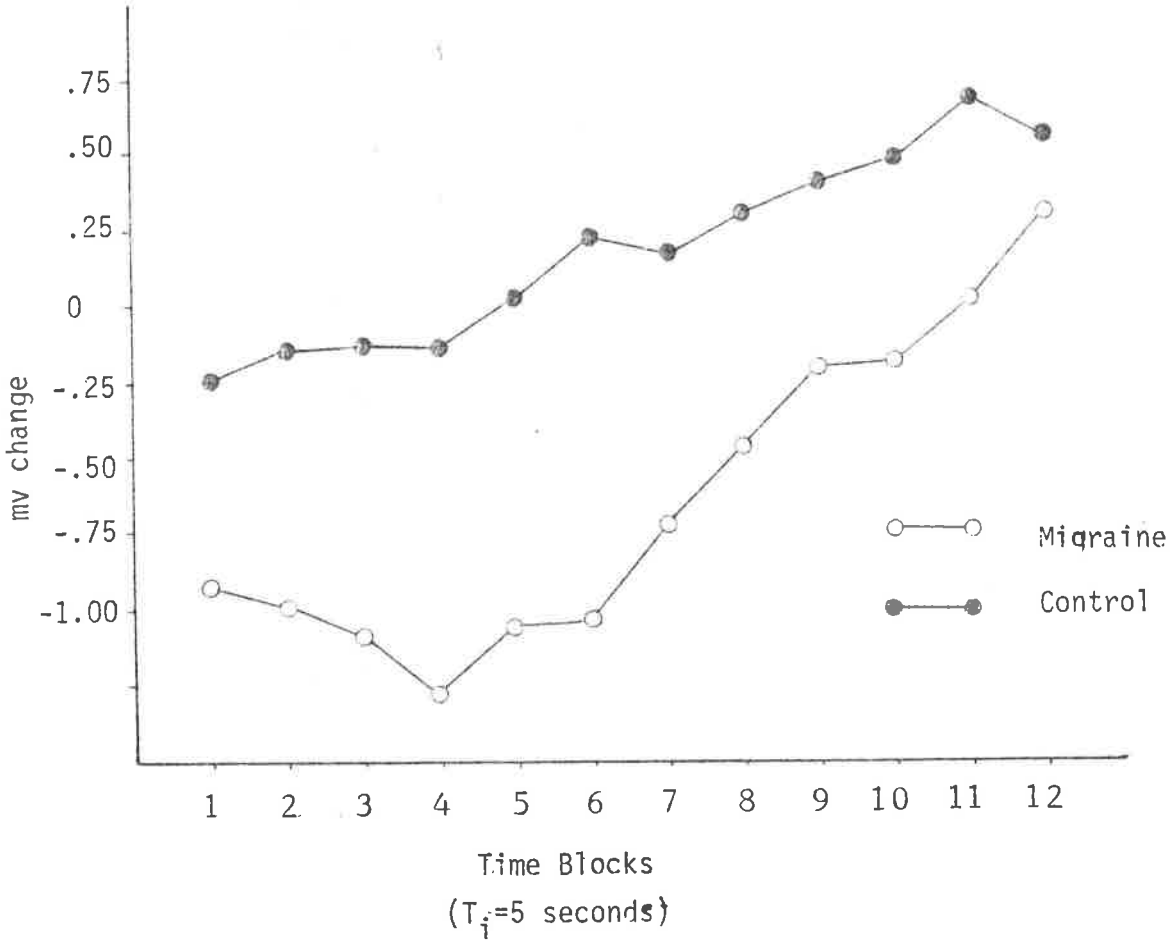


Table 5

Multivariate Repeated Measures Analysis of
Migraine vs. Control Blood Volume
Change During Word-naming

Source of variation	Degrees of freedom	*F*	*p* less than
Group	1,52	4.1456	.0469
Time blocks	11,42	2.9813	.0052
Group X Time Blocks	11,42	1.8564	.0744

Table 6

Step-down Fs and Standardized Discriminant Function Coefficients on Orthogonal Polynomials for Group X Time blocks Interaction for Blood Volume Change During Word-naming

Orthogonal polynomial	Step-down *F*	*p* less than	Coefficient
P_1	.9922	.3239	.3402
P_2	5.7047	.0207	.8392
P_3	.5528	.4607	-.3840
P_4	2.8296	.0990	.4996
P_5	2.0972	.1514	.3772
P_6	4.9667	.0307	.5304
P_7	.4082	.5261	.0523
P_8	.5794	.4506	-.1496
P_9	.5519	.4616	-.3064
P_{10}	.0660	.7986	-.0450
P_{11}	1.0774	.3052	-.3110

variate analysis of these repeated measures data showed non-significant Group and Group X Time effects, indicating that migraine and control groups did not differ in amount of pupil size change during word-naming (see Table 7). The Time main effect was significant with F (11,42)=1.9824, $p < .0054$. Within the Time effect, one trend, cubic, was significant with step-down F(1,52) of 11.8454, $p < .0012$. The cubic trend was also associated with the highest standardized discriminant function coefficient, thus indicating that the combined migraine-control group profile changed slope or direction twice during the word-naming period.

Post Stress

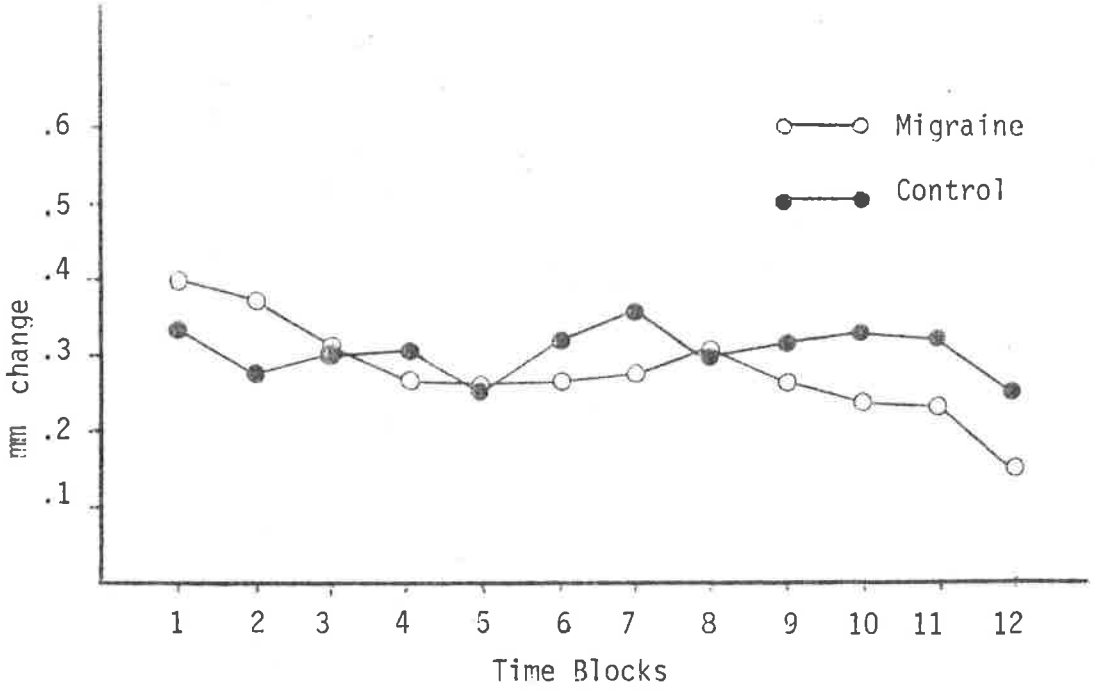
Migraine and control group means on pupil size change and blood volume change are shown in Table 8. Standard deviations are shown in Table 9. Bivariate correlations of pupil size change with blood volume change at each time block were low for both migraine and control groups (see Table 10). Pupil size change and blood volume change correlated significantly within the migraine group at time blocks 15,16, and 17, however; r^2 was relatively small and a strong linear relationship between pupil size change and blood volume change at each time block was not indicated.

Blood Volume Change. Migraine and control group profiles on blood volume change post word-naming are shown in Figure 3. Neither the group main effect nor the Group X Time Blocks interaction reached significance in the multivariate analysis of the repeated measures (see Table 11).

Figure 2

Pupil Size Change

During Word-naming



(T_i=5 seconds

Table 7

Multivariate Repeated Measures Analysis of
Migraine vs. Control Pupil Size
Change During Word-naming

Source of variation	Degrees of freedom	F	p less than
Group	1,52	.0831	.7743
Time blocks	11,42	1.9824	.0054
Group X Time Blocks	11,42	.9796	.4795

Table 8

Group Means on Pupil Size Change and Blood Volume Change Post Word-naming

	Control		Migraine	
Time blocks	Pupil size	Blood volume	Pupil size	Blood volume
T_1	.0659	.4370	-.0115	.1667
T_2	-.0685	.0241	-.1300	.0185
T_3	-.1167	.1093	-.2004	-.1481
T_4	-.1833	-.0463	-.2726	.1667
T_5	-.2019	-.1574	-.2819	.5259
T_6	-.2389	.1370	-.2578	.4925
T_7	-.2481	.2722	-.3115	.7852
T_8	-.3204	.3370	-.4133	.8963
T_9	-.3630	.4222	-.4089	1.0481
T_{10}	-.4074	.5148	-.4911	1.2685
T_{11}	-.4500	.6278	-.4800	1.2870
T_{12}	-.4630	.7648	-.4540	1.3370

Table 9

Group Standard Deviations on Pupil Size Change and Blood Volume Change Post Word-naming

	Control		Migraine	
Time blocks	Pupil size	Blood volume	Pupil size	Blood volume
T_1	.4713	1.7340	.4742	2.1186
T_2	.4373	1.8256	.4841	2.3177
T_3	.4218	2.0785	.4460	2.4205
T_4	.3952	2.2136	.4017	2.2619
T_5	.4199	2.2818	.3990	2.3088
T_6	.3699	2.3113	.3649	2.3135
T_7	.3870	2.2447	.4277	2.2813
T_8	.3809	2.2414	.4036	2.2372
T_9	.3876	2.1340	.4290	2.4229
T_{10}	.3885	2.2017	.4021	2.5103
T_{11}	.3656	2.2320	.3332	2.2159
T_{12}	.4028	2.2615	.3688	2.2394

Table 10

Bivariate Correlations of Pupil Size Change with

Blood Volume Change Post Word-naming

Time blocks	Control	Migraine
T_1	-.0384	.0011
T_2	-.0932	-.1073
T_3	-.1771	-.3287 *
T_4	.0513	-.3195 **
T_5	-.2054	-.3243 ***
T_6	-.0627	-.2167
T_7	-.1577	.0241
T_8	-.1176	.0454
T_9	-.0993	-.0074
T_{10}	-.0582	-.0874
T_{11}	.0457	-.0546
T_{12}	-.0857	.1163

* $\underline{p}$=.047, r^2=.108

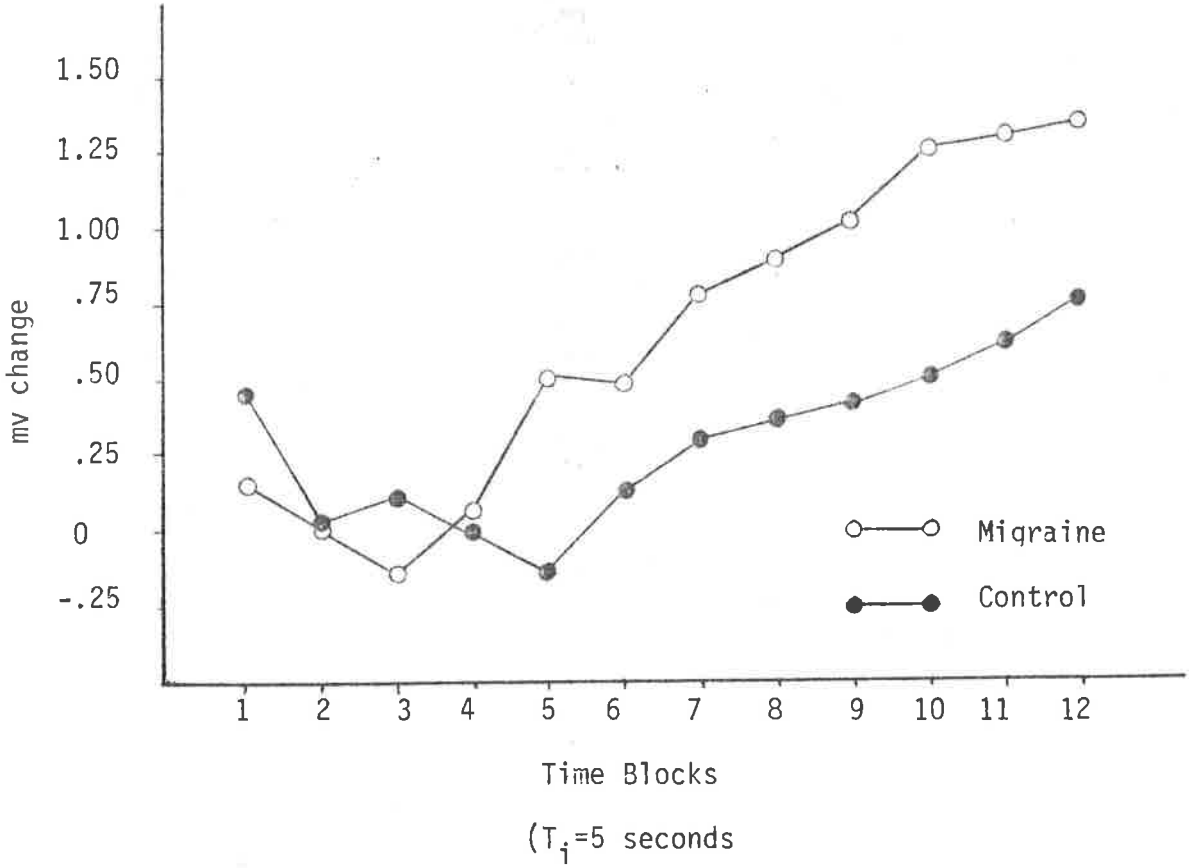
** $\underline{p}$=.052, r^2=.102

*** $\underline{p}$=.049, r^2=.105

Figure 3

Blood Volume Change

Post Word-naming



(T_i=5 seconds

Table 11

Multivariate Repeated Measures Analysis of Migraine vs. Control Blood Volume Change Post Word-naming

Source of variation	Degrees of freedom	F	p less than
Group	1,52	.4214	.5191
Time blocks	11,42	4.1420	.0004
Group X Time blocks	11,42	1.4794	.1757

The hypothesis that migraineurs would show differences in post stress recovery from controls was thus not supported. The Time main effect was significant ($F(1,52)=4.1420$, $p < .0004$) with linear (F $1,52=19.3217$, $p < .0001$), cubic ($F(1,52)=8.2687$, $p < .0059$), and ninth order ($F(1,52)=4.8237$, $p < .0334$) trends. Standardized discriminant function coefficients indicated that the quadratic trend contributed most to the Time main effect. Visual inspection of Figure 3 clarifies the nature of the quadratic trend. Both groups, taken together, showed vasoconstriction from during stress blood volume change levels early during the post stress period.

Pupil size change. Pupil size change for migraine and control groups is shown graphically in Figure 4. Visual inspection of Figure 4 suggests the presence of neither between group differences nor a Group X Time blocks interaction. Multivariate analysis of the repeated measures showed non-significant Group and Group X Time blocks effects (see Table 12). The Time blocks main effect was significant with $F(11,42)$ of 8.1314 ($p < .0001$). Only the orthogonal polynomial for linear trend showed a significant step-down F ($F(1,52)=13.29$, $p < .0001$). The linear trend also showed the highest standardized discriminant function coefficient. In sum, migraine and control groups did not show differences in post-stress recovery on pupil size change. Both groups showed a linear decrease in pupil size to below baseline levels at the end of the recovery period.

Figure 4
Pupil Size Change
Post Word-naming

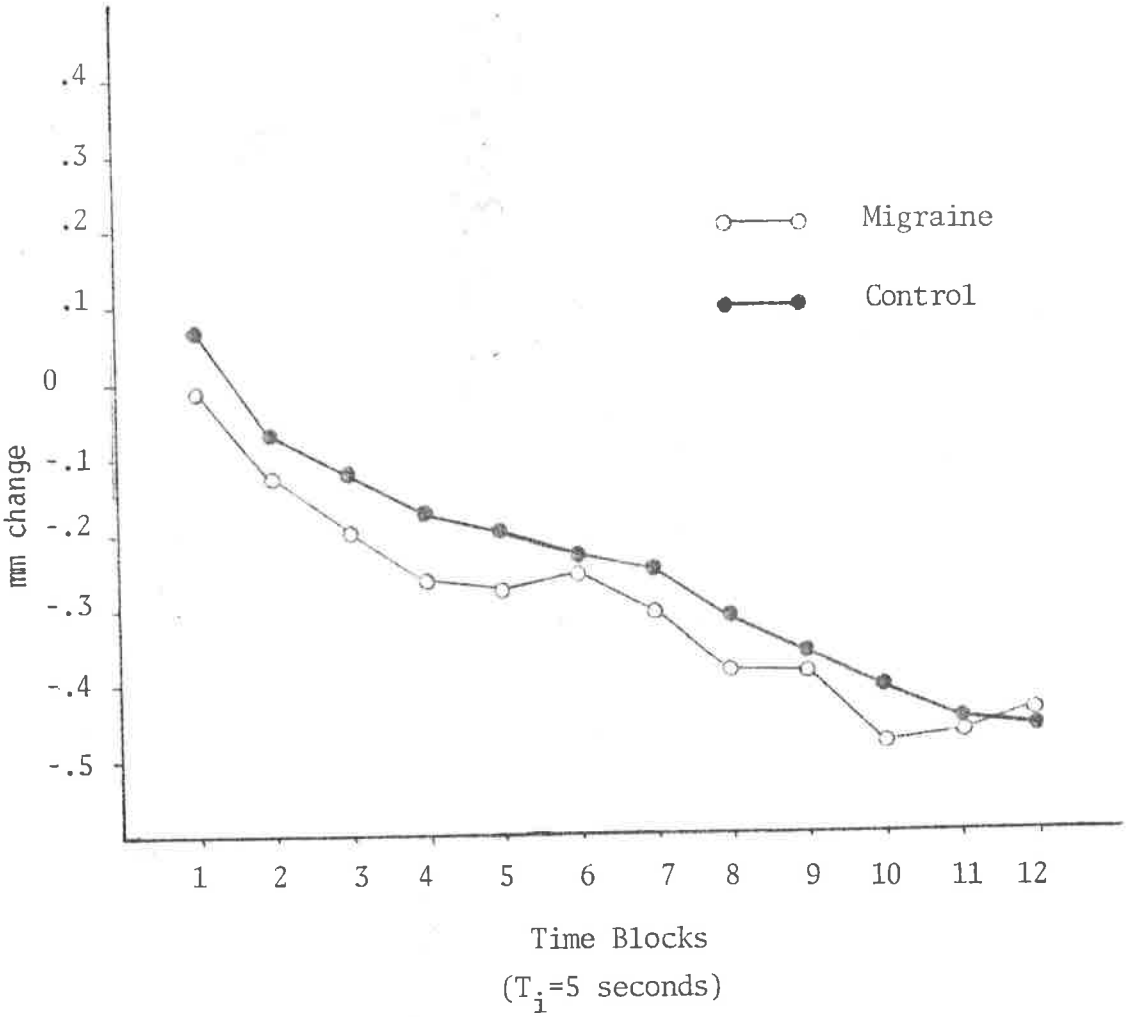


Table 12

Multivariate Repeated Measures Analysis of
Migraine vs. Control Pupil Size
Change Post Word-naming

Source of variation	Degrees of freedom	F	p less than
Group	1,52	.3558	.5535
Time blocks	11,42	8.1314	.0001
Group X Time blocks	11,42	1.0534	.4200

Experiment 2 - Cold Pressor

During Stress

Tables 13 and 14 show migraine and control group means and standard deviations on pupil size change and blood volume change during the cold pressor. No bivariate correlations of pupil size change with blood volume change at each time block during the cold pressor were significant (see Table 15), indicating the absence of a linear relationship between the dependent variables.

Blood Volume Change. Blood volume change profiles for migraine and control groups during the cold pressor are shown in Figure 5. The summary of the multivariate analysis of these data is shown in Table 16. The visual impression of a strong Group effect was supported by a significant Group main effect with $F(1,52)$ of 10.2007, $p < .0001$. Post hoc comparisons within the Group effect showed that migraineurs vasoconstricted significantly more than controls from time block 2 through time block 6 (HSD=.927, $p < .05$). Visual inspection of Figure 5 suggests a Group X Linear interaction, however; the multivariate test of the orthogonal polynomials for interaction did not reach significance ($F < 1$). The step-down F for Group X Linear interaction term did approach significance ($F(1,52)=3.3803$, $p < .0717$). The Time main effect, which again represented the blood volume responses of both migraine and control groups taken together, showed a significant multivariate F (5,48) of 9.8269 with $p < .0001$. Within the Time effect, linear, quadratic, and cubic trends showed significant step-down Fs (linear - $F(1,52)=$

Table 13

Group Means on Pupil Size Change and Blood Volume Change During Cold Pressor

Time blocks	Control		Migraine	
	Pupil size	Blood volume	Pupil size	Blood volume
T_1	.5756	.2889	.5678	-.5815
T_2	.4533	-.3074	.4270	-1.6037
T_3	.3785	-.4648	.3900	-3.0185
T_4	.2237	-.3037	.3214	-1.9667
T_5	.2200	-.3056	.3122	-2.0000
T_6	.2941	-.3796	.3067	-2.0815

Table 14

Group Standard Deviations on Pupil Size Change and Blood Volume Change During Cold Pressor

Time blocks	Control		Migraine	
	Pupil size	Blood volume	Pupil size	Blood volume
T_1	.2717	1.0789	.3950	1.0363
T_2	.2756	1.6217	.3640	1.5646
T_3	.3018	1.9021	.3480	1.7418
T_4	.3740	1.9777	.3562	1.8504
T_5	.4037	1.9673	.3735	2.0381
T_6	.3957	2.1622	.3786	2.2518

Table 15

Bivariate Correlations of Pupil Size Change with Blood Volume Change During Cold Pressor

Time block	Control	Migraine
T_1	-.1416	.2826
T_2	-.1109	-.1333
T_3	-.0519	.0129
T_4	.1224	.0628
T_5	.0195	.0061
T_6	.1452	.1397

Figure 5
Blood Volume Change
During Cold Pressor

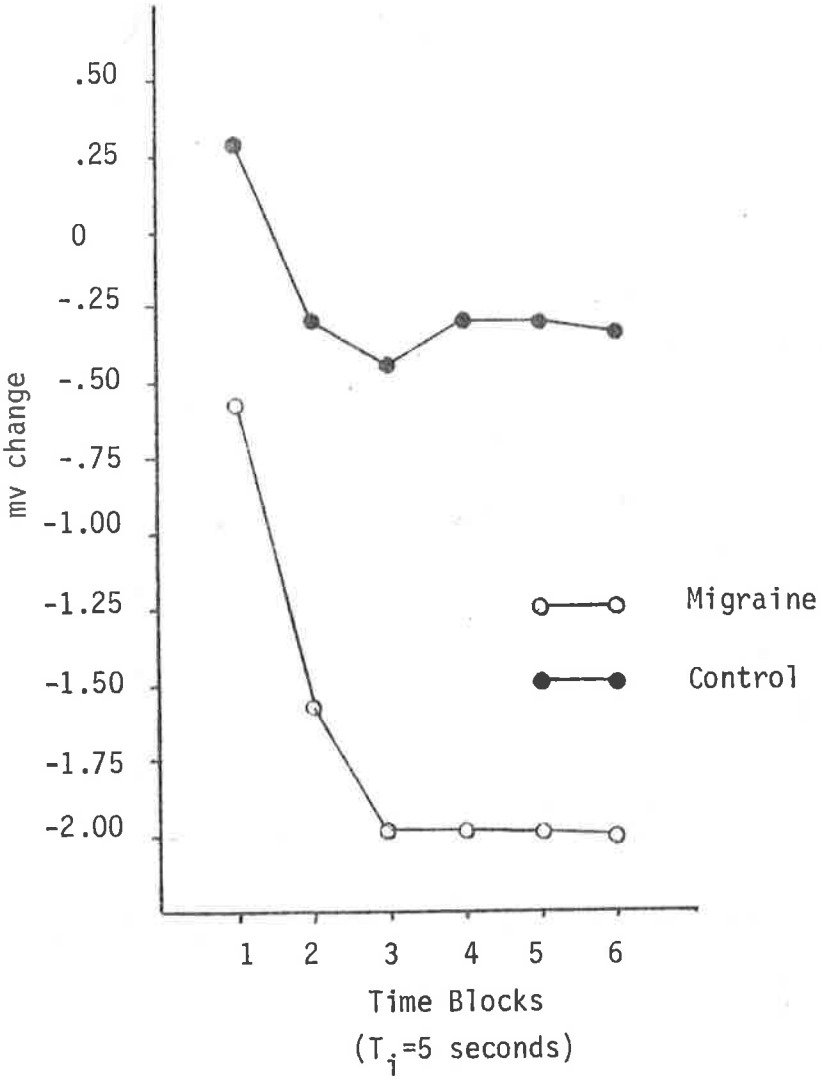


Table 16

Multivariate Repeated Measures Analysis of
Migraine vs. Control Blood Volume
Change During Cold Pressor

Source of variation	Degrees of freedom	F	p less than
Group	1,52	10.2007	.0024
Time blocks	5,48	9.8269	.0001
Group X Time blocks	5,48	.7616	.5820

15.8165, $p < .0003$; quadratic - $F(1,52)=11.5324$, $p < .0014$; cubic - $F(1,52)=12,1326$, $p < .0001$. Standardized discriminant function coefficients indicated that cubic and quadratic trends respectively contributed the majority of the variance to the Time main effect. (See Table 16 for the summary of the multivariate analysis of variance.)

During cold stress, then, the hypothesis that migraineurs would show greater overall vasoconstriction was supported. Vasoconstriction differences between migraine and control groups were significant from time block 2 through time block 6. Group profiles suggested that migraineurs constricted at a different rate over time blocks, however; the test of the Group X Time blocks interaction did not reach significance.

Pupil size change. Migraine and control group pupil size change profiles during the cold pressor are plotted in Figure 6. Neither the Group main effect nor the Group X Time blocks interaction reached significance in the multivariate analysis of the repeated measures (see Table 17). The Time main effect showed an F of 8.3884 with $p < .0001$. Step-down Fs and standardized discriminant function coefficients showed a strong linear trend for both groups taken together ($F(1,52)=37.8005$, $p < .0001$. In sum the hypothesis predicting that migraineurs would show greater pupillary dilation in response to the cold pressor was not supported. Both groups showed approximately equal dilation to the stressor followed by a linear decrease in dilation over time blocks.

Figure 6
Pupil Size Change
During Cold Pressor

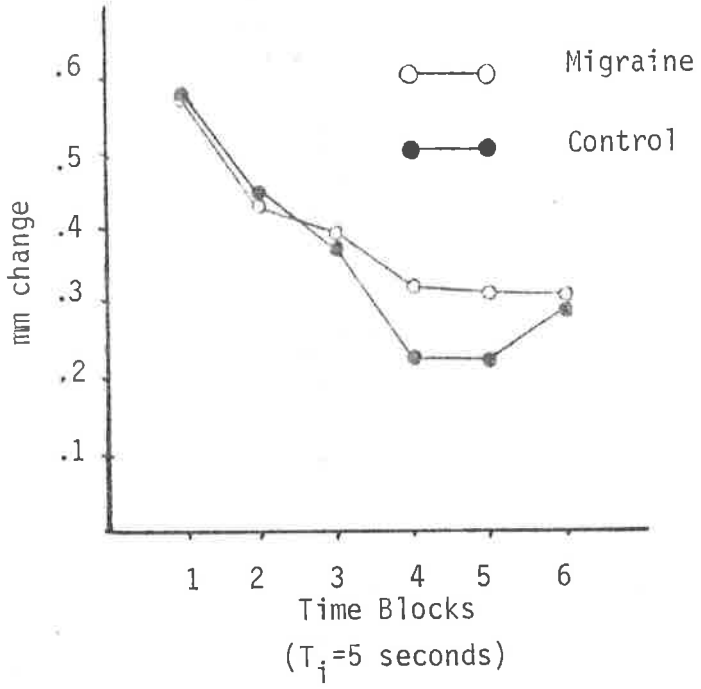


Table 17

Multivariate Repeated Measures Analsis of Migraine vs. Control Pupil Size Change During Cold Pressor

Source of variation	Degrees of freedom	F	p less than
Group	1,52	.1266	.7235
Time blocks	5,48	8.3884	.0001
Group X Time blocks	5,48	.5349	.7488

Post Stress

Migraine and control group means and standard deviations on pupil size change and blood volume change during the cold pressor recovery period are shown in Tables 18 and 19 respectively. No bivariate correlations of pupil size change with blood volume change reached significance for either group, again indicating the absence of a linear relationship between the dependent variables at each time block (see Table 20).

Blood volume change. Figure 7 shows migraine and control group blood volume change profiles over the cold pressor recovery period. The multivariate repeated measures analysis of variance showed significant Group ($F(1,52)=3.9137$, $p < .0533$) and marginally significant Time blocks ($F(1,52)=1.8293$, $p < .0793$) main effects. The test of the Group X Time blocks interaction did not reach significance (see Table 21).

Within the Group main effect, post hoc pair-wise comparisons employing Tukey's HSD procedure showed that migraineurs vasoconstricted more than controls from time block 1 through time block 4 (HSD=.89, $p < .05$). Within the Time blocks main effect, linear and quadratic orthogonal polynomials showed significant step-down Fs with the quadratic trend showing the highest standardized discriminant function coefficient (linear - $F(1,52)=6.5967$, $p < .0132$; quadratic - $F(1,52)=6.5444$, $p < .0136$. The quadratic trend within Time blocks indicated that the combined migraine-control blood volume change profile made one significant

change in direction. Inspection of Figure 7 suggested that this change involved vasodilation toward baseline from approximately time block 6 through time block 12. As was the case for blood volume change during the cold pressor, visual inspection of Figure 7 suggested the presence of a Group X Linear interaction. The Group X Linear univariate step-down F did reach significance ($F(1,52)=4.2132$, $p<.0452$), however; this result cannot be interpreted owing to the non-significant multivariate F for the Group X Time blocks interaction.

On post-cold pressor, then, migraineurs continued their during stress response pattern and vasoconstricted more than controls over the 12 time block period. The test of the Group X Time blocks interaction failed to provide clear evidence for a migraine vs. control difference in post stress recovery rate over time. The significant Group main effect appeared to be the result of migraineurs greater vasoconstriction during the cold pressor period.

Pupil size change. Migraine and control group pupil size change profiles are shown in Figure 8. The tests of the Group main effect and the Group X Time blocks interaction did not show significant F ratios (see Table 22), indicating no between group differences in level or rate of pupil size change post-cold pressor. The Time main effect reached significance ($F(11,42)=18.3730$, $p<.0001$) with step-down Fs and standardized discriminant function coefficients showing a strong linear trend ($F(1,52)=181.0240$, $p<.0001$). Thus, the hypothesis predicting that migraineurs would show slower post-cold pressor

Table 18

Group Means on Pupil Size Change and Blood Volume Change Post Cold Pressor

	Control		Migraine	
Time blocks	Pupil size	Blood volume	Pupil size	Blood volume
T_1	.2989	-.5056	.2956	-2.2148
T_2	.1719	-.6222	.2474	-2.4111
T_3	.0052	-.6404	.0289	-2.3593
T_4	-.1320	-.8130	-.1156	-1.8444
T_5	-.2078	-.8241	-.1933	-1.5704
T_6	-.1967	-1.0163	-.2230	-1.5296
T_7	-.2200	-.7222	-.3026	-1.2481
T_8	-.2367	-.6037	-.3415	-1.0704
T_9	-.3107	-.6370	-.3933	-.8778
T_{10}	-.3719	-.6400	-.4119	-.9296
T_{11}	-.3919	-.3926	-.4748	-.8741
T_{12}	-.3689	-.3204	-.6378	-.8778

Table 19

Group Standard Deviations on Pupil Size Change and Blood Volume Change Post Cold Pressor

	Control		Migraine	
Time blocks	Pupil size	Blood volume	Pupil size	Blood volume
T_1	.3948	2.1752	.3835	2.3777
T_2	.3016	2.1885	.3774	2.4063
T_3	.2881	2.0524	.4489	2.1161
T_4	.2666	1.7285	.4123	1.7723
T_5	.2570	1.5889	.3969	1.5701
T_6	.2535	1.8040	.3381	1.8055
T_7	.2793	2.1416	.3719	1.5373
T_8	.3185	2.0342	.3510	1.6040
T_9	.3098	1.8994	.3551	1.6223
T_{10}	.3295	1.8413	.3751	1.7950
T_{11}	.3528	1.9203	.3697	1.7819
T_{12}	.3665	1.8284	.7919	1.8341

Table 20

Bivariate Correlations of Pupil Size Change with

Blood Volume Change Post Cold Pressor

Time block	Control	Migraine
T_1	.1395	.1230
T_2	.2657	.1192
T_3	.0959	.2918
T_4	.1181	.2211
T_5	.2165	.0026
T_6	.1824	-.0899
T_7	.1434	-.1440
T_8	.1926	-.1756
T_9	.2000	-.0375
T_{10}	.2624	-.0093
T_{11}	.1935	.0089
T_{12}	.1401	-.0334

Figure 7
Blood Volume Change
Post Cold Pressor

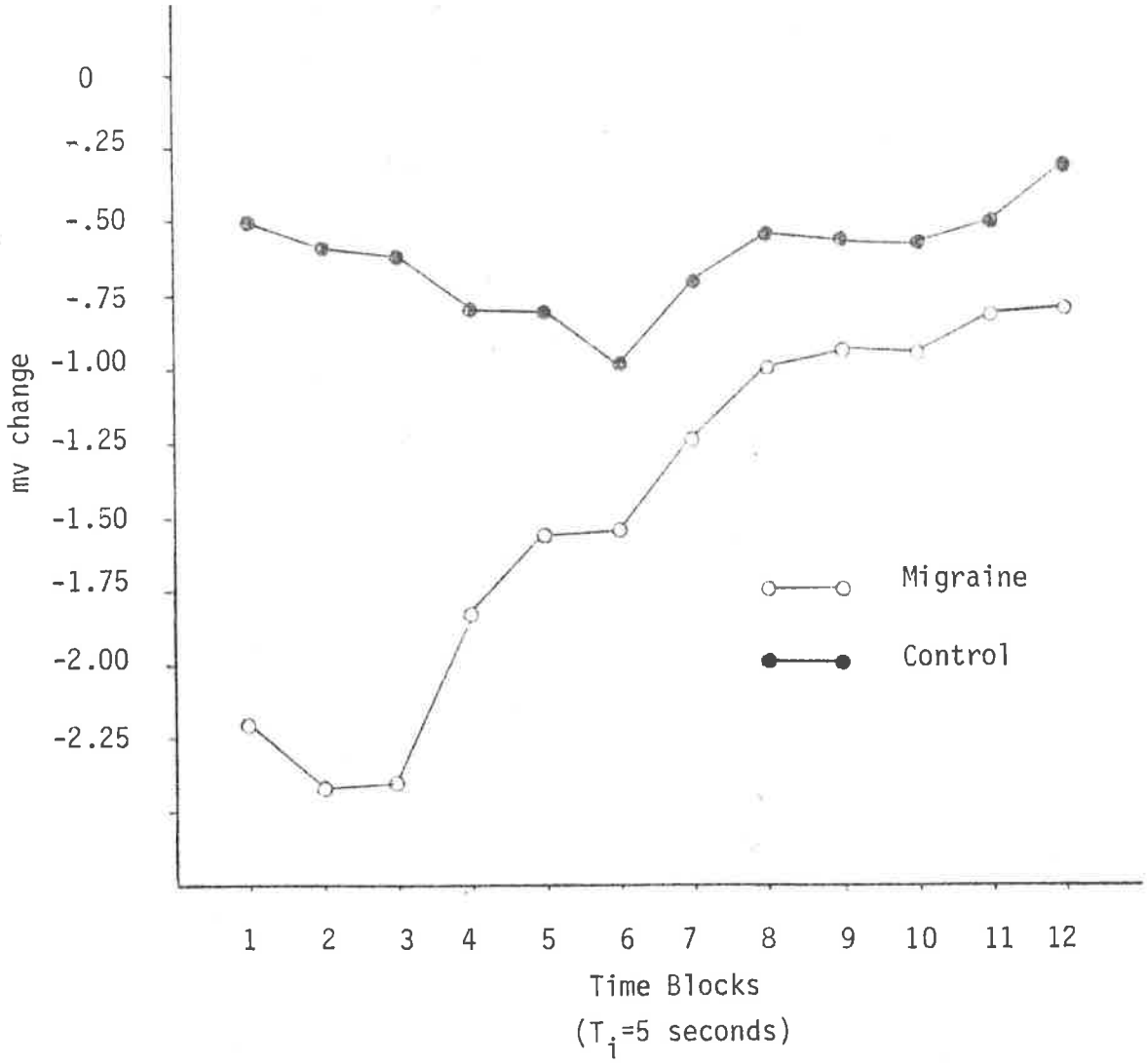


Figure 8
Pupil Size Change
Post Cold Pressor

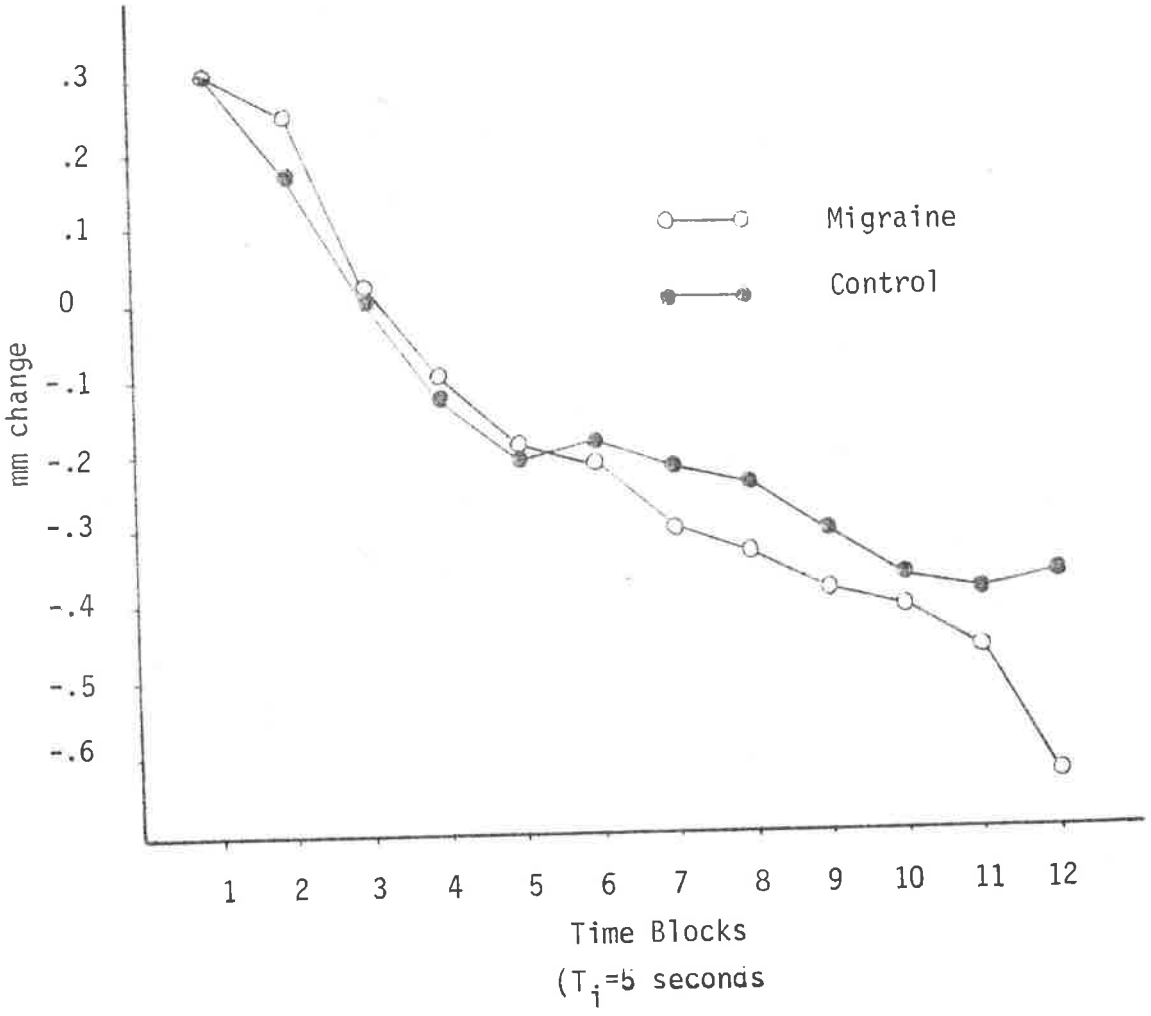


Table 21

Multivariate Repeated Measures Analysis of
Migraine vs. Control Blood Volume
Change Post-Cold Pressor

Source of variation	Degrees of freedom	F	p less than
Group	1,52	3.9137	.1533
Time blocks	11,42	1.8293	.0793
Group X Time blocks	11,42	1.0859	.3954

Table 22

Multivariate Repeated Measures Analysis of
Migraine vs. Control Pupil Size
Change Post-Cold Pressor

Source of variation	Degrees of freedom	F	p less than
Group	1,52	.3158	.5766
Time blocks	11,42	18.3730	.0001
Group X Time blocks	11,42	1.5525	.1493

recovery than controls on pupil size change was not supported. For both groups, pupil size decreased linearly throughout the recovery period. Figure 8 shows that the decrease was to levels below pre-stress baselines.

Experiment 3 - Pupillary Light-reflex

Non-stressed pupillary light-reflex and light-reflex during word-naming and cold pressor were recorded as pupil size in mm at one second intervals. Pupil size at the onset of the light stimulus was used as the first observation, followed by 6 during light stimulus observations. Stress-inhibition of the light-reflex was assessed using the difference between each subject's non-stressed pupil size and stressed pupil size at each time block. Group differences in stress-inhibition were tested using a 2 group X 7 time block multivariate repeated measures analysis of these difference scores.

Migraine and control group pupillary light-reflex means and standard deviations under non-stressed, word-naming, and cold pressor conditions are shown in Tables 23 and 24 respectively. Group profiles on these raw scores are shown in Figure 9. Migraine and control groups did not differ significantly on pre-light stimulus pupil size under non-stressed, word-naming, or cold pressor conditions.

Profiles of difference scores between stressed and non-stressed pupillary light-reflex for migraine and control groups under word-naming and cold pressor conditions are shown in Figure 10. Under word-naming, the multivariate analysis of repeated measures showed neither a significant Group main effect nor a significant Group X Time blocks interaction (see Table 25). As shown in Figure 10

both groups showed light-reflex inhibition during word-naming, however; neither the overall level of inhibition nor the rate of inhibition change over time was different for migraine vs. control groups. The Time main effect showed a significant $F(6,47)$ of 5.3502 ($p <$ .0003) with the quadratic trend showing significance ($F(1,52) =$ 16.0111, $p <$ .0014. The quadratic trend was also associated with the highest standardized discriminant function coefficient. Visual inspection of Figure 10a suggests that, for both groups taken together, stress inhibition of the light reflex was greatest at the beginning and at the end of the light stimulus period. The significant quadratic trend within Time supports this impression.

The multivariate analysis of variance for migraine vs. control group differences in light-reflex inhibition under the cold pressor yielded results similar to those under word-naming (see Table 26). Neither the Group main effect nor the Group X Time blocks interaction reached significance, again indicating neither overall level nor rate of change over time difference between groups. Although the non-significant Group effect precludes post-hoc level comparisons between groups, visual inspection of Figure 10 suggests that controls rather than migraineurs tended to show greater light-reflex inhibition. The Time main effect was significant with F of 2.4410 ($p <$ .0390). with significant step-down Fs on linear, quadratic, cubic, and quintic trends. Discriminant analysis showed the cubic trend to be the greatest contributor to the overall Time effect.

For Experiment 3, then, the effects of interest in terms of reflecting migraine vs. control differences (i.e. Group main effect and

Table 23

Migraine and Control Group Pupillary Light-Reflex Means under Three Conditions

	Control			Migraine		
Time blocks	Non-stress	Word-naming	Cold Pressor	Non-stress	Word-naming	Cold Pressor
Pre-stimulus	4.4630	4.8704	4.6300	4.3889	4.6407	4.6260
T_1	4.2719	4.6437	4.3667	4.2778	4.4241	4.3241
T_2	3.6789	3.9363	3.8426	3.7222	3.8796	3.7611
T_3	3.7511	4.0248	3.8441	3.8297	3.9444	3.8241
T_4	3.7926	4.1426	4.0056	3.9093	4.1889	3.8667
T_5	3.8604	4.2900	4.0537	3.8167	4.3130	3.9704
T_6	3.8656	4.3770	4.0222	3.8630	4.3556	3.9815

Table 24

Migraine and Control Group Pupillary Light-Reflex

Standard Deviations under Three Conditions

	Control			Migraine		
Time blocks	Non-stress	Word-naming	Cold Pressor	Non-stress	Word-naming	Cold Pressor
Pre-stimulus	.7658	.9091	.7038	.6620	.6059	.6970
T_1	.7912	.9780	.7979	.7927	.7192	.8497
T_2	.5866	.7979	.6496	.6564	.7235	.7648
T_3	.6097	.7586	.6361	.7271	.6440	.6669
T_4	.6332	.6850	.6158	.7956	.7495	.8106
T_5	.7248	.7108	.7715	.6618	.7428	.6447
T_6	.6414	.7264	.6321	.6374	.9962	.6935

Figure 9

Pupillary Light-reflex
Under Three Conditions

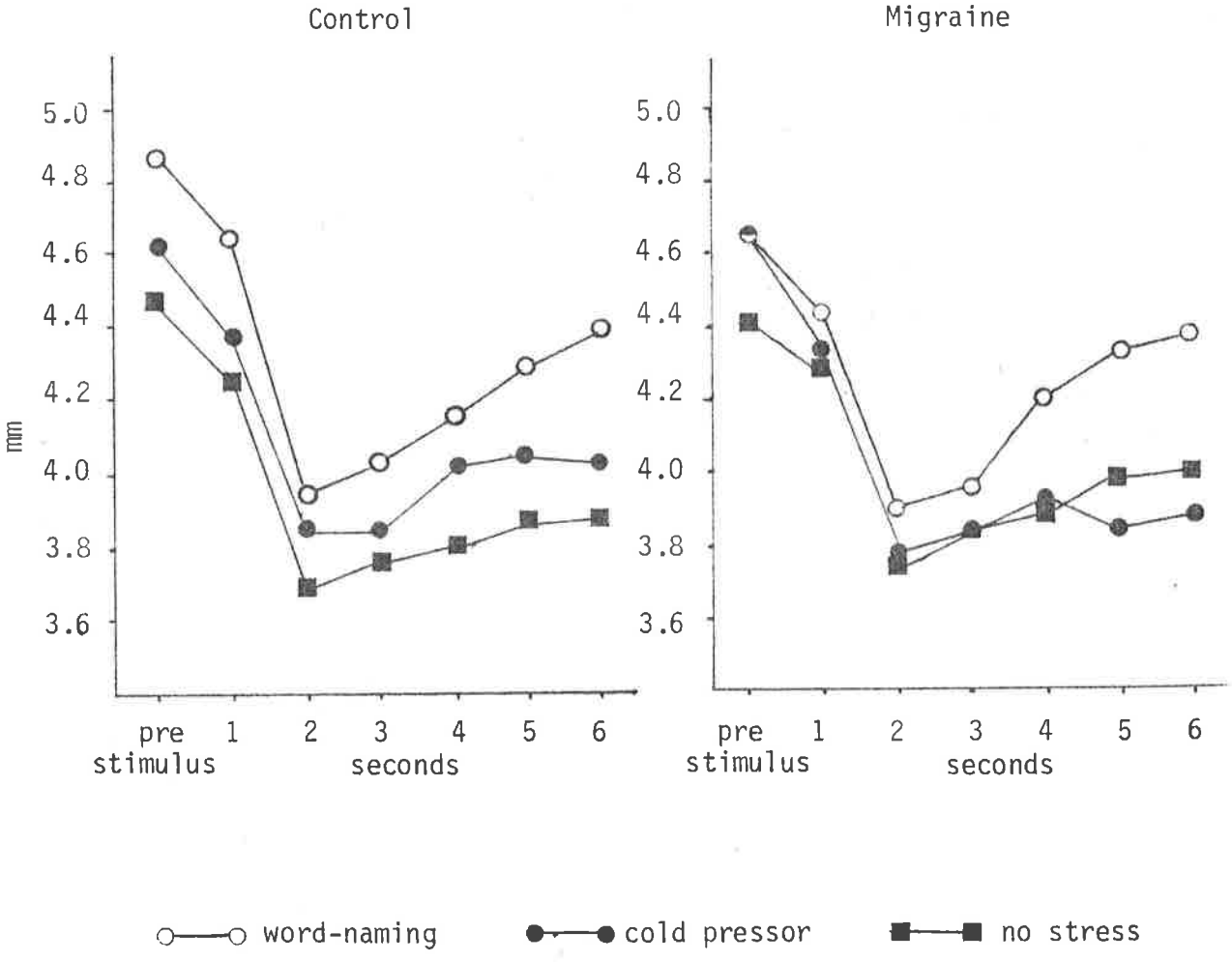


Figure 10
Light-reflex Inhibition
Under Three Conditions

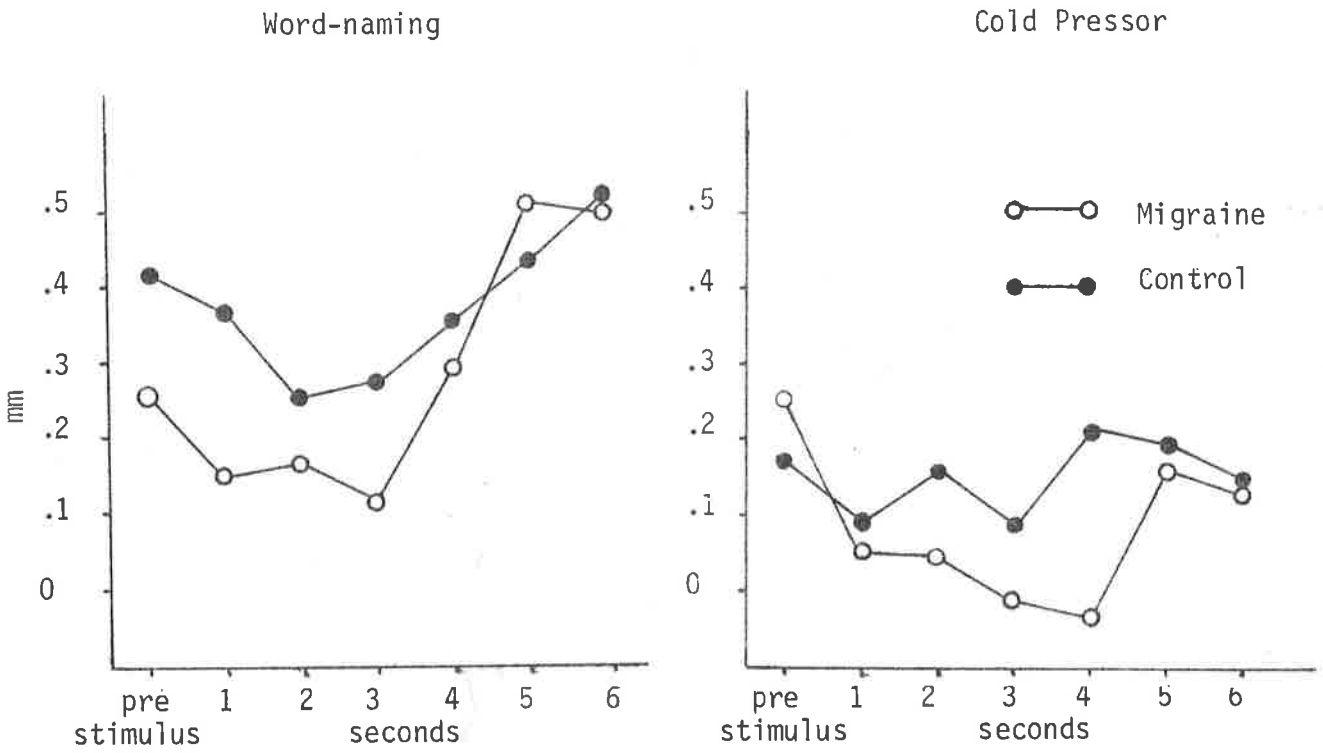


Table 25

Multivariate Repeated Measures Analysis of Migraine vs. Control Pupillary Light-Reflex Inhibition under Word-Naming

Source of variation	Degrees of freedom	F	p less than
Group	1,52	1.0518	.3099
Time blocks	6,47	5.3502	.0003
Group X Time blocks	6,47	1.4171	.2282

Table 26

Multivariate Repeated Measures Analysis of Migraine vs. Control Pupillary Light-Reflex Inhibition under Cold Pressor

Source of variation	Degrees freedom	F	p less than
Group	1,52	.7851	.3797
Time blocks	6,47	2.4410	.0390
Group X Time blocks	6,47	1.4127	.2298

Group X Time blocks interaction) failed to reach significance under both word-naming and cold pressor conditions. Hypotheses predicting greater stress inhibition of the pupillary light-reflex among migraineurs were not supported.

Personality Factors

Group Differences

Migraine and control group means and standard deviations on neuroticism, state anxiety, and trait anxiety are shown in Table 27. Bivariate correlations among these measures are shown in Table 28. Because the three personality measures correlated fairly highly, they were treated as a package and were submitted to a multivariate analysis. The multivariate test of group differences on the three variable package yielded a significant $F(3,50)$ of 2.6314 with $p < .0477$. Examination of the univariate Fs associated with each personality measure indicated that migraineurs showed significantly higher neuroticism and trait anxiety than controls. State anxiety did not show a significant difference between groups (see Table 29). Discriminant analysis was performed in order to determine the relative contribution of each variable to the overall multivariate F. Examination of the standardized discriminant function coefficients showed that trait anxiety was the most highly weighted variable in terms of distinguishing between migraine and control groups (see Table 29).

Accordingly, the hypotheses predicting that migraineurs would show higher neuroticism, state anxiety, and trait anxiety were partially supported. Migraineurs showed significantly higher neuroticism and trait anxiety than controls but they did not report feeling more

anxiety in the actual experimental situation (state anxiety). Statistical analyses showed that trait anxiety was the most powerful discriminator between migraine and control groups.

Personality Measures and Blood Volume Change

The finding that migraineurs and controls differed significantly on the package of personality measures justified further investigation of how personality factors might relate to physiological responses. Previously, migraineurs' blood volume change during word-naming and during cold pressor was shown to be greater than that of controls while no differences were found in pupil size change. Blood volume changes during word-naming and cold pressor were thus chosen as criterion measures and neuroticism, state anxiety, and trait anxiety were used as predictors in an analysis of covariance. A significant multiple R of predictors with criterion would indicate some predictability of blood volume responses from personality scores and would speak to the hypothesis of personality factors mediating physiological responses.

Before proceeding with the analysis of covariance, covariate regression slopes were examined for the assumption of equality in the population. The null hypothesis of no differences in regression hyperplanes was not rejected for both word-naming and cold pressor conditions, thus permitting the covariance hypothesis tests of predictive interest.

During word-naming, the regression analysis using the three predictor variables of neuroticism, state anxiety, and trait anxiety on the criterion of total blood volume change yielded a non-significant

Table 27

Migraine and Control Group Means and Standard Deviations of Three Personality Measures

	Control		Migraine	
	Mean	Standard Deviation	Mean	Standard Deviation
Neuroticism	9.852	4.204	12.444	4.677
State Anxiety	33.593	6.271	34.963	8.760
Trait Anxiety	33.370	5.982	38.852	8.926

Table 28

Correlation Matrix of

Personality Measures

	Neuroticism	State Anxiety	Trait Anxiety
Neuroticism	1.000		
State Anxiety	.577	1.000	
Trait Anxiety	.707	.593	1.000

Table 29

Univariate Fs and Standardized Discriminant Function Coefficients for the Multivariate Test of Three Personality Variables

Variable	F	p less than	Coefficient
Neuroticism	4.5897	.0369	.3580
State Anxiety	.4369	.5116	-.5610
Trait Anxiety	7.0269	.0107	.9718

multiple R of .2066 ($F(3,49)=.7281$, $p<.5402$). Only 4.27% of the between group variability could be accounted for by the package of personality variables. The analysis of covariance for during cold pressor similarily yielded non-significant results ($R=.1387$, $R^2=.0192$, $F(3,49)=.3203$, p .8107). Consequently, the hypothesis predicting that migraine vs. control group personality differences mediated or accounted for observed blood volume change differences was not supported under either word-naming or cold pressor conditions.

Diastolic Blood Pressure and Blood Volume Change

As reported earlier, sitting blood pressure was taken for all subjects prior to their participation in the experimental treatments. This was done to ensure that no hypertensives were exposed to the stressors of the treatments. It was found that migraineurs showed significantly higher diastolic blood pressure than controls. No hypotheses were forwarded concerning blood pressure differences between migraine and control groups, however; the possibility that diastolic blood pressure differences were related to group differences in blood volume change during word-naming and during cold pressor was investigated in a post hoc analysis of covariance. Total blood volume change during each stressor was used as the criterion and diastolic blood pressure was used as the predictor or covariate.

Under both word-naming and cold pressor conditions the F statistic for the test of parallelism of regression hyperplanes failed to reach significance, indicating that the assumption of equal regression slopes in the population was tenable. For word-naming, the correlation of the diastolic blood pressure covariate with the total blood volume change criterion was .4394 ($r^2=.1931$) with $F(1,51)=12.2061$

($p < .001$. Although this correlation reached significance it was not large enough to conclusively show that an important portion of blood volume variance could be accounted for by diastolic blood pressure differences. The comparison of the difference between the statistical test of the Group main effect before and after accounting for the diastolic blood pressure covariate provided some clarification. Before partialling out diastolic blood pressure, the test of the word-naming Group main effect reached significance with $F(1,52)$ of 4.1456, p less than .0469. The test of the Group main effect after covariate adjustment did not reach significance ($F(1,52)$= 1.0967, $p < .2999$.

The same analysis of covariance procedures were applied to the total blood volume change during cold pressor data. The correlation of the diastolic blood pressure covariate with the total blood volume change criterion was .4105 (r^2=.1685) with $F(1,51)$=10.3341, $p < .0023$. The test of the Group main effect before covariate adjustment yielded an $F(1,52)$ of 10.2007 with $p < .0024$. After covariate adjustment, the during cold pressor Group main effect remained significant with $F(1,51)$=4.2556 and $p < .0443$.

In sum, the analysis of covariance indicated that the migraine vs. control group difference on total blood volume change during word-naming did not hold its significance after adjustment for differences on the diastolic blood pressure covariate. In other words, diastolic blood pressure differences "explained away" group differences in blood volume change during word-naming. Even though the regression of total blood volume change on diastolic blood pressure was of approximately

the same magnitude for both word-naming and cold pressor conditions, the Group effect during the cold pressor was sufficiently large to remain significant after blood volume change means were adjusted for differences on the diastolic blood pressure covariate.

CHAPTER IV

Discussion

The present study investigated the hypothesis that migraine sufferers respond to stressful stimuli with excessive sympathetic outflow when compared to a group of subjects who do not suffer from migraine. Two dependent measures, digital blood volume and pupil size were used as indicators of sympathetic responsiveness in two stressful situations, word-naming and cold pressor. A third experiment investigated migraine versus control group differences in sympathetically mediated inhibition of the pupillary light reflex under the same two stress conditions of word-naming and cold pressor. Migraine versus control differences in state anxiety, trait anxiety, and neuroticism were examined as possible mediators of excessive sympathetic responsiveness to stress in migrainous subjects. An ancillary analysis of the relationship between diastolic blood pressure and blood volume responses to the stressors was performed in order to investigate any possible relationship between these two variables.

Physiological Responses to Stress

Blood Volume During Stress

Hypotheses predicting that migraineurs would show greater overall digital blood volume reduction than controls were supported during both word-naming and cold pressor conditions. Under word-naming, the migraine group demonstrated the expected response of increased sympathetic outflow as shown by digital vasoconstriction. For migraineurs, constriction was greatest during the first 30 seconds of word-naming, followed by a gradual return to baseline levels by the

end of the 1 minute stress period. Controls did not show significant vasoconstriction at any point during word-naming. The control group profile actually showed a slight dilation to above baseline levels (time blocks six through 12). Post hoc comparisons of migraine and control group blood volume means revealed that the groups differed significantly from time blocks two through seven. Migraineurs' early response to the word-naming stressor thus contributed most to the overall Group main effect. Migraineurs appeared to show signs of recovery from their initially high vasoconstriction levels following time block seven and no group differences were apparent following time block eight.

During cold stress, migraineurs again demonstrated the expected significant response of increased sympathetic outflow as shown by digital vasoconstriction. Controls also responded in the expected direction, however the magnitude of change for controls was small and not significantly different from baseline levels. Comparisons of migraine and control group means showed significant differences from time blocks two through six. Thus migraineurs showed greater vasoconstriction early in the cold pressor period and, as a group, they continued to show greater constriction throughout the stress period.

Overall then, group comparisons indicated that migraineurs, on the whole, showed the expected response of digital vasoconstriction in response to both stressors while the control group, on the whole, showed little or no response to either stressor. However, reliance solely on group profiles and group means gives the mistaken impression of response homogeneity within groups. It was not the case that

all migraineurs responded in the appropriate direction while no one in the control group showed the expected responses. Within the migraine group, 23 of 27 subjects showed vasoconstriction while controls were considerably more variable with 17 of 27 showing vasoconstriction in response to both word-naming and cold pressor. Migraineurs thus appeared to show a more uniform "readiness" to react to stress with the vasomotor response of digital vasoconstriction whereas controls were much more heterogeneous, the majority showing constriction but a large minority showing dilation.

Because photoplethysmographically measured blood volume responses provide only an index of change in blood volume, a migraine versus control group initial value comparison was not possible for this variable. The question of initial values would have been addressed had resting finger temperature been included in the dependent variable package however this procedure was not used. Other data from the current study as well as data presented by other researchers suggest that if an initial value difference had been operative, it would have acted to minimize or nullify the significant blood volume effects.

Werbach and Sandweiss (1978) found resting finger temperatures to be significantly lower among migraine sufferers than among other patient groups. Lower finger temperature suggests less blood flow and, accordingly, lower blood volume values. In the current study, resting diastolic blood pressure was significantly higher in migraineurs than in controls. All other circulatory factors held constant, higher diastolic blood pressure suggests lower initial blood volume levels in digital vascular beds. According to the Law of Initial Values (Wilder, 1957), lower initial blood volume values would result in less

blood volume reduction in response to a stressful stimulus. Thus, although the present study presented no data speaking directly to the question of migraine versus control initial blood volume values, related findings suggest that the peripheral vascular anomalies demonstrated by migraineurs were not invalidated by initial value differences. Furthermore, it is possible that the effects observed in this study were apparent despite a possible initial value bias against the observance of a significant effect.

Pupil Size During Stress

Hypotheses predicting that migraineurs would show greater overall pupillary dilation than controls in response to stress were not supported under either word-naming or cold pressor conditions. Effect sizes in terms of peak dilation were comparable to those observed by Janisse and Dumoff (1977) however no migraine versus control group differences in initial values or responses to stress were found.

During word-naming both groups showed prompt pupillary dilation which was maintained throughout the stress period however, group profiles were virtually indistinguishable from one another. Similarily, under cold pressor, both groups showed pupillary responses in the expected direction of dilation but neither the between group comparisons nor the group by time block interactions were significantly different. Examination of individual subjects' profiles also failed to differentiate migraine and control groups. Under word-naming, 23 of 27 controls and 24 of 27 migraineurs responded in the expected direction. During cold-pressor, all 27 controls and 23 of 27 migraineurs showed pupillary dilation.

Physiological Responses Post-stress

Blood Volume Post-stress

The hypotheses predicting that migraineurs would show slower post-stress recovery than controls on blood volume were not supported under either word-naming or cold pressor conditions. In terms of the statistical analysis, the effects of most interest, the Group by Time blocks interactions, did not reach statistical significance. The Group effect on post-cold pressor reached significance and will be discussed in the light of two possible confounds.

On post-word-naming the issue of stress recovery was essentially moot in that migraine and control group profiles ceased to differ significantly following time block eight of the during stress period. Migraineurs had recovered to their own baseline level and to a level not significantly different from controls by the end of the during stress period. For both groups, a kind of rebound vasodilation to above baseline levels was evident during the latter part of the recovery period. Had this rebound been exclusive to the migraine group, speculations might have been made regarding the "sympathetic overshoot" hypothesis of Sargent, Walters, and Green (1973). While migraineurs showed slight greater dilation above baseline post-stress the statistical test of the between group effect did not reach significance.

On post-cold pressor the Group by Time Blocks interaction also did not reach significance and hence no conclusions can be drawn regarding group differences in rate of stress recovery over time on blood volume change. While the overall Group effect did reach significance, two factors confound clear interpretation. The first factor concerns

the variability in the direction of controls' vasomotor responses during the cold pressor. As pointed out earlier, 10 of 27 controls showed vasodilation rather than the expected response of vasoconstriction. Combining these individual data into group means resulted in a during stress profile showing no significant vasoconstriction to stress for controls. Consequently, discussing post-stress recovery differences between migraine and control groups makes little sense when controls did not show significant blood volume reduction from which to recover. The second complicating factor involves differences in initial values at the beginning of the stress recovery period. Whereas controls showed virtually no vasoconstriction during stress, migraineurs showed strong vasoconstriction which was maintained throughout the stress period. At the end of the stress period and consequently at the beginning of the recovery period, migraine and control groups differed widely in terms of initial blood volume values. The test of the Group effect on post-cold pressor was thus not statistically independent of the significant Group effect during cold pressor. The large initial value difference was responsible for the significance found for the post-cold pressor Group effect.

Migraineurs did in fact recover from stress appropriately as shown by migraine and control group profiles being statistically indistinguishable from one another (following time block four of the post-cold pressor period).

Pupil Size Post-stress

As was the case during word-naming and cold pressor, migraine and control group profiles were not significantly different under both

stress recovery conditions. Post-word-naming, migraine and control groups had reached levels not significantly different from baseline after only 5 seconds of the recovery period. For both groups, a gradual linear constriction to below baseline was observed for the remainder of the recovery period. On post-cold pressor, both groups reached baseline levels after 15 seconds of the recovery period, followed by a linear constriction to below baseline levels. Thus, under both stress conditions and during both stress recovery periods there was no indication that aberrant sympathetic nervous system activity was observable in the pupillary responses of migraineurs.

Light-Reflex Inhibition

While experiments one and two of the current study investigated the question of migraine versus control differences in the largely adrenergic pupillary response to stress (Lowenstein & Loewenfeld, 1950; Loewenfeld, 1958), the third experiment addressed the more interactive question of whether differences in adrenergic-cholinergic balance were apparent when migraine and control groups were compared. It was hypothesized that stress inhibition of the pupillary light reflex would be greater in migraineurs than in controls when either word-naming or cold pressor were presented contiguously to the light stimulus. These hypotheses were formulated under the assumption that experiments one and two would show excessive pupillary dilation to stress in migraineurs. It would follow, then, that excessive dilation in response to stress would result in excessive inhibition of the light reflex. Given that neither word-naming nor cold pressor experiments showed aberrant pupillary dilation to stress in migraineurs it was not surprising that migraineurs did not show excessive pupillary light-

reflex inhibition under either word-naming or cold pressor conditions.

Under word-naming, both migraineurs and controls showed the expected elevation of the overall light-reflex curve however, neither the overall level of change in pupil size over non-stressed levels nor, rate of change over time, were different in the statistical comparisons of groups. Similarily, under cold pressor, both groups showed the appropriate elevation in the light-reflex curve but again neither level nor rate of response were different in the between group comparisons.

Autonomic Tuning in Migraine

The evidence presented thus far has shown that migraineurs responded to stress with excessive digital blood volume reduction in comparison to controls. These vasomotor abnormalities were apparent under both word-naming and cold pressor situations. On the other hand, data did not support the contention that pupillary responses to stress were aberrant in migraineurs. Dependent variable correlations were consistently low within both groups. These data fail to support the notion of a generalized ergotropic tuning as being characteristic of migraine sufferers (Gelhorn, 1970). It cannot, then, be assumed that the migrainous individual is constitutionally predisposed to react to stress with an indiscriminate, en masse sympathetic nervous system discharge as has been suggested by some authors (Lennox, 1960; Selby & Lance, 1960). Rather, the migraine sufferers exhibited greatest autonomic reactivity in a specific organ system, the vasomotor system. These data are more consistent with Lacey and Lacey's (1958) hypothesis of response specificity and Wolff's (in Dalessio, 1972) notion of somatic vulnerability. Migraineurs, individuals prone to a disorder of the

the vascular system, appeared to be "vulnerable" to exaggerated vascular responsiveness to stress, at least with respect to the peripheral vascular response of digital vasoconstriction.

Peripheral and Cerebral Blood Flow

Given data suggesting abnormal responsiveness to stress in the peripheral vascular structures of migraineurs it is now important to link peripheral vascular behavior to the cranial vascular responses thought to be instrumental in the initiation of migraine. The "sympathetic overshoot" hypothesis of Sargent et al. (1973) suggests that migraineurs respond to stress with exaggerated constriction of cranial and cerebral vascular structures. This constriction is thought to be sufficiently strong to induce cerebral eschemia which in turn launches a rebound vasodilation which seeks to "repay" the brain for lost blood flow. The dilation is excessive and results in the pain of migraine.

To date, no studies have directly addressed the question of cerebral vascular responses to stress in migraineurs, however recent evidence has suggested a similarity between peripheral and cerebral vascular behavior in migraineurs. Claghorn et al. (1981) and Mathew et al. (1980) monitored hemispheric and regional cerebral blood flow changes accompanying directional skin temperature self-regulation in migrainous and non-migrainous subjects. In the former, hand-warming was associated with increases in cerebral blood flow while hand-cooling was associated with decreases in cerebral flow. In the latter subjects, hand-warming and hand-cooling groups did not show differential cerebral blood flow changes.

Extending these observations to the findings of the present study, it does not seem unreasonable to suggest that the digital blood volume

reductions demonstrated by migraineurs in response to stress may have been accompanied by cerebral blood flow reduction. Further studies utilizing a stress paradigm similar to the current study but including cerebral blood flow changes as a dependent measure would clearly be fruitful in the elucidation of the relationship between stress responses and brain blood flow in migraine.

Diastolic Blood Pressure and Blood Volume

An ancillary analysis of covariance was performed to investigate the relationship between resting diastolic blood pressure and blood volume responses under word-naming and cold pressor conditions. The rationale for this analysis was two-fold. First, diastolic blood pressure and digital vasomotor responses are related in that they are both vascular in nature. Because migraine versus control differences were apparent on both variables, it seemed appropriate to pay further attention to whether a significant statistical relationship existed between the two measures. Second, practitioners and researchers in the area of migraine have long suspected a link between hypertension and migraine although to date no data have appeared in the literature to substantiate this speculation. Notwithstanding, the same beta-receptor blocking agents used in hypertension prophylaxis have been used with some success in migraine prophylaxis (eg. Wideroe & Vigander, 1974; McCann, 1982). A link between blood pressure differences and vascular stress response anomalies would suggest a possible relationship between these two disorders.

Statistical analyses showed that a relatively small but significant portion of the migraine versus control group difference in overall blood volume change was accounted for by the diastolic blood

pressure covariate. The significant Group effect on word-naming was nullified after adjustment for differences in diastolic blood pressure. Under cold pressor, the magnitude of the relationship between group differences in total blood volume change and diastolic blood pressure was approximately the same as under word-naming, however, the cold pressor effect, although reduced in size, maintained its significance. A positive relationship between diastolic blood pressure and blood volume reduction was thus confirmed under both stress conditions. These relationships were found even though higher diastolic blood pressure suggests lower initial blood volume values and, according to the Law of Initial Values (Wilder, 1957), less ability for the organ system to respond in the direction of further blood volume reduction.

With respect to the underlying mechanism of migraine, two speculations may be made on the basis of these data. First, higher diastolic blood pressure values suggest a resting state characterized by a generalized over-constriction of vascular structures. This over-constriction in the resting state may increase the potential for total vascular occlusion and blood flow stoppage in response to further strong sympathetic stimulation as in a stress situation. Secondly, these data suggest that migraineurs are vascular hyperresponders to stress, at least with respect to the peripheral vascular response of digital vasconstriction. As discussed previously, there is some inferential evidence that peripheral vascular behavior may have cerebral concomitants. Hyperresponsiveness to stress, coupled with higher potential for vascular occlusion and its consequent cerebral eschemia thus may result in the rebound vasodilation that causes the pain of

migraine.

The effect of beta-blockers may also be two-fold. Initially, they decrease vascular tone and consequently reduce the potential for serious reductions in blood flow. Secondly, phasic sympathetic vasoconstrictive responses to stress may be reduced. These two effects taken together reduce both tonic and phasic vascular responses and the potential for vascular occlusion and the consequent rebound vasodilation that results in migraine pain.

Tonic and phasic effects of beta-blocking agents in migraine prophylaxis would be further clarified by further research. Tonic, effects would be addressed by comparing resting blood flow levels in peripheral and cerebral vascular structures under drug and no drug conditions. Secondly, a study using a stress paradigm similar to the one presented here could compare phasic responses to stress in migraineurs under both drug and no drug conditions. Recording of both peripheral and cerebral vascular responses would provide exciting and hopefully fruitful data.

Personality

Two related questions regarding the role of personality factors in migraine initiation were addressed in the present study. The first question asked whether group differences between migraineurs and controls were apparent on self-report measures of state anxiety, trait anxiety and neuroticism. Second, given significant personality differences, was there a statistically significant relationship between group differences on the package of personality measures and group differences in physiological responses to the experimental stressors?

The first hypothesis received partial support. The migraine versus control group comparison on the multivariate package of personality variables was significant with trait anxiety and neuroticism showing significant univariate differences. Migraineurs thus reported feeling more anxious in general (trait anxiety). As well, they reported more characteristics consistent with neuroticism, or in Eysenck's words, an individual predisposed to "emotional overresponsiveness" (Eysenck & Eysenck, 1964). No differences were found with respect to how anxious the groups felt in the actual experimental situation (state anxiety).

It is important to note that migraine versus control group differences were statistically significant but not necessarily psychologically significant in the sense of demonstrating psychopathology in migraineurs. Migraineurs' trait anxiety levels were not significantly different from the norms given for the general population by Spielberger et al. (1970). Similarily, mean neuroticism levels for migraineurs were lower than norms for various neurotic, psychotic, or normal standardization groups.

The analyses concerning the relationship between personality differences and differences in digital vasoconstriction responses to stress failed to show significant effects. The correlation of the personality variable package with overall blood volume response under both stressors was low and the covariance analyses both showed that a significant portion of blood volume response group difference was not accounted for by group differences in personality. Consequently, although the present study found statistically significant personality differences similar to those found by other researchers (eg. Henryk-gutt and Rees, 1973),

the hypothesis that migraineurs' personality constellations mediate or account for exaggerated vascular responsiveness to stress forwarded by Wolfe (in Dalessio, 1972; Mitchell & Mitchell, 1971) was not supported.

These results were not surprising considering the controversial status of the literature on the relationship between migraine initiation and personality. Even if large differences in personality were apparent, the majority of the evidence in psychophysiology fails to show that particular psychological states are specific to particular patterns of physiological responses (Greenfield & Sternbach, 1972). In that the personality differences observed between migraine and control groups in this study were small and given that migraineurs did not score within clinically significant ranges, the expectation that these small differences would be significantly related to physiological responses was clearly unreasonable. On the basis of these data, practitioners and researchers in the area would be well advised to at least suspend judgment regarding the existence of a particular psychopathological profile as being either characteristic of the migraine sufferer or instrumental in the initiation of migraine.

Implications for Treatment

The results of the current study speak to both theoretical and practical issues with respect to the psychophysiological treatment of migraine. The theoretical base for biofeedback treatments which claim that migraineurs respond to stress with excessive sympathetic nervous system activity received support, at least with respect to the peripheral vascular response of digital vasoconstriction. In terms of practical

issues, the literature concerning the outcome of various biofeedback treatments, relaxation regimes, and hypnotic interventions remains too plagued by methodological difficulties to provide a clear picture of differential effectiveness among these techniques (Adams, Feurstein, & Fowler, 1980). Most of these treatments appear to show positive effects, at least in the short term. Blanchard, Theobald, Williamson, Silver, and Brown (1978) have suggested that the final common pathway for positive treatment effects under varying procedures is the development of the ability of the migraineur to relax and consequently reduce both tonic and phasic sympathetic reactivity. With respect to the current study, migraineurs clearly showed differences from controls in digital blood volume reduction in response to stress. The procedurally simple and relatively inexpensive biofeedback index of finger temperature provides a reasonable analogue to digital blood volume and thus appears to be both a practical and theoretically appropriate method of increasing migraineurs' abilities to control tonic and phasic responses to stress and consequently reduce migraine susceptibility.

CHAPTER V

Summary and Conclusions

Researchers have suggested that the vasoconstriction phase of the migraine sequence is the result of aberrant autonomic responsiveness to stressful stimulation (eg. Sargent, Walters, & Green, 1973). The migrainous subject is thought to respond to stress with excessive sympathetic outflow. To date, no data directly addressing the question of whether migrainous and non-migrainous subjects differ with respect to their responses to stress have appeared in the literature.

In the present study, the question of migraine versus control group differences in sympathetically mediated responses to stress was addressed in the following manner. Twenty seven migrainous and 27 non-migrainous women matched on relevant variables were recruited through newspaper advertisements and radio announcements. All subjects participated voluntarily. Digital blood volume and pupil size, two responses known to be primarily sympathetically mediated, were used as dependent variables under two stress conditions, word-naming and cold pressor. Stress recovery was also monitored following each stress condition. A third experiment examined whether migraine versus control group differences in stress inhibition of the parasympathetic pupillary light-reflex were apparent when migraine and control groups were compared. This was done by presenting light stimulation to the pupil contiguously with the stress stimuli of word-naming and cold pressor.

The data indicated that migraineurs' overall blood volume reduction was significantly greater than that of controls during both word-

naming and cold pressor conditions. There were no clear indicators of post-stress recovery differences between groups. Migraine versus control group differences were not found with respect to during stress or post-stress pupil size responses. As well, group differences in pupillary light-reflex inhibition were not found. These data were interpreted as supportive of the notions of response specificity (Lacey & Lacey, 1958) and somatic vulnerability (Wolff, in Dalessio, 1972). Migraineurs, individuals prone to a disorder of the vascular system, appeared to be "vulnerable" to exaggerated responsiveness to stress with respect to the peripheral vascular response of digital vascular constriction. Data presented by other researchers (Claghorn et al., 1981; Mathew et al., 1980) have suggested that peripheral vascular anomalies shown by migraineurs may have cerebral vascular concomitants. A potentially fruitful avenue for further research would be the examination of cerebral vascular responses to stress in migrainous subjects.

The serendipitous finding that migraineurs showed higher diastolic blood pressure than controls led to further analyses which indicated a significant positive relationship between diastolic blood pressure and digital vasoconstriction responses to stress in migraineurs. These data were viewed as suggestive of a relationship between migraine and hypertension and possibly supportive of the current medical treatment strategy of prescribing daily prophylactic doses of beta-recorder blocking agents in cases of severe migraine. Additional research aimed at clarifying the effects of beta-blockers on vascular responses to stress in migraineurs should be pursued.

A second group of hypotheses considered the proposition that per-

sonality factors mediate excessive sympathetic responsiveness to stress in migraineurs (Mitchell & Mitchell, 1971). Migraine and control groups completed self-report measures of trait anxiety, state anxiety, and neuroticism. The relationship between group means on these measures and differences in physiological responses to stress were examined by means of analysis of covariance. Migraineurs were significantly higher on trait anxiety and neuroticism but differences were not found with respect to state anxiety. Even though migraineurs scored significantly higher than controls on trait anxiety and neuroticism, their mean levels were not clinically significant. Furthermore, group differences in anxiety and neuroticism were not significantly related to group differences in digital vasoconstriction responses to stress. Given these data, the question of cause and effect confusion also raises itself. Migrainous women may have scored higher on these personality measures as a result of their migraine experiences rather than vice versa. Practitioners and researchers in the area of migraine are cautioned against assuming that a particular psychopathological profile is either characteristic of the migraine sufferer or instrumental in the initiation of migraine.

Both theoretical and practical issues for the biofeedback treatment of migraine were addressed by the outcomes of the current study. The theoretical premise of finger temperature biofeedback treatment received support; migraineurs reacted to stress with excessive sympathetic nervous system discharge with respect to the peripheral vascular response of digital vasoconstriction. From the practical standpoint, the frequently used biofeedback index of finger temperature re-

presents a reasonable analogue to the finger blood volume measure used in the current study and, as such, targets an organ system that has been shown to be anomalous in migrainous subjects.

Footnotes

[1] Considerable variability in the amount of light stimulation necessary to achieve one millimeter of pupillary constriction was noted within migraine and control groups. Rheostat settings were noted for all subjects. Subsequent statistical analysis showed no significant difference between migraine and control group light intensity levels ($\bar{X}$ migraine = 4.70, $\bar{X}$ control = 4.60).

[2] Discriminant function coefficients are similar to standardized regression weights in a multiple regression equation. Each coefficient represents the relative importance of a given variable with the effects of all other variables partialed out (Tatsuoka, 1970).

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Appendix A

Newspaper Advertisement Requesting Volunteer Migraineurs

Female migraine sufferers are needed for a study of the nature of migraine headache. This research is being conducted at the Psychology Department of the University of Manitoba. Interested individuals may obtain more information by calling G. Bednarczyk at 489-7042 or 474-9338.

Appendix B

Newspaper Article Requesting Volunteer Migraineurs

George Bednarczyk, a graduate student at the University of Manitoba department of psychology is doing research on the cause of migraine headaches. His PhD thesis: Differences in Pupillary and Peripheral Vascular Responses to Stress in Migrainous and Non-migrainous Subjects.

He would like to get in touch with women who have migraine headaches to take part in his research. They must be older than 18, pre-menopausal, and have a diagnosis of migraine from a medical doctor. The research project takes place in June and is not painful.

Interested women with migraines should phone George at 489-7042 or 474-9338.

Appendix C

Radio Announcements Requesting Volunteer Migraineurs

Re. Public Service Announcement Request

The following public service announcement is self-explanatory. I would be grateful if your station could air the request during the week of May 22 through May 25. Thank you for your co-operation.

> Female migraine sufferers are needed for a study of the nature of migraine headache. This research is being conducted at the Psychology Department of the University of Manitoba. Indviduals interested in volunteering approximately one hour of their time may obtain more information by calling G. Bednarczyk (pronounced Bednarchick) at 489-7042 or 474-9338.

Sincerely,

G. Bednarczyk

Appendix D

First Contact Information Form

Name_____Age_____Phone#_____

Main inclusion characteristics:

frequency/month_____

unilateral_____throbbing_____

nausea_____vomiting_____

family history_____

ergot response_____

M.D. diagnosis_____M.D. name_____

purpose elaborated?_____

control strategy response_____

glasses_____B.C. pills_____

pregnant_____medications_____

Headache Questionaire (M)

Name_____ Age_____

Medical History

Have you ever been diagnosed as having any of the following:

hypertension_____seizures_____

systemic illness_____circulatory disorder_____

Have you ever experienced any severe head injury? If so specify nature of injury _____

Medication History

What drugs have you taken for migraine in the past??

_____

What drugs are you currently taking for migraine?

_____

What was the last (most recent) medication you took for migraine?

_____ When did you take this medication?_____

Headache Characteristics

Are you aware of any triggers for your migraines?

_____

_____

Are you aware of any cyclical causes of you migraines? (e.g. weekends, holidays, menstruation etc.)_____

_____

Do you get any warnings before a headache is about to begin?_____ Describe any warning signs_____

_____

On the average, how long do your migraines last?_____hours

About how often a month do you get migraines _____times

Do you experience more than one kind of headache?_____

When was your most recent migraine?_____

When did your last menstrual period begin (date)_____

List any drugs of any kind taken in the last 48 hours

_____

Are you currently on birth control pills?_____

Appendix F

Headache Questionaire (C)

Name_____Age_____

Medical History

Have you ever been diagnosed as having any of the following:

hypertension_____seizures_____

systemic illness_____circulatory disorder_____

Have you ever experienced any severe head injury? If so specify nature of injury_____

Do you experience headaches of any kind?_____

Are your headaches usually on one side of your head or on both sides?_____

Are your headaches ever accompanied by nausea and/or vomiting?_____

Is your headache pain throbbing or steady?_____

Do any of your blood relatives experience migraine headaches? If so, who?_____

How often per month do you get headaches?_____

What drugs have you taken in the past to relieve a headache? (please list)_____

What drugs do you currently take for a headache? (please list)_____

How long do your headaches usually last?_____hours

When was the last time you had a headache?_____

List any drugs taken for your last headache_____

_____

List any drugs of any kind taken in the last 48 hours.

_____

When did your last menstrual period begin (date)_____

Do you experience more than one kind of headache?_____

Are you currently on birth control pills?_____

Appendix G
Experimental Instructions

This experiment will consist of five separate procedures. You will be given detailed instructions before each procedure. For now, I'll briefly describe the whole experiment to you. The first procedure will involve naming words that begin with a certain letter of the alphabet. You will be given a letter and then you will hear a series of tones. Your task will be to name a new word that begins with that letter after you hear each tone. The second procedure is called the cold pressor. This task involves having your left hand placed in a bucket of ice water for 30 seconds. After the cold pressor task is completed we will examine the response of the pupils of your eyes to light. A small light will be shone into your right eye and the changes occuring in your pupils will be recorded. For the fourth task we will repeat the word-naming procedure but this time the light will be shone in your eye during the time you are naming words. The last procedure will be to repeat the cold pressor task. The light will again be presented during the time that your hand is in the water. The experiment will be completed at this point.

Throughout these procedures we will be recording the activity of the pupil of your left eye and the blood flow activity of the middle finger of your right hand. In order for us to get accurate recordings it is very important that you keep your head and right hand very still during all procedures. It is also important that you keep your eyes wide open while we are measuring your pupil. So try and keep your eyes a bit more open than normal during the tasks and try to blink as little as possible. To keep your eyes correctly positioned a chart has been placed on the front wall. Focus your eyes on the centre of this chart during all procedures.

Are there any questions before we begin the first procedure?

(Pause for questions)

The first procedure is called word-naming. After I have alligned

Appendix G (contd.)

the pupillometer and you are comfortable you will hear a series of five tones that sound like this (3 sample tones presented). Following the fifth tone you will hear a letter and a word beginning with that letter. You will then hear the same tone you heard before. Your task will be to name a new word beginning with that letter after you hear each tone. The tone will be repeated every few seconds and you will name a new word beginning with the same letter after each tone. Don't use any proper nouns or people's names and don't worry if you happen to miss a word. Just continue naming new words after each tone.

Here is an example of what the word-naming task sounds like.

(5 tones)...."e" as in "eat"
(tone) "earth"
(tone) "end"
(tone) "eagle"

Now let's do a brief trial run to make sure you understand the instructions. Are there any questions before we begin the trial run.

(Pause for questions)

Let's begin. (Subject not yet positioned at pupillometer)
(5 tones)...."s" as in "sand"
(tone) _____
(tone) _____
(tone) _____

Now we are ready to begin the word-naming task. I will now position you at the pupillometer. (pause) Remember to remain as still as possible and to keep your eyes wide open as you are naming words. Also remember to focus on the centre of the target in front of you. You will hear the word "relax" after the word-naming task is completed. Do not mave when you hear the word "relax" but remain in place so we can monitor your responses for another few minutes. Remember, the first letter will be presented after you hear the first five tones.

Appendix G (contd.)

(Subject positioned at pupillometer)

(5 tones)...."b" as in "boy"

(12 tones, each 5 seconds apart)

"Relax" (60 second post-stress period)

The next part of the experiment will be the cold pressor. After you have been positioned at the pupillometer, I will place your left hand in a bucket of ice water. Your hand will remain in the water for 30 seconds after which it will be removed from the water, wrapped in a towel, and placed on the arm of the chair. Stay in place as you did before so we can continue to monitor your responses for a few minutes. During the time that your hand is in the water you will again hear tones. This time I would like you to say one letter of the alphabet after you hear each tone. Start with "a" and go on to "b", "c", etc. As before you will hear the five quick tones just before I place your hand in the water. Remember to remain as still as possible and to also remember to focus on the centre of the target in front of you. Are there any questions before we begin?

(Pause for questions)

Let's begin.

(5 tones)....Hand placed in water for 30 seconds with tones presented 5 seconds apart.
Hand removed from water, wrapped, placed on arm of chair.
60 second post-stress period.

In the next part of the experiment we will examine your pupillary light-reflex. A small light will be shone into your right eye several times until I have determined the exact amount of light necessary to produce a certain amount of response. The light shouldn't be too bright but don't hesitate to let me know if you find it unpleasant. You are not required to say anything for this part of the experiment. Are there any questions before we begin.

(Pause for questions)

Appendix G (contd.)

Be sure to focus on the target and keep still and keep your eyes wide open during this procedure. Blink as little as possible.

(Experimenter establishes light-reflex value)

The next part of the experiment will be the same as the first word-naming task. You will hear five quick tones followed by a new letter. You will then hear the tones that signal you to name a word that begins with the letter that has been given. The only difference from the first word-naming procedure is that while you are naming words, the light will be shown into your right eye for a few seconds. Are there any questions before we begin.

(Pause for questions)

Let's begin.

(5 tones)...."m" as in "man"

(5 tones, each 5 seconds apart. Light stimulus presented)

The last part of the experiment will be a repetition of the cold pressor task. This time you do not have to say anything while your hand is in the water. The light will be turned on again at some point while your hand is in the water. As before, focus on the target, keep still, keep your eyes wide open, and blink as little as possible. Are there any questions before we begin?

(Pause for questions)

Let's begin.

(5 tones)....Hand placed in water. Light stimulus presented.

Hand removed from water, wrapped, placed on arm of chair.

This completes the experiment. Thank you very much for your participation.