INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

U·M·I

University Microfilms International
A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor, MI 48106-1346 USA
313/761-4700 800/521-0600

Order Number 9417476

Pupillary response to noxious electrodermal stimulation in varying conditions of intensity, delay and information

Iglesias, Irmgard Isabel, Ph.D.

City University of New York, 1994

Copyright ©1994 by Iglesias, Irmgard Isabel. All rights reserved.

U·M·I
300 N. Zeeb Rd.
Ann Arbor, MI 48106

PUPILLARY RESPONSE TO NOXIOUS ELECTRODERMAL STIMULATION IN VARYING CONDITIONS OF INTENSITY, DELAY AND INFORMATION

by

Irmgard I. Iglesias

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

1994

c1994

IRMGARD I. IGLESIAS

All Rights Reserved

This manuscript has been read and accepted for the Graduate Faculty in Psychology in satisfaction of the dissertation requirement for the degree of Doctor of Philosophy.

Jan 31 1994
Date

Gad Hakerem
Gad Hakerem, Ph.D.
Chair of Examining Committee

February 1, 1994
Date

Arthur Reber
Arthur Reber, Ph.D.
Executive Officer

W. Crawford Clark, Ph. D.

Philip Ramsey, Ph. D.

Wilma Winnick, Ph. D.

Supervisory Committee

The City University of New York

Abstract

PUPILLARY RESPONSE TO NOXIOUS ELECTRODERMAL STIMULATION IN VARYING CONDITIONS OF INTENSITY, DELAY AND INFORMATION

by

Irmgard I. Iglesias

Adviser: Professor Gad Hakerem

The pupillary response to noxious and non-noxious electrodermal stimulation at four intensity levels was studied in 24 paid volunteers, under conditions of information about intensity, information about delay, and after four, five, eight and nine second delays.

Pupil diameter size was recorded every 20 milliseconds during a three second period, starting at stimulus onset. Ratings of the pain experience using a 12 item scale were also recorded.

As expected, higher intensity noxious stimuli resulted in significantly larger changes in pupil size and higher intensity ratings. Both measures accurately reflected the stimulus intensity levels. The pupillary response was concluded to be an accurate indicator of the pain experience and a viable method in pain measurement.

Information about intensity and, or, delay was expected to influence the subjects' perception of stimulus intensity and to result in smaller responses because of the association between uncertainty and anxiety. Shorter delays were expected to result in smaller responses because of their association with better predictability.

Neither Delay, nor Information about Intensity or Delay, nor Order resulted in significant differences. However, a relative chronicity effect of Intensity Information was suggested because responses at the initial sessions were in the opposite direction as those of latter sessions.

The lack of significant differences due to Delay was explained in part by an information processing component believed to contribute to pupil size increases following short delays. Hypothetically, these increases offset the larger pupil dilations expected after longer delays.

Discriminability and response criteria were obtained from pain ratings data through Signal Detection Analysis. Discriminability was significantly higher when low intensity pairs of stimulus intensities were compared, and response criteria were significantly lower when high intensity pairs were compared. Neither Delay Information, nor Intensity Information nor Delay were found to significantly affect these responses. Further post-hoc analyses on sex reflected some subtle differences on these measures but due to uneven sample sizes data are inconclusive, but suggestive.

Conclusions arrived at from pupillary data were consistent with discriminability data , adding validity to the use of pupillometry in pain research.

Acknowledgements

In the course of carrying out this study, I have come in contact with many who have offered me, not only their time and knowledge, but also, and most importantly, the opportunity to see much beyond the confines of this work. I would like to thank all, though I can only recognize a few individually.

I wish to thank my adviser, Dr. Gad Hakerem, who guided me wisely along the various stages of this work, for transmitting to me his enthusiasm about the pupil, for long hours of arguing with the computer until it finally did what we wanted it to do, and especially, for his patience and support over the years.

I also wish to thank Dr. W. Crawford Clark for sharing with me valuable insights on his vast knowledge of Pain; Dr. Wilma Winnick and Dr. Philip Ramsey, for their valuable advice on all aspects in the process of analysis and interpretation of facts; and Dr. Malvin Janal, for his help in performing SDT analyses. These were done at the Mental Health Clinical Research Center of the New York State Psychiatric Institute.

My thanks also to Mr. Sirio Alvarez Cruz, programmer at the University of Puerto Rico Centro de Servicios de Computación Académica; and to the University of Puerto Rico Medical Sciences Library staff.

Posthumous thanks to Dr. Samuel Sutton, whose bright light, shining at the initial stages of this work, is still remembered; and to Maurice Rosengarten, who engineered the electrical stimulator and was crucial in the experimental set-up.

Very special thanks to Dr. Richard E. C. White, Faculty Research Adviser at the Queens College Academic Computer Center, who taught me dedication with no other reward than the enjoyment of a challenge and the discovery of a solution.

Finally, and most especially, thanks to my husband, Ramón Figueroa, and my children, Luis and Nicol, from whom I robbed valuable time so I could work on the completion of this study. I dedicate this work to them.

Table of Contents

page

List of Tables

List of Figures

List of Appendices

Introduction

The experience of pain is universal. It can be induced by a wide variety of stimuli, and is followed by easily identifiable changes in behavior, such as vocalizations and attempts to escape. It can be accompanied by autonomic signs such as perspiration and changes in heart rate. Recognition by the subject is unequivocal. Yet, the experience of pain, so obvious and common to all, is an elusive clinical phenomenon.

Pain has been defined traditionally as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage" (Manheimer, 1984, p.80). Obviously, "unpleasant" and "emotional" are not quantitative evaluations, and, even if "degrees of unpleasantness" and "emotionality" were quantifiable, there would still be ample room for subjective interpretation. This lack of objectivity precludes an exact measurement of the experience of pain.

Our access to this experience is through the sufferer's judgement of its intensity and threat to tissue integrity. But there exists a dissociation between the presumed intensity of the noxious stimulus and the subject's reaction to it. According to Clark, "...pain is paradoxical in the extent to which the presumed intensity of the noxious stimulus (amount of apparent damage) is dissociated from the subjective or behavioral reactions to it. The report of pain, particularly chronic pain, is less veridical than reports about hearing, vision or touch, in which the response can be predicted quite exactly in most instances once the intensity of the stimulus is known." (Clark, 1992) Pain may not necessarily be accompanied by tissue damage, or, may not be present when in fact there is tissue damage. Further, a noxious stimulus of a given intensity may not necessarily produce an equally intense response in different individuals, or even in the same individual at different times. The inability to predict the sufferer's report of pain when the intensity of the noxious stimulus is known is based upon this dissociation.

Important distinctions have been recognized between "pain" and "nociception", and consequently, between "suffering" and "pain behavior", that clarify some of these issues. Fordyce (1988) defines nociception as the input of noxious stimulation on specialized nerve endings through A-delta and C fibers on to the central nervous system, signifying that aversive events are occurring. Pain, which he says is commonly confounded with nociception, is the sensation that arises from nociception but it may also arise centrally in the absence of peripheral stimulation. Nociception may be perceived, in which case pain is felt (sensed), or it may not be perceived, in which case there is no pain.

Suffering, Fordyce (1988) continues, is an affective response which may or may not be observed, that is triggered by nociception, pain or other aversive events. Pain behavior is the set of observable actions taken by those who experience nociception or pain, e.g., crying, wincing, writhing, withdrawal from the noxious stimulus, etc.

The dissociation between magnitude of injury, or intensity of stimulation, and the response to it, can then be uderstood by variations in the amount of suffering triggered, and the role of central processes that determine and modulate the perception of nociception and the response to it. The latter, according to these distinctions would constitute both suffering and pain behaviors.

Since suffering is not easily measured, it is pain behavior that is essentially the basis of pain measurement and made equivalent to pain response, of which it is only a part. These pain behaviors are usually socially adaptive and motivated, and include the report of pain. Such behaviors are intimately related to the reflexive actions designed to insure survival, and to the autonomic changes that facilitate these actions. Social learning and conditioning may, to a certain degree, influence these reflexive behaviors. An infant can modulate crying according to perceived consequences. Crying in public may be repressed by the adult, but despite social learning, wincing and crying in public may become unavoidable at times. The pain response thus varies, depending at the same time on social learning and specific circumstances, and does not necessarily correlate with the intensity of the noxious stimulus or event.

Individual differences in pain detection thresholds (the minimum intensity at which a stimulus begins to be labeled as painful), and intra-individual threshold variability, defy traditional methods of pain measurement. This is so even when physical conditions in the laboratory, as well as the psychophysical characteristics of the stimuli, are controlled and kept constant.

These difficulties in measurement have induced some scientists like A. Brodal to question the classification of pain among the other senses by saying: "The central processes related to pain perception appear to be extremely complex. It may indeed be misleading to consider 'pain sensibility' a sensory quality of a kind similar to, for example, tactile and joint sensibility. This is suggested especially by the fact that pain sensations are far more closely linked with emotion than any other sensation, a well known experience from daily life." (Brodal, 1981, p.126)

Research on the human temperature sense, for example, has yielded data suggesting that the required temperature range for maximum discharge of "warmth" fibers is between 38 and 43 degrees centigrade and between 16 and 27 degrees centigrade for "cold" fibers. This allows for fairly predictable responses to temperature changes in human subjects (Brodal, 1981).

By contrast, mean thresholds obtained for (noxious) radiant heat stimulation vary by as much as 166 mcal/sec/cm2, and an individual's threshold range can be as large as 302 mcal/sec/cm2 (Clark, 1969a). This is too wide a spectrum to allow reliable prediction of pain responses.

The ability to predict based on cause and effect relationships is one of the hallmarks of science. This can be done with a fair amount of accuracy in some sensations, such as hearing and vision, but not pain. To place the "sense of pain" in the realm of science requires the investigation of factors that interact with the known stimulus parameters. It is a valid scientific assumption to say that with the eventual knowledge and control of these factors, the measurement, and most importantly, the control of pain, is possible. It is the aim of this investigation to contribute to the further evaluation of psychological variables affecting the pain experience, and to examine the viability of an alternate method of measurement in the assessment of pain.

Mechanisms of pain transmission

The receptors for the pain sensation are believed to be free nerve endings. There are no specific nociceptors since there is multiple overlap on pain sensitive tissue. For example, fibers serving temperature, touch and pain sensibility in one region may converge on the same peripheral nerve which in turn overlaps with adjoining nerves serving the same region (Clark, 1992).

It is now believed that the pain impulse is transmitted by thinly myelinated A-delta fibers (conveying sharp, well localized,rapidly conducted pain impulses), which are modality specific, usually to intense mechanical stimulation. Smaller unmyelinated C fibers are also involved (conveying dull, poorly localized, slowly conducted pain impulses, usually from intense heat or cold, strong mechanical stimulation and irritant chemicals).

These fibers of primary afferent neurons converge in the dorsal horn of the spinal cord. Here they contact second order neurons of the spinal cord. At this level, impulses from pain afferents converge with other peripheral input, as well as with somatomotor, autonomic and descending central nervous system (CNS) impulses. They are integrated and transformed (inhibited or facilitated) here, and relayed on to the thalamus. Some of these second order neurons, especially those in the phylogenetically older nociceptive system, first send axons to the reticular formation and periaqueductal gray, and then to the thalamus. Third order neurons in the thalamus project fibers to the somatosensory cortex areas I and II, as well as other areas of the cortex (limbic system and prefrontal areas). The somatosensory cortex is said to be related to the sensory-discriminative dimension in the pain experience, and the limbic and prefrontal areas to the motivational-emotional dimension (Clark, 1992).

Two major pain pathways have been recognized: the newer spinothalamocortical, which is associated with brief, well localized pain, and the older spinoreticulothalamic tract, associated with chronic, diffuse pain (Clark & Hunt, 1971). Integrity of the thalamus vis a vis other cerebral structures seems to be the only requirement for pain to be experienced, although the participation of other structures, such as the hypothalamus, limbic system and neocortex in the pain experience indicates that other sensory inputs, attention, and emotion, have a role in the pain experience. Projections to the limbic system appear to be implicated in emotional defensive aspects of pain-related behavior, and projections to the parietal cortex in the processing and discrimination of the pain sensations (Clark & Hunt, 1971).

Pain modulation at the spinal cord level can take various forms. Direct stimulation of primary nociceptive afferents such as in acupuncture or in trans-cutaneous electrical nerve stimulation (TENS) inhibits spinothalamic neurons that transmit pain. That is, one form of noxious stimulation can inhibit the transmission of another (Melzack, 1991).

Non-noxious stimuli on large A-beta fibers can also inhibit transmission of pain sensations. This is reflected in the common occurrence of relieving pain by gentle touch, rubbing, and temperature stimulation of an injured area.

Descending impulses are another modulatory mechanism that are closely related to the cognitive and emotional factors that defy prediction of pain report based on stimulus intensity. A complex network of connections between limbic and prefrontal areas with the thalamus, responsible for an extensive system of descending fibers that can inhibit or facilitate nociceptive transmission at the dorsal horn level, has been confirmed (Clark, 1992).

Within this context are the psychological factors that seem to affect the subjective evaluation of the noxious stimulus. These factors can be grouped into three broad categories -- cognitive, emotional and sensory -- although they are highly interrelated. Cognitive factors include information and beliefs one has regarding the pain report, which may be obtained through learning experiences, instructions or suggestion, among others. Emotional factors include the aversion one may have towards pain, or towards a particular situation or stimulus one perceives as potentially harmful. The level of anxiety and expectancies regarding the stimulus, including its relative immediacy or delay, are also emotional factors. Sensory input that can increase arousal or distract attention from the noxious stimulus can also influence the perception of pain. The input of these factors are centrally processed and can result in descending impulses that modulate the pain experience.

In addition, there are endogenous and non-opioid analgesic systems localized at the brain stem level, which are activated naturally upon exposure to noxious stimulation. Electrical stimulation of the periaqueductal gray produces analgesia to noxious stimulation. This analgesic effect appears to be mediated by serotonin containing fibers from the raphe nucleus to the spinal cord. According to Grau (1987), higher neural processes can also activate these analgesic systems as well as block them by maintaining or displacing an aversive event from working memory.

The Gate Control theory of pain as proposed by Melzack and Wall (1965) has waxed and waned in the course of the various findings in pain research. Current neurophysiological advances have confirmed the role of the descending impulses discussed above. Other influences by local neurons, nociceptive and otherwise, have also been found to facilitate or inhibit ascending nociceptive fibers (Clark, 1992). Although some specific concepts have been disproven, the original basic hypothesis that pain "gates" open and close at the dorsal horn level has in general been supported.

To summarize: a sensory message about a noxious stimulus can traverse through several alternate routes in the nervous system. This is subject to the influence of several central processing centers as well as of several analgesic systems in the brain which can modulate the sensation. The panorama is one in which several pain transmission and pain blocking systems interact, while long-term social learning as well as circumstances present at the moment of stimulation combine to produce a unique pain experience each time. This is the basis for the subjectivity of the pain experience and the relative unreliability of the response to noxious stimuli.

Measurement of the pain experience

It is of interest to both clinician and scientist to be able to evaluate the pain experience accurately in order to test the efficacy of pain treatment procedures and analgesic drugs. A good number of pain measurement methods have been devised. Most are based on the method of limits which involves stepwise increases in stimulus intensity to establish a minimum intensity at which pain is first reported and a maximum intensity at which withdrawal from the stimulus occurs or is requested.

In magnitude estimation procedures the subject is asked to estimate the intensity of the stimulus according to a given ratio. Sternbach's (Echternach, 1987) pain estimate method is one such procedure in which a number scale from 0 to 100 ("the suicide point") is used. Further, verbal estimations attempt to use similar ratio scaling with varying verbal descriptors. Visual analogue scales use a 0 to 100 mm line in which points in the line correspond to ratings of increasing value similar to Sternbach's number scale. However, conflicting and inconsistent results, and extremely unreliable, wide ranging thresholds are obtained with these methods, making it impossible to set standards (Echternach, 1987).

Can there be an objective measure of a subjective phenomenon?

Although in the philosophical sense this would seem like an impossible endeavor, scientists have attempted to measure subjective phenomena with some degree of success. Feelings like anxiety, depression, fear and elation, to name just a few, have been measured by first being defined operationally as an overt response believed to reflect the feeling. It is possible to then measure the response more discreetly than the overall feeling.

Scales have also been designed that include verbal or numerical descriptors that reflect levels of the feeling, as judged by an observer or by the subjects themselves. In this way measurement units are applied to what in reality is a continuous phenomenon, but which is now made more amenable to scientific investigation.

Another approach towards measurement has been to analyze the phenomenon in its parts, each by a different measuring tool. For example, indices like heart rate, motor responses, vocalizations, etc. have been used to assess the physiological components. Evaluation through rating scales, questionnaires or other tests deemed appropriate have been used to measure the subjective components.

Another approach has been that of Signal Detection Theory (SDT) which has attempted to measure pain by separating its components, but, without using different measurement tools. SDT takes a single response from which it then derives the components, or rather, a mathematical representation of them.

SDT has been applied to pain perception studies since the 1960's, and has addressed quite successfully some of the problems encountered by traditional methods. It postulates that these methods confuse pain thresholds with the sensory component of the pain experience and thus cannot explain wide fluctuations due to nonsensory factors. According to SDT, thresholds are not pure indicators of sensory sensibility because they are influenced by subjective biases. Thresholds are considered to be perceptual judgements which reflect both the subject's decision processes and their sensitivity (Clark & Yang, 1983).

SDT assumes that the pain experience has an objective sensory component and a subjective emotional component which can be separated and measured accurately. The neurosensory component, d', is an index of discriminability and reflects the functional state of the (nociceptive) sensory system. A high d' reflects a subject's greater ability to distinguish between stimuli of varying intensities, while a low d' reflects lower discriminability (associated presumably with duller neural activity and relative insensitivity to noxious stimulation).

The subjective component, Lx, or the response criterion, is an index of the subject's response biases. It is an attitudinal parameter in that it reflects the subject's readiness, or reluctance, to label a stimulus intensity as "painful" depending on the social demand characteristics of the situation. A high Lx indicates that the subject is not willing to classify a sensory experience as painful until it is unquestionably so in his/her own mind. A low Lx indicates that the subject is more likely to report pain more often and at lower stimulus intensities. This refers to the traditional detection threshold.

The subjective component also includes tolerance thresholds, or the highest level at which the subject is willing to accept stimulation without withdrawal. The response criterion depends on the perceived social value of a response, which would bring acceptance or embarrassment, and which is molded individually and influenced by the various subjective factors mentioned above.

Neither pain detection nor pain tolerance is purely neurosensory, as demonstrated by Clark and Goodman (1974), since both of these can be altered simply by the experimenter's instructions while leaving sensory discriminability unchanged. Clark (1969b) questions the notion of detection thresholds as "lower limits of sensitivity" since these limits can be altered by subjective factors, and even in the absence of stimulation subjects have yielded false affirmative responses.

The reduction of d' corresponds to the attenuation of the amount of neurosensory information reaching higher centers (Clark & Yang, 1983). The correctness of SDT in pain measurement is based on the fact that analgesic drugs reduce or dull neural activity mediating pain, while they also reduce the ability to discriminate between intensities (Clark & Goodman, 1974). If d' is reduced by a treatment condition, it is assumed that less information about the stimulus is reaching the higher processing centers. The subject has increasing difficulties distinguishing stimulus from noise. This is assumed to be a result of decreased sensory input, or reduced neural activity, which ameliorates the intensity of the sensation. If d' remains constant after administration of a treatment condition, neurosensitivity of pain fibers is assumed also to be unchanged, and the treatment probably has not produced analgesia.

Clark and Yang (1983) caution against equating decreased d' with analgesia in every instance, despite the high correlation that exists between the two as the basis of the SDT assumption concerning pain. As the intricacies of pain mechanisms are uncovered this correlation may not necessarily always stand, and ultimately, may only be just that, a correlation, and not two inexorably linked phenomena.

The two parameter analysis of SDT enables one to quantify the components of the pain experience isolating a "relatively pure" measure of sensory sensitivity. With it one can determine which, if any, of the components reflect a treatment effect, i.e., whether pain responses obtained are the result of a true change in sensory sensibility, or merely a change in the response criterion due to anxiety, suggestion, or other subjective influences (Clark, 1969a).

SDT is thus useful in evaluating the effectiveness of analgesics as well as of other procedures used for pain relief. Theoretically it has proven quite useful in clarifying issues such as the sex, age and ethnicity differences often obtained in pain studies. It has been used to demonstrate that no sensitivity differences could be supported when the data were subjected to SDT analysis, and that the differences reported could be accounted for instead by changes in response criteria (Clark & Yang, 1983). Similarly, it has been used to evaluate the role of the various subjective factors that appear to influence pain ratings.

Subjective factors in the pain experience

The early literature on pain control, despite methodological problems, sheds some light on the relative importance of subjective factors affecting the perception of pain. Concentrating on surgical and chronic pain patients, they set the basis for later more rigorously controlled laboratory work applying SDT analysis. A brief review gives an idea on the role of such factors as learning, information, anxiety, and delay on the perception of pain and the modulation of the pain response.

A. Learning. Society imposes demands on its members who, over time, adapt to these demands and incorporate them as cultural make-up. The response to pain appears to be influenced by this kind of social learning. In Spanos, Cross and Watson (1987) among others, men reported less pain than women, suggesting a gender difference in pain sensitivity. However, Clark and Mehl (1971) and Clark and Goodman (1974) found identical pain discriminability in men and women, suggesting equal sensitivity. What they did find was a difference in the willingness to report pain and in their responsivity to suggestion instructions. Socially it is more acceptable for women (as the "weaker sex") to feel more and tolerate less pain. In fact, when sensitivity and reporting biases are evaluated separately by SDT analysis, it is found that only the latter reflects a gender difference.

Further, although Chapman and Jones (1944), among others, obtained higher pain thresholds for subjects of increasing age, it has been determined recently that age does not necessarily bring about a change in pain sensitivity, but rather a higher criterion for reporting pain. Clark and Mehl (1971) speculate that individuals adapt to their chronic pain over the years. They learn to cope with it more effectively and as adults progressively treat pain more stoically than as children, thus their higher tolerance thresholds.

Older studies on ethnicity concluded that there are differences in pain sensitivity among different nationalities and races. However, it has been found that social learning biases pain reporting differentially. It has also been reported that subjects who come from a different ethnic group than the experimenter tend to show higher pain tolerance thresholds (Wolff & Langley, 1968).

Clark and Clark (1980) reported higher pain thresholds following electrical stimulation among Nepalese subjects than among Western controls, despite equal sensory pain discriminability (d'), as demonstrated by SDT analysis. They concluded that a cultural difference accounted for a higher criterion in reporting pain among the Nepalese (despite equally functioning sensory systems).

The motivation to respond to social demand or challenge is acquired through learning. Kanfer and Goldfoot (1966) found that subjects who were instructed to watch the clock with the purpose of extending as much as possible the tolerance for a noxious stimulus, were more tolerant than those told to simply pay attention to the noxious stimulus in order to report on it accurately. The implicit challenge in the experimenter's instructions to the first group was apparently taken up and resulted in an increase in tolerance thresholds.

Social norms and expectations result in specific patterns of behavior. As members of a cultural or social group, we tend to act in ways acceptable to that group, rather than risk embarrassment or ostracism. This tendency to conform was described by Orne (1962) as the influence of "social demand characteristics". If the demand characteristics of a situation change, the expected pattern of behavior also changes, showing that such behavior is learned, not biologically determined. This is what happens when individual, social or cultural norms are challenged or covertly criticized, as was the case in the above and the following study.

Minority group subjects, who were told that they were unable to stand pain as compared to a majority group, actually increased their tolerance significantly (Wolff & Langley, 1968). The alleged majority group's greater tolerance for pain appears to have presented a challenge to the minority group who responded by exersizing greater stoicism than culturally expected of them.

These studies suggest that indeed pain tolerance cannot be considered a stable sensory quality of individuals or of ethnic groups. Rather, it appears to be a learned response acquired over time through participation in a socio-cultural environment, and, something that can be altered if social demands are altered.

B. Information. The positive effect of information on pain relief has been well established. Information can be conveyed in the form of knowledge about the noxious stimulus or about circumstances surrounding the painful event. It can also be conveyed in the form of suggestion. Suggestive information can be subtle, as in the placebo effect, or quite overt, as when specific instructions are imparted to subjects. Hypnosis is an extreme form of suggestive information where the consciousness of the subject is altered. It too has been proven to affect the experience of pain.

Being informed about a noxious stimulus has been associated with reductions in the autonomic response to pain. Lykken (1959) reported that the galvanic skin response (GSR) to noxious electric shock was reduced when preceded by a warning tone, compared to GSRs after unexpected shock. He claims many subjects volunteered that the shock felt less strong when previously informed (warned) about it. Unless the reduced GSRs are attributed to the tone itself, it appears that this index of pain, unreliable as it may be, reflected the effect of information on the impact of the noxious stimulus. Although it cannot be said that the intensity of the sensation was reduced, the GSR reflected a reduction of some dimension of the pain experience.

Egbert, Battit, Welch and Bartlett (1964) reported that surgical patients who received information regarding the nature of post operative pain required less narcotic medication than controls. It cannot be determined from this study whether these patients experienced less pain, or simply less "anxiety" as the authors speculate. Objectively, however, information enhancing the patients' appraisal of the experience contributed to the attenuation of a specific pain response: the demand for relief.

Similarly, Andrew (1968) reported a decrease in recovery time in patients who had been prepared prior to surgical procedures with information about the forthcoming operation and recovery. The authors suggest that the information helped reduce the patients' anxiety to make pain more tolerable thus facilitating the process of recovery.

Jones, Bentler and Petry (1966) provided subjects with information regarding the intensity and time of onset of an electrical stimulus. Reduction of uncertainty proved to be a powerful positive reinforcement as suggested by instrumental responses requesting such information as a function of degree of uncertainty.

Greater tolerance for pain was obtained by Tursky (1974) in subjects who received more information regarding the nature of the noxious stimulation with electric shock. Informed subjects' pain reports required higher intensities than those of uninformed subjects.

Johnson (1981), and Anderson and Masur (1983) obtained lower "distress" reports when the information provided was towards expecting higher levels of pain. The authors gave information about onset, duration, intensity, and sensory qualities of noxious events and were able to minimize the distress shown by patients undergoing invasive medical and dental procedures. Actual pain measurements were not taken.

Information prior to noxious stimulation is thus reported to reduce distress, facilitate recovery and increase tolerance, but, is a noxious stimulus really less painful when forewarned? A review by Tan (1982) suggests that preparatory information given as a cognitive coping strategy has been generally effective in reducing anxiety but that data on pain attenuation per se are not convincing since pain ratings were either not taken, or, when taken, were not found to be lower as a result of information.

Another angle of investigation was Wallace's (1985) manipulation of surgical patients' expectations of pain. She varied the level of intensity as well as the direction of the pain, by telling some patients they should expect high levels when in fact they would be receiving lower levels, and told others to expect low levels when they would be receiving higher levels. Patients expecting high levels and getting low reported less distress, while patients expecting low and getting high reported higher distress.

Wallace (1985) challenges the existing "clinical wisdom" hypothesis based on simple suggestion concerning the effect of information and cognitive processing. Her theory states that the direction of the dicrepancy between the information and actual intensity determines attenuation or exacerbation of pain. On the other hand, the "clinical wisdom" hypothesis claims that the pain experience following information results in higher tolerance for pain regardless of discrepancy. Wallace's results do not disprove either theory because the direction of the discrepancy did not directly produce changes in pain reports. It did however alter the amount of distress experienced by subjects, pointing to the role of anxiety as the mediating factor in information studies.

According to the above-mentioned studies, informed patients ask for less narcotic medication, or complain less, thus facilitating recovery. Similarly, informed subjects score lower on distress tests and tolerate higher stimulus intensities. Thus, although the sensation of pain may not have been altered (SDT was not performed), the information provided affected the subject's appraisal of the noxious stimuli or events and resulted in changes in the response to pain. Although information could not be attributed an analgesic effect, it appears that an attenuation of the emotional component of the experience can result in changes of pain-related behavior.

Information provided as a suggestion has also been very effective, especially when conveyed by a person in position of authority. Covert suggestion in the form of specific instructions to subjects is another example of information affecting the perception of an incoming stimulus.

Clark and Goodman (1974) studied the effect of instructions on pain detection and pain tolerance. They found that by simply imparting instructions tending to either lower or raise pain detection and tolerance criteria these could be altered in the direction expected. They were in fact able to get subjects to start reporting thermally induced very faint pain sensations at higher levels of stimulation (than at their presuggestion experimental sessions), and to tolerate intense thermal stimuli at higher levels as well. But again, based on SDT analysis, an analgesic effect of suggestion was not supported because the subjects' d' was unchanged from presuggestion to suggestion sessions.

The efficacy of an analgesic drug has been shown to be effectively augmented by suggestive information. A fixed amount of nitrous oxide, given to subjects who were told it had high analgesic potency, was a more efficient analgesic than when no information was given. The subjects in the suggestion group actually reported lower pain levels to a fixed intensity of the noxious stimulus than controls (Dworkin, Chen, Schubert & Clark, 1984).

The placebo effect is another form of suggestive information. Clark (1969a) administered a placebo described to subjects as a "potent pain-killer" while presenting them with radiant heat stimuli. He found through SDT analysis that although the placebo did not alter the subjects' d', it did raise their response criteria, that is, the intensity at which they called the stimulus "painful" was higher. The mechanism of action of the placebo effect is unclear, but it appears that the

the way in which the subjects perceived the experimental situation, now demanding more tolerance from them. Believing that the thermal stimulus should be less painful because of the analgesic, would make a pain response potentially embarrassing. This induced the subjects to act as expected by complying to the covert suggestion. According to the SDT analysis performed, an analgesic effect of the placebo was not supported, since the subjects' d' remained unchanged while response criteria increased, presumably because of the demand characteristics of the experimental situation.

Findings similar to Clark's were obtained by Farthing, Venturino and Brown (1984), who conveyed suggestive information to their subjects (that their hands were numb) in a cold pressor test. They obtained a reduction of pain ratings among a group of highly hypnotizable subjects though not in a low hypnotizable group (hypnotic trance was not induced).

Marino, Gwynn and Spanos (1989), also with a cold pressor task, obtained a decrease in reported pain through suggestion. Their subjects were told to imagine a pleasant experience. It was then suggested to them that this strategy would (or would not) work given a personality study performed on them. The positive (will work) suggestion group produced larger pain report reductions, i.e., these subjects developed more stoical attitudes than the negative group.

Finally, in hypnosis, the strongest form of suggestive information, a case study is noteworty (Kaplan, 1960). During hypnotic trance, a subject was told that his left arm was insensitive, but that he could write with his right hand. During the trance, he was pricked repeatedly on his left hand. He complained in writing with his right hand, but after the trance ended he could not remember being hurt at all. Obviously, the sensation was transmitted and acted upon, but somehow repressed from conscious thought. Hypnotic analgesia was therefore not supported, although suggestive information appeared to affect the perception of pain at the conscious level.

It was established earlier that information about an impending noxious event resulted in changes in pain related-behavior, mediated apparently by the attenuation of the emotional component of the experience. The question of whether or not information of this type can in fact attenuate the sensation of pain needs further investigation, especially since no SDT analyses were reported in this area.

In studies where information was conveyed in the form of instructions or suggestion, pain ratings or tolerance levels were typically altered, mediated apparently by a change in the demand characteristics of the situation. While the few studies that utilized SDT analysis suggest that no analgesic effect could be attributed to information (because only response criteria were affected), it has become well established as a factor influencing the subjective component of the pain response.

C. Anxiety and arousal. The subjective or emotional component of the pain experience can also be influenced directly. It is commonly agreed upon that both trait and induced anxiety can influence the ability to cope with and tolerate pain. Increasing anxiety levels have been associated with decreasing tolerance for pain.

It has been reported that subjects scoring high on the extraversion and psychotic ends of personality scales show higher tolerance for pain (Lynn & Eysenck, 1961). These are personality traits associated with low anxiety levels.

Bobey and Davidson (1970) studied the effect of anxiety on the perception and tolerance of pain. They compared psychiatric patients, classified as anxiety cases or neurotics, with other psychiatric patients and normal subjects, and found the former to have lower pain tolerance thresholds. They argued that reducing anxiety should increase the tolerance for pain and were able to increase pain tolerance thresholds in young female students through relaxation techniques. However, their results were inconclusive when they attempted to lower these thresholds through tape recordings of women during labor and childbirth designed to induce anxiety. This "anxiety" treatment showed significant differences from the controls in tolerance levels, but only when the experimenter was male. With the female experimenter the tolerance level of the presumably anxious group did not differ significantly from controls. The combined anxiety tapes and the male presence were necessary to produce a change in tolerance levels. This suggests that the tape treatment was not sufficiently anxiety-provoking, or that a different social dynamic was produced with the male experimenter which changed the demand characteristics of the situation.

High anxiety levels have also been associated with lower tolerance for pain by Lepanto, Moroney and Zenhausern (1965). They found that when subjects lacked control over the noxious stimulus (when only the experimenter had the power to stop it), they exhibited lower pain perception levels than controls who could control the stimulus. Presumably, lack of control subjects experienced higher levels of anxiety and thus were more likely to report pain quicker. More motor responses associated with pain, like grimaces and arm movements, were observed in these subjects.

Unfortunately, without the benefits of SDT analysis, it is not known whether sensitivity and, or, response criteria were different.

The threat of electric shock was used by Haslam (1966) as an anxiety-provoking agent in studying laboratory pain. She too obtained significantly lower pain thresholds in the anxiety-induced group. Further, subjects who were dropped from the experiment (because the threat of shock was not successful in producing anxiety in them), had even higher pain thresholds than the control non-threat group, lending additional support to the association between anxiety and lower pain perception thresholds.

Hill, Kornetsky, Flanary and Wikler (1952) studied the effects of anxiety on the ability to judge an electric shock as "stronger" or "weaker" than a standard. Anxiety was manipulated through differences in the degree of "formality" in the attitude of the experimenter toward the subject and in procedural differences, such as allowing self-administration of shock in the informal, but not the formal group. These groups were further divided into morphine and placebo-treated subgroups.

The "formals" tended to overestimate the intensity of the stimulus, a reflection of lower pain thresholds attributed to a presumed higher level of induced anxiety. However, when treated with morphine, the estimates became significantly more accurate. This effect of a 15 mg dose of morphine on intensity estimations occured only among the formal group. In the informal group, where anxiety had been dissipated procedurally, estimation of intensities was the same for morphine and placebo groups, and there was no significant overestimation.

This selective effect of morphine on the formal group only, suggests that its analgesic action consists on a reduction of anxiety (which in turn results in greater accuracy), rather than a direct effect on sensory functions. Although morphine does not act as relief generally for all types of anxiety, it is evident that the anxiety produced in this experiment (fear and anticipation of pain) was susceptible to its effect. And thus the role of anxiety in comparative pain estimations, a crude measure of sensory discrimination, is suggested in this 1952 study.

Dougher (1979) examined trait anxiety using instructions as an experimental procedure to modulate the presumed effects of anxiety on pain detection thresholds. He compared clinically diagnosed anxious and non anxious individuals given instructions that tended to either facilitate or inhibit them to report pain quickly. Overall, the highly anxious group reported pain significantly sooner than the low anxious. Those who received facilitatory instructions reported pain significantly sooner than the inhibitory ones, but only on the last four trials relative to the first two. Inhibitory instructions resulted in higher pain thresholds on the last four trials as well. The high anxious inhibitory group reported sooner than the low anxious facilitatory group, suggesting that the effect of trait anxiety superseded the effect of instructions.

SDT analysis allowed the author to conclude that the high anxious subjects were no different in d' than the low anxious, and thus that instructions did not modify their sensitivity. The differences however, were in response criteria, in their subjective tendency or reluctance to report pain. However, the author cautions that even after SDT analysis, the relation between anxiety and response biases is not conclusively established because trait anxiety individuals were diagnosed as such in part through their questionnaire answers regarding pain, thus falling into circular reasoning.

Other aspects of the role of emotion on the pain experience have also been manipulated with similar results. Zelman, Howland, Nichols and Cleeland (1991) induced depression or elation through cognitive means. They obtained no significant differences in verbal pain ratings, but the length of time their subjects were willing to tolerate varied significantly. Those with induced depression showed shorter tolerance times. Apparently, the effect was not based on expectations because even in those subjects who expected the opposite of the experimenters (they believed that depression would lengthen tolerance time), the direction of the effect was the same as with other subjects. Without the benefits of SDT analysis, these authors obtained altered response criteria with unchanged discrimination functions.

Many investigators like those discussed above, who successfully manipulate cognitive or emotional states relative to pain typically obtain changes in pain ratings. After treating data with SDT analysis, in order to separate the affective from the sensory component of the pain response, they generally obtain unaltered sensory function or d', with changes occuring only in response criteria. However, Malow (1981), Malow, West and Stuker (1987), and Malow, West and Sutker (1989) are notable exceptions.

Using SDT analysis, Malow (1981) showed that indeed anxiety can affect the ability to discriminate between noxious stimuli. He induced anxiety through threat of shock and obtained a decrease in pain sensory discriminability. He also obtained a decrease in the tendency to report pain but only in the group with combined verbal and physiological indexes of anxiety, who also showed the largest decrease in sensitivity. These results lend support to the theory that anxiety can modify the neural impulses reaching the brain from a peripheral noxious stimulus by intercepting, inhibiting or altering the stimulus enough to affect the subject's sensory experience of it.

Previous studies with data subjected to SDT analysis have mostly demonstrated changes in pain report bias or in tolerance levels, but not in sensory discrimininability (d'), which is presumed to reflect neural function. It is possible that Malow's use of a tonic pain stimulus (pressure) rather than a phasic stimulus, a different procedure in obtaining d', or his method of independently verifying anxiety by verbal report and physiological measures, could account for the unusual results. In addition, Malow's results question the generally accepted conclusion that greater anxiety produces a greater reaction to noxious stimuli.

To confirm these findings Malow et al (1989) used highly anxious detoxified substance abusers, half of whom significantly lowered their state anxiety scores over treatment. They obtained lower pain ratings in the lowered anxiety group. Subjected to SDT analysis, the data yielded that this improved anxiety group not only increased its criteria on pain detection significantly (the typical finding), but also significantly increased its sensory discriminative ability (the atypical finding).

After the introduction of SDT analysis of pain research data it has become generally agreed upon that cognitive and affective manipulations only affect the decisional aspects of the pain response, while discriminative aspects remain unchanged. Malow's results suggest that both could be affected.

These findings tend to support Melzack's (1982) hypothesis that central nervous system (CNS) activity can modulate incoming impulses arising from peripheral noxious stimulation. It is possible that increased CNS activity generated by severe states of anxiety, or increased states of agitation during other pathologic mental or affective states interfere with sensory processing of the noxious stimulus, thus affecting discriminative ability. This would be in addition to the already commonly accepted interference of central processing of cognitive functions involved in the decisional aspects of the pain response.

This hypothesis could explain apparently inconsistent findings on the effect of anxiety, arousal and stress on the discriminative and reactive components of the pain response. For example, findings by Hill et al (1952), who obtained improved intensity estimates in morphine treated, highly anxious subjects, are consistent with changes in discriminative ability due to relief of high levels of anxiety.

Further , it is well known that tolerance for pain in athletes undergoing strenous physical activity, and of soldiers during battle, contrasts sharply with that observed when out of the gym or off the war zone. This phenomenom called "stress-induced analgesia" is produced in situations of high arousal or during activities associated with high sensory input. The phenomenom can be interpreted as due to increased sensory and proprioceptive input competing with incoming noxious stimuli (for fibers and for the subject's attention, i.e., for sensory and cognitive processing). It has also been interpreted as due to the increased hormonal secretion that occurs after prolonged exercise, stress and arousal, which activates the brain's antinociceptive system. Janal, Colt, Clark and Glusman (1984) found that after an intense 6.3 mile run, their subjects gave reduced reports for ischemic and thermal pain, while they experienced mood elevation, and showed increased plasma hormonal levels. They concluded that it was central sensory input that was probably reduced because SDT analysis yielded reduced discriminability and not a change in response bias, when components of the reduced pain ratings were separated.

Regardless of interpretation, stress-induced analgesia is at odds with the commonly held linear relationship between increasing anxiety /arousal/CNS activity, increasing pain ratings and decreasing pain tolerance. Stress-induced analgesia however, is consistent with a curvilinear relationship where extreme levels of anxiety (arousal and CNS activity) can reverse the direction of responses observed in the laboratory when anxiety is relieved or augmented.

The non-linear relationship between anxiety and the discriminative and decisional aspects of the pain response fits more data more appropriately than the linear interpretation. Increasing anxiety would still be associated with decreasing pain tolerance as well as decreasing reluctance to report pain. But this would occur up to a point where severe anxiety, stress and arousal would tend to increase these as is the case in for example, stress-induced analgesia.

Similarly, anxiety, stress and arousal would also be related in a curvilinear fashion to discriminative ability. In this case, relatively low levels of anxiety would be associated with high d', but both increasing or decreasing anxiety would be associated with diminished sensory discrimination ability.

There is a point at which extremely low levels of anxiety and arousal are of course associated with diminished sensory discrimination ability because of neural inhibition or low neural activity overall, as when analgesics are administered or the subject is somnolent.

In the studies discussed in this section, both trait anxiety and anxiety induced by experimental procedures (such as lack of control over the noxious event, threat of shock, formality between experimenter and subject, specific instructions and depression) were examined. The results were generally changes in pain ratings, specifically in the tendency to report pain, and in tolerance, though in a few cases discriminability seems to have been altered as well. Since these changes did not always occur in the same direction, a non-linear relationship between anxiety and the pain experience was considered. However, regardless of the shape of this relationship, anxiety stands out as a crucial part in the "puzzle of pain".

D. Warning signal and delay. The element of surprise, or expectancy, is believed to have high emotional impact. Accordingly, the delay between a warning signal and the stimulus onset is considered a factor in the size of the stimulus' impact on the organism. Not knowing when an impending noxious event will occur can increase the level of anxiety in a subject. In addition, the longer the delay the harder it is to predict when the stimulus will occur. Expecting a stimulus that takes long in arriving may also increase the subject's anxiety level. Thus, uncertainty about the duration of the delay, as well as the length of the delay itself, could both be influential factors in the experience of pain. There is evidence in the literature that delay may indeed be an important factor, but its precise role is still unclear.

Jones, Bentler and Petry (1966) suggest that the reduction of uncertainty acts as a positive reinforcement serving to modify behavior. They studied the effect of uncertainty about the temporal occurrence of a shock, and about its intensity, on an instrumental response capable of reducing that uncertainty. Information about both intensity and delay, or about intensity alone or delay alone, was provided upon request to subjects. It was reported that requests for information were higher at higher levels of uncertainty, and requests for information about delay were significantly higher than requests for information about intensity. Requests for information about both were very slightly more, though not significantly so. These results suggest that information may reduce anxiety associated with uncertainty and that reduction of anxiety due to temporal uncertainty has a higher motivational value than reduction of uncertainty regarding intensity.

The authors speculate that reduction of uncertainty may be reinforcing because it may allow the subject to produce other responses that could help minimize the pain experience. That is, the warning signal may not just reduce anxiety by reducing uncertainty, but may also allow the subject to prepare for the noxious event.

Cacioppo and Sandman (1978) reported that a warning signal enhances whatever pattern of physiological preparatory responses are developed for a specific task. For example, a warning signal prior to viewing autopsy slides, which are associated with heart rate deceleration, resulted in further deceleration. A warning signal prior to tasks requiring a high level of cognitive processing and which are accompanied by heart rate acceleration, resulted in greater acceleration. The authors presented the warning signal 5 seconds prior to the task or stimulus.

According to Jones et al (1966), preparatory responses may be ideational, such as "I can be relaxed for another minute", or postural/motor, such as grinding the teeth, which provides competing sensory input. The suggested preference for reduction of temporal uncertainty is consistent with this because it allows the subject to know just how much time is available, and when to perform the ideational or postural adjustments that help to cope with the pain. According to the subjects' own accounts, ideational responses were more often used.

If information about delay is preferred, and if ideational responses are more prominent as coping strategies during the delay, intuitively one might expect that relatively longer delays would be preferred. This would presumably allow the coping or preparatory responses to develop more fully. However, a longer delay is less effective in enhancing preparatory responses because the predictability of the stimulus onset is lessened when more time elapses between warning signal and stimulus.

In fact, Hare, Krebs, Creighton and Petrusic (1966) found that shorter delays are preferred by subjects when given a choice. The latency of self-administration of shock was generally one second even though subjects had up to 15 seconds. This was unrelated to the intensity or the uncertainty levels of the shock. The authors consider that one second appears to be sufficient for the subjects to devise coping responses that prepare them for the shock.

Lykken (1962) measured the GSR to noxious electric shock in rats under various delay conditions. Similar to Hare et al (1966), he had found that the effect of a warning signal in reducing GSRs was strongest when the delay between signal and shock was one second long. He concluded that, within limits, the shorter the delay the greater the accuracy in the prediction of stimulus onset. He speculates that the delay is necessary for the organism to elaborate the preparatory responses that seem to ameliorate the impact of the noxious stimulus. Although during the longer intervals (5, 10 seconds) the warning signal produced smaller GSRs than with no warning, the effect was smaller than with a one second interval. Apparently, the longer interval does not allow the subject to predict the onset of the shock as accurately as with the short interval. The 0.5 second interval was better than the longer intervals, but not quite as effective as the one second interval in potentiating the GSR reduction by the warning signal. Although it allowed relatively accurate prediction of time occurrence for the shock, it may not have allowed sufficient time for preparatory responses to develop fully.

Altogether these studies suggest that certainty about the temporal occurrence of a noxious stimulus has a high motivational value. They also suggest that the delay between the warning signal and stimulus onset is probably used for the preparation of a certain pattern of responses that presumably help the subject cope with the noxious event. Finally, it has been suggested that a relatively short delay is preferable to a longer one.

But, while preferred by subjects, does the presence of these conditions lead to an amelioration of the pain experience itself?

Klemp and Rodin (1976) studied the effect of delays (5 to 20 seconds) and the reduction of temporal uncertainty on subjective ratings of anxiety and on intensity ratings by the subject. They obtained significantly lower pre-stimulus anxiety in the reduced temporal uncertainty and the shorter delay conditions. However, the subjects' reported intensity of the shocks did not change with either manipulation.

Similarly, Katz (1984) compared the effect of predictable and unpredictable delays prior to an electric shock stimulus. A light signal told the subjects exactly when the shock would occur in the predictable trials. Lack of information regarding the timing of shocks resulted in significantly higher responses in electrodermal measures as well as in verbal ratings of the perceived aversiveness of the stimulus. In addition, significantly fewer subjects preferred the unpredictable condition and more distress was reported in an anxiety questionnaire by subjects when in this condition.

Katz's predictable delays were 3 seconds in duration while Klemp and Rodin's (1976) ranged between 5 and 20 seconds. In addition, Klemp and Rodin used only mild shocks empirically predetermined as uncomfortable but not painful for most subjects. This lack of intensity in the stimulus could explain the absence of a pattern of preparatory and actual pain responses observed in other studies, and the nonsignificant effect of uncertainty in intensity ratings.

Unfortunately, Katz (1984) did not utilize SDT analysis, so it is not known either whether increased verbal ratings in uncertainty conditions in his study reflect a sensory, or a response bias difference.

Another negative finding was that of Baltissen and Boucsein (1986) who did not obtain differences in verbal ratings to aversive white noise stimulation between signalled and unsignalled presentations. However, they did obtain differences in electrodermal measures and interpreted these as changes in the orienting response, rather than as predictability attenuating arousal through a selective inhibitory process on nociception (Lykken's "preception" hypothesis in Lykken, 1959). Their use of white noise as aversive stimulus may not have been sufficiently noxious to affect subjective ratings, so their results are inconclusive as well.

The issue of preference towards predictable and unpredictable conditions, and of which is more stressful, was addressed by Abbott, Schoen and Badia (1984). They review animal studies and suggest that apparently conflicting results may be reconciled when methodological differences such as the use of different dependent measures, stimulus parameters, number and length of experimental sessions and signal parameters, are considered.

By grouping together studies with common features, they were able to conclude that overall, short term predictable conditions are less stressful than unpredictable ones. This was demonstrated according to them by less weight loss, less gastric ulceration and less susceptibitlity to immunologic disease in rats under these conditions. This effect appears to be reversed in long term studies where predictability appears to be more stressful, as suggested also by these physiological indexes. They explain this reversal through arousal mechanisms.

They speculate that normally, in the short-term predictable condition, the organism alternates between periods of relaxation and arousal depending on the delay between warning signal and noxious stimulus. In the short-term unpredictable condition, a state of chronic arousal is generated which ends in exhaustion and is thus more stressful for the subject. However, after prolonged exposure to noxious stimulation, the organism cannot maintain chronic arousal and exhaustion, and instead, habituation occurs in the long-term unpredictable condition. On the other hand, in the long-term predictable condition, alternating between relaxation and arousal is still physiologically possible, but the constant alternation causes more physiological strain, retards habituation to stress, and becomes more aversive over time.

Further, the authors report that behavioral studies on rats demonstrate a strong preference for predictable conditions in short term studies. They studied preference over time and reported a change from 90% to 50% preference for predictable conditions, and further decreases when session durations were increased.

Applicability of these conclusions to human subjects must of course be cautious, but recognition of the role of procedural factors and of a possible reversal of preference over time in humans as well, are important in attempting to reconcile conflicting results in human studies.

Arthur (1986) disagrees with the Abbott et al (1984) classification of studies in short and long term categories, and presents some evidence that warning signals add stress rather than diminish it. He speculates that increased weight loss and ulceration in unpredictable conditions are due to eating and shock contingencies, rather than to greater stress in unpredictability. He argues that the rat reduces ingestion because it is accidentally paired with shock. However, even if this were the case, unpredictable shock is no less stressful because of an indirect relation with the physiological index of stress.

Abbott and Badia (1986), in their rebuttal of Arthur (1986), present new evidence regarding preference for predictable over unpredictable shock in short term studies. Rats presented more stomach ulceration when receiving shocks on variable-time rather than fixed-time schedules. Further, they justify their short-term, long-term classifications by clarifying their inclusion of studies over long periods of time but with brief experimental sessions as constituting acute stress. They include as long-term those studies which may not have lasted over 24 hours but which had long and numerous experimental sessions. They classify this as chronic stress.

In sum, despite conflicting results and interpretations, the importance of delays and temporal uncertainty, as variables to be controlled for in pain studies, is a clearly indicated fact. Whether or not the presence of delays, the length of the delays, and information about the delays, affect pain sensitivity and, or, pain response criteria, is not clearly established and still very much an empirical question.

The pupil as an index of the pain experience

The limitations of SDT methods stem from the fact that d' and Lx are indirect measures, obtained from a mathematical formula, and based on the assumption that neural activity and sensory discriminability vary concomitantly. While the assumption is good, given the vast amount of evidence that supports it, it does not necessarily always hold.

Due to the subjectivity of the pain experience, the unreliability of the pain response and the ensuing problems in measurement, and despite the advances made by SDT, it would be useful to consider indexes of the pain sensation other than the pain report. These should not be seen as substitutes, but as alternate or complementary methods, and as ways to validate the SDT analyses.

It is well known that the pain experience is correlated with a number of autonomic reactions such as perspiration, heart rate changes, etc. However, the subjective pain report continues to be a more valid index than the "more objective" physiological indicators of pain studied up to now (Clark & Hunt, 1971). Along with signalling pain, these autonomic responses also signal emotions like fear and surprise which occur together with pain. In addition, strong autonomic responses occur to non-noxious environmental stimuli such as tones, lights etc. which sometimes accompany the noxious stimuli in pain research. It is not always possible to separate the effects of one or the other. Besides, these autonomic responses correlate poorly with changes in stimulus intensity, which makes them unreliable predictors of the pain response.

Pupil dilation is one of the autonomic responses associated with pain (Janisse, 1977). In one of the few studies on pain and pupil relations, Krueger and Fazel-Madjilessi (1978) obtained increased pupillary dilations after applying electrodermal stimulation to the forearm. The effect of noxious stimuli on pupillary motility suggests that it can play a role as a source of information regarding the pain experience, and perhaps as an alternate method of measurement.

The sphincter muscle of the iris constricts to light but it also responds to stimulation from multiple regions of the brain and from the periphery, including noxious stimulation. The light reflex arc consists of afferent fibers from the retina to the pretectal nuclei whose fibers extend to the oculomotor complex. Oculomotor neurons send efferent axons to the ciliary ganglion and these in turn to the sphincter muscle of the iris.

Afferents are both crossed and uncrossed, enabling a consensual light reflex; efferents are ipsilateral. After an afferent lesion the consensual reaction remains present unless only the eye of the affected side is exposed to light, in which case the light reflex is abolished on both sides. An efferent lesion results in elimination of the light reflex on the side of the lesion.

In general it is agreed that constriction of the pupil is produced by excitation of parasympathetic fibers, while dilation is produced by excitation of sympathetic fibers. Although this is correct as a general principle, research findings suggest that it is not that simple (Brodal, 1981). These findings show that pupil size changes are an expression of the influence of parasympathetic fibers of the oculomotor nerve, while sympathetic fibers play a subordinate role.

Reflex dilation following noxious stimulation in animal studies is not abolished when sympathetic impulses are eliminated by transection of afferent fibers. Noxious stimulation of two ascending pathways from the spinal cord, which appear to end in the Edinger-Westphal nucleus, produce pupillary dilation. This occurs even if both sympathetic fibers are transected. Secondarily, excitation of sympathetic fibers results in pupillary dilation by producing a constriction of vessels and activation of secondary dilator muscles of the iris (Brodal, 1981).

Pupillary size changes are thus more accurately said to be due to tonic changes in the parasympathetic fibers, and, to a lesser extent, to sympathetic impulses. Specifically, dilation is due primarily to inhibition of parasympathetic fibers of the oculomotor nerve, and secondarily to sympathetic excitation. The active role of both systems will of course produce maximal dilation.

Pioneering work was carried out by Lowenstein and Lowenfeld (1950), demonstrating that pupillary dilations are correlated with strong emotions. Much of the work that followed was plagued by contradictory and inconclusive results that led to the decline in pupillary motility research (Hakerem, 1973), but the data made it conceivable to view the pupillary reflex as an "objective indicator" of certain behavioral phenomena.

Hakerem (1973) studied pupillary responses as objective indicators of conceptual processes. He obtained pupillary responses simultaneously with evoked potentials, which reflected some of the processes involved in a complex conceptual task requiring guessing. These responses showed high intra-individual consistency despite much inter-individual variation. He also reported that in another study, monozygotic twins showed strikingly similar response curves while dyzygotic twins showed considerable discrepancies. The author speculates that the processes being reflected by these pupillary responses could be dependent upon inborn neuronal connections, even though elements of social learning were probably also embedded in the responses.

Further, Hakerem and Lidsky (1975) also tested pupillary reactions as objective indicators of psychopathology. They compared schizophrenic subjects and normal controls, and found that the psychiatric patients had significantly smaller pupils, and more importantly, significantly less constriction as a response to light. After ruling out the Law of Initial Values and long term intake of phenoziazines as explanations for these striking differences, they concluded that the pupillary responses could serve with about 80% accuracy to classify subjects into these two groups.

Richer, Silverman and Beatty (1983) obtained pupillary dilations that could serve as objective indicators of motor responses. They reported dilations 1.5 seconds prior to manual responses, peaking 0.5 second after the response. These dilations coincided quite precisely with increases in muscle tone and in excitability of spinal reflexes known to occur prior to contingent movement. Thus the pupil served as a marker for, and as part of, the overall autonomic activation component of a motor response.

One related study by Perry, Heller, Kamiya and Levine (1989) suggests, though inconclusively, a relationship between subjective factors and the pupillary response. The authors measured the pupillary light reflex function in chronic pain patients with and without demonstrable organic basis, and in normal controls. They found a significant autonomic alteration in both pain groups. These groups had a reduced constrictive pupillary response compared to normals. However, pain levels were not significantly correlated with any of the parameters of altered autonomic function. These findings suggest the possible susceptibility of the pupil for reflecting both objective and subjective factors involved in the pain experience, since tissue damage was present in only one group, although both presented with autonomic alterations. Of course, the absence of demonstrable tissue damage does not necessarily mean that there is no organic basis for the pain.

If the pupil could serve as an objective indicator of cognitive, emotional and motor activities, why not of the pain experience?

These pupillary findings, the reflexive nature of the pupillary response to noxious stimulation, and the possibility of a genetic component in pupillary reaction patterns as suggested by monozygotic twin studies (Hakerem, 1973), make the pupil an excellent candidate for consideration as "objective indicator".

This is not to negate the subjectivity of the pain experience, but it implies that the pain sensory component can be measured. The questions raised were: Can the organism, by way of the pupil, tell us the intensity of the stimulus being administered, and if so, can the pupil tell us in clinical situations and in analgesic drug research when the intensity of the noxious event is not known, how much pain is being felt? In other words, can the message detour around the brain and come to autonomic nervous system fibers to reflect a "pure" message, free of influence from cognitive or affective factors, and give us an objective measure of stimulus intensity? Can the pupil reflect with some degree of accuracy changes in stimulus intensity?

Also, what determines the shape of pupillary responses, inborn neural connections or subjective factors and learning? More concretely, does the pupillary pain response reflect stimulus intensities independently of the subjective components of the pain experience, or are these part of the response?

It was hypothesized that the message originated by the noxious stimulus reaches autonomic fibers before being transformed at higher centers of the brain, before CNS processing, and thus, before modulation of the experience by subjective factors. If such a detour existed, the pupil would reflect neurosensory function, and not the subjective aspects of the pain experience.

It was our aim to test the susceptibility of the pupil to changes in stimulus intensity and delay, and to changes in information that could possibly alter the subjective experience of pain.

Experimental variables and hypotheses

Our working hypothesis regarding the pupillary response was that, given its reflexive, involuntary nature, and given its suggested genetic component, it would reflect stimulus intensities accurately, and perhaps bypass the psychological factors that affect the subjective ratings.

Electrodermal stimulation was chosen as the noxious event based on the advantages of repetitive electrical stimulation as the model most closely approximating clinical pain. It does not produce noticeable tissue damage, even after prolonged use, and it is convenient because of the relative ease with which stimulus intensities can be quantified and changed from trial to trial (Myers, Janal, Pai & Clark, 1982).

The intensity of the electrodermal stimulus, and the delay (between information and stimulus onset) were varied. Stronger intensities and longer delays were expected to result in higher pain ratings and larger pupil dilations.

Information about stimulus parameters was also varied. It was expected that information would ameliorate the impact of the stimulus either by reducing the effect of anxiety (produced by fear of the noxious stimulus, or by uncertainty about it), by allowing preparatory responses that help cope with the noxious event, or simply by reducing the size of the pain response which is presumed to be larger when the intensity of the noxious stimulus is not known. It was hypothesized that regardless of the mechanism, more information provided to the subject would result in reduced intensity ratings. Based on preference results from Jones et al (1966), it was hypothesized that information about delay would produce smaller pain ratings than information about intensity. Absence of information was expected to yield the highest pain ratings, given the larger anxiety component associated with this condition.

The effect of these conditions was examined through two dependent variables: the subject's rating of the intensity of the sensation, and the changes in pupillary diameter.

A subjective report measure was used because it is superior to any of the physiological indexes used up to date. A verbal scale was used because it appears to be the scale of choice in pain ratings. According to Linton and Gotestam (1983), who compared a verbal rating scale with a visual analogue scale and found greater discrepancies with the visual scale, it is the more reliable instrument.

Changes in pupillary motility and in ratings resulting from intensity, delay and information variables could help further clarify normal pain mechanisms. It could contribute as well to set standards for comparison with clinical populations displaying abnormal responses to noxious stimulation, such as depressed patients

(Potts, Carson & Carson, 1984). Finally, the pupillary pain response could be used as an alternate method in testing the efficacy of analgesic drugs, especially in the case of patients in whom a verbal response is precluded.

Method

Subjects

Twenty-four normal paid volunteers who served as subjects completed the experiment. They read and signed an informed consent form regarding the experiment, which was approved by the local Institutional Review Board (see Appendix A). The consent form explained some aspects of the experiment such as the possibility of discomfort or pain, the safety of the equipment, and the confidentiality of the results. It included a statement by the subject regarding age, health, and the consumption of medication, alcohol, illegal drugs, etc.

The subjects' ages ranged from 19 to 50 years, and averaged 32 years, with median age being 30. They included college students and personnel, and Hispanic-American workers. There were 10 females and 14 males. (See Appendix B for sample characteristics.)

One person was excused at his request in the course of the experiment, and two others, not suitable because of excessive blinking, were also excused.

Apparatus and materials

An in-house constant current electrical stimulator, was used to deliver the electrical stimulus. The intensity, onset and duration of delivery were pre-programmed through a Digital Corporation Mink laboratory computer. A tone generator on line with the computer system was programmed for tone delivery onset, duration and pitch.

An infrared video pupillometer was used to focus on the subject's pupil and to measure its diameter. The pupillometer was also on line with the computer system to measure and store the properly calibrated pupil diameter sizes.

The experiment was conducted in a dark, sound-proof chamber where the camera was located. The subject sat on a relatively comfortable adjustable chair. An infrared light source with filtered wavelengths below 800 mu was used to focus and measure the pupil. This light did not affect pupil size. A small, red fixation light was used, to stabilize the subject's gaze.

A "bite-board" was devised to minimize the subject's head movement, and thus keep the pupil in focus throughout the experiment. This was done with a Kerr dental compound which was first heated to soften. When soft, the subject would bite on it, leaving a permanent dental impression. After the dental impression, or bite-board, hardened, it was affixed to the camera apparatus.

The pupil was brought into focus by adjusting the position of the chair, the bite-board, and the camera. After the best possible focus was obtained, the bite-board insured that the position of the head, and thus the pupil, was maintained. The subjects had to retract from the bite-board at the end of each trial to give the rating of the stimulus. With the bite-board, only minimal if any readjustments of focus were necessary throughout the experiment.

A video monitor was placed in a room adjacent to the sound-proof chamber where the experimenter could closely follow pupil events from trial to trial while conducting the experiment. Pupil data were stored automatically through computer pre-programming. Ratings were entered manually by the experimenter, and stored along with the pupil data. An intercom facilitated experimeter-subject communication. The intercom was always open only on the subject's side. This prevented extraneous noises from entering the subject's chamber.

Two Grass electrodes were used to deliver the current originating from the stimulator. They were placed with electrode cream on the skin of the upper surface of the index and middle fingers of the subject's left hand. The hand rested on a table placed in front of the subject where the pupillometer was also located. Insulation was placed between the two fingers to avoid shunting.

An ohmmeter was used to insure the adequate operating conditions and proper placement of the electrodes. Skin resistance was measured prior to the initiation of each block for this purpose. The skin was cleaned with alcohol swabs and scrubbed vigorously to insure a resistance below 20,000 ohms.

A rating scale including twelve categories and their numerical equivalents ranging from "0" to "11" described the increasing stimulus intensities. Twelve were chosen to allow the subject enough alternatives to choose from when describing each intensity of pain, and so as not to disclose how many stimulus intensities were being used. The categories were:

0 = Nothing
1 = Very Faint Sensation
2 = Mild Sensation
3 = Moderate Sensation
4 = Strong Sensation
5 = Uncomfortable but not painful
6 = Faint Pain
7 = Mild Pain
8 = Moderate Pain
9 = Strong Pain
10 = Strong Pain
11 = Very Severe Pain

Instructions

Prior to the initiation of the experiment uniform instructions (see Appendix C) were given to all subjects regarding the four experimental blocks, the experimental procedures, and what was expected of them at each point. A time sequence chart was used to illustrate the sequence of events in each trial (see Appendix D).

The 12 category pain rating scale was provided to the subjects. They were encouraged to use all categories and to answer with a number from the scale. They were asked to rate the sensation as accurately as possible, regardless of the information received. They were assured that deceitful information would not be provided. Before each block instructions were repeated regarding the meaning of the tone combinations to be presented during that specific block. The subjects knew that stimulus intensities would be either "painful" or "non-painful" according to their own pretested sensitivities, and that delays would be either short or long . They were not told how many delay levels would be used, nor how many intensity levels would be presented, in order to encourage the use of all twelve categories in the pain rating scale.

The subjects were instructed to signal the experimenter when they were ready to start a new trial by returning to position in the apparatus, which the experimenter was monitoring. They could rest at will after each trial. In this sense the experiment was subject-paced, although the timing and sequence of events during the trial were computerized and pre-programmed.

Procedure

After a preliminary introduction to the experiment and signing of the consent form, the bite-board was prepared, and the electrodes were affixed on the subject's fingers. The subject then entered the experimental chamber where the height of the chair was adjusted, as well as the position of the head and bite-board, in order to achieve maximum precision in the focusing of the pupil. Further adjustments were made in the placement of the camera until the monitor showed a well focused pupil. Instructions were then given to the subject as well as explanations to any question that may arise.

Skin resistance was measured at this point to make sure that the electrodes were properly placed and working. Individual differences in electrodermal sensitivity required preliminary testing in order to choose the stimulus intensity levels to be used with each individual subject. A given intensity could be considered painful by one subject and non painful by another. Through pre-testing the desired range in intensities was obtained (from lowest noticeable to highest tolerable) and then the four intensities were chosen.

Stimulus intensities were chosen through preliminary individual testing. Very low intensity stimuli were first applied and then gradually increased.

The subjects were asked to report when the stimulus was first felt, and to indicate when they reached the upper limit of their tolerance. The subjects were instructed to assign a number, corresponding to one of the twelve categories of the verbal scale, to each stimulus. They were asked to try to tolerate stimuli at the highest intensity possible. Intensities ranging from the lowest felt to the highest tolerated were then randomly presented again asking the subject to rate the stimuli.

Two low intensity stimulus levels were chosen by first picking the lowest felt, rated most frequently by the subject as "1" or "2", though also rated (less frequently) as "0", "3", "4" or "5". The second intensity was chosen as the stimulus most frequently rated as "3" or "4" by that subject, but also rated (less frequently) as "0", "1", "2" or "5". These two intensity levels were the low intensity pair. They partially overlapped in terms of ratings, and were not easily discriminable by the subject.

Two high intensity stimuli were chosen by first picking the highest tolerable stimulus intensity rated by the subject most frequently as "10" or "11", and then picking the second highest from those rated by the subject most frequently as "8" or "9". Similarly, the high intensity pair partially overlapped in response ratings and was not easily discriminable by the subject.

The difference between high and low intensity pairs was larger than between the two high intensities or the two low intensities. They did not overlap in response ratings, and were easily discriminable by the subject. This preliminary procedure was adapted to the response patterns of individual subjects. It served the purpose of pre-training as well, where the subjects became familiar with the apparatus and it was ascertained whether they understood the use of the response scale . A brief pre-training with the information tones was also performed so that subjects could learn to distinguish the information signalled by the various tone combinations.

Four experimental blocks of 64 trials each were performed. Each block contained all four levels of the stimulus intensity, and all four levels of the delay. They differed only on the information provided about intensity and delay. Prior to each block the subject was told which information condition was to follow, i.e. whether the tones would provide information about intensity and delay, information about intensity alone, information about delay alone, or,no information at all.

As the subject was instructed to enter the bite-board (to bite on the dental impression) the focused pupil would become visible on the monitor. This signalled readiness to begin. The timing and presentation of all tones and electrical stimuli was pre-programmed. Each trial was started by the delivery of two sets of "information" tones. The first set of one or two high pitched tones provided information about intensity. One brief tone meant relatively low intensity. Two brief tones meant relatively high intensity. A single longer tone meant no information. Two seconds later a second set of one or two low pitched tones would follow with information about delay. One brief tone meant a relatively short delay. Two brief tones meant a relatively longer delay, and a single longer tone meant no information (see Table 1).

All trials were thus preceded by auditory stimuli (tones), whether or not information was conveyed. In this way, auditory stimulation was kept relatively constant while electrodermal stimulus intensity and delay were varied. A differential effect of tone VS no tone was thus avoided.

The delay "information" tones were followed by a variable interval which could last four, five, eight, or nine seconds. These four pre-stimulus delay intervals were chosen to parallel intensity levels by having a short delay pair and a long delay pair, easily discriminable between but not within pairs.

After the variable delay, the electrical stimulus was delivered. The four stimulus intensities were presented randomly, with the restriction that each

Table 1

Meaning of "Information" tones

INTENSITY INFORMATION TONES:

One short, high pitched = Low intensity

Two short, high pitched = High intensity

One long, high pitched = No information

DELAY INFORMATION TONES:

One short, low pitched = Short delay (4-5 secs.)

Two short, low pitched = Long delay (8-9 secs.)

One long, low pitched = No information

intensity level was presented 16 times and combined in equal frequency with each delay level. Three seconds later, a last "response" tone was delivered, signalling to the subject that it was time to respond by rating the stimulus with one of the twelve categories in the verbal scale. The experimenter recorded this response and waited until the subject's pupil was again in full view on the monitor in order to continue with the next trial.

Pupil size measurements were taken every 20 milliseconds (ms) for three seconds, between stimulus onset and response tone, yielding 150 data points for each trial. (See Figure 1 for time sequence of events in one trial.)

These data points were averaged across trials to obtain an average response curve for each treatment level for each subject. This was necessary because of the high variability in size of the normal individual pupil. Computer corrections were made for eye blinks. Trials with excessive blinking, eye closure, or head movement were programmed to be rejected automatically.

After giving a rating, the subject entered the bite-board again. Each trial lasted a minimum of 12 and a maximum of 17 seconds up to the "response" tone. The variable rest period between response tone and the onset of a new trial lasted about 20 seconds. Each of four information blocks (containing 64 trials each) lasted

IT: Intensity tones
DT: Delay tones
S: Stimulus
PM: Pupil measurement
RT: Response tone

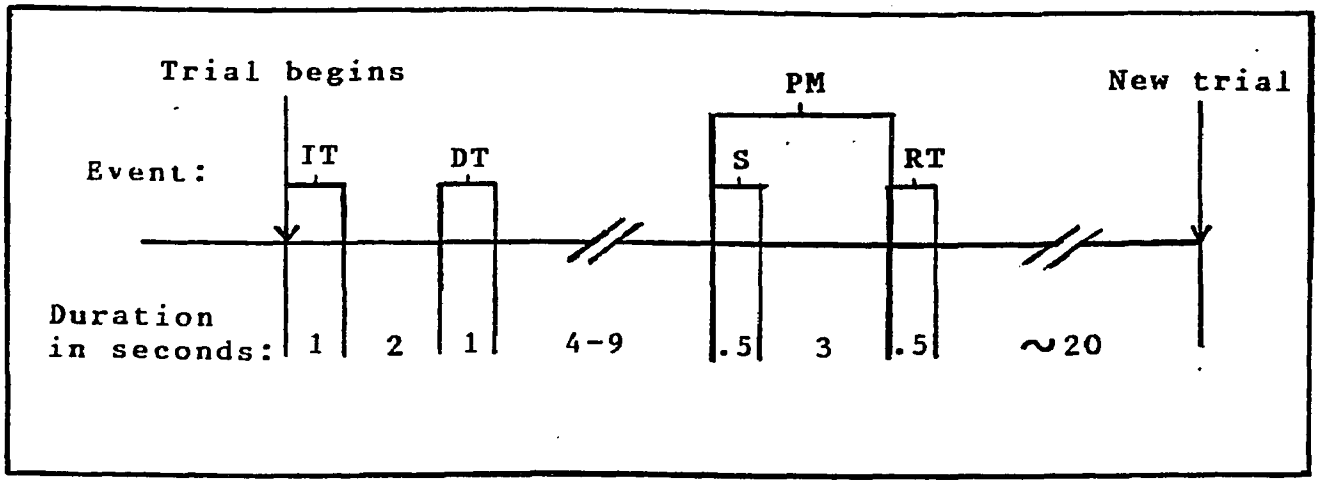


Figure 1. Time sequence of events in one trial.

lasted about 45 minutes. The entire procedure, including preparation time, lasted from 4 to 5 hours. All segments were performed consecutively, in full, on the same day, to avoid day to day changes in electrodermal sensitivity or in response criteria due to non experimental causes.

Design

Originally, the design included four Independent Variables (each with four treatment levels): Stimulus Intensity, Delay, Information, and Order of presentation. All subjects received all treatment conditions so the experiment had a repeated measures design. However, Information was separated and analysed as two distinct variables: Intensity Information and Delay Information. And Sex and Ethno-cultural background were added post-hoc. The two Dependent Variables were Pupillary Response and Ratings, as well as Discriminability and Response Criteria derived from the ratings through SDT analysis.

Independent Variables. The parameters of the electrodermal stimulus that were varied were intensity and delay. Information about these two parameters was also varied. In each of four separate blocks of 64 trials the information received by the subject could be either:

1.) information about both intensity and delay,
2.) information about delay only,
3.) information about intensity only, or
4.) no information.

Two low intensity and two high intensity stimuli were chosen which were previously labelled by the subject as "non painful" and "painful" respectively. Delay levels chosen were two relatively short ones (of four and five seconds each), and two relatively long ones (of eight and nine seconds each). Symmetry was obtained by varying stimulus intensity and delay parameters in similar ways. Low and high stimulus pairs were easily discriminable between, but not within pairs. Similarly, short and long delay pairs were chosen which were easily discriminable between, but not within pairs.

Each treatment condition of each variable was presented on an equal number of trials. That is, each of four intensities was presented 16 times in each information block of 64 trials. Each of four delays was presented 16 times in each information block. And each intensity level was combined with each delay level in equal frequencies in each information block. This resulted in a random arrangement of intensity and delay presentations, with the restrictions imposed by the symmetry just discussed.

The order in which information blocks were presented was considered a factor that could possibly mask their effects. Electrodermal sensitivity, as well as psychological variables such as boredom and anxiety, could change in the course of the experiment and have differential effects interacting with the information treatment. A Latin Square procedure was thus used to counter a potential order effect. There were 24 possible order combinations for the four information blocks, so 24 subjects were chosen. In this way, each information block was presented first, second, third or fourth in equal number of frequencies. (See Appendix B for order combinations per subject.)

Dependent Variables. The pupillary reaction was evaluated by measuring the diameter of the pupil at stimulus onset and during three seconds thereafter. This yielded a pupil size dilation curve from which a baseline (an average of the first 10 data points), and a peak value (the highest point in the dilation curve), were obtained. The difference between peak and baseline value was the pupil size change in millimeters (mm), used as a dependent variable. This was done because there is a constant small range variability in the size of the normal pupil which is independent of the stimulus. In addition, the pupil's reaction is a relatively slow process, which does not show the stimulus' effects immediately after its onset. Absolute peak size was not used as dependent variable because pupil size varies individually and thus is not an appropriate measure of changes due to treatment.

The subjective evaluation was measured by a rating scale. It consisted of numbers from "0" to "11" and their verbal equivalents, chosen by the subject at the end of each trial. A total of 256 values were obtained, 64 at each block. These ratings were subjected to signal detection analysis, thus yielding two additional dependent variables: discriminability and response bias.

Further, since pupil data required averaging across trials, pupil size change after a specified stimulus intensity concomitantly with a specified delay could not be obtained. For this reason, pupil sizes had to be sorted separately, by intensity and by delay and consequently, for purposes of statistical analyses, had to be treated as two separate dependent variables.

Results

Due to complexities in the design, different approaches to the Information and Order variables had to be devised. As mentioned, Information was originally intended as a single variable with four levels. These levels represented the four blocks of trials which differed in the type of information provided, and in the position of the block in the sequence in which it was administered to each subject.

The levels of Information were really qualitatively diverse and not a simple matter of degrees of difference. Therefore, in order to clarify this source of variation, Information was split into two variables: Information about delay (ID), and Information about intensity (II). Each of these had two treatment levels: Information, and No Information. For example, for Delay Information: trials providing information about intensity and delay, and trials providing information about delay only, were considered the Information level; trials providing information about intensity only, and trials providing no information, were considered the No Information level. All tables will present these two variables separately.

Further, the Order variable presented quite a challenge for statistical analysis. To control for changes over time, information blocks were administered in different sequences. Each subject was assigned a different combination of sequences which was not replicated within the experiment. There were 24 subjects and 24 possible sequences or order combinations. Thus Order was totally confounded with subjects.

One alternative to bypassing this problem was to treat Order as a within subjects variable. However, when it was treated as such it could not be crossed (and therefore analyzed jointly) with Information, since the data corresponding to one level in one variable was identical to that of the other variable. When they were tested separately, each yielded a non significant effect. However, this was not an adequate test because it did not allow addressing the question of the relationship between receiving information and when, in the course of the experiment, it was received. This was an important question because a comparison of the means for Information and No Information at each of the four sequence positions suggested an interesting crossover effect.

Treatment of the data as a Fixed Factor Factorial design appeared to "solve" this problem and in fact yielded significant Order by Information effects, but this was not the appropriate statistical procedure for a Repeated Measures design. Other means of looking at the data had to be devised.

Subjects were then re-grouped according to how close to the beginning or the end of the experiment they received information about intensity or about delay. Since they received information in two blocks, and no information in two others, the groups were characterized according to the relative proximity or position of those blocks to the beginning or end. This approach yielded two new between subjects variables: "Order of information about delay" (IDO), and "Order of information about intensity" (IIO), (in keeping with the separation between the two information variables). These two "order" variables reflected block positions, and most importantly, could be crossed with Information variables in Repeated Measures Analyses of Variance.

The levels of IDO (and IIO as well) were as follow:
Level 1 = Information in the first and second blocks.
Level 2 = Information in the first and third blocks.
Level 3 = Information in the first and fourth blocks.
Level 4 = Information in the second and third blocks.
Level 5 = Information in the second and fourth blocks.
Level 6 = Information in the third and fourth blocks.

Obviously, level 1 represents data obtained earliest in the experiment, level 6 represents data obtained latest in the experiment, and middle levels represent combinations that are relatively closer to one or the other. IDO and IIO levels were replicated in four subjects and became analyzable variables that could be crossed with Information. Although this is not the ideal way of accessing the interaction between Information and Order because it requires collapsing of some data, it was the only acceptable way of approaching the problem without violating statistical principle. This discussion should be kept in mind when interpreting results further on.

Pupil size sorted by intensity

The mean stimulus intensities were: 23.2, 28.4, 63.1, and 68.6 volts. (See Appendix F for intensities per subject.) The size of the pupil increased, in all subjects, as the intensity of the electrodermal stimulus increased. An example of the course of change in the pupil of one subject following electrodermal stimulation appears in Appendix E.

This subject is typical of the sample which presented a similar pattern of slow rise, followed by rapid peaking, reaching maximum dilation 1 to 1.5 seconds after stimulus onset, and a slower return to baseline.

The mean pupillary response showed a steady increase as a function of intensity from .20 mm at the lowest intensity, to .23 mm, .37 mm, and .41 mm at the highest intensity. These pupil size changes were independent of baseline pupil size. (See Figure 2.) The mean pupil size changes as a result of variations in stimulus intensity, as well as of all other variables, appear in Table 2.

Analyses of variance showed that indeed pupil size changed significantly as the stimulus intensity varied ((F(3,15) = 20.2725, P = .0001)). (See Table 3 for ANOVA results.)

Information given the subject about the intensity or the delay of the stimulus had no appreciable effect on the size of the pupil. Each produced a .30 mm increase, compared to a .31 mm increase when no information was provided. The difference was not significant.

Lack of information about intensity produced larger mean changes during the first two sessions (.33 and .34 mm), and smaller mean changes during the latter two (.27 and .28 mm), while information about intensity produced smaller mean changes during the first sessions and larger changes during the latter. (See Figure 4 for a graphic representation of this relationship.) However despite this suggested relative effect of information over time, neither Order of information about intensity (IIO), nor any of its interaction effects, were significant. It should be noted at this point that the Intensity Information by IIO, and the Delay Information by IIO interactions showed very similar patterns which were extremely consistent across all four intensities. A closer examination of the subjects included in each of the six "order" positions was undertaken by computing overall mean pupil size changes for each subject

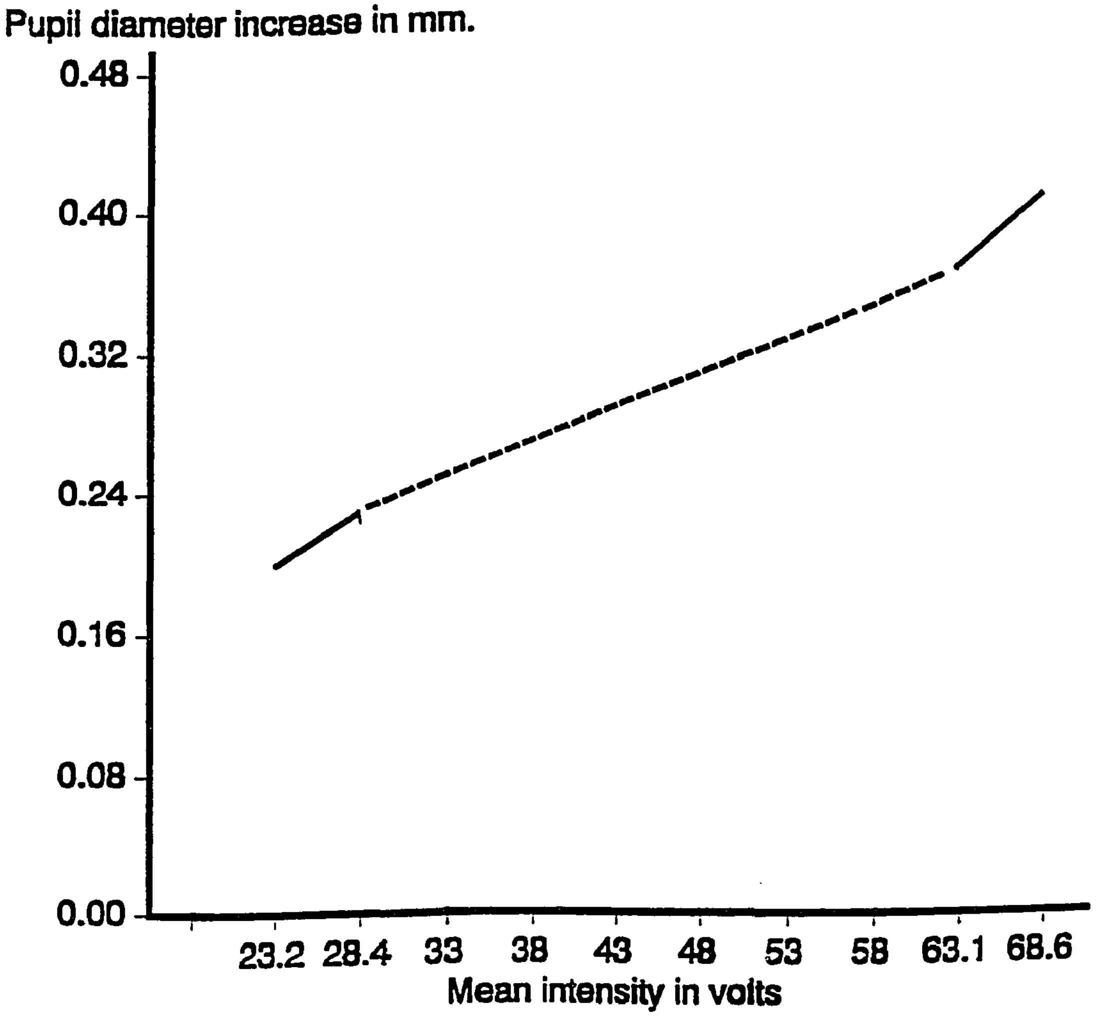


Figure 2. Effect of intensity on pupillary response. Pupil size increased as intensity increased. Broken line represents values not used.

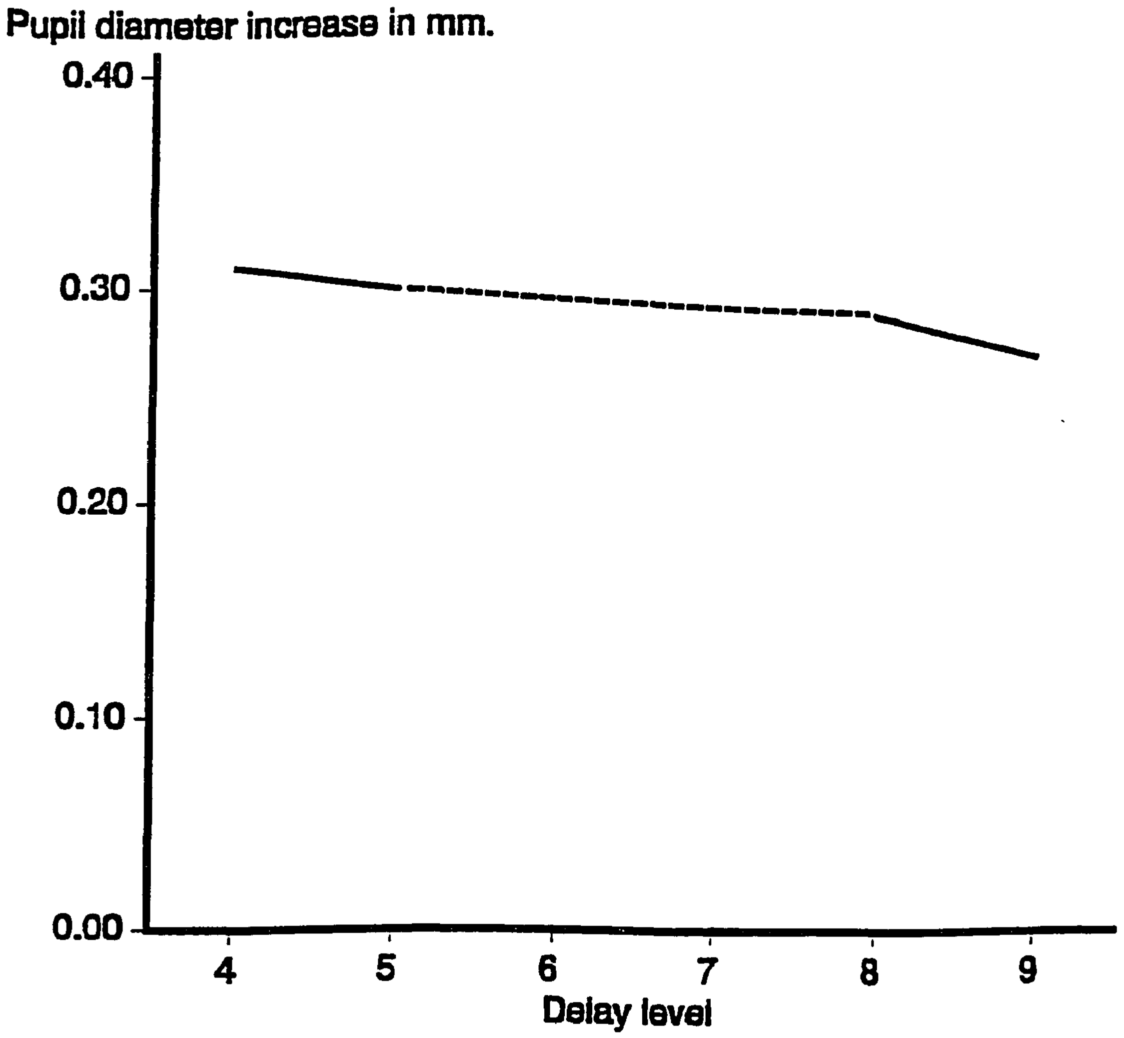


Figure 3. Effect of delay on pupillary response. Pupil size tended to decrease as delay increased. Broken line represents values not used.

individually. The top "high dilators" and the bottom "low dilators" were then located along the overall II X IIO and DI X IIO interaction curves. This revealed clusters of "high dilators" at the high points in the curve, and clusters of "low dilators" at the low points in the curve, suggesting that the apparent differences between these positions were more closely related to differences between the subjects themselves than to the two positions in which they were receiving information.

Males showed larger pupillary dilations than females, despite lower intensities, but the difference was not significant. Average stimulus intensities were 18.1, 22.8, 61.8 and 66.8 volts for males, and 30.3, 36.2, 64.9 and 71.3 for females. (See Appendix F for intensities per subject.)

Pupil size sorted by delay

Changes in pupillary response were somewhat larger after the shortest delay and decreased in size as the delays became longer. These were .31, .30, .28 and .27mm average increases in size after the 4, 5, 8, and 9 second delays. (See Figure 3.)

As with pupil size sorted by intensity, pupil size sorted by delay showed essentially no differences as a result of information about the intensity of the stimulus or about its delay. However, a significant interaction between Delay Information and Delay showed that, as

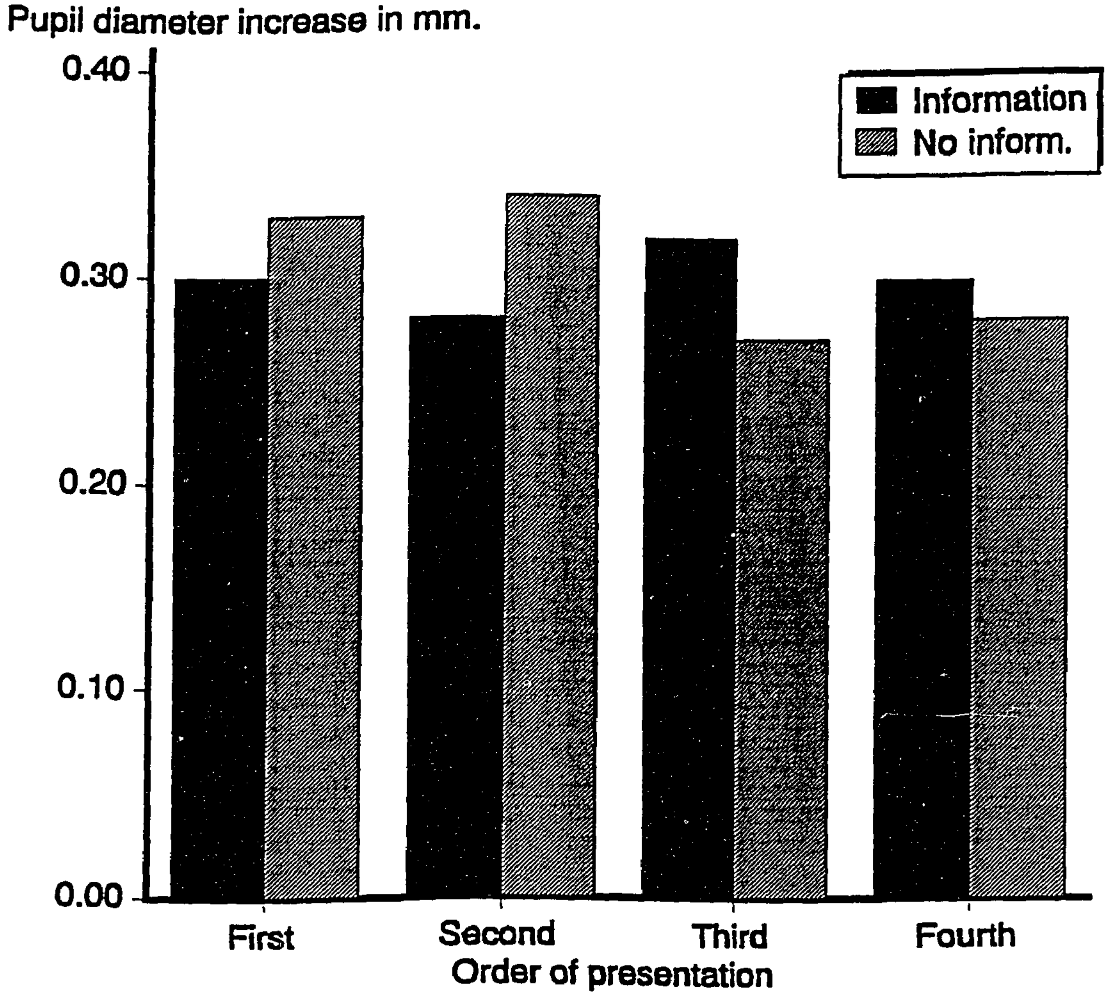


Figure 4. Effect of Intensity Information and Order on pupillary response. No information resulted in larger increases at the first two sessions and smaller ones at the last two.

Table 2

Means for pupillary response data in mm (sorted by intensity)

	Information	No Information
Delay Information	0.30	0.31
Intensity Information	0.30	0.31

	1	2	3	4
Intensity	0.20	0.23	0.37	0.41

	F	M
Sex	0.28	0.32

	1	2	3	4	5	6
Int.Inf.Order (IIO)	.31	.34	.25	.24	.28	.38

Table 3

<u>Summary of ANOVA performed on pupillary response data (sorted by intensity) (* = significant result)</u>

Delay Information	F (1,17) = 2.3144, P = .1466
Intensity Information	F (1,17) = 0.1068, P = .7479
Intensity	F (3,15) = 20.2725, P = .0001*
Sex	F (1,17) = 0.3900P P = .5431
Int. Inf. Order (IIO)	F (5,17) = 0.4300, P = .8243

Table 4

Means for pupillary response data in mm (sorted by delay)

	Information	No Information
Delay Information	0.30	0.29
Intensity Information	0.30	0.29

	1	2	3	4
Delay	0.31	0.30	0.29	0.27

	F	M
Sex	0.27	0.31

	1	2	3	4	5	6
Del. Inf. Order (IDO)	.25	.36	.41	.21	.34	.18

		1	2	3	4
Delay Inf. X Delay	(Inf.)	.30	.29	.29	.26
	(No Inf.)	.31	.32	.28	.28

		1	2	3	4
Delay X Sex	(F)	.25	.27	.26	.28
	(M)	.35	.32	.30	.27

Table 5

Summary of ANOVA performed on pupillary response data (sorted by delay) (* = significant result)

Delay Information	F (1,17) = 0.8119, P = .3802
Intensity Information	F (1,17) = 0.0465, P = .8319
Delay	F (3,15) = 2.0840, P = .1453
Sex	F (1,17) = 0.1800, P = .6771
Delay Inf. Order (IDO)	F (9,17) = 1.6900, P = .1912
Delay X Sex	F (3,15) =10.7061, P = .0005*
Delay Inf. X Delay	F (3,15) = 4.3628, P = .0213*

expected, lack of information about delay resulted in larger pupil dilations after 4, 5, and 9 seconds. However, after 8 seconds information about delay resulted in larger dilations. The fact that the effect was not consistent at all four stimulus delays may explain in part why Information about Delay was not significant overall.

Males showed larger dilations than females, despite lower intensities, but this was not a significant effect. A significant Delay by Sex interaction showed that males' pupils responded to the length of the delays quite differently than females'. Male subjects' pupils showed decreased pupillary responses as delays became longer, while females' pupils tended to increase as delays lengthened, and the change was not as dramatic as in males.

Again, lack of information about intensity resulted in larger pupil size increases during the first two sessions, and smaller increases during the last two. However, the Order of Delay Information (IDO) effect was not significant. (Overall means appear in Table 4 and ANOVA results in Table 5.)

<u>Ratings</u>

As expected, ratings increased significantly as stimulus intensity increased, independently of all other variables. The average ratings for stimuli of increasing

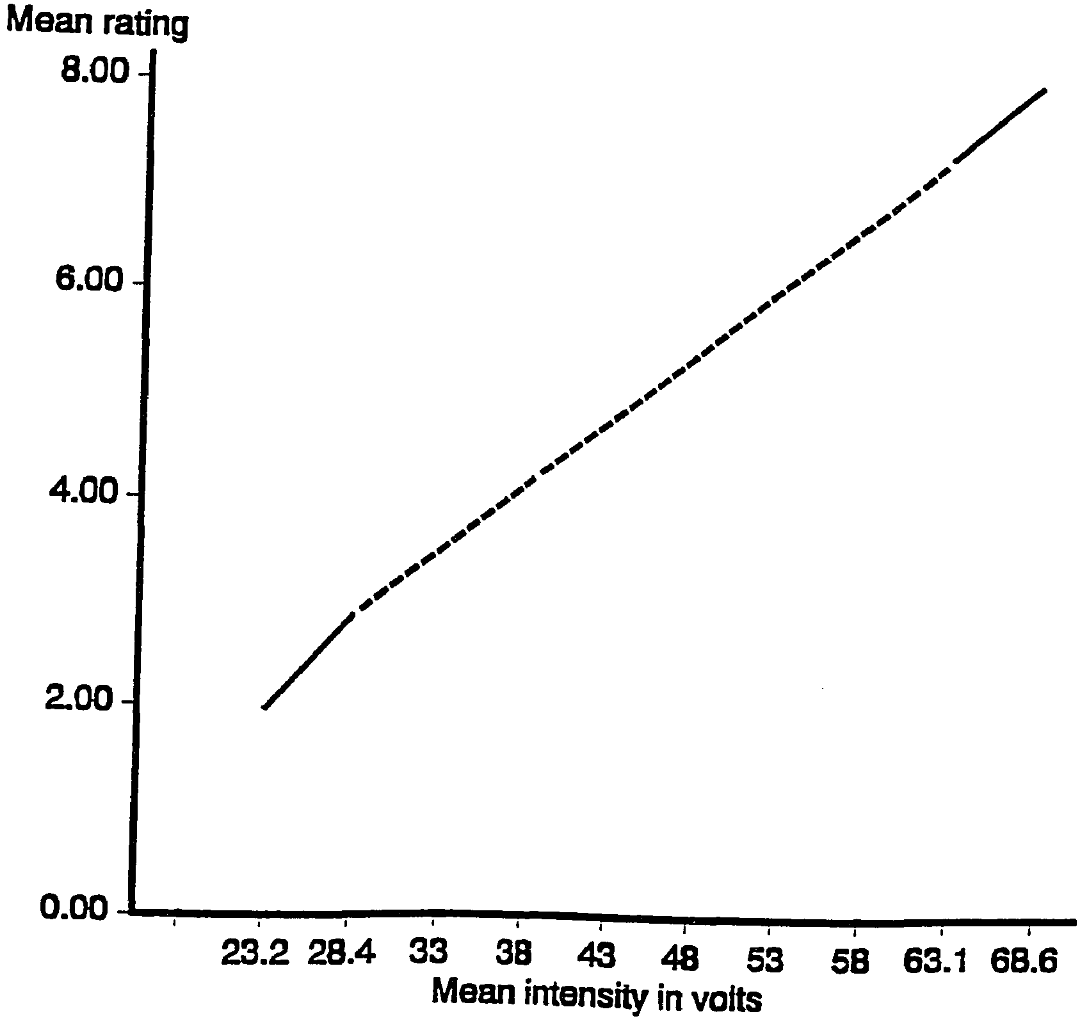


Figure 5. Effect of stimulus intensity on ratings. Ratings increased as intensity increased. Broken line represents values not used.

intensities were 1.96, 2.86, 7.31, and 7.96. (See Figure 5.)

Mean ratings were practically identical after all 4 delay lengths. Ratings were also nearly identical in all order presentations. Neither Order about Intensity Information (IIO), nor Order about Delay Information (DIO) showed significant effects.

As with pupillary responses, ratings were essentially the same regardless of whether or not information about delay, or information about intensity was provided. A significant Information about delay by Delay interaction does not change these results. Ratings continue to be higher after long delays for both Information and No information trials. The interaction is significant because Information results in higher ratings after four and eight seconds, and No information results in higher ratings after five and nine seconds __ a probably spurious finding.

Male subjects responded with higher mean ratings (5.20), than females (4.77), despite receiving lower intensity stimuli, but this effect was not significant. This could be so because when ratings were examined at each level of intensity (in the Sex by Intensity interaction effect), it was found that males responded with higher ratings than females only at the higher sets of intensities. ((F(3,10) = 3.3577, p = .0634)) (Means for all variables appear on Table 6, and ANOVA results on Table 7.)

Discriminability

Ratings were submitted to SDT analysis in order to obtain separate measures for discriminability (d') and response criteria.

This analysis was carried out on low intensity and high intensity stimulus pairs. It was found that discriminability was higher between low intensity stimuli than between high intensity stimuli. This difference was statistically significant, and was independent of other variables such as information, order and sex.

Discriminability depends on the functional state of the sensory system, on the difference in intensity between the stimuli, and on the level of intensity at which stimuli are being compared. The difference between intensities was determined for individual subjects based on their responses in a pre-test, and not on any formula that automatically set their difference at a constant, although this was the intent. The intensities varied according to the subjects' ratings, and ranged from 3.4 to 52.4 volts at the low end, and from 23.6 to 154.4 volts at the high end. Therefore, the d' values computed for these subjects, who received different sets of intensities of electrodermal stimulation, are not directly comparable unless an adjustment is made. To

Table 6

Means for ratings

	Information	No Information				
Delay Information	5.00	5.05				
Intensity Information	5.03	5.02				
	1	2	3	4		
Intensity	1.96	2.86	7.31	7.96		
Delay	4.98	5.00	5.08	5.07		
	F	M				
Sex	4.77	5.20				
	1	2	3	4	5	6
Del.Inf.Order (IDO)	5.04	5.05	5.02	5.03	5.00	5.01
Int.Inf.Order (IIO)	5.04	5.06	5.01	5.04	5.00	5.01

Table 7

Summary of ANOVA performed on ratings data

(* = significant result)

Delay Information	F (1,12) = 00.0000,	P = 1.0000
Intensity Information	F (1,12) = 00.0000,	P = 1.0000
Intensity	F (3,10) = 95.6918,	P = .0001*
Delay	F (3,10) = 01.4450,	P = .2875
Sex	F (1,12) = 00.3900,	P = .5444
Int.Inf.Order (IIO)	F (5,12) = 00.4800,	P = .7876
Del.Inf.Order (IDO)	F (5,12) = 00.1200,	P = .9850
Intensity X Sex	F (3,10) = 03.3577,	P = .0634
Del. Inf. X Delay	F (3,10) = 03.8457,	P = .0457*

allow comparison between subjects, another measure of discriminability, Unit d', introduced by Clark (1974) was used. Unit d' is equivalent to the "intensity difference between higher and lower intensity stimuli which is required in order to achieve d' = 1.0" (Clark, 1974). It is similar to the "just noticeable difference" of classical psychophysics. (To compute, Unit d' = Higher intensity - Lower intensity / d'.) Thus the dimensionless value of d' is transformed into Unit d', which expresses the difference in number of volts necessary to achieve a d' equal to unity. Consequently, the lower values of Unit d' mean superior discriminability, since they reflect that the subject can discriminate stimulus intensities that are less different.

After making these adjustments, it was found that discriminability was 1.56 volts per d' better for low intensity pairs of stimuli than for high intensity pairs: F(1,12)=7.5403, p=.0177.

Discriminability was higher when information about intensity was provided, but not significantly so. On the other hand Delay Informatin resulted in lower discriminability, also not significantly. This may be explained by a significant interaction between Information about Delay and Intensity in which Delay Information was associated with lower discriminability at high intensities only. Due to collapsing of data within the two information variables it is not clear whether the lower discriminability might be due to information about delay, or, lack of informaton about intensity which could occur when information about delay was provided.

Means for discriminability were higher at the latter two sessions than at the first two. An attempt to analyse this effect through the IIO and IDO variables yielded non significant results.

Males and females differed somewhat in their ability to discriminate between different intensity stimuli. Males needed 3.08 less volts, than females to discriminate at the d' = 1 level but this difference was not significant. (See Tables 8 and 9 for means and ANOVA results.)

Response bias

Response bias, the tendency to respond in a particular way, influenced by psychological factors that are independent of stimulus intensity, was also obtained through SDT. Response bias was measured as the response criterion, B. A higher response criterion meant that the subjects were less willing to report pain, or to give a stimulus intensity a high rating on the scale.

As expected, stimulus intensity influenced the subjects' response criteria. For the low intensity pairs of stimuli, the mean response criterion was 9.72, and for the high intensity pairs it was 3.72. Naturally, subjects

Table 8

Means for discriminability data adjusted for intensities (Unit d'), in volts per d'

	Information	No Information
Delay Information	8.03	7.26
Intensity Information	7.57	7.73

	Lo	Hi
Intensity	6.87	8.43

	F	M
Sex	9.45	6.37

	1	2	3	4	5	6
Del.Inf.Order (IDO)	8.01	7.70	7.78	7.52	7.60	7.28
Int.Inf.Order (IIO)	8.01	7.70	7.78	7.52	7.60	7.29

Table 9

Summary of ANOVA performed on discriminability (Unit d') data (* = significant result)

Delay Information	F (1,12) =	1.7218,	P = .2140
Intensity Information	F (1,12) =	0.0134,	P = .9096
Intensity	F (1,12) =	7.5403,	P = .0177*
Sex	F (1,12) =	1.3300,	P = .2706
Del. Inf. Order (IDO)	F (5,12) =	0.8500,	P = .9544
Int. Inf. Order (IIO)	F (5,12) =	0.2000,	P = .5388
Del. Inf. X Intensity	F (1,12) =	5.0712,	P = .0438*

were less willing to label low intensities as painful, and more willing to label high intensities as painful.

It was found that the information (or lack of it) regarding the intensity or the delay of the stimulus did not bias the response criteria. Responses to a given stimulus intensity did not vary depending on whether or not the subjects were told that the stimulus would be of high or low intensity, or that the delay would be short or long.

Response criteria did not change over time and IDO and IIO did not reflect significant differences in the way subjects responded as a result of the grouping of information blocks towards the beginning or the end of the experiment.

Males set lower response criteria than females, but not significantly so. A Sex by Intensity interaction was found, showing that males set higher response criteria than females at the low intensities, but lower criteria at the high intensities: $F(1,12) = 13.4274$, $p = .0032$. (See Figure 6.) Overall means and ANOVA results appear in Tables 10 and 11.

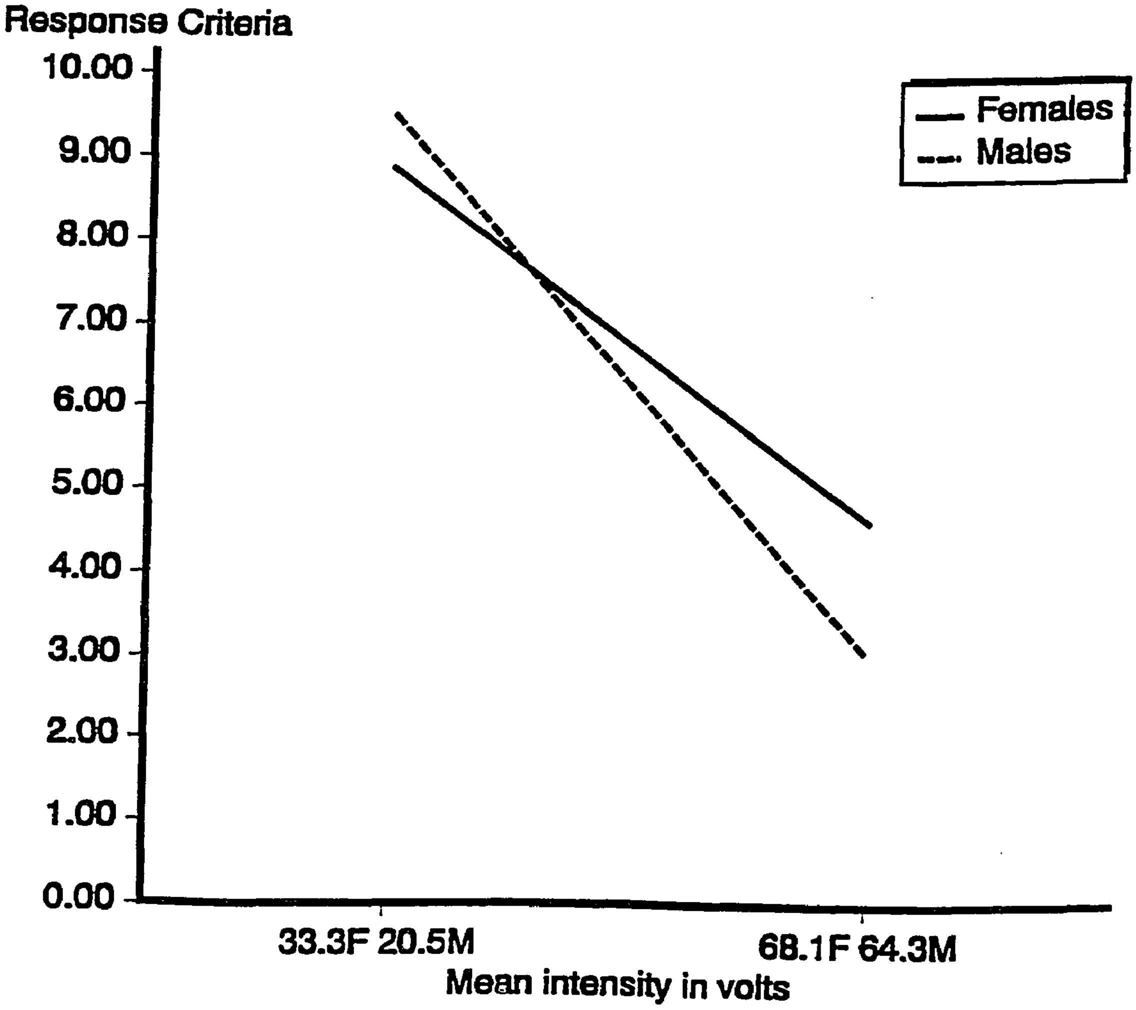


Figure 6. Effect of Sex and Intensity on Response criteria. Males set higher response criteria than females at low intensities but lower criteria at higher intensities.

Table 10

Means for response critera

	Information	No Information
Delay Information	6.45	6.51
Intensity Information	6.48	6.47

	Lo	Hi
Intensity	9.23	3.72

Sex	F	M
	6.76	6.27

	1	2	3	4	5	6
Del.Inf.Order (IDO)	6.46	6.42	6.52	6.44	6.54	6.50
Int.Inf.Order (IIO)	6.47	6.42	6.52	6.44	6.53	6.48

Table 11

Summary of ANOVA performed on response criteria data (* = significant result)

Delay Information	F (3,12) = 0.2458, P = .6290
Intensity Information	F (1,12) = 0.0063, P = .9381
Intensity	F (1,12) =331.9992, P = .0001*
Sex	F (1,12) = 0.6400, P = .4402
Int.Inf.Order (IIO)	F (5,12) = 0.5300, P = .7477
Del.Inf.Order (IDO)	F (5,12) = 0.1300, P = .9837
Intensity X Sex	F (1,12) = 13.4274, P = .0032*

Discussion

The efforts towards attaining symmetry of design in this study, intended to obtain more control and information, resulted in extreme difficulties accessing and interpreting the data. Too many variables and levels required an excessive amount of trials which made the experiment too long and overwhelming for the subjects. The problems in analysing Order and Information compounded the difficulties. Besides, pupillary responses resulting from delay and information manipulations could not be accessed simultaneously so they had to be analyzed separately, as if two different experiments.

In retrospect, a few shorter experiments with more subjects would have been more fruitful in setting the basis for more complex investigations. The appropriate length of delays, the effect of conveying verbal information through auditory stimuli, the introduction and measurement of anxiety, the changes occurring over time, and so on, needed to be examined individually, prior to combining into one experimental pot.

Initially, a pilot study suggested that delays and information had an effect on pupil size and verbal ratings. However, when all possible order sequences were filled by the 24 subjects, and data were submitted to the rigors of statistical analysis, the effects dissipated, some of them becoming mere trends. But, these difficulties notwithstanding, it was possible to draw some important conclusions from the study.

The Pupil as an "objective indicator"

The primary aim of this study was to evaluate the use of pupillometry as a possible method in assessing the intensity of the pain experience. Pupil size measurements, time-locked with electrodermal stimulation reflected highly significant increases as the intensities of the stimuli were increased. This occurred consistently in all 24 subjects studied. The "pupillary pain response", or increase in pupil diameter size due to electrodermal stimulation, was in fact a reliable indicator of the intensity of the noxious stimulus.

Thus, the viability of pupillometry was unquestionably demonstrated as a method in pain measurement. It may not be the elusive "objective indicator" but it is a highly reliable index, comparable to ratings, in reflecting changes in stimulus intensity. The pupillary pain response is not to be discarded along with the many other autonomic responses that have been tried out unsuccessfully as indices of noxious stimulus intensity. It may be used with confidence as a complement to verbal response, or as an independent index of electrodermal stimulus intensity when verbal responses are precluded.

Ratings also differed significantly as stimulus intensities changed. This was an expected result which validated the pupillary findings. Pain ratings were expected to be more influenced by subjective factors than the pupillary response. However, the issue of relative vulnerability to these factors could not be resolved here because the psychological factors studied did not have a significant effect on pupillary responses nor on ratings. The issue of whether the pupil may represent a "detour" around the brain that could bypass central processing by receiving a direct message and thus provide a "more objective" measure of stimulus intensity was thus not resolved.

Subtle sex findings which did not reach significance provided further evidence in support of the role of the pupillary response as an index of the pain sensation. Results on sex differences showing higher pupillary responsivity in male subjects were consistent with findings on their higher d'. Since the latter is considered an indicator of neurosensory status, the fact that pupil findings paralleled discriminability findings suggests that the pupil may also be an index of the status of the nociceptive neurosensory system.

In addition, a sex by intensity interaction occurring in pain ratings and in response criteria, but not in pupillary response, indicates that at higher (noxious) intensities the correspondence between stimulus intensity and response breaks down for pain ratings while it does not for the pupillary responses. Males and females dilated systematically at all levels of intensity. This may indicate that the sex biases that affect ratings at noxious levels of stimuluation do not affect the pupillary response, thus adding to its value in pain research.

The importance of the pupil as an alternate measure of the pain experience is further exemplified in the attempts to clarify the role of information, or of a given cognitive process intended to divert the subject's attention from a noxious stimulus in order to ameliorate its impact. For this type of investigation it would be necessary to use a pain response other than pain ratings. When a rating is requested the subject must place conscious attention on the stimulus in order to rate it as accurately as possible. In this way the diversion cannot be effective. The pupillary pain response provides an excellent alternate measure. The subject can concentrate on the information without the need to consciously attend to the stimulus in order to rate it, and the pupil would provide the intensity ratings.

The role of information

Information as a factor in the modulation of the experience of pain was not supported by the data. Neither Delay Information, nor Intensity Information, yielded significant differences on the pupillary response, ratings, discriminability, or response criteria.

Further, it was expected that Delay Information would reduce more uncertainty anxiety than Intensity Information. Accordingly, Delay Information should have resulted in smaller pupil sizes and lower ratings, but this was not the case. Jones et al's finding (1966) that subjects prefer information about delay over information about intensity, presumably because it permits the subject palliative responses, led to this unsupported hypothesis.

Although Order was not significant (tested separately, or as IDO and IIO), changes over time did occur, which may have affected the visibility of other effects. In fact, the pupillary response means for Information and No Information for each of the four blocks suggest that the role of information may have depended on a time factor that was not evident by itself. Pupillary responses were larger during the initial experimental sessions when no information about intensity was provided to the subjects. The inverse occurred during the latter sessions when it was having such information that resulted in larger pupil size increases.

The hypothesis regarding information was that lack of information would result in larger pupil dilations due to the increased anxiety associated with not knowing.

This hypothesis was supported, during the first half of the experiment but not during the latter half. Larger increases in pupil size due to no information were obtained only during the initial sessions.

It is possible that the crossover occurred at some point in time during the second or third sessions in which the role of information about intensity changed from attenuating the effect of the noxious stimulus at the initial sessions, to intensifying its effects at the latter sessions.

This crossover phenomenon can be explained with the concept of the relative chronicity of noxious stimulation suggested by Abbot et al (1984). They note that information has a positive effect alleviating acute noxious stimuli in short studies, and a negative effect in long experimental sessions and long term studies. In the latter, information becomes more, rather than less, stressful to the organism because constant alternation between arousal and relaxation is preferable for relatively short periods of time, but more aversive in the long run. Abbot et al speculate that this is so because the sustained arousal produced during no information treatments cannot be tolerated indefinitely and thus leads faster to habituation in long term studies.

In the present study, noxious stimulation during the first session can be considered acute since the experiment was just beginning, and information seemed to have a positive role. Subjects are naturally more anxious when they start a pain experiment, and it appears that information, intended to lower that anxiety, worked initially.

However, after four sessions, the effect of noxious stimulation becomes chronic and it was lack of information that seemed to acquire the positive role. The end result of this crossover phenomenon would be non-significant main effects for information. Jones et al (1966) were able to obtain a significant information effect probably because their experiment involved only 36 shocks in three 12-minute conditions (compared to 256 shocks in four 45-minute conditions in our study). Their experiment could be considered short term, while ours is a combination of a both short and long-term study.

Because of the constraints of the order variable confounded with subjects effects it was impossible to conclude that this is a subjects effect due to individual variability, or to the crossover hypothesis. The IDO and IIO variables devised for the purpose of testing this hypothesis fell short because it was revealed post-hoc that "high dilators" and "low dilators" were not evenly distributed among the six groups. Future studies undertaken to clarify this relationship could pre-test subjects to determine their pupillary responsivity before assigning to groups. If repeated measures are used, the repetition over time should be of the same condition so one can then examine order effects as a within subjects variable in a repeated measures design.

A relative chronicity relationship was also identified in ratings and response criteria. Uncertainty about how strong the stimulus would be was expected to produce some anxiety in the subjects. As anxiety is associated with less tolerance for pain, uncertainty conditions in which no information was provided were expected to result in higher ratings and lower response criteria. However, in this case, having information about the intensity of the stimulus and about the delay as well resulted in higher ratings and lower response criteria at the initial sessions and the inverse at the end. That is, subjects rated a stimulus intensity as higher and reported more pain when informed than when not informed at the beginning of the experiment, and the inverse at the end.

It appears that at the outset of the experiment expectancies about impending electrical shocks were higher than those actually received, and the subjects could adjust their ratings but only when information was provided. At the end, information led to lower ratings because initial expectancies were no longer operating.

This pattern of adjusting ratings when informed, implies that the power of suggestion can lead to reporting more, or less, pain according to the information received. The suggestion component in information seems to have been the driving force behind the ratings, rather than the reduction of uncertainty stress as was the case with pupillary responses. In sum, as the more "organic" measure, pupillary responses appear to be affected by the stress of uncertainty, whereas ratings, as the more "subjective" measure, appear to be affected by the suggestibility aspect of information.

In this way, the role of information was distinct in each of the two responses (pupil size and ratings). The interactions observed in both may explain in part the non-significant differences in Intensity Information as a main effect. Other explanations were also considered:

A. Subjects' understanding of the information. The subjects were pretested to confirm their understanding of the information conveyed by tone combinations. However, as the experiment proceded, subjects may have become bored, forgotten, or become less effective in attending to tone combinations and interpreting their meaning. If the information was not clear enough, or not attended to, its effect would be weakened or eliminated.

B. Information processing versus anxiety. When information was provided, the subject had to first convert the information that was conveyed symbolically through tone combinations into verbal information, then process the verbal information, and then develop the appropriate preparatory response.

The process of interpreting verbally the meaning of the information tones constituted an additional information processing step that presumably involved additional pupillary activity. It is possible that the stress of uncertainty was counterbalanced by the information processing activity. Thus the lack of significant differences.

C. Strength of noxious stimulation. Despite significant differences in both ratings and pupil size due to different intensities, the pain experienced may not have been strong enough for information per se to make a difference. For ethical reasons the intensities used could not be increased. Subjects were told that they would receive only the highest intensities acceptable to them.

At moderate levels of intensity the pain sensory system is less variable, responses are more predictable, less influenced by subjective factors. In fact, some investigators that used uncomfortable but non-painful stimulus intensities (such as Klemp and Rodin, 1976, and Baltissen and Boucsein, 1986) were unable to obtain significant differences in the reported intensity of the stimulus as a result of uncertainty reduction.

The "specificity theory", developed originally by Von Frey, incorrect in its psychological aspect of prediction, assumed a one-to-one correspondence between the physical aspects of the stimulus and the organism's response to it (Melzack & Wall, 1982). This correspondence is more true of senses other than pain. Exact prediction of the pain response is impossible because each individual has an accumulation of psychological experiences (memories) regarding pain that are not apparent. In addition there are factors simultaneous with the experience, that may alter it. Past cultural and individual history factors, and present psychological factors cancel the specificity between noxious stimulus and pain response. Even if the receptors, the pathways, and their destination in the brain were indeed "specific", the effect of the intervening factors that modulate pain would have to be computed in order for the outcome to be predicted accurately.

The "specificity model" is closer to reality at more moderate levels of intensity because the emotional aspects are less at play, as in the traditional senses (of touch, warmth, etc.). If not enough pain was produced in our study the "specificity model" would apply and the various treatments would not have a significant effect in altering the experience.

D. Level of anxiety. Malow (1981) was able to successfully demonstrate the effects of anxiety on pain perception by first documenting the presence of anxiety independently of the experimental manipulation. He used self-report as well as physiological indices to define the level of anxiety in his subjects. He induced anxiety through threat of shock, independently of the experimental manipulation of pressure pain. In another study (Malow, 1987), he used severely anxious subjects, identified through test scores, who were submitted to therapy for anxiety reduction. Again, reduction of anxiety was independently measured, not assumed. In both studies he obtained significant differences in both discriminability and response bias as a result of the anxiety treatment.

In our study, anxiety was not measured independently. We cannot say with certainty that anxiety was present in a significant way in the subjects. The atmosphere during the study was overall a relaxed one. In addition, the information tones served as a warning signal in all trials across all conditions and may have possibly reduced any existing level of anxiety.

Providing information, or denying it, may not have effectively reduced anxiety or produced a significant amount of it. Although it is probably true that uncertainty is associated with some degree of anxiety, and also probably true that anxiety can be reduced by reducing uncertainty, it is not necessarily true that anxiety was felt by subjects in this experiment.

Thus the role of information as an anxiety reducing agent could not be observed.

E. Information processing as a diversion of attention. Cognitive methods of pain control, that is, coping strategies, have been described as a way of ameliorating the impact of a noxious stimulus. A variety of techniques, such as singing a song, imagining pleasant thoughts, examining the surroundings, and many others, have been reported to be effective in diverting the subjects' attention from the noxious stimulus and increasing tolerance (Wack & Turk, 1984).

This role of information was also considered. But in our study the subjects'primary focus of attention had to be on the stimulus in order to give an accurate rating, and not on the information provided. Thus information processing could not act as an effective diversion from pain and its role as such was not in effect.

In a related study, Spanos et al (1987) were similarly unsuccessful in reducing pain reports with a redefinition strategy. They asked subjects to focus their attention on sensations during noxious stimulation so attention to the noxious experience seems to have precluded any pain-reducing role that the information on expectancies could have had.

F. Were pain ratings the proper tool? Measures other than pain ratings, perhaps more sensitive to the influence of psychological factors, may have been a more appropriate tool in assessing the role of information.

Both pain threshold and pain tolerance measures correlate highly, but each reflects specific aspects of the pain experience. Wolff (1964) concluded that the pain detection threshold is more sensitive to physiological or sensory variables while pain tolerance more sensitive to psychological variables. Studies like Zelman et el's (1991) seem to support this as they obtained changes only in tolerance time, as a result of cognitive manipulations. Tursky (1974) found no consistent differences in detection thresholds but did find highly significant differences in tolerance levels due to ethnocultural background.

However, the relative vulnerability of pain detection and pain tolerance to psychological variables is still controversial. Studies such as Clark and Goodman's (1974) show that both are influenced, although even in their case there was a somewhat larger effect of suggestion on pain tolerance than on pain detection.

Regardless of which is more vulnerable, it is clear that neither detection nor tolerance thresholds are fixed sensory parameters, but rather, measures that respond to psychological manipulation and which represent different criterion locations along the pain decision axis (Clark & Goodman, 1974).

It is also clear that assessment tools can be relatively different in their ability to access specific sensory/affective components of the pain experience. For example, Zelman et al (1991), who altered the emotional state of their subjects through mood induction procedures, were able to change the length of time subjects were willing to tolerate a noxious stimulus but unable to affect verbal pain magnitude ratings.

Perhaps a more direct measure of pain tolerance such as withdrawal time, rather than pain ratings, would have been a more suitable tool to bring out the effect of the information variables.

G. Clinical versus experimental pain

It is possible that, unlike clinical situations in which knowledge about the noxious events seems to at least help the patient cope, information does not act as a significant factor in the laboratory.

There is some evidence to indicate that experimental pain is qualitatively different from clinical pain in various aspects. Price (1988) proposed a two-stage theory of pain, the first of which is the immediate sensation that covaries with the intensity of the noxious stimulus. The second stage is dependent upon contextual factors and perceived implications or meaning of the pain sensation. It is more susceptible to alterations in the stimulus-response function.

Price reports that, while cancer patients rated pain sensation intensities at comparable levels with patients of other less life threatening conditions, their affective ratings were higher. This is presumably because of the implications associated with the pain in each case (Price, Harkins & Baker, 1987). Further, Chapman, Dingman and Ginzberg (1965) reported that proven analgesic agents did not alter the detection of experimentally induced radiant heat pain.

The experimental situation, because of less meaning attached to the experience, is less emotional, less susceptible to alteration by contextual or psychological factors. Its context is comparatively benign and involves no implications of present or future bodily harm, nor of further pain, and no interruption of one's life in any significant way. Davidson and Neufeld (1974) failed to obtain increases in situational anxiety in their pain group, a result they describe as specific to the experimental pain situation in contrast to typical clinical pain.

However, this should not cast doubts on the usefulness of experimental pain in analgesic drug research. Yang, Clark, Ngai, Berkowitz and Spector (1979) obtained reduced discriminability as well as increased pain report criteria to radiant heat stimulation with intravenous administration of morphine, and to a lesser extent, with diazepam. Yang, Clark, Dooley and Mignogna (1982) also obtained lower pain reports to ischemic pain after intranasal application of cocaine. The effect was analgesic, and not due to affective or motor changes, because according to the authors the dosage used was smaller than that necessary to produce euphoria. Further, breathing nitrous oxide induced analgesia, and produced an increase in response criteria to ischemic pain (Yang, Clark & Ngai, 1980).

These studies suggest that dose levels and routes of administration (oral versus intravenous or intranasal) are important and may explain the lack of results in Chapman's studies, and also that diazepam, as an anxiolitic agent, appears to be less effective than morphine or cocaine in reducing pain ratings.

Further, Haslam (1966) effectively introduced anxiety into the experimental situation by adding threat of shock to the experimental radiant heat procedures and obtained lower pain thresholds. These results tend to support the notion that when experimental pain is accompanied by anxiety, psychological factors can be more effective.

In conclusion, despite obvious differences between clinical and experimental pain, it is possible, though more difficult, to alter the pain experience in the laboratory, given that the affective aspects in experimental pain are indeed weaker than in clinical pain.

Our study did not include the inducement of anxiety, and the subjects were given assurances that the equipment was safe and amply tested, and that stimuli would not result in any damage whatsoever. These assurances, perhaps excessive, could have further contributed to the reduction of the affective component, and consequently, to the lack of significant effects.

The role of delays

Knowing the length of the delay before stimulus onset allows the organism to get "ready" for the stimulus. Shorter delays allow better predictability and are preferred by both human and animal subjects (Hare et al, 1966). They result in lower anxiety ratings (Klemp and Rodin, 1966). Thus they were assumed to be less stressful and expected to result in smaller responses. However, the length of the delay did not make a significant difference on any of the variables measured.

Several significant interactions regarding delay were observed. Information about delay by Delay was significant in both pupillary responses and ratings.

Delay by Sex was significant in pupillary data and Information about delay by Intensity was significant in discriminability data. These could be indicative of an effect that needs to be more defined and isolated in future studies so that it can surface more clearly.

Contrary to expectations, non-significant but slightly larger pupil dilation curves were obtained following shorter delays. It was hypothesized that after shorter delays pupillary activity reflected an information processing component in addition to that associated with the electrodermal stimulus. Auditory stimuli were presented in different combinations and their meaning had to be interpreted by the subject. This required cognitive processing which results in pupillary activity (Hakerem, 1973), in addition to that produced by the noxious stimulus.

Further, the preparatory responses believed to take place during the shorter interval may also be associated with additional pupillary activity lasting beyond stimulus onset. Simple motoric responses for example, were shown to involve pupillary activity lasting two seconds, and occuring prior to and after movement onset (Richer & Beatty, 1985).

Preparatory responses are not as likely during longer delays, or when length of delay is not known. During longer delays information processing is completed before stimulus onset and thus no added pupillary activity would be observed.

The lack of significant differences between dilations following short and long delays may then be the result of these different pupillary mechanisms interacting. That is, the increase in pupil size due to noxious stimulation after short delays may also be reflecting the activity of an information processing component, and a preparatory response component. After long delays only the noxious stimulation may be reflected.

This pupillary information processing component should not affect pain ratings. The effect of long delays, which make stimulus onset less predictable and thus, presumably more stressfull, should be reflected by the ratings. In fact, pain ratings tended to be higher for the longer delays, but not significantly.

Another factor that may have obscured the effect of delays and information about delays is the optimal length of the delay for achieving predictability. Likken (1962) determined that one second was the optimum delay length for obtaining smaller autonomic responses to noxious stimulation in rats.

Katz's (1984) subjects always received an electric shock exactly three seconds after a certain light went on. Katz also used verbal ratings and an autonomic index (skin resistance) to assess the effects of information about delay. He obtained smaller autonomic responses in predictable conditions, paralleling both the subjects' lower rating of their anticipatory distress and their lower perceived aversiveness of the shock itself. In our study the delay was 4-9 seconds and the subjects were only informed that the delay would be "short" or "long", but not how long. Thus predictability was considerably lower, perhaps enough to explain the lack of significant results.

Sex differences

Typically, males have been found to tolerate higher levels of pain than females, but reports of no difference, of females' higher tolerance, also abound in the literature. To illustrate, Spanos et al (1987) using pain reduction strategies, obtained less pain reports from males than from females. Yet, in a previous study (Spanos, Hodgins, Stam & Gwynn (1984), using the same noxious stimulus intensities and conditions, they found no sigificant sex difference.

SDT treated data more commonly reflect equal discriminability between the sexes and higher stoicism among males. It has been argued that results are not due to differences in sensitivity but to culturally acquired differences in criteria for reporting pain.

In the present study, subtle sex differences were obtained (perhaps due to unequal group sizes and different ethnic compositions) in ratings, pupil size, response criteria and discriminability, though none were significant. Males started reporting sensation at a point 12 volts lower than females and their highest tolerable intensity was 5 volts lower. Their lower tolerance level could be related to a lower detection level as in the "psychological anchor effect" (Clark & Hunt, 1971), in which the standards set by the subject vary according to an anchor point.

A "sensitivity range", which may be operationally defined as the difference between the first felt and highest tolerated intensities, was 49 volts for males compared to 41 volts for females. Males may have given higher ratings at the high point because they experienced a broader range of stimulus intensities than females relative to their anchor point.

On the other hand, the results may have been due to the relative stresfullness of the experimental situation for each group. Female subjects may have been relatively more relaxed in the presence of a same-sex experimenter. Bobey and Davidson (1970), when attempting to induce anxiety in female subjects in order to reduce tolerance levels, were successful only with a different-sex (male) experimenter. Besides, the presence of a Hispanic experimenter could also explain some of the differences.

Wolff and Langley (1968) reported on the tendency of ethnic groups to behave according to the perceived standards of the experimenter's ethnic background. In our case, 90% of females, compared to only 64% of males, were of a similar ethno-cultural background as the experimenter. Females may have been more relaxed given that their standards were not being challenged, while males were under the stress of a different-sex, and a different-ethnic background experimenter.

A significant Delay by Sex interaction in pupillary data reveals that larger dilations after short delays are evidenced only in males. Since males are believed to have been under more stress than females, it is plausible that they were more involved in the experimental procedure __ that they wanted to "do well" more so than females. The added pupillary activity resulting from information processing and preparatory responses may be reflected in their larger dilations, especially after short delays. Females on the other hand show little difference in dilations after short or long delays, and if anything, they show more activity after long delays.

Definite conclusions on sensitivity and stoicism among the sexes are unwarranted, given unequal group sizes, and all the above mentioned contaminants.

But whatever the interpretation of results, it is noteworthy that findings on "sensitivity" based on detection and tolerance thresholds are consistent with results on d' and on pupillary responses.

Conclusions and future studies

The fact that the pupil can discriminate between intensities reliably, at a level comparable to the verbal response, is an important contribution to pain research. Its usefulness in investigating pain mechanisms and in analgesic drug testing is clear.

The shape of the normal pupillary response curve associated with noxious electrodermal stimulation was drawn. The normal average magnitude or peak diameter size change, peaking delay, and duration were obtained, and the slopes before peak and during return to baseline, were drawn. These can be compared in future studies to those of clinical populations, especially those involving autonomic nervous system deseases, or those involving central cholinergic activity. This could turn the pupil from a descriptive tool into a useful diagnostic tool, as Lepore (1985) suggests.

A future study would have to confirm the role of the information processing component suggested by the data to see if indeed it is present and for how long. Studies on the type and duration of pupillary activity associated with the conversion of auditory stimuli into verbal information and consequently, the processing of the latter, could help to clarify this question.

Another interesting hypothesis that should be further investigated is the applicability to humans of Abbot et al's (1984) notion on the relative effect of pain chronicity in animals. Findings on a possible crossover effect, lead to speculations that two components of the pain response can be identified separately in pupillary responses and in pain ratings. The stress produced by uncertainty appears to weigh more on the pupillary response, while the suggestibility of information appears to modulate ratings. Based on this, the pupil can be said to be more vulnerable to organic factors, and ratings to subjective ones.

A final question remains: As a neurosensory index vulnerable to the stress of uncertainty, is the pupil's response truly specific tc stimulus intensity, or is it merely a reaction to the stress and anxiety produced by the noxious stimulus and by the uncertainty surrounding it? Is the pupil really a "detour from the brain", or is the noxious message reflected in the pupil only after it has been transformed by modulation at higher centers in the brain?

Obviously, findings in this study support the use of pupillometry in the task of unravelling the "mysteries of pain", but, most importantly, these findings challenge us with many more new questions for future research.

Appendix A

INFORMED CONSENT

New York State Psychiatric Institute
722 West 168th Street
New York, N.Y. 10032

I have been asked to participate in a research study on my responses to various intensities of electrical stimulation ranging from just noticeable to painful. The purpose of this study is to better understand the relationship between painful and nonpainful stimuli and the changes they produce in pupil size. (These changes are believed to be related to the arousing or emotional properties of the stimulus.) I understand that you are not interested in the amount of pain I can tolerate, but wish to know how good I am at detecting the presence of a minimal amount of pain.

At present I am not receiving any medical treatment, nor am I taking any medication. I do not take more than two drinks of alcohol a day, use illegal drugs, or smoke over 10 cigarettes a day.

I understand that electrodes will be attached to my fingers. Then, in order to establish the electrical intensities which are acceptable to me, brief (0.5 second) stimuli will be presented in a slowly increasing series beginning at the just noticeable level. After the stimulus intensities have been determined they will be presented randomly with respect to their intensity. The noxious stimulus intensity has been pre-determined by trials on ourselves and is safe. The total number of stimuli over a 5 hour period will be 64 at each intensity. The actual pain testing will take about 3 hours, with an additional 2 hours for rest pauses. Only a single, 5 hour session will be needed.

The circuitry in the electrical stimulator has been approved by our electrical engineer. During the past eight years of electrical stimulation we have experienced no problems. The electrical stimulation may produce a slight reddening of the skin for a few minutes.

I will receive $75.00 for participation in this study. I will be paid at the rate of $13.00 an hour for the first 3 hours and at $18.00 an hour for the last two hours.

I understand that this study will not benefit me directly. However, the study may lead to a greater understanding of how emotions affect pain perception and thus help in the medical treatment of others. My participation is voluntary, and I may discontinue the procedures at any time without the loss of any benefits to which I am otherwise entitled.

The results of the tests will be considered confidential and kept in the Psychiatric Institute. Only the research staff will have access to these files. When the results of the study are presented, no individual identifying information will be used under any circumstances.

I understand that if I have any questions about these procedures or my responses to them, I may call Dr. Crawford Clark, Ph.D. at (212) 960-2480 (work).

The New York State Psychiatric Institute-Columbia University Department of Psychiatry Institutional Review Board has approved the recruitment of subjects for this study.

I understand that any injuries resulting from my participation in this study, and which might occur from the known or unknown risks of the research described to me, will receive immediate medical care and treatment, including hospitalization if necessary. Emergency medical treatment within the capability of New York State Psychiatric Institute, will be provided free of charge. If I require additional hospitalization I understand that funds are not available to cover additional medical treatment or other compensation.

I have read this form and all of my questions have been answered satisfactorily. If I wish additional information concerning my rights as a research subject I may call the Institutional Review Board Coordinator at (212) 960-5758. I am over 18 years of age. I have been given a copy of this consent form to keep.

NAME (Print) --

Signature --

Date --

Address ---

Telephone ---

Social Security no. ---------------------------------

Appendix B

Subject No.	Age	Sex	Order	Ethno-cultural
01	24	F	ACBD*	N**
02	50	M	BACD	N
03	37	M	DBCA	H
04	25	M	CADB	N
05	21	M	ABDC	H
06	34	M	BDAC	N
07	35	F	CDAB	H
08	33	F	ADBC	H
09	19	F	DCAB	H
10	19	F	DABC	H
11	35	F	BADC	H
12	29	F	BCDA	H
13	40	F	ACDB	H
14	23	M	DACB	N
15	27	F	CABD	H
16	40	M	ABCD	H
17	21	M	CBDA	H
18	46	M	CDBA	H
19	31	F	DBAC	H
20	47	M	BDCA	H
21	28	M	CBAD	H
22	37	M	DCBA	H
23	28	M	BCAD	N
24	29	M	ADCB	H

Sample characteristics

* A = Information about intensity and delay
B = Information about delay
C = Informtion about intensity
D = No information

** N = North American Caucasian
H = Hispanic

Appendix C

INSTRUCTIONS TO SUBJECTS

1. Purpose. The purpose of the experiment is to measure the changes in the size of the pupil as a result of electrical stimulation. Current will be delivered to these two fingers, in varying intensities and in random order. Meanwhile, a camera focused on your eye will be measuring your pupil.

2. Overall. The experiment is divided into 4 parts of 64 trials each. The difference between each part will be the information that I will give you about the current in each. I will place these electrodes on your fingers and I will prepare an impression of your teeth in a clay compound so that you will have no trouble staying still while the pupil is being measured. In each trial you will receive an electrical current that will be less than 1/2 second long. Sometimes the current will be mild, sometimes it will hurt, although it is not harmful in any way. You will determine the highest intensity to be used in the experiment by showing me what is the highest that you can tolerate in a preliminary test.

3. Information. During each trial you will hear some tones that give you the information about the current, and hopefully will help you prepare yourself for it. Three aspects of the tones give information:
    a) When they appear within the trial (i.e., first, here, or second, here - show diagram).
    b) Whether they are short or long (I will demonstrate shortly).
    c) Whether they are one or two tones.

4. Trials. The sequence of events in each trial is like this (show diagram).
    a) The first set of tone or tones give information about intensity:
        1 long tone means NO information.
        1 short tone means that the current will be low.
        2 short tones mean that the current will be high.
    b) The second set of tones give information about time, or the delay between the tone(s) and the current itself.
        1 long tone means NO information.
        1 short tone means a relatively short delay.
        2 short tones mean a relatively longer delay.

I will explain these again before each session of the experiment, and I will tell you what you can expect regarding the information tones before each part begins.

I will <u>not</u> try to trick you. the information will always be accurate.

c) After the delay tones there will be a delay that will vary in length randomly, and then you will feel the current. Three seconds later you will hear a last tone that tells you the trial is over. You then relax and describe the sensation by saying a number according to this scale from "0" to "11". (Show scale and explain it.)

5. <u>Blinking.</u> Since the purpose of the experiment is to measure the pupil, it is very important to be perfectly still, to fix your eye on this red light, and <u>not</u> to blink when the pupil is being measured. This happens immediately after the delay tones here (show diagram) up until you hear the last response tone. You should especially not blink during or after the current is on. Blinking is OK after that last tone. As soon as you are ready for the next trial you should go back on the bite board by biting on the dental impression. When I see your eye on that monitor I will start a new trial.

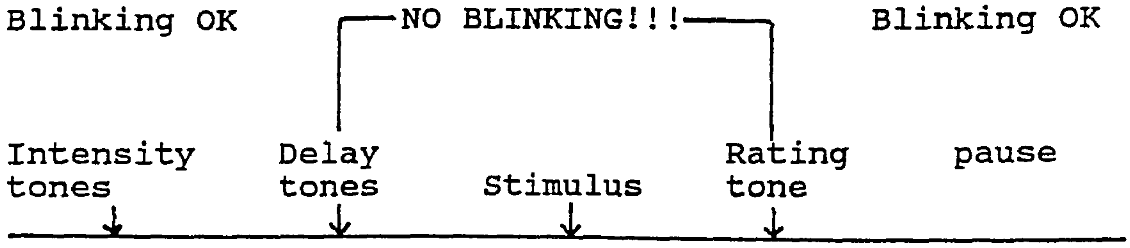
6. <u>Rests.</u> Periodically, I will tell you what trial number we are on. You can take a rest in between sessions. If you need to rest at any time within any of the 4 sessions, you simply tell me, or you don't go back on the bite board. When I don't see you eye on the monitor I will assume you are not ready for the next trial and thus I will not continue until I do.

7. <u>Pretest.</u> Before we start the experiment we will do a preliminary test to determine your sensitivity to electrical stimulation. In this test I will start by giving you very low current, and I will increase the intensity as we go along. You will give me a number using the "0" to "11" scale each time to describe your sensation. When you reach "7" I will alternate lower and higher intensities until you reach the highest intensity you are able to tolerate in this experiment. That will be <u>your</u> number "11". I will then continue to do some additional trials using intensities randomly, to make sure of your sensitivity. During the experiment itself I will use several of the intensities within the range of what you labeled "0" to "11". These will not exceed the intensity you have rated as "11".

Any questions?

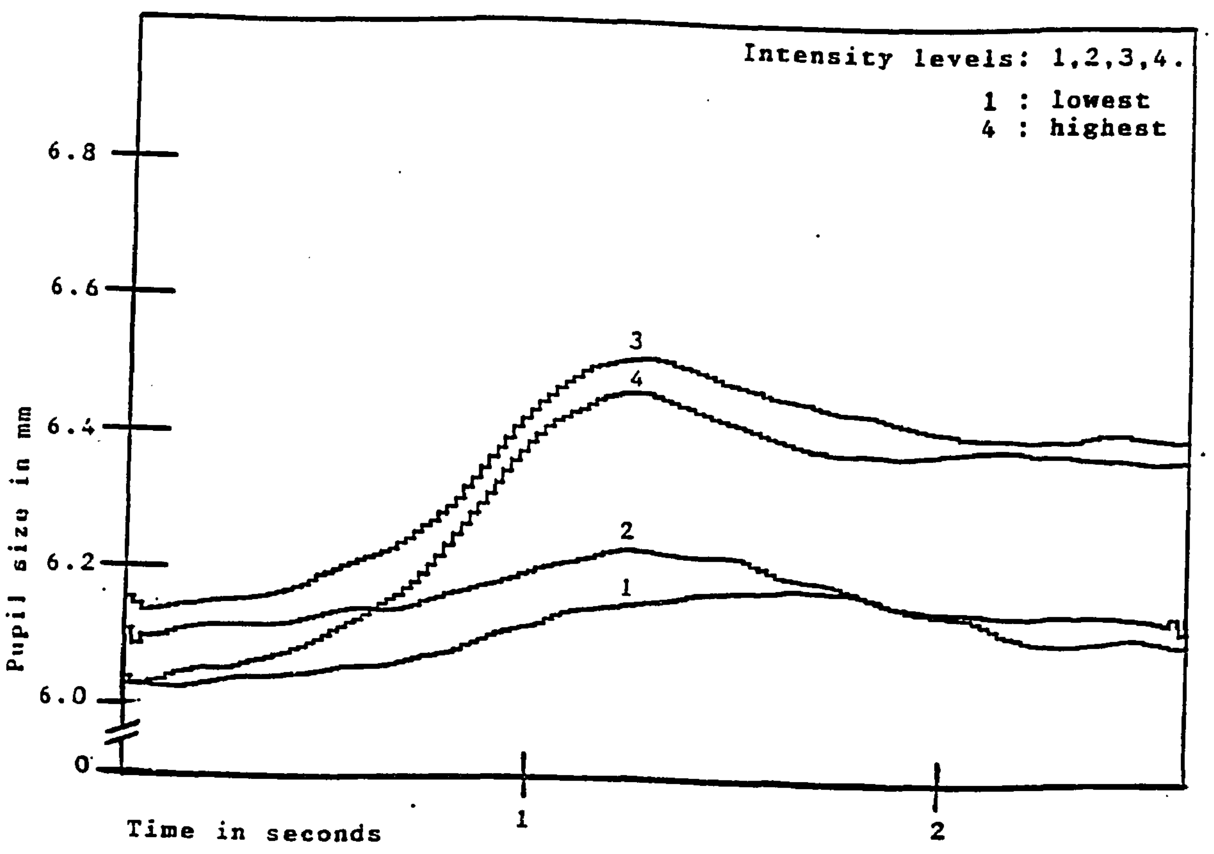
Appendix D

Sequence of events in one trial:



Sequence of events chart used as part of instructions.

Appendix E



Sample pupil size increase after stimulus onset, at each of four stimulus intensities.

Appendix F

	Intensity level:				Means by sex:	
Subj. no.	1	2	3	4	F	M
01	10.5	18.2	39.4	52.5	30.2	
02	04.8	16.8	40.0	52.0		28.4
03	03.6	06.0	21.8	23.6		13.8
04	08.5	10.6	62.3	67.6		37.2
05	07.3	11.0	54.9	59.3		33.1
06	44.4	53.8	145.0	154.4		99.4
07	45.1	50.0	94.2	99.1	72.1	
08	30.3	37.7	77.0	83.1	57.0	
09	40.2	47.5	91.7	99.1	69.6	
10	18.1	27.9	42.6	50.0	34.6	
11	32.8	37.7	59.8	64.7	48.8	
12	18.1	23.0	40.2	47.5	32.2	
13	15.6	20.5	37.7	42.6	29.1	
14	03.4	05.5	31.9	34.0		18.7
15	45.1	47.5	72.1	74.5	59.8	
16	08.2	13.2	23.0	27.9		18.1
17	08.2	10.7	23.0	27.9		17.4
18	25.4	27.9	74.5	79.4		51.8
19	47.5	52.4	94.2	99.8	73.5	
20	23.0	27.9	74.5	79.4		51.2
21	52.4	57.4	97.4	99.8		76.8
22	13.2	18.1	94.9	99.8		56.5
23	23.0	25.4	67.2	69.6		46.3
24	27.9	35.3	54.9	59.8		44.5
Mean:	23.2	28.4	63.1	68.6	50.7	42.4

Intensities administered per subject (in volts).

References

Abbott, B.B., Schoen, L.S. & Badia, P. (1984). Predictable and unpredictable shock: Behavioral measures of aversion and physiological measures of stress. Psychological Bulletin, 96, 45-71.

Abbott, B.B. & Badia, P. (1986). Predictable versus unpredictable shock conditions and physiological measures of stress: A reply to Arthur. Psychological Bulletin, 100, 384- 387.

Anderson, J.L. & Masur, F.T. (1983).Psychological preparation for invasive medical and dental procedures. Journal of Behavior Medicine, 6, 1-14.

Andrew, J. (1968). Coping style, stress-relevant learning and recovery from surgery. Dissertation Abstracts, 28, 1182-B.

Arthur, A.Z. (1986). Stress of predictable and unpredictable shock. Psychological Bulletin, 100, 379- 383.

Baltissen, R. & Boucsein, W. (1986). Effects of a warning signal on reactions to aversive white noise stimulation: does warning "short-circuit" habituation?. Psychophysiology, 23, 224-231.

Bobey, M.J. & Davidson, P.O. (1970). Psychological factors affecting pain tolerance. Journal of Psychosomatic Research, 14, 371-376.

Brodal, A. (1981). Neurological Anatomy (3rd ed.). New York: Oxford University Press.

Cacioppo, J.T. & Sandman, C.A. (1978). Physiological differentiation of sensory and cognitive tasks as a function of warning, processing demands, and reported unpleasantness. Biological Psychology, 6, 181-192.

Chapman, L.F., Dingman, H.F. & Ginzberg, S.F. (1965). Failure of systemic analgesic agents to alter the absolute sensory threshold for the simple detection of Pain. Brain, 88, 1011-1022.

Chapman, W.P. & Jones, C.M. (1944). Variations in cutaneous and visceral pain sensitivity in normal subjects. Journal of Clinical Investigations, 23, 81-91.

Clark, W.C. (1969a). Sensory-decision theory analysis of the placebo effect on the criterion for pain and thermal sensitivity (d'). Journal of Abnormal Psychology, 74, 363-371.

Clark, W.C. (1969b). The effect of information feedback and reference tones on d' and Lx: A further analysis of Nash and Adamson's data. Psychonomic Science, 16, 93-94.

Clark, W.C. (1974). Pain sensitivity and the report of pain: An introduction to sensory decision theory. Anesthesiology, 40, 272-287.

Clark, W.C. (1992). Pain and suffering. Chapter to appear in J.A Downey (Ed.), Physiologic basis of rehabilitation medicine. New York: Demos Publications.

Clark, W.C. & Clark, S.B. (1980). Pain responses in Nepalese porters. Science, 209, 440-442.

Clark, W.C. & Goodman, J.S. (1974). Effects of suggestion on d' and Cx for pain detection and pain tolerance. Journal of Abnormal Psychology, 83, 364-372.

Clark, W.C. & Hunt, H.F. (1971). Pain. In J.A. Downey & R.C. Darling (Eds.), Physiological basis of rehabilitation medicine (pp 373-401). Philadelphia: W.B Saunders Co.

Clark, W.C. & Marmor, E. (1969). Comparison of sensory sensitivities (d') determined from verbal and autonomic responses to electrical stimulation. Paper presented to the Eastern Psychological Association, April 12, 1969.

Clark, W.C. & Mehl, L. (1971). Thermal pain: A sensory decision theory analysis of the effect of age and sex on d', various response criteria and 50% pain threshold. Journal of Abnormal & Social Psychology, 78, 202-212.

Clark, W.C. & Yang, J.C. (1983). Application of sensory decision theory to problems in laboratory and clinical pain. In R. Melzack (Ed.), Pain measurement and assessment (pp 15-25). New York: Raven Press.

Davidson, P.O. & Neufeld, W.J. (1974). Response to pain and stress: A multivariate analysis. Journal of Psychosomatic Research, 18, 25-32.

Dougher, M.J. (1979). Sensory decision theory analysis of the effects of anxiety and experimental instructions on pain. Journal of Abnormal Psychology, 88, 137-144.

Dworkin, S.F., Chen, A.C.N., Schubert, M.M. & Clark, D.W. (1984). Cognitive modification of pain: Information in combination with N2 O. Pain, 19, 339- 351.

Echternach, J.L. (1987). Evaluation of pain in the clinical environment. In J.L. Echternach (Ed.), Pain. Clinics in Physical Therapy (pp 39-59). New York: Churchill Livingstone.

Egbert, L.D., Battit, G.E., Welch, C.E. & Bartlett, M.R. (1964). Reduction of postoperative pain by encouragement and instruction of patients. New England Journal of Medicine, 270.

Farthing, G.W., Venturino, M. & Brown, S.W. (1984). Suggestion and distraction in the control of pain: Test of two hypotheses. Journal of Abnormal Psychology, 93, 266-276.

Fordyce, W.E. (1988). Pain and suffering: A reappraisal. American Psychologist, 43, 276-283.

Grau, J.W. (1987). The central representation of an aversive event maintains the opioid and nonopioid forms of analgesia. Behavioral Neuroscience, 101, 272-288.

Hakerem, G. (1973). The effect of cognitive manipulation on pupillary diameter and evoked vertex potentials. In E. Dodt & K.E. Schrader (Eds.), Prodeedings of the Symposium der D.O.G. (pp 239-245). Munchen: J.F. Bergmann Verlag.

Hakerem, G. & Lidsky, A. (1975). Characteristics of pupillary reactivity in psychiatric patients and normal controls. In Experimental Approaches to Psychopathology (pp 61-72). New York: Academic Press.

Hare, R.D., Krebs, D.L., Creighton, T.D. & Petrusic, W.M. (1966). Latency of self-administered shock as a function of its intensity and probability. Psychonomic Science, 6, 79-80.

Haslam, D.R. (1966). The effect of threatened shock upon pain threshold. Psychonomic Science, 6, 309-310.

Hill, H.E., Kornetsky, C.H., Flanary, H.G. & Wikler, A. (1952). Effects of anxiety and morphine on discrimination of intensities of painful stimuli. Journal of Clinical Investigation, 31, 473-480.

Janal, M.N., Colt, E.W.D., Clark, W.C. & Glusman, M. (1984). Pain sensitivity, mood and plasma endocrine levels in man following long distance running: Effects of Naloxone. Pain, 19, 13-25.

Janisse, M.P. (1977). Pupillometry. New York: Wiley and Sons.

Johnston, M. (1981). Emotional distress immediately following surgery. In J.W.G. Tiller & P.R. Marki (Eds.), Behavioural Medicine. Melbourne: Geigi.

Jones, A., Bentler, P.M. & Petry, G. (1966). The reduction of uncertainty concerning future pain. Journal of Abnormal Psychology, 71, 87-94.

Kanfer, F.H. & Goldfoot, D.A. (1966). Self-control and tolerance of noxious stimulation. Psychological Reports, 18, 79-85.

Kaplan, E.A. (1960). Hypnosis and pain. Archives of General Psychiatry, 2, 567-567.

Katz, R. (1984). Unconfounded electrodermal measures in assessing the aversiveness of predictable and unpredictable shocks. Psychophysiology, 21, 452-458.

Klemp, G. & Rodin, J. (1976). Effects of uncertainty, delay and focus of attention on reactions to an aversive situation. Journal of Experimental-Social Psychology, 12, 416-421.

Krueger, H. & Fazel-Madjilessi, A. (1978). Quantitative determination of sensitivity to pain. Arzeneimittel - Forschung, Sonderdruck.

Lepanto, R., Moroney, W. & Zenhausern, R. (1965). The contribution of anxiety to the laboratory investigation of pain. Psychonomic Science, 3, 475.

Lepore, F. E. (19850. Diagnostic pharmacology of the pupil. Clinical Neuropharmacology, 8, 27-37.

Linton, S.J. & Gotestam, K.G. (1983). A clinical comparison of two pain scales: correlation, remembering chronic pain and a measure of compliance. Pain, 17, 57-65.

Lowenstein, O. & Lowenfeld, I. (1950). Mutual role of sympathetic and of parasympathetic in shaping of the pupillary reflex to light. Archives of Neurology and Psychiatry, 64, 341-377.

Lykken, D.T. (1959). Preliminary observations on the preception phenomena. Psychophysiology Measurement Newsletter, 5, 2-4.

Lykken, D.T. (1962). Preception in the rat: autonomic response to shock as a function of length of warning signal. Science, 137, 665-666.

Lynn, R. & Eysenck, H.J. (1961). Tolerance for pain, extraversion and neuroticism. Perceptual and Motor Skills, 12, 161-162.

Malow, R.M. (1981). The effects of induced anxiety on pain perception: A signal detection analysis. Pain, 11, 397-405.

Malow, R.M., West, J.A. & Sutker, P.B. (1987). A sensory decision theory analysis of anxiety and pain responses in chronic drug abusers. Journal of Abnormal Psychology, 96, 184-189.

Malow, R.M., West, J.A. & Sutker, P.B. (1989). Anxiety and pain response changes across treatment: sensory decision analysis. Pain, 38, 35-44.

Manheimer, J.S. (1984). Differential evaluation for the determination of T.E.N.S. effectiveness in specific pain syndromes. In J.S. Manheimer & G.N. Lampe (Eds.), Clinical transcutaneous electrical nerve stimulation, (pp 63-189). Philadelphia: F.A.Davis Co.

Marino, J., Gwynn, M.I. & Spanos, N.P. (1989). Cognitive mediators in the reduction of pain: The role of expectancy, strategy use, and self-presentation. Journal of Abnormal Psychology, 98, 256-262.

Melzack, R. (1991). The gate control theory 25 years later: New perspectives in phantom limb pain. In M.R.Bond, J.E. Charlton & C.J. Woolf (Eds.), Proceedings ofthe VIth World Congress on Pain, pp.9-21, Amsterdam:Elsevier.

Melzack, R & Wall, P.D. (1982). The challenge of pain. Harmondsworth: Penguin Press.

Melzack, R. & Wall, P.D. (1965). Pain mechanisms: A new theory. Science, 150, 971-979.

Myers, S.J., Janal, M.N., Pai, L.T. & Clark, W.C. (1982). A model of clinical pain. Technique for evaluation of analgesic agents. American Journal of Physical Medicine, 61, 1-10.

Moltner, R., Holzl, R. & Strian, F. (1990). Heart rate changes as an autonomic component of the pain response. Pain, 43, 81-89.

Orne, M.T. (1962). On the social psychology of the psychological experiment. American Psychologist, 17, 776-783.

Perry, F., Heller, P.H., Kamiya, J. & Levine, J.D. (1989). Altered autonomic function in patients with arthritis or with chronic myofascial pain. Pain, 39, 77-84.

Potts, Carson, T. & Carson, R.C. (1984). The affective disorders. In H.E. Adams & P.B. Stutker (Eds.), Comprehensive Handbook of Psychopathology (pp 349-381). New York: Plenum Press.

Price, D.D. (1988). Psychological and neural mechanisms of pain. New York: Raven Press.

Price, D.D., Harkins, S.W. & Baker, C. (1987). Sensory affective relationships among different types of clinical pain and experimental pain. Pain, 3, 1-8.

Richer, F. & Beatty, J. (1985). Pupillary dilations in movement preparation and execution. Psychophysiology, 22, 204-207.

Richer, F., Silverman, C. & Beatty, J. (1983). Response selection and initiation in speeded reactions: A pupillometric analysis. Journal of Experimental Psychology: Human Perception and Performance, 9, 360-370.

Spanos, N.P., Cross, W.P. & Watson, E. (1987). Expectancy, redefinition and reported pain. Perceptual and Motor Skills, 64, 355-358.

Tan, S. Y. (1982). Cognitive and cognitive-behavioral methods for pain control: A selective review. Pain, 12, 201-228.

Tursky, B. (1974). Physical, physiological and psychological factors that affect pain reaction to electric shock. Psychophysiology, 11, 95-112.

Wack, J.T. & Turk, D.C. (1984). Latent structure of strategies used to cope with nociceptive stimulation. Health Psychology, 3, 27-43.

Wallace, L.M. (1985). Surgical patients' expectations of pain and discomfort: Does accuracy of expectations minimize post-surgical pain and distress? Pain, 22, 363-373.

Wolff, B.B. (1964). The relationship of experimental pain tolerance to pain threshold: A critique of Gelfand's paper. Canadian Journal of Psychology, 18, 249-253.

Wolff, B.B. & Langley, S. (1968). Cultural factors and the response to pain: A review. American Anthropologist, 70, 494-501.

Yang, J.C., Clark, W.C., Ngai, S.H., Berkowitz, B.A. & Spector, S. (1979). Analgesic action and pharmacokinetics of morphine and diaxepam in man: an evaluation by sensory decision theory. Anesthesiology, 51, 495-502.

Yang, J.C., Clark, W.C. & Ngai, S.H. (1980).Antagonism of nitrous oxide analgesia by naloxone in man. Anesthesiology, 52, 414-417.

Yang, J.C., Clark, W.C., Dooley, J.C. & Mignogna, F.V. (1982). Effect of intranasal cocaine on experimental pain in man. Anesthesia and analgesia, 61, 358-361.

Zatzick, D.F. & Dimsdale, J.E. (1990). Cultural variations in response to painful stimuli. Psychosomatic Medicine, 52, 544-557.

Zelman, D.C., Howland, E.W., Nichols, S.N. & Cleeland, C.S. (1991). The effects of induced mood on laboratory pain. Pain, 46, 105-111.