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THE EFFECT OF PAIN ON EARLY ATTENTIONAL PROCESSING

by

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Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy

at

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ABSTRACT

Three studies were carried out to investigate pain's effects on early attentional processes. Previous research has found that pain can disrupt attentional processing. The Mismatch negativity (MMN) event-related potential has been established as a hardwired index of early auditory pitch difference detection. It is elicited independent of active attentional focus but can be modulated by focused attention and attentional demand. In the present studies, participants' MMN was used to compare early attentional processing between no-pain and pain conditions. In Experiment 1, healthy volunteers' MMN was recorded using a passive auditory paradigm where auditory stimuli were presented during a simple visual task. Recordings were taken during no-pain, experimentally induced cold pressor pain, and experimentally induced ischemic pain conditions. No difference was found in MMN amplitude or latency between these conditions. In Experiment 2, MMN in another group of healthy volunteers was compared between no-pain and experimentally induced ischemic pain conditions using passive and active auditory attention paradigms. The attentional demand of the visual task in the passive condition was greater than in Experiment 1. As well, the discrimination difficulty level of the auditory stimuli was also varied in both attention conditions. As in Experiment 1, no differences were found in MMN amplitude or latency between the pain conditions. The attentional demand of the auditory task did not affect pain's effects on MMN. Experiment 3 used the same auditory paradigms as Experiment 2. However, participants were individuals with intractable chronic pain. These participants were tested before and after receiving nerve block injections for their pain. Although pain did not affect MMN during the active auditory attention task, it did decrease MMN amplitude during the passive auditory task. The findings of these studies suggest that the nature and level of pain may be a key factor during cognitive processing of attentionally demanding tasks.

LIST OF ABBREVIATIONS AND SYMBOLS USED

BDI-II	Beck Depression Inventory – Second Edition
CPMCQ	Chronic Pain Memory Complaint Questionnaire
DST	Digit Symbol Test
EEG	Electroencephalogram
ERP	Event-Related Potential
FMS	Fibromyalgia Syndrome
m	meters
ms	milliseconds
μV	microvolts
MMN	Mismatch Negativity
MOQ-2	Memory Observation Questionnaire – Second Edition
MPQ	McGill Pain Questionnaire
MSPQ	Modified Somatic Perception Questionnaire
N1	Negative deflection event-related potential occurring approximately 100 milliseconds post-stimulus.
Nd	Negativity difference event-related potential.
NRS	Numerical Rating Scale
P3	Positive deflection event-related potential occurring approximately 300 milliseconds post-stimulus.
PASAT	Paced Auditory Serial Attention Task
PCS	Pain Catastrophizing Scale

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Introduction

The increase in the body of research that investigates pain's effects on cognition reflects the growing acknowledgement of the importance of these effects. While the methodologies used vary considerably (Eccleston, 1995a; Rainville et al., 1997; Grace et al., 1999; Derbyshire, 1999; Hutchison et al., 1999), the rationale of these studies is consistent. Few would argue that pain interferes with one's ability to function on many levels, including cognitively, however how this interference occurs is not well understood. It has only been with the development of sophisticated measurement strategies that the details of the relation between pain and cognitive processes such as attention have been more broadly and effectively investigated empirically.

This dissertation discusses the results of three studies aimed at further clarifying pain's effects on cognitive processes. In particular, pain's effects on the attention-related processes that occur during the early stages of stimulus processing are examined. Prior to the presentation of these results, relevant empirical studies will be discussed in order to create a context in which to discuss the rationale for these studies and the implications of their results. This research review includes work that has investigated the effects of pain on attention as well as neuroimaging studies that have examined where in the brain pain might exert its effects on attention. A review of the literature relevant to the study of early auditory attentional processing using event-related potentials (ERP's) is also included in order to provide a link between the existing literature related to imaging pain's effects on attention and the three studies reported thereafter.

Pain and attention

The study of pain's effects on cognition has important implications in the domains of basic level science and clinical science. From a clinical perspective, this is a particularly relevant area of study because many chronic pain patients report pain-related cognitive deficits including

problems with attention and concentration. It is important to note that among the studies that will now be reviewed, some of these studies have reported the subjective effects of pain by patient report on attention while others have examined these effects using empirically based, objective measures. Studies of the subjective effects of pain offer important insight into the changes and functional deficits that occur in individuals who experience pain, particularly chronic pain. It is noteworthy to mention here that many patients with chronic pain suffer from some disorder or injury that caused the pain that may create additional complications other than just pain. Some disorders may include other factors that create attentional disruption other than pain (e.g., anxiety or depression). Thus, it is not easy to attribute differences between individuals with pain, including chronic pain, and those without pain solely to the effect of the pain. Empirical studies provide information that allows us to compare performance between individuals who experience pain from those who do not. However, some empirical studies have control procedures built into the experimental design that may reduce the ecological validity of the results. Despite the limitations inherent to both of these kinds of studies, each method provides us with very useful and complementary information regarding how pain affects cognitive function.

In an early study, Westin (1973) reported a higher prevalence rate of concentration and memory deficits in pain patients compared to matched controls. Astrand (1987) later found that back pain patients showed deficits on verbal and nonverbal cognitive tasks. Jamison and colleagues (1988) highlighted the widespread impairments in daily functioning that were suggested to result from pain. In this study, individuals with chronic pain reported a range of difficulties with attention and memory. In order to evaluate the extent of these complaints more objectively, Jamison and colleagues used a screening inventory consisting of a 90 symptom item checklist (Symptom Checklist 90; SCL-90), a pain evaluation questionnaire, and subjective

physician ratings of the levels of patient nervousness, depression, irritation, and symptom dramatization and exaggeration. Patients who reported more problems with concentration and memory also reported more psychosocial and functional problems such as disharmony in family and other social relationships, difficulty in performing household chores, recreational activities, and physical activity, including exercise. An increase in anxiety and depression as well as increased sleep disturbance was also reported. Results were also cited from a subgroup of these patients who were evaluated following treatment in a six-week multidisciplinary pain program that suggested that patients who reported more problems with concentration (attention) and memory were less likely to be able to return to active employment and normal daily functioning. As a result of their findings, Jamison and colleagues called for further and more objective empirical evaluation of the extent of cognitive deficits in pain patients, citing that the evaluation of attention and memory deficits in this population had previously been given little attention in the literature.

Despite this call from Jamison and colleagues, only a small body of research was carried out aimed at empirically examining how pain affects cognitive function. This work used both quantitative and qualitative measures and focused primarily on pain's effects on attention and memory. Kewman and colleagues (1991) investigated the incidence of cognitive impairment in patients who experienced chronic musculoskeletal pain. Signs of cognitive dysfunction were assessed using the Neurobehavioral Cognitive Status Exam (NCSE), a brief standardized screening test of cognitive function. These researchers reported that while most healthy adults achieve nearly perfect scores on the NCSE, 32% of their pain patient sample scored in the impaired range on one or more test index. Most of these impaired scores fell in the domain of attention or memory. Both patient pain ratings, duration of pain, and a measure of disability were

significantly correlated with NSCE scores ($p < .001$). However when a measure of psychological distress was held constant, these correlations were no longer significant. As a result of their findings, Kewman and colleagues also called for an extension of work such as theirs using tools such as a more comprehensive neuropsychological assessment battery and diagnostic imaging.

Two later papers attempted to further address pain-related cognitive deficits. Unfortunately, the conclusions put forth by both were severely constrained by methodological weaknesses. Schnurr and MacDonald (1995) examined the prevalence of memory complaints in two groups of chronic pain patients, one group who had chronic pain and a head injury as a result of a motor vehicle accident, and another with chronic pain due to work-related musculoskeletal pain. Memory complaints from these groups were compared to the frequency of memory complaints of a group of pain-free psychotherapy patients and a group of pain-free controls. The measures used in this study consisted only of an extensive questionnaire, the Chronic Pain Memory Complaint Questionnaire (CPMCQ) designed for the study, the Beck Depression Inventory, the State-Trait Anxiety Inventory, and the Memory Observation Questionnaire – 2 (MOQ-2), a standardized questionnaire that was developed and validated for use with geriatric and demented populations. Schnurr and MacDonald reported that results from the MOQ-2 and the CPMCQ indicated that both groups of chronic pain patients felt that they had more problems with memory than that two pain-free control groups. Unfortunately, they did not collect actual performance measures to compare the levels of functioning of these patients to that of pain-free controls. Of related importance, both of the chronic pain groups were found to report more anxiety and depression than both of the pain-free psychotherapy and control groups. Given the many prior empirical studies linking depression to memory and attention deficits (e. g., Whitehouse, Turanski, & Murray, 2000; Sweeny, Wetzler, Stokes, & Kocsis, 1989), it is possible

that these differences in anxiety and depression could account for an increase in the reported cognitive deficits. In fact, when the depression scores were covaried out, differences in memory complaints between groups disappeared on the MOQ-2 but not on the CPMCQ. Schnurr and MacDonald also called for further study with more objective and standardized measures in order to further clarify the nature of pain's effects on cognition.

Another report that examined cognitive problems related to pain was published by Grigsby and colleagues (1995). This methodologically limited study, a retrospective chart review that did not include a control group, also suggested the importance of pain's disruptive effect on cognition. Grigsby and colleagues compared achievement on the Human Performance Measurement System – Basic Elements of Performance I (HPMS – BEP I) of a group of chronic pain patients to a group of pain-free head trauma patients. The HPMS – BEP I consists of a series of computerized tasks that evaluate measures of motor speed, motor coordination, visual short-term memory, and processing speed. Of primary interest in this study was patients' performance on processing speed tasks that progressively increased in complexity and cognitive demand during task performance. With the exception of one motor coordination and two visual short term memory tasks where pain patients scored nearly equally well with head trauma patients, the pain patients scored significantly lower on two measures of central processing speed and markedly, but not statistically significantly, lower on all of the seven remaining measures. It is very interesting to note the consistent trend in this study of poorer cognitive performance by chronic pain patients compared with head trauma patients who would be expected to show cognitive deficits due to their head injuries.

A few studies have investigated pain's effects on cognitive function using more objective and better standardized measures and experimental paradigms. Using standardized

neuropsychological assessment techniques, Sletvold and colleagues (1995, 1997) examined information processing deficits evident in chronic pain patients with a primary diagnosis of Fibromyalgia Syndrome (FMS). The performance of these pain patients was compared to the performance of a group of patients diagnosed with major depressive disorder, and a group of healthy controls. In their first report, Sletvold, Stiles, and Landro (1995) reported the performance of their three experimental groups on a test of psychomotor performance (Digit Symbol Test, DST), a test of attention and speeded response (Trail Making Test, TMT), and a test of information processing capacity related to working memory (Paced Auditory Serial Addition Task, PASAT). When comparing the differences in the performance of the three groups, it was found that both depressed and FMS patients performed significantly more poorly than the healthy controls on the Digit Symbol Task and the memory Paced Auditory Serial Addition Task. These effects were true of both depressed and non-depressed FMS patients and lead Sletvold and colleagues to suggest that cognitive deficits manifested in their pain patients could be related to the patients' pain syndromes. In the second report from this group, Landro, Stiles, and Sletvold (1997) reported data from the same participants on a battery of memory measures. These measures included a test of auditory working memory (Digit Span Forward), long term memory (Randt Memory Test), retrieval from long term memory after interference (Code Memory Test), semantic memory (The Word Fluency Test), and recognition memory (Kimura Recurring Recognition Figures Test). Patients in the major depression and FMS groups showed performance deficits on the Randt Memory Test, the Code Memory Test, and the Word Fluency task compared to the healthy control group. However, in contrast to Sletvold et al. (1995), only Fibromyalgia patients with a history of depression showed these deficits. Although it is unclear why memory deficits were linked to depression in FMS patients while other

information processing deficits were not, it is still noteworthy that the Sletvold et al. (1995) data provided further evidence of pain's disruptive effects on cognition and suggested the need for research to further clarify these effects.

Eccleston performed a series of studies that investigated the effects of chronic pain on attention. These studies used an attentionally demanding numerical interference task first reported by Windes (1968). Eccleston (1994) examined the performance of groups of chronic pain patients was reported using two variations of this task. In the first experiment, a group of chronic pain patients separated into high and low pain groups and a group of healthy controls were presented with the image of a single stimulus resembling a numerical playing card on a computer screen (see Figure 1). Each card contained a variable number of digits where each digit on each card was of the same numerical value. Participants were required to respond by giving either the value of the digit displayed on the card, or a more difficult task of choosing how many digits were displayed on the card in separate blocks. Both participant groups performed the digit value naming task trials significantly faster than trials where they reported the number of digits on the card. However, no differences were seen in reaction time between pain patient groups or between patients and controls. As Eccleston was unsure whether the cognitive task employed in experiment one was sufficiently difficult, he performed a second experiment. In experiment two, other chronic pain patient and healthy control groups performed a more attentionally demanding task. In this experiment, participants were presented with a pair of the previously used cards as stimuli (see Figure 2). Participants were required to perform two task blocks as in the first experiment where they either chose the card with the digit of the highest value or a more difficult block where they were required to choose the card with the largest number of digits. As was found in the first experiment, participants took longer in responding to the trials where they

responded to the number of digits on the card. However, on this more attentionally demanding task, chronic pain patients in the high pain group took significantly longer to respond than did the low pain and control groups who did not differ significantly from each other. The results of these experiments suggested that the effects of pain become most pronounced in situations where attentional demand is high and when pain intensity is high.

Shortly after his first report of the interaction between pain intensity and attentional load, Eccleston (1995a) performed a follow-up study that elaborated on his initial findings. One unanswered question following Eccleston's 1994 report was whether the lack of a difference in performance between patients in the low pain group and the control group was a result of the experimental task not being attentionally demanding enough to enable pain to disrupt performance. Two experiments were performed to replicate and extend Eccleston (1994). Experiment one of Eccleston (1995a) replicated experiment two of Eccleston (1994) and found that chronic pain patients experiencing high intensity pain performed more poorly on an attentionally demanding task than patients reporting low intensity pain and healthy controls. No performance differences were found on the experimental task with a low attentional demand. In Eccleston (1995a) experiment two, an additional, particularly attentionally demanding task was added to the previously performed task blocks. Participants were required to perform a block of trials where the criteria for choosing one of the two displayed cards alternated on each trial between choosing the card with the digit of highest numerical value and the card displaying the largest group of numbers. This task carries with it an increased attentional demand in order to perform it properly and was given to participants in order to examine whether this very demanding task would differentiate the low intensity chronic pain group from the healthy controls. The primary question being studied using this task was whether pain, even of low

intensity would interfere with the performance of a task of high attentional load. The pattern of performance results on this attentionally demanding switch task closely mirrored the pattern seen in Eccleston's prior report. While all participants took significantly longer to perform the switch task than task blocks using only one rule per block, only the high pain intensity group of patients performed significantly worse than the control group. These findings added further support to previous work that found that pain exerted an interfering effect only in patients reporting high levels of pain when performing attentionally demanding tasks but not on tasks with low attentional demand.

Eccleston, Crombez, Aldrich, and Stannard (1997) and Crombez and colleagues (1999) later published findings that added further knowledge about the relationship between pain and attention. These studies again used groups of chronic pain patients split into high and low pain intensity groups that were required to perform the numerical interference card choice task. Eccleston et al. (1997) again found significant differences between patient groups only on the most attentionally demanding task block. Each of the patient groups were then split into groups reporting low and high levels of somatic awareness as reported on the Modified Somatic Perception Questionnaire (Main, 1983). Novel to this study was the finding that the group of patients reporting high pain levels *and* high levels of somatic awareness was the only group to show a performance decrement on the most attentionally demanding task. Along with this finding, it was found that the patients reporting high somatic awareness also reported increased levels of depression and anxiety. These findings suggested that pain intensity alone may not account for performance deficits on attentionally demanding tasks and that vigilance toward somatic sensations may play a role in pain's disruptive effects on attention.

Crombez and colleagues (1999) further examined attentional disruption in chronic pain patients by looking at the relationship between attentional interference and pain-related fear. They again measured performance decrements on the numerical interference card choice task in a group of chronic pain patients. An analysis of patient performance indicated that pain severity alone did not account for performance decrements but that attentional disruption was best predicted by an interaction between pain severity and pain-related fear. This effect was found to be independent of patients' levels of negative affect.

Using a neuropsychological assessment battery, Grace, Nielson, Hopkins, and Berg (1999) reported that a group of patients with FMS showed performance deficits on standardized memory tasks and on an attentionally demanding task compared to a well-matched control group. The FMS patients performed significantly more poorly on the Wechsler Memory Scale – Revised (WMS-R) General Memory Index, particularly on the Verbal memory component of this index. These patients also performed more poorly on the WMS – R Delayed Recall Index. In contrast, on attention-related tasks, the FMS group only showed performance decrements compared to the control group on the most attentionally demanding test, the Paced Auditory Serial Additions Test (PASAT) while performing as well as controls on other attention-related tasks. This finding supports Eccleston's (1994, 1995a) prior findings that pain seems to become disruptive when attentional demands are high. As Fibromyalgia Syndrome is a disorder with a complex clinical presentation, Grace and colleagues performed post hoc analyses in order to ascertain how pain and other factors may have played a role in the attention and memory deficits that were observed in the FMS group. These analyses found that the impaired performance scores were significantly correlated with pain severity and anxiety on measures of both memory and attention but not with depression or sleep quality.

In order to further clarify attentional deficits in chronic pain patients, Dick, Eccleston, and Crombez (submitted) attempted to extend Grace et al.'s (1999) findings. While taking a number of factors such as medication use, sleep quality, mood, and somatic awareness into account, they sought to further investigate the relationship between attention deficits, pain severity, and pain-related disability in chronic pain patients. Three groups of pain patients were recruited along with an age-matched healthy control group. The patient groups included a group of patients with rheumatoid arthritis, a group of patients with FMS, and a group of patients with chronic pain from a variety of sites including musculoskeletal and osteoarthritic joint pain. All participants were administered a neuropsychological test that provided indices related to selective attention, sustained attention, attention switching, and auditory-verbal working memory. It was found in this study that pain-free participants had significantly less pain-related disability, catastrophic thinking about pain, and depression. Patients with Fibromyalgia Syndrome were found to report higher levels of somatic awareness than patients with rheumatoid arthritis. On an overall composite score of attentional functioning, all chronic pain patients groups performed more poorly than pain-free controls. Chronic pain patients' selective attention index score was also significantly lower than that of pain-free controls. Patients with rheumatoid arthritis performed significantly worse than pain-free controls on an index of sustained attention. No differences were observed between groups on the index of attention switching. Finally, pain-free controls performed significantly better than patients with Fibromyalgia Syndrome and rheumatoid arthritis on the index of auditory-verbal working memory. Of note, all of these between group differences remained significant when depression and anxiety were covaried out. This study was the first to compare attentional performance *between* chronic pain groups and while it did not find consistent significant differences between patient groups, it did provide

additional evidence that chronic pain has a significant disruptive effect on different kinds of attention.

In order to provide a theoretical framework that is capable of explaining the effects of pain on attention, two primary models of attentional disruption have been proposed . The first model follows a classic theory of attention (Kahneman, 1973) where attention is thought to exist as a finite pool of resources that are allocated to the tasks undertaken by the cognitive system. Using this model, pain has been framed as a consumer of attentional resources that limits resources available for task performance when pain is present. This model would project that as pain increases and consumes increasing amounts of attentional resources, task performance would decline accordingly.

More recently, Eccleston and Crombez (1999) have proposed a model of pain's effects on attentional processing. This model incorporates an underlying cognitive framework of attention that is based largely upon Normal and Shallice's (1986) model of attention. In this model, attention is seen as a mechanism of 'selection for action' where incoming inputs are prioritized for processing by a "Supervisory Attentional System" (SAS). This model has attention acting to maintain efficient task performance while allowing for interruption by incoming high priority stimuli. Eccleston and Crombez (1999) have conceptualized pain as a stimulus that interrupts, distracts, and is difficult to disengage from. Pain is also proposed in this model to redirect attention toward the source of the pain, a selective role that is highly prioritized and that leads to behavior aimed at escape from pain stimuli. This highly prioritized function of pain makes it potentially extremely disruptive to behavior during pain stimulation. Pain qualities that have been proposed to affect the priority level of pain during cognitive tasks are the intensity, predictability, and novelty of pain where more intense, less predictable, and more novel pain

inputs will most easily capture attentional priority. While Eccleston and Crombez' (1999) model could be argued to provide little more predictive power of how pain and attention interact than the resource allocation model of pain, it provides an elegant and much more specific working model of how pain acts as a disrupter by using Norman and Shallice's (1985) Supervisory Attentional System. For this reason, the remaining discussion of pain's effects on attention will be framed using Eccleston and Crombez' (1999) model.

Imaging pain's effects on brain attention centres

The existing literature showing pain's effects on attention and the availability of theoretically driven models of attention and pain such as put forth by Eccleston and Crombez (1999), provide a strong impetus to build on and broaden our understanding of how pain functions within the cognitive system. While the literature regarding pain's effects on attention using methodologies involving behavioral responses or neuropsychological assessment provides valuable theoretical and clinical information, other methodologies offer a complementary evaluation of these effects. There is a steadily increasing body of literature that has investigated these effects using brain imaging techniques. The refinement of imaging technology during recent years is rapidly increasing the opportunities available to investigate how and where in the brain pain interacts and interferes with cognitive processing.

Over fifty years ago Hebb (1949) postulated that pain as a *psychological* entity, must exert significant influence at the cortical level. A group of groundbreaking studies during the last decade of the twentieth century fuelled what has been a major increase of research regarding how pain acts at the level of the cortex (e.g., Rainville, Duncan, Price, Carrier, & Bushnell, 1997; Talbot, Marrett, Evans, Meyer, Bushnell, & Duncan, 1991; Jones, Brown, Friston, Qi, & Frackowiak, 1991). These important studies highlighted areas that may be the cortical location

where pain intrudes on cognition and, more specifically, on attentional processing. These studies examined the link between pain and attention in the anterior cingulate area of the brain, an area now widely acknowledged as being a major centre of attentional processing (Carter et al., 1998; Whalen et al., 1998; Peterson et al., 1999; Davis et al., 2000). By implicating the anterior cingulate region as a possible centre involved in pain processing, these studies turned the interest of a number of researchers toward the influence of pain on this important cortical region.

Using positron emission tomography (PET), Jones et al. (1991) first reported significant cortical activity related to pain in areas outside of somatosensory cortex. This research found that painful heat stimulation did not cause a notable change in primary somatosensory cortex activity but that a marked increase in regional cerebral blood flow activity occurred in the anterior cingulate cortex (area 24) contralateral to the painful stimulation. Using both PET and magnetic resonance imaging (MRI), Talbot and colleagues (1991) later reported a study that detected changes in regional cerebral blood flow due to painful heat stimulation more clearly. They reported increases in regional cerebral blood flow in the anterior cingulate (area 24) and clear but lesser increases in regional cerebral blood flow activity in both primary (SI) and secondary (SII) somatosensory cortex. Between the SI and SII areas of somatosensory cortex a relatively greater increase in SII regional cerebral blood flow was observed, again confirming the contribution of somatosensory cortex in pain processing. The finding of increased activity in area 24 provided further evidence that this widely held attention-related area also plays a role in pain processing. Talbot and colleagues (1991) also noted that the anterior cingulate region in which a substantial increase in regional cerebral blood flow was observed is the same area that is sometimes surgically removed in patients with intractable pain. Following this operation, patients do not tend to report a noticeable change in their pain levels however they do tend to report their pain to

be much less distressing. Talbot et al. (1991) went on to postulate that the increase in regional cerebral blood flow in the anterior cingulate was related to cortical processing of the affective component of pain. It is also possible that by removing this area, attention was no longer as strongly directed toward pain, thereby reducing the disruptive and distressing nature of the perceived pain.

A later paper by Rainville et al. (1997) used an elegant experimental design to further clarify previously reported findings. Using hypnotic suggestion that increased or decreased the perceived unpleasantness of painful heat stimuli, Rainville et al. were able to experimentally separate the affective and sensory components of painful heat stimulation. Using both PET and MRI to image changes in regional cerebral blood flow, their measurements showed that anterior cingulate activity was primarily related to the level of emotional unpleasantness of participants' pain. Referring to the proximity of this portion of the anterior cingulate to other anterior cingulate regions previously found to play important roles in nociception, motor function and attention, Rainville and colleagues went on to propose that many behavioral changes related to pain such as the modulation of attention could be a result of the activation of this area. Rainville et al. (1997) cautioned that because strong anatomical connections exist between the anterior cingulate and primary and secondary somatosensory cortex, we must acknowledge the highly interactive nature of pain processing regions in the brain.

Following these initial reports of changes in activity in the anterior cingulate region as a result of pain induction, another wave of research was undertaken aimed at clarifying the effects of pain on attention in attention-related brain areas. Using an fMRI paradigm to observe differences in anterior cingulate activity during attentionally demanding tasks with and without painful electrocutaneous stimulation, Davis and colleagues (1997) contributed further evidence

of the processing of painful stimuli in the anterior cingulate. Their participants underwent separate periods of mild pain, moderate to intense pain, and a block where they performed an attentionally demanding task without painful stimulation. The results indicated that a small posterior portion of the anterior cingulate was active during moderate to intense but not during mildly painful stimulation. They also found that a more anterior portion of the anterior cingulate appeared to be involved in the attentionally demanding tasks. Thus, their findings are in line with Eccleston and colleagues' (1994, 1995a, 1997) reports that high intensity pain appears to be required before pain will disrupt attentional processing. However, their investigation was not able to find a specific area that was activated by both pain and attentionally demanding tasks.

In a later study, Derbyshire, Vogt, and Jones (1998) used PET and fMRI imaging techniques to further investigate whether anterior cingulate sites activated during painful stimulation overlapped with sites activated during an attentionally demanding Stroop task. On this task, individuals are required to read colour words or name the colour or these words that are printed in various colours. The attentional demand of this task is increased by printing the words in colours that either match or do not match the colour named by the word. Similar to Davis et al. (1997), they found that areas of the anterior cingulate were activated in both painful stimulation blocks and during performance of this task. However, Derbyshire et al. (1998) found a partial overlap of the areas activated in these different blocks in the midcingulate area at the group level of their analysis. These effects were not found consistently in data from individual participants. Derbyshire and colleagues therefore concluded that while they were able to confirm that pain appears to be processed in the anterior cingulate, inter-individual differences in the locations of pain sites activated and sites activated during attentionally demanding task were highly variable and did not consistently point to a specific area where pain and attention are processed together.

Hutchison et al. (1999) have suggested that an interaction between the anterior cingulate and attention-related cortical areas may account for the link between pain and attention. Using single cell recordings in anterior cingulate regions of patients undergoing bilateral cingulotomy, this group reported finding neurons whose activity was affected by painful thermal and mechanical stimuli. They also found that while some anterior cingulate neurons were only responsive to very small receptive fields, others appeared to be active primarily during more complex, integrative cognitive processing of pain. This report provided evidence at a very basic anatomical level suggesting that pain and attention may interact. It is possible that this type of interaction is an example of the underlying mechanisms of the previously noted disruptive effect of pain on attention.

A later report by Kwan and colleagues (2000) employed a design that allowed them to propose a contrasting map of areas related to pain processing and attention functions. Despite finding considerable variability between individual study participants' specific areas of anterior cingulate activation, a consistent activation pattern was observed where the anterior region of the anterior cingulate was activated by non-specific attentional activation. It was also found that more posterior portions of the anterior cingulate showed an increase in activity during painful stimulation. It appears from the progression of this line of study that with continued refinement of methodology and enhanced imaging technology, a clearer understanding of how and where pain and attention interact in the brain is an increasingly attainable goal.

Imaging pain's effects on attention using ERP's

In addition to previously mentioned studies of pain's effects on cognitive processing that have used blood flow monitoring imaging methods, other measurement techniques exist that offer valuable complementary contributions. One such method records event-related potentials

(ERP's). This technique capitalizes on the ability to detect and record the electrical activity of neurons at the scalp. These potentials are recorded by averaging windows of electroencephalographic (EEG) activity that are time locked to specific stimuli. By doing this, EEG activity not related to the signal will average to zero, leaving only a measure of the response to stimuli. ERP's allow for measurement of cognitive events at a very high level of temporal resolution (Polich, 1993) and are increasingly being used to map differences in cortical activity across the scalp. This mapping function can allow the monitoring of changes on a fairly general regional level at the scalp. By providing a measure of brain activity with a temporal resolution at a millisecond level, this technique provides valuable complementary information to imaging techniques such as MRI, magnetoencephalography (e. g., Yamasaki et al., 1999) and single cell recordings (e.g., Hutchison et al., 1999).

Event-related potentials have been used previously in a wide variety of research paradigms and clinical settings as a means of better understanding a number of psychophysiological processes (Brandeis & Lehmann, 1986; Polich, 1993a; Polich, 1993b). While a large number of studies have examined sensory evoked-potentials created by discrete pain events,(see Zaslansky et al., 1996a & 1996b for a review), there have been far fewer ERP studies that have examined how pain affects ERP's, which are very useful in indexing higher cognitive functions such as attentional processes. While attention has generally been found to not significantly affect the earliest evoked potentials (Woldorf, Hackley, & Hillyard, 1991), there are a number of late components that have been found to be modulated by attention. One late ERP component that has been thoroughly investigated as an index of cognitive processing, the P3, has been studied in order to investigate variations in attentional functions during task performance (Isreal, Chesney, Wickens & Donchin, 1980a; Polich 1993b). A number of

experiments that have studied the P3 and its relation to attention have found that it can be reliably used as an index of attentional resource demands taken up by a task (Isreal, Chesney, Wickens & Donchin, 1980a; Isreal, Chesney, Wickens & Donchin, 1980b). In one such study, Wickens, Kramer, Vanasse & Donchin (1983) used a resource capacity model (e.g., Kahneman, 1973) and reported that the amplitude of the P3 was related to the attentional resources allocated to the task that elicited it. In their experiment, ERP's were measured during performance of a dual-task paradigm. It was found that as the resource demands required by a primary visual tracking task increased, the P3 amplitude for a secondary auditory task decreased. This P3 decrease was modeled as a result of a decrease in the allocation of attentional resources to the secondary task.

Using these findings an important link can now be drawn between the literature regarding pain's effects on attention discussed above and event-related potential studies. As a number of previous studies have found behavioral performance decrements due to pain on attentionally demanding tasks (e. g., Eccleston 1994, 1995a), ERP paradigms can be constructed that objectively monitor changes in evoked brain potentials during similar tasks. The previously mentioned research that has highlighted the interesting relationship between pain and attention lends itself well to the design of such studies. As well, the findings of many of these studies can plausibly be fitted under Eccleston and Crombez' (1999) theoretical model that pain disrupts attentional functioning and interferes with the Supervisory Attentional System that prioritizes stimulus processing and task performance. If an attentionally demanding task that is highly prioritized by the Supervisory Attentional System is forced to compete with a high level of pain, task performance will likely suffer. Further, ERP's whose magnitudes are related to attentional processes enlisted by such a task will be reduced due to pain's disruptive effect.

As pain perception can be decreased due to attentional distraction (e.g., McCaul & Mallotte, 1984) and pain interferes with task performance (e.g., Eccleston, 1995a), a logical step to study pain's effects on attention using ERP's would be to construct a dual task paradigm where pain functions as a primary task. As such, an auditory oddball paradigm commonly employed in P3 research is a useful paradigm to potentially use as an objective measure of pain's effect on task performance. The first two reported studies using this type of design were performed by Rosenfeld and Kim (1991) and Rosenfeld, Johnson, and Koo (1993). These studies were carried out in order to ascertain whether individuals feigning pain could be identified when compared to people experiencing pain by using ERP measurements. In the 1991 study, pain was induced using a finger press device and results indicated that individuals who feigned pain could be reliably differentiated from real pain participants only if pain levels were being consciously tracked by the participants. Thus, when pain level was not being tracked, people faking their pain appeared to be able to alter their cognitive processes enough that their P3 waves showed comparable decrements to those found in the group who really did experience pain. These findings were interpreted using an attentional resource allocation model. In the real pain and feigned pain groups that were not monitoring their pain levels actively, pain did not "use up" sufficient attentional resources to significantly change the amplitude of the P3 wave as compared to intra-individual modulation of attention. Only when additional resources were allocated to monitoring real or feigned pain levels did the P3 amplitude differentiate the groups. It would also appear from these findings that tracking pain required more attentional resources than faking pain tracking when pain was not present. This finding that pain affected cognitive processing most notably during a task that increased cognitive load is also in line with Eccleston and colleague's work (1994, 1995a, 1997).

Rosenfeld, Johnson, and Koo (1993) later carried out a follow-up study where a blood pressure cuff was used in order to create ischemic pain. Ischemia-induced pain was used due to concerns about the inconsistency of pain levels induced by the finger press in the initial study. These follow-up results were somewhat different from those of the initial study. The only condition where a significant change in the amplitude of the P3 was observed between groups was in a high pain condition when participants were *not* tracking their pain. However, the findings of this study at the group level were still in line with Rosenfeld's original hypotheses that pain would lead to a diminution of the P3. At the same time, it is somewhat surprising that when an increase in the use of cognitive resources occurred due to the task of tracking pain, the group differences that were observed during the 1991 study disappeared. While the hit rate for detecting individuals feigning pain in this study increased to 91% from the unsatisfactory 66% in the 1991 study, the differences in results between these two studies leads to a number of additional questions. The results of these studies are different enough that one cannot help but question if some significant experimental or cognitive factors other than pain magnitude were different between studies. One cannot help but wonder about the existence and role of additional intervening cognitive and/or affective variables that were not controlled between these studies.

Lorenz & Bromm (1997) found additional evidence in support of the hypothesis that pain acts as a disrupter of attention. In this study, parietal P3 amplitude was significantly reduced due to the presence of ischemic pain during both a visual memory search task and during an auditory oddball task. No early ERP components were found to be affected by pain. However, a significant fronto-central N275 wave enhancement was found during the memory search task in the pain condition. What is also of note is that it appeared possible to separate participants in this study according to the effect of pain on them as indexed by the amount that their error rates

increased after the introduction of pain. Lorenz & Bromm found a wide range of effects of pain on the P3 between participants. Those participants whose error rates were higher on the memory task (apparently due to disruption by pain) showed trends of reductions in both their visual N275 and P3 amplitudes when compared to participants whose error rates did not show a marked change. One participant, whose error rate increased 14% after the introduction of pain, showed this effect especially clearly. Further, some participants whose error rates did not change markedly did not show significant changes in their ERP's due to pain. Although Lorenz and Bromm hypothesized that their effects were due to differences between participants in effort (as manifested in some participants as an the increase in the N275), another possible explanation for their findings exists. These findings could suggest that participants in this study showed differential decrements both in performance and in P3 amplitude according to the degree to which pain intruded on their cognitive processes. Although the pain induction technique used was standardized across participants, what may have varied between participants was the degree to which the pain stimulus was disruptive. Given past findings (e. g., Rainville et al., 1997) that the distressing nature of pain affects pain processing, it would be of considerable value to know whether the range of differences between participants in this study could be attributed to differences in the levels of pain-related distress.

In another study, Michalski (1998) reported that ERP's evoked by light flashes as well as auditory evoked potentials were affected by pain. In this study, healthy participants experienced pain due to immersion of a hand in cold water. Compared to a control condition where their hand was immersed in warm water, the amplitude of the P3 evoked by deviant target stimuli was significantly reduced in both the auditory and visual modality, suggesting a disruptive effect of pain on attentional processing of both kinds of stimuli.

In an study that sought to extend Lorenz and Bromm (1997), Houlihan and colleagues (submitted) examined pain's effects on attention using ERP's while requiring participants to perform a Sternberg memory task during pain and no-pain conditions. This task requires individuals to respond to visual probes following the display of groups of probes (typically letters). By changing the number of probes used, one can increase the difficulty of this task. Using an increasing memory load in the Sternberg paradigm allowed this group to test whether the disruptive effect of pain would increase with increasing cognitive load. The behavioural data from this study showed that accuracy decreased and response time increased with the increasing cognitive load in both pain and no pain conditions. Accuracy was also significantly worse in pain than in no-pain conditions. The amplitude of the P3 was reduced in pain compared to no-pain conditions. However, this effect was found to be strongest in the easiest memory load condition. It is possible that this finding was not primarily related to the increasingly disruptive effect of pain during easy tasks, rather it was also related to the natural decrease in P3 amplitude during increasingly difficult cognitive tasks. As the difficulty of the task increased, the resulting P3 decreased. In a sense, fewer attentional resources were available to be depleted and the difference between pain and no-pain conditions decreased. Despite this limitation, this study provided support to the theory that pain disrupts attentional functioning as this disruptive effect was observed even on low cognitive load tasks. Unfortunately, this report was not able to clarify whether a task of increasing cognitive load was affected significantly more by pain than performance on tasks of low cognitive load.

Lorenz, Beck, and Bromm (1997a; 1997b) went on to test a parallel hypotheses with chronic pain patients. They reported a small P3 amplitude enhancement in a group of chronic pain patients after the patients received orally administered sustained release morphine. Thus, the

disruptive effect of pain appeared to be reversed with analgesic use. After examination of the early sensory components of the patients' ERP's, it was suggested that this change in the P3 was not a result of the level of patients' sedation or their ability to focus on the tones but that the analgesic effect of the morphine was the factor most strongly related to the change in the P3. Following Eccleston and Crombez' model, as pain was decreased due to analgesia, the Supervisory Attentional System was able to prioritize other incoming stimuli and the resulting neural response to these stimuli was larger and manifested by an increase in P3 amplitude.

Pain's effects on early attentional processes

These previously reported ERP studies have examined how pain affects active cognitive processing, primarily using the late component P3. Unfortunately, in addition to pain, a number of intra-individual factors such as alertness, motivation, and effort have been found to affect the P3 (Picton, 1995). Due to the variability that may exist between participants on these factors, it is sometimes difficult to confidently interpret changes in P3 during pain experiments (Lorenz & Bromm, 1997). One way of avoiding these problems would be to measure the effects of pain on earlier attentional processes that are not as strongly controlled by factors such as effort in participants.

In an attempt to address this need Houlihan et al., (in preparation) have examined how pain affects the P3a component elicited by unexpected novel stimuli embedded in an auditory stream. The novelty P3a has become a component that has been increasingly studied as an indicator of involuntary attention switching (Alho et al., 1998). This component, while still considered a "late" ERP component, is elicited by an earlier passive attentional mechanism. Escera and colleagues (1998) reported that the later component of the P3a exhibited attentional modulation and suggested that it reflects an attentional orienting response. This means that this

component represents a process that when activated, "alerts" other brain centers that focus one's conscious attention to a particular stimulus. Of note, the earlier component of the P3a was not affected by attention and was therefore described by these authors as reflective of a neural process more closely linked to sensory processing. Although the P3a appears to occur as a result of a hardwired, passive process, Houlihan et al.'s data suggests that the P3a can be reduced by experimentally induced cold pressor pain. While many of the previously mentioned studies have found that pain affects active attention (e.g., Eccleston, 1995a; Lorenz and Bromm, 1997) the Houlihan et al. data has provided findings that pain may affect attention during cognitive processing. This finding calls into to question the point during perceptual processing at which pain begins to become disruptive of attention.

Mismatch Negativity (MMN)

While the Houlihan et al. (in preparation) work examines a relatively earlier, more passive effect of attention than previously studied by the Rosenfeld, Michalski, and Lorenz research groups, there are still earlier ERP components that have been reported to be enhanced or attenuated through the modulation of attention. No research has previously examined how pain affects these early attentional processes. One early component reported to be affected by attention is the Mismatch Negativity (MMN), an early ERP component proposed to act as a mechanism for eliciting attentional orienting responses such as the P3a (Escera et al., 1998). This mechanism's actions and functions are such that they can plausibly be incorporated as a component within Norman and Shallice's (1985) Supervisory Attention System model as they act to detect incoming stimulus information and alert the cognitive system of the potential importance of this information.

The MMN has features that make it a potentially interesting ERP component to use to examine early attentional processes and the effect of pain on these processes. The MMN was first reported by Näätänen, Gaillard, and Mäntysalo (1978) as an electrophysiological manifestation of the detection of stimulus difference in early auditory processing. This and later studies (see Näätänen, 1990 for a review) found MMN to be reliably generated between 150 and 250 msec after a deviant tone that differed in pitch, intensity, or duration from a stream of standard tones in which it was imbedded (Alho, 1995). The MMN has been found to occur as a result of the detection of change in a stimulus, meaning that an initial auditory stimulus will not elicit the MMN, it will only occur when a deviant stimulus follows previous standard stimuli (Sams et al., 1985; Novak et al.,1990). Näätänen and colleagues (1993) demonstrated that the MMN increases as the memory trace that is used to detect stimulus differences is strengthened with repeated presentation of standard stimuli. The MMN is found by subtracting the waveform elicited by standard tones from the waveform elicited by the deviant tones. The amplitude of MMN has been found to be enhanced by factors such as increasing the magnitude of stimulus difference between standard and deviant stimuli and by decreasing the latency between standard and deviant stimuli (Sams, Paavilanen, Alho, and Näätänen, 1985b).

Näätänen, Gaillard, and Mäntysalo (1978) proposed that the MMN was generated in primary and association areas of auditory cortex. Most later reports have found that the MMN generators exist on the supratemporal plane (Alho et al., 1998;Woldorf et al., 1998). It is becoming increasingly evident that the MMN is a very good indicator of a person's accuracy of sound discrimination and the integrity of a person's central sound representation of auditory stimuli (Näätänen & Alho, 1997). Näätänen (1992) has proposed that the MMN is generated as a result of a *preconscious* comparison of stimulus features using a neural echoic memory trace

formed by the presence of a number of standard stimuli presented prior to a deviant stimulus. A number of reports have provided data that support this proposal. In one such report, Tiitinen and colleagues (1994) provided clear evidence that behavioral responses elicited during an auditory task were controlled by early sensory memory processes. They showed that behavioral response latency and accuracy were both very tightly linked to the amplitude, duration, and latency of the MMN. Cowan and colleagues also provided data supporting the echoic memory trace hypothesis by showing that deviant stimuli must be preceded by two or three standard stimuli before the MMN will be elicited (Cowan, et al., 1993). In another series of experiments Näätänen and colleagues (1993) found that the memory trace underlying the MMN was built slowly and strengthened over time. This effect was found to occur even when very complex auditory stimuli that differed only slightly from each other were used.

Näätänen and Alho (1995) have emphasized that the available evidence suggests that the MMN is a result of a neural sensory memory system rather than a system that relies on feature-specific stimulus detection mechanisms. They proposed that the underlying neurophysiological mechanism that generates the MMN functions based upon the relative difference between excitatory and inhibitory processes. They suggested that repeated standard stimuli cause neurons that detect differences in auditory stimuli to be inhibited, leading to an inhibitory "memory trace" for these standard stimuli. Stimuli that deviate from these standard stimuli will lead to neural firing to the degree that the stimulus deviates from standard stimuli. Thus, stimuli that deviate only slightly tend to generate a small MMN or no MMN at all if the difference is very slight. They further proposed that when the MMN generated is large enough, it triggers a later attention switch response that is instrumental to the stimuli later being perceived consciously.

Näätänen, Gaillard, and Mäntysalo (1978) proposed in their initial report on the MMN that the basic MMN generator functions independently of attention. They found that the MMN was elicited by auditory feature deviance whether or not participants were attending to auditory stimuli. A large number of subsequent studies have supported this theory (for extensive reviews see Näätänen, 1990 and Näätänen, 1992). For example, using a dichotic listening paradigm, Alho and colleagues (1989) showed that while the MMN was reliably elicited by auditory feature differences, the active direction of attention toward deviant stimuli did not change the MMN significantly. Paavilainen et al. (1993) found that even very small pitch changes presented in a dichotic listening task at a very fast rate to the unattended ear elicited MMN. Näätänen et al. (1993) also used a dichotic listening task and found that MMNs to deviant auditory stimuli that differed from standard stimuli in their pitch were not significantly different when attention was directed to or away from these stimuli.

The existing data have made it abundantly clear that the MMN can be elicited irrespective of the attention of participants to stimulus differences. Näätänen and Michie (1979) proposed that a component of the MMN manifested at the scalp may be generated in the frontal region of the brain. They suggested that the underlying mechanisms that generate this frontal MMN component were responsible for the previously mentioned preconscious attentional switch response. They suggested that this response orients attention toward the deviation in stimulus features and leads to conscious perception of the stimulus deviance. Näätänen (1986) later reported that while the MMN is not necessarily the key mechanism leading to an orienting response to stimulus difference, it likely plays a central role in the generation of such a response. Näätänen (1986) highlighted the strong similarities of the MMN and neuronal mechanisms in a model of orienting response generation put forth in a theory by Sokolov (1975). Sokolov's

(1975) neural model proposed that the repetition of environmental stimuli would lead to an inhibition of an orienting response to repeated stimuli but not to novel stimuli. Näätänen (1986) proposed that this orienting response is related to an attention-switching process that functions very much like an alarm. When stimulus deviances are detected by the basic MMN response, this leads to an orienting response toward deviant stimuli.

Modulation of the MMN by Attention

It should be noted here that there are reports (Woldorf & Hillyard, 1990; Woldorf, Hackley, & Hillyard, 1991; Woods, Alho, & Algazi, 1992; Alho et al., 1992) that have provided evidence that the MMN can be affected by attention. These papers will be discussed in more detail below in Experiment 2. For present purposes, it is important to note that these reports found that the MMN may be attenuated in the absence of attention. However, it was also evident in these studies that the MMN was still elicited even when attention was strongly focused elsewhere. This continues to support Näätänen, Gaillard, and Mäntysalo's (1978) initial proposal that the MMN is generated with or without active attention to the stimuli presented.

As an explanation for the apparent potential for the MMN to be attenuated when attention is strongly focused elsewhere, Näätänen, Paavilainen, Tiitinen, Jiang, and Alho (1993) re-emphasized a model proposed by Näätänen (1991). They reported results that suggested that the MMN cannot be eliminated in the absence of attention to auditory stimuli. Näätänen's (1991) model suggested that two groups of neurons are active during the generation of the MMN. One group was hypothesized to be responsible for the basic mismatch detection response that responds to even the slightest stimulus deviation. These neurons were labeled as "computational" or informational neurons. The second group, called "amplifying" or modulating neurons, receive and amplify the signal from the computational neurons. By proposing that this second group of

amplifying neurons takes part in the enhancement of the MMN, Näätänen's (1991) model is able to account for the attention-related attenuation of the MMN when attention is strongly focused elsewhere. While the computational neurons respond with or without active attention, the model proposes that few or none of the amplifying neurons are activated when attention is directed elsewhere. Näätänen (1991) further proposed that the activation of the amplifying neurons is linked to the attention-switching "alarm" function. Thus, if amplifying neurons are not sufficiently activated to create the attention-switch alarm response, the MMN may be reduced in the absence of attention.

While the existing data have made it abundantly clear that the MMN can be elicited irrespective of the attention of participants to stimulus differences, Näätänen and Michie (1979) proposed that a component of the MMN manifested at the scalp was generated in frontal areas. They suggested that the underlying mechanisms that generate this frontal MMN component were responsible for a preconscious attentional switch response. They proposed that this response orients attention toward the deviation in stimulus features and leads to conscious perception of the stimulus deviance. Näätänen (1986) later proposed that while the MMN is not necessarily the key mechanism leading to an orienting response to stimulus difference, it likely plays a central role in the generation of such a response. Näätänen (1986) also highlighted the strong similarities of the MMN and neuronal mechanisms in a model of orienting response generation put forth in Sokolov's (1975) theory.

Cerebral Generators of the MMN

Scherg, Vajsar, and Picton (1989) used a dipole source analysis technique to examine where the MMN is generated and whether more than one brain source exists that generates the MMN. They reported that their findings supported a two-component MMN model. This two-

component model bears some similarity to Näätänen's (1991) model where two (computational and amplifying) components are proposed to generate the MMN. Scherg and colleagues proposed that one MMN generator occurred at the same location as and was related to the generator of the N1 component. This generator was found to be bilateral and vertically oriented on the supratemporal plane (i.e., projecting through the top of the scalp). This first generator was proposed to represent the activation of non-refractory cells in the N1 generator and was found to have a larger response at larger levels of stimulus deviance. Thus, a stimulus that is very different from standard stimuli would be predicted to cause additional non-refractory frequency-specific cells to fire, leading to a larger response. The second MMN generator was found to be slightly anterior to the first generator and more frontal and lateral in its orientation compared to this generator. This dipole was found to increase in its latency of activation and decrease in its degree of activation as deviance from standard tones decreased. Scherg and colleagues proposed that this component represents the "true" neural generator of mismatch detection. The second component reported by Scherg et al. (1989) that is related to mismatch detection represents Näätänen's (1991) computational component that is fundamentally activated at the detection of pitch deviance. Scherg et al.'s (1989) N1-related component also fits with Näätänen's (1991) proposed amplifying component as it appeared to increase with large degrees of stimulus deviance and to decrease with small levels of stimulus deviance. This finding is very similar to what Näätänen et al. (1993) proposed would occur at small levels of deviance. Escera et al.'s (1998) report provides further support of Näätänen's (1991) model in that a N1-related MMN enhancement was found that increased with the degree of deviant difference along with a later but overlapping MMN process related to pitch detection.

Using current source density analysis, Giard and colleagues (1990) provided data that also suggests the possible existence of a third, frontal MMN generator. This generator is relevant to the previously mentioned studies that have linked that anterior cingulate area to attentional processes. Using a dichotic listening task, Giard et al. reported findings suggesting the presence of MMN generators in primary auditory cortex and in the frontal scalp region, likely in the frontal or prefrontal cortex. They suggested that their findings supported Näätänen and Michie's (1979) proposal that when a pitch difference is detected in primary auditory cortex, a frontal area responsible for an orienting response and attention switching is activated. A later report by Levänen and colleagues (1996) provides further support for the existence of a frontal generator related to the MMN. Using magnetoencephalography, they found a frontal dipole in a minority of their study participants and suggested that the frontal dipoles may have been radial to the magnetoencephalography sensors (and therefore undetectable by these sensors) in their other participants. In a report that may provide a key link between the anterior cingulate region, attentional functioning, and the MMN, Alho (1995) suggested that the frontal attention switching mechanism, when activated, might feed back to auditory cortex and thereby lead to an amplification of the MMN. He suggested that this feedback could lead to improved detection of other relevant stimulus differences that accompany earlier occurring deviant stimuli. Further evidence of the possibility of the existence of a frontal generator was provided by Rinne and colleagues (2000). They hypothesized that if a frontal MMN generator that is activated by MMN generators in the temporal lobes existed, the frontally generated component would have a later latency than the temporal MMN component. Rinne et al. (2000) found that in their EEG data, following the MMN maximum generated at temporal sites, the source current distribution became more anterior during MMN generation. They noted that this frontal effect was not

evident in the concurrent magnetoencephalography data they collected. They therefore proposed that the frontal MMN generator or generators were oriented radial to the magnetoencephalography sensors and were likely located in deeper brain structures. In interpreting these reports, it should be noted that one reason why it is difficult to conclusively locate a frontal generator of the MMN is the orientation of the bilateral auditory cortex MMN generators. The vertical supratemporal dipoles created by these generators produce electrical potentials that are maximal at the frontal midline scalp region that likely affect the signal recorded at the scalp that is generated in the anterior cingulate region.

Kropotov and colleagues (1995) were able to make intracranial recordings at a number of sites in patients with Parkinson's disease or Obsessive Compulsive Disorder who received exploratory procedures prior to stereotactic surgery. While the location of the electrodes was limited to those sites relevant to surgical necessity for the patients, useful information was gained from the recordings that were made. From the recordings collected it was found that the MMN was generated in the temporal cortex and that it was generated independently of attention. It was also found that the attention-dependent P3 component was generated in areas distinct from the temporal cortex where the MMN was generated. While this report was not able to definitively describe all MMN generator sites, it did provide important evidence that at least one major generator component of the MMN is attention independent.

Kropotov and colleagues (2000) went on to make intracranial recordings in patients awaiting stereotaxic surgery using an auditory oddball task. Their findings suggested that three processes occurred during the detection of differences in auditory tones. One response process was pitch-dependent and occurred in primary auditory cortex. Another process occurred in secondary auditory cortex and was sensitive to changes in the interstimulus interval. The third

process was found to represent the basic MMN pitch detection mechanism and occurred in auditory association cortex. Of note, an additional process was noted to be activated when stimuli were being actively attended to. This process was found to occur in basal ganglia-thalamic circuits. These findings are important in that they demonstrate what may be the biological underpinnings of the MMN. They also point to additional mechanisms outside of auditory cortex that may be involved in the attentional processes that may affect the MMN.

Additional Modulators of the MMN

As the MMN is a hardwired auditory response, it is important to know how common it is for environmental influences internal and external to the body might influence it. There is a small body of literature that suggests additional ways of modulating the MMN. A few reports (Grillon et al., 1995; Jääskeläinen et al., 1995a; Jääskeläinen et al., 1995b; Jääskeläinen et al., 1996; Jääskeläinen et al., 1998) have reported varying effects of alcohol on the MMN and one report has suggested that the MMN can be affected by nitrous oxide (N2O). Although Grillon and colleagues (1995) found that a moderate dose of ethanol did not affect the MMN, a number of reports by Jääskeläinen and colleagues have suggested that the MMN may be affected by alcohol consumption. For example, Jääskeläinen and colleagues (1995a; 1995b) found that MMN amplitude was reduced and MMN latency increased following alcohol consumption, even at a low dosage (1995b). In both of these reports, the authors interpreted their results to suggest that alcohol disrupts the early passive detection of auditory stimulus differences, outside the scope of conscious attention. Of special note, Jääskeläinen et al. (1995b) reported that the attenuation of the MMN by alcohol was especially strong when small stimulus deviance was being processed. This finding suggests that alcohol may have interfered with the "amplifying" component of the MMN. Jääskeläinen and colleagues (1996) also reported a decrease in MMN amplitude but that

this decrease was only seen in frontal scalp sites. They proposed that this finding may be indicative that alcohol only affects the frontal MMN generator and not generators found in auditory cortex. Jääskeläinen and colleagues (1998) found that MMN latency was increased by alcohol consumption. This reaffirmed their proposal that alcohol appears to affect the early attentional processes related to the MMN and it's function in stimulus feature processing. Finally, Pang and Fowler (1999) found that the anaesthetic gas N2O decreased the amplitude of the MMN. They interpreted their results to suggest that the change in arousal brought about by the introduction of N2O affected early attentional mechanisms linked to the generation of the MMN. Although it is possible that N2O affects different neurobiological mechanisms than alcohol, the key common element between these reports is that despite the fact that the MMN is a hardwired, preconscious process, it can be disrupted by changes in the neurological environment.

Modulating the MMN with Pain

The description of the nature of the MMN generators and the manner in which these generators act as outlined in Näätänen and Alho (1998) is of great importance to the hypotheses of the following experiments. They propose that the brain's auditory sensory memory system holds the stimulus representation. When a newly presented stimulus deviates from this representation, the MMN is generated. They further suggested that the magnitude of the MMN depends on the degree of overlap between excitatory and inhibitory neural elements activated by stimulus perception. When little overlap exists, more excitatory neurons fire and a larger MMN response is elicited. When a large enough MMN response occurs, Näätänen and Alho (1998) propose that an attention switch process occurs that increases the likelihood that the stimulus will be consciously perceived. It is important to note that Näätänen and Alho proposed that these processes function at a very basic, automatic level. Of special note, they suggested that while

stimuli that only differ slightly from the sensory memory trace may not generate the MMN, the degree of attention directed toward stimulus discrimination can have an influence on this process. Thus, if stimulus differences are being attended to, previously undetected stimuli may be detected and stimuli that would have elicited a small MMN response may evoke a larger MMN.

The attentional switch component proposed to act as one of the components that generates the MMN is also of primary interest in the present research. As previous findings have shown a possible disruptive effect of pain on attention during tasks requiring focused attention to attentional switch tasks, the question arises as to whether pain will affect earlier, passive cognitive processes reflected by the MMN and thought to underlie attentional switching that underlies the generation of the MMN. If pain could be found to disrupt such early processes, it would suggest that the MMN could be used as an early index of pain's disruptive effects. This would avoid the previous methodological difficulties where concentration, motivation, and effort affected task performance and related ERP's such as the P3.

The first investigation of pain's effect on early attentional processing using the MMN was presented by Dick and colleagues (1999). They hypothesized that if pain acted as a disrupter of the early attentional processes, MMN amplitude would be decreased during pain compared to no-pain conditions. This effect was found in eight of twenty healthy participants undergoing pain induction by immersion of a forearm in cold water (see Figure 3). However, contrary to the original hypothesis, nine of the twenty participants showed a significant increase in MMN amplitude in pain versus no pain conditions (see Figure 4). Dick and colleagues (1999) proposed that this increase in MMN amplitude may have reflected an increased orienting response to the auditory stimuli during pain in these participants. No effect of pain was found in three

participants who showed extremely large (5-7 microvolt) MMN amplitudes (see Figure 5). Unfortunately, it was not possible to differentiate the groups on the basis of participants' levels of reported pain on a numerical rating scale (NRS). As well, no difference were observed between the three groups on measures of the perceived sensory or affective qualities of pain using the McGill Pain Questionnaire (MPQ; Melzack, 1975), or on levels of pain catastrophizing (Pain Catastrophizing Scale – PCS; Sullivan, Bishop, and Pivik, 1995). Unfortunately, the cold water used to create pain was only maintained at 4-5 degrees Celsius and may not have provided a strong enough pain stimulus. However, by suggesting that pain may affect early attentional processing in some individuals, this preliminary report provided a starting point for further investigation of how pain may affect early attentional processing.

The following three experiments were carried out in order to replicate and extend Dick et al. (1999). In Experiment 1, the effect of pain on early auditory attentional processes as manifested by changes in MMN was examined. This experiment was primarily aimed at replicating earlier findings while generating data with an improved signal-to-noise ratio. Pain stimulation in the cold water pain induction condition was increased by decreasing the water temperature to between one and two degrees Celsius and by holding the temperature at this lower level by circulating the water in the tank. This experiment also employed a second pain induction technique using ischemic pain as reported in Lorenz & Bromm (1997). This manipulation was carried out in order to ascertain whether different methods of pain induction lead to different levels of disruption of attentional processing. Measures of pain intensity (Numerical Rating Scale), pain catastrophizing (Pain Catastrophizing Scale), and the sensory and affective qualities of pain (McGill Pain Questionnaire) were also recorded.

The primary hypothesis of Experiment 1 was that pain would disrupt the early attentional "amplifying" component of the MMN and be manifested as a decrement in MMN amplitude. It was also hypothesized that as the perceived pain level, the sensory and affective qualities of pain, and pain catastrophizing level increased, the magnitude of the MMN would decrease. It was not expected that either pain induction technique would disrupt the basic sensory discrimination or "computational" component of the MMN. Thus, while MMN amplitude was expected to be reduced by pain stimulation, it was not expected to disappear completely. Finally, it was expected that in accordance with previous MMN studies, the MMN would be largest over the frontal scalp region. As this region is above the anterior cingulate region, it was also hypothesized that the reduction of MMN by pain would be greatest in this region.

Experiment 2 was designed to test whether increasing the task difficulty of the distracter task would tax participants' cognitive systems enough to allow pain to disrupt the attentional processes involved in the generation of the MMN. Experiment 3 used a design analogous to Experiment 2 but was carried out using volunteers who suffered from high levels of chronic pain.

Experiment 1

Method

Participants

Informed consent was obtained from all participants following the protocol approved by the appropriate local human research ethics boards. Fifteen adult volunteers (eight females, seven males) with normal hearing, corrected visual acuity, and no history of psychiatric problems or head trauma were recruited for this study. One female participant was found to be left handed using the Edinberg Handedness Questionnaire (EHQ; Oldfield, 1971). Data from one right-

handed female participant were discarded due to excessive ocular artifact. The remaining 14 participants had a mean age of 19.9 years (range = 17 - 27 years, SD = 2.5 years).

All participants were screened when recruited for any medical conditions that could have precluded them from safely participating in the cold pressor or ischemic pain procedures. None of the volunteers were screened out of the study due to these criteria. Participants were also screened on a day prior to testing to ascertain their ability to tolerate the cold pressor and ischemic pain tasks for one minute periods. Six participants (four females, two males) who attended screening sessions chose not to return for testing due to an inability to tolerate pain induction.

All participants received compensation for participation in screening sessions and testing sessions. Undergraduate student participants who were eligible to receive course credit points for participation in research were offered either one credit point or ten dollars per hour for each hour (or part of an hour) required by the experiment. Participants who were not eligible for course credit points received ten dollars per hour (or part of an hour) required by the experiment.

Pain Induction Techniques

Two pain induction techniques were used in this study. In one pain condition, experimental pain was induced using the cold-pressor test (see Turk, Meichenbaum, & Genest, 1995) The cold pressor apparatus consisted of a cooler equipped with a modified arm lever upon which participants rested their forearms. The cooler was filled with water maintained at 1-2 degrees Celsius. Water temperature was maintained by keeping ice inside of a wire mesh container immersed in the cooler water while water was circulated in the tank using a circulating pump.

In the second pain condition, ischemic muscle pain was induced using the upper arm tourniquet test following a protocol outlined in Smith, Egbert, Markowitz, Mosteller, and Beecher (1966). Blood flow was occluded in the upper arm using a blood pressure cuff (Baumanometer Calibrated V-Lok Cuff) inflated to 250 mmHg. A hand dynamometer (Preston Smedley-Type, model PC 5032P) was used to measure grip strength during ischemic pain induction.

Participants were given pain induction in both arms where only one arm had pain in a given session and each arm only had one type of pain induction method assigned to it. Pain induction method was assigned randomly and balanced across participants for both left and right arms. The order of the control and the two pain condition testing sessions were also randomized and balanced across participants.

Auditory Stimuli

The auditory oddball stimuli used in the present experiment followed a classic oddball paradigm to elicit MMN. Each recording block was composed of a sequence of 1000 tones. Using Neuroscan Stim software, these tones were presented binaurally through Panasonic RP-HT247 headphones at an ISI of 600 milliseconds. Each tone was presented at 60 dB SPL for 60 ms with 10 ms rise and fall times. Two hundred oddball tones (20% of the sequence) at a frequency of 1100 Hz were presented within the stream of 800 standard (1000 Hz) tones in each block. The presentation of the oddball tones within the standard tone stream was pseudorandom with the constraint that each oddball tone was preceded by at least two standard tones.

Visual Stimuli

Innocuous nature videos were shown to participants on a Panasonic CT - 2084Y television placed 1.75 m (just outside of the testing room) from the chair in which the participant

was seated. This allowed participants to easily view the video while minimizing the electrical noise created in the room by the television monitor. The content of the nature videos dealt primarily with marine scenes with slow moving images, thus decreasing involuntary eye movements.

Questionnaire Measures

Demographic information including current health and a brief medical history was taken using a simple questionnaire. Additional information related to participants' pain experience during the experiment and thought patterns of catastrophic thinking related to pain were collected using the following standardized questionnaires.

Pain Catastrophizing Scale (PCS). The PCS (Sullivan, Bishop, and Pivik, 1995) contains 13 items outlining thoughts and feelings that an individual may have when experiencing pain. Respondents are required to rate the degree to which they have the listed thoughts and feelings when they are experiencing pain. Three factors have been found to be assessed by this scale, rumination, magnification, and helplessness. Evaluation of the psychometric properties of this scale has found that this measure demonstrates good reliability and validity in measuring these factors.

McGill Pain Questionnaire (MPQ). The MPQ (Melzack, 1975) is composed of items related to sensory, affective, and evaluative aspects of pain. Respondents are required to endorse pain-related adjectives listed on the forms. The adjectives are grouped according to their similarity in description of a pain experience and are listed in a graded fashion in terms of intensity. The MPQ's purported strengths lie in its ability to provide a quantitative measure of these aspects of pain, it's sensitivity to detect differences in pain levels, and differences in the underlying qualities of pain (Melzack, 1975).

Numerical Pain Rating Scale (NRS). Pain levels were rated using an 11 cm numerical rating scale (NRS) affixed to the bottom of the television screen. The NRS was anchored and labeled at zero and ten. A rating of zero represented "no pain" and a rating of ten represented "the worst pain imaginable".

Electrophysiological Data Acquisition

Continuous EEG data was recorded using a 32 channel Ag/AgCl electrode Neuromedical Supplies Quik-Cap. Recordings were taken over the sites: FPz, FP1, FP2, Fz, F3, F4, F7, F8, FT7, FT8, FCZ, FC3, FC4, Cz, C3, C4, CPz, CP3, CP4, Pz, P3, P4, P7, P8, T7, T8, TP7, TP8, Oz, O1, and O2. The electrode at AFz was used as a ground electrode. Electrode placement in the cap followed the International 10/20 system (Jasper, 1958). All electrodes were referenced to linked ears through a 10 KΩ resistor. Inter-electrode impedances were kept below five KΩ. Horizontal eye movements were monitored using an electro-oculogram (EOG) with Ag/AgCl electrodes placed over the outer canthus of the right and left eyes. A vertical EOG was also monitored using Ag/AgCl electrodes placed above and below the right eye.

Analogue EEG recordings were made using a Synamps 32 channel amplifier at a bandpass of DC - 100 Hz and used a digital sampling rate of 2000 Hz. A 60 Hz notch filter was enabled during recording in order to control for effects of electrical fields generated by electrical lines in the recording area. Continuous EEG data was epoched around a recording window from 50 ms before the presentation of each tone until 462 msec after tone presentation. Baseline correction was performed using the portion of the epoch recorded during the 50 msec prior to tone presentation. All data was then filtered digitally offline at a bandpass of 0.5 -20 Hz. Trials in which absolute EOG activity was greater than $\pm$ 75 microvolts (μV) were rejected and excluded from statistical analysis. Average files were then created for each of the two tones present in the

tone stream. In order to obtain the MMN, averaged waveforms for the standard tone were subtracted from averaged waveforms elicited by the deviant tones in each condition. Peak scoring for the MMN was carried out by marking the highest negative peak at electrode Fz between 140 and 250 ms post-stimulus in the subtraction file for each condition. Following this procedure, the average amplitude value was calculated for the waveform in the area $\pm$ 25 ms on either side of the peak for statistical analyses. Peak scoring was also carried out for the N1 deflection using the highest negative peak at electrode Fz between 80 and 140 ms post-stimulus.

Procedure

Prior to the day of testing, a screening session was held where health and handedness questionnaires were administered in addition to informed consent forms. The Pain Catastrophizing Scale (Sullivan et al., 1995) was also administered during this session. Upon completion of these forms, participants took part in brief pain induction sessions where using both the cold pressor and ischemic pain induction techniques. Participants were then given the choice following the screening session of whether they wished to return for inclusion in the study.

On the day of testing, participants were seated in an armchair in a shielded room adjacent to where the EEG recording equipment was located. Experimental procedures were re-explained to participants. They were also instructed to avoid moving and blinking their eyes as much as possible and instructed to blink if necessary when giving their pain ratings. During EEG recording in pain and no-pain conditions, participants were also instructed to carefully watch the nature video while ignoring the tone stream played through the headphones. They were informed that they would be questioned regarding the content of the video during each testing session.

Every 30 seconds tone presentation was stopped and participants were asked to report their level of pain using the visual analogue scale placed at the bottom of the television screen.

The ten minute cold pressor testing block was divided into at least three blocks of a maximum of 3.5 minutes. This was done because previous research (Eccleston, 1995b) has shown that pain levels decrease during the cold pressor task due to numbing after approximately four minutes. Participants were given the option of performing the control and ischemic pain sessions without a break. Each pain recording session was followed by a break of sufficient length to allow the limb in which pain had been induced to recover to either a comfortable temperature or a comfortable level of blood circulation as reported by the participant. Immediately following the stoppage of EEG recording, the video was stopped and participants were asked to report what had occurred during the video sequence just viewed in order to monitor the level of attention directed at the video. At the end of each ten minute pain condition recording block, the McGill Pain Questionnaire was filled out by participants. When all three condition blocks were completed, the modified Pain Coping Strategies Questionnaire was completed by participants and participants were debriefed.

Statistical Analyses

All statistical analyses were carried out using a personal computer version of the Statistical Package for the Social Sciences, version nine (SPSS 9.0). Amplitude of the MMN was compared to the mean amplitude of the 50 ms pre-stimulus baseline period with paired t-tests using Bonferroni corrections to control for the inflation of alpha. Analysis of ERP waveform differences between control and pain sessions was carried out using a repeated measures ANOVA. This repeated measures ANOVA was carried out for the three pain condition levels (no pain control, cold pressor pain, ischemic pain) and separately for electrode site using

normalized data for a reduced montage (McCarthy & Wood, 1985) at sites Fz, Cz, Pz, C3, C4, T7, and T8. Descriptive statistics for demographic and questionnaire data were calculated and can be found in Table 1.

A repeated measures ANOVA was also carried out to test whether pain ratings were significantly different across the three experimental blocks. All repeated measures ANOVAs were carried out using conservative Greenhouse-Geisser corrections for degrees of freedom. All t-tests were carried out using Bonferroni corrections to control for the inflation of alpha.

The analysis and discussion of spatial analysis and mapping were performed separately (Brauer et al., unpublished data).

Results and Discussion

The length of time that participants were able to keep their arms in the cold pressor water ranged from 30 seconds to 3.5 minutes. Tolerance of ischemic pain ranged from 3.5 minutes to 10 minutes. Participants divided their control sessions into two five-minute or one ten-minute session. Participants' average pain ratings during cold pressor conditions ($\underline{M} = 6.41$, $\underline{SD} = 1.66$) did not differ significantly [$F(1, 13) = 0.31$, *ns.*] from their average pain ratings during ischemic pain ($\underline{M} = 6.25$, $\underline{SD} = 1.19$). A repeated measures ANOVA found that a significant difference existed between pain ratings across the three experimental conditions [$F(2, 26) = 208.78$, $p < .0001$]. Post hoc examination confirmed that both pain rating averages during pain conditions differed significantly from average pain ratings ($\underline{M} = 0.0071$, $\underline{SD} = 0.0027$) during control conditions.

The MMN waveforms elicited in Experiment 1 were clear and well defined in each experimental condition. The average amplitude around the peak of the MMN was found to be

significantly different from zero on each comparison ($p < .0001$). Grand average MMN waveforms peak amplitudes at electrode Fz of control (- 2.89 μV), cold pressor (- 2.84 μV), and ischemic pain (- 2.53 μV) conditions were in a range that suggested that the aim to improve signal-to-noise ratio of the MMN in this experiment had been accomplished (Lang et al., 1995). No differences were found in MMN amplitude ($F(2,39) = 0.012$, *ns.*) or latency ($F(2,39) = 0.78$, *ns.*) between experimental conditions (see Figure 6). The amplitude of the MMN was found to differ significantly between electrode sites [$F(2,15) = 13.42$, $p < .0001$]and was found to be largest at electrode Fz ($p < .0001$) relative to other sites. No differences were found in the amplitude of the N1 to standard tones amplitude [$F(2,39) = 0.15$, *ns.*] or latency ($F(2,39) = 0.41$, *ns.*) between pain conditions The amplitude of the N1 was found to differ significantly between electrode sites [$F(2,15) = 21.73$, $p < .0001$] and was found to be largest at electrode Fz ($p < .0001$).

Data collected from participants' McGill Pain Questionnaire - Pain Rating Index were not different between the two pain conditions ($t(13) = 0.35$, *ns.*). As there were no differences found between participants or conditions in the MMN, no further analyses were carried out on questionnaire data. Qualitatively, all participants were able to respond with a high level of detail to the questions posed to them regarding the content of the nature video. It appeared that they had little difficulty in staying focused on the content of the video. In fact, one female participant remarked during her debriefing that when she was experiencing pain, in addition to attending to the details of the video, she would "sometimes follow the pattern of high beeps" to distract herself from the pain, even though she had been clearly instructed to ignore the tones.

It appears from these data that experimentally induced pain did not have an effect on early passive auditory attentional processing as manifested by the MMN. There is little question

that the experimental paradigm used elicited a MMN waveform that was within normal limits for healthy young adults such as those tested in this study. There is also little question that participants' MMN's were generally unaffected by pain in both of the pain induction conditions. This was seen both in the individual waveforms and in the group results.

These results suggest that the auditory difference detection mechanism that generates the MMN is indeed a very basic, hardwired mechanism whose function is not affected by pain. However, there may be reasons that might explain why pain still did not have an effect on the processes underlying the MMN. Although participants performed very well at recalling very specific details of the video, this task may not have been difficult enough to keep their attention away from the tones. The participant who sometimes attended to the tones and possibly other participants may not have ignored the tone stream as instructed. This possible turning of attention toward the auditory stimuli may have resulted in an amplification of the MMN in such participants. This would be a problem if participants monitored the tone stream when they were in pain as the amplification of the MMN due to attention could reduce the effect that pain had on their MMN. In addition to this possibility, it is possible that the task of watching the nature video and reporting on even minute details of the video (e.g., the color of diver's gloves) was not difficult enough to sufficiently tax these participants' cognitive systems. If, as Eccleston has previously reported (1994, 1995a), a high level of pain must be present during the performance of an attentionally demanding task for attention to be disrupted, then additional modifications may be necessary to obtain the predicted effect. A more attentionally demanding task may be required. As well, while the pain induction methods used in Experiment 1 were reported by participants to have produced substantial levels of pain, the pain was time limited and escapable

according to the desire of the participant. This kind of pain is qualitatively different from the pain experienced by Eccleston's participants who suffered from chronic pain.

Experiment 2

As the data from Experiment 1 showed no effect of pain on basic passive early attentional processing manifested by the MMN, it was decided to examine whether pain would affect the amplifying component of the MMN when participants took part in an active auditory attention paradigm. It was also decided that a more attentionally demanding task would be used as a distracter task in the passive auditory condition to ensure that participants focused on something other than the tones. The Windes (1968) task was chosen as this distracter task. By choosing this task, it provided an attentionally demanding task and also allowed for a broad comparison with Eccleston's (1994; 1995a) findings.

As has been briefly mentioned earlier, a number of reports have suggested that the amplitude of the MMN can be changed by modifying the attentional load of the experimental paradigm. While previous research has provided very strong evidence that the MMN can be generated independent of active attention to stimulus differences, some reports have shown that in conditions where participants were required to actively monitor a tone stream for deviant tones, MMN amplitude was increased. It has now been widely accepted that attention can affect the MMN. However, questions remain as to whether attention can affect the basic stimulus feature ("computational") detection MMN generators or whether it merely acts on the relatively later ("amplifying") MMN generators.

In one of the earliest reports of this effect, Woldorf, Hackley, and Hillyard (1991) used a dichotic listening task where standard tone streams that contained deviant stimuli were played to participants who were highly trained on the task. Deviant stimuli differed from standard tone

stimuli in their intensity. In both of the experiments reported in Woldorf et al. (1991), participants' MMN amplitude was significantly higher to deviant tones in the tone stream that was attended than was the MMN to the unattended stream. Woldorf and colleagues (1991) argued that MMN amplitude was not attention independent. It was clear from this study that MMN amplitude could be influenced by active attentional processing of stimulus differences. This argument was later strongly challenged by a number of studies that showed that the basic MMN generating mechanism operates independently of attention (for a review see Näätänen, 1995).

In two later studies, Alho, Woods, and colleagues reported a series of parallel experiments where they examined whether attention to stimuli would modulate the MMN. Woods, Alho, and Algazi (1992) presented a tone stream to participants that included two deviant tones. One of these deviant tones differed from their standard (1000 Hz) tone by 64 Hz ("difficult-to-detect" tone) and the other deviant tone differed by 500 Hz ("easy-to-detect" tone). The experimental tone stream was presented to participants in two attentional conditions. In one condition, participants performed a simultaneous attentionally demanding visual task and ignored the tone stream. In the second attentional condition, participants were required to respond to the deviant tones. They found that the MMN amplitude was increased with attention to the difficult-to-detect deviants but not to the easy-to-detect deviants. Alho, Woods, Algazi, and Näätänen (1992) found that MMN amplitude also showed a small but significant increase when more difficult-to-detect 1050 Hz deviant tones were actively responded to. Again, in contrast to this effect, they reported that while participants' MMN amplitudes elicited by the 1500 Hz deviant tones were much larger than the MMN elicited by the 1050 tones, there was no difference in the MMN elicited by the easy-to-detect tone between active and passive attentional conditions. Consequently, Alho and

colleagues suggested that attention may only noticeably affect MMN amplitude during processing of small stimulus changes. They further proposed that it is possible that large stimulus differences are processed in an automatic fashion whether or not attention is directed at incoming stimuli.

It is noteworthy to mention that the changes in the MMN to difficult-to-detect tones in the Alho et al. (1992) and the Woods et al. (1992) studies were quite small increases (Alho, personal communication, August 2000). This is important to note because Alho, Woods, and Algazi (1994) used an auditory tone stream that was in many ways similar to those used in the two previously mentioned studies (Woods et al., 1992; Alho et al., 1992) and were unable to replicate their MMN findings. Attention did not enhance the MMN elicited by small frequency deviances in Alho, Woods, and Algazi (1994). However, it was noted that the tones that only deviated slightly from standard tones were never actively targeted by participants in Alho, Woods, and Algazi (1994). It was also pointed out that it is possible that the effects found in Woods et al. (1992) and Alho et al. (1992) were related to the contribution of the N2b to the MMN elicited by small stimulus deviances. This possibility will be further discussed hereafter.

More recently, Trejo and colleagues (1995) reported a variation of active and passive MMN testing blocks. Participants in this study were presented binaurally with a standard (1200 Hz) tone stream containing two deviant (1000 and 1400 Hz) tones which was played simultaneously with a recorded narrative. In the passive MMN condition participants were instructed to ignore the tone stream and were required to respond each time they heard the word *and* in the narrative. In the active MMN condition, participants responded when they detected one of the deviant tones and ignored the narrative. The results of this work showed an increased MMN in the active attend condition elicited by the deviant tones that had been responded to. Whether this difference

is solely due to an increase in the MMN in the active condition or whether the passive condition MMN was decreased due to the attentionally demanding word tracking task is unclear.

Woldorf and colleagues (1998) strongly argued that the MMN can be gated or suppressed by modulating attention. Using magnetoencephalographic recordings, they presented participants in their study with an attentionally demanding dichotic listening task similar to the one used in Woldorf et al. (1991). They found that the MMN elicited by tones that deviated in their intensity which were presented in the unattended ear were significantly smaller than those presented in the attended ear. They proposed that these results further supported their argument that the MMN is not attention independent and that Näätänen's (1991) model of computational and amplifying divisions of the MMN was both circular and unparsimonious in its argument. While it is possible that deviants differing in intensity may present a unique case in the generation of the MMN (see also Näätänen et al., 1993) it is likely that the exact nature of the influence of attention on the mechanisms that generate the MMN will remain a subject of argument until further methodological or technological developments allow for a more precise investigation of these mechanisms.

Regardless of the exact nature of the mechanisms underlying the MMN, it appears clear that the MMN can be affected by attention. In order to examine whether pain would disrupt this early attentional modulation that has been reported to increase MMN amplitude, Experiment 2 was designed. This study used a paradigm similar to the paradigm reported in Woods, Alho, and Algazi, (1992). The aim in using this paradigm was to provide an opportunity to examine whether pain would interfere with the early attentional processes that act along with the basic MMN generating mechanisms. The primary question was whether pain would interfere with the secondary, amplifying mechanism involved in the increase in MMN amplitude during an active

attention task. The question of how pain would affect the MMN while an attentionally demanding task was being performed was also a focus. Further, another important question was whether this effect would be most pronounced on more difficult tasks such as when participants were required to detect the difficult-to-detect tones. It was hypothesized that the MMN enhancement generated by active attention to difficult-to-detect tones would be disrupted by pain. A second hypothesis was that using a more demanding distracter task in the passive MMN condition would tax attentional mechanisms and thereby have a more disruptive effect on these mechanisms and lead to a larger reduction in MMN amplitude to the difficult-to-detect tones. Finally, it was expected that the decrement of the MMN due to pain would be the largest over the frontal scalp region over the anterior cingulate.

Method

Participants

Participants were recruited using on-campus postings and were given the same compensation for participation as the volunteers in Experiment 1. All participants read and signed the informed consent forms approved by the appropriate local research ethics boards prior to taking part in experimental tasks. Inclusionary criteria outlined in Experiment 1 were also used in Experiment 2.

Sixteen right-handed adult volunteers (11 female, 5 male; $\underline{M}$ age = 21.8 years, $\underline{SD}$ = 7.1 years, range = 18 – 43 years) chose to take part following screening sessions for health, hearing, and willingness to tolerate pain induction. All participants were able to detect the difficult-to-detect deviant tone at at least an 80% accuracy rate. One right-handed female participant chose not to return for testing because of the distressing nature of the pain induced.

Pain Induction Technique

As Experiment 1 showed that there was no difference between pain induction techniques in terms of pain intensity ratings or their effects on the MMN, for convenience, only ischemic pain was used in Experiment 2. The ischemic pain induction protocol used in Experiment 1 (Smith et al., 1966) was again used in this study. This pain induction technique was chosen because it allows for longer pain sessions and requires less recovery time between pain blocks. Pain recording sessions lasted a maximum of eight minutes following pain induction starting when participants rated their pain as at least four out of ten on the NRS. A total of 16 minutes of recordings were taken while participants experienced pain in each of two experimental (active and passive) auditory conditions. All participants were informed that they were permitted to remove the blood pressure cuff at any time during testing without losing compensation for participation.

As all participants in Experiment 2 were right-handed, the blood pressure cuff was placed on the left (non-dominant) arm during testing. During no-pain recording sessions, the cuff was placed on the left arm but was not inflated.

Auditory Stimuli

Each recording condition block was composed of a sequence of 1600 tones. Using Neuroscan Stim software, these tones were presented binaurally through Panasonic RP-HT247 headphones at an ISI of 600 milliseconds. Each tone was presented at 60 dB SPL for 60 ms with 10 ms rise and fall times. Two hundred and ten difficult-to-detect oddball tones (13% of the sequence) at a frequency of 1020 Hz and 210 easy-to-detect oddball tones (13% of the sequence) at a frequency of 1500 Hz were presented within the stream of 1180 (74%) standard (1000 Hz) tones in each block.

The pitch of the difficult-to-detect (1020 Hz) tones was chosen following pilot testing of pain-free healthy volunteers who did not take part in Experiment 2. These healthy volunteers were asked to perform the experimental tone detection task with difficult-to-detect tones of varying pitches. Their ability to detect these tones was monitored starting with 1050 Hz difficult-to-detect tones. Following each block, the pitch of the difficult-to-detect tones in the stream were decreased by 10 Hz. When 1020 Hz tones were used in the tone stream, all healthy volunteers reported a (subjective) marked increase in detection difficulty yet remained able to detect these tones at an accuracy of at least 80%. Further, difficult-to-detect tone detection performance became very poor when 1010 Hz tones were used, therefore 1020 Hz difficult-to-detect tones were chosen. This choice of a 20 Hz difference being a point at which the MMN can begin to be reliably elicited in healthy participants is confirmed by other previous reports (Sams et al., 1985; Näätänen, 1990; Tiitinen et al., 1994). For example, Tiitinen and colleagues (1994) reported that at a frequency difference of 20 Hz the MMN began to be reliably elicited while it was not reliably elicited in some individuals at smaller pitch differences.

The presentation of the oddball tones within the standard tone stream was pseudorandom with the constraint that each oddball tone was preceded by at least two standard tones. In the active detection condition, participants were instructed to press a button as quickly as possible with the index finger of their dominant hand whenever they heard either of the deviant tones. In the passive condition, participants were instructed to ignore the tone stream and to concentrate maximally on the visual task presented to them.

Visual task

The visual task was the same visual paradigm (Windes, 1968) previously used by Eccleston in a number of previous reports (Eccleston et al., 1994, 1995, 1997, 1999). This

paradigm was chosen for two reasons. First, this paradigm provides an engaging visual task with minimal motor requirements and generally elicits fairly minimal eye movements. In these ways, this task is similar to the visual task used in Woods et al. (1992). Second, by using this paradigm, the opportunity was provided to compare behavioral results in this study with those previously published by Eccleston and colleagues.

Stimuli were presented using a Macintosh 190E laptop computer placed approximately 1.5 m away (to reduce eye movement) from each participant. Each visual stimulus trial was made up of two adjacent cards measuring approximately 85 mm X 60 mm. The cards in each pair were placed approximately 25 mm apart (see Figure 2). Upon each card were displayed one to nine numbers chosen from numbers between one and nine (inclusive). A constraint was included on all stimuli such that the number of numbers on each card never equaled the value of the numeral of that card. For example, there were never three three's on a stimulus card. Also, the same numerical digit presented on a card was never the same on consecutive trials. A brief pause was taken at approximately the four-minute mark of each eight minute session. This break typically lasted approximately one minute or less.

Participants were instructed to choose the card that contained the highest number of numbers on it. This rule was the most attentionally demanding rule for participants to follow as reported by Eccleston (1994) in his first report that used this task. Stimulus pairs remained on the computer screen until a response was made. Responses and reaction times were recorded by the computer. Participants were also instructed to respond as quickly as possible using left or right keys marked on a computer keyboard placed in their laps using the index and middle fingers of their dominant hand. Their fingers were kept over the two response keys between responses to facilitate faster responding.

Questionnaire Measures

Demographic, health, medical history, medications taken, and handedness data were collected using the same forms as in Experiment 1. As well, as in Experiment 1, information concerning participants' pain experience during the experiment (MPQ) and pain catastrophizing (PCS) was again collected. As was the case in Experiment 1, pain levels were reported by participants using an 11 cm numerical rating scale (NRS).

In addition to these measures, level of depressive mood over the past two weeks was recorded using the Beck Depression Inventory II (BDI – II). This measure examines 21 symptoms and attitudes rated by the respondent on a four point severity scale. The items of this scale are related to the cognitive, affective, somatic, and vegetative dimensions of depression. This measure takes very little time to complete and is high in face validity. Psychometric evaluation of this test have found that it has good internal consistency (Dozois, 1998), reliability (Osman et al., 1998), and good content, construct, and concurrent validity (Steer et al., 1998).

Electrophysiological Data Acquisition

Continuous EEG data was recorded in all participants using Synamps amplifiers. Participants' EEG data were recorded using a 128 channel Ag/AgCl electrode Neuromedical Supplies Quik-Cap. Cap electrode placement followed the International 10/20 system (Jasper, 1958). All electrodes were referenced to an electrode placed on the nose. This location for the reference was chosen in order to avoid the potential problems that can occur when using a linked-ear reference (Picton, Lins, & Scherg, 1995). The electrode placed at position AFz was used as a common ground. Inter-electrode impedances were kept below five kΩ. Horizontal eye movements were recorded using an electro-oculogram (EOG) with Ag/AgCl electrodes placed

over the outer canthus of the right and left eyes. Right and left vertical EOG recordings were also made using Ag/AgCl electrodes placed above and below both eyes.

Analogue EEG recordings were made at a bandpass of 0.1 - 100 Hz at a digital sampling rate of 500 Hz. A 60 Hz notch filter was enabled during recording. All data was filtered digitally offline at a bandpass of 0.5 -20 Hz. Following offline filtering, an ocular artifact correction algorithm was used to model eye blinks and mathematically remove them from the filtered continuous EEG files. The choice to use an ocular correction technique in addition to artifact rejection was made because of reports published by Croft and Barry (2000a, 2000b) that have shown that this method provides some advantages over simple artifact rejection. One primary advantage of using this technique is that as there is an ethical limit on the amount of time that one can inflict pain on volunteers, individuals who produce a high amount of ocular artifact (that often appears worse during painful stimulation) can still provide adequate data for analysis.

Filtered, artifact corrected continuous EEG data was epoched from 50 ms before the presentation of each tone until 462 msec post-stimulus. Artifact rejection was then carried out for epochs containing EEG artifact that was greater than $\pm$ 100 μV at electrodes Fz, Cz, Pz, FC3, FC4, FT7, FT8, CP3, CP4, TP7, and TP8. This step was taken as a precautionary measure for the presence of electrode or movement-related artifact in any of these electrodes not related to EOG artifact. Artifact rejection was then again carried out on remaining epochs where EOG artifact was greater than $\pm$ 75 μV existed in the HEOG channel. Baseline correction was performed using the portion of the epoch recorded during the 50 msec prior to tone presentation and averaged files were then created for each of the three tones in the tone sequence. In order to obtain the MMN, averaged waveforms for the standard tone were subtracted from averaged waveforms elicited by the deviant tones in each condition. Peak scoring for the MMN was

carried out by marking the highest negative peak at electrode Fz between 140 and 250 ms post-stimulus in the subtraction file for each condition. Following this procedure, the average amplitude value was calculated for the waveform in the area $\pm$ 25 ms on either side of the peak for statistical analyses. Peak scoring was also carried out for the N1 deflection to standard tones in each condition using the highest negative peak at electrode Fz between 80 and 140 ms post-stimulus and for the P3 using the highest positive peak between 280 and 550 ms post-stimulus at electrode Pz. For the purpose of statistical analyses, the peak amplitude values for the N1 and P3 deflections were taken.

Procedure

Prior to the day of testing, each participant took part in a screening session that was the same as screening sessions held during Experiment 1 except for the addition of a practice session for the active auditory task. During this auditory practice task, participants listened to the tone stream through headphones and were told to press a button as quickly as possible whenever they detected either of the two deviant tones. This addition was carried out in order to ensure that participants were able to detect the difficult-to-detect tones. During testing, participants were seated in a comfortable armchair in a shielded room adjacent to the room where EEG recording equipment was located. Electrodes were then applied using Electro-Cap International Electro-gel at the above mentioned sites and inter-electrode impedances were checked.

The experimental protocol was then explained to participants. Participants were instructed to avoid unnecessary eye movements and blinking but were instructed to blink if necessary. Every 60 seconds tone presentation was stopped and participants were asked to report their level of pain using the numerical rating scale placed below the computer screen screen.

Participants were also encouraged to blink if needed during these breaks while their pain ratings were being taken.

During passive auditory recording blocks, participants were instructed to focus maximally on their performance of the visual card choice task while ignoring the tones played to them. They were told to respond to each card pair as quickly as possible while committing as few errors as possible. Five practice trials were given to each participant in order to help familiarize participants with the task.

In the active auditory condition, participants were instructed to focus on the auditory tone stream and to press a button on a key pad whenever they detected either of the deviant stimuli. They were also instructed during this condition to keep their eyes fixated on the computer screen where one pair of the playing card stimuli was being presented. A short tone detection practice period was given to each participant to help them familiarize themselves with the auditory task prior to testing.

Participants were permitted to stop recording sessions and remove the blood pressure cuff as they desired. Sixteen minutes of recording data was collected in each of the four conditions (passive attention with no pain, passive attention with pain, active attention with no pain, active attention with pain). Participants were given the option of performing the control and ischemic pain sessions without a break to a maximum of eight minutes at a time in each condition. All pain recording sessions were followed by a break of sufficient duration to allow the arm in which pain had been induced to return to a comfortable level of blood circulation as reported by the participant. The order of the active and passive conditions and the order of pain and no-pain conditions were counterbalanced.

Participants were administered the MPQ following their final pain recording block and the BDI-II at the end of testing. Following completion of these questionnaires, participants were debriefed and compensated.

Statistical Analyses

All statistical analyses were carried out using SPSS 9.0. The MMN was compared to the mean amplitude of the 50 ms pre-stimulus baseline period using paired t-tests and Bonferroni corrections to control for the inflation of alpha. A repeated measures ANOVA was carried out using the MMN amplitude and latency data for the variables of pain condition (no-pain vs. pain), attentional condition (active vs. passive), and tone detection difficulty (easy- vs. difficult-to-detect). A repeated measures ANOVA was also performed for electrode site using normalized data (McCarthy & Wood, 1985) at sites Fz, Cz, Pz, CP3 CP4, TP7, TP8. Repeated measures ANOVAs were also carried out for peak amplitude and latency of the N1 and P3 deflections.

Additional repeated measures ANOVAs were carried out for participants' behavioural performance data on the active tone detection task using the variables of pain (no-pain vs. pain) and difficulty (easy- vs. difficult-to-detect tones). Paired t-tests were carried out for the first 20 trials on the Windes (1968) task in the no-pain and pain conditions for both accuracy and response latency. Only the first twenty trials were used for analysis because a significant practice effect occurs for this task after the first 20 trials of a block (Eccleston, personal communication, September, 2000). Clearly, as participants were required to perform this task over two 16-minute periods, when the second passive session was carried out (no-pain or pain) most participants had completed approximately 1000 trials in the previous session. Despite this limited usefulness for comparison, this task chosen primarily because it is attentionally engaging for the volunteers.

Repeated measures ANOVAs were also carried out for participants' pain ratings using the factors of pain condition (no-pain vs. pain) and attention (active vs. passive). Descriptive statistics for age and questionnaire data were calculated and are displayed in Table 2.

All repeated measures ANOVAs were carried out using conservative Greenhouse-Geisser corrections for the degrees of freedom used in these calculations. All t-tests were carried out using Bonferroni corrections to control for inflation of alpha.

The analysis and discussion of spatial mapping recorded from the 128 channel array will to performed separately.

Results and Discussion

Participants' pain ratings differed significantly [$F(1,15) = 247.74$, $p < .0001$] between no-pain and pain conditions. They did not differ significantly [$F(1,15) = 0.38$, *ns.*] between the active and passive attentional conditions (see Table 2). Although the verbal anchors on the NRS were the same for each participant, it must be acknowledged that there was a considerable amount of variability between participants as to what each conceptualized as "worst pain imaginable". However, all participants reported that the pain they experienced was unpleasant and not easy to endure.

The repeated measures ANOVA for MMN amplitude at electrode Fz using the variables of pain condition, attentional condition, and tone detection difficulty found no effect of pain [$F(1,15) = 1.82$, *ns.*], attention [$F(1,15) = 0.36$, *ns.*], or tone detection difficulty [$F(1,15) = 0.11$, *ns.*]. These findings were consistent when performing this analysis for the area under the curve 25 ms on each side of the MMN peak and when 25 ms intervals between 150 and 250 ms post-stimulus were analysed. While nine of the 16 participants (as in Dick et al., 1999) showed MMN decrements due to pain, there was no theory-based method to separate these participants based

on other information collected from participants who did not show a change in MMN in the pain condition. No effect of pain [$F(1,15) = 1.43$, *ns.*] or attention [$F(1,15) = 0.93$, *ns.*] was found on MMN peak latency. The MMN to the easy-to-detect tones was significantly earlier than the MMN to the difficult-to-detect tones [$F(1,15) = 7.13$, $p < .01$].

Upon inspection of the relevant interactions, a significant interaction was found between attentional condition and tone detection difficulty [$F(1,15) = 9.38$, $p < .009$]. This interaction was found to be a result of larger amplitude MMN's elicited by the difficult-to-detect tones in the active attentional condition than were elicited by the easy-to-detect tones (regardless of pain condition). This result was confirmed using the 25 ms interval analysis method mentioned above as the MMN to easy-to-detect tones was largest in the first two intervals and the MMN to the difficult-to-detect tones was largest in the last two intervals [$F(3,15) = 18.44$, $p < .000$]. As well, smaller amplitude MMN's were elicited by the difficult-to-detect tones than were elicited by the easy-to-detect tones in the passive attention condition (regardless of pain condition). Planned comparisons carried out in order to examine whether attention increased MMN amplitude found that, similar to Alho et al. (1992) and Woods et al. (1992), the MMN elicited by the difficult-to-detect tone was larger in the active attention condition than in the passive attention condition when participants were experiencing pain [$t(15) = -2.79$, $p < .02$]. This effect occurred in the last two interval windows [$F(3,15) = 9.97$, $p < .007$]. While the classic pattern of smaller MMN's being elicited by deviant tones with smaller pitch deviance was observed in the passive attention condition, the reverse was seen when these participants were actively attending to these difficult-to-detect tones. It appears that not only was the MMN amplified to the difficult-to-detect tones in the active condition, it became substantially larger than the MMN elicited by the easy-to-detect tones. Although a number of previously reported studies have found increases in the MMN as a

result of attention to auditory stimuli, none have reported this kind of effect. It may be that the presence of a high level of experimental pain focused these healthy volunteers more intensely on the difficult auditory task and lead to an increase in attention to the difficult-to-detect tones (see Figures 7, 8, and 9).

The repeated measures ANOVA for MMN latency using the variables of pain condition, attentional condition, and tone detection difficulty found no effect of pain [$F(1,15) = 0.98$, *ns.*] or attentional condition [$F(1,15) = 1.41$, *ns.*]. The MMN to difficult-to-detect tones was found to occur significantly later than the MMN to easy-to-detect tones [$F(1,15) = 6.21$, $p < .001$]. This pattern of delayed latency of the MMN to deviant tones with smaller degrees of deviance is in line with previous findings (Näätänen, 1990).

With respect to participants' behavioural performance in the passive attention condition on the computerized Windes (1968) task, no difference was found in either error rate [$t(15) = -0.45$, *ns.*] or reaction time [$t(15) = -0.34$, *ns.*] between no-pain (M errors = 1.06, SD = 1.18; M rt = 532.15 ms, SD = 88.08) and pain conditions (M error = 1.25, SD = 1.48; M rt = 546.93 ms, SD = 105.21). On the deviant tone detection task in the active attention condition between pain conditions, no difference was found on measures of accuracy [$F(1,15) = 1.36$, *ns.*] or latency [$F(1,15) = 0.83$, *ns.*] for easy- or difficult-to-detect tones. Detection accuracy was significantly higher [$F(1,15) = 18.43$, $p < .001$]and reaction times shorter [$F(1,15) = 67.32$, $p < .0001$] to easy-to-detect tones than to difficult-to-detect tones (see Table 3).

Results from repeated measures ANOVAs for the N1 amplitude at electrode Fz to standard tones using factors of pain condition and attentional condition found no effect for pain [$F(1,15) = 0.01$, *ns.*] or attentional condition [$F(1,15) = 0.45$, *ns.*]. In terms of N1 latency, there was also no effect of pain [$F(1,15) = 0.25$, *ns.*] or attentional condition [$F(1,15) = 0.07$, *ns.*]. In

these participants, neither the introduction of experimental pain or active focus of attention changed the magnitude or the timing of initial stimulus processing related to the standard tones.

Following repeated measures ANOVAs for the P3 amplitude at electrode Pz, no difference was found due to pain [$F(1,15) = 0.35$, *ns.*] or tone detection difficulty [$F(1,15) = 1.22$, *ns.*]. The mean amplitude of the P3 during this task was generally quite small. Of note, P3 latency was significantly shorter [$F(1,15) = 5.70$, $p < .04$] during pain than no-pain conditions and significantly later to difficult-to-detect tones [$F(1,15) = 56.58$, $p < .0001$]. This finding of a reduced P3 latency during pain fits well with the proposal that these healthy participants may have been more focused on the tone detection task during pain sessions as P3 latency tends to decrease as attention to task increases (Polich, 1993a).

Repeated measures ANOVAs for electrode site carried out for MMN, N1, and P3 data across the reduced montage (see Figures 10 and 11) found that the amplitude was greatest and latency earliest for the MMN at electrode Fz, for the N1 at Fz, and for the P3 at Pz (all significant at at least $p < .05$). These findings are in accordance with previous scalp topography findings for each of these deflections (Näätänen, 1990, Polich, 1993a). Using the 25 ms interval analyses, it was found that the MMN elicited by the easy-to-detect tones was most negative at Fz in the earliest two intervals and that the MMN elicited by the difficult-to-detect tones was most negative in he last two intervals [$F(3,15) = 4.25$, $p < .004$].

Although the results of Experiment 2 again found that pain did not affect the processes related to the MMN, the most notable finding of this study was that an increase in attention to the difficult auditory task of detecting the 1020 Hz tones lead to a substantial increase in MMN amplitude, but only during the pain condition. Rather than being disrupted by pain, the presence of pain seemed to enhance these healthy adults' early attentional processing toward the difficult-

to-detect tones. As no behavioural decrements occurred in either accuracy of speed of task completion, it appears that these participants were able to perform both behavioural tasks as well when they were in pain than when they had no pain. This effect is similar, albeit at a very general level, to the results found in nine of the 20 participants in Dick et al. (1999) who showed an increase in the MMN during pain. Direct comparison between these results is not possible because of the considerable differences between the designs and paradigms used in these experiments. Future study of performance and/or processing changes designed to clarify the underpinnings of this phenomenon could include variations in task difficulty and attentional focus in order to attempt to replicate and extend this finding.

A major issue that remains and that has gone unanswered in the line of research discussed here, is the magnitude and quality of the experimental pain experienced by the participants in these studies. There is no question that the pain induced in these experiments was substantial and quite distressing for participants. However, it is quite reasonable to postulate that a qualitative difference might exist between healthy individuals who experience a time-limited, escapable, pain stimulus and individuals who suffer from chronic, intractable pain. Chronic pain is by nature disruptive, distressing, and difficult to distract oneself from. Eccleston and Crombez (1999) have also suggested that chronic pain may become a disorder of chronic distraction due to the presence of an unending noxious stimulus. In order to examine whether the early attentional processes that affect the MMN would be disrupted by chronic pain, Experiment 3 used a similar design and the same paradigms as were used Experiment 2.

Experiment 3

Experiment 2 suggested that while the attentional processes involved in the generation of the MMN were not disrupted by experimental pain, these participants showed the increased MMN to

difficult-to-detect tones as reported in Alho et al. (1992) and Woods et al. (1992) when they were experiencing pain. However, Eccleston's (1994, 1995a) findings that only chronic patients who reported high levels of pain showed attentional disruption provide an impetus for further investigation with respect to the nature of the pain experienced by participants in Experiments 1 and 2. The pain induced in these healthy participants had predictable onsets and endings, and participants knew they were free to end pain stimulation at any time. Consequently, it is possible that the pain in these first experiments was less distressing and therefore potentially less disruptive to their task-related cognitive processes.

In order to ascertain whether the nature of participants' pain had an effect on the findings in Experiments 1 and 2, a group of chronic pain patients was recruited. The patients chosen were a unique population recruited from a local pain management service. These patients received therapeutic nerve block injections for their persistent chronic intractable pain. These patients provided an almost ideal experimental group as they typically report very high levels of pain prior to their injections and also generally report significant pain relief following their injections. These clinical features provide the potential to compare a clinical population to the healthy participant groups tested in Experiments 1 and 2 as they can be tested in pain and in significantly less- or no-pain situations.

By testing this patient group, our primary aim in this experiment was to explore whether high levels of chronic, intractable pain have more of a disruptive effect on early attentional processing as manifested by decrements in the MMN. It was hypothesized that in Experiment 3, chronic pain would be more disruptive to early attentional processing than the experimentally induced tonic pain used in Experiments 1 and 2 and result in a significant decrement in MMN amplitude. It was also hypothesized that this disruptive effect would be greatest on the most

difficult task and be observed as a decrease in the MMN resulting from the difficult-to-detect tone. As well, it was again predicted that the scalp area where the effect of pain would be most pronounced would be in the frontal scalp area over the anterior cingulate region.

Method

Participants

Patients with a diagnosis of chronic pain for at least six months were recruited through the Pain Management Unit at the Queen Elizabeth II Health Sciences Centre in Halifax, Canada. Potential participants were initially contacted by a nurse at the pain management unit. Thirty-four of those patients who consented to discuss the experiment with the primary investigator were then contacted via telephone and given a brief summary of the experimental protocol. Three patients who reported significant hearing loss did not take part in this study. Of the other patients contacted, four were unable to attend due to physical illness or physical limitations that made testing impossible. Nine other patients chose not to participate due to travel constraints (a number of patients travel in excess of three hundred km to receive nerve blocks and only traveled to Halifax when they had high levels of pain). Basic inclusionary and exclusionary criteria outlined in Experiments 1 and Experiment 2 were also used in this experiment.

Eighteen patients agreed to attend testing sessions. Of these patients, one 53 year-old male attended an initial no-pain testing session but did not experience a return of his pain prior to his subsequent nerve block and therefore could not take part in a second test. Another 41 year-old male attended a pain recording session but chose not to return because he experienced considerable nausea during his first testing session. A 49 year-old male who attended both pain and no-pain sessions reported almost exactly the same pain ratings at both sessions. His data were therefore not included in the analysis. Three patients who had limited success during the

practice tone detection task for the difficult-to-detect tones were found to perform at less than chance level at detecting the difficult tones and were excluded from analysis. The remaining group of 12 patients (6 females; 6 males) had a mean age of 52.8 years (SD = 7.48; range = 37 – 63 years). Eleven of these participants were found to be predominantly right handed using the Edinberg Handedness Questionnaire (EHQ). Mean length of time since the onset of chronic pain in these patients was 13.75 years (SD = 8.83years). Table 4 contains age and questionnaire data from these patients. A detailed record was taken at the beginning of both testing sessions regarding the medications being taken by patients. Most patients took a number of medications for a variety of medical conditions. However, in each case, the medications taken by patients was consistent between the two testing sessions. This included the use of any oral analgesics. Testing was scheduled according to patients' personal schedules and the timing of their referrals. Three patients attended their first testing session while their nerve blocks were still providing them with substantial pain relief. These participants returned for testing a number of weeks later when their pain had increased. The other nine patients attended their first testing session while experiencing high levels of pain a few days or a few hours before a nerve block. These individuals were re-tested following their nerve blocks when their pain had decreased by at least 40 percent (by self-report). All participants were compensated at a rate of $10.00 per hour of time taken by the experiment and were reimbursed for their parking fees.

Nerve block procedure

Patients received pain relief through a variety of procedures that almost always involved the injection of medications. These procedures included epidural injections, facet joint rhizotomies, and sympathetic nerve blocks. A general description of these procedures and the medications used to perform them can be found in Wall and Melzack (1999). The side effects of

these procedures and the medications used for these blocks typically do not include direct cognitive effects. Their primary aim is to provide pain relief in specific areas of the body. While these procedures are not always effective for some individuals, those who receive pain relief following the procedure report dramatic reductions in their pain and substantial increases in their ability to function in daily activities.

Auditory Stimuli

The auditory stimulus paradigm used in this experiment was the same as that used in Experiment 2. Task instructions were also the same as those given to participants in Experiment 2. A potential problem that was foreseen was the natural reduction of the MMN that has been reported with age (Pekkonen et al., 1996; Czigler, Czibra, & Csontos, 1992). As the patient group in Experiment 3 was much older and probably had worse hearing than the volunteers in Experiment 2, the use of a deviant tone only differing by 20 Hz was a possible limitation. Fortunately, all patients were able to detect at least a few of these 1020 Hz deviants during their initial practice session. Most patients did quite well at detecting them. However, as was previously mentioned, three of the patients performed at worse than a chance level during some testing sessions and their data were therefore no included for statistical analysis.

Visual task

The visual task paradigm (Windes, 1968) and task instructions used in this experiment were the same as those used in Experiment 2.

Questionnaire Measures

Background information on demographics, health, medical history, medications taken, and handedness data were collected using the same forms as in Experiments 1 and 2. Patients'

information related to pain experienced during testing (MPQ), pain intensity (NRS), pain catastrophizing (PCS), and mood (BDI – II) were collected as in Experiment 2 (see Table 4).

Electrophysiological Data Acquisition

Patient data was recorded using a 32 channel Ag/AgCl electrode Neuromedical Supplies Quik-Cap where only the electrodes located at sites Fz, Cz, Pz, CP3, CP4, TP7 and TP8 were prepared and used for recording. Participants' continuous EEG was recorded using a Synamps 32 channel amplifier in the same laboratory setting as in Experiment 2. A reference electrode at the nose was used and inter-electrode impedances were kept below five kΩ. Horizontal eye movements were recorded using Ag/AgCl electrodes placed over the outer canthus of the right and left eyes. Vertical EOG recordings were also made using Ag/AgCl electrodes placed above and below the left eye.

Analogue EEG recordings were made using a bandpass of 0.1 - 100 Hz with a 60 Hz notch filter enabled during recording, sampled at 500 Hz. Offline digital filtering was carried out at a bandpass of 0.5 -20 Hz. After offline filtering, the same ocular artifact correction algorithm that was used in Experiment 2 was used to model and mathematically remove eye blinks from the filtered continuous EEG files.

The filtered, artifact corrected continuous EEG data was epoched from 50 ms pre-stimulus until 462 msec post-stimulus. Artifact rejection was then carried out using a similar protocol to the one used in Experiment 2. Epochs containing EEG artifact that was greater than $\pm$ 100 μV were rejected at all scalp electrodes in order to remove any electrode or movement-related artifact in any of these electrodes not related to EOG artifact. Remaining epochs were again subjected to artifact rejection where epochs containing deflections of greater than $\pm$ 75 μV in the HEOG channel were also excluded from analysis. Baseline correction using the portion of

the epoch recorded during the 50 msec prior to tone presentation was performed and averaged files were then created for each of the three tones in the tone sequence. Scoring for amplitude and latency were carried out as outlined for Experiment 2.

Procedure

Each patient read and signed informed consent forms approved by the appropriate local research ethics boards prior the commencement of the experiment. At the beginning of the first testing session, patients filled out demographic, health, and handedness questionnaires as well as the PCS. Detailed information regarding patients' medication use over the previous week was recorded prior to each testing session. Patients were then introduced to the experimental protocol and requirements using the same instructions as in Experiment 2.

During both visits, patients performed the active auditory task once and the passive auditory task once. Both conditions were carried out following the same experimental protocol as in Experiment 2 and block order was counterbalanced for attentional condition and for pain condition. As all of these patients reported considerable physical discomfort and high pain ratings during the testing day when they had pain, many exhibited a great deal of motor and ocular movement artifact. If during recording the presence of a considerable amount of artifact was noted two to four extra minutes of the tone sequence was added on to each condition in order to enhance signal-to-noise ratio and thereby improve the likelihood of collecting viable data. At the end of the testing session on the day when the patient was experiencing pain, patients filled out the MPQ and BDI-II.

A second testing session was booked with each patient after there had been at least a 40% absolute change in the patient's pain ratings. During this testing session, each participant took part in experimental conditions following the same protocol as during the first visit. Following

the completion of the second testing session, all participants were fully debriefed regarding the rationale, hypotheses, and experimental manipulations of the experiment.

Statistical Analyses

All statistical analyses were carried out using SPSS 9.0. Participants' pain ratings were compared though a repeated measures ANOVA using the factors of pain condition (no-pain vs. pain) and attention (active vs. passive). Paired t-tests were used to compare the mean 50 ms MMN amplitude window to the mean amplitude of the 50 ms pre-stimulus baseline period. Amplitude and latency data for the MMN were analysed using a repeated measures ANOVA for the variables of pain condition (no-pain vs. pain), attentional condition (active vs. passive), and tone detection difficulty (easy- vs. difficult-to-detect). Normalized data (as in McCarthy & Wood, 1985) was also subjected to a repeated measures ANOVA across the electrode sites Fz, Cz, Pz, CP3 CP4, TP7, TP8. Peak amplitude and latency of the N1 and P3 ERP's were also analysed using a repeated measures ANOVA.

Behavioural performance data on the active condition tone detection task was carried out through additional repeated measures ANOVAs where the variables of pain (no-pain vs. pain) and difficulty (easy- vs. difficult-to-detect tones) were entered. As was the case in Experiment 2, only the first 20 trials on the Windes (1968) task were used for comparison in a paired t-test between no-pain and pain conditions for both accuracy and response latency. As the participants in this study were tested on two separate days with at least three intervening days, any possible practice effect between the two passive pain testing sessions was likely avoided.

All repeated measures ANOVAs were carried out using conservative Greenhouse-Geisser corrections for the degrees of freedom used in these calculations. All t-tests were carried out using Bonferroni corrections to control for inflation of alpha.

Results and Discussion

As expected, pain ratings reported by the chronic pain patients were found to differ significantly [$F(1,11) = 146.26$, $p < .0001$] between no-pain and pain conditions. They did not differ significantly [$F(1,11) = 0.13$, *ns.*] between the active and passive attention conditions (see Table 4). From a qualitative perspective, it was evident while interacting with these patients that factors such as past experience with pain and strategies used to cope with pain likely influenced each person's definition of "worst pain imaginable".

Planned comparisons were carried out in order to examine whether there was an increase in the MMN to the difficult to detect tones due to attention. As was the case in Experiment 2, this effect did not occur in the no-pain condition [$t(11) = 0.90$, *ns.*] but did occur in the pain condition [$t(11) = -2.66$, $p < .03$]. This result was confirmed and extended using the 25 ms interval analyses mentioned in Experiment 2. It was found that this effect was strongest in the last two intervals [$F(3,11) = 7.32$, $p < .009$]. Again, the data do not replicate the results reported by Alho et al. (1992) and Woods et al. (1992) when pain is not present. However, when pain was present, there was a trend that the MMN was significantly larger when the tones were being actively attended to than when they were being ignored. In terms of absolute values for MMN amplitude, it was found that the MMN elicited by deviant tones was larger in the active condition than in the passive condition and was larger to easy- than to difficult-to-detect tones. However none of these comparisons were statistically significant.

In contrast to the findings in the previously reported experiments where experimentally induced pain did not interfere with the attentional processes related to the generation of the MMN, a repeated measures ANOVA found that pain did significantly reduce MMN amplitude [$F(1,11) = 5.44$, $p < .04$]. This effect was found primarily to be a result of a reduction in the

MMN in the passive condition when pain was present. Post-hoc comparisons found that in the active attention condition, there was no difference between easy- [$t(11) = -0.31$, *ns.*] or between difficult-to-detect tones [$t(11) = 1.15$, *ns.*] between pain conditions (see Figure 12). However, the MMN elicited by the difficult-to-detect tones in the passive condition were significantly smaller during pain than in no-pain sessions [$t(11) = -2.40$, $p < .04$] (see Figure 13). A marginally significant difference [$t(11) = -1.82$, $p = .096$] was found where the MMN elicited by the easy-to-detect tones was also less in the pain condition than in the no-pain condition. Thus, it appeared, that when chronic pain patients were engaged in an attentionally demanding task, processing of the difficult-to-detect tone was impaired by pain. This was not the case when these patients were carrying out a relatively easier tone detection task.

There was no overall effect of attentional condition on MMN amplitude [$F(1,11) = 2.15$, *ns.*]. However, there was a significant effect of tone detection difficulty [$F(1,11) = 5.41$, $p < .04$] where the MMN elicited by easy-to-detect tones was larger than the MMN elicited by difficult-to-detect tones. Pain [$F(1,11) = 1.27$, *ns.*]and attention [$F(1,11) = 1.51$, *ns.*] did not affect MMN peak latency. The peak latency of the MMN to the easy-to-detect tones was significantly earlier than MMN peak latency to difficult-to-detect tones [$F(1,11) = 4.89$, $p < .05$].

Qualitatively, it is worth noting that the participant who reported almost identical pain ratings during his no-pain and pain testing sessions showed very little difference in his waveforms between no-pain and pain conditions. However, the majority of chronic pain patients showed a visible decrease in MMN amplitude in pain conditions. There was no pattern as to which attentional condition showed more of a decrease in MMN as a result of pain. As was suggested in Dick et al. (1999), it may be that intra-individual factors lead to these differences.

A repeated measures ANOVA for the amplitude of the N1 found no effect of pain [$F(1,11) = 4.05$, *ns.*] or attention [$F(1,11) = 0.183$, *ns.*]. A similar procedure was carried out for N1 latency and also found no effect of either pain [$F(1,11) = 0.19$, *ns.*] or attention [$F(1,11) = 0.01$, *ns.*]. This suggests that the finding of a significant effect of pain on the MMN was not due to a change in the N1 generators that are related to the MMN but more likely on the pitch detection processes that occur shortly after the N1 is elicited.

The amplitude of the P3 was not affected significantly by pain [$F(1,11) = 0.11$, *ns.*] or tone detection difficulty [$F(1,11) = 1.10$, *ns.*]. P3 latency was also not significantly affected by pain [$F(1,11) = 1.25$, *ns.*] or tone detection difficulty [$F(1,11) = 1.44$, *ns.*]. While the amplitude of the P3 elicited by both target tones was again found to be quite small, a trend was found that P3 amplitude was smaller and slightly earlier in the pain than in the no-pain conditions. It is unclear why the P3 was so small in both Experiment 2 and Experiment 3. Larger P3 deflections tend to be elicited by a target tone such as the easy-to-detect tone (Picton, 1992). It may be that the increased attentional load created by the task of detecting the difficult-to-detect deviant tone reduced the P3 elicited by both targeted deviant tones.

On the Windes (1968) task, patients did not exhibit an effect of pain on task performance accuracy [$t(11) = 1.15$, *ns.*]. In fact, they made very few errors in both the no-pain ($\underline{M} = 0.50$ errors, $\underline{SD} = 0.80$) and pain ($\underline{M} = 0.25$ errors, $\underline{SD} = 0.45$) conditions. However, response latencies were significantly affected by pain [$t(11) = -2.29$, $p < .05$]. Mean reaction time was longer during pain ($\underline{M} = 969.69$ ms, $\underline{SD} = 290.73$) than in no-pain ($\underline{M} = 802.17$ ms, $\underline{SD} = 177.54$) conditions. Thus, while patients performed just as well on the computerized task while in pain, they did not perform the task as quickly.

When performing the active condition task of detecting both deviant tones, there was no effect of pain on accuracy [$F(1,11) = 1.01$, *ns.*]. A significant effect of tone detection difficulty was found [$F(1,11) = 14.81$, $p < .004$] where easy-to-detect tones were more accurately detected than difficult-to-detect tones (see Table 5). Response latency on this task was significantly decreased by pain [$F(1,11) = 5.22$, $p < .05$]. Difficult-to-detect tones, when accurately detected, were responded to significantly faster than to easy-to-detect tones [$F(1,11) = 61.31$, $p < .0001$]. It appears that although the participants in this experiment had difficulty detecting the difficult-to-detect tones, they were quite vigilant in listening for those tones. It may be that they were more focused on this behavioural task during pain. Possible explanations for this finding will be discussed hereafter.

Repeated measures ANOVAs were also carried out for the variable of electrode site at the seven electrodes for the MMN, N1, and P3 deflections. These analyses found that MMN amplitude was largest and occurred earliest at electrode Fz (see Figures 14 and 15). The N1 was largest and earliest at electrode Fz, and the P3 was largest and earliest at electrode Pz (all significant at the $p < .05$ level).

While the healthy volunteers in Experiment 2 cannot be used as controls for the chronic pain patients in Experiment 3, it is worth noting some of the differences on demographic and questionnaire measures. It is obvious that a considerable age gap existed between the two participant groups [$t(26) = 11.09$, $p < .0001$]. This is not an unusual finding as the incidence of chronic pain increases with age and the participants in Experiment 2 were almost all young adults. Chronic pain patients also reported significantly higher levels of pain catastrophizing [$t(26) = 3.24$, $p < .005$] and higher levels of pain during the no-pain testing sessions [$t(26) = 4.00$, $p < .003$]. It is also not surprising that these patients who have been through extended

periods with high levels of pain would show increased catastrophizing related to pain. The patients reported significantly higher levels of pain than the volunteers in Experiment 2 during their no-pain sessions [$t(26) = 3.84$, $p < .001$]. The healthy volunteers rarely reported any pain during the no-pain sessions while most of the chronic pain patients still reported low levels of pain even though they often described the results of their nerve blocks as "miraculous". No significant differences were found between the two participant groups on any of the measures of pain from the MPQ, subjective pain ratings during pain sessions, or on a measure of depression. Reference to these comparisons will be made in the following section.

General Discussion

The primary goal of the studies reported in this dissertation was to examine whether pain would affect the early attentional processes related to the generation of the MMN. It was hypothesized in each of these studies that pain would disrupt attentional processes following Eccleston and Crombez' (1999) model because, as a stimulus, it has a high priority for processing. Previous research using event-related potential measures had found that pain does seem to have a disruptive effect on attention. However, that small body of work tended to show that the effects of pain varied considerably along with intra-personal variables such as motivation. In pilot ERP research carried out in preparation for the present studies (Dick et al., 1999), data was produced that suggested that early processes elicited independent of attention (mismatch negativity) were disrupted in some individuals. However, in other individuals tested, pain seemed to enhance these processes. In a sense, it appeared that pain may have focused this latter subset of people and increased their processing of experimental stimuli.

The three studies reported here sought to extend the findings from this pilot work and increase our understanding of how pain affects early attentional processes. Experiment 1 used a

high level of experimentally induced pain in young healthy adults using two different pain induction techniques and found that neither pain induction technique consistently interfered with passive early attentional processing. No consistent changes were observed in the MMN. This finding suggested that the basic generating mechanisms of the MMN were not affected by pain. The next experiment attempted to capitalize on an innovative experimental design used in previously published research (Alho et al., 1992; Woods et al., 1992) in order to examine whether experimentally induced pain would interfere with early attentional processes when participants' focus of attention and the attentional demand of experimental tasks were varied. Experimentally induced pain was again not found to disrupt early attentional processes in this study. However, a very interesting result was found where, only during pain conditions, the MMN elicited by a difficult-to-detect tone was larger when attended to than when ignored. This is the same effect found in the Alho et al. (1992) and Woods et al. (1992) studies but could not be replicated in the no-pain conditions. On a very general level, it may be that this effect is similar to that found in some of the pilot participants in Dick et al. (1999) who appeared to be more focused by pain. The third study used a very different group of participants who reported high levels of chronic pain and who had experienced severe chronic pain for extended periods. The main purpose in recruiting these participants was to examine whether there would be a difference between the effects of a high level of experimentally induced pain and high levels of chronic intractable pain. The MMN was found to be disrupted in the chronic pain patients when they had pain prior to nerve block injections, suggesting that some features of the different types of pain may have differentially affected cognitive processing.

In terms of basic electrophysiological findings, the pattern of results of these studies were in line with the general body of previously published MMN work. The MMN was reliably

elicited by the detection of differences in the pitch of deviant tones in all three experiments. The magnitude and latencies of the MMN in each experiment were within normal limits suggested by previous reports (e.g., Lang et al., 1995) for each experimental group. In the final two experiments, the MMN elicited by easy-to-detect deviant tones was larger than the MMN to difficult-to-detect tones in the passive attention conditions and in the patients in the active attentional condition. An unexpected result that will be discussed later was found in that the MMN to difficult-to-detect tones was larger than the MMN to easy-to-detect tones in the participants in Experiment 2 when they were actively attending to the deviant tones. The MMN to the easy-to-detect tones was consistently found to be as early or earlier than the MMN to difficult-to-detect tones. Differences in the MMN found due to pain in the third experiment were not found in the N1 data for that experiment. This suggests that pain's effects occurred during stimulus difference detection, the process typically thought to be represented by the MMN and not the response to basic stimulus features manifested by the N1 response. Further, in Experiments 2 and 3, the P3 component, predicted when participants were attending to and detecting deviant tones, was elicited in the active attention conditions but not in the passive attention conditions. The P3 found in these experiments was quite small, likely due to the high attentional demand of the tone detection task. The MMN, N1, and P3 deflections were found to be maximal at scalp regions predicted by previous research. It is important to note these general findings as evidence that the data collected in these experiments did not contain anomalies that might have influenced their findings. It is also important to note that the MMN was largest in the frontal region of the scalp and that the decrease in MMN was largest in this area. This finding is in line with previous reports that pain interferes with and thereby decreases cortical activity in the anterior cingulated region that is under this frontal scalp area.

An important contribution made by the methodological modifications in Experiments 2 and 3 allow us to see the effects of increasing the attentional demand of the experimental tasks. First of all, the use of the Windes (1968) task increased the cognitive load of the distracter task in the passive attention conditions in Experiments 2 and 3. This helped alleviate the concern that participants could have been attending to the tones in Experiment 1. It also allowed us to compare the performance of the participants in these experiments to those tested in Eccleston's (1994; 1995a) previous studies. The use of a deviant tone whose pitch deviance was quite difficult to detect also increased the cognitive processing load on participants' cognitive systems in both attentional conditions. The small P3 deflections elicited by the deviant tones in both of the final experiments provide supportive evidence that task difficulty was indeed high.

Each study in this series of studies has helped to clarify how pain affects attentional processes during the very early stages of auditory stimulus processing. The first study suggested that experimentally induced pain does not disrupt the attentional processes that underlie the MMN. The second and third studies found that pain appears to augment the brain's response to difficult-to-detect tones when they are being attended. The third study also suggested that chronic intractable pain does disrupt attentional functioning related to the MMN. It is important to note that there were consistencies in some of the key findings of these studies. There are reasons why it was not completely surprising that Experiments 2 and 3 did not replicate the effects reported in Alho et al. (1992) and Woods et al. (1992) in all experimental conditions. The MMN increases in these previously published studies that was a result of attention to difficult-to-detect tones was small and was not replicated in all later studies of this effect. This may have been due to the relatively small MMN signal. Although the MMN can be modulated, there are likely limits to how much it can be changed by attention. Unfortunately, as this effect was not

replicated in the no-pain conditions in Experiments 2 and 3, it was not possible to test the hypothesis that pain would disrupt this amplification of the MMN on the difficult task. However, what is extremely interesting is that the effects found in Alho et al. (1992) and Woods et al. (1992) *were* found when pain was present in the participant groups in the final two experiments of this study. This pattern occurred even though these two groups of people were quite different in terms of their age, their health status, and their pattern of responses to the tones in the two attentional conditions. For example, the healthy adult volunteers who experienced experimentally induced pain in the second experiment had larger MMN's to the difficult-to-detect tones than their MMN's to easy-to-detect tones in the active attentional condition. In contrast, the chronic pain patients showed a less marked difference in their responses to the easy- vs. difficult-to-detect tones. There appear to be two primary reasons for these findings. First, the MMN to these difficult-to-detect tones was increased or "amplified", to use Näätänen's (1991) term, in the active attentional condition. This trend was only seen in the pain condition. Second, the MMN to the difficult-to-detect tones was smallest in the passive attentional conditions during pain in both experiments. This reduction was probably a combination of a smaller MMN being elicited in the passive condition, a decrease in this MMN due to the disruptive effect of pain, and as the MMN may have been reduced due to the relatively largest attentional load present during this condition. This finding is in line with Eccleston's previous findings (1994, 1995a) where individuals who showed marked performance decrements while experiencing high levels of pain *and* when the attentional load of the task they were performing was also high.

On behavioural measures, the effects of pain on attention were less consistent between the final two experiments. Pain had no effect on behavioural performance in the young adult volunteers in Experiment 2 on either the computerized Windes (1968) task in the passive

attention condition or on the deviant tone detection task in the active condition. It may be that these healthy young adults were not sufficiently taxed cognitively for pain to have a disruptive effect on their early attentional processes affecting the MMN. Future research could address this issue by further increasing the demand of the tasks presented to such participants and noting whether the effects become similar to those reported by Eccleston (1994, 1995a) result.

The behavioural results in the chronic pain patient group in Experiment 3 show a very different pattern from the findings in Experiment 2. The chronic pain patients only showed a significant decrease in response latency on the Windes (1968) task. Their accuracy was not affected by pain. However, on the active tone detection task, pain affected response accuracy, primarily to the detection of the difficult-to-detect tones. It did not affect response latency to the tones. Thus, if the tones were detected, they were responded to just as quickly when participants were experiencing pain as when they were not experiencing pain. Although it was somewhat disappointing that the results of behavioural measures did not match the electrophysiological results, this discrepancy is not entirely unexpected. The level of processing represented by the MMN reflects early sensory detection of stimulus feature differences whereas motor responses to either auditory or visual stimuli occur at a much later processing stage after a number of other cognitive processing steps have been carried out.

There are some obvious and very important differences between the pain experienced between patient groups in Experiments 1 and 2 compared to Experiment 3. These differences may explain one reason why pain was found to only disrupt attention in Experiment 3. Clearly, experimentally induced pain was escapable and less threatening than the pain experienced by the chronic pain patients. This is important in light of Crombez et al.'s (1999) findings that fear of pain played a key role in their observed disruption of performance due to pain. Further, the

patients reported significantly higher levels pain catastrophizing, suggesting that they tended to ruminate more about their pain, magnify their pain, and feel helpless as a result of pain. These are features that could lead to an increased fear of pain and additional disruption due to pain. As well, as the experimentally induced pain in the healthy volunteers was time-limited, it's effects were more brief and would have been less likely to have the effect of wearing down these participants. It appeared from the results in the final two experiments that healthy young adults who experienced experimentally induced pain more strongly processed stimulus information while the participants with chronic pain were impaired by their pain during stimulus processing. Chronic pain by nature is chronically disruptive (Eccleston & Crombez, 1999) and makes it increasingly difficult for an individual with chronic pain to sustain attention on a task for extended periods (Dick et al., submitted). It may be that after extended periods of disruption by chronic pain, the extent of cognitive disruption becomes more pervasive and observable in a patient's performance. The behavioural performance of the patients with chronic pain in Experiment 3 supports this proposal. As well, as has been mentioned earlier, because chronic pain is often associated with other factors that may impair cognitive processes (e. g., anxiety or depression), it is very difficult to only measure the effect of pain on cognition.

An interesting comparison can also be made between the results of Experiment 3 and Lorenz, Beck, and Bromm's (1997) report of the effects of orally administered morphine on attention. Those researchers recorded the P3 in chronic pain patients before and after morphine induced analgesia. They found that, as indexed by an increase in the P3, attentional processing improved following analgesia. Most patients in Experiment 3 were first tested while experiencing a high level of pain and then re-tested following the analgesic effects of their nerve blocks. While a similar trend in the P3 was observed in these patients (see Figure 11), this effect

was not significant. However, the MMN was found to be increased following analgesia, suggesting decreased disruption by pain of early attentional processes.

A number of methodological limitations in these studies should be acknowledged at this time and dealt with in future studies. Due to the recruitment method of the participants in Experiments 1 and 2, it is quite possible that there was a sampling bias toward individuals who were less fearful of pain. It is impossible to know how many students who initially heard about these studies chose not to sign up for them. It would be ideal to be able to randomly select a group of young healthy adults and perform Experiment 2 with them using experimentally induced pain. It is also not possible to know without further study how much of a factor the age difference between experimental groups in the final two studies affected the results of these studies. Previous research (e.g., Rogers, 2000) has found that as people age, their ability to sustain attention to tasks and optimize performance over an extended period declines. One way to respond to this limitation would be to test a group of pain free adults age-matched to the chronic pain patients in Experiment 3. However, as Experiment 3 used a within-subjects design with a number of design controls, pain appeared to be the primary difference between the two pain conditions. It will also be important to replicate the effects found in Experiment 3 as they were small effects. Although patients consistently showed decrements in MMN amplitude during pain, particularly during the more attentionally demanding passive attention condition, these were not very large effects. This is likely due at least in part to the small signal of the MMN. Unfortunately, at present, the MMN cannot be used as an objective index of the level of pain experienced by an individual. It is very possible that there may be other factors that may interact with pain that affect how pain affects attentional processing.

In order to answer the call of many researchers such as Jamison et al. (1988) for further study of how pain affects attention and other cognitive processes, it will be useful for future studies of how pain affects early attentional processing to examine how these effects correlate with and how they are related to everyday functional disabilities related to pain. While attentional disruption is increasingly being recognized as a common report of individuals who suffer from chronic pain, it would be helpful if a link could be drawn between disruption at early cognitive processing levels and reported impairments in everyday functions such as concentration and memory. It will also be useful to measure additional cognitive variables that could modulate the effects of pain on attention such as working memory abilities. It may be that individuals with larger working memory capacities will not be disrupted by pain until the cognitive load of a task being performed during pain is increased to the point that it strongly taxes working memory. As there is also an increasing body of evidence that fear of pain and somatic awareness may be important variables related to one's vulnerability to attentional disruption, these variables should be recorded and used in interpreting the effects found in future studies. While attempting to better understand the effects found in Experiments 2 and 3 in younger and older adults, it would also be interesting to extend the use of these paradigms to include adolescents and children who suffer from chronic pain. Such studies could look at developmental differences in how chronic pain affects individuals differentially at different stages across the lifespan and how the chronicity of pain affects functional outcomes and disabilities.

As Näätänen (1995) has suggested that the MMN represents a hard wired, sensory discrimination process that plays a very important role in auditory processing, it would not be particularly advantageous from a selective perspective for it to be easily disrupted by an

occurrence as common as pain. In fact, it may be advantageous for pain to enhance performance in order to increase the likelihood of successful escape from the cause of noxious stimulation. The findings of Experiment 2 suggest that the sensory processes related to the MMN may actually be enhanced when pain is present. The findings of Experiment 3 suggest that when attention is chronically disrupted by pain, even hard wired cognitive processes may be more easily disrupted and thereby impaired by pain.

Attentional deficits have clear implications for patients in their daily functioning. The importance of efficient, undisrupted attentional processing is important to ongoing mental activity. The aim of basic research such as the studies reported in this dissertation is to improve our understanding of the very basic level effects of pain on attention. By better understanding these basic effects and where in the brain these effects are exerted , it is hoped that we will increase our ability to help individuals overcome these effects.

Appendix A

Measure	Possible Score Range	M (SD)
Age (years)	N/A	19.93 (2.50)
Pain rating (NRS) (Cold Pressor Pain)	0 – 10	6.41 (1.66)
Pain rating (NRS) (Ischemic Pain)	0 – 10	6.25 (1.19)
Pain Catastrophizing Scale	0 – 42	15.71 (7.36)
McGill Pain Questionnaire (Cold Pressor Pain)		
Sensory Index	0 – 42	17.08 (5.98)
Affective Index	0 – 14	1.87 (1.21)
Pain Rating Index (total)	0 – 78	21.00 (10.37)
McGill Pain Questionnaire (Ischemic Pain)		
Sensory Index	0 – 42	14.81 (5.29)
Affective Index	0 – 14	1.74 (1.46)
Pain Rating Index (total)	0 – 78	18.50 (9.65)

Table 1. Age and questionnaire data for participants taking part in Experiment 1. Included are columns indicating the possible range of scores for each measure as well as the mean (M) and standard deviations (SD) for the data obtained from participants.

Measure	Possible Score Range	M (SD)
Age (years)	N/A	21.81 (7.11)
Pain rating (NRS)		
No Pain, Active Condition	0 – 10	0.06 (0.22)
No Pain, Passive Condition	0 – 10	0.06 (0.24)
Pain, Active Condition	0 – 10	6.55 (1.55)
Pain, Passive Condition	0 – 10	6.42 (1.72)
Pain Catastrophizing Scale	0 – 42	15.38 (8.46)
McGill Pain Questionnaire		
Sensory Index	0 – 42	14.50 (6.47)
Affective Index	0 – 14	1.13 (1.36)
Pain Rating Index (total)	0 – 78	22.00 (10.28)
Beck Depression Inventory–II	0 – 63	6.40 (6.79)

Table 2. Age and questionnaire data for participants taking part in Experiment 2. Included are columns indicating the possible range of scores for each measure as well as the mean (M) and standard deviations (SD) for the data obtained from participants.

Condition	M Accuracy (SD)	M Latency (SD)
No Pain, Active Attention, Easy tone	96.84 (2.69)	316.40 (53.0)
No Pain, Active Attention, Difficult tone	62.94 (13.13)	468.27 (105.71)
Pain, Active Attention, Easy tone	96.66 (3.68)	319.06 (75.33)
Pain, Active Attention, Difficult tone	60.99 (12.99)	492.74 (115.70)

Table 3. Means and standard deviations for behavioural responses in the active attention condition to easy- and difficult-to-detect tones for volunteers in Experiment 2. (Accuracy measured in percent correct, latency in milliseconds.)

Measure	Possible Score Range	M (SD)
Age (years)	N/A	52.83 (7.48)
Pain Chronicity (years)	N/A	13.75 (8.83)
Pain rating (NRS)		
No Pain, Active Condition	0 – 10	1.67 (1.67)
No Pain, Passive Condition	0 – 10	1.90 (1.58)
Pain, Active Condition	0 – 10	6.27 (1.50)
Pain, Passive Condition	0 – 10	6.15 (1.98)
Pain Catastrophizing Scale	0 – 42	26.92 (9.91)
McGill Pain Questionnaire		
Sensory Index	0 – 42	15.50 (5.28)
Affective Index	0 – 14	2.58 (2.60)
Pain Rating Index (total)	0 – 78	24.08 (10.53)
Beck Depression Inventory–II	0 – 63	9.76 (7.31)
Time between testing sessions (days)	N/A	40.17 (29.77)

Table 4. Demographic and questionnaire data for participants taking part in Experiment 3. Included are columns indicating the possible range of scores for each measure as well as the mean (M) and standard deviations (SD) for the data obtained from participants.

Condition	M Accuracy (SD)	M Latency (SD)
No Pain, Active Attention, Easy tone	91.14 (16.84)	413.70 (217.89)
No Pain, Active Attention, Difficult tone	58.27 (21.59)	513.16 (245.51)
Pain, Active Attention, Easy tone	88.44 (26.75)	424.56 (202.36)
Pain, Active Attention, Difficult tone	43.53 (24.36)	560.75 (156.08)

Table 5. Means and standard deviations for behavioural responses in the active attention condition to easy- and difficult-to-detect tones for chronic pain patients in Experiment 3. (Accuracy measured in percent correct, latency in milliseconds.)

Appendix B

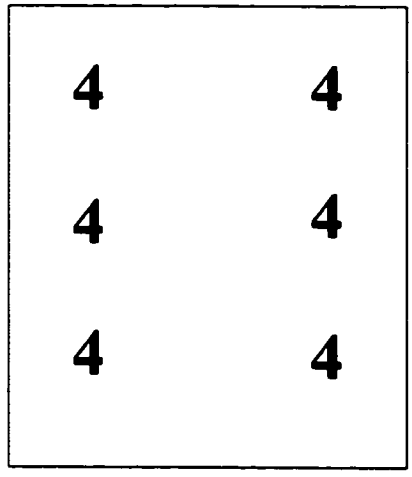

Figure 1. An example of a sample stimulus from the Windes (1968) paradigm used in Eccleston (1994).

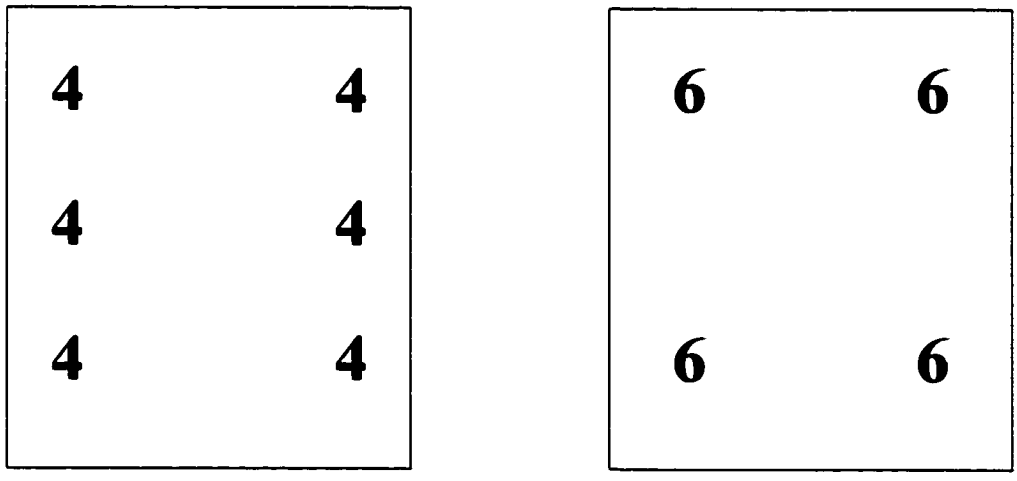

Figure 2. An example of the two-card stimulus items used in Eccleston (1995a) and in Experiments 2 and 3 of this dissertation.

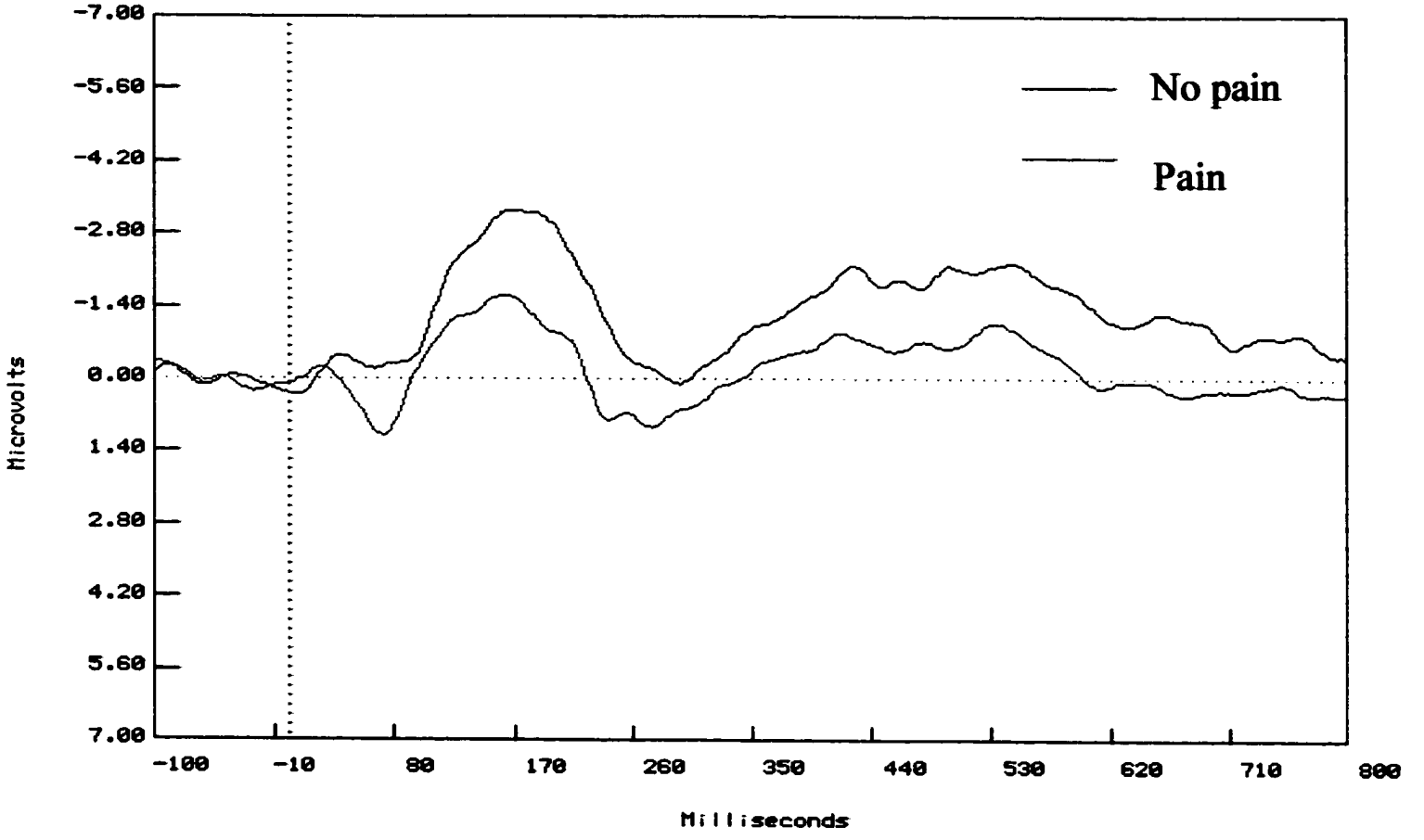

Figure 3. Grand average waveforms at electrode site Fz for the eight participants showing a decrease in MMN amplitude. From Dick et al., (1999).

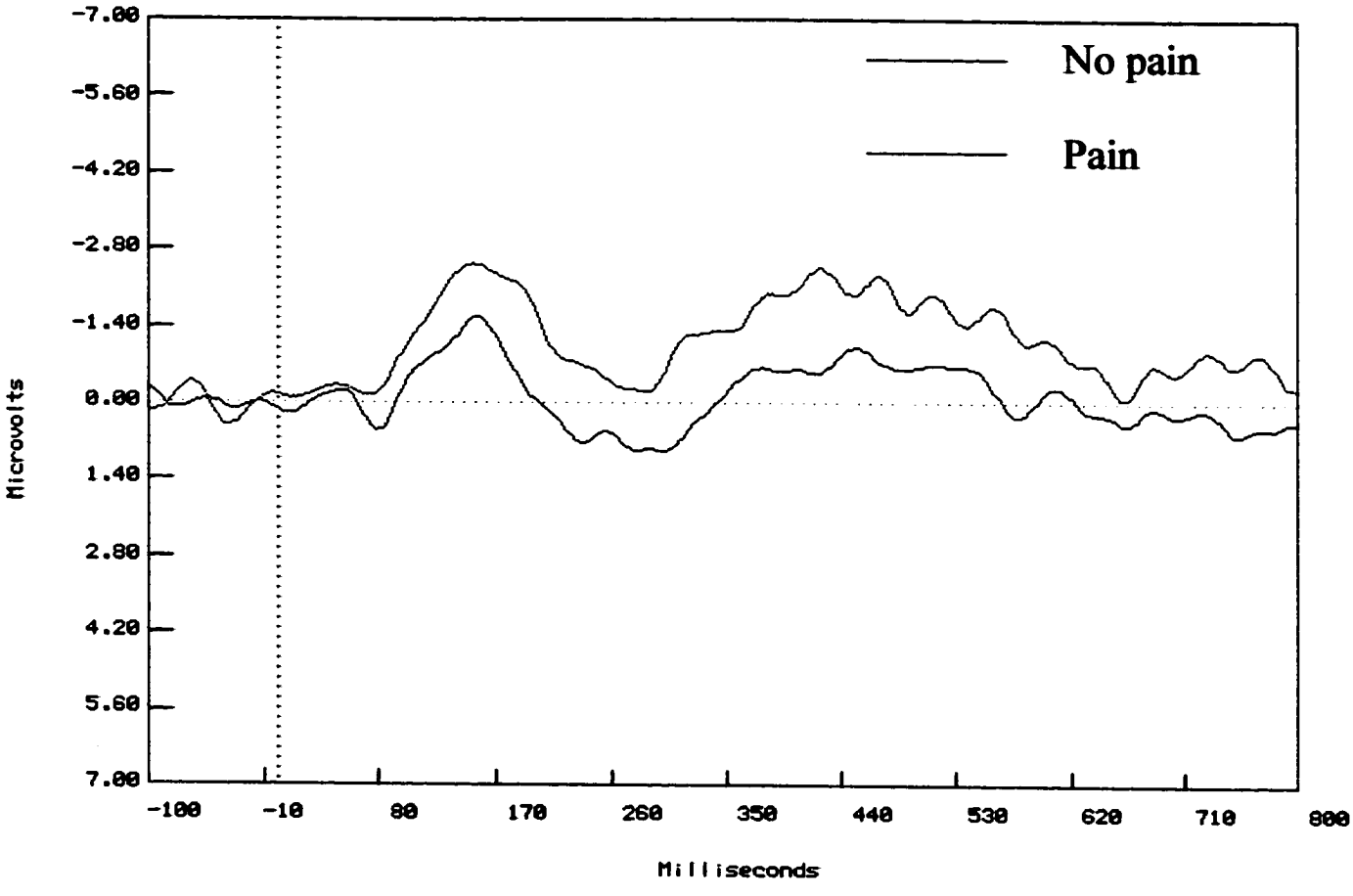

Figure 4. Grand average waveforms at electrode site Fz for nine participants showing an increase in MMN amplitude. From Dick et al., (1999).

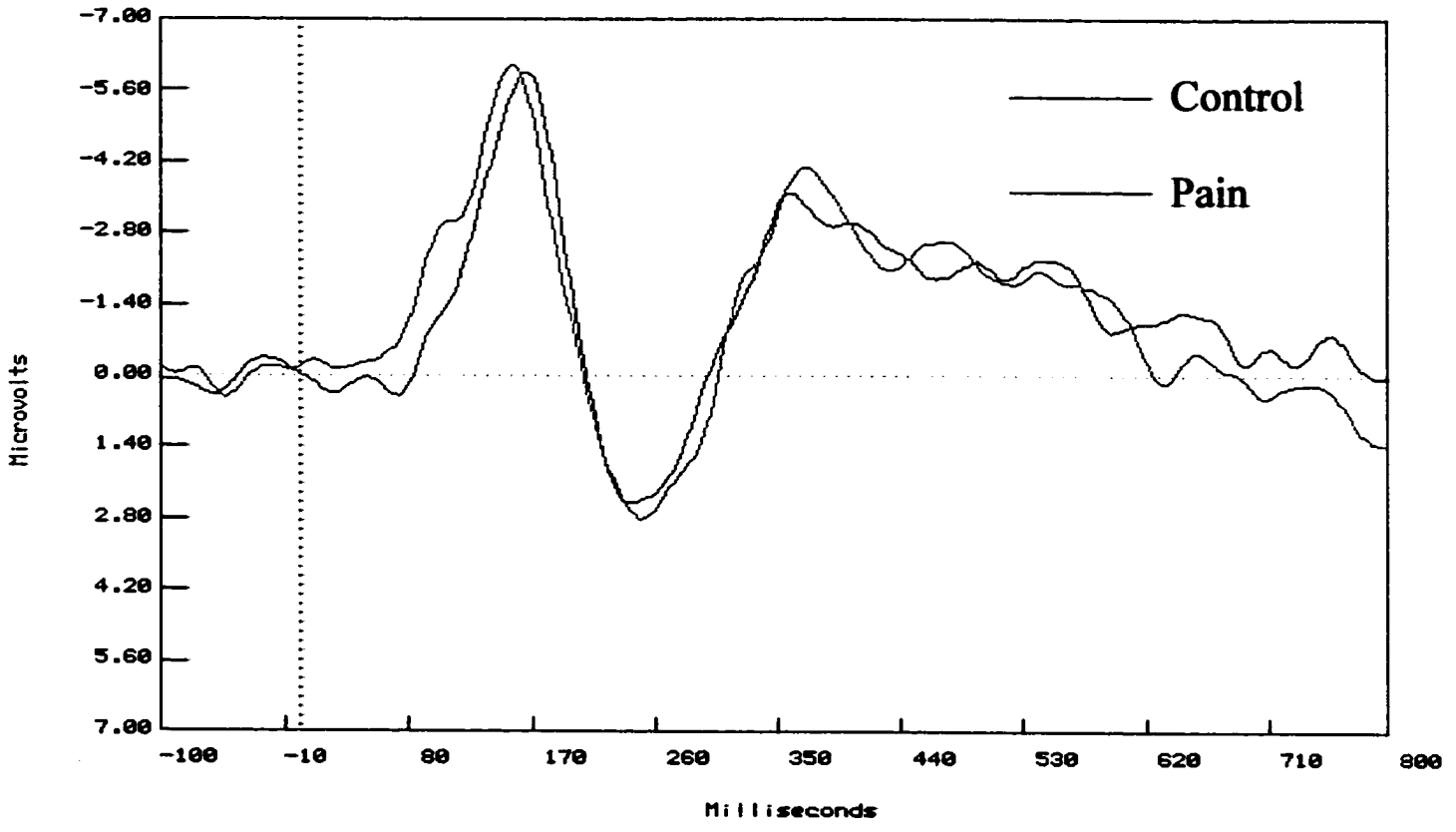

Figure 5. Grand average waveforms at electrode site Fz for the three participants showing no change in MMN amplitude. From Dick et al., (1999).

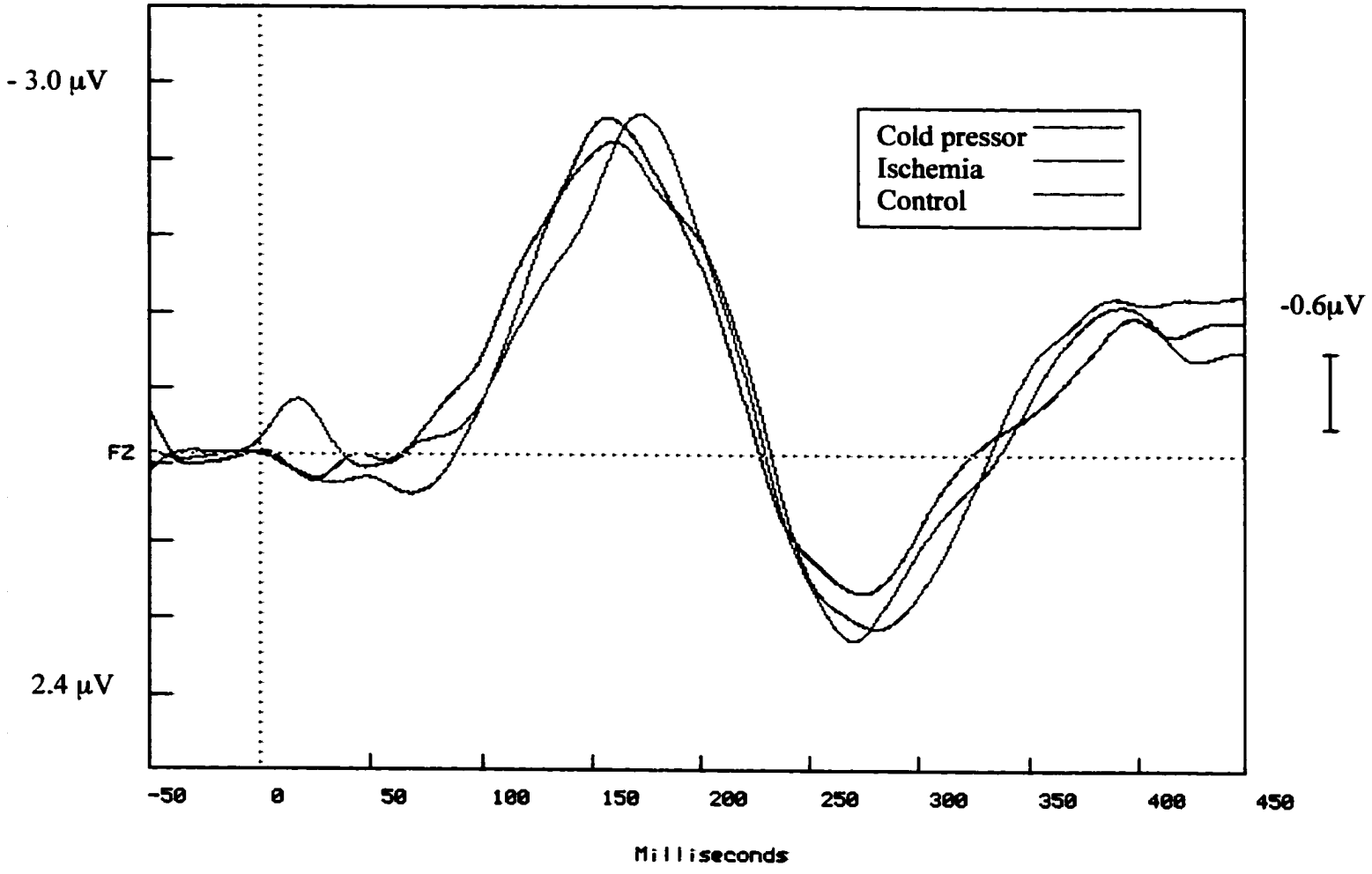

Figure 6. Grand average MMN waveforms for cold pressor pain, ischemic pain, and no-pain conditions at electrode site Fz in Experiment 1. MMN is well defined in all three conditions. Little difference is evident in the amplitude and latency between conditions.

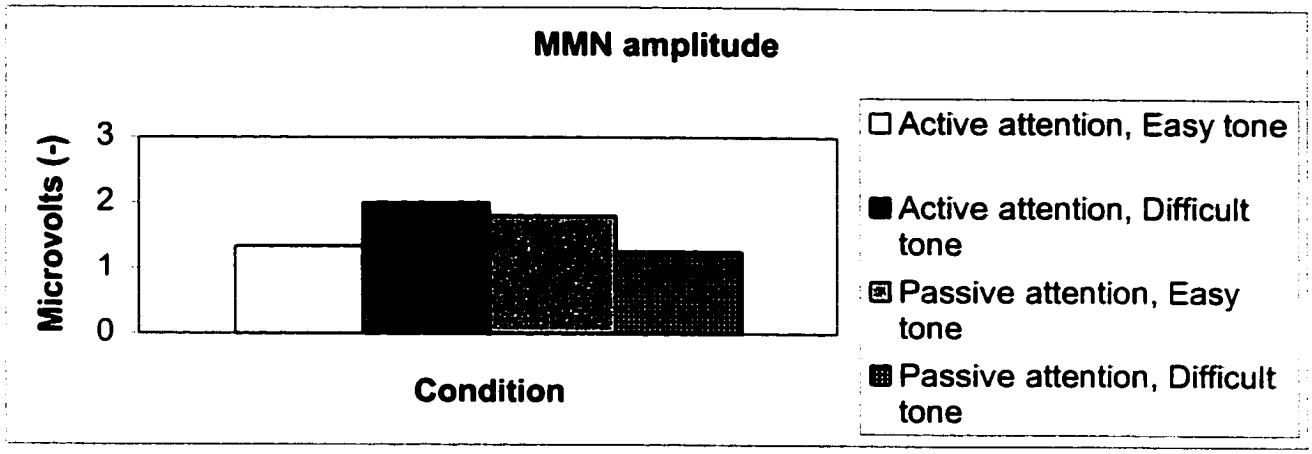

Figure 7. MMN amplitude in healthy volunteers in Experiment 2 without pain during active and passive attentional conditions for easy- and difficult-to-detect tones.s

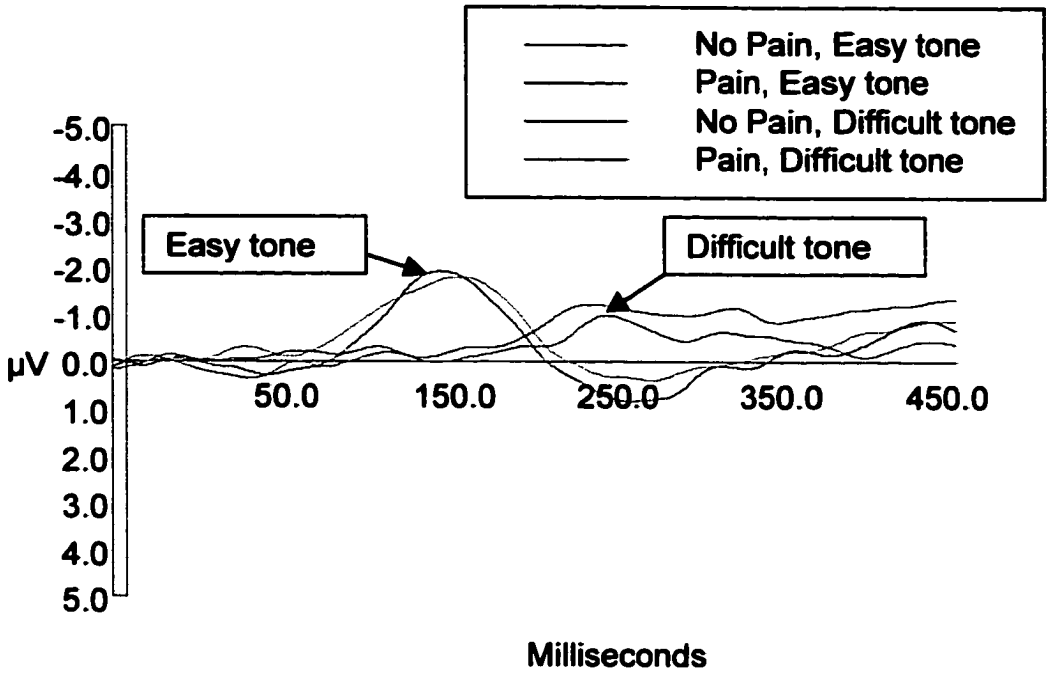

Figure 8. Grand average MMN waveforms (labeled at peak) for healthy volunteers in Experiment 2 during the passive attention condition at electrode Fz.

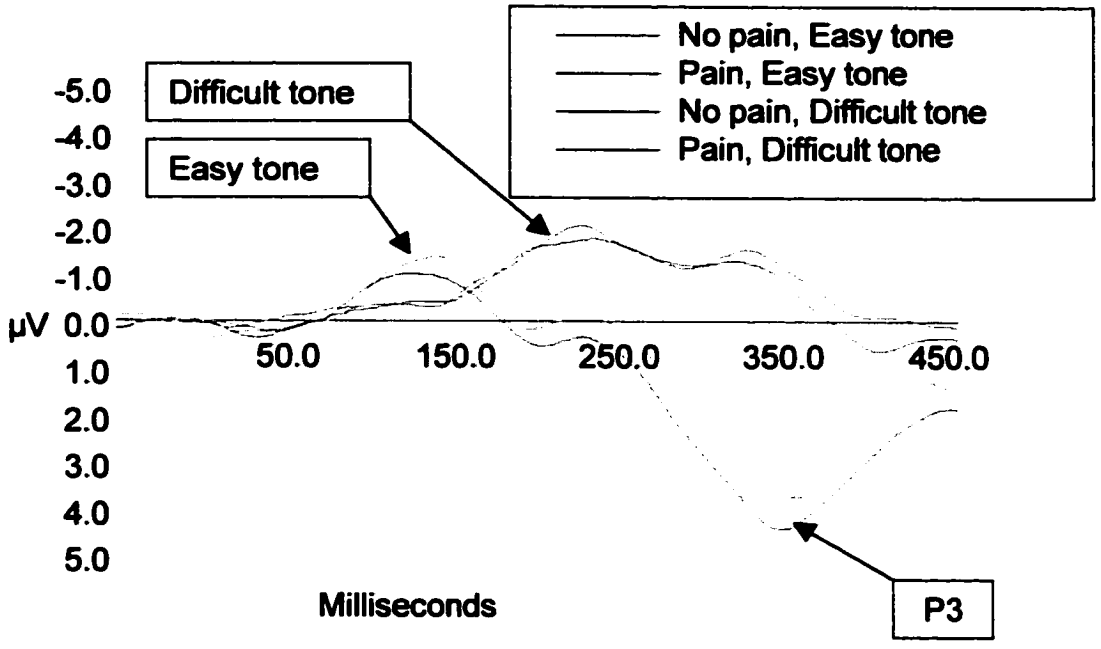

Figure 9. Grand average MMN and P3 waveforms (labeled at peak) for healthy volunteers in Experiment 2 during the active attention condition at electrode Fz.

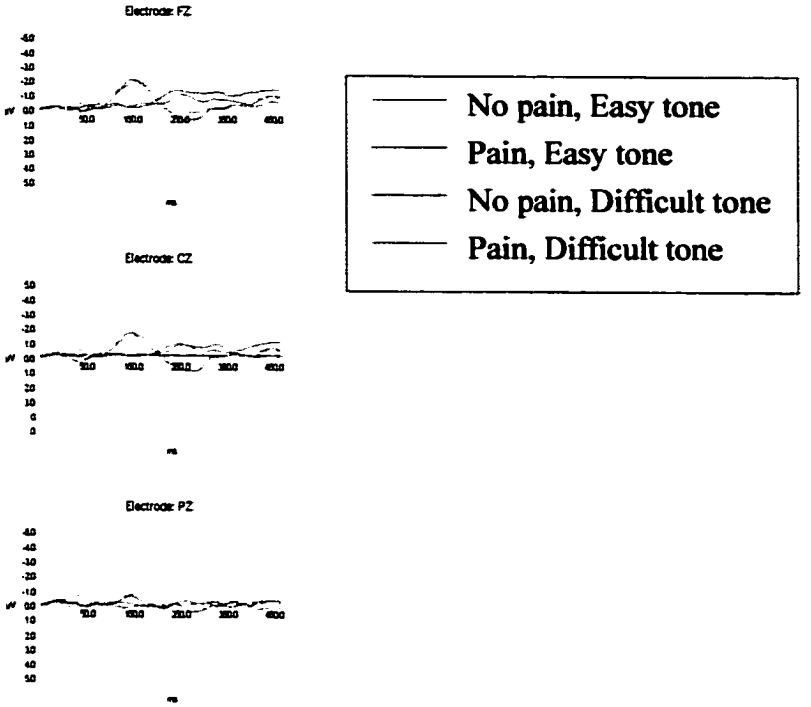

Figure 10. Grand average MMN waveforms for healthy volunteers in Experiment 2 during the passive attention condition at electrodes Fz, Cz, and Pz.

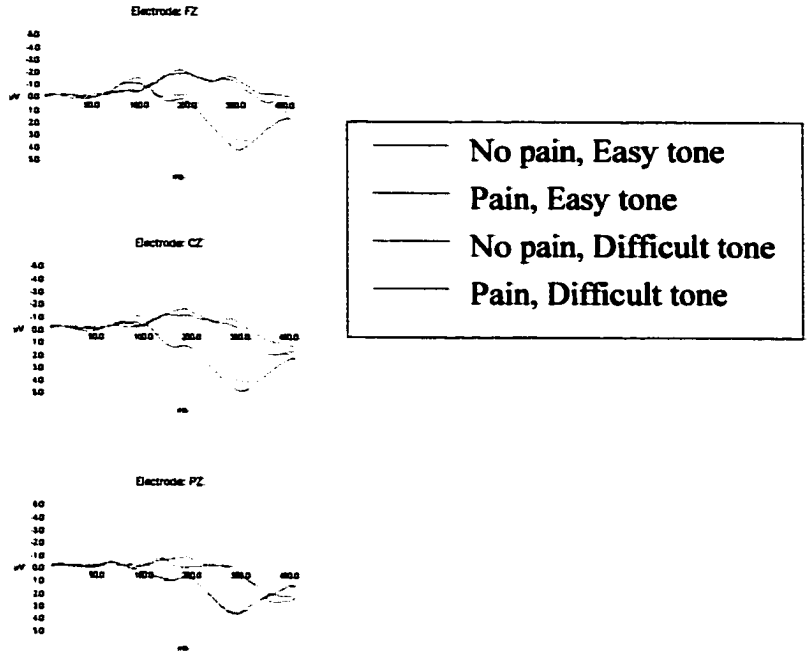

Figure 11. Grand average MMN waveforms for healthy volunteers in Experiment 2 during the active attention condition at electrodes Fz, Cz, and Pz.

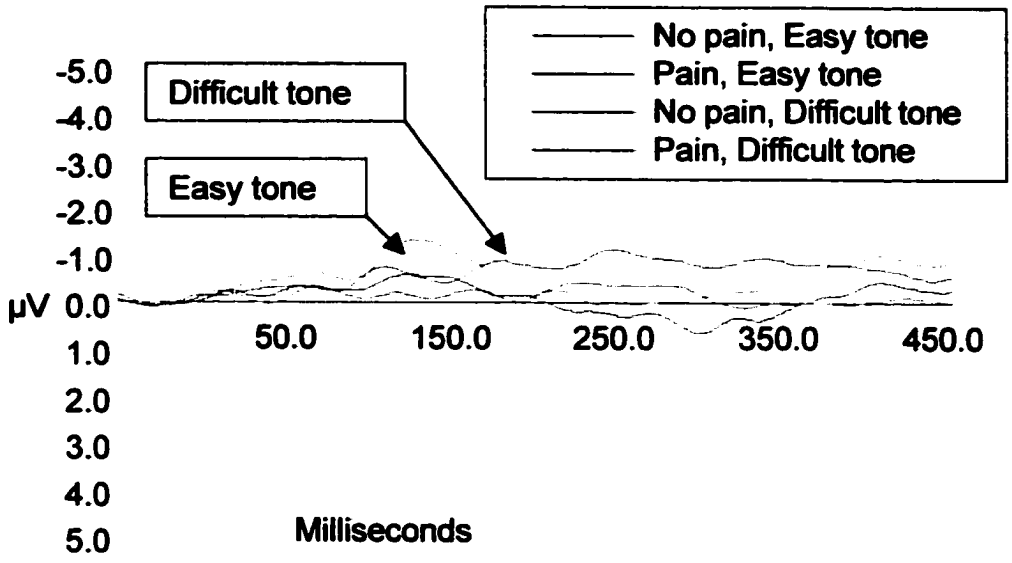

Figure 12. Grand average MMN waveforms (labeled at peak) for chronic pain patients in Experiment 3 in the passive attention condition at electrode Fz.

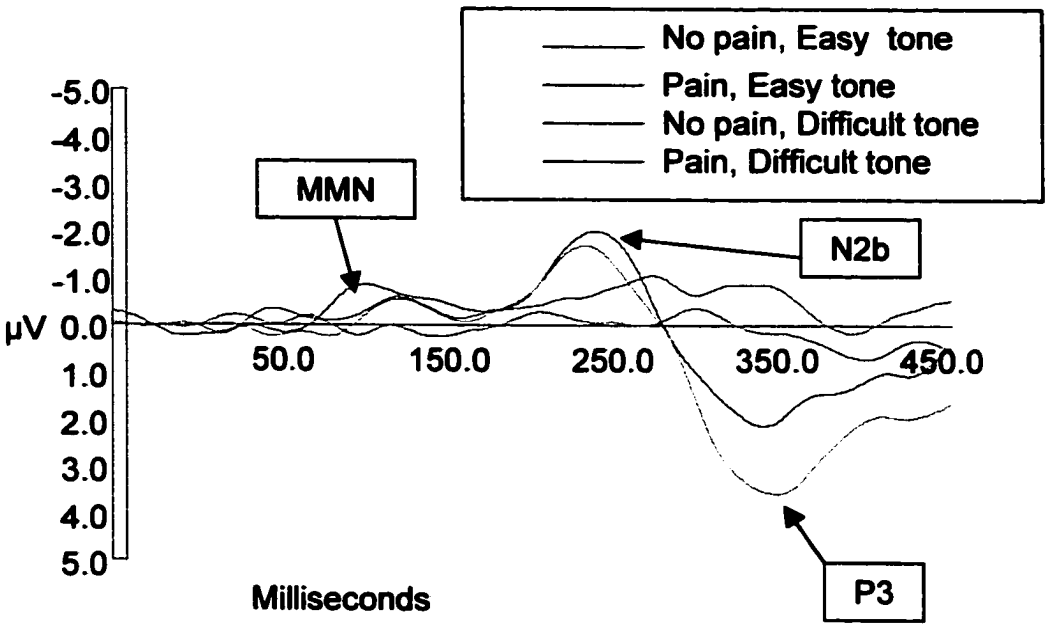

Figure 13. Grand average MMN and P3 waveforms (labeled at peak) for chronic pain patients in Experiment 3 the active attention condition at electrode Fz.

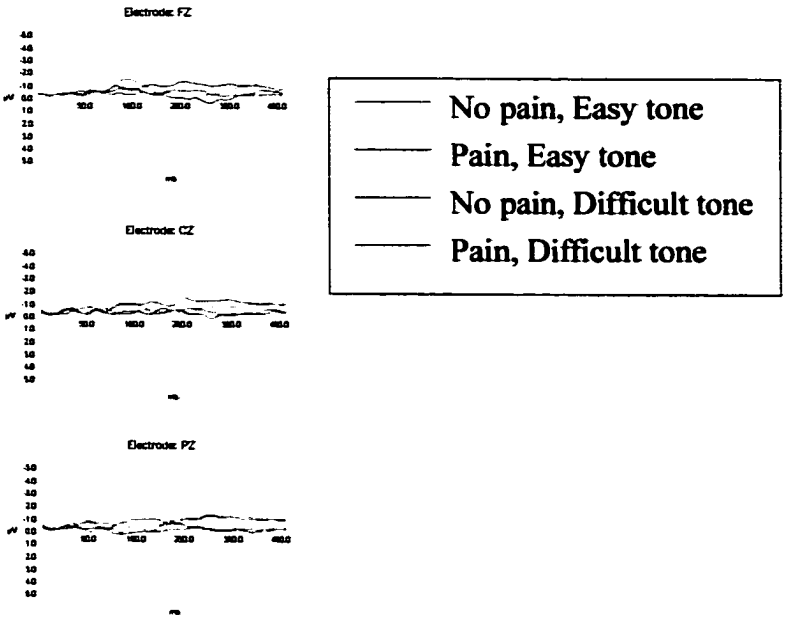

Figure 14. Grand average MMN waveforms for patients with chronic pain in Experiment 3 during the passive attention condition at electrodes Fz, Cz, and Pz.

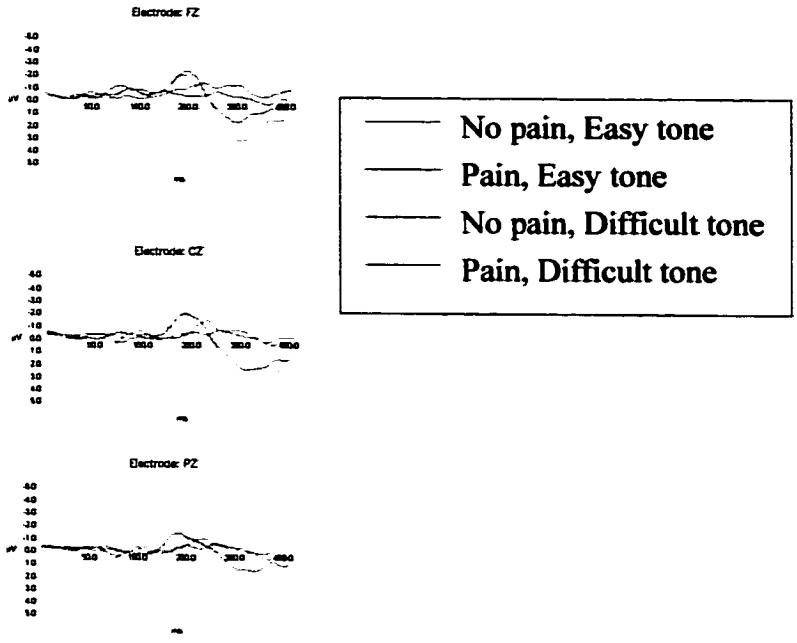

Figure 15. Grand average MMN waveforms for patients with chronic pain in Experiment 3 during the active attention condition at electrodes Fz, Cz, and Pz.

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