Neurophysiological Differences in Pain Reactivity:

Why Some People are Tolerant to Pain

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(ABSTRACT)

Pain is a complex, ubiquitous phenomenon that can be debilitating and costly. Although it is well known that some individuals can easily tolerate pain while others are more intolerant to pain, little is known of the neurophysiological bases of these differences. Because differences in sensory information processing may underlie variability in tolerance to pain and because measures of sensory gating are used to explore differences in sensory information processing, sensory gating among college students (N = 14) who are tolerant or intolerant to pain was investigated. This investigation explored the hypothesis that those who were more tolerant to pain would evidence greater sensory gating. Pain tolerance was first determined using a cold pressor task. Sensory gating was then determined by the amount of attenuation of the amplitude of a second painful, electrical, somatosensory stimulus (S2) in relation to the amplitude of an identical first stimulus (S1) in a paired-stimulus evoked potential (EP[1]) paradigm. The results obtained showed the intolerant group exhibiting greater physiological reactivity than the tolerant group, indicating that the tolerant group attained greater sensory gating than the intolerant group.

[1] The term, evoked potential (EP), was used early in the research involving brain potential measurement because it was thought that the potentials reflected basic sensory processes that were 'evoked' by the presentation of the stimulus. Now the term event-related potential (ERP) is often used because it was realized that some potentials might be related to a variety of processes that are 'invoked' by the psychological demands of the situation (Rugg & Coles, 1995). Although this study throws into question possible processes involved in the generation of the short latency P50, the earlier and more common term for the P50 (EP), will be used in this paper.

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Introduction

Pain is a complex phenomenon that can impact negatively on an individual's quality of life, resulting in tremendous costs in both human suffering and economic resources. Pain patients may report decreased activity levels, depressed mood, decreased socialization, impaired enjoyment of life, decreased ability to work, poor sleep, decreased ability to practice their religion and concern about finances (Taylor, Chun, Renking, Stegman, & Webster, 2004). It is well known that some individuals can easily tolerate pain while others are more reactive and intolerant to pain. These differences are obtained in both clinical and experimental settings, with much research emphasis directed toward behavioral and learned precursors to pain intolerance, such as catastrophizing (e.g., Jones, Rollman, White, Hill, & Brooke, 2003), maternal behavior (e.g., Chambers, Craig, & Bennett, 2002) and various other psychosocial factors (e.g., Zaza, & Baine, 2002). Other work (e.g., Bromm & Lorenz, 1998) suggests there may also be neurophysiological bases to these individual differences. Understanding what mechanisms may be involved in tolerance to pain would be of value in the treatment and control of various pain maladies in order to improve the quality of life for those suffering from such conditions. Therefore, this study was conducted to examine the neurophysiological bases of pain tolerance.

Pain is an unpleasant sensory and emotional experience that is subjective and complex, involving psychological as well as physiological processes. Pain is perhaps more complicated than other somatosensory experiences, since various psychological factors, such as stress, attention and arousal can easily change one's perception of that pain (Kakigi, et al., 2003; Tracey, et al., 2002), with the degree of subjective pain being affected by the amount of attention to and distraction from painful stimuli (e.g. Eccleston, 1995; Eccleston, & Crombez, 1999; Lorenz, & Garcia-Larrea, 2003; McDermid, Rollman, & McCain, 1996). To experience pain, various afferent and efferent messages must be integrated and modulated by central processes (Hadjistavropoulos & Craig, 2004).

Pain modulation: The pain system consists of various nociceptors and spinal cord neurons that transmit peripheral input to such structures as the brainstem, thalamus, cortex and limbic system by way of the dorsal horns of the vertebral column. As the pain signal travels from the nociceptor to brain structures involved in perception and cognition, it is subject to a variety of interneuronal networks in the dorsal horn and thalamus that both facilitate and inhibit activation (Bromm & Lorenz, 1998). For many years the prevailing one-dimensional model conceptualized pain as the result of a direct connection between the source of injury and a pain center in the brain (Craig & Rollman, 1999). Knowledge existed concerning a variable link between injury and pain, such that despite sustaining considerable injury, athletes or soldiers, for example, were able to complete their duties and not experience any pain, while others were incapacitated by what might seem a minor injury or no discernible injury at all. Melzack and Wall (1965), with their 'Gate Control' theory of pain, were the first to articulate the existence of a specific pain modulatory system, wherein supraspinal influences acted on nociceptive inputs. Additionally, they were the first to acknowledge that psychological variables have an impact on the perception and interpretation of pain, and to integrate that knowledge into a plastic, multidimensional network model (Skevington, 1995). This theory helped the medical and biological sciences to accept that the brain was not merely a passive transmission system but a dynamic, active system that filters, selects and modulates inputs (Melzack & Katz, 2004). The theory postulated that descending fibers from many brain areas project to the dorsal horns and can inhibit these cells from firing (closing the gate), depending on the integration of the descending messages regarding current cognitive and affective state, and information coming from the periphery, and thus influencing the perception of pain (Asmundson & Wright, 2004). This pain modulation can occur at any level of the CNS during sensory input filtering, and can be set and reset as that input is analyzed and acted on by the brain. Following Melzack and Wall's postulation of the 'Gate Control' theory of pain, it was found that electrical stimulation of discrete brain sites could lead to highly specific suppression of responses to noxious stimulation and the existence of this stimulation-produced analgesia strongly supported the hypothesis of descending systems contributing to pain modulation (Fields & Basbaum, 1994).

The thalamic role in sensory processing: Although knowledge of descending inhibitory processes at the level of the dorsal horns is valuable in understanding pain, there is much more to the story of sensory processing. It is well known that in sensory processing the thalamus provides a vital link between sensory receptors and the cerebral cortex for all modalities except olfaction. However, the thalamus is more than just a passive relay station for sensory information. It is actively involved in enhancing or inhibiting specific information depending on an individual's behavioral state (Amaral, 2000).

The thalamus is a complex almond shaped structure that is made up of at least 50 well-defined nuclei, located deep within the brain, dorsal to the hypothalamus. Some nuclei are considered specific relay nuclei, such that they receive ascending sensory input and project to well defined cortical areas that are related to specific functions. Other thalamic nuclei project to association areas of the cortex, subcortical regions or connect diffusely to various cortical regions (Carpenter, 1991). The reticular nucleus, a thin outer shell of the thalamus, receives inputs from both thalamic nuclei and from the cerebral cortex. Fibers that emanate from thalamic nuclei destined for specific cortical areas give rise to collateral branches that terminate in the reticular nucleus, while corticothalamic fibers passing to the thalamic nuclei project collaterals to the same portion of the reticular nucleus. In addition, those portions of the reticular nucleus that received thalamic and cortical collaterals, project back to those same thalamic nuclei. Virtually all cells of the thalamic reticular nucleus produce γ-Aminobutyric acid (GABA), which acts as an inhibitory neurotransmitter. When reticular nucleus neurons fire, they hyperpolarize thalamic relay neurons, thus preventing thalamic relay neurons from reaching firing threshold in response to sensory inputs (Saper, 2000). Thus, sensory input activates the thalamic reticular nucleus, which in turn inhibits and changes the firing pattern of the thalamic relay cells (Pinault, 2004). Therefore it is in a position to gate the flow of information between thalamus and cortex. Thus, in order to prevent the flooding of higher cortical centers with irrelevant information, which may lead to brain dysfunction, the central nervous system (CNS) has the ability to inhibit or suppress its response to incoming sensory input. This ability to inhibit is sometimes called sensory gating.

The inhibitory role of the prefrontal cortex: The prefrontal cortex (PFC) plays an important role in regulating this flow of thalamo-cortical information. Skinner and Yingling (1977), working with cats, presented the first physiological evidence for a multi-modal, prefrontal-thalamic inhibitory system that regulates sensory flow to primary cortical regions. By cooling the cat prefrontal cortex (cryogenic blockade) they increased the amplitudes of evoked responses recorded in primary cortex. By stimulating the nucleus reticularis of the thalamus, they produced modality specific suppression of activity in the primary sensory cortex. This could be interpreted as a modulating excitatory prefrontal pathway that projects to the nucleus reticularis thalami, which in turn, sends inhibitory projections to sensory relay nuclei, thus providing a mechanism by which selective sensory suppression might occur (Guillery, Feig, & Lozsadi, 1998). Thus, prefrontal cortex, which regulates inhibition and excitation in distributed neural networks, through corticothalamic projections that reflect attention, recent memories and behavioral goals, is thought to modulate this sensory processing (Behrendt, 2003; Knight, et al., 1999; Saint-Cyr, Bronstein, & Cummings, 2002).

The thalamus and pain processing: As stated above, pain signals, as well as most other sensory signals (excluding olfactory signals), when entering the CNS pass through the thalamus, which acts as an active relay or 'gating' system, before being projected to different areas of the cortex. Many neuroimaging studies have consistently indicated an involvement of the thalamus in pain processing. Peyron, Laurent, and Garcia-Larrea (2000) in their review of functional imaging of brain responses for the years 1991-1999 cite 25 studies that found thalamic activation during pain stimulation in normal subjects. The majority of this activation was bilateral, which may suggest an attentional or arousal reaction to pain. These robust results are obtained with differing pain stimuli, activation sites, imaging techniques, data processing approaches, and other details. Davis (2000) reports on several studies carried out in her laboratory using fMRI to investigate the human pain experience. These studies included administration of electrical stimulation, heat stimuli and cold stimuli at both noxious and innocuous levels in alternating periods of painful stimuli with non-painful control stimuli. She found the thalamus was activated by all stimuli

Clinical studies in which lesions are performed on the thalamus to alter pain support thalamic involvement in pain processing. White and Sweet (1969, as cited in Price, 1999) reported that depending on the location of the thalamic nuclei, they could produce pain relief in patients suffering intractable pain. Head and Holmes (1911, as cited by Price, 1999) found that several patients with damaged thalami showed reduced pain responses to stimuli on the side of the body contralateral to the damage. Several studies of electrical stimulation of the human thalamus in which stimulation of specific nuclei resulted in pain in conscious humans provide evidence of thalamic involvement in pain processing (Price, 1999).

The somatosensory cortex and pain processing: Many neuroimaging studies as well as clinical lesion studies in humans and experimental lesion studies in animals indicate the involvement of the primary somatosensory cortex (SI) in the perception of pain (Kenshalo & Douglass, 1995). This area exhibits responses to painful stimuli that are not seen with non-noxious stimuli. Bushnell et al. (1999) investigated the factors that might contribute to variable results among studies investigating the role of SI in pain perception. They provide evidence that SI is modulated by such cognitive factors as attention and previous experience, which alters pain perception. An examination of this and other factors lead them to the conclusion that SI cortex plays a prominent and highly modulated role in the sensory aspects of pain. Price (1999) cites several studies that support the role of the somatosensory cortex in sensory discriminative aspects of pain. He states, "Thus, the effects of lesions and electrical stimulation of the human post-central gyrus, though producing somewhat equivocal results, tend to be consistent with animal neuroanatomical and neurophysiological studies that provide evidence for the role of the primary somatosensory cortical area in sensory aspects of pain" (p. 115). Although Peyron et al. (2000) in their review of brain responses to pain report only 63% of the cases found significant pain-related activation of SI, they hypothesize differences in spatial and temporal summation and attention may contribute to this finding, rather than a lack of involvement of SI in pain processing.

The prefrontal cortex and pain processing: Along with thalamic and SI involvement in pain processing, which is fairly well established, the involvement of prefrontal areas in pain processing has need of consideration. Although this involvement

has been less well established or understood (Talbot, et al., 1991), continuing investigations have supported a functional role for prefrontal activity in pain processing. Peyron et al. (2000) again in their review of functional imaging of brain responses for the years 1991-1999 cite 25 studies in which activations in dorsolateral prefrontal (DLPF) or medial prefrontal (MPF) cortex or both were found during pain induction. Raij, Numminen, Narvanen, Hiltunen, and Hari (2005) in a study using fMRI found both DLPF and MPF activation in normal subjects whose pain was induced either hypnotically or by laser pulses to the skin. Derbyshire, Whalley, Stenger, and Oakley (2004) compared physically and hypnotically induced pain with imagined pain in normal subjects and found similar activations in PFC (BA 9, 10, 46) for the physically and hypnotically induced pain. Lu et al. (2004) used gastric distention to induce pain in normal subjects and found PFC activation. Other studies utilizing various pain populations such as chronic pain patients (Newburg, et al., 2005, Apkarian, 2004) and fibromyalgia patients (Gracely, et al., 2004; Cook, et al., 2004) found involvement of the PFC during pain induction.

Sensory gating: Although neuroimaging techniques such as PET and fMRI have good spatial resolution, they are less helpful in following the time course of pain induction and processing. Because differences in sensory information processing may underlie differences in tolerance to pain and because measures of sensory gating are often used to investigate sensory information processing, the paired stimulus paradigm is a more useful tool for investigating the evolvement of sensory information processing. Within an electrophysiological paradigm utilizing electroencephalograms (EEG), sensory gating is commonly assessed by measuring event related potentials (ERP) which are voltage deflections that are time locked to sensory, cognitive or motor events that can be measured in several sensory modalities (i.e. visual, auditory, and somatosensory). The positive and negative peak components thus produced represent the field potentials generated by the synchronous activity of sizable neural populations at various locations in the sensory pathways. In order to extract the signal (the time-locked ERP) from the noise (the background EEG), several repetitions of the stimulus are presented and then all epochs containing the EEG values for each time-point are averaged. The positive P50 waveform (occurring at 35-70 ms post stimulus in the auditory system) is the most

commonly studied component in relation to sensory gating. For the P50 waveform sensory gating is considered to occur if there is a relative attenuation of the amplitude of a second stimulus (S2) in relation to the amplitude of a first stimulus (S1) in a paired-stimulus ERP paradigm. The normal P50 suppression to the second stimulus is thought to reflect a sensory gating mechanism, important for protection against information overload (Bramon, Rabe-Hesketh, Sham, Murray & Frangou, 2004).

Abnormal sensory gating: Because there is involvement of a prefrontal inhibitory pathway, damage to the prefrontal cortex may disrupt inhibitory modulation of sensory inputs, thereby interfering with the ability of the CNS to filter out irrelevant sensory information. Abnormalities in prefrontal function and structure have been extensively documented in schizophrenia (Weinberger & Berman, 1996; for reviews see: Antonova, Sharma, Morris, & Kumar, 2004; Heinz, Romero, Gallinat, Juckel, & Weinberger, 2003; Volk & Lewis, 2002; Tekin, & Cummings, 2002; Torrey, 2002; Weinberger, et al., 2001). Inefficiency in sensory filtering processes may lead to flooding by sensory input, thereby contributing to the characteristic symptoms of schizophrenia. These information-processing inefficiencies that characterize schizophrenia are associated with impaired auditory sensory gating (Thoma, et al., 2005). The abnormal sensory gating that is characteristic of schizophrenic patients is well documented (for a meta-analysis see; Bramon, et al., 2004), and is also found in their first- degree relatives (e.g. Myles-Worsley, 2002), those diagnosed with Post-traumatic stress disorder (PTSD) (e.g. Ghisolfi, et al., 2004) and other populations (Jessen, et al., 2001; Cadenhead, Light, Geyer, & Braff, 2000). In their meta-analysis of the auditory P50 waveform in schizophrenia, Bramon et al. (2004) examined twenty P50 studies that were suitable for analysis and which altogether included 421 patients and 401 controls. Their meta-regression analyses of these studies demonstrated that the P50 ratio (S2/S1; a higher value indicates an impairment in gating) was significantly larger in the patients compared to healthy volunteers, while there were no differences in latency.

Somatosensory evoked potentials and sensory gating: Although auditory processing is now the most commonly pursued modality in assessing sensory gating, somatosensory evoked potentials (SEP) have recently come under scrutiny. Arnfred, Eder, Hemmingsen, Glenthoj and Chen (2001) in a study examining both the SEP and

AEP in a non-pain gating paradigm, administered paired auditory clicks and median nerve stimulations to healthy men. For both modalities, they found that gating was most pronounced at an inter-stimulus level (ISI) of 500 ms. They concluded that it is possible to use median nerve stimulation in a paired P50 gating paradigm. It appears that the effects of the auditory and the somatosensory paradigms are comparable. Their results indicated that they were measuring similar information–processing modulation at P50 in the two modalities and that these components are manifestations of similar subcortical processes. However, since the gating was not correlated across modalities, they concluded that it is not a cross-modal modulation.

SEPs and pain: Although a few studies have examined SEPs and pain (DePascalis, Magurano, & Bellusci, 1999; Kropotov, Crawford, & Polyakov, 1997; Miltner, Johnson, Braun & Larbig, 1989; Wang, et al., 2003) none have used the paired stimulus paradigm. One study (Johnson & Adler, 1993) used a cold-pressor task as a transient stressor on P50 auditory gating. The cold-pressor test diminished P50 auditory gating in nine out of ten normal controls, all of which had previously demonstrated normal auditory P50 gating. They report the degree of impairment in gating was highly variable among subjects. This result might be expected due to the subjects' varying levels of tolerance to pain, that was not measured.

Rationale for and hypothesis of this study: It is not known why some individuals are more intolerant or reactive to pain than others, but a better understanding of pain information processing may lead to better management of or reduction in disabling conditions due to pain. Because it is postulated that sensory gating is related to the inhibition or suppression of the CNS response to incoming sensory input, this study was conducted to test the hypothesis that those who are intolerant to pain will have greater physiological reactivity or reduced sensory gating in comparison with those more tolerant to pain. This hypothesis was tested using paired painful somatosensory stimuli, with higher S2/S1 ratios (related to an increase in S2) and lower S1 – S2 differences indicating greater physiological reactivity or a lesser degree of sensory gating.

Method

Participants

Participation involved two phases to the study, a preliminary screening for tolerance and intolerance to pain and the measurement of sensory gating. Participants in the preliminary screening included 60 (male = 29, female = 31) volunteers from the Virginia Tech undergraduate psychology subject pool, ranging in age from 18 to 32 (M = 20.22; SD = 2.49) years of age. These 60 participants were originally solicited to participate in a study examining various biopsychosocial factors relating to pain tolerance. Of these, using the criteria of being able to leave one's hand in 0-1° C cold water for 3 min in two consecutive dips, 38 (male = 20, female = 18) were tolerant to pain and 22 (male = 9, female = 13) were intolerant to pain. Of these 60 participants who were screened, only those who met the following criteria were included in the sensory gating phase: non-smoker (by self report), strongly right-handed as indicated by a self report handedness questionnaire (see Appendix A), no previous concussion or other neurological disorders, which might impact EEG, and no diagnosis of ADHD or other learning problems as per medical screening questionnaire (see Appendix B). Of the 60 original participants, 14 (male=10, female = 4) participants ranging in age from 18 to 27 (M = 20.8; SD = 2.94) met the criteria and agreed to continue with the sensory gating phase of the study. All participants received extra credit for psychology courses.

Procedure

Preliminary Screening. Participants underwent a preliminary screening for inclusion into a pain tolerant (TOL) or pain intolerant (INTOL) group. Each participant read and signed a consent form (see Appendix C) explaining the procedure of the experiment. Participants completed a medical form (see Appendix B) ensuring they had no medical problems that would preclude them from being exposed to ice water, such as arthritis, heart disorders or other such difficulties or problems that would interfere with neurological recordings. Participants were then instructed to leave their left hand submerged in ice water (0°C) for as long as possible, but to remove it when they could no longer bear it (see Appendix D for administered instructions). Participants were not told that the maximum submersion time was 180 sec, thus providing a measure of participants' tolerance to this pain. Participants were also instructed to rate both their sensory pain and distress pain according to a graduated 11- item scale for each type of pain when the experimenter said 'report'. Sensory pain is related to the extent that the

cold hand is experienced as being physically painful. The second type of pain relates to the distress or annoyance that the cold hand induces. It is emotional and motivational, the 'suffering' component of pain, and related to how much one would like to be rid of the pain. The sensory pain scale ranges from 0 (no pain) to 10 (unbearable) and the distress scale ranges from 0 (no distress) to 10 (excruciating) (see Appendix E for scales). Participants were instructed as to the meaning of these 2 types of pain and asked if they understood. If the participants indicated that they did not understand the difference, further explanation was supplied until they indicated understanding.

The experimenter lowered each participant's left hand into the ice water and began timing. Participants were asked to report their rating of sensory and distress pain every 20 seconds from the time their hand was submerged until they removed their hand or until 180 sec had elapsed, whichever occurred first. After a 3-min interval a second dip of the same hand was performed under the same conditions. During the 3-min interval the ice water was thoroughly stirred and a second reading of the temperature was made, to ensure that the water remained at 0°C. Based upon the length of submersion time participants were categorized into two groups: INTOL (less than 90 sec for each of 2 dips) and TOL (180 sec for each dip).

Physiological Recordings. For measurement of the electroencephalogram (EEG), each participant was fitted with a 29 scalp-site Lycra electrode cap (Electro-Cap International, Easton, Ohio) referenced to linked earlobes, after reading and signing the consent form (see Appendix F). The positions of the electrodes were in accordance to a 10-10 system as proposed by the American Electroencephalographic Society (1994), a revision of the International 10-20 system with an additional nine electrode sites equally spaced between the frontal line (F7 to F8) and central line (T3 to T4) and between the central line and parietal line (T5 to T6). Eye movements were recorded from electrodes placed directly above and below the eye (vertical measurement) and outer canthus of each eye (horizontal measurement). Electrode impedances were kept below 5Kohm and balanced throughout as equally as possible (less than 500 ohm difference). Continuous EEG data, with stimulus presentation marked for subsequent EP analyses, was collected using SCAN 4.0 with Neuroscan bioamplifiers. The EEG was sampled at 500 Hz with a low bandpass cut-off of 100 Hz. Offline the SEP data was filtered for a low bandpass of

30 Hz. The accompanying Neuroscan STIM that is interfaced with the SCAN acquisition program controlled stimulus generation, and the EEG data was marked simultaneously with stimulus onset. A digital signal was generated using STIM software that activated a Grass s10DSCM somatosensory stimulator and an SIU8T stimulus isolation unit (maximum output voltage approximately 150 volts). This isolation unit ensures the safety of the equipment for use with human subjects.

Stimulus Intensity Determination. Analgesia research should utilize painful stimuli that are clearly and definitely painful (e.g. Becker, Yingling, & Fein, 1993). Participants were aware that it is necessary to provide stimuli that are strongly painful but bearable in order to assess electrophysiological responses to painful stimuli. Sensory threshold, pain threshold and pain tolerance levels were assessed using an ascending method of limits (Gescheider, Sklar, Van Doran, & Verrillo, 1985). Since some habituation to the stimuli may occur with multiple trials, 3 ascending trials were given to determine when the stimulus was perceived as being strongly painful but bearable. This perception was based on participants' ratings of their sensory pain on the same scale used during the preliminary screening. Of the three trials administered, the highest rating was used for determining stimulus voltage. Stimuli rated as painful but bearable fell within 70 to 90 volts. There was no statistical difference in voltage administered between the TOL and INTOL groups. A practice block of 5 stimuli at the chosen level was used to familiarize the participants with the sensations of finger stimulation and verify SEP recording.

Stimuli. For each group, stimuli consisted of 50 sets of paired square-wave electrical pulses of 0.2 msec duration (rise/fall time of 20 μsec), with an ISI between pairs of 500 msec and a 3 sec interval between sets. Each pulse was delivered to the left and right hand separately in the center of the palmar surface of the distal phalange of the second finger by a Grass S10DSCM somatosensory stimulator with an SIU8T stimulus isolation unit (maximum output voltage approximately 150 volts) triggered externally by the Neuroscan STIM package. The participant's finger was prepared by having the participant rub the skin with an emery board, followed by the experimenter's vigorous cleaning of the area with NUPREP and an alcohol swab.

Data Reduction and Analyses. EEG analog records were first divided into –50 to 462 ms analysis periods or epochs. In EP recording, a period of recording before the stimulus (pre-stimulus period) is often used as an estimate of the residual noise in the average and can be used as a baseline against which to measure the amplitude of EP peaks (Spehlman, 1985). The total time period of the epoch (512 ms) is an integral multiple of the fundamental frequency of 2 Hz, which allows frequency analyses using Fourier transforms (Transnational College of LEX). Epochs were then submitted to the SCAN automatic rejection program for trials contaminated by excessive eye movements (exceeding ± 35 μV on the EOG channel) or electromyographic artifacts. Baseline adjustment was made using the mean amplitude at latency –2 ms to 0. Smoothing programs were applied. Subsequently each epoch was scanned visually for verification and noting of further eye movement, muscle, or other artifacts. Those SEP epochs containing artifacts were not included in the data analyses.

Visual identification of waveforms at Cz was performed. The electrode site Cz was chosen because it has been reported to be the location with the highest amplitudes within the sensory gating paradigm (Arnfred, et al., 2001; Nagamoto, Adler, Waldo, Griffith & Freedman, 1991; Wan, 2004, unpublished thesis). The P50 waveform was identified as the positive peak closest to 50ms falling within a latency window of 35 to 80ms. Peak amplitude is the voltage difference between a peak and a reference level, generally representing zero amplitude (Spehlmann, 1985). However, if the baseline is not stable, this method is not optimal. In this case, peak-to-peak amplitude may be used. Measurements are taken of the vertical distance between successive peaks of opposite polarity (Arnfred & Chen, 2004). Because the baseline in this study was noisy, amplitude was calculated as the difference in amplitude between the preceding negative waveform and the identified positive peak . These amplitude data were exported to statistical software (SPSS v. 10.1) for further analysis. The data were examined for statistical differences of sensory gating between the TOL and INTOL group using t-tests and two-factor mixed factorial analysis of variance tests (ANOVA) having stimulus condition as the within subjects factor and pain tolerance as the between subjects factor.

Results

Because each participant received both of the paired stimuli (S1 and S2) of each set, stimulus condition was treated as a repeated measure, and thus considered a within subjects factor. Because each group (TOL and INTOL) consisted of non-overlapping participants, pain tolerance was treated as a between subjects factor. Based on the resulting 2 x 2 (Pain Tolerance x Stimulus Condition) mixed A x (B) factorial ANOVA, a significant main effect for amplitude between the paired stimuli (S1 and S2), F (1, 12) = 7.501, $p < .05$, was obtained with overall S1 amplitudes (M = 2.296, SD = 1.886) being significantly larger than S2 (M = 1.421, SD 1.564) amplitudes. However, of more importance to this study, based on the above ANOVA, a significant two-way interaction of the factors was obtained, F (1,12) = 5.356, $p < .05$. Subsequent t-tests resulted in a significant difference between S1 and S2 for the TOL group only, t (8) = 3.789, $p < .01$, with S1 (M = 2.301, SD = .961) obtaining a larger amplitude than S2 (M = 1.001, SD = .961). Independent samples t-tests revealed no significant difference between TOL and INTOL for S1 and S2. No main effect was observed for pain tolerance. (See Figure 1.)

Two separate measures of sensory gating were employed; differences obtained by subtracting S2 from S1 (S1 – S2) and the ratio obtained by dividing S2 by S1 (S2/S1). Since S1-S2 is the difference between the amplitudes of the first and second stimuli, and since S2 is either less than or equal to S1 depending on the activity of sensory gating, as the value for S1-S2 increases, so does the level of sensory gating. And in the opposite direction, as S2 approaches the value of S1, the difference decreases, indicating a smaller degree of sensory gating. For S2/S1 the ratio obtained will approach the value '1' as sensory gating lessens and inversely, will decrease from '1' with greater gating. In other words, an inverse relationship exists between the value of the ratio and the extent of sensory gating, such that as the ratio increases, sensory gating decreases. Using independent samples t- tests for the measures of gating, S1-S2 differed significantly, t (12) = 2.314, $p < .05$, between the TOL (M = 1.3002, SD = 1.029) and INTOL (M = .1092, SD = .659) groups, indicating a greater degree of gating for the TOL group. The S2/S1 ratios differed significantly, t (12) = 2.974, $p < .05$, between the INTOL (M = .962, SD = .389) and TOL (M = .435, SD = .275) groups, also indicating a more active process of sensory gating. (See Figure 2.)

In order to evaluate whether the TOL and INTOL groups differed in their subjective experience of pain as well as their reaction to pain (leaving their hand in or retracting their hand from ice water), an independent samples t test was performed on the pain report data (see Appendix E for pain rating scale values). The ratings for sensory pain for dip 1 and dip 2 were averaged separately, and then the obtained values were averaged to produce an overall pain sensory rating value. The same process was performed for the pain distress ratings to obtain an overall pain distress rating value. These values were compared using an independent samples t test. There were significant differences for both sensory pain (intensity) and pain distress between the two groups. For sensory pain TOL differed significantly from INTOL, $\underline{t}$ (12) = 3.138, $\underline{p} < .01$ with TOL obtaining $\underline{M}$ = 5.84 and $\underline{SD}$ = 1.29 and INTOL obtaining $\underline{M}$ = 7.99 and $\underline{SD}$ = 1.29 (the higher the rating, the more the intensity). For distress pain TOL differed significantly from INTOL, t (12) = 4.55, $p < .01$, with TOL obtaining $\underline{M}$ = 4.55 and $\underline{SD}$ = 1.10 and INTOL obtaining $\underline{M}$ = 7.25 and $\underline{SD}$ = 1.13 (the higher the rating, the more the distress). (See figure 3.)

Discussion

The present study is the first to use paired somatosensory stimuli in the investigation of pain tolerance. The resultant data support the hypothesis of greater physiological reactivity in those individuals with greater intolerance to pain. This greater physiological reactivity is indicated by the lack of suppression of the second stimuli in a paired stimulus paradigm, which is considered a reduction in sensory gating. However, the term 'gating' is a hypothetical psychological construct that does not elucidate the neural mechanisms involved.

P50 and inhibition: This gating of the P50 component is related to a central inhibitory function which occurs at the neuronal level and which may be "hard-wired" (Smith, Boutros, & Schwarzkopf, 1994) and/or associated with attentional modulation (White & Yee, 1997). Mueller, Keil, Kissler and Gruber (2001) using the double click paradigm in the auditory system observed that earlier components (Po, Na, Pa and Nb) as well as the P50 and later components (N100and P200) exhibited amplitude suppression to the second click. They contend that auditory gating occurs very early, possibly at a subcortical level. This experiment does not elucidate whether this suppression is related

to a hard-wired inhibitory process or something else. Whether the PFC is involved in this inhibitory process is yet to be determined.

Prefrontal involvement in P50 suppression: Because reduced P50 suppression is consistently found in the schizophrenic population (Bramon, et al., 2004) and because abnormalities in prefrontal function and structure have been extensively documented in schizophrenia (e.g., Antonova, et al., 2004) it may be deduced that the activities of prefrontal regions may also be involved in P50 suppression and therefore pain tolerance.

Knight et al. (1999) presented the most direct evidence for frontal involvement in P50 amplitude reduction. Patients with prefrontal lesions failed to suppress the second stimulus in a paired click paradigm. Wiesser et al. (2001) presented the only other direct support for frontal lobe involvement in auditory P50 suppression. Using MEG and EEG for spatio-temporal source analysis, they were able to identify a frontal source as well as temporal auditory cortex contributions to the P50 scalp potential.

It is not known precisely what structures are responsible for the generation of the P50 component because there is no correlation between each waveform peak and one structure. As Spehlmann (1985) states, "…more than one structure may contribute to the production of one peak, and each generator may contribute to more than one peak" (p. 13). Because the gating effect is measured most effectively at CZ, it might seem to preclude an involvement of the PFC. EEG signals, however, are measuring the postsynaptic activity of a large number of fibers projecting onto neuronal processes. Thus, if the PFC were communicating with thalamic neurons, those projecting axons would be synapsing at the thalamic region. Therefore you would expect to observe more activity, and thus more amplitude, at the vertex than more frontally.

The fact that the P50 suppression effect occurs so early in sensory processing may appear to preclude prefrontal involvement. Several studies provide evidence that the early P50 component may involve preattentive sensory processes (Boutros, Belger, Campbell, D'Souza & Krystal, 1999; Boutros, Korzyukov, Jansen, Feingold, & Bell, 2004; Kisley, Noecker & Guinther, 2004; & van Luijtelaar, 2003). Evoked potentials occurring early in the information processing stages are called sensory or exogenous components because they are highly sensitive to physical stimulus attributes such as modality, intensity, duration, or repetition rate (Lorenz & Garcia-Larrea, 2003). Evoked

responses that occur between 40 and 250 ms post-stimulus are often considered exogenous, that is, are generated by sensory stimulation without influence from mental operations (Boutros, et al. 2004). However, Foxe and Simpson (2002) using high-density ERP recordings and scalp current density mapping, provided evidence in the visual system for prefrontal involvement between 56 and 80ms post stimulus.

Mauguiere (1999) maintains that neural responses in the P50 range are modulated by cognitive factors. Attentional focus has been shown to modulate activity as early as 15 ms post-stimulus in the auditory modality (Hackley, 1993) and at 40 ms post-stimulus in the somatosensory modality (Desmedt, Bourguet, Nguyen Tran, & Delacuvellerie, 1984).

It is well known that hypnotic suggestion in hypnotizable individuals can attenuate if not eliminate the experience of pain. Crawford and Gruzelier (1992) present a neurophysiological model of hypnosis and pain that involves an anterior inhibitory function. Crawford (1994), considering somatosensory evoked potential study results, proposes an involvement of far frontal cortex in assessing incoming painful events. Relevance is determined and the frontal region is then involved in inhibiting irrelevant somatosensory information coming from the thalamic region. Birbaumer, Elbert, Canavan, and Rockstroh (1990) review evidence that supports the involvement of far frontal regions in an inhibitory feedback circuit associated with the regulation of thalamocortical activities. Although the effects of hypnosis on later components, such as the N100 and P300, have been studied (e.g., DePascalis, Bellusci, Gallo, Magurano, & Chen, 2004; DePascalis, et al., 1999; Jensen, Barabasz, Barabasz, & Warner, 2001) no study has identified the effects of hypnosis on earlier components, such as the P50. Because participants were not screened for hypnotizability, nor were pain coping strategies assessed, this study could not address alternate mechanisms by which tolerant subjects may be achieving sensory gating. Future studies could help elucidate the role of hypnosis, coping strategies and anterior cortices on P50 suppression and pain tolerance.

Although the P50 component is thought by many to be a preattentive, stimulus driven phenomenon, it appears that involvement of prefrontal areas may require a reconsideration of that assumption. Although the prefrontal cortex has been implicated in diverse cognitive processes or "executive functions", wherein information processing is coordinated and action controlled, that involvement was thought to occur later in the time

course of information processing than 50 ms. Casey, Morrow, Lorenz, and Minoshima (2000) by appropriately timing PET acquisition with changes in experimental conditions, found cortical activation that preceded thalamic activation. However, they could not rule out that a small amount of thalamic activation that could not be measured may have generated the cortical activity, which would fit with the extensive divergence of thalamocortical fibers. They also could not rule out the possibility that unidentified factors in the environment or anticipation, anxiety or fear, independent of the sensory stimulation, may have generated the cortical activation. This early cortical activity could be influencing subcortical nociceptive transmission. Thus, further investigation into the time course of prefrontal activations in pain processing and tolerance would be illuminating.

Although there are strong indications for an involvement of the prefrontal cortex in pain tolerance and sensory gating, it has yet to be elucidated just which areas or network of areas are contributing to these processes. PET and fMRI alone, because of poor temporal resolution cannot specify which SEP component may be generated (Ohara, Crone, Weiss, Treede & Lenz, 2004; Spiegel, Tintera, Gawehn, Stoeter, & Treede, 1999). Because PET and fMRI offer excellent spatial and SEP excellent temporal resolution, a combination of these techniques would allow a more detailed analysis of which areas might be functioning at which time in the course of the repetitions. Measures of executive functioning in pain tolerant and intolerant individuals could help elucidate some of these issues. Based on the current study's results, one would hypothesize that pain tolerant subjects would perform better on measures of executive function.

Sequential and/or parallel components of pain: Although this study supports differences in gating related to tolerance to pain, it does not tell the whole story of pain tolerance. The pain experience consists of a multidimensional integration of sensory-discriminative, affective-motivational and cognitive-evaluative qualities (Peyron, et al., 2000). These components of pain are often presented as separate mechanisms involving disparate neural processes and networks. Price (1999) integrates psychological, physiological and anatomical evidence, proposing that the sensory-discriminative, arousal and some motor responses associated with pain appear to be activated in parallel. He contends, however, that psychological and neurophysiological evidence exists to show

that affective emotional states depend on sequential processing using cognitive processes. Melzack and Casey (1968) contend that processing in the sensory and affective level can occur in parallel. In light of the results of this study, investigations into the mechanisms of these processes and their relationship and interactions would be of value.

Pain ratings and sensory cortices: Because those individuals who were intolerant to pain demonstrated impairment in their reduction of the second stimulus and because of the apparent involvement of prefrontal cortex in pain processing and the P50 component, it is suggested that prefrontal-thalamic networks may influence pain tolerance. This could be interpreted as being congruent with differing prefrontal inhibitory activation, leading to a lack of thalamic gating, resulting in the CNS being flooded with pain sensory input. In support of this interpretation, the present study found those who were tolerant to pain by the criteria of leaving their hand in ice water for 180 seconds also rated their pain intensity and distress significantly lower than those who were intolerant to the pain (retracted their hand from the ice water in less than 90 seconds). Coghill, McHaffie, & Yen (2003) examined neural correlates of pain tolerant and intolerant individuals during administration of thermal pain. Using fMRI to assess brain activation, they found more frequent and more robust pain-induced activation of SI (as well as prefrontal cortex) in those intolerant to pain as compared to those more tolerant to pain. However, because SI involvement in pain processing is not clear at this time, future studies to illuminate SI activity and pain processing would be indicated.

Pain modulation systems and gating: Does a lack in sensory gating really result in flooding the CNS with pain sensory input or might some other mechanism be involved? Several distinct pain modulatory (analgesic) systems have been identified under controlled laboratory condition (Price, 1999). Could such endogenous opioid systems be involved in the sensory gating reduction in pain intolerant individuals? VonRee (as cited in Price, 1999) found that microinjections into the nucleus medialis dorsalis of the thalamus resulted in analgesia. However, one would think sensory gating reduction in pain intolerant individuals would relate to sensory discriminative aspects of information processing, and not be related specifically to the endogenous opioid systems since gating occurs in other modalities as well, which are not involved in pain sensory inputs.

Arousal and pain tolerance: Because there were no significant differences between S1 amplitudes between the tolerant and intolerant groups in this study (see figure 1), it would appear that greater general arousal for the intolerant group is not the main contributing factor to gating suppression ineffectiveness. However, since arousal and attention are so intimately related, and attentional factors may be contributing to differences in sensory gating, future studies might assess what specific contribution arousal may have in this process. Other contributing factors may be assessed, such as blood pressure, since there is evidence of functional interactions between cardiovascular and pain regulatory systems (Bruehl & Chung, 2004).

Developing pain tolerance: If those individuals who are intolerant to pain demonstrate a lesser degree of sensory gating, does this difference indicate a precursor to intolerance, or is the lack of sensory gating a result of pain intolerance? Tolerance to pain may involve a predisposition that results from genetic makeup, social learning, prior trauma or some combination of each (Asmundson & Wright, 2004). Studies of pain tolerance and sensory gating beginning in infancy and as a developmental process would help shed light on this issue.

Gender, sensory gating and pain: Because the relationship between gender, sensory gating and pain is not simple, further evaluation of this issue as it relates to pain tolerance and intolerance would be of value. For example, in experimentally induced pain studies, the majority of studies show women are comparatively less tolerant and more sensitive to noxious stimulation than men (Fillingim, 2003; Fillingim, Browning, Powell, & Wright, 2002; Fillingim & Maixner, 1995; Riley, Robinson, Wise, Myers, & Fillingim, 1998). However, not all studies report this result. Although the differences in pain tolerance between men and women are small (Berkley, 1995), the discrepancies shown across studies may be influenced by the significant variability in pain responses between individuals (Fillingim & Maixner, 1995). Evidence also exists to suggest men and women experience different clinical pain experiences (Fillingim, 2000). These differences between men and women may change from condition to condition, and may also vary across the life span (LeResche, 1999), while some begin to emerge during adolescence and persist under extreme life circumstances and therefore may be mediated, in part, by biological factors (Unruh, 1996). Whether these differences are due to

biological factors, such as hormonal fluctuations and/or psychosocial influences is yet to be determined. Gender differences have also been reported in gating paradigms. Hetrick et al. (1996) obtained results from a study on gender differences in gating using the paired click auditory evoked potential in normal subjects. They found that although the P50 potential amplitudes to S1 were not significantly different between men and women, the women had significantly higher S2 amplitudes, and greater S2/S1 ratios. This indicates a lesser degree of gating for women than men. To further complicate the issue, menstrual cycle may act as a confounding factor. For example, Walpurger, Petrowsky, Kirschbaum, and Wolf (2004) investigated auditory ERPs in healthy women at three different phases of their menstrual cycle and found menstrual cycle-associated changes.

In order to elucidate the intricacies of tolerance, gating and gender, comparisons between men and women in both pain tolerance and sensory gating would be important considerations for future studies. These future studies would also benefit from an examination of the effects of menstrual phase within women. Although, in this study, a chi-square test examining the relationship between tolerance and gender showed no significant association between the variables, the low number of participants in this study may throw in doubt the lack of significance. A chi-square test comparing tolerance and gender may not be valid since one cell would have an expected frequency of less than 5. Although not everyone agrees, leading authorities proscribe the use of chi-square when any of the expected frequencies is less than 5 (Gray & Kinnear, 1998). However, males and females were proportionally distributed within the TOL and INTOL groups, which would minimize possible gender confounds in this study,

Number of sweeps: In this study, measurement of the P50 component was difficult, possibly due to the low number of paired repetitions. Arnfred et al. (2001), in the first study to use the somatosensory modality in an EP gating paradigm, recommend averaging at least 60 sweeps in order to identify an SEP P50 component. However, they administered non-painful stimuli. Because pain responses may change with repeated stimulation, 50 pairs of stimuli were used in this study to minimize the effects of repeated stimulation. Because this study was the first to use paired painful somatosensory stimuli to investigate pain tolerance, future studies would be of benefit to assess the number of

repetitions needed to produce measurable P50 components, while minimizing changes in the pain response.

Alternative considerations: At this time the functional significance of the P50 suppression effect is not known. Although the P50 suppression effect is often interpreted as a being associated with a sensory gating mechanism important for preventing the flooding of an organism from irrelevant or harmful stimuli, it is not known whether it reflects such a psychologically relevant process or a more basic neurophysiological process. What is known is that when identical paired stimuli are presented at regular intervals (500 ms) the second of the pair is smaller in amplitude at P50 in most individuals. Whether this attenuation occurs as a result of habituation, adaptation, refractory periods or recovery cycle processes of neural generators is not known at this time. Intriguing is a study in which Rosburg et al. (2004) presented 100 trains of 6 auditory clicks (5 identical, the 6^{th} deviating in frequency and duration) with each click separated by 500 ms and each train separated by 8 seconds. They found a significant amplitude reduction for the P50 component from the 1^{st} to the 2^{nd} stimuli, but no further amplitude decrease from the 2^{nd} to the 5^{th}. They offer this as evidence against habituation as the origin of the amplitude attenuation but rather '…as a result of the refractory period of those assemblies of neurons involved in the generation of the observed signal" (p. 248). Whether this interpretation will stand the test of time or other explanations will become more illuminating and explanatory is yet to be seen.

Summary: Pain is essential for an organism's immediate awareness about actual or threatening injury to enable protective behavior. However, being overwhelmed by pain reduces an individual's ability to respond appropriately. Thus a balance in pain tolerance is indicated, placing importance on understanding greater intolerance to pain. This study supports greater physiological reactivity or a reduction in suppression to a second somatosensory stimulus in those individuals who are intolerant to pain. This reduction may relate to dysfunctional prefrontal-thalamic activity that may involve attentional or pre-attentional processes. Since the term 'gating' is a hypothetical psychological construct that does not elucidate the neural mechanisms involved, perhaps future research will unravel such mechanisms. A better understanding of these processes may lead to better pain modulation so that individuals in the future may be able to regulate more

readily their tolerance to pain and thus reduce the disabling and costly effects that pain can inflict on individuals as well as society.

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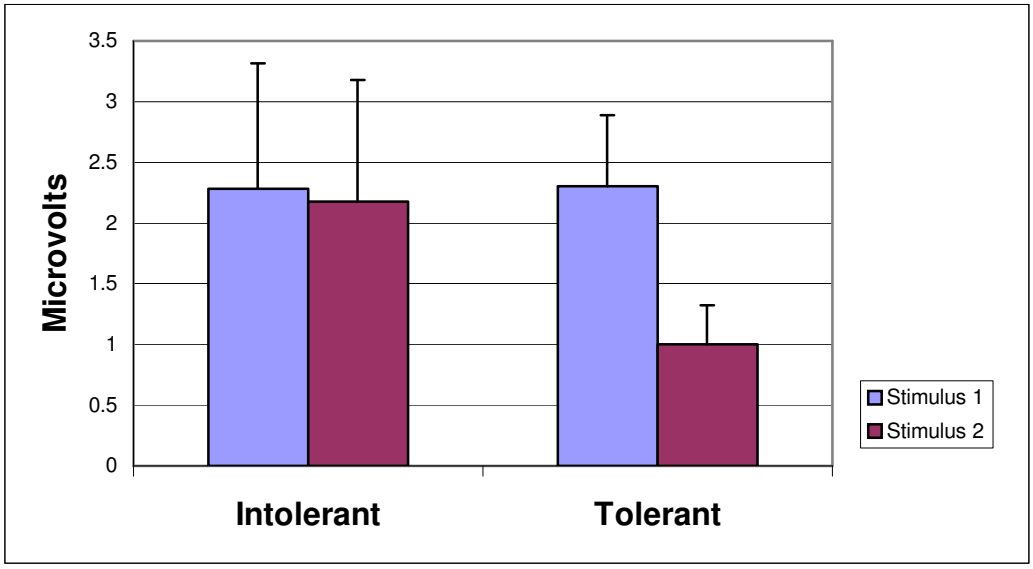

Figure 1. P50 stimulus 1 and stimulus 2 amplitudes (and S.E.) for the intolerant and tolerant pain groups reported in microvolts. Significant differences were revealed for stimulus (S1 > S2, $p < .05$) and S1 and S2 within the tolerant group ($p < .01$).

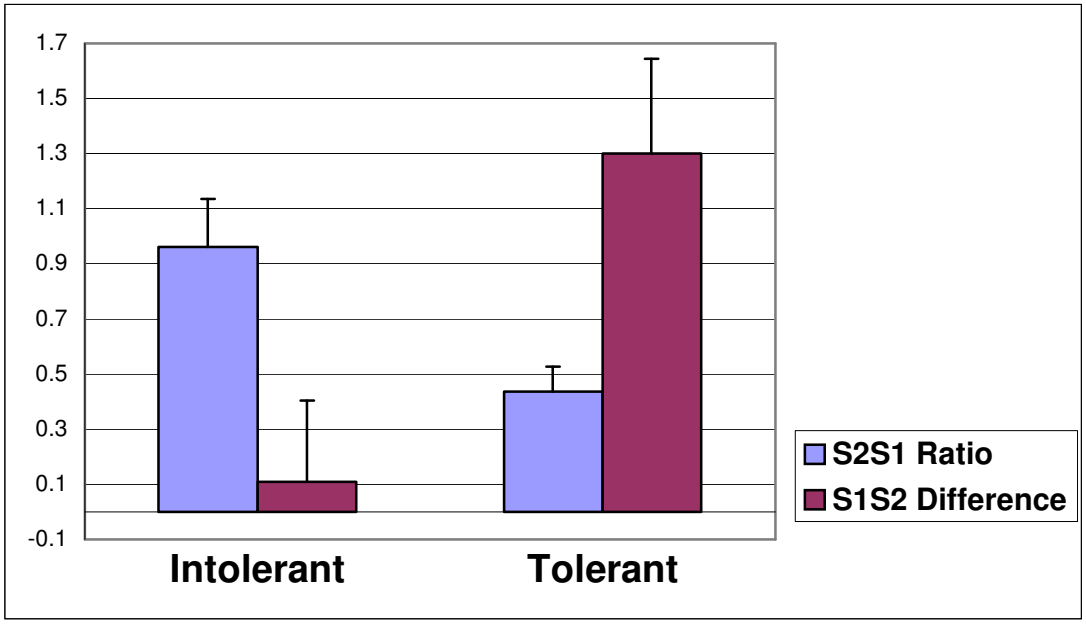

Figure 2. The S2/S1 ratio and S1-S2 difference (and S.E.) reported for the pain tolerant and intolerant groups. Both the ratio and the difference are significant at $p < .05$.
*Note: The larger the ratio and the smaller the difference, the less the sensory gating.

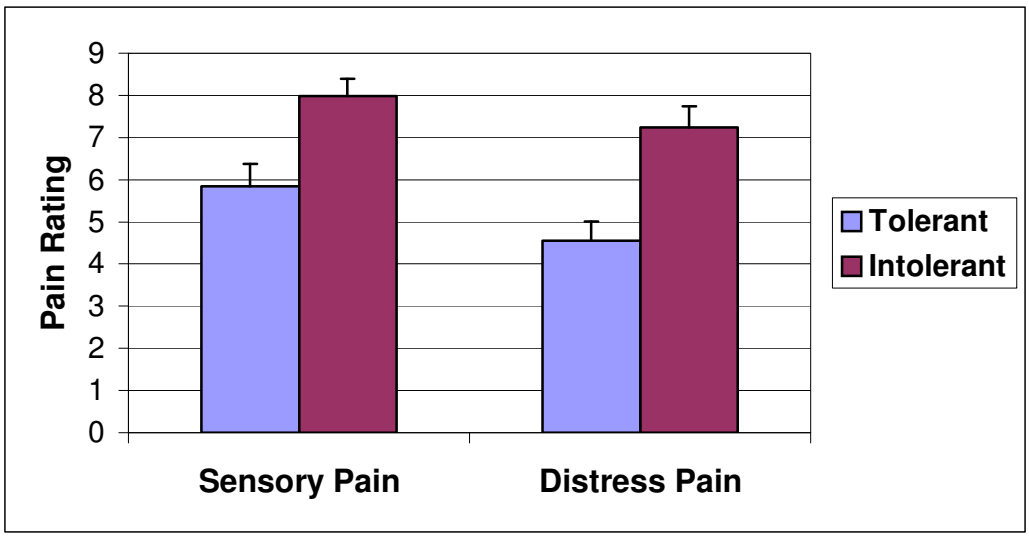

Figure 3. Averaged sensory and distress pain ratings (and S.E.) for TOL and INTOL groups. There were significant differences between TOL and INTOL at $p < .01$ for both sensory and distress pain.

Appendix A

Handedness Questionnaire

Subject #: _____

Circle the appropriate number after each item.

	Right	Left	Both
With which hand would you throw a ball to hit a target?	1	-1	0
With which hand do you draw?	1	-1	0
With which hand do you use an eraser on paper?	1	-1	0
With which hand do you remove the top card when dealing?	1	-1	0
With which foot do you kick a ball?	1	-1	0
If you wanted to pick up a pebble with your toes, which foot would you use?	1	-1	0
If you had to step up onto a chair, which foot would you place on the chair first?	1	-1	0
Which eye would you use to peep through a keyhole?	1	-1	0
If you had to look into a dark bottle to see how full it was, which eye would you use?	1	-1	0
Which eye would you use to sight down a rifle?	1	-1	0
If you wanted to listen to a conversation going on behind a closed door, which ear would you place against the door?	1	-1	0
If you wanted to listen to someone's heartbeat, which ear would you place against their chest?	1	-1	0
Into which ear would you place the earphone of a transistor radio?	1	-1	0

#of Right + # of Left = Total Score

_____ + _____ = _____

Is mother left or right hand dominant? _____

Is father left or right hand dominant? _____

*Note: participants were considered right handed with a score of 7 or above (Porac, Coren & Duncan, 1980).

Appendix B

Medical Screening Questionnaire

The following information is required by the Institutional Review Board to screen for possible participation in subsequent EEG studies. We must know if you have had any medical problems that might keep you from participating. It is important that you be as honest as you can. This is kept confidential.

Name_____ Age _____ Sex: Male ___ Female _____

1. Since birth have you ever hand any medical problems? Yes __ No __ If yes, please explain.

2. Since birth have you ever been hospitalized? Yes___ No___ If yes, please explain.

3. Have you ever hit your head and experienced a concussion? Yes ___ No ___ If yes, please explain.

4. Did you ever have problems where you saw a counselor, psychologist or psychiatrist? Yes___ No ___ If yes, please explain.

5. Do you use tobacco (smoke, chew)? Yes ___ No ___ If yes, please explain.

6. Have you had any hearing problems? Yes ___ No ___ If yes, please explain.

7. What is your current weight and height?

8. Do you currently have or have you ever had any of the following? Circle yes or no.

Yes	No	Strong reaction to cold weather
Yes	No	Circulation problems
Yes	No	Tissue disease
Yes	No	Skin disorders (other than facial acne)
Yes	No	Arthritis
Yes	No	Asthma
Yes	No	Lung problems
Yes	No	Heart problems/disease
Yes	No	Diabetes
Yes	No	Hypoglycemia
Yes	No	Hypertension
Yes	No	Low blood pressure

Yes No High blood pressure

Yes No Hepatitis

Yes No Neurological problems

Yes No Epilepsy or seizures

Yes No Brain disorder

Yes No Stroke

If you have circled yes to any of the above conditions, please explain.

9. Have you ever been diagnosed formally to have had:

Yes No Learning deficiency or disorder

Yes No Reading deficiency or disorder

Yes No Attention deficit disorder

Yes No Attention deficit hyperactivity disorder

10. Do you have:

Yes No Claustrophobia (high fear of smaller closed rooms)

Yes No High fear of needles or blood

11. List any over the counter prescription medications you are presently taking:

12. Do you have or have you ever had any other medical conditions that you can think of? If yes, please not them below

Appendix C

Consent Form for Experiment #1: Pain Experiences, Cognitive Processing and Personality Styles

1. PURPOSE OF EXPERIMENT

We are interested in learning more about individual differences in how healthy individuals experience pain and relationships to various psychological and physiological factors. We hope this information will help others in the future learn to seek control over pain. Today you are invited to fill out some questionnaires (they are in the packet and you may look them over before signing this consent form). These questionnaires assess individual differences in and relationships between pain experiences, reactivity to pain, attitudes towards pain, vividness of painful memories, physiological sensitivity, noise sensitivity, emotional intensity, absorptive attention, and personality characteristics. You will also be asked to fill out a short medical questionnaire. If you show no medical problems and continue to be interested, you will be asked to place your hand into ice-cold water. If the water becomes too uncomfortable during immersion, you may remove your hand from the water at any time. You will do this twice. After the completion of this experiment, if you meet certain criteria and are interested, you will be invited to participate in a study of brain dynamics during painful stimulation of your left and right middle fingers.

2. PROCEDURE TO BE FOLLOWED IN THE STUDY:

To accomplish the goals of the study, you will be asked to complete individually a series of self-report instruments that assess your handedness, neurological history (brief), past pain experiences, attentional styles, and personality styles. The experimenter will examine your medical questionnaire to verify that you do not have any medical problems that would preclude you from placing your hand into cold water.

The second part involves placing your hand in ice water for as long as you can bear it. Every 20 seconds you will be asked to report pain and distress being experienced at that time on a scale from 0 (no pain or distress) to 10 (most excruciating pain or distress imaginable). You may take your hand out of the water at any time you desire.

3. ANONYMITY OF SUBMECTS AND CONFIDENTIALITY OF RESULTS:

The results of this study will be kept strictly confidential. At no time will the researchers release your results to anyone without your written consent. The information you provide will have your name removed and only a subject code will identify you during analyses and any write-up of the research. Should you report that you may harm yourself or others (on the Beck Depression Inventory), the researcher has the obligation to break confidentiality and report this information to the appropriate agency.

4. DISCOMFORTS AND RISKS FROM PARTICIPATING IN THE STUDY:

There are minimal risks to you from participation in this study. The questions may remind you of things that could make you feel uncomfortable. Should you wish to discuss material covered in the questionnaires, we recommend that you contact the local crisis center, RAFT, or the student counseling center.

If you place your hand into the cold water, you will experience pain and this will be uncomfortable. If the pain is too uncomfortable you may stop at any time. You have been chosen as having no known medical problems that might interfere.

5. BENEFITS OF THIS PROJECT:

No personal benefit is promised you. Your participation in this project today will help advance the scientific knowledge of the interrelationships between responses on these questionnaires and pain responsivity.

6. FREEDOM TO WITHDRAW:

Your are free to withdraw from this study at any time without penalty.

7. COMPENSATION:

Participation will be totally voluntary. You will receive one hour's credit for participation in this project regardless of whether or not you complete the experiment today. Please check your course syllabi for information as to worth of this extra credit and for alternative ways by which to receive extra credit.

8. USE OF RESEARCH DATA:

The information from this research may be used for scientific or educational purposes. It may be presented at scientific meetings and/or published and reproduced in professional journals or books, or used for any other purpose that Virginia Tech's Department of Psychology considers proper in the interest of education, knowledge, or research.

9. APPROVAL OF RESEARCH:

This research project has been approved by the Human Subjects Committee of the Department of Psychology and by the Institutional Review Board of Virginia Tech. You will receive a copy of this consent form.

10. SUBJECT'S PERMISSION:

I have read and understand the above description of the study. I have had an opportunity to ask questions and have had them all answered. I hereby acknowledge the above and give my voluntary consent for participation in this study. I further understand that if I participate I may withdraw at any time without penalty. I understand that should I have any questions regarding this research and its conduct, I should contact any of the persons named below:

Primary Researcher: Helen J. Crawford, PhD.	Phone number
Co-Researcher: Susan Daugherty, M.S. graduate student	Phone number
Chair, Human Subjects Committee: D. Harrison, Ph.D.	Phone number
Chair, Institutional Review Board: David Moore	Phone number

SUBJECT'S SIGNATURE: _____

SUBJECT'S PHONE: _____

DATE: _____

You will be given a copy of this consent form.

Appendix D

Instructions for Cold Pressor Task

"As you know, this experiment will concern assessing pain levels to experimental pain that uses cold ice water. It has been shown that one can place one's hand in such cold water for 15 minutes without producing any harm as long as you do not have any medical difficulties. Can you think of anything, such as arthritis or skin disorders or heart problems that would stop you from putting your hand into cold water?" (Verify medical questionnaire).

"I want you to leave your hand in the ice water as long as possible. When you cannot endure it any longer, please take your hand out immediately."

"When I say "report", please give me a rating (0-10 scale) for two types of pain: sensory pain and distress pain. You can distinguish between the cold of the water and the pain produced. The sensory pain is related to how physically painful the cold of the arm is. The second type of pain is distress or annoyance that differs from sensory pain. It is emotional and motivational, the suffering component of pain, how much you would like to be rid of the pain. For example, you probably have woken up in the morning and had a toothache. It is a moderate level of sensory pain, but you figure it will go away so you are not distressed. By the early afternoon you still have the same level of sensory pain, but now you are much more distressed. So there are two components of pain: the sensory pain and the distress pain. They can vary together or separately with any pain. Do you understand the difference?" (Discuss if necessary)

"You will immediately report first the sensory pain and then immediately the distress pain each time I say, "report". Do not hesitate in your reporting. You are to look at the scale in front of you while maintaining your attention on your hand in the water." (Review the scale in front of the subject)

"Remember, I want you to leave your hand in the ice water as long as possible. When you cannot endure it any longer, please take your hand out immediately."

(Subject keeps eyes open and looks at the rating scale. Rating starts when the subject puts his hand into the ice water.)

Rating is at 0, 20, 40, 80, 100, 120, 140, 180 seconds, three minutes total, and then experimenter takes hand out of water for subject. Subject dries it with a towel.

Appendix E

Pain Rating Scales

Pain Intensity Scale		Pain Distress Scale	
0	no change	0	no change
1	barely cool, no pain	1	comfortable
2	cool, no pain	2	discomforting
3	cold, no pain	3	unpleasant
4	slight pain	4	irritating
5	mild pain	5	distressing
6	moderate pain	6	miserable
7	moderately-strong pain	7	awful
8	strong pain	8	horrible
9	severe pain	9	agonizing
10	unbearable pain	10	excruciating

Appendix F

Consent Form for Experiment #2: Somatosensory Event-Related Potentials to Noxious Stimuli and Auditory Sensory Gating in Pain Tolerant and Pain Sensitive Individuals

1. PURPOSE OF EXPERIMENT:

Based upon several criteria, you have been invited to assess your brain wave activity that is recorded with an electroencephalographic machine. The purpose of this experiment is to examine somatosensory evoked potentials and EEG brain wave activity during and following stimulations to the middle finger of your left and right hands under differing conditions. You will be given 6-7 minutes of electrical stimulations (6-10 seconds apart) to your third finger of the left and right hands. The stimulation will be quite short in duration and will feel like a moderately painful electric shock. The equipment is completely grounded and isolated and therefore safe; it has been approved for human use. The levels will be determined at the beginning of the experiment by presenting very low level stimulations and enhancing them in intensity to reach your rating of the stimulation as moderately painful, but bearable. In addition, you will be given pairs of tones to listen to for approximately 7 minutes.

2. PROCEDURE TO BE FOLLOWED IN THE STUDY:

To accomplish the goals of this study, you will be asked to put on an electrode cap which has electrodes permanently placed in the cap; the cap is like a swimming cap and may be slightly uncomfortable as it is attached to a harness that is fastened lightly around your chest to hold the cap in place. We will also place electrodes on your left and right ear lobes, and four near your eyes to measure eye movements. The somatosensory electrodes will be placed on your middle finger of your left and right hands and held in place by a band that goes around the finger. Your skin will be cleaned with a mildly abrasive cleanser and may cause slight discomfort. If you have skin allergies, we will only use alcohol as a cleaner. To insure your safety from infection, the experimenter has thoroughly sanitized the electrodes and washed the electrode cap. The experimenter will wear clean rubber gloves while attaching the electrodes.

Following this, you will be given several short sets of stimulations to determine where the pain is perceived as moderately painful but bearable. We will verify your EEG with a

trial of 5 stimulations. After that you will be given the regular set of stimulations, at the predetermined level you chose. Afterwards, we will discuss your experiences and you will be able to see your recorded brain activity.

This experiment will take approximately two hours.

You are to report to the experimenter if you are on any medications or under doctor's treatment. You are not to have ingested alcohol in the last 24 hours. You are to report any recent history of using tobacco, either smoked or chewed. Your are to inform the experimenter of any skin reactions from lotions or anything else you have had in the past. You are to inform the experimenter of all medical and psychiatric problems that you have had that might interfere with the experiment.

3. ANNONYMITY OF SUBJECTS AND CONFIDENTIALITY OF RESULTS:

The results of this study will be kept strictly confidential. At no time will the researchers release your results to anyone without your written consent. The information you provide will have your name removed and only a subject code will identify you during analyses and any write-up of the research. Should you report that you may harm yourself or others (on the Beck Depression Inventory), the researcher has the obligation to break confidentiality and report this information to the appropriate agency.

4. DISCOMFORTS AND RISKS FROM PARTICIPATING IN THE STUDY:

There are minimal risks to you from participation in this study. You will experience pain and this will be uncomfortable. If the pain is too uncomfortable you may stop at any time. You have been chosen as having no known medical problems that might interfere in your participation in the research. In addition, you do not know of any medical problems that might interfere in your participation.

5. BENEFITS OF THIS PROJECT:

No personal benefit is promised you. Your participation in this project today will help advance the scientific knowledge of the interrelationships between your physiological reactivity to the painful stimuli and prior measures taken in Experiment 1.

6. FREEDOM TO WITHDRAW:

You are free to withdraw from this study at any time without penalty.

7. COMPENSATION:

Participation will be totally voluntary. You will receive two hours credit for participation in this project regardless of whether or not you complete the experiment today. Please check your course syllabi for information as to worth of this extra credit and for alternative ways by which to receive extra credit.

8. USE OF RESEARCH DATA:

The information from this research may me used for scientific or educational purposes. It may be presented at scientific meetings and/or published and reproduced in professional journals or books, or used for any other purpose that Virginia Tech's Department of Psychology considers proper in the interest of education, knowledge, or research.

9. APPROVAL OF RESEARCH:

This research project has been approved by the Human subjects Committee of the Department of Psychology and by the Institutional Review Board of Virginia Tech. You will receive a copy of this consent form.

10. SUBJECTS'S PERMISSION:

I have read and understand the above description of the study. . I have had an opportunity to ask questions and have had them all answered. I hereby acknowledge the above and give my voluntary consent for participation in this study. I further understand that if I participate I may withdraw at any time without penalty. I understand that should I have any questions regarding this research and its conduct, I should contact any of the persons named below:

Primary Researcher: Helen J. Crawford, PhD.	Phone number
Co-Researcher: Susan Daugherty, M.S. graduate student	Phone number
Chair, Human Subjects Committee: D. Harrison, Ph.D.	Phone number
Chair, Institutional Review Board: Thomas Hurd	Phone number

SUBJECT'S SIGNATURE: _____

SUBJECT'S PHONE: _____

DATE: _____

You will be given a copy of this consent form.

CURRICULUM VITA

SUSAN ATLEE DAUGHERTY, PhD, LPC

PERSONAL INFORMATION

School address: Department of Psychology
Virginia Polytechnic Institute and State University
Blacksburg, Virginia 24061-0436
E-mail: sdaugher@vt.edu

Home Address: 3671 Bower Road
Roanoke, Virginia 24018

EDUCATION

Virginia Polytechnic Institute and State University, Blacksburg, Virginia, 1999-present Accepted into PhD. Program, Psychological Sciences. **PhD**, December 2005, Psychology.
Dissertation: Neurophysiological Differences in Pain Reactivity: Why Some People are Tolerant to Pain

Virginia Polytechnic Institute and State University, Blacksburg, Virginia, 1986 Accepted into PhD program in Clinical Psychology, terminated due to pregnancy.

University of Illinois at Chicago Circle, Chicago Illinois, 9/1974-5/1975 Undergraduate Psychology, **MA,** 1980 Clinical /Physiological Psychology

Wayne State Medical School, Detroit, Michigan, 9/1973-5/1974 Medical Microbiology and Immunology

Albion College, Albion Michigan, **BA**, Cum Laude, 1973 Major: Biology

Honors: Mortar Board, Dean's List.

Spent one year abroad-India

LICENSURE

Licensed Professional Counselor, Virginia Board of Professional Counselors, 1991.

RESEARCH ACTIVITIES

Virginia Tech: 1999-present

Alternate Methods of Pain Management in Elderly Populations project: Participated in developing project guidelines and direction, performed literature searches, assessed research instruments,

Pain Tolerance/Intolerance: Conducted research with 60 subjects in pain tolerant/intolerant study. Included soliciting subjects and measuring pain tolerance and intolerance using ice water, administering 11 biopsychosocial questionnaires and analyzing the data for the 60 subjects.

Pain: solicited subjects and conducted pain research using electrical stimulation and EEG for 20 subjects

Music, Mood and EEG: (extended class project) Developed project, solicited subjects, conducted emotion research using music, script and EEG and analyzed data for over 20 subjects

FMRI: Participated as subject in fMRI study in Charlottesville, attended fMRI workshop, identified localization of brain activity using Talairach coordinates on fMRI scans, analyzed data

Hypnosis: Trained and assisted in conducting group hypnosis, conducted group hypnosis using the Harvard Scale for over 60 subjects, scored hypnosis screening instruments

Hypnosis Questionnaires: Prepared packets of biopsychosocial questionnaires, scored and analyzed for over 100 subjects

Tobacco study: attended lab meetings, helped in running control subjects using electrical pain stimulation and EEG

Training: Trained undergraduates in various aspects of EEG, hypnosis, and pain research

PUBLICATIONS

Daniel J. Cox, PhD, **Susan A. Daugherty LPC,** Lee Ritterband Ph.D., Boris P. Kovatchev, PhD, Linda A. Gonder-Frederick, PhD, William L. Clarke, MD. *The Nature Of Driving Mishaps Among Adults With Type 1 Diabetes Mellitus (T1DM).* (Submitted for publication, July 2005.)

PRESENTATIONS

Helen J. Crawford, James E. Horton, Greg S. Harrington, Traci Hirsch Downs, Datrina Fox, **Susan Daugherty**, J. Hunter Downs III. **Attention and Disattention (Hypnotic Analgesia) to Noxious Somatosensory TENS Stimuli: fMRI Differences in Low and Highly Hypnotizable Individuals.** (Paper) for Human Brain Mapping Conference, San Antonio, TX, June 12-16, 2000.

Joe McArdle, **Susan Daugherty**, and Helen J. Crawford. **Earlobe vs. Nose Reference: Differential Impact on Auditory and Visual Odd-Ball ERPs**. (Poster) presented at APS Conference, June 9, 2000, Miami Florida.

Jennifer N. Alfaro, **Susan AtLee Daugherty** and Helen J. Crawford. **Music, Mood and EEG: An Analysis of Mood Induction and Hemisphericity.** Poster presented at SPR 41st Annual Meeting in Montreal, Canada, October 10-14, 2001.

Susan AtLee Daugherty, Jennifer N. Alfaro and Helen J. Crawford. **Effects of Music on Brain Activity: Music vs. Verbal Script Induction of Self-Generated Emotion.** Poster presented at Virginia Tech GSA 18th Annual Research Symposium, April 2, 2002.

Susan AtLee Daugherty and Helen J. Crawford. **Why Are Some People Intolerant to Pain?** Poster presented at Virginia Tech GSA 18th Annual Research Symposium, April 2, 2002.
Awarded 2nd place for Social Sciences Category

HONORS

Inducted into the **Honor Society of Phi Kappa Phi** for academic excellence and sound character, April 2002.

PROFESSIONAL EXPERIENCE

2005: Part-time position administering QEEG and other neuro/psychological tests.
1999-2002: Graduate Teaching assistant. Two semesters as recitation instructor for Introductory Psychology, Two semesters as Advanced cognitive Psychology laboratory instructor, one semester as Advanced Developmental Psychology laboratory instructor, and one semester Advanced Learning Psychology laboratory instructor

1994-1999: Private Practice in Roanoke, Virginia. Licensed Professional Counselor. Assessed clients using interview and observation. Diagnosed clients using DSM-III and IV. Performed individual and group therapy using an eclectic approach, including client centered, cognitive, behavioral, and play therapy. Managed cases by consulting with

support persons including doctors, school counselors, principals and teachers, other family members and the court system. Made referrals when appropriate.
1995-1996: The Family Place with Commonwealth Catholic Charities. Licensed Professional Counselor. Same counseling responsibilities as above
1989-1994: Lewis-Gale Hospital Business Health Services. EAP Counselor. Provided assessment, counseling and referral to a wide range of clients, especially children. Trained employees and supervisors in the appropriate use of EAP. Acted as liaison between companies and EAP. Wrote reports reflecting quarterly and annual usage rates. Developed and presented parenting seminar. Developed and marketed assertiveness and grief groups Provided clinical supervision for EAP staff. Developed forms for statistical use. Provided counseling at various health screenings, especially related to stress.
1984-1985: Parents United. Group Counselor for abused children and siblings of abused teens.
1983-1986: Comprehensive Counseling Services. Child Psychotherapist. Same counseling responsibilities as above.
1981-1983: Mental Health Services. Child Psychotherapist. Same counseling responsibilities as above.

PROFESSIONAL DEVELOPMENT

Beyond Psychology: Expanding Our Models of Relationship, Change and Consciousness, 28th annual Networker Symposium, Washington, DC
Expanding the Frontiers of Pain, Wake Forest University
Using Matlab, Virginia Tech
The fMRI Experience IV, Bethesda, Maryland
Winter Brain Meeting,
American Psychological Society 12th Annual Convention
Workshop on Functional Neuroimaging and Theories of Cognitive Dynamics, Duke University
Cognitive Neuroscience society Annual Meeting

Attentional Processes In Perception and Working Memory Symposium, Satellite Symposium of the Cognitive Neuroscience Annual Meeting

Brain and Communication: Conscious and Unconscious Processing, Satellite conference to the cognitive Neuroscience Society Meeting

Ongoing Psychodrama Group for Personal and Professional Development, Blue Ridge Human Relations Training Institute

Neuropsychological Assessment of Brain Injured Children, Dr. Arthur MacNeil Horton, The Fielding Institute,

Frontal Lobes, Executive Functions and Human Behavior, Dr Elkhonon Goldberg. The Fielding Institute

Theory and Methods in the Assessment of Normal and Disordered Attention, Dr. Allen Mirsky, The Fielding Institute

Supervision Group Focusing on Psychotherapy with Children, Stephanie Pratola, Roanoke, Virginia,

Object Relations, Betty Etzler, Roanoke, Virginia, workshops

Creativity and Madness, American Institute of Medical Education, Santa Fe, New Mexico

Adlerian Play Therapy, Terry Kottman, Washington, D.C.

Healing the Incest Wound, Adult Survivors in Therapy, Christine Curtois, Roanoke, Virginia

Advanced Treatment Issues in Child Sexual Abuse, Eliana Gil, Hampton, Virginia

Play Therapy, Group Play Therapy, Filial Therapy, Gary landreth, Greensboro, North Carolina

Tears of the Children, Mental Health Association of the Roanoke Valley

Co-dependency, Facts, Fiction or Fantasy, Mukesh Patel, Roanoke, Virginia

DEPARTMENTAL COLLOQUIA ATTENDED

The Developmental Psychopathology of Anxiety: Experimental and Clinical Findings, Dr. Peter Muris

Crime, Brain Mechanisms, and Development, Dr. Arian Raine

Scents and Sensibility: The Intersection of Odor and Cognition, Dr. Tyler Lorig

Cognitive-Behavioral Treatment of School-Refusing Children: The Perspectives from Down Under, Neville J. King

ADHD Research and Intervention in Southeastern Virginia, Dr. Gretchen LeFever

Infant EEG and the Development of Internally Controlled Attention, Dr. Tatiana Stroganova

Sleep Disorders, Donald Zedalis

Treating Explosive, Non-compliant Children, Ross Greene

Lateralization and Negative Affect in Visual Formesthesias, Jason Parker

Self-Regulation in Behavioral Development, Dr. Susan Calkins

OCD in Children, David Evans

Why Primates Don't Have Language

Memory Functioning in Adults, Richard McNally

Psychosocial Treatments for Generalized Anxiety Disorder, Tom Borkovec

Social Development in a Monogamous Primate, Kurt Hoffman

Mediators and Moderators: Who's on First? Grayson Holmbeck

Visual Processing, Physics dept. colloquium

Family Relationships and Psychosocial Adjustment in Adolescents with Spina Bifada, Grayson Holmbeck

RELEVANT COURSE WORK

Seminar in Neurocognition, Seminar in Frontal Lobe Development, Seminar in Neurocognition and EEG, seminar in EEG Oscillations, Statistics for social Science Research I and II, Research Methods, Proseminar in Learning, Neurochemical Regulation, Biological Bases of Behavior, Cognitive Psychology, Developmental Psychology

PROFESSIONAL AFFILIATIONS

Southwest Virginia Pain Initiative

American Psychological Society

Cognitive Neuroscience Society

Society for Psychophysiological Research