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Factors that Contribute to Susceptibility of the Placebo/Nocebo Effect in Experimentally Induced Ischemic Arm Pain

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Abstract

Placebo's (positive expectancies producing positive outcomes) and nocebo's (negative expectancies producing negative outcomes) are real and measurable effects. Real as these effects may be, predicting individuals that may be susceptible to placebo/nocebo effects has been inconsistent. The present study examined whether measures designed to assess somatization (MSPQ), catastrophizing (PCS) and childhood trauma (CTQ) would predict placebo and nocebo membership. In addition, measures designed to assess anxiety (ASI) anxiety about pain (PASS) and depression (BDI) were evaluated to determine whether anxiety or depression mediates responsiveness. The Hargreaves Thermal Withdrawal test and the submaximal effort tourniquet technique were employed as pain vehicles for the measurement of group differences. No significant effects of planned analyses were observed. However, unplanned analyses of childhood trauma subscales indicated that physical and emotional abuse predicted placebo response. Additionally, emotional neglect trended toward predicting nocebo responsiveness. These results indicate that further studies, correcting for weaknesses, is warranted.

Keywords: placebo, nocebo, somatization, catastrophizing, childhood trauma, anxiety

Introduction

Placebo (I will please) and nocebo (I will harm) are real phenomenon that have been extensively studied but are not well understood (Benedetti et al. 2007). The term placebo is practically ubiquitous in contemporary language and has a lengthy history. The use of the word placebo dates back several centuries in medical literature with the first reported controlled placebo study conducted in 1799 (Price, Finniss, & Benedetti, 2008). Geers, Helfer, Kosbab, Weiland and Landry (2005) pointed out that "placebos have been described as one of the most powerful agents of symptom relief in medicine" and argue that prior to the beginning of the 20th century most treatments for illness and disease were placebo.

Nocebo, on the other hand, is a newer term that is rarely used in lay language or academia. According to Benedetti and Amanzio (1996) the term nocebo was introduced by Kissel and Barrucand in 1974 to distinguish "the pleasing and salubrious effects of placebo from the noxious effects." This distinction, though important, does little to eliminate confusion between the two terms. For example, if one does a PubMed search for nocebo, large numbers of papers will be found with placebo in the title and nocebo in the text. It seems clear that the field generally considers nocebo to fall under the umbrella of placebo, an assumption that may be dispelled by considering precise definitions of the two terms. As noted by Grünbaum (1981), a fundamental problem to advancing the field of placebo research has been one of definition.

Important Distinctions

The author will begin by clarifying the difference between placebo and the placebo effect. While it may seem intuitive that there is a difference, the distinction is

often muddled or missing in related literature. For example, Olchansky (2007) states a "placebo is a sham, often a pill, but any intervention purported to be therapeutic. Without direct physiologic or pharmacologic activity, a placebo somehow provides benefit or apparent benefit. Nocebo is a sham, without direct physiologic or pharmacological activity, that causes harm or apparent harm." Note the lack of distinction for placebo effect.

On the other hand, Stewart-Williams and Podd (2004) posited the following definitions that included such a distinction. "A *placebo* is a substance or procedure that has no inherent power to produce an effect that is sought or expected." Followed by a definition for placebo effect, "A *placebo* effect is a genuine psychological or physiological effect, in a human or another animal, which is attributable to receiving a substance or undergoing a procedure, but is not due to the inherent powers of that substance or procedure."

Benedetti, Carlino and Pollo (2010) echo the immediately preceding definition by stating "A real placebo effect is a psychobiological phenomenon occurring in the patient's brain after the administration of an inert substance, or of a sham physical treatment such as sham surgery, along with verbal suggestions (or any other cue) of clinical benefit." Colloca and Benedetti (2007) then state for nocebo and nocebo effect the following, "If positive verbal suggestions, which are typical of the placebo effect, are reversed in the opposite direction, a nocebo effect can be obtained. Therefore, the study of the nocebo effect is the study of the negative psychosocial context around the patient and the treatment, and its neurobiological investigation is the analysis of the

effects of this negative context on the patient's brain and body." In short, nocebo is the opposite of placebo either with pill or procedure and its observed effect or effects.

Taken together, the Stewart-Williams and Podd definitions provide the most complete framework from which to work. Now one only needs to make a minor amendment to clarify the meaning of nocebo and nocebo effect:

> A *placebo* or *nocebo* is a substance or procedure that has no inherent power to produce an effect that is sought or expected.
>
> A *placebo effect* is a genuine *positive* psychological or physiological effect, in a human or another animal, which is attributable to receiving a substance or undergoing a procedure, but is not due to the inherent powers of that substance or procedure. A *nocebo effect* is a genuine *negative* psychological or physiological effect, in a human or another animal, which is attributable to receiving a substance or undergoing a procedure, but is not due to the inherent powers of that substance or procedure.

The author argues that the amendment is necessary because it provides effect directionality and thus, more clearly, delineates placebo from nocebo. Now that working definitions for placebo and nocebo have been established, the remaining discussion will encompass a brief review of issues related to placebo/nocebo effects, pain and its relationship to the placebo response.

What is known: A brief review.

Much of the knowledge of the placebo effect comes from pain studies with and without neuropharmacological approaches (Amanzio and Benedetti, 1999; Benedetti & Amanzio, 1997; Hoffman et al., 2005). The literature generally suggests that placebo and nocebo responses are a function of conditioning and/or expectation (Benedetti et al., 2003; 2007; Colloca and Benedetti, 2007; Colloca et al. 2008; Enck et al. 2008; Geers et al., 2006; Klosterhalfen and Enck, 2008; Klosterhalfen et al., 2009; Olshancky,

2007; Stewart-Williams, 2004; Stewart-Williams and Podd, 2004; Voudouris et al., 1990),with reward, social learning and memory also implicated (Benedetti, Carlino & Pollo, 2010).

Expectancy

Expectancy theory has gained ground in recent years, largely supplanting similar mental constructs such as faith and hope (Peck & Coleman, 1991). Expectancy as a construct embodies an intuitive understanding of what the placebo effect is, “A placebo produces an effect because the recipient expects it to. The placebo elicits an expectation for a particular effect, and the expectation produces that effect” (Stewart-Williams and Podd, 2004).

Benedetti, Carlino & Pollo (2010) highlight two studies that demonstrate how strongly expectation is linked to pain and placebo responsiveness. Both studies investigated the role of the prefrontal cortex and placebo responsiveness. In the first study, Benedetti et al. (2006) studied Alzheimer patients in initial stages and after one year to evaluate the effectiveness of a placebo component of therapy the patients were receiving. The placebo component of therapy was correlated with a cognitive status as assessed by the Frontal Assessment Battery (FAB) test and functional connectivity among different brain regions assessed by electroencephalographic connectivity analysis. It was found that patients with lower FAB scores had lower placebo treatment responsiveness. Additionally, it was observed that disruption of placebo responsiveness occurred at the same time that prefrontal lobe connectivity to the rest of the brain was reduced.

Next, Krummenacher et al. (2010) used repetitive transcranial magnetic stimulation (rTMS) to transiently disrupt right and left dorsolateral prefrontal cortex (r/l dlpfc) functioning in a heat pain paradigm. This study found that placebos significantly increased pain threshold/tolerance and that disruption of r/l dlpfc using rTMS completely blocked placebo analgesia. In other words, “no prefrontal control, no placebo response” (Benedetti et al., 2010).

Conditioning

Classical conditioning comprises the second major theoretical approach to the placebo effect. In general, applying conditioning to the placebo effect requires the drug or active ingredient to be the unconditioned stimulus (US) and the unlearned response to the active ingredient to be the unconditioned response (UR). In the course of any number of paradigms, the US would be paired with a neutral stimulus such as pill casings, syringes or even to objects, places, people and the procedures themselves. Through repeated associations with the US the neutral stimuli become conditioned stimuli (CS) capable of producing an effect similar to that of the active ingredient, which would be considered a conditioned response (CR). Thus, in a conditioning framework the placebo would be considered the CS and the placebo effect the CR (Stewart-Williams and Podd, 2004).

Much of the support for the classical conditioning paradigm comes from research on nonhuman animals and has been demonstrated with a variety of drugs and systems. Hernstien (1962) demonstrated that rats conditioned with injections of amphetamines when injected with saline exhibited behavior similar to that seen by amphetamine injection. Ader and Cohen (1975) paired novel saccharine flavored liquid with

cyclophosphamide, an immunosuppressant. After several pairings, the saccharine solution (CS, placebo) would elicit immunosuppression (CR, placebo effect). This was groundbreaking work as it was not generally believed at the time that conditioning could affect the immune system (Stewart-Williams and Podd, 2004).

As with many academic topics, scholars tend to prefer one theory over another, in this case pitting expectancy (Kirsch, 1991) against conditioning (Voudouris et al., 1989; 1990). However, as with many dichotomies there is often the overlooked third choice of both. In 2003, Benedetti et al. demonstrated in experimental pain models and Parkinson models that "conditioning is actually mediated by expectations and that expectations do not affect conditioned responses." While it may not be clear what relationship expectancy and conditioning might have with each other, the literature shows that expectancy or previous exposure (conditioning) or both are necessary for the placebo effect to take place.

Mechanisms and diseases

Pain, as previously mentioned, is the paradigm utilized most when studying placebo and nocebo effects. It provides an easy platform from which to manipulate variables. This flexibility has enabled researchers to articulate the neurological mechanisms involved with pain and placebo/nocebo responses. It has been demonstrated placebos activate endogenous opioids (analgesia) that decrease pain response and nocebos activate an opponent hyperalgesic nonopioid system (cholecystokinin, CCK) that increase pain responsiveness (Amanzio and Benedetti, 1999; Benedetti, 2007; Benedetti & Amanzio, 1997; Benedetti et al., 2007; Colloca and

Benedetti, 2007; Colloca et al., 2008; Enck et al., 2008; Klosterhalfen and Enck, 2008; Kong et al., 2008).

Though pain has been one of the most intensively studied areas of placebo and nocebo, a number of other conditions have been studied using a placebo paradigm. As a result, researchers are better able to articulate the mechanisms involved. Next to pain, Parkinson's disease has been well described and studied in placebo settings. It is generally thought to generate an expectation induced release of dopamine in the striatum and recorded changes of firing patterns of sub-thalamic nucleus neurons as a result have been observed (Benedetti et al., 2004). According to Benedetti's (2008) review of placebo and placebo effects across diseases and treatments, depression has differential metabolic responses in different brain regions, thought to be related to inhibition of serotonin reuptake. Furthermore the review showed that addiction had demonstrated changes in metabolic activity in various brain regions and the cardiovascular system has demonstrated reductions of β-adrenergic activity, all in response to placebo. Additionally, it was also shown that conditioning of opioid receptors in respiratory centers has been seen as a result of pharmacological preconditioning and the immune system has been documented to respond to pharmacological preconditioning as well, especially to immunosuppressive drugs. Finally, it was reported that conditioning of some hormones has been observed for the endocrine system as a result of pharmacological preconditioning with 5-HT receptor agonists.

Arguments against the placebo effect

Despite the wealth of evidence documenting real placebo and nocebo effects, it is important to note that the literature is not consistent. Three meta-analytic studies have shown that depending on design placebo effect sizes can range from small in placebo only treatment designs (Hrobjartssen & Gøetsche, 2001; 2004) to large effect sizes in analgesic pain studies (Hrobjartssen & Gøetsche, 2006). These studies suggest that many placebo effects can be attributed to poor study design, spontaneous remission and regression to the mean and is, therefore, not as ubiquitous as the literature might suggest or even non-existent. Though it is important to note that poor design, remission and statistical regressions could influence the effect size of placebo response, it is also important to note that these meta-analyses have been challenged on a number of methodological issues. The primary complaint was one of directly comparing conditions that are not readily comparable (Meissner et al., 2007; Stewart-Williams and Podd, 2004). Regardless of the effect size that may or may not be observed in a particular set of studies it is clear that the literature as a whole considers the placebo and nocebo effects to be real effects and one of serious academic inquiry.

Susceptibility to the placebo and nocebo effect

Scholars like Liberman (1968) and Jospe (1978) have endeavored to find evidence of a placebo-prone personality. The results, however, have been generally weak and insignificant (Gelfand, Gelfand & Rardin, 1965; Shapiro and Shapiro, 1997; Turner et al., 1994) or inconsistently present across different trials (Kaptchuk et al, 2008). Geers et al. (2005) suggested that basic methodological problems, poor instrument reliability and factors such as spontaneous remission or regression to the

mean rather than a placebo effect may be impacting whether or not placebo personality traits or situations can reliably emerge. These are the same problems mentioned in the studies by Hrobjartsson and Gøtzsche (2001, 2004, 2006) and recognized by others (Stewart-Williams, 2004; Stewart-Williams and Podd, 2004; Enck, Benedetti & Schedlowski, 2008; Benedetti, Carlino & Pollo, 2010).

The literature is clear, however, that placebo responders do exist. Kosterhalfen and Enck (2008) report that the overall placebo response rate to be around 40%, with variations on response rates depending on the disorder examined. For example, response rates of 29% in depression and 21% in migraine prophylaxis were reported while response rates of 26.9% to 56% were found in pain studies (Price, Finniss & Benedetti, 2008) and 75% placebo response rates found in a metaanalytic study of anti-depressive medication trials by Kirsch and Sapirstein (1998).

Recently, two genetic studies have tried to identify placebo responders. One study examined genetic variants related to serotonin and its role in placebo responding and social anxiety. It was found that only subjects homozygous for the long allele of the 5-HTTLPR (serotonin transporter-linked polymorphic region) or the G variant of the TPH2 (tryptophan hydroxylase-2) gene promoter G-703T exhibited reduced stress related activity in the amygdala during placebo response. Additionally, the TPH2 polymorphism was found to be a significant predictor of clinical placebo response (Furmark et al. 2008). The next genetic study examined the relationship between placebo responsiveness and polymorphisms in genes encoding for the monoamines catechol-*O*-methyltransferase (COMT) and monoamine oxidase A (MAO A) in participants with major depressive disorder. It was found that individuals with G or G/G

forms of MAO A had significantly lower magnitude of placebo response compared with other genotypes and that individuals with the ValMet COMT polymorphism showed a trend toward lower magnitude of placebo response (Leuchter et al. 2009). Exciting as finding placebo responders through genetic techniques may be additional studies are needed to confirm and elaborate these results.

In General, research that utilizes placebo is assessing medical treatment effectiveness by comparing active treatment groups with placebo groups but not with a no-placebo control group (Geers et al., 2006; Ader, 2000). Less than 4% of placebo studies have included a no-placebo control group in which to evaluate the effect claimed (Ernst and Resch, 1995; Fisher, 2000; Geer et al., 2005). A major problem with omitting a no placebo group is that it calls into question the comparative accuracy of the effect sizes observed and reported in such groups. Given this problem, the certainty that no consistent placebo responder can be found is called into question.

Pain as a Vehicle for Understanding Placebo and Nocebo

Pain is mentioned throughout this paper as the most understood and articulated modality for placebo and nocebo effects. It is a useful paradigm for examining these effects as it is easily manipulated in experimental situations and avoids some ethical dilemmas that may be seen in other placebo/nocebo studies (e.g. giving suggestions of symptom worsening to major depressive individuals). It is necessary then to discuss briefly pain and factors that are known to influence it.

The International Association for the study of Pain (IASP) has defined pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage” (Merskey and Bogduk, 1994).

Loeser and Melzack (1999) describe three broad categories of pain. 1) Transient pain, which is elicited by activation of nociceptive transducers in the skin and other tissues of the body but do not require tissue damage. This type of pain is ubiquitous in daily life and is rarely a cause in seeking health care. 2) Acute pain, which is activated by substantial injury of bodily tissue and the activation of nociceptive transducers at the local site of tissue damage. Individuals typically seek medical care for this type of injury. 3) Chronic pain, which is pain that is commonly triggered by an injury or disease and is commonly perpetuated by factors other than the cause of the pain. Loeser and Melzack (1999) further suggest that all types of chronic pain lead people to seek health care, however treatment is often not effective. They state that chronic pain is unrelenting and attribute this to stress, environmental and affective factors that may be superimposed on the original damaged tissue, contributing to its intensity and persistence.

The American academy of Pain Management (2003) claims that for the previous year approximately 57% of adult Americans reported experiencing recurring or chronic pain, 62% of which reported being in pain for more than one year with 40% noting they were in constant pain. Gatchel (2004a, 2004b) indicates the pervasive nature of pain is a medical problem by stating that it affected over 50 million Americans, incurs a cost of over $70 billion annually in health care and lost productivity and accounts for more than 80% of all clinical visits. Indeed the U.S. congress, in recognition of the problem, declared 2001-2010 as the Decade of Pain Control and Research. Further, the Joint commission on Accreditation of Healthcare Organization has implemented a requirement that physicians consider pain to be the fifth vital sign, in addition to pulse, blood pressure, core temperature and respiration (Gatchel et al. 2007).

Nonphysiological Factors that Influence the Experience of pain

Pain has an urgent primitive quality that is responsible for its emotional qualities that are unlike any other sensory experience and the intensity with which it is experienced can be affected by a number of subjective experiences that produce differing responses by individuals under comparable circumstances (Kandel, Schwartz and Jessel, 2000). Conceptually there are a number of nonphysiological factors that can influence the perception of pain, for this discussion the factors being considered are anxiety, catastrophizing, somatization, depression and childhood trauma.

Anxiety

Anxiety is generally considered to be worry about future events and can lead to misinterpretation of body states, a generalized state of worry, phobias or specific disorders related to specific traumatic events (DSM-IV-TR; American Psychiatric Association, 2000). It is known to have physiological effects such as increased arousal (Cuthbert et al., 2003), and has been demonstrated to have a significant impact on the perceived intensity of painful stimuli, specifically in the context of placebo and nocebo studies (Colloca & Benedetti, 2007; Benedetti et al., 2006). It has been demonstrated that reduction of anxiety in placebo studies will reduce pain perception and that increases in anxiety during nocebo studies will increase pain perception (Benedetti and Amanzio, 1997; Benedetti et al., 1997; Benedetti et al., 2006; Colloca and Benedetti, 2007)

Because of its strong association with pain and pain perception (Benedetti et al., 2006; 2007; Colloca and Benedetti, 2007; Gatchel et al., 2007; Geers et al., 2005; Keogh et al., 2006; Loeser and Melzack, 1999; Ploghous et al., 2001) and the degree to

which it has been experimentally manipulated made anxiety an examined variable in this study.

Catastrophizing

Catastrophizing is considered a tendency to exaggerate, focus and emphasize negative aspects of painful situations (Turner & Aaron, 2001). It has been characterized as a coping mechanism and appraisal or belief system (Sullivan et al., 2001). Individuals with a tendency to catastrophize are thought to reflect a persistent life course trait (Sullivan, Bishop & Pivik, 1995).

Sullivan et al. (2008) conducted a study to evaluate the relationship between catastrophizing and placebo responsiveness and found that high catastrophizers were more likely to respond to placebo suggestion than low catastrophizers and while receiving active treatment high catastrophizers responded significantly less than low catastrophizers. This suggests that catastrophizers may be more susceptible to nocebo suggestions than non-catastrophizers. Due to its consistent relationship to painful situations, well-articulated foundation and the important role it plays in the perceived intensity of painful experience and emotional distress (Sullivan et al., 2001), catastrophizing was a variable of interest in this study.

Somatization

> It is important to understand that certain patients use their physical symptoms as a way of dealing with, and communicating about, their emotional lives (*somatization*). That is to say, in this type of symptom magnification, physical symptoms may be easier to accept as causing current unhappiness and discontent than admitting that some psychological reason is contributing to it (Gatchel, 2004).

Geers, Helfer, Wieland & Kosbab (2006) examined the role somatic focus might have in placebo responders. They hypothesized that somatic focus would influence the response rates of individuals in an unconditional situation as compared to individuals in a conditional situation or controls. Results indicated that individuals given an unambiguous (unconditional) situation and told to focus on physical symptoms (somatic focus) were indeed more likely to report more placebo symptoms than the other two groups.

This study suggests that somatizer's would be susceptible to both placebo and nocebo effects due to their attention to physical changes by definition. Because of somatization's relationship to pain as a coping mechanism and the influence it may have on placebo/nocebo effects, it was considered a factor in this study.

Depression

Depression is another psychological factor whose relationship to pain cannot be ignored. A literature review by Bair, Robinson, Katon and Kroenke (2003) found that on average 65% of patients with depression experienced one or more pain symptoms and that depression was observed in anywhere from 5 to 85% of patients with pain conditions.

As mentioned earlier, the meta-analysis conducted by Kirsch and Sapirstein (1998) indicating a 75% placebo response rate in anti-depressive medication trials dictates that depression needed consideration as a variable in this study.

Childhood Trauma

Of additional interest is the consideration the role childhood trauma may have on pain perception. Research has demonstrated that early childhood trauma and adversity

is predictive for the onset of back pain in adulthood (Kopec and Sayre, 2005) and has been related to poor outcome following back surgery (Shofferman et al., 1993). It is believed that childhood trauma involving abuse or neglect may influence the way one perceives future painful events (Fillingim and Edwards, 2005; Heckman and Westefeld, 2006) based on past experiences and was therefore included as a consideration in this study.

Purpose and hypotheses

Given the information presented thus far, it is the author's goal to evaluate whether the nonphysiological factors of anxiety, catastrophizing, somatization, depression and childhood trauma will influence an individual's response to placebo and nocebo conditions. This study evaluated these factors using a placebo group, nocebo group and control group design, which allowed the clearest distinction between groups.

Based on evaluation of material presented to this point the author hypothesized that subjects given an inert pill and a positive verbal suggestion (placebo) will report experiencing less pain than controls and that subjects given an inert pill and negative verbal suggestion (nocebo) will report experiencing more pain than controls in a study utilizing ischemic arm pain,. Additionally, based on the literature, it is the author's assertion that somatization, catastrophizing and childhood trauma represent a stable coping style and unchanging personal experiences, respectively, where anxiety and depression represent transient variable states. Given this assertion, the author hypothesized that individuals in the top ten percent of somatizers (high somatizers) will report lower levels of pain in the placebo condition in comparison to the bottom fifty percent of somatizers (low somatizers) and controls with the top ten percent reporting

higher pain ratings in the nocebo condition than the bottom fifty percent and controls. In the case of childhood trauma, the author suggests that these negative experiences will present a negative outlook (expectation) in painful situations. Thus, it was hypothesized that individuals in the top 10 percent of trauma victims (high trauma) will report higher pain ratings in the nocebo condition as compared to those in the bottom 50 percent (low trauma) and those in placebo and control conditions. In addition, it is hypothesized that anxiety and depression will mediate responses to the Nocebo and Placebo groups.

Methods

Participants

90 healthy participants, 62 females and 28 males, were recruited from psychology classes at the University of New Orleans and randomly assigned to one of three groups (nocebo, placebo and control) after screening for chronic or current pain, to include back pain, neuropathic pain and headaches; mental distress; cardiovascular disorders; asthma; arthritis; as well as those who indicate they have taken aspirin or any other analgesic (prescription or over the counter), cough medicine, sedatives, tranquilizers, antidepressants or alcohol consumption on the day of testing. Following the screening process all subjects signed a written informed consent form in which the experimental procedure was described in detail.

An evaluation of a large data set from a questionnaire distributed at the University of New Orleans (2008) that contained two of the questionnaires to be included in this study (the MSPQ and PCS), was conducted to determine the minimum number of participants that would be required to conduct this study. Results indicated that 135 participants (45 per group) is the minimum number necessary for reasonable

assurance that random assignment to each group will include enough members for each variable to allow comparisons. The proposed number of 135 participants was approved by committee, however, due to unanticipated time constraints the number or participants at the time of writing is 90.

Measures

Modified Somatic Perception Questionnaire.

The MSPQ is administered to measure somatic arousal. It is a 13 item 4-point Likert scale ranging from 1 (not at all) to 4 (very much) that demonstrates adequate validity and reliability (Main, 1983).

Pain Catastrophizing Scale.

The PCS is a 13 item 5-point Likert scale ranging from 0 (not at all) to 4 (all the time). It assesses pain related catastrophizing by asking individuals to recall painful experiences and rate the frequency with which they experience catastrophic thoughts and feelings. The PCS has well established reliability and validity (Osman et al, 2000; Sullivan, 1995).

Childhood Trauma Questionnaire.

The CTQ is a 28 item scale indicating levels of retrospective childhood abuse and neglect. It contains four scales (physical and emotional abuse, emotional neglect, sexual abuse, and physical neglect) containing 5-point Likert scale items ranging from 0 (never) to 4 (very often). The CTQ has demonstrated adequate reliability and construct validity (Rosen and Martin, 1996).

Anxiety Sensitivity Index

The ASI is a 16 item questionnaire designed to assess the tendency to fear anxiety-related bodily sensations based on the belief they may have harmful consequences. Each item is rated on a 5 point Likert scale rating from 0 (very little) to 4 (very much). The ASI has good validity and reliability and has been shown to predict fear of pain, escape and avoidance behaviors (Asmundson and Carleton, 2005; Asmundson and Taylor, 1996; Norton and Asmundson, 2004).

Pain Anxiety Symptoms Scale.

The PASS is a valid 20-item questionnaire that measure anxiety associated with pain. Each item is rated on a 6-point Likert scale ranging from 0 (never) to 5 (always). The PASS possesses adequate construct and concurrent validities (Staats et al., 2001).

Beck Depression Inventory.

The BDI is one of the most widely used instruments for depression screening in psychiatric patients and normal populations (Whisman, Perez & Ramel, 2000). The BDI consists of 21 items on a 4-point Likert scale ranging from 0 to 3, with greater responses indicating greater degrees of depression. Scores are summed to yield a score of 0 to 63.

Pain measures

*Hargreaves Thermal Withdrawal Test**.***

This test measured phasic (brief escapable pain). Subjects were asked to place their non-dominant hand, palm-down, on a glass table suspended above a halogen heat source. Subjects were asked withdraw when they can no longer tolerate the

temperature. Latency to withdraw was recorded. If subjects failed to withdraw, the light was terminated after 20 seconds to prevent tissue injury.

Modified Submaximal Tourniquet Procedure.

This test induced exercise ischemic pain in the arm that increases over time (Amanzio and Benedetti 1999; Benedetti, 1996; Benedetti et al., 2006; Smith et al., 1966). The pain felt is that of a strong cramp similar to what one might experience during a strenuous workout. Subjects had the venous blood of the non-dominant arm exsanguinated by elevating it above the heart for 30 seconds, after which a sphygmomanometer (blood pressure cuff) was placed around the upper arm. The pressure cuff was inflated to a pressure of 300 mmHg. After this the subject was asked to start squeezing a hand exerciser 12 times, each squeeze to last 2 seconds followed by a 2 second rest. The discomfort experienced increases over time and the subject was asked to rate the intensity of their discomfort on a visual analog scale rating from 0 (no pain) to 10 (worst possible pain) every minute until conclusion. At the five minute mark subjects were asked to squeeze the hand exercise 5 more times and twice more at the eight minute mark. The test continued until the subject indicated a desire to withdraw or a maximum of 10 minutes have elapsed. Once a desire to withdraw has been verbally indicated the pressure cuff was immediately removed. Time to withdraw and intensity ratings were recorded.

Procedure

Qualified participants in all conditions had both sensory measures explained to them in detail and a brief description of the “drugs” to be given. Next, each subject was given the Hargreaves Thermal Withdrawal test for a base line measurement. Once the

Hargreaves test was conducted each subject was given the MSPQ, PCS and CTQ respectively. Upon completion of these three assessment measures each participant rolled three di numbering from one to three in a variety of colors. The participant would then show the experiment what blue number di they had drawn and was lead to believe that this determined which experimental group they had been assigned to. The purpose of which was to allow participants to have a sense of control in the selection process. The true assignment, however, had been randomly predetermined.

Following the “randomization” process the experimenter left the room to retrieve the “drug” of study which in each case was a size 4 red and white colored gelatin capsule containing pure cornstarch. Upon returning, the experimenter explained to the participant which drug they were to receive and any potential side effects.

Placebo group.

Subjects assigned to this group were told that they would were told the following “For the next part of the study you will be given an anxiolytic, which is a drug that reduces anxiety. This drug (P-533), in addition to reducing anxiety, has been documented to be a pain reliever as well. This drug is safe and has no negative reactions with other medication. It can have the following side effects: sense of wellbeing and occasional reports of drowsiness.” After consumption of the pill participants were left alone in the testing room without distractions (e.g. cell phones, ipods) for 15 minutes to give the “drug” time to take effect. While in truth the purpose of the lapse was to allow participants time to ruminate over the coming pain measures for 15 minutes, which presumably increased test anxiety and increasing group divergence allowing for easier statistical discrimination.

After 15 minutes had elapsed the experimenter returned to give the remaining questionnaires, which consisted of the ASI, PASS and BDI, respectively. Once the questionnaires were completed subjects were given a 2nd Hargreaves test followed by the tourniquet procedure. After conclusion of the pain measures participants were thanked for their time and dismissed. Due to the possibility of participant contamination full debriefings are to be conducted at the end of the study. Participants will be contacted by email (obtained from informed consent forms) and fully debriefed at that time.

Nocebo group.

Subjects assigned to this group were told the following "For the next part of the study you will be given a vasoconstrictor, a drug that constricts the blood vessels. This drug (N-3556) has been documented to increase pain sensitivity in certain situations, specifically with ischemic pain and heat. This drug is safe and has no negative reactions with other medication. However, it can have the following side effects: increased heart rate, mild headache, increased anxiety and constipation have all been reported. These effects have all been documented to be short lived, however." After consumption of the pill participants were left alone in the testing room without distractions (e.g. cell phones, ipods) for 15 minutes to give the "drug" time to take effect. While in truth the purpose of the lapse was to allow participants time to ruminate over the coming pain measures for 15 minutes, which presumably increased test anxiety and increasing group divergence allowing for easier statistical discrimination.

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questionnaires were completed subjects were given a 2nd Hargreaves test followed by the tourniquet procedure. After conclusion of the pain measures participants were thanked for their time and dismissed. Due to the possibility of participant contamination full debriefings are to be conducted at the end of the study. Participants will be contacted by email (obtained from informed consent forms) and fully debriefed at that time.

Control group.

Subjects assigned to this group were told the following “For the next part of the study you will be given an inert talc pill. This pill has no active effects and is being given to you because you have been assigned to a control group.” After consumption of the pill participants were left alone in the testing room without distractions (e.g. cell phones, ipods) for 15 minutes to give the “drug” time to take effect. While in truth the purpose of the lapse was to allow participants time to ruminate over the coming pain measures for 15 minutes, which presumably increased test anxiety and increasing group divergence allowing for easier statistical discrimination.

After 15 minutes had elapsed the experimenter returned to give the remaining questionnaires, which consisted of the ASI, PASS and BDI, respectively. Once the questionnaires were completed subjects were given a 2nd Hargreaves test followed by the tourniquet procedure. After conclusion of the pain measures participants were thanked for their time and dismissed. Due to the possibility of participant contamination full debriefings are to be conducted at the end of the study. Participants will be contacted by email (obtained from informed consent forms) and fully debriefed at that

time. Table 1 indicates the characteristics of all three groups by sex, age and mean scores for all six assessment measures.

Group	Sex (male/female)	Age (SD)	MSPQ (SD)	PCS (SD)	CTQ (SD)	ASI (SD)	PASS (SD)	BDI (SD)
Placebo	9/21	22.03 (2.9)	4.47 (3.58)	13.30 (10.51)	51.26 (8.62)	33.63 (9.43)	51.23 (12.22)	28.10 (6.48)
Nocebo	9/21	22.13 (4.2)	4.50 (3.25)	13.87 (11.30)	53.13 (6.60)	33.37 (8.10)	51.30 (11.99)	28.13 (4.61)
Control	10/20	20.16 (8.8)	4.87 (3.77)	13.10 (10.53)	54.00 (7.79)	32.57 (7.99)	48.67 (14.21)	28.60 (8.45)

Table 1. Characteristics of groups

Statistical Analysis.

MANOVA's were conducted to establish that all three groups were equitable for the predictor variables MSPQ, PCS and CTQ and to establish whether significant group differences existed for the hypothesized mediating assessment measures, ASI, PASS and BDI, respectively. Repeated measures ANOVA's and ANCOVA's were conducted to evaluate mean group differences, with and without predictors, for the Hargreaves pain measure. Latent Growth Curve Analysis and Cox Regression survival analysis were utilized to evaluate the Ischemic arm pain measure, with and without predictors. Differences were considered to be statistically significant at $p < 0.05$.

Results

A one-way MANOVA was conducted to establish whether the groups were equitably distributed for the predictor variables MSPQ, PCS and CTQ. These three variables were treated as dependent variables for this test. Means and standard

deviations are presented in Table 1. Box's Test of Equality was not significant, $p > 0.7$, indicating the use of Wilk's Criterion. The combined DV's were not significant $F(6, 170) = .386$, $p=.887$, indicating an equitable distribution of predictor variable scores.

Pain Measure: Hargreaves

To test the hypothesis that a difference between group assignment would be found a one way ANOVA was conducted. Prior to running the analysis Pre and Posttest variables for the Hargreaves were consolidated into one variable, maximum Percent Effect (MPE). MPE allows for the clearest distinction of pre and post test scores for the individual and was calculated with the following formula: ((test – baseline) / (20 – baseline)) X 100. There was no significant difference between groups, $F(2,54)=1.080$,$p = .271$. Table 2 reports the means and SD for the MPE variable.

Group	N	MPE Mean	MPE SD
Placebo	17	-6.7041	132.17
Nocebo	20	-135.842	393.28
Control	20	-61.515	189.860

Table 2. Means and SD for Pre MPE.

To evaluate whether the top 10 percent compared to the bottom 50 percent of each predictor variable would identify placebo and nocebo responders a new variable was created. The large (2008) dataset that established the number of subjects for this study was used to establish cut off values for the MSPQ and PCS 10/50 split. Any MSPQ score ≥ 12 and ≤4, PCS score ≥ 34 and ≤ 12, and CTQ score ≥ 65 and ≤ 51 were compiled into a single variable. Any score meeting the top 10 percent cut off was coded a 1 and those meeting the bottom 50 percent cut off was coded 0, resulting in 61 subjects, 14 in the top 10 percent and 47 in the bottom 50 percent. After creating the

splitting variable a new ANOVA was conducted with the splitting variable added to group membership.. Results, once more, indicate no statistically significant difference for group membership ($F(2,48) = .727$, $p = .489$) and an interaction of ($F(2,48) = .274$, $p = .761$. Table 3 reports the means and (SD) for this test.

Group	10/50	N	MPE Mean	MPE SD
Placebo	50	14	-12.697	145.737
	10	3	21.263	16.696
Nocebo	50	13	-186.359	480.588
	10	5	-79.615	103.727
Control	50	14	-38.662	173.002
	10	5	-84.669	247.046

Table 3. Means and SD for MPE.

Pain Measure: Ischemic Arm Test

Due to the way this test was measured two types of statistical tests were conducted. A Latent growth curve analysis was conducted to handle pain values over time and a Cox-Regression Survival analysis was conducted to examine survival membership over time.

In order to establish a meaningful growth curve model a graph depicting each groups mean pain rating over the 10 time points was evaluated (see Figure 1). After

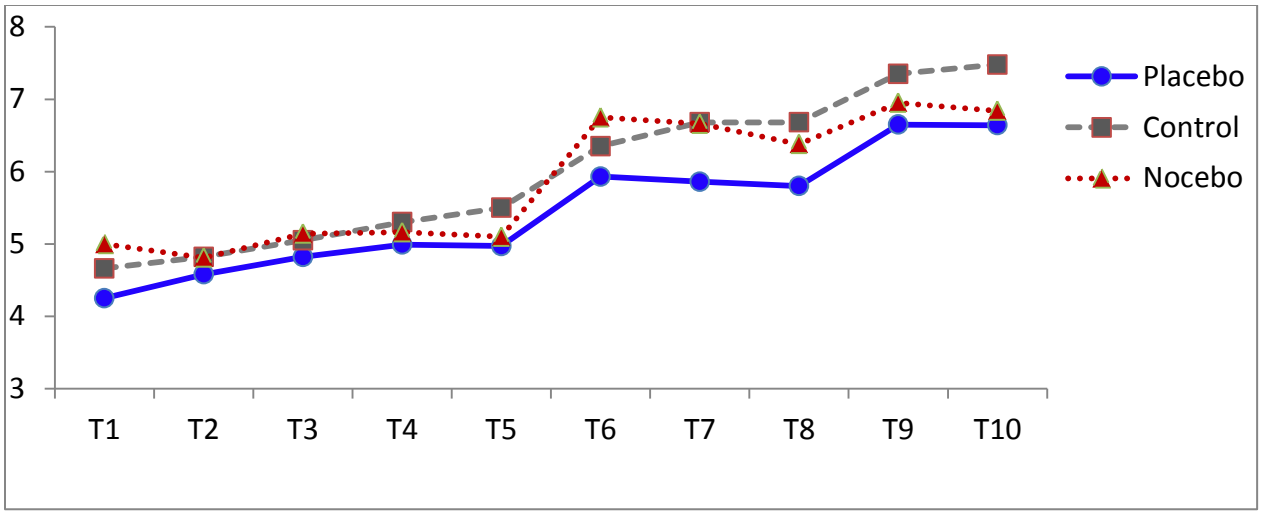

Figure 1, mean pain rating by group

examining the graph a piecemeal model (Figure 2) was selected for two reasons, 1) it was believed to best represent the data, as illustrated by the means plot (figure 1) and 2) it made methodological sense as there was a participant instruction to squeeze the hand calipers five more times between time points 5 and 6 resulting in increased pain reporting, which is clearly represented in Figure 1. Next, two dummy variables were created to allow clearer distinction between groups for the model. Dummy 1 represents the placebo group and control while Dummy 2 represents the nocebo group and control.

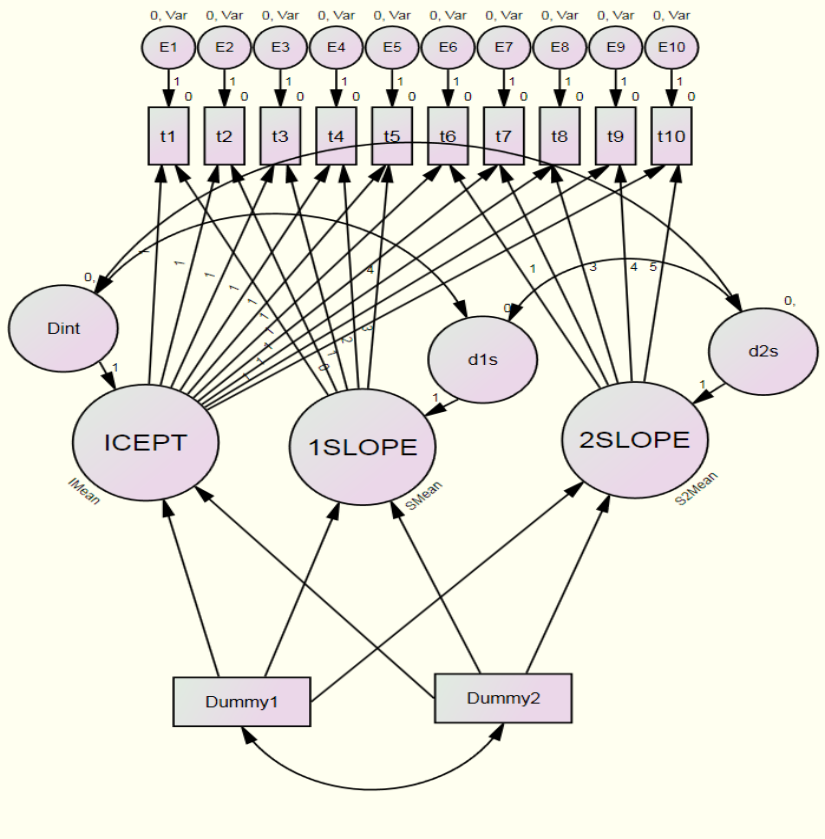

Figure 2, Growth Curve Piecemeal model, without predictors.

Results from the estimation of the model depicted in Figure 2 yielded X^2 (68, *N*=90) = 367.430, *p* < .001 suggesting a poor model fit (Byrne, 2010). The RMSEA (Root Mean Square Error of Approximation) value for this model is .222 and a CFI (Comparative Fit Index) value of .684. Byrne (2010) suggests that a RMSEA value < .05 and a CFI value of > .95 is recommended for good model fit. Thus it can be concluded that this model is a poor fit of the data. Table 4 provides the regression estimates and p values for this model.

		Estimate	S.E.	C.R.	*p*
Icept	←Dummy1	-.164	.650	-.252	.801
1slope	←Dummy1	.101	.149	.678	.498
2slope	←Dummy1	.025	.272	.093	.926
Icept	←Dummy2	.421	.650	.648	.517
1slope	←Dummy2	-.128	.149	-.862	.389
2slope	←Dummy2	-.096	.272	-.351	.726

Table 4

Next a model adding predictors was evaluated (see Figure 3). The first predictor to be evaluated was MSPQ total score. Estimation results from this model yielded X^2 (93, *N*=90) = 420.428, *p* < .001, a RMSEA value of .199 and a CFI value of .719.

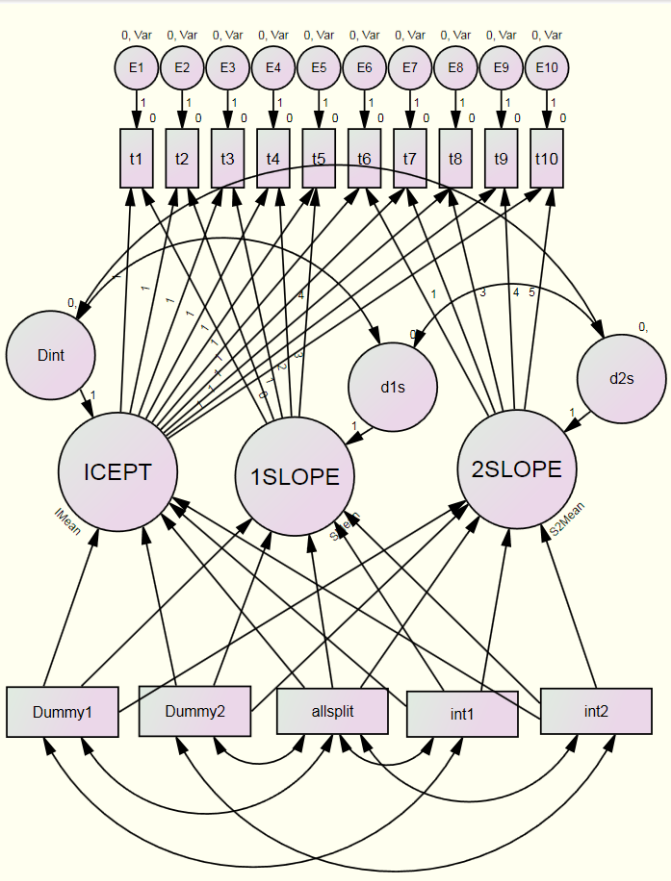

Figure 3, Growth Curve Piecemeal model with predictor

Though there was some improvement in RMSEA and CFI values, results indicate this model is a poor fit to the data. Examination of regression weights yielded no significant p values.

Next, a model replacing MSPQ total scores with PCS total scores was evaluated. Estimation results for this model yielded X^2 (93, *N*=90) = 407.391, *p* < .001, a RMSEA value of .195 and a CFI value of .730. Examination of regression weights yielded no significant p values.

The next model to be evaluated replaced PCS total scores with CTQ total scores. Estimation results for this model yielded X^2 (93, *N*=90) = 407.391, *p* < .001, a RMSEA value of .195 and a CFI value of .730. Examination of regression weights yielded no significant p values, however, the interaction term for placebo and CTQ trended toward significance (see table 5).

		Estimate	S.E.	C.R.	*p*
Icept	←CTQ	-.001	.034	-.029	.977
1slope	←CTQ	.006	.008	.807	.419
2slope	←CTQ	.007	.014	.510	.560
Icept	←CTQ int1[1]	.094	.055	1.704	.088
1slope	←CTQ int1[1]	-.022	.011	-.139	.090
2slope	←CTQ int1[1]	-.043	.023	-1.845	.065
Icept	←CTQ int2	-.034	.048	-.706	.480
1slope	←CTQ int2	-.002	.011	-.139	.890
2slope	←CTQ int2	.012	.020	.586	.558

Table 5, regression weights; [1] interaction term for CTQ and placebo.

Finally, the model depicted in Figure 3 was evaluated with the predictors MSPQ, PCS and CTQ combined into one variable using the top 10 percent, bottom 50 percent split described earlier. Estimation results for this model yielded X^2 (93, *N*=90) = 419.260, *p* < .001, a RMSEA value of .199 and a CFI value of .680. Examination of the regression weights yielded no p value that approached significance. Taken together, all models examined exhibited poor model fit and no significant p values. Considering, however, the trend toward significance for the interaction term of the CTQ and Placebo,

unplanned secondary analyses were conducted on each of the five subscales (emotional abuse, physical abuse, sexual abuse, emotional neglect and physical neglect) to determine if any significant effect may have been washed out by only examining a total score.

Each of the subscales were summed and centered and an interaction term created for both Dummy1(placebo) and Dummy 2(nocebo) variables. The subscales and their interaction terms were plugged into the model one at a time. Model fit remained poor for all subscales, however, a significant effect was found for placebo and physical abuse and for placebo and emotional abuse. In addition, a trend toward significance was found for emotional neglect and nocebo. Table 6 reports these regression weights and p values. No significant effect or trend was observed for sexual abuse or physical neglect and were not included in the following table.

Physical Abuse	Estimate	S.E.	C.R.	*p*
Icept ←Dummy 1	-6.138	1.818	-3.377	***
1slope ←Dummy 1	.708	.438	1.618	.106
2slope ←Dummy 1	1.219	.792	1.540	.124
Icept ←PA x Dummy1	.888	.258	3.435	***
1slope ←PA x Dummy1	-.086	.062	-1.378	.168
2slope ←PA x Dummy1	-.176	.113	-1.567	.117
Emotional Abuse				
Icept ←EA x Dummy1	.519	.182	2.857	.004*
1slope ←EA x Dummy1	-.092	.043	-2.142	.032*
2slope ←EA x Dummy1	-.178	.079	-2.255	.024*
Emotional Neglect				
Icept ←EN x Dummy2	-.326	.178	-1.834	.067
1slope ←EN x Dummy2	.005	.041	.117	.907
2slope ←EN x Dummy2	.078	.074	1.052	.293

Table 6, *** p <.001; * p < .05.

Next, a Cox-Regression survival analysis was conducted to evaluate whether ASI, PASS and BDI would predict faster dropout rates beyond that of group

membership and the top 10, bottom 50 percent split. The dummy code variables for group membership used in the growth curve analysis were used in this analysis as recommended by Tabachnick and Fidell (2007) for regression analysis. Group membership (dummy1 and dummy2) and the 10/50 split (allsplit) were entered as covariates in the first block, ASI, PASS and BDI scores were entered into the second block. At no time did the model become significant ($X^2(6) = 5.753$, p = .451), however, ASI scores contributed significant variance to the prediction of dropout rates (see Table 7 for results).

	B	SE	Wald	DF	Sig	Exp(b)
Dummy1	.506	.487	1.077	1	.299	1.658
Dummy2	.402	.501	.644	1	.422	1.494
Allsplit	.175	.512	.117	1	.732	1.191
ASI	.059	.028	4.383	1	.036	1.061
PASS	-.012	.018	.438	1	.508	.988
BDI	-.032	.036	.825	1	.364	.968

Table 7

Finally, no mediation tests were conducted for anxiety and depression variables due to a lack of significance on any model examined thus far. A SOBEL mediation test requires a significant direct path correlation before the indirect path can be examined.

Discussion

In this study, an attempt was made to identify placebo/nocebo responders based on coping styles that were hypothesized to affect expectation. These coping styles were described as somatization, catastrophizing and child-hood trauma all of which have been documented to influence pain perception and outcomes (Sullivan et al., 2001; Fillingim and Edwards, 2005; Heckman and Westefeld, 2006; Geers et al., 2006). Additionally, an attempt was made to evaluate the extent anxiety and depression might

mediate placebo/nocebo responsiveness. The results of planned analyses indicated that the anxiety sensitivity index (ASI) contributed significantly to drop out rates in the survival analysis. This is not surprising as anxiety has been repeatedly demonstrated to influence placebo and nocebo responses, with reduced anxiety associated with placebo effects and increased anxiety associated with nocebo effects (Benedetti et al., 2006; 2007; Colloca and Benedetti, 2007; Gatchel et al., 2007; Geers et al., 2005; Keogh et al., 2006; Loeser and Melzack, 1999; Ploghous et al., 2001). This contribution, however, failed to significantly improve the overall survival model and was the only component of any planned analysis to reach significance. There was, however, an encouraging trend found in childhood trauma scores and placebo responsiveness that warranted further unplanned analysis.

The placebo/nocebo effect is a well-established phenomenon that has been demonstrated using a variety of pain paradigms by numerous studies (Amanzio and Benedetti, 1999; Benedetti, 2007; Benedetti & Amanzio, 1997; Benedetti et al., 2007; Colloca and Benedetti, 2007; Colloca et al., 2008; Enck et al., 2008; Klosterhalfen and Enck, 2008; Kong et al., 2008). Considering the well-established nature of the placebo/nocebo effect it is surprising that little to no effect was observed for the proposed hypotheses. One could reasonably conclude a methodological flaw is washing out these primary effects.

The discussion, then, will focus on two areas. First, the author will discuss the unplanned childhood trauma results. Second, the potential pitfalls and limitations that may have negatively affected the outcome and suggestions for models that would overcome these deficits are covered.

Unplanned Analyses: Childhood Trauma

Because childhood trauma questionnaire total scores trended toward a significant interaction between childhood trauma and placebo responsiveness further analyses were conducted on each of the five subscales contained in the CTQ. It was believed that such analyses might reveal effects that were washed out by the combination of all scales into a single score.

The initial hypothesis about childhood trauma was that it would be an experience resulting in a negative coping style, thus resulting in more susceptibility to negative information. In this case the suggestion of pain worsening (nocebo). As mentioned previously, research has demonstrated that early childhood trauma and adversity is predictive for the onset of back pain in adulthood (Kopec and Sayre, 2005) and has been related to poor outcome following back surgery (Shofferman et al., 1993). Additionally, It is believed that childhood trauma involving abuse or neglect may influence the way one perceives future painful events (Fillingim and Edwards, 2005; Heckman and Westefeld, 2006) based on past experiences.

The results indicated that childhood trauma does indeed influence future painful events. Apparently, it is not unidirectional, as the author hypothesized. Physical and emotional abuse significantly predicted placebo responsiveness but not nocebo responsiveness. This finding is clearly opposite to the model posited. Sexual abuse did not influence responsiveness in either direction, nor did physical neglect. Emotional neglect, however, trended toward nocebo responsiveness but not placebo.

It is not immediately clear why such divergence in responsiveness was found. The literature provided the author with little information directly related to the topic.

Fillingim and Edwards (2005) noted that subjects who self-reported sexual and physical abuse had a decreased sensitivity to repetitive thermal stimulation but not to ischemia pain. They also indicated that those with self-reports of abuse perceived themselves to be in poorer health and reported greater negative affect than non-abuse groups. The authors had no clear explanation for why there was a difference in response to brief pain versus more intense pain. They did, however, suggest that somatic focus could be a contributing factor. In fact, Geers et al. (2006) investigated the role of somatic focus and placebo responding and found that individuals who were instructed to somatically attend to a drug's effects were more likely to be a placebo responder than those that were not attending. This is in keeping with this study's inclusion of somatization as a factor in placebo/nocebo responsiveness.

It is problematic, however, in that somatization as a predictor did not produce an effect in this study. This does not rule out the possibility that somatic focus could be a mechanism interacting with physical and emotional abuse in such a way that predisposes an individual to look for positive information that a painful condition is about to be relieved. It is also possible somatic focus of negative information is an outcome of emotional neglect. One must keep in mind that this study focused on non-clinical populations and such a mechanism may only be temporarily effective, if it exists at all. In a clinical pain population it may be that physical and sexual abuse then increases the likelihood of poorer outcomes as the literature indicates.

The one clear point is that much more research needs to be conducted to elucidate the mechanisms involved. Additionally, caution must be used in any interpretation of this data as the population was non-clinical. This naturally resulted in

small samples for the abuse, neglect subscales of the CTQ and could very well be random occurrence. Though little difference was found between groups in this study as a whole, it is encouraging that significant effects were observed for childhood trauma and placebo/nocebo responsiveness. Even if the effects were the result of statistical randomness further investigation is warranted, which leads to the remaining discussion of this study's strengths, weaknesses and suggested modifications.

Study Strengths

Although there were no significant statistical main effect findings one can still optimistically conclude that a number of sound design elements existed in this study. The choice of predictor variables has been demonstrated to influence pain perceptions and outcomes (Sullivan et al., 2001; Fillingim and Edwards, 2005; Heckman and Westefeld, 2006; Geers et al., 2006) and has been scrutinized for validity and reliability (Main, 1983; Osman et al, 2000; Sullivan, 1995; Rosen and Martin, 1996).

Though no mediation tests could be conducted on the anxiety measures their inclusion for consideration is in keeping with the literature. Additional support for inclusion of anxiety measures in this study comes indirectly from the Cox Regression survival analysis. The ASI contributed significant variance to the prediction of dropout rates, $p = .036$, however, failed to bring the total model to significance. Thus, caution is warranted in interpreting this result. That said, it could reasonably be concluded that a similar study would benefit from the inclusion of anxiety measures.

The Hargreaves Thermal Withdrawal test is not generally conducted in placebo/nocebo studies. However, it is the author's opinion that inclusion of this pain

measure can be considered a study strength for two reasons. First, the measure is brief which allowed for a pre and posttest in the same experimental session. Second, the following table, illustrates the differences between groups that are traditionally expected. A clear indication the measure is sound.

Group	N	MPE Mean	MPE SD
Placebo	17	-6.7041	132.17
Nocebo	20	-135.842	393.28
Control	20	-61.515	189.860

Table 8. Means and SD for Pre MPE.

Inclusion of the ischemic pain measure can generally be considered a study strength. It is a well-established measure first developed by Smith et al., (1966) and validated by Smith et al., (1968) for use in analgesia pain studies. Since its development it has been commonly and reliably used to detect placebo and nocebo effects, especially by the Benedetti research group (Amanzio and Benedetti 1999; Benedetti, 1996; 1997; Benedetti et al., 1997 Benedetti et al., 2003; Benedetti et al., 2006). Further support of this measure can be gleaned from examination of Figure 1, in which mean scores of the VAS 10 time points are trending toward expected results.

Lastly, as noted in the introduction fewer than 4% of placebo studies have included a no-placebo control group in which to evaluate claimed effects (Ernst and Resch, 1995; Fisher, 2000; Geer et al., 2005). Not only did this study include a control group the groups were conditional. Price, Finniss and Benedetti (2008) reported “Verbal suggestions that induce certain expectations of analgesia induce larger placebo responses than those inducing uncertain expectations.” In other words, groups that are told what to expect (conditional) experience larger placebo effects than groups that are

not told what to expect (unconditional). Despite the many perceived strengths of this study, clearly there were significant weaknesses that managed to diminish the outcome.

Study Weaknesses

Though there is no real way in which to quantify the weaknesses of this study, reflection on the procedures used and revisiting the literature has provided the author with several suspected deficiencies. The primary suspected deficiency was the strength of the suggestions used. There are gradations of suggestion strength in regards to the placebo/nocebo response. Olshansky (2007) states:

> Placebo strength varies by the type of intervention. A dose response exists. Blue (vs. pink) placebo pills are sedating. Yellow (vs. green) placebo pills are stimulating. Red (vs. beige) placebos encourage a cardiac response. Branded ismore effective than generic. Four-times-a-day is more potent than twice-a-day. Larger capsules are stronger than smaller ones. Interventions, injections, andsurgery give larger effects than pills.

The above statement was echoed by Benedetti and Amanzio (1997) and Williams (2004).

Participants in this study told that the “drugs” being investigated were of a short duration and considered safe to take with other medications with few side effects. The purpose of the generally weak suggestion was to alleviate participant concerns, thus increasing participant numbers. However, reviewing the literature found Benedetti using phrases like “powerful” and “strong” when explaining pill or injection effects (Benedetti et al., 2006). If, as posited in the introduction, placebo and nocebo effects are contingent on expectancies then a weak expectancy could very well have driven the weak to non-existent results found in this study. Without a primary difference observed between groups then all other analyses would necessarily fail.

Though listed as strengths both pain measures also had their weaknesses that is believed to have contributed to the difficulties observed in this study. The primary pain measure in this study was ischemia pain induced by the tourniquet technique. This study used a modified version of the technique described by Benedetti (1996). Amanzio and Benedetti (1999) noted that tolerance and pain variability was observed if the sphygmomanometer cuff was not maintained at 300mmHg and an Esmarch bandage (pressure bandage) maintained on the forearm for the duration of the test (10 minutes).

In this study the sphygmomanometer cuff was maintained at 300mmHg, however, due to concerns about potential participant injury an Esmarch bandage was not applied to the forearm. In revisiting the literature the author determined a misunderstanding about the Esmarch bandage had taken place. Originally the Esmarch bandage was a rubber tube approximate the width of a finger and could be tightened into a tourniquet. More recently the Esmarch bandage is a wider latex bandage, also known as a Martin bandage, and is used primarily as a pressure bandage, not as a tourniquet (Fletcher and Healy, 1983). The initial literature review led the author to believe that inappropriate application of an Esmarch bandage could lead to participant injury and was thus discarded from consideration.

Additionally, the ischemia test was only applied once. Initial consideration was given to a repeated measures administration but was discarded for concern it would have a significant impact on continued subject participation. In other words, there was concern that subjects would drop from the study once they had experienced the discomfort generated by this test. Returning to the literature has convinced the author

that repeating this test would be the most effective technique in establishing placebo/nocebo responses.

Finally, the ischemic arm test was measured and analyzed using a VAS pain rating each minute over a ten minute time frame. Though this was the main measure used by Benedetti (1996; 2006), alternative applications of this technique were modified to be measured as length of time from last hand caliper squeeze to unbearable pain. This measure generally induces ischemic arm pain quickly and becomes unbearable in about 13 to 14 minutes (Amanzio and Benedetti 1999; Benedetti, 1996; 1997; Benedetti et al., 1997 Benedetti et al., 2003; Benedetti et al., 2006). This study did not observe a quick increase in pain. In fact, several subjects noted a lessening in discomfort after the initial application of the blood pressure cuff. Taken together, this measure, as utilized in this study, likely contributed significantly to the lack of effect observed between groups.

Turning next to the Hargreaves Thermal Withdrawal test, though also listed as a strength in the study it too had observable weaknesses. During administration of the test it was suspected that a number of subjects misunderstood the verbal instructions of the test. Several others complained the glass top was cold to the touch and perhaps interfered with detection of the heat stimulus. Finally, several subjects in a row timed out on the pre and post test leading the experimenter to believe that the apparatus settings had been altered in some fashion. In all, 25 subjects had to be eliminated for ceiling effects on analyses that involved this test potentially contributing to non-significant effects.

Finally, it should be considered that contamination of the subject pool may have influenced expectations. A number of participants mentioned to the experimenter that

they had discussed the study with other participants prior to their appointment and knew what to expect in terms of procedure and drug strength. It is not clear to what degree, if any, this foreknowledge may have influenced outcome.

Conclusion

The author believes that this study was fundamentally sound but methodologically weak in the areas noted above. To address these issues two potential study designs could be considered. First, a study primarily identical to this one with the following changes in design. 1) Moving from a weak suggestion to a strong suggestion and including an injection instead of a pill would largely alleviate this weakness. 2) Modifying the ischemic arm test to include an Esmarch bandage to increase exsanguination speed and reduce variations in pain responsiveness. 3) Moving from a VAS measurement of pain to a time to unbearable pain measurement would likely alleviate the considerable subjective ambiguity observed in the VAS measurement. An instruction of “tell me when the discomfort is unbearable” is much less confusing than a scale containing “worse pain imaginable”. It was observed that a number of subjects in the current study gave significant consideration to the “meaning” of “worse pain imaginable”. 4) Moving to a repeated measure of the Ischemia test would enhance detection of effects and be more in keeping with existing literature. 5) Finally, instructions clarifying the Hargreaves test, a daily settings check and efforts to alleviate the “cold” sensation of the glass table top would conclude modifications to a subsequent study based on the initial premises.

Alternatively, an animal neglect model could be proposed. Moving to an animal model would allow more objective testing on several hypotheses considered in the

present study. Though somatization and catastrophizing could not be directly assessed in an animal model childhood trauma could be manipulated and its effects on pain could be directly observed. Such a model would involve separating rat pups for extended periods of time from their mothers to approximate emotional neglect and surgically injuring others to approximate physical abuse. Though such manipulations might seem cruel, an Institutional Animal Care and Use Committee (IACUC) approval has been given at UNO for a similarly designed study.

Manipulating rearing situations and comparing them to non-manipulated animals has the obvious advantage of control of conditions. Fewer subjects can be used because all subjects have known histories with precisely controlled interventions. This is unlike human studies in which larger numbers of participants are needed to obtain adequate numbers of individuals with desired predictor variable scores. Even then, large variations in personal histories and experiences will exist in a human subjects study creating the possibilities that some experience or another may have been overlooked in design consideration.

Deception is a primary component of placebo and nocebo studies. Considering this, one might wonder how you lie to a rat. The answer would presumably be that you violate conditioned expectations. Hernstien (1962) and Ader and Cohen (1975) demonstrated that placebo responses could be conditioned in animals. Thus, by extension, a model that manipulates conditioning would mimic the deception process used in human models. For example, over the course of several trials a drug like morphine or valium could be administered to an animal and given a saline solution injection (placebo) on a final trial to violate expectancies. Nocebo might be

accomplished by giving several trials of saline solution followed by Complete Freund's Adjuvant (CFA), a water-in-oil emulsion that contains a pain inducing agent, mimicking a negative violation of expectancy. Though an extensive literature review is necessary to completely work out the mechanics of an animal model it should be clear that such a model is possible and would have distinct methodological advantages.

In summary, it is the author's assertion that though the present study had no significant primary findings it has a number of sound premises which was illustrated by the unplanned CTQ analysis. A more comprehensive study built from the information here that addresses the weaknesses mentioned by utilizing a subsequent human model study or more precisely controlled animal model is warranted.

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Appendix

University Committee for the Protection of Human Subjects in Research University of New Orleans

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Campus Correspondence

Principal Investigator: Kevin W. Greve

Co-Investigator:Steve T. Brewer

Date: November 30, 2010

Protocol Title: "Factors that Contribute to Susceptibility of Placebo/Nocebo Responding in Experimentally Induced Ischemic Arm Pain"

IRB#: 06Oct10

Your proposal was reviewed by the full IRB. The group voted to approve your proposal pending that you adequately address several issues. Your responses to those issues have been received and you have adequately addressed all of the issues raised by the committee. Your project is now in compliance with UNO and Federal regulations and you may begin conducting your research.

Please remember that approval is only valid for one year from the approval date. Any changes to the procedures or protocols must be reviewed and approved by the IRB prior to implementation. Use the IRB number listed on this letter in all future correspondence regarding this proposal.

If an adverse, unforeseen event occurs (e.g., physical, social, or emotional harm), you are required to inform the IRB as soon as possible after the event.

Best of luck with your project!
Sincerely,

Robert Laird, Ph.D., Chair
Committee for the Protection of Human Subjects in Research

Vita

Steve Brewer was born in Sallisaw, Oklahoma and earned his B.S. in Psychology with a minor in Alcohol and Drug Abuse Counseling from Rogers State University in 2008. In 2009, Steve enrolled into the University of New Orleans to earn his M.S. and PhD. in Applied Biopsychology. Upon completion of the current document he will have earned his M.S and will be on track to complete his PhD. in 2013.