To my parents, the most supportive and generous individuals I have ever known
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The interest in placebo responding has existed for a number of years, and a variety of studies have investigated placebo responding in numerous settings. In response, several theoretical concepts have been suggested to explain placebo responding; however, the exact mechanisms of placebo responding remain unknown. This study sought to further understand the roles of somatic focus, expectation for pain and desire for pain relief as they relate to sensory discriminability and response bias. One hundred and twenty (65 female and 55 male) asymptomatic individuals, recruited from the University of Florida, were randomized into one of two groups: a placebo induction group and a repeated baseline group. This study included a 4-stage experimental design, used in an effort to elicit placebo responding through a conditioning and verbal suggestion paradigm. It was discovered that only a minority of participants (28.9%) in the placebo induction group actually were placebo responders, and of those individuals showing a placebo response, 70% were male. Contrary to our a priori hypotheses, results indicate no significant relationship between a measure of somatic focus and sensory discriminability in placebo responding. Additionally, there were no significant relationships between expectation for pain or desire for pain relief with the component of response bias. Exploratory analyses were also conducted, and 44.9% of individuals randomized to the placebo
induction group were found to be nocebo responders. Additional analyses indicated a sex
difference between those individuals exhibiting placebo responses and those exhibiting nocebo
responses. Specifically, females were more likely to be nocebo responders, while males were
more likely to exhibit placebo responses. Results of these exploratory analyses also indicate that
a single-item question of attention was the strongest contributor to membership in either the
placebo or nocebo groups.
CHAPTER 1
INTRODUCTION

Background

The notion of “placebo” has existed for a number of years; however, throughout much of its history the potential benefits of the placebo phenomenon have been ignored. The fact that placebos lead to significant changes can no longer be overlooked, especially as much research has shown that placebo responding is associated with magnitudes of effectiveness similar to “active” treatments and have been shown to accompany changes in neural activity (Craggs, Price, Perlstein, Verne, & Robinson, 2008).

Interest in the placebo effect significantly increased after Henry Beecher’s 1955 article delineated the history of research completed in the area of placebo responding. This longstanding interest in placebo responding is somewhat due to the belief that placebo responding is partially responsible for favorable outcomes in most areas of healthcare (see Harrington, 1997; Jospe, 1978; Kirsch, 1999; Moerman, 2002; Peters, 2001; Shapiro & Shapiro, 1997; White, Tursky, & Schwartz 1985). In response to this interest, healthcare providers have used a variety of theoretical concepts to explain the placebo phenomenon. Although the concepts of “placebo responding” and “placebo analgesia” have existed for a number of years, they have often been poorly defined (Voudouris, Peck, & Coleman, 1985). However, in 2004, Vase and colleagues provided adequate definitions to differentiate the many terms used in this area of research. These authors define “placebo analgesia effect” as the “measured difference in pain across an untreated and treated group or across an untreated and placebo treated condition within the same group” (Vase, Price, Verne, & Robinson, 2004). Additionally, they define “placebo analgesia response” as a “reduction in pain in an individual that results from his or her perception of the therapeutic intervention” (Vase et al., 2004).
Despite the improvements in differentiating these terms, no consensus exists for the exact psychological or physiological mechanisms involved in placebo analgesia (Vase et al., 2004). The majority of the theories seeking to explain placebo responding have investigated the external factors responsible for placebo responding. However, in the past several years, many theorists seeking to explain placebo responding have shifted their attention from environmental factors to human perceptions and meanings (Harrington, 1997). Both external and perceived factors have been shown to produce placebo responding (Amanzio & Benedetti, 1999; Gracely, Dubner, Deeter, & Wolskee, 1985; Price et al., 1999; Pollo et al., 2001; Vase, Riley, & Price, 2002; Voudouris et al., 1985, 1989, 1990). More specifically, investigations have revealed that classical conditioning, suggestion, expectancy, and desire for pain relief all play a role in placebo analgesia.

**Classical Conditioning**

As previously stated, the degree of placebo analgesia is dependent on several factors, and one of the major theories used to explain the mechanisms of placebo responding is the conditioning theory. Researchers have suggested that placebo analgesia is partially due to the effects of conditioning (Chung et al., 2007; Voudouris et al., 1985, 1989, 1990). The conditioning theory asserts that certain stimuli (e.g., medical setting, white lab coat, pills/syringes/ointments) may become conditioned stimuli when an individual receives an inert agent (unconditioned stimulus) that leads to an analgesic response (unconditioned response). As the measurement of placebo responding matured, inclusion of a repeated baseline control condition became necessary in experimental studies (Fields & Levine, 1981). The first researchers to use this repeated baseline in a study assessing the contribution of conditioning in placebo was Voudouris and colleagues (1985, 1989, 1990). Voudouris and colleagues provided evidence that it is possible to condition placebo analgesia in human participants during an
experimental study. In this paradigm, participants were subjected to three consecutive conditions (pre-test, manipulation, post-test) with electric stimuli and either with or without the use of a placebo cream. The pre-test employed an electrical stimulus that was applied to the participants’ skin to determine the participants’ individual thresholds. The manipulation included the pairing of an inert cream with a reduced electrical stimulus to suggest an analgesic effect, and the post-test involved the use of an inert cream applied to the skin and an electrical stimulus that was increased to its original level at the pre-test. Voudouris and colleagues found that the participants reported experiencing reduced pain with the placebo cream and they concluded that this placebo response was due to the result of conditioning.

**Suggestion**

Both verbal and nonverbal suggestions for pain relief have also been shown to influence placebo responding. Research has provided evidence for the contributions of both direct and indirect suggestion in experimental placebo designs (Pollo et al., 2001; Price et al., 1999; Vase et al., 2002). In addition to the relative contribution of each, it appears that conditioning and suggestion combine to produce an additive effect of placebo analgesia (Vase et al., 2002). More specifically, Vase and colleagues found that the overall effect size of the placebo analgesia was significantly higher than the effect size in double-blind, randomized clinical studies, with this huge difference being explained by the verbal instructions given to the participants (Enck & Klosterhalfen, 2005; Vase et al., 2002).

**Expectancy**

The expectancy theory is another of the major theories used to explain the mechanisms of placebo responding, and research has suggested that an individual’s expectation of reduced pain may be sufficient in producing pain relief for that individual. Vase and colleagues (2004) described expectancy as “the experienced likelihood of an outcome or an expected effect.” They
wrote that expectancy can be measured simply by inquiring about the level of pain that each participant expects to experience prior to the presentation of pain stimuli (Vase et al., 2004). Researchers have noted that these experiential factors of placebo analgesia (expectancy and desire) are not mutually exclusive from the external factors (conditioning and suggestion). In fact, an investigation by Benedetti and colleagues (2001) concluded that conditioning and suggestion induce individual expectations for pain relief.

**Desire**

Desire has been defined as “the experiential dimension of wanting something to happen or wanting to avoid something happening,” and research suggests that this concept is likely involved in placebo responding (Vase et al., 2004). Price and colleagues (1999) became the first researchers to measure participants’ levels of desire in a study investigating placebo analgesia. Results from this study suggested that desire for pain relief was not associated with the degree of placebo analgesia; however, this finding is likely due to the brevity of painful stimuli in the experimental setting (Price et al., 1999). Desire has been shown to influence an individual’s perception; thus, it becomes a factor in placebo analgesia. Vase, Robinson, Verne and Price (2003) concluded that participants’ expected pain levels and their desire for pain relief account for a large amount of the variance in placebo responding. They reported that the combination of desire for pain relief and expectations of pain accounted for 81% of the variance in pain ratings during a study investigating rectal pain (Vase et al., 2003).

**The Debate**

In 2001, Hrobjartsson and Gotzsche conducted a meta-analysis that included 29 studies of placebo analgesia, and suggested that the small placebo analgesia effect (Cohen’s d = 0.27) was due to confounding variables such as response bias, rather than any of the previously discussed mechanisms that have been theorized to be associated with placebo analgesia. Response bias can
be defined as a type of cognitive bias in which the participant responds the way he or she believes the experimenter wants him or her to respond rather than relying on one’s true perceptions. An example of this would be a participant’s reporting of decreased pain during an experimental task because the participant believes the researcher desires a decreased pain rating, rather than the participant providing an accurate rating of his or her pain. Garnering additional information regarding the external and experiential factors associated with placebo analgesia is crucial in squelching the belief that placebo responding is merely due to confounding variables like response bias.

**Discrimination Tasks and Somatic Focus**

As McNicol (1972) points out, human decisions are made on the availability of evidence; furthermore, these decisions are frequently made with some degree of uncertainty. There is evidence that individuals vary in the amount of time spent attending to various environmental cues, including the degree to which an individual attends to his or her own somatic cues (Anderson & Pennebaker, 1980). Individuals also vary in their abilities to discriminate between these cues (Pennebaker & Skelton, 1981). Furthermore, individuals may likely describe identical stimuli in very different ways. For example, some individuals may describe a thermal stimulus of a particular temperature and duration as “painful,” whereas other individuals may describe this same sensation as “non-painful.” Conclusions from a review by Wool and Barsky (1994) suggest that women somatize more than men. A more recent study by Hiller and colleagues (2006) also report that increased somatization is associated with being female. It is unclear, however, whether this difference in pain perception is due to sensory or non-sensory factors, such as psychological distress. A recent study by Soetanto, Chung and Wong (2004) found that a sample of females showed enhanced sensory discriminability compared to the sample of males in their study. Additionally, these researchers concluded that women were less stoical in their
responses to pain (Soetanto et al., 2004). These results led these researchers to conclude that this enhanced discriminability in females may explain why females tend to report more pain and seek healthcare more frequently than do males. Additionally, other researchers have suggested that placebo analgesia is partially due to a patient's tendency "to try to please the investigator and report improvement when none has occurred" (Hrobjartsson & Gotzsche, 2001). Despite previous research, additional investigations are warranted in order to determine the mechanisms responsible for placebo responding, including establishing the role of sensory discriminability and response bias in pain reporting and placebo responding.

Somatic focus refers to an individual’s tendency to notice and attend to their physical symptoms. Considering the role of somatic focus as a mechanism of placebo responding draws from the literature on expectancy. As Geers and colleagues theorized and concluded, placebo responding is partially due to an individual’s expectations that consistently guide his or her detection and interpretation of somatic cues (Geers, Helfer, Weiland, & Kosbab, 2006). The meaning that individuals give to their sensations can have immense implications for their psychological and physical health (Cioffi, 1991). Additionally, the relationship between somatic focus and pain (including both clinical and experimental pain) is largely unknown. Data suggest, however, that individuals suffering from chronic pain conditions may exhibit hypersensitivity to experimental stimuli. A recent study reported that a group of veterans with chronic gastrointestinal symptoms exhibited visceral and cutaneous hypersensitivity compared to control participants; these individuals also had significantly higher scores on a measure of somatic focus, which accounted for a large amount of the variance in their reports of pain (Dunphy et al., 2003). Additionally, recent research has suggested that somatic focus has a role in placebo responding
This study concluded that individuals’ degree of somatic focus moderated the effect of placebo expectations on placebo responding.

Garnering additional information about placebo analgesia would provide a greater understanding of the mechanisms associated with human pain. Placebo analgesia provides several advantages to other methods of pain reduction; for instance, placebo analgesia may be noninvasive and may lack many of the side effects of various pain medications. Research has shown that the use of placebo has been shown to produce analgesic effects in asymptomatic controls (Amanzio & Benedetti, 1999; Chung et al., 2007; Montgomery & Kirsch, 1996; Price et al., 1999; Voudouris et al., 1985, 1989, 1990). Conditioning and expectancy explain some of the effects of placebo responding, while other factors, such as an individual’s level of somatic focus, may contribute to additional effects. Each of the advancements in the study and measurement of placebo analgesia will contribute to a better understanding of the mechanisms of this phenomenon and improvements in the clinical treatment of the pain conditions. To increase the knowledge of placebo effects within experimental designs, with both asymptomatic and symptomatic samples, has extensive implications for the psychological and medical fields.

Signal Detection Theory (SDT) and the Placebo: A Brief Overview of Previous Research

In 1969, Clark applied methodology based on the Signal Detection Theory (SDT) to analyze his data obtained during experimental pain testing. Clark’s research included a placebo group and a control group. Those participants in the placebo condition were asked to ingest an inert substance that they were told would decrease the sensations of the radiant stimuli and would decrease the pain experienced from these stimuli. Both of these groups were asked to rate the intensities of a number of radiant stimulation. Subsequently, those individuals in the placebo condition rated significantly fewer painful responses compared to those individuals in the control condition. The SDT analysis employed by Clark revealed that the effect of the placebo altered
the participants’ biases toward reporting a given stimulus as “painful”; however, Clark reported that the sensory discriminability did not differ between conditions. A few years later, Feather, Chapman and Fisher (1972) provided additional support for the general conclusions drawn by Clark in 1969. These researchers reported that the placebo effects of their study could be explained by a decreased bias toward reporting the stimuli as painful.

Additional research examines similar components of the signal detection theory. In an additional investigation, Clark and colleagues investigated the effects of acupuncture on pain responding in an experimental setting. Using an SDT framework, these researchers reported decreased biases to report stimuli as painful in the acupuncture condition, but they noted no differences in response bias in the control group. However, other researchers attempting to explain analgesic effectiveness have suggested that in addition to changes in participants’ biases to report pain, there may also be decreased sensory discriminability (Chapman, Gehrig, & Wilson, 1975a, 1975b). As proposed by Chapman, Murphy and Butler (1973), the analgesic response to radiant heat stimulation was found to be due both to reductions in sensory discriminability and a response bias toward labeling the experimental stimulation as less painful.

Preliminary Studies and Future Directions

Researchers have investigated the various aspects of a number of acute and chronic pain conditions as well as experimentally induced pain. The various aspects under investigation have included both the psychological and physiological components of pain as they related to the individual and his or her subjective experience of pain. Chung and colleagues (2007) recently completed an investigation using a placebo design with verbal placebo suggestion and conditioning to induce placebo responses in a sample of asymptomatic controls. This study also examined the effects of providing information regarding participants’ placebo responses on future pain responses. They discovered that there were no significant differences between
participants who were told they experienced a placebo response versus those who were not told. Additionally, these researchers found that the placebo effect persisted (even though the magnitude of the response decreased somewhat) when a second inert cream was used after participants were told that the first cream used in the study was a placebo.

Furthermore, an investigation by Chung and colleagues (2007) assessed the role of somatic focus on overall pain response. This researcher found that a measure of somatic focus was predictive of participants’ experiences of a first placebo response. Results from this study also found that desire was a more consistent predictor or placebo analgesia than was expectation.

Researchers have effectively induced placebo analgesia through verbal suggestion and have developed a successful conditioning paradigm to condition placebo analgesia in an experimental setting with asymptomatic control individuals (Chung et al., 2007; Voudouris et al., 1985, 1989, 1990). Research has also assessed the experiential factors of expectancy and desire in placebo responding. Additionally, this research has shown that placebo analgesia is related to somatic focus in both clinical and asymptomatic samples. Gaining a better understanding of the precise relationship of somatic focus with placebo analgesia is needed, and this study intends to decompose the mechanisms of placebo analgesia.

**Proposed Study**

The proposed study employed a verbal suggestion and conditioning paradigm similar to the one used previously by Chung and colleagues (2007). This study intended to induce placebo responses in asymptomatic participants during several thermal stimulation trials. The purposes of this study are to investigate the relationships of sensory discriminability and response bias to placebo responding, and to determine the relationships of these variables to somatic focus and the experiential factors of placebo responding (expectancy and desire).
By employing this proposed paradigm, we tested two competing hypotheses: a “traditional analgesic response hypothesis” and a “somatic focus hypothesis.” Previous research on signal detection theory (SDT) and analgesic effectiveness suggests that a decrease in a participant’s discriminability is associated with an analgesic response (Chapman et al., 1975a, 1975b; Chapman, Murphy, and Butler, 1973). Additionally, the placebo analgesic response has been shown to be associated with biases for reporting thermal stimulation as less painful (Chapman et al., 1975a, 1975b; Clark, 1969; Clark & Yang, 1974; Clark, Yang, & Hall, 1975; Feather et al., 1972; Yang, Richlin, Brand, Wagner, & Clark, 1985). For the purposes of this study, we defined the “traditional analgesic response hypothesis” as a decrease in sensory discriminability and a bias toward reporting stimuli as “not painful.” Therefore, in the case of this first competing hypothesis, we expected to see a decrease in discriminability associated with placebo responding and a bias toward decreased reporting of a stimulus as “painful.” That is, we expected to observe decreased pain intensity ratings during the placebo manipulation due to a decrease in sensory discriminability.

However, data assessing the role of somatic focus in placebo responding, suggests that increased reports of somatic focus are associated with increased placebo responding (Geers et al., 2006). This information suggests that an increase in somatic focus may be associated with an increase in discriminability, as individuals are focusing more attention to somatic cues. This increased discriminability may be associated with a change in the response bias component of a participant’s report of pain, with individuals having a bias toward perceiving and reporting all thermal stimuli as less painful.

This proposed experimental design will add to the current placebo literature by providing detailed information regarding the mechanisms of placebo responding. Support for these
hypotheses would be inconsistent with claims that the placebo response is wholly a function of response bias or demand characteristics of the experimental procedure as put forth by Hrobjartsson and Gotzsche (2001). Additionally, these anticipated findings will support our hypothesis that the placebo analgesic response is largely due to a reinterpretation of nociceptive input as a result of interplay between somatic focus and the expectation of pain relief from placebo instructions and placebo conditioning.

**Power Analysis**

A study investigating the role of somatic focus on expectations and placebo responding in a 2-group sample of asymptomatic control individuals achieved statistically reliable results with a sample size of 54 (Geers et al., 2006). We assumed similar large effect sizes (Cohen’s d of 1.04 to 1.16), indicating a total sample size in the range of 20 to 26 in order to achieve a power of 0.8 with alpha at 0.05. Another study investigating pain conditioning and use of a topical ointment in a 2-group sample of asymptomatic control individuals achieved statistically reliable results with a sample size of 77 (Chung et al., 2007). We assumed similar moderate to large effect sizes, (Cohen’s d of 0.60 to 0.99), indicating a total sample size in the range of 28 to 72 in order to achieve a power of 0.8 with alpha at 0.05. This previous study by Chung and colleagues (2007) found that a majority (83%) of participants demonstrated a placebo response; however, approximately one-sixth of participants in the placebo induction group did not exhibit a placebo response (as defined in their study). Given that not all participants who are randomized into a placebo induction group will exhibit a placebo response, we over-sampled participants. This oversampling was especially important for this study, as the initially proposed analyses were to include only those individuals who demonstrated a placebo response (as defined as a change score greater than zero). As proposed, participants who did not demonstrate a placebo response were to be excluded from statistical analyses.
CHAPTER 2
MATERIALS AND METHOD

Participants and Setting

The participants were one hundred and twenty asymptomatic adults, 65 female (54.2%) and 55 male (45.8%). Fifty-nine participants were randomly assigned to the placebo condition and 51 participants were randomly assigned to the repeated baseline condition. Additionally, ten other participants were tested in the placebo condition by an experimenter of a different gender. The average age was 22.7 (SD = 4.4) years and the mean years of formal education was 15.6 (SD = 1.9) years. The racial/ethnic background for the sample was as follows: 78 Caucasian (65.0%), 13 African American (10.8%), 12 Hispanic (10.0%), 12 Asian Americans (10.0%), and 4 individuals of another racial or ethnic background (3.3%). The majority (85.8%) of this sample are full-time students, and 14 (11.7%) are employed full-time.

These participants were recruited via advertisements posted throughout the University of Florida. Prior to inclusion in this study, a brief screening was conducted. Before beginning the experimental protocol, all participants read and signed an institutionally approved consent form; this consent form provided information about the nature of the noxious thermal stimulation to be used during this investigation. At this time, the participants were advised that they could withdraw their consent at any time without it negatively affecting them. As approved by the institutional review board, all participants received either monetary compensation or class credit at the University of Florida for their participation in this study.

Individuals were excluded from this study if they endorsed a previous history of heart conditions, hypertension, diabetes mellitus, asthma, seizures, frostbite, past trauma to the hands, lupus erythematosus or arthritis. Additionally, individuals who were currently taking pain medication were excluded from participation in this study. Participants were required to read,
understand and respond to verbal and written English. All participants were tested in an experimental testing room in the Center for Pain Research and Behavioral Health at the University of Florida.

**Apparatus**

All thermal stimuli were delivered via a computer-controlled Medoc Thermal Sensory Analyzer. This device is a peltier-element-based stimulator that is frequently used in experimental pain testing. Additionally, this computer-controlled device is capable of reaching a variety of temperatures, including those in the noxious range of 45°C to 51°C. More specifically, the range of temperatures of this device range from a resting, nonpainful temperature of 33°C to noxious temperature of 51°C; this range of temperatures has been used in a variety of previous studies and has been shown to be safe in both asymptomatic individuals and pain patients (Chung et al., 2007; Robinson, Wise, Gagnon, Fillingim, & Price, 2004). Stimuli were applied in a random order to the forearms by a contact thermode, and the duration of the stimulus presentation was three seconds per trial. Additionally, the stimulus presentation was timed so that the same site on a participant’s forearm would not be closer in time than three minutes; this precaution was taken in order to avoid sensitization of any of the testing sites.

**Placebo Cream**

The placebo-conditioning paradigm included the use of an inert cream acting as a placebo analgesic. This cream consisted of a mixture of over-the-counter cold cream, linalool/oil of thyme in a ratio of 8:1. The components of this placebo cream have a distinctive, medicinal smell and have been used in previous conditioning studies by Voudouris and colleagues (1990) and by Chung and colleagues (2007). The control cream consisted of a mixture of over-the-counter cold cream and water in a ratio of 8:1. Both of these creams were placed in two identical labeled bottles, and the creams were applied to the ventral areas of the forearms.
**Mechanical Visual Analog Scale (VAS)**

Participants were asked to use visual analogue scales to rate their experimental pain, his or her expectation of pain, and his or her desire for pain relief. The end points of these scales were designated as “no pain” and as “the most intense pain imaginable.” Visual analogue scales have been validated as ratio scale measures of sensory intensity and affective magnitude in chronic pain. Additionally, a VAS will be used in this study to assess each participant’s mood. This will take into account a variety of negative feelings that may be associated with the pain experience, including: depression, anxiety, frustration, fear, and anger. The end points for these mood rating were designated as “none” and “the most severe imaginable.”

**Measures**

All participants were assessed via a multidimensional testing battery, which included a measure of somatic focus. Individuals were randomized to either complete this packet of questionnaires prior to sensory testing or after sensory testing.

**Demographic Questionnaire**

Participants completed a questionnaire assessing for age, sex, race/ethnicity, highest level of education completed, income, occupation, and marital status. This demographic questionnaire also included information on previous pain experiences.

**Pennebaker Inventory of Limbic Languidness (PILL)**

The PILL (Pennebaker, 1982) is a 54-item scale that measures the frequency of a set of common physical symptoms and sensations. Participants provide responses using a five-point Likert scale. The scores of these 54 items can simply be summed to create a total score. The PILL has been shown to be a good measure of the level of somatization in asymptomatic individuals (Gijsbers van Wijk, van Vliet, & Kolk, 1996).
**Somatosensory Amplification Scale (SAS)**

The SAS is a 10-item self-report measure and participants rate the degree to which each of these 10 items is characteristic of them. The SAS uses an ordinal scale, and participants are asked to rate using a 1 to 5 scale. The total scores can range from 10 to 50, with higher scores indicating greater symptom amplification. Research indicates that the score of the SAS is a predictor of impairments in physical, psychological and social functioning (Kroenke et al., 1994). Additionally, SAS scores correlate closely with the number of somatic symptoms in patients (Nakao, Barsky, Kumano, & Kuboki, 2002).

**Illness Attitude Scale (IAS)**

The IAS (Kellner, Abbott, Winslow & Pathak, 1987) is a self-report measure consisting of 9 subscales. These subscales are designed to assess attitudes, fears and beliefs associated with hypochondriasis. The IAS has been shown to have high test-retest reliability in normal subjects and is positively related to other measures assessing hypochondriacal and somatization concerns (Sirri, Grandi, & Fava, 2008).

**Beck Depression Inventory - Second Edition (BDI-II)**

The BDI-II (Beck, Steer, & Brown, 1996) is a 21-item self-report measure of the existence and severity of a variety of depressive symptoms. The total score is determined by summing all items, and this score can range from 0 to 63. Scores of 0 to 13 are considered to be in the "minimal" range, scores in the 14-19 range are considered "mild," moderate scores are in the range of 20 to 28, and scores above 29 are considered to be "severe."

**Procedure**

This study consisted of a series of four consecutive pain testing stages that occurred during one experimental session. All participants participated in four, consecutively administered pain testing stages. Participants were informed that they would be participating in an experimental
pain study investigating the effects of an ointment on pain responding. After participants expressed an interest in and met inclusion criteria for participation in this study, informed consent procedures were conducted as approved by the Institutional Review Board of the University of Florida. Each participant was randomized into one of two groups, either a placebo group or repeated baseline group. All participants underwent a series of testing stages in which they received a series of heat stimuli applied to eight areas of their forearms.

Additionally, the study design consisted of a total of 44 thermal stimuli presentations plus the number of thermal stimuli (maximum of 9) required to determine the idiosyncratic temperatures to be used in later stages (as determined by the ascending series).

**Ascending Series (Stage 1)**

During the first stage, the following set of instructions was provided to each participant:

You will consecutively undergo several sensory-testing sessions using a heat thermode. During these sessions, you will receive several brief heat pulses of varying temperatures applied to different areas of your forearms. These heat pulses will range from undetectable to painful. You will also be asked to provide responses to several questionnaires about yourself and your health and mood.

One-half of the participants were randomly assigned to complete this battery of questionnaires prior to receiving the experimental thermal stimuli, while the other half of participants completed these questionnaires at the end of all four stages.

The first stage consisted of calibration trials conducted to control for individual differences in pain perception. An ascending series of trials was conducted in order to determine individual thresholds and to determine a “control temperature” and “placebo temperature” to use in later stages (described below). During the ascending series, temperature of the thermal stimuli began at 43°C and increased by 1°C over the course of trials up to 51°C. This stage included a maximum of nine trials. The participants were asked to rate the pain intensity immediately following the thermal stimuli through the use of a mechanical visual analogue scale (M-VAS).
following each trial. On a 0 to 10 scale, the temperatures at which the patients rated his or her pain intensity between a 0 and 2 and between 4 and 6 were noted; the former temperature served as a "placebo temperature," while the latter temperature served as a "control temperature." These individually determined temperatures were used in later stages.

**Baseline Rating Task (Stage 2)**

In this stage, participants participated in a baseline rating task where they were presented with 18 stimuli at 6 different temperatures. These 6 different temperatures were idiosyncratically determined based on ratings during the ascending series. The first two temperatures used were the individual’s “control temperature” and “placebo temperature,” as determined by the ascending series. Adding and subtracting 1 C˚ from these control and placebo temperatures determined the additional thermal stimuli temperatures to be used. Immediately following each stimulus, participants were asked to rate the pain intensity through the use of an M-VAS. The presentation of heat stimuli was randomized within blocks, so that a stimulus of a given temperature would not be presented until all six temperatures within that block were presented.

**Suggestion and Conditioning (Stage 3)**

During the third stage, each participant in the placebo condition was provided with further details about the nature of this study, including the explanation of the use of the "analgesic cream." These participants were told, “The cream you have just been given is known to significantly reduce pain in some patients. The level of stimulation during this session will remain constant throughout all trials.” Each individual received a series of eight thermal stimuli trials that were counterbalanced for forearm location. We chose to use a series of eight trials because repeated pairings are necessary for conditioning to occur. The use of the placebo cream accompanied four of these trials, while the other four trials were completed without the use of any cream. The thermode was placed on a randomly selected site on one of the forearms and the
thermal stimuli were applied. The temperature of the stimulus was lowered with the use of the placebo cream, in order to produce the conditioning effect. Each participant was asked to rate the pain intensity using an M-VAS immediately following each trial.

Those participants assigned to the repeated baseline condition were told that they are in the control condition and that they will receive an inactive cream throughout the study. These participants underwent a series of 8 trials at his or her individually determined control temperature without any reductions in stimulus intensity, as to prevent conditioning from occurring in this group. Expectations for pain and desire for pain relief (both rated using a VAS) were assessed from both groups before the initiation of the thermal stimuli.

**Post-Suggestion and Post-Conditioning (Stage 4)**

During the fourth stage, participants were presented with another 18 thermal stimuli, three trials of six unique temperatures. These six temperatures were the same idiosyncratically determined temperatures used in the baseline rating task (Stage 2). Again, the participants in the placebo group were told, “We will retest the cream, now using various degrees of temperatures. The cream you have just been given is known to significantly reduce pain in some individuals.” Those individuals in the repeated baseline group were, again, informed that they are in the control condition and they will receive an inactive cream. Immediately following each stimulus, participants were asked to rate the pain intensity through the use of an M-VAS. The presentation of thermal stimuli was, again, randomized within blocks, so that a given temperature was not repeated until all six temperatures within that block have been presented. At the end of this stage, all participants were asked: “How easy was it to pay attention to these stimuli?” They were asked to provide a rating on an M-VAS.
Table 2-1. Protocol for the placebo and repeated baseline groups.

<table>
<thead>
<tr>
<th>Recruiting Information Prior to Consenting</th>
<th>Placebo Group</th>
<th>Repeated Baseline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants were told they would be participating in a study examining the effects of an ointment on pain.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Randomization</th>
<th>Placebo Group</th>
<th>Repeated Baseline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants were randomized into one of two groups (Placebo Group or Repeated Baseline Group).</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Information</th>
<th>Placebo Group</th>
<th>Repeated Baseline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants were told: “You will consecutively undergo several sensory-testing sessions using a heat thermode. During these sessions, you will receive several brief heat pulses of varying temperatures applied to different areas of your forearms. These heat pulses will range from undetectable to painful. You will also be asked to provide responses to several questionnaires about yourself and your health and mood.”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Questionnaires</th>
<th>Placebo Group</th>
<th>Repeated Baseline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants received the same packet of questionnaires. (Half completed these questionnaires prior to Stage 1, while the other half completed these questionnaires following Stage 4.)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ascending Series (Stage 1)</th>
<th>Placebo Group</th>
<th>Repeated Baseline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants were asked to rate their perceived pain intensities of heat pulses beginning at 43 C° and increasing by 1 C°. These ratings determined the idiosyncratic temperatures to be used in the remainder of the protocol.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Rating Task (Stage 2)</th>
<th>Placebo Group</th>
<th>Repeated Baseline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>All participants were presented with 18 stimuli at 6 different temperatures (as idiosyncratically determined in previous step). Participants were asked to rate the pain intensity immediately following each stimulus presentation.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Suggesting and Conditioning (Stage 3)</th>
<th>Placebo Group</th>
<th>Repeated Baseline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants were told: “The cream you have just been given is known to significantly reduce pain in some individuals.”</td>
<td></td>
<td>Participants were told: “You are in the control condition, and we will be testing the inactive cream in your condition.”</td>
</tr>
<tr>
<td>Participants were presented with a series of 8 trials. Participants’ placebo temperature and use of cream will be used in 4 trials, while 4 trials will use participants’ control temperatures.</td>
<td></td>
<td>Participants were presented with a series of 8 trials, with their control temperature used in all 8 trials.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-Suggestion and Post-Conditioning (Stage 4)</th>
<th>Placebo Group</th>
<th>Repeated Baseline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants were told: “We will retest the pain relieving cream, now using various degrees of temperatures. Again, the cream you have just been given is known to significantly reduce pain in some individuals.”</td>
<td></td>
<td>Participants were told: “You will now receive more heat pulses, and again we will be testing the inactive cream in your condition.”</td>
</tr>
<tr>
<td>All participants were presented with 18 stimuli at 6 different temperatures (same temperatures as used during the Baseline Rating Task). Participants were asked to rate the pain intensity immediately following each stimulus presentation. Additionally, all participants will be asked: “How easy was it to pay attention to the stimuli?”</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CHAPTER 3
RESULTS

Verification of the Placebo Effect

We calculated the grand means of pain ratings across all six temperatures used in Stage 2 and in Stage 4. Each participant’s placebo response was calculated by subtracting their grand mean of pain ratings during Stage 4 from their grand mean of pain ratings during the baseline rating task of Stage 2. Individuals were considered to be “placebo responders” if they had difference scores greater than zero. Twenty of 69 (28.9%) of participants demonstrated a placebo response and only these individuals were considered for the following analyses. Of individuals receiving a placebo response, 14 (70%) were male and 6 (30%) were female. The mean age of placebo responders was 21.85 years. The racial/ethnic breakdown is as follows: Caucasian (65%), African American (5%), Hispanic (10%), Asian American (10%), and 10% identified themselves of a different racial/ethnic background than the categories listed. Additionally, 31 individuals demonstrated a nocebo response, which was defined as a difference score greater than zero. Another 18 individuals were excluded from completing the entire sensory testing protocol, because of their pain intensity ratings. Four of these 18 (22.2%) individuals provided pain ratings too high to continue with the study, while the majority (77.8 %) provided pain ratings too low to continue with the study.

Pain Intensity Ratings

We examined the main and interaction effects of group, time, and level of stimulation. To do this, we conducted a mixed model repeated measures ANOVA with time as a within subject factor (2), idiosyncratically determined temperature as a within subject factor (6) and group as a between subject factor (2). Results indicated a non-significant main effect of pain intensity ratings for group (F(1, 55) = .000, p = .991); however, results indicated a significant time (Stage
2 and Stage 4) by group (placebo group and repeated baseline group) interaction (F(1, 55) = 7.48, p < .01), with the placebo group reporting less intense pain at Stage 4 compared to Stage 2 and the repeated baseline group reporting more intense pain across stages. Temperatures and pain intensity ratings for all groups are listed in the Appendix.

![Figure 3-1](image)

**Figure 3-1.** Pain ratings at baseline (Time 1) and post-conditioning (Time 2)

* p < 0.05

**Response Bias and Discriminability: Placebo Responders Only**

In order to assess pain perception in the placebo group, we examined both discriminability (represented by slopes) and response bias (represented by intercepts). First, we calculated the mean of the M-VAS pain intensity ratings at each of the idiosyncratically determined temperatures for each participant. We then calculated individual slope and intercept values for each participant and used these values in subsequent analyses. Two separate regressions were run to test the hypotheses that scores on a measure of somatic focus (PILL) are positively related to the component of sensory discriminability, while expectations for pain are positively related to response bias and desire for pain relief is negatively related to response bias. Analysis of the regression equations revealed that there is no relationship between sensory discriminability
(represented by slope values) and PILL scores ($R^2 = .055$, $F(1, 17) = 0.929$, $p = .349$), IAS total scores ($R^2 = .058$, $F(1, 18) = 1.051$, $p = .320$) or SAS total scores ($R^2 = .009$, $F(1, 19) = 0.164$, $p = .690$). These analyses also revealed no relationship between response bias (represented by y-intercept values) and expectation of pain ($R^2 = .004$, $F(1, 18) = 0.069$, $p = .796$). There was also no relationship between response bias and desire for pain relief ($R^2 = .000$, $F(1, 18) = 0.004$, $p = .948$).

**Mood**

The main and interaction effects of group (placebo group and repeated baseline group) by time (Pre and Post) for the five assessed mood variables (depression, anxiety, frustration, anger, fear) were examined. Repeated measures ANOVAs were conducted to examine these effects. Tests of between-subject effects revealed no significant main effects of condition for depression, anxiety, frustration, anger or fear. Tests of within-subject effects revealed no changes for time in depression, anxiety, frustration or anger. However, significant changes for time were found in fear ($F(1, 55) = 4.631$, $p < 0.05$). There was a significant time by condition interaction for the M-VAS rating for depression ($F(1, 55) = 5.288$, $p = 0.05$). Those individuals who were placebo responders reported significantly higher scores on the BDI-II ($M = 11.100$, $SD = 6.300$)

<table>
<thead>
<tr>
<th>Mood</th>
<th>Placebo Group</th>
<th>Repeated Baseline Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>Depression</td>
<td>M = 0.760</td>
<td>M = 0.605</td>
</tr>
<tr>
<td></td>
<td>SD = 1.133</td>
<td>SD = 1.207</td>
</tr>
<tr>
<td>Anxiety</td>
<td>M = 0.575</td>
<td>M = 0.960</td>
</tr>
<tr>
<td></td>
<td>SD = 0.689</td>
<td>SD = 1.415</td>
</tr>
<tr>
<td>Frustration</td>
<td>M = 0.480</td>
<td>M = 0.385</td>
</tr>
<tr>
<td></td>
<td>SD = 0.879</td>
<td>SD = 0.728</td>
</tr>
<tr>
<td>Anger</td>
<td>M = 0.190</td>
<td>M = 0.130</td>
</tr>
<tr>
<td></td>
<td>SD = 0.430</td>
<td>SD = 0.234</td>
</tr>
<tr>
<td>Fear</td>
<td>M = 0.470</td>
<td>M = 0.145</td>
</tr>
<tr>
<td></td>
<td>SD = 0.607</td>
<td>SD = 0.415</td>
</tr>
</tbody>
</table>
compared to the scores of those individuals in the repeated baseline group (M = 7.02, SD = 11.192) (F(69) = 3.739, p = 0.05).

**Nocebo Responders**

Given that so few of the participants demonstrated a placebo response as it was initially defined, we wanted to obtain additional information about the characteristics of these other participants. Although not hypothesized, a number of individuals demonstrated a nocebo response. Individuals were considered to be "nocebo responders" if they had difference scores less than zero (calculated by subtracting their grand mean of pain ratings during Stage 4 from their grand mean of pain ratings during the baseline rating task of Stage 2). Of individuals demonstrating a nocebo response, 12 (38.7%) were male and 19 (61.3%) were female. The mean age of nocebo responders was 23.74 years. The racial/ethnic breakdown is as follows: Caucasian (64.5%), African American (6.5%), Hispanic (9.7%), Asian American (12.9%), and 6.5% identified themselves of a different racial/ethnic background than the categories listed.

![Figure 3-2. Pain ratings at baseline (Time 1) and post-conditioning (Time 2) for all participants. * p < 0.05  ** p < 0.001](image-url)
Response Bias and Sensory Discriminability: Placebo and Nocebo Responders

In order to assess pain perception in our entire sample, additional regressions were run to examine sensory discriminability and response bias. As previously described, the mean pain intensity ratings were calculated at each of the idiosyncratically determined temperatures for all participants. We then calculated individual slope and intercept values and these values were used for subsequent analyses. The first of two regressions was run to test the hypothesis that scores on the PILL are positively related to the component of sensory discriminability. The second regression was conducted to test the hypotheses that expectations for pain are positively related to response bias and desire for pain relief is negatively related to response bias. Analyses of these regressions revealed that there is no reliable relationship between discriminability (as represented by slope values) and PILL total score ($R^2 = 0.002$, $F(1, 42) = 0.087$, $p = 0.770$; $t = 0.295$, std. $\beta = 0.046$), SAS total score ($R^2 = 0.086$, $F(1, 42) = 0.310$, $p = 0.580$; $t = 0.557$, std. $\beta = 0.086$) or IAS total score ($R^2 = 0.015$, $F(1, 43) = 0.677$, $p = 0.415$; $t = 0.823$, std. $\beta = 0.124$).

Additionally, there is no reliable relationship between response bias (represented by y-intercept values) and expectation of pain ($R^2 = 0.024$, $F(1, 45) = 1.077$, $p = 0.305$; $t = -1.038$, $p = 0.305$, std. $\beta = -0.155$) and desire for pain relief ($R^2 = .001$, $F(1, 45) = 0.029$, $p = 0.866$; $t = 0.170$, $p = 0.170$, std. $\beta = 0.026$).

Pain Intensity Ratings: All Participants

Given that relatively few participants demonstrated a placebo response, as defined as having a change score greater than 0, we hypothesized that differing degrees of sensitization may have been associated with the observed separation between “placebo responders” and “nocebo responders.” In order to re-examine the hypotheses, we included all individuals who were randomized into the Placebo Induction group (irrespective of their increases or decreases in pain intensity ratings over time) and compared these participants to those randomized into the
Repeated Baseline group. We re-examined the main and interaction effects of group (Placebo Induction group by Repeated Baseline group), time, and level of stimulation. To do this, we conducted a mixed model repeated measures ANOVA with time as a within subject factor (2) and group as a between subject factor (2). Results indicated a significant main effect for time, with both groups reporting increased pain intensity ratings from Stage 2 to Stage 4 (F(1, 81) = 11.482, p = .001). However, there was no significant main effect for group (F(1, 81) = .725, p = .397) and no significant time by group interaction (F(1, 81) = .034, p = .855). The pain intensity ratings for the two groups at each time point can be seen in Figure 3-3.

![Figure 3-3. Pain intensity ratings at Time 1 and Time 2 for placebo induction and repeated baseline groups.](image)

**Response Bias and Discriminability: All Participants**

After collapsing both the placebo responders and nocebo responders into one group, we then re-examined the hypothesized relationships between discriminability and somatic focus and between expectations and desire with response bias. The mean M-VAS pain intensity ratings at each of temperatures was calculated for each participant. Next, individual slope and intercept values for each participant were calculated and these values were used in the following analyses.
We ran these regressions to test the hypotheses that scores on measures of somatization (i.e., PILL, IAS, SAS) are positively related to the component of sensory discriminability, while expectations for pain are positively related to response bias and desire for pain relief is negatively related to response bias. Analysis of the regression equations revealed that there is no relationship between sensory discriminability and PILL scores ($R^2 = .000$, $F(1, 78) = 0.025$, $p = .874$), SAS scores ($R^2 = .000$, $F(1, 78) = 0.004$, $p = .947$) or IAS scores ($R^2 = .001$, $F(1, 78) = 0.095$, $p = .759$). These analyses revealed that the relationship between response bias and expectation of pain is approaching statistical significance ($R^2 = .043$, $F(1, 82) = 3.666$, $p = 0.059$). However, there was also no relationship between response bias and desire for pain relief ($R^2 = .004$, $F(1, 82) = 0.299$, $p = 0.586$).

**Exploratory Analyses of Group Differences**

As previously mentioned, the placebo induction was successful for only 20 participants, while 31 participants exhibited a nocebo response. Due to this, we examined both groups to determine if any differences existed between placebo and nocebo groups. Analyses of placebo responders and nocebo responders revealed a statistically significant difference between groups on a single-item rating of attention (i.e., “How easy was it for you to pay attention to these [thermal] stimuli?”) [$F(1, 42) = 6.374$, $p = 0.015$, Cohen’s $d = 0.79$], with nocebo responders reporting that they were better able to pay attention to these stimuli compared to placebo responders. Additionally, analyses revealed that there were statistically significant sex differences between placebo responders and nocebo responders, with males being more likely to have a placebo response while females were more likely to be nocebo responders [$\chi^2(1, 51) = 4.763$, $p < 0.05$]. A discriminant analysis was performed to determine the contribution of a variety of variables to group membership. Individuals' responses to a question of attention and
participant sex were the strongest contributors to group membership. Other contributors to group membership are provided in Table 3-2. These analyses revealed that 77.3% of cases were correctly classified based on these variables.

Table 3-2. Pooled within-groups correlations between discriminating variables

<table>
<thead>
<tr>
<th></th>
<th>r</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention to Stimuli</td>
<td>.452</td>
</tr>
<tr>
<td>Sex</td>
<td>.401</td>
</tr>
<tr>
<td>Marital Status</td>
<td>.282</td>
</tr>
<tr>
<td>PILL Total</td>
<td>-.253</td>
</tr>
<tr>
<td>SAS Total</td>
<td>-.251</td>
</tr>
<tr>
<td>Age</td>
<td>.156</td>
</tr>
<tr>
<td>BDI Total</td>
<td>-.147</td>
</tr>
<tr>
<td>IAS Total</td>
<td>.015</td>
</tr>
</tbody>
</table>

As previously mentioned, 18 participants were excluded from this study following the Ascending Series trial. These individuals were excluded from continued participation because their ratings of pain intensity did not fall within the predetermined range for this study. In an effort to determine if any differences existed between participants included versus those excluded, we compared all individuals who were initially randomized to the placebo induction group. We found that those 18 individuals excluded from participation based on their initial pain ratings had significantly lower PILL scores compared to both the placebo responders and the nocebo responders \[F(1, 58) = 3.193, p = 0.048\]. Although not statistically different, there was a trend for these excluded individuals to have lower scores on a variety of outcome measures (see Table 3-3). There were no significant differences for these excluded individuals on demographic variables compared to the placebo or nocebo responders.

Table 3-3. Means and standard deviations for outcomes measures

<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo Responders</th>
<th>Nocebo Responders</th>
<th>Excluded Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>PILL</td>
<td>M= 114.47 SD= 27.91</td>
<td>M= 102.67 SD= 26.41</td>
<td>M= 92.24 SD= 21.83</td>
</tr>
<tr>
<td>SAS</td>
<td>M= 17.65 SD= 6.95</td>
<td>M= 15.04 SD= 5.37</td>
<td>M= 13.53 SD= 5.44</td>
</tr>
<tr>
<td>IAS</td>
<td>M= 33.12 SD= 14.31</td>
<td>M= 33.41 SD= 8.35</td>
<td>M= 30.29 SD= 13.57</td>
</tr>
<tr>
<td>BDI</td>
<td>M= 11.10 SD= 6.30</td>
<td>M= 6.63 SD= 7.79</td>
<td>M= 6.82 SD= 7.58</td>
</tr>
</tbody>
</table>
Correlations Among Measures of Mood, Somatization and Attention

In order to examine the relationships among the measures used in this study, we conducted correlational analyses using total scores for the BDI-II, the PILL, the SAS, and the IAS. Additionally, the M-VAS ratings of the 5 assessed mood variables (depression, anxiety, frustration, anger and fear) were included, as was the M-VAS rating of the single-item assessment of attention paid to thermal stimuli. These analyses suggest that the BDI-II is significantly correlated with all three measures of somatization: PILL (r(76) = .547, p < 0.001), SAS (r(76)= .294, p .009), and IAS (r(76) = .284, p = .012). The BDI-II is also significantly correlated with several of the single-item mood variables: depression (r(79) = .550, p < 0.001), frustration (r(79) = 0.289, p = 0.009), and anger (r(79) = .231, p = 0.038); however, the BDI-II was not significantly correlated with the single-item assessment of anxiety. All three measures of somatization are significantly correlated: PILL and SAS (r(74) = 0.462, p < 0.001), PILL and IAS (r(74) = 0.479, p < 0.001), and IAS and SAS (r(74) = 0.680, p <0.001). The PILL total score was not significantly correlated with the single-item measure of anxiety (r(77) = 0.121, p = .287). The single-item assessment of attention paid to the thermal stimuli was not significantly related to any of the measures of somatization, suggesting that item is measuring a different construct from somatic focus or somatization. The measure of attention was negatively correlated with a single-item assessment of anger (r(80) = -0.262, p = 0.018). Table 3-4 includes a complete listing of these correlations.
Table 3-4. Correlation matrix for measures of mood, somatization and attention

<table>
<thead>
<tr>
<th></th>
<th>BDI</th>
<th>PILL</th>
<th>SAS</th>
<th>IAS</th>
<th>Attention</th>
<th>Depression</th>
<th>Anxiety</th>
<th>Frustration</th>
<th>Anger</th>
<th>Fear</th>
</tr>
</thead>
<tbody>
<tr>
<td>BDI</td>
<td>--</td>
<td>.547**</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PILL</td>
<td>.294**</td>
<td>.462**</td>
<td>--</td>
<td>.284*</td>
<td>.479**</td>
<td>.680**</td>
<td>.004</td>
<td>--</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAS</td>
<td></td>
<td></td>
<td>.284*</td>
<td>.134</td>
<td>.121</td>
<td>.078</td>
<td>.152</td>
<td>-.262*</td>
<td>.231*</td>
<td>.312**</td>
</tr>
<tr>
<td>IAS</td>
<td></td>
<td></td>
<td></td>
<td>.134</td>
<td>.037</td>
<td>.016</td>
<td>.598**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Attention</td>
<td>.004</td>
<td>-.037</td>
<td>-.093</td>
<td>-.215</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>.550**</td>
<td>.114</td>
<td>.022</td>
<td>.030</td>
<td>-.057</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>.134</td>
<td>.121</td>
<td>-.031</td>
<td>.037</td>
<td>-.016</td>
<td>.598**</td>
<td>--</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Frustration</td>
<td>.289**</td>
<td>.246*</td>
<td>.078</td>
<td>.152</td>
<td>-.196</td>
<td>.480**</td>
<td>.476**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger</td>
<td>.231*</td>
<td>.055</td>
<td>.202</td>
<td>.136</td>
<td>-.262*</td>
<td>.345**</td>
<td>.234*</td>
<td>.705**</td>
<td>--</td>
<td></td>
</tr>
<tr>
<td>Fear</td>
<td>.030</td>
<td>.312**</td>
<td>.313*</td>
<td>.282*</td>
<td>-.173</td>
<td>.076</td>
<td>.317**</td>
<td>.284**</td>
<td>.235*</td>
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</table>

* Correlation is significant at the 0.05 level (2-tailed).
** Correlation is significant at the 0.01 level (2-tailed).
Since Henry Beecher's 1955 article outlined the history of the placebo responding, interest in the area of placebo responding has grown significantly. Numerous investigations have been completed examining the various mechanisms potentially responsible for the placebo phenomenon. Although much work has been done in this area and many mechanisms of placebo responding have been demonstrated, the exact physiological or psychological mechanisms remain unknown. There have been relatively few studies investigating the roles of somatization, expectation for pain, and desire for pain relief in placebo responding. Additionally, there are no known studies investigating the relationships between somatic focus and sensory discriminability and between expectations and desire with the notion of response bias. The main goal of this study was to explore these relationships in an experimental pain task.

We discovered that only a minority of individuals randomized to the placebo induction group responded to the experimental manipulation; that is, only 20 of 69 individuals exhibited placebo responses (i.e., difference scores greater than zero). This percentage of placebo responders is significantly less compared to a previous study using a similar conditioning and verbal suggestion paradigm, in which approximately 83% of individuals were placebo responders (Chung et al., 2007). Interestingly, in this study, a majority of the individuals (70%) who were found to be placebo responders were male. Again, these results are contrary to those in the Chung study (2007), in which results suggest that there were no sex differences for either exhibiting a first or second placebo response. A review of the current literature found only two studies reporting information specifically on sex differences in placebo analgesia response. One of these studies revealed that placebo analgesia was found in males, but not females (Flaten, Aslaksen, Finset, Simonsen, & Johansen, 2006). These researchers also examined the role of
social support in pain responding and found that males who received social support from the 
opposite gender were found to have lower levels of cortisol compared to females who received 
social support from the opposite gender. This information suggests that males and females may 
respond differently during placebo induction tasks, and these differences in placebo responding 
appear to be affected by direct or indirect social support provided during experimental settings. 
Furthermore, males and females appeared to respond differently to the social support provided 
during this task, with males responding more favorably (as measured by decreased cortisol 
levels).

Despite the relatively few number of studies reporting sex differences in placebo analgesia, 
there have been a number of studies demonstrated sex differences in pain responding. 
Specifically, research has shown that females exhibit greater sensitivity to experimentally-
induced pain compared to males and this greater sensitivity has been shown to persist across 
different stimulus modalities (e.g., thermal stimulation, pressure) (Berkley, 1997; Fillingim & 
Maixner, 1995; Riley, Robinson, Wise, Myers, & Fillingim, 1998). Additionally, it has been 
well documented that females and males respond differently to analgesics, specifically with 
regards to pharmacologically induced analgesia (Fillingim, 2002). For example, the current 
body of research suggests that females exhibit significantly greater opioid analgesia compared to 
males (Kest et al., 2000; Craft, 1998). Alternatively, Robinson, Riley, Brown and Gremillion 
(1998) reported that males reported greater analgesia in response to lidocaine compared to 
females, and Walker and Carmody (1998) reported that male subjects reported decreased 
experimental pain compared to female participants following the use of a nonsteroidal anti-
-inflammatory drug. A majority of the research assessing sex differences in analgesia include 
clinical samples and/or pharmacological methods of analgesia, while this study consisted only of
the use of an inert cream used with healthy, asymptomatic participants. Currently, there is no conclusive evidence for the exact psychosocial factors involved in sex differences found in placebo and nocebo responding for asymptomatic individuals; however, a number of possibilities (e.g., differences in anxiety) exist to explain these differences. Further studies are needed to examine these psychosocial factors that may be associated with the sex differences observed in this study.

One of the factors associated with sex differences may be state or trait anxiety experienced by participants. It has been shown that females often report experiencing higher levels of anxiety compared to males (e.g., Linzer et al., 1996). Additionally, anxiety has been shown to be positively correlated with increased endorsement of physical symptoms and increased sensitivity to experimental pain (Kroenke & Spitzer, 1998; Fillingim, Keefe, Light, Booker, & Maixner, 1996). This study included only a single-item assessment of anxiety, and ratings of this assessment did not correlate significantly with any of the three measures of somatization employed in this study. This lack of correlation was surprising given the previously mentioned literature on the relationship between anxiety and somatization. The measure of anxiety used in this study is highly face-valid, and participants may have been less likely to endorse experiencing anxiety on this measure. Given that anxiety has been shown to be an important variable related to somatization and one’s experience of pain, and because sex differences have been reported in the experience of anxiety, implementation of a more thorough measure designed to assess state and trait anxiety may have proven beneficial in helping to delineate any differences found in the current sample.

This study might have also benefited by having an additional measure/assessment of attention included. Results of the discriminant analysis revealed that the self-reported degree of
attention paid to the thermal stimuli was the strongest predictor of placebo or nocebo responses. Additionally, a specific region of the brain [the anterior cingulate cortex (ACC)] has been shown to be involved in both attentional regulation and placebo analgesia (Petrovic, 2005). These investigations have suggested that experiencing a placebo is associated with decreases in cortical activity in areas typically associated with nociception. In the current study, participants who reported greater ease at attending to the experimental stimuli were less likely to experience placebo analgesia. One hypothesis is that these individuals who reported an increased ease of attending to the thermal stimuli may have had increased activity in the ACC, potentially eliminating a placebo response. Given this information, that attention and placebo analgesia have both been shown to be associated with activity in particular brain areas, future studies may benefit from an increased assessment of the role of attention during the pain task and in placebo responding.

We examined two hypotheses of placebo responding: a traditional analgesic response hypothesis and a somatic focus hypothesis. We discovered that there was no significant relationship between sensory discriminability and a measure of somatic focus in placebo responders. Additionally, we found that there was no significant relationship between an individual's expectation for pain and desire for pain relief with the component of response bias. Previous research has shown that a patient’s expectations account for a large amount of variance (up to 49%) in pain ratings following an experimental manipulation (Montgomery & Kirsch, 1997). Studies assessing desire have reported slightly different results, with some studies reporting that desire is not significantly related to magnitudes of placebo analgesia (Price et al., 1999). The lack of significance of desire for pain relief may be due to the brief nature of experimentally induced pain. Thus, desire for pain relief, as it relates to placebo responding,
necessitates further examination in clinical pain samples, where pain duration is often of an unknown and unpredictable nature.

Mood was examined in two different ways, with each participant completing a measure of depression and providing pre- and post- mood ratings on a VAS. We determined that there was a significant difference between groups on a measure of depression, with participants in the placebo group reporting significant higher levels of depressive symptoms. It is important to point out, however, that the mean score of this measure of depression fell in the "minimal" range of experience of depressive symptoms. We determined that there were no significant mood changes for either group on ratings of depression, anxiety, frustration or anger over the course of this experimental session. However, there were significant decreases in participants' levels of fear over time, and this was consistent across groups.

**Limitations**

One of the major limitations to this study is that the experimental manipulation employing conditioning and verbal suggestion worked for relatively few individuals who were randomized to the placebo induction group. Initially, only 17 of 59 (28.8%) individuals who were randomly assigned to the placebo group were placebo responders. This is in stark contrast to a previous study that examined placebo responding in a sample of asymptomatic individuals. This study employed a similar conditioning and verbal suggestion protocol and found that 83% participants demonstrated a placebo response (Chung et al., 2007). Given this information, two initial hypotheses arose when comparing this investigation with Chung's study. First, the number of stimuli in this study was significantly more than the number used in Chung's investigation. This study used up to 53 stimuli [44 plus the number of stimuli (up to 9) required for the ascending series]; Chung's study, on the other hand, used a maximum of 29 stimuli. Although precautions were taken (avoiding retesting one location within 3 minutes) to avoid sensitization, it is possible
that the sheer number of stimuli led to sensitization. It is plausible that the observed increases in pain intensity ratings over time for the repeated baseline group and the nocebo responders are an artifact of peripheral sensitization. If this is the case, that sensitization occurred due to the number of stimuli, it could be expected that the placebo manipulation might not be effective for the majority of participants. This hypothesis may also support the small magnitude of pain intensity reductions found in the placebo group.

A second hypothesis as to why there were so few responders was regarding the sex of the experimenter. All of the participants in Chung's study were tested by a female experimenter, and the previously mentioned 59 individuals in this study were tested by a male experimenter. In an effort to determine if sex of the experimenter might be the cause of such discrepancy, a female experimenter ran 10 additional subjects in the placebo condition. Of these ten subjects who completed the exact protocol, only 3 of 10 (30%) individuals were determined to be placebo responders. This information suggests that lack of placebo responding is not due to the sex of the experimenter.

Another limitation of this study is that approximately one-fourth of participants were excluded from this study because they did not provide pain ratings that fell within the range needed for completion of this study (VAS pain intensity ratings of 0 to 2 and 4 and 6). Specifically, of the total sample of 120 participants, 32 (26.67%) were not able to complete the protocol due to their pain ratings, with the majority of these individuals providing pain ratings too low to be included. These initial pain ratings did not appear to be affected by the sex of the experimenter. When tested by a male experimenter, 30 of 110 (27.27%) participants provided initial ratings (during the Ascending Series) that excluded them from completing the entire set of stimuli; similarly, when tested by a female experimenter, 2 of 10 (20%) of participants provided
ratings inconsistent with continued inclusion in the protocol. Those individuals who were initially randomized to the placebo induction group and who were later excluded from the study due to their pain ratings were found to have significantly lower ratings of somatic focus (as measured by the PILL) than either the placebo or nocebo groups. It is plausible that these individuals with decreased scores of somatization may have attended differentially to the thermal stimuli present during the study and thus provided lower pain ratings compared to the placebo and nocebo responders.

Another limitation to this current study is that we do not have sound data regarding the number of individuals who have participated in previous pain studies. Anecdotally, however, a small proportion of individuals volunteered information that either they or their friends had been in previous studies investigating an ointment on pain responding. A recent study, which was completed in this same laboratory, included a protocol that informed participants that they received an inert cream rather than an active ointment (Chung et al., 2007). When retested during the Chung experiment, these individuals continued to demonstrate a placebo response, however the magnitude of this response was diminished. It is possible that the magnitude of placebo responding might continue to diminish should these individuals be enrolled in additional studies. Therefore, it would likely prove beneficial to determine whether participants are experienced with or naïve to research protocols using similar stimuli (e.g., inert creams, thermal stimuli). Additional studies also suggest the importance of prior experience on the magnitude of the placebo response (Colloca & Benedetti, 2009). Specifically, this study demonstrated that social observation learning increased the magnitude of the placebo response, and this response was greater than the magnitude observed by either a conditioning or verbal suggestion paradigm. Given the low number of responders in the current study (and the small magnitudes of response
for those exhibiting a placebo response), it could prove beneficial to add a social observational component to increase the magnitude of placebo responses in future studies. Colloca and Benedetti also note that prior experience (whether effective or ineffective) have long-lasting effects on the outcome of subsequent treatment, providing additional data to assess prior experience prior to beginning a protocol similar to the one employed in this study.

There is some evidence that placebo responding may be due, in part, to a variety of personality variables. For instance, the previously mentioned study by Colloca and Benedetti found that a measure of empathy was positively correlated with placebo responding. Geers and Lassiter (2005) also demonstrated that the variables of optimism and pessimism were correlated with placebo responding during some experimental conditions, with individuals classified as “pessimists” being more apt to report experiencing the expected symptoms. Although, the current literature has found few personality variables consistently associated with placebo or nocebo responding, it may be important that additional studies attempt to determine the role of personality variables on placebo-nocebo responding.

**Conclusions and Future Directions**

Gaining a better understanding of the physiological and psychological mechanisms contributing to placebo responding is important. Results from this study do not support the tested hypotheses; however, the sample size of placebo responders was not large enough to make firm determinations. Despite the limitations of this study, it did shed light on the important role of attention and somatic focus in placebo responding. This study found that a single-item assessment of attention paid to the thermal stimuli (i.e., “How easy was it for you to pay attention to these stimuli?”) was the largest contributor to group membership between those who received a placebo response and those who received a nocebo response. Our results indicate that the placebo induction was unsuccessful for participants reporting greater ease of paying attention.
to the study stimuli, suggesting that the easier it is for a participant to attend to the stimuli (as rated on a single-item self-report assessment of attention), the decreased likelihood of exhibiting a placebo response. Additionally, individuals who were excluded from the study because of low pain ratings were found to have significantly lower scores on a measure of somatic focus, suggesting that decreased somatic focus is related to decreased reporting of pain intensity. In 2007, Chung and colleagues reported that a measure of somatic focus (i.e., PILL) predicted first placebo responding, but noted that other measures of somatization (e.g., IAS) did not predict placebo responding. These differences were not surprising, given that each of these measures likely captures different constructs. Although the PILL is a symptom-checklist designed to be a measure of somatic focus, it may also measure other constructs (e.g., anxiety, catastrophizing) without being face valid. The IAS, however, is a face valid measure assessing beliefs and worries about illnesses, and this measure may not be the most appropriate measure for relatively healthy, young study participants. Furthermore, the single-item question used in this study to measure attention likely is capturing components much different than those measured by either the PILL or the IAS. As additional studies are designed, it important to gain an increased understanding of these measures and of constructs captured within each of these measure. Additionally, given that attention was found to be the strongest contributor to group separation between placebo and nocebo responders, it would likely prove beneficial to include a measure of attention to pain.

Results from this study also indicated that there were significant sex differences in pain responding, with males being much more likely to exhibit a placebo response while women were more likely to exhibit a nocebo response. Given these findings, future studies are needed to
further delineate the roles of attention, somatic focus and sex differences in placebo and nocebo responding.
### APPENDIX A
### TEMPERATURE AND PAIN RATINGS FOR ALL PARTICIPANTS

<table>
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<tr>
<th></th>
<th>Minimum Temp.</th>
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<th>SD</th>
<th>Minimum Pain</th>
<th>Maximum Pain</th>
<th>Mean Pain</th>
<th>SD</th>
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# APPENDIX B
TEMPERATURE AND PAIN RATINGS FOR PLACEBO RESPONDERS ONLY

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### APPENDIX C
TEMPERATURE AND PAIN RATINGS FOR REPEATED BASELINE GROUP ONLY

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## APPENDIX D
TEMPERATURE AND PAIN RATINGS FOR NOCEBO RESPONDERS ONLY

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LIST OF REFERENCES


BIOGRAPHICAL SKETCH

Robert Corey McCulloch graduated from the University of Mississippi in May 2004, where he received Bachelor of Arts degrees in psychology and sociology. While at the University of Mississippi, Corey held research assistant positions in the Departments of Environmental Toxicology (2000-2002), Pharmacognosy (2002-2004), and Psychology (2002-2004). In August 2004, Corey began his doctoral training in the Department of Clinical and Health Psychology and joined the Center for Pain Research and Behavioral Health. Corey received his Master of Science degree in May 2006 from the University of Florida. His master’s thesis examined the associations of mood, pain, and cognitive performance in individuals receiving opioid medications for chronic low back pain. As a member of the Center for Pain Research and Behavioral Health, Corey also participated in investigations that examined placebo responding in irritable bowel syndrome patients and assessed patient-centered outcomes in chronic pain groups. Corey completed an APA-accredited internship in clinical psychology at the University of California, San Diego (UCSD) in June 2009. He received a doctoral degree in clinical psychology from the University of Florida in August 2009.