ACUPRESSURE AS A NON-PHARMACOLOGICAL TREATMENT FOR NEUROLOGICAL INSULT AND STRESS REDUCTION: THEORY, MECHANISMS, AND EFFICACY

by

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Acupressure as a non-pharmacological treatment for neurological insult and stress reduction: theory, mechanisms, and efficacy

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ABSTRACT

Acupressure is a form of complementary and alternative medicine (CAM) that involves stimulation of acupoints using fingertip pressure. Acupoints are areas of skin designated as such by Traditional Chinese Medicine, with stimulation thought to elicit distinct effects from stimulation of non-acupoints. As such, the studies in this thesis compare effects of active acupressure treatments (with stimulation of acupoints) to those of placebo acupressure treatments, which control for all aspects of active acupressure treatments, but stimulate non-acupoints rather than acupoints. Specifically, the effects of acupressure on cognitive function following traumatic brain injury (TBI) were investigated, as well as the efficacy of acupressure for stress reduction in healthy college students. A series of eight acupressure treatments were found to improve cognitive function and reduce perceived stress over and above improvements seen following placebo acupressure in TBI survivors. The cognitive benefits seen could be a result of active acupressure-associated stress reduction, possibly mediated via the autonomic nervous system. No group differences in stress response reduction were found after a single administration of active acupressure, placebo acupressure or a relaxation CD in the stress study, possibly due to insufficient "dosing". As attitudes can contribute to placebo effects in both active and placebo interventions, the impact of attitudes towards CAM and conventional medicine on treatment outcome in both studies were assessed, to further delineate possible placebo effects. Although having less of an influence on outcome than hypothesized, attitudes

towards both CAM and conventional medicine did affect a number of outcome measures, as well as measures at baseline and during the intervention itself, suggesting that attitudes towards CAM and conventional medicine should be taken into account both in clinical studies and regular clinical practice. These studies highlight the importance of rigorous scientific research of CAM therapies, incorporating randomization, blinding procedures, and appropriate control conditions.

DEDICATION

To Sean:

*"*Let it never be said that my anal retentive attention to detail never yielded positive results*." -Kevin Smith, "Dogma"*

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CHAPTER 1

GENERAL INTRODUCTION

Introduction to acupressure

Complementary and alternative medicine (CAM) refers to medical treatments not considered to be in the mainstream of modern medicine. Many therapies fall under the wide umbrella of this term, such as massage, chiropractic therapy, and meditation. Although termed complementary and *alternative* medicine, CAM is most often used in a manner complementary to conventional medicine, and is often viewed as a way to supplement healthcare in a more complete way than the use of conventional medicine alone (Ruggie, 2004). For example, surveys have found that up to 69% of patients with cancer use CAM in addition to conventional medical treatments rather than as a substitute for conventional medical care, often to treat symptoms resulting from conventional treatments (e.g., nausea from chemotherapy) (Pham and Primack, 2003). Also, up to 71% of patients with HIV/AIDS report using CAM in addition to conventional medical treatments, largely to combat side effects from antiretroviral therapy as well as disease symptoms (Palmer, 2008). The studies in this thesis investigate a CAM modality, specifically acupressure, which lends itself well as an adjunct treatment to conventional medicine.

Acupressure is a CAM therapy that involves using the fingertips to apply pressure to the skin on areas called *acupoints*. Acupoints are areas of the skin designated as such by Traditional Chinese Medicine (TCM). Acupressure has most commonly been studied for its utility as a therapy to alleviate nausea and vomiting, post-operatively (Alkaissi et al., 2002), in pregnancy (Streitberger et al., 2006), following chemotherapy (Streitberger et al., 2006; Dibble et al., 2007), and in motion sickness (Streitberger et al., 2006). It has also shown success in treating lower back pain (Hseih et al., 2006), anxiety (Agarwal et al., 2005), fatigue (Tsay, 2004), dysmenorrhea (Cho and Hwang, 2010), and menopausal hot flashes (Zhou et al., 2009).

Traditional Chinese Medicine (TCM) theory

TCM is a system of health and healing with a holistic approach, emphasizing the importance of balance between our constantly changing internal and external environments (Stux and Pomeranz, 1997; Bauer, 2005). In brief, TCM theory focuses on the balance of *qi*, an energy or "vital force" that is said to flow throughout the human body (Stux and Pomeranz, 1997; Bauer, 2005). According to TCM theory, qi flows through the body in pathways called *meridians* which connect acupoints (Kavoussi and Ross, 2007). Acupoints are thought to be the areas on the skin where qi is closest to the surface (Stux and Pomeranz, 1997). Because blockage of qi is thought to be the cause of illness, stimulation of acupoints is believed to free qi that has become "stuck" and restore balance and health (Stux and Pomeranz, 1997; Bauer, 2005). The studies in the following chapters investigate Jin Shin acupressure, a treatment that derives from traditional TCM acupressure theory. Finger pressure at acupoints during Jin Shin acupressure is thought to promote the flow of energy throughout the body and restore balance.

This view of healing and health does not translate well to Western science and medicine. As such, scientists have attempted to find ways to explain possible mechanisms of acupressure (and acupuncture, a CAM treatment also involving stimulation of acupoints, but using needles rather than fingertips) that will fit better with Western science. The goal is to discover the physiological mechanisms that could be driving effects derived from acupoint stimulation.

Physiological differences between acupoints and non-acupoints

The studies that will be detailed in this thesis ask the question of whether applying pressure to acupoints elicits a differential response than applying pressure to non-acupoints. Many researchers have attempted to determine what might be unique about acupoints that could explain why acupoint stimulation might elicit distinct effects from stimulation of non-acupoints.

Acupuncture studies using fMRI have found differential brain activation when acupoints versus non-acupoints are stimulated (Yan et al., 2005). Importantly, Yan et al. also found stimulation of different acupoints to activate different areas in the brain, such that stimulation of an acupoint on the foot showed a distinct response pattern than did stimulation of a hand acupoint (Yan et al., 2005). Zhang et al. conducted a similar study, but investigated brain activation differences (using fMRI) when stimulating two acupoints within the same spinal segment. They compared two pairs of acupoints to each other and, similarly to Yan et al., found distinct response patterns from stimulation of different acupoints, even when in the same spinal segment (Zhang et al., 2004). These results support the use of different acupoints for distinct purposes, as is taught in TCM.

One long-standing theory suggests that acupoints have lower electrical resistance and increased electrical conductivity than surrounding skin, although results have been mixed (Ahn et al., 2005; Pearson et al., 2007; Colbert et al., 2009; Kramer et al., 2009). A possible reason for contradictory studies in the literature could be that studies use a multitude of devices to measure electrical resistance. A common method has been to use a single electrode at the tip of a pen-shaped device that is pressed against the skin manually (Pearson et al., 2007; Kramer et al., 2009), which can create measurement problems by allowing variability in the pressure and angle used (Kramer et al., 2009). Other researchers have developed more complex and reliable methods of measuring electrical resistance at acupoints, in attempts to detect any unique electrical properties at acupoints compared to surrounding skin. Kramer et al. used an array of 64 electrodes on a flexible surface, which they placed over an area of skin on the arm that included both acupoints and non-acupoints. This allowed them to compare six acupoints to surrounding skin at the same time, with the same pressure and angle. However, their results

were still inconclusive: across the six points used, they found 62.8% of measurements to show no change between acupoints and the surrounding skin, 26.9% of measurements to find acupoints to have lower resistance than surrounding skin, and 11.3% of measurements to demonstrate acupoints having higher resistance than surrounding skin. They hypothesized that this could be due to skin resistance perhaps being transient in nature (Kramer et al., 2009). Colbert et al. found similar results using an automated 8-channel system called "the Octopus". They measured electrical skin resistance for two continuous hours at eight skin sites, which consisted of two acupoints and one non-acupoint on the toe, two acupoints and one non-acupoint on the wrist, and one acupoint and one non-acupoint on the leg. For the toe and wrist, they averaged the resistance from the two acupoints for comparison to the corresponding non-acupoint. Similar to Kramer et al. (2009), they found mixed results, with only the acupoints on the toe showing significantly lower resistance than the corresponding non-acupoint. There were no significant differences between the acupoints and non-acupoints on the wrist or leg (Colbert et al., 2009). Given the mixed results in the literature, it is difficult to make any definitive conclusions regarding electrical differences between acupoints and non-acupoints. The disparity in results could be due to the variety of methods used to measure electrical resistance (e.g., number and size of electrodes used, acupoints measured, length of recording time), challenges in electrodermal recording (e.g., variability in skin hydration, pressure used, presence of sweat ducts (Ahn and Martinsen, 2007)) and possibly the transient nature of electrical resistance at acupoints (Ahn and Martinsen, 2007; Kramer et al., 2009).

Another theory is that there may be circulatory differences between acupoints and non-acupoints. To investigate this, Hsiu et al. have utilized laser Doppler flowmetry, a non-invasive technique revealing red blood cell concentration and flow in areas of the skin. Using this

technique, they found skin at acupoints to have increased blood flow and concentration compared to that at non-acupoints (Hsiu et al., 2007). As a result, it has been theorized that acupressure may exert its effects by modulating microcirculatory blood flow (Hsiu et al., 2010). That acupoints have different microvasculature than non-acupoints would be fitting with this theory. Indeed, Hsiu et al. found improved microcirculatory blood flow at an acupoint (again using laser Doppler flowmetry) when the same amount of pressure was applied to both an acupoint and a non-acupoint (Hsiu et al., 2010). However, since this study only focused on a single acupoint, additional research is needed to determine if stimulation of other acupoints would elicit differential microvascular effects than stimulation of non-acupoints.

Although acupressure has shown efficacy in treating a variety of medical conditions, there is a dearth of research on acupressure employing appropriate scientific rigor. To be able to attribute observed treatment effects to acupoint stimulation and not to other components of treatment, it is important to employ an experimental design that includes randomization, blinding procedures, and appropriate placebo controls.

The placebo effect

Placebo effects must be taken into account in any trial of a medical treatment, and may need additional consideration in research of CAM treatments. The placebo effect involves the context surrounding treatment, anything that the patient would not encounter were they not receiving clinical treatment (Benedetti, 2008). These are effects in addition to the "active" effects of the treatment and can influence treatment outcome.

Expectations and the placebo effect

A classic example of placebo effects can be seen in trials involving placebo pills. When a pill is given for a certain ailment, many factors are involved. If the pill is real, there are the

actual pharmacological effects of the drug. Importantly, even in active treatments, there will be placebo effects present. A strong contributor to placebo effects is expectancy, which can be manipulated in a number of ways. For one, the doctor will prescribe the pill with the instruction that it should help the ailment for which it is being prescribed, which leads to an expectation of efficacy. Additionally, simply being in a medical setting (e.g., in a doctor's office, surrounded by medical equipment, with a doctor in a lab coat) can increase expectations (Price et al., 2008).

Expectations can have a large impact on treatment outcome. Frankenhaeuser et al. found that patients given an inert pill (a "placebo" pill) and informed that it was a stimulant showed both physiological (increased heart rate and blood pressure) and behavioral (increased reaction speed) symptoms expected from a stimulant. Alternately, patients given the same placebo pill and told it was a depressant showed the opposite effects, demonstrating reduced heart rate and blood pressure, as well as slowed reaction speed (Frankenhaeuser et al., 1963). So, even when the only difference between two treatments is the suggestion provided with it, the treatment can elicit opposite effects. Expectancy has been found to influence "real" treatments in a similar manner. Volkow et al. found that the effects of methylphenidate (a stimulant) on cocaine addicts were amplified when expectations were increased. Participants were broken into four groups, such that they were given either methylphenidate or placebo and told to expect either methylphenidate or placebo. Those given methylphenidate and expecting methylphenidate showed increased effects (measured via subjective ratings and brain glucose metabolism) compared to those given methylphenidate and expecting placebo (Volkow et al., 2003). Similarly, Amanzio et al. found that "hidden" injections of analgesic drugs were less effective in relieving pain than were "open" injections of the same drugs. Open injections were given in full view of the patient, by a doctor who told the patient the drug was a powerful painkiller. Hidden

injections were administered via a pre-programmed infusion machine, with no doctor present, so the subject was unaware of when the drug was being administered. As such, the open injections involved raised expectations not present in the hidden injections. That open injections were found to be more efficacious at reducing subjective pain ratings indicates that placebo effects enhanced the effects of the analgesic drugs (Amanzio et al., 2001). Also demonstrating the influence of expectancy-induced placebo effects on treatment outcome, Yee et al. found that patients with higher preoperative expectations showed greater improvement in a number of functional measures (measured with the SF-36 Health Survey) following spinal surgery (Yee et al., 2008).

The attitude of the medical provider can also influence expectations surrounding treatment. A positive interaction with a healthcare provider can provide nonspecific benefits, such as improved mood, anxiety reduction, and stress relief (Verheul et al., 2010; Oken, 2008). If a physician is enthusiastic and positive about a treatment, it can increase patient expectations; similarly, a negative attitude can decrease patient expectations (Thomas, 1987). Thomas (1987) found that a physician's attitude towards treatment during a doctor's visit had an important impact on patient outcome. Patients presenting with symptoms but no definitive diagnosis were randomly assigned to receive either a "positive" consultation with or without treatment, or a "negative" consultation with or without treatment. Two weeks later, Thomas found that significantly more of those who received positive consultations (which included a definitive diagnosis, more time with the physician, and a more optimistic outlook from the physician than the negative consultations) reported feeling better than those who received negative consultations, but found no significant differences between those who were given treatment compared to those who were not (Thomas, 1987). In another study, physicians gave one group

of patients recovering from acute tonsillitis more time and information than another group of patients, and were also friendlier with the first group. Two days later, significantly more of the patients who were given more attention from a friendly physician reported symptom improvement than those in the other group (Olsson and Tibblin, 1989). These studies demonstrate the important influence physician attitude and attention can have on outcome. Other variables that can influence patient expectations include prior experiences with medical care (Colloca and Benedetti, 2006), religious or cultural beliefs surrounding a treatment (Bausell, 2007), and how the philosophy behind a treatment agrees with their own life philosophies (Ruggie, 2004).

Conditioning and the placebo effect

Additionally, there can be an element of conditioning involved in eliciting placebo effects. If a patient has taken a pill for a condition previously and subsequently experienced improvement, the mere act of taking a pill can lead to relief, even when a pharmacological effect has not begun to affect the ailment, or when the drug is inappropriate for the condition and wouldn't be expected to elicit improvement, such as when an antibiotic is unnecessarily prescribed for a viral infection (Bausell, 2007). This conditioned effect is due to repeated past pairings between taking a pill and experiencing relief. In a similar example, patients can be conditioned to experience pain relief following a saline injection after being conditioned with multiple morphine injections (Amanzio and Benedetti, 1999). Conditioning can work with expectancy, such that conditioning leads to expectations that a certain response will follow a certain stimulus, which can lead to increased expectations (Kirsch, 1997) and influence outcome (Volkow et al., 2003).

CAM and the placebo effect

It has been suggested that CAM modalities may be more susceptible to placebo effects than conventional medical treatments (Kaptchuk, 2002). There are many possible reasons why this might be so. For one, practitioners of CAM are not bound to scientific evidence as doctors are, so can be more openly optimistic about treatments with patients, even without scientific proof of treatment efficacy (Kaptchuk, 2002). This could influence patient attitudes towards treatment, important since positive expectations can lead to improved outcome (Amanzio et al., 2001; Volkow et al., 2003; Yee et al., 2008). Additionally, CAM treatments are often administered in a less professional setting than conventional medicine (usually administered in hospitals or doctor's offices), which could be less intimidating to patients. The nature of the illnesses CAM treatment is used in can also contribute to the development of placebo effects (Kaptchuk, 2002). The conditions for which CAM is most often used are the same conditions that appear most susceptible to placebo effects themselves, such as chronic diseases with fluctuating courses of symptoms (e.g., chronic pain), disorders with subjective symptoms (e.g., depression), or affective disorders (e.g., anxiety). It has also been suggested that because CAM emphasizes personal responsibility in treatment, this can facilitate adherence to treatment (Kaptchuk, 2002).

One challenge in CAM research is that it can be difficult to find an appropriate placebo condition for some modalities. A placebo condition should control for all aspects of treatment that could contribute to placebo effects (e.g., atmosphere, practitioner/patient interaction), while only differing in the aspect of the treatment thought to be "active". This way, any additional effects seen in the group receiving active treatment can be attributed to the active aspect of treatment, not to the elements of treatment eliciting placebo effects. As the studies in this thesis

investigate acupressure, it was necessary to design a placebo acupressure procedure to control for all but the active elements of acupressure. While the mechanism behind acupressure is not known, it is thought that the stimulation of acupoints is responsible for "active" effects of acupressure. Therefore, an appropriate acupressure placebo would need to control for all elements of the active treatment, except for the stimulation of acupoints. To accomplish this, our laboratory developed a placebo procedure to control for time, touch, atmosphere, and practitioner attention (Hernández et al., 2003}.

Acupressure procedure

A brief description of the acupressure protocol follows, as the rationale behind it is an important precursor to the following chapters. The acupressure treatment studies in this thesis all used a placebo-controlled design, with a placebo acupressure treatment that controlled for all aspects of the active acupressure treatments, but involved stimulation of non-acupoints rather than acupoints. A set of placebo acupressure points (Hernández et al., 2003) not found on established acupressure point charts were identified, each of which was assigned a number. To determine which acupoints to stimulate during a treatment, the acupressure practitioner used "pulse diagnosis", a TCM method used in regular acupressure practice. Pulse diagnosis is a process in which the practitioner holds the radial aspects of the participant's wrists and "listens" for a pulse that feels like a blood pulse, but contains all elements of body health. Through this method, the practitioner assesses where the greatest "need" is, in terms of which meridians should be stimulated, by ascertaining where energy is moving well and where it is blocked. Based on this, the practitioner decides where to treat to unblock the energy (Clancy et al., 1996; Burmeister, 1997; Ho and Lisowski, 1997). According to TCM theory, the practitioner acts as a kind of "conduit", enabling the patient's energy to flow between the points (Clancy et al., 1996;

Burmeister, 1997). Using a random number generator, the placebo points were put into a matching sequence for each customary Jin Shin (acupressure) treatment. Consequently, if pulse diagnosis dictated treatment of the gall bladder, there was a placebo gall bladder treatment containing the same number of steps in matching sequence to the standard active gall bladder treatment.

The procedure itself is as follows. During treatment sessions, participants lay face up on a massage table, fully clothed with shoes removed, as is common practice for acupressure treatments (Mines, 1982; Burmeister, 1997). A Jin Shin (acupressure) practitioner with over 20 years of clinical and educational experience and appropriate certification administered treatments (active or placebo) behind a closed curtain. The practitioner was also trained in use of the placebo acupoints (Hernández et al., 2003). The practitioner began treatment administration by holding the radial aspect of the participant's wrists (i.e., pulse diagnosis) with her fingertips, which determined the appropriate treatment sequence to begin the session. During treatment, the practitioner applied pressure with her fingertips to different sites (e.g., points) on the body, in sequence. After a sequence was complete, the radial wrists of the participant were held again by the practitioner to determine the next treatment sequence. The entire treatment, itself, lasts 40 minutes.

The placebo control procedure was designed to be indistinguishable from the active treatment session, to last the same duration, and contain the same amount of physical contact. As with the active treatment, the practitioner began by holding the radial aspect of the participant's wrists for pulse diagnosis. To guarantee matching practitioner/participant interactions for both treatment types, only scripted dialogue was used.

Cardiovascular effects of acupressure in stroke survivors

Using this procedure, a previous study in our laboratory investigated the effects of acupressure on stroke survivors (McFadden and Hernández, 2010). Participants at least 19 months post-stroke were included in the study, and had had a unilateral stroke with resulting persistent deficits, such as hemiplegia. A randomized, placebo-controlled, single-blind, crossover design was used. Pilot data from our laboratory suggested that active acupressure was associated with greater heart rate reduction than placebo acupressure (Hernández et al., 2003). As such, this next study utilized a crossover design as a next logical step in the research prior to a study with separate groups for each treatment type. In the crossover design, participants received a 40-minute acupressure treatment (either active or placebo) once per week for eight weeks. Outcome measures were taken before and after this series of treatments, and then participants did not come in to the laboratory during an eight-week washout phase. Following this, participants received an identical series of treatments of the other treatment type; participants were randomized to receive either active treatments for the first eight-week treatment phase and placebo the second (condition A), or placebo treatments for the first eight-week treatment phase and active the second (condition B) (see Table 1.1). Participants and researchers were blinded to the treatment order assigned, with only the acupressure practitioner knowing which type of treatment was administered.

Random Assignment to A or B		
First 8 weeks	**Second 8 weeks**	**Third 8 weeks**
A. Active phase	Washout period	Placebo phase
B. Placebo phase	Washout period	Active phase

Table 1.1. Experimental design for the stroke study.

As the study population was one with cardiovascular disorder, analyses focused on cardiovascular measures, specifically heart rate and blood pressure. Analyses found active acupressure treatments to reduce heart rate significantly more and faster than placebo acupressure treatments (see Figure 1.1), suggesting an induction of the relaxation response in both groups, but more so for the active treatments. A significant treatment effect on blood pressure was not found, but this could be due to 67% of study participants taking antihypertensive medications during the study.

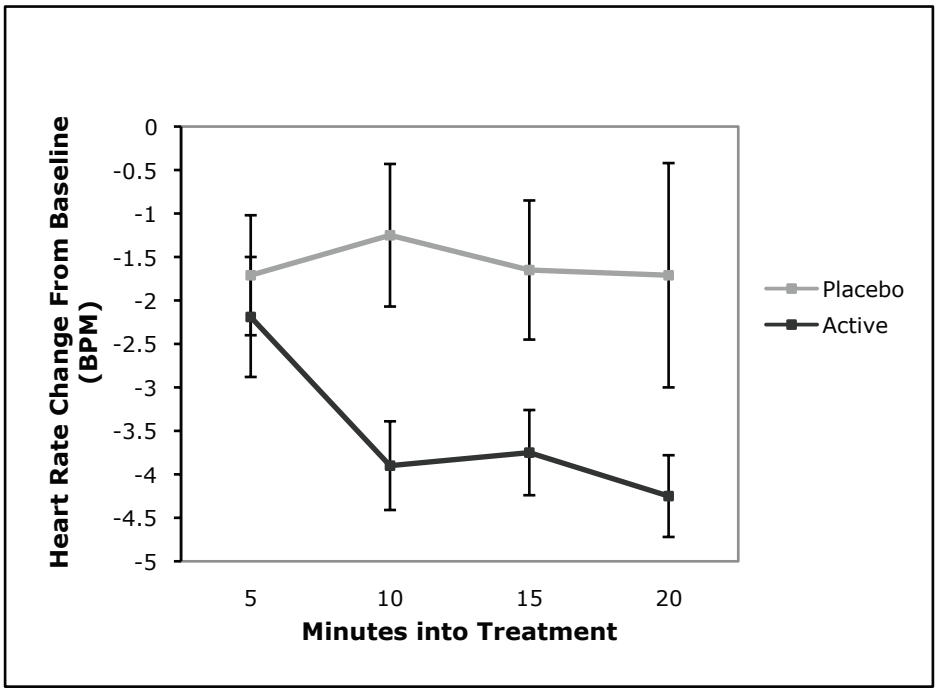

Figure 1.1. Mean (± SEM) heart rate change in the first 20 min of treatment sessions, averaged across the last 4 weeks of each treatment phase.

Previous studies have also found acupressure to reduce heart rate (Felhendler and Lisander, 1999; Sugiura et al., 2007), although appropriate control conditions were not employed, making it difficult to attribute heart rate differences definitively to the stimulation of acupoints versus non-acupoints. This reduction in heart rate may indicate a faster and greater induction of the relaxation response during active acupressure treatments. The stress response

has been linked to disease (Esch et al., 2002) and it has been suggested that the relaxation response could break the stress-disease link by reducing the response to stress (Esch et al., 2003). This could be particularly useful in a population with cardiovascular disease if short-term induction of the relaxation response could facilitate stress resilience, which could lead to reduced risk of further cardiovascular disease (Esch et al., 2002; Esch et al., 2003). If this relaxation response induction leads to a reduction in the stress response, it could help determine other populations for which acupressure could be a useful adjunct treatment.

Thesis overview

The following chapters will expand upon the stroke study, by examining the effects of acupressure in traumatic brain injury (TBI) survivors, as well as in healthy college students. While evidence of an increased relaxation response during active acupressure treatment was found in the stroke study, the functional benefits of this remain to be seen. As is a normal experimental progression (White and Ernst, 2001), the following studies both used a randomized, placebo-controlled, single-blind design, but without crossover into the opposite treatment.

In the TBI study (Chapter 2), the effects of acupressure on cognitive function in TBI survivors were investigated, using a neuropsychological test battery and event-related potentials (ERPs) during Stroop (Stroop, 1935) and auditory oddball tasks. Additionally, state of being questionnaires were used to assess if acupressure affected such things as perceived stress or depression in this population. This study used a randomized, placebo-controlled, single-blind design, comparing a group receiving active acupressure treatments to one receiving placebo acupressure treatments. As described above, the only difference between the two treatment types was the stimulation of acupoints vs. non-acupoints. Eight 40-minute acupressure treatments were administered (2 per week for 4 weeks), with measurements taken both before (within a

week of beginning the treatment series) and after the treatment series (within 48 hours of the last treatment). It was hypothesized that active acupressure treatments would be associated with greater cognitive improvement than placebo acupressure treatments.

Results from this study should tell us a number of things. First, this study will investigate if acupressure is an effective adjunct treatment for cognitive function following TBI. Also, in the TBI study we aimed to see if treatment effects would be seen if 8 treatments were administered in a shorter time-frame. The TBI study utilized the same number of treatments as the stroke study, but in a more condensed fashion. Both studies involved a series of 8 treatments, but treatments were administered once per week in the stroke study (for 8 weeks) and twice per week in the TBI study (for 4 weeks). While the stroke study suggested a number of treatments necessary to elicit an acupressure-associated effect on heart rate, it remains to be seen what an optimal timing schedule might be. Given that participants were receiving two treatments per week rather than one, it was thought that this might even lead to an enhancement of treatment effects (i.e., a more concentrated "dose").

In the next study (Chapter 3), participants were healthy college students. This study tested the effects of acupressure on the reduction of the stress response in a healthy population. Again, a randomized, placebo-controlled single-blind design was used, but an additional control group was incorporated into this study, in an effort to further parse out placebo effects from treatment effects. As described above, the placebo acupressure group controls for all but the stimulation of acupoints vs. non-acupoints. A relaxation CD control group was added into the stress study, in which participants lay on the massage table and listened to a relaxation CD for the same length of time as the acupressure treatments (40 minutes). This allows for a group that controls for laying down and relaxing, but does not receive any physical touch or practitioner

attention. Participants completed the study in a single session and were randomly assigned to receive a single administration of either active acupressure, placebo acupressure, or the relaxation CD. To test the effects of each intervention on the stress response, a math task stressor was administered before and after the intervention. The hypothesis in this study was that while all three groups would experience a reduced stress response to the post-intervention math task stressor, those in the active acupressure group would show additional stress reduction compared to the placebo acupressure and relaxation CD groups.

Results from this study should tell us if acupressure is an effective treatment for stress reduction in a healthy population. Results will also help in examining appropriate "dosing" necessary to elicit treatment effects. The stroke study found most of the active acupressure-associated treatment effect on heart rate to occur during the last four treatments of the 8-treatment series rather than the first four. This important discovery indicates an appropriate "dose" of acupressure necessary to elicit treatment effects in this population. These results suggest that while 4 treatments may have been necessary, they were not sufficient to observe a treatment effect in this study. However, while this study suggested more than four treatments may be necessary to elicit a treatment effect in stroke survivors, studies on healthy populations have previously found acupressure-associated effects following a single treatment administration (Felhendler and Lisander, 1999; Sugiura et al., 2007). The stress study aimed to see if a single acupressure treatment would be sufficient to elicit an acute effect on stress-reduction in a healthy population, when the intervention was immediately preceded and followed by the administration of a stressor.

In Chapter 4, the effects of participants' attitudes towards CAM on treatment outcome are explored. This study involved performing additional analyses on data from both the TBI and

stress studies. In both studies, the Complementary, Alternative, and Conventional Medicine Attitudes Scale (CACMAS) (McFadden et al., in press) was administered prior to any intervention. This questionnaire was included to assess participants' attitudes towards CAM. As attitudes can contribute to a placebo effect, this measure was added so that group differences (*TBI study*: active vs. placebo acupressure; *stress study*: active acupressure vs. placebo acupressure vs. relaxation CD) in CAM attitudes could be assessed. How those attitudes may have influenced intervention-associated outcome in the TBI study and the stress study is investigated in Chapter 4. It was hypothesized that having a more positive attitude towards CAM treatments would lead to an increased effect of the intervention, as this could enhance placebo effects (in active treatments as well as controls). Additionally, it was hypothesized that dissatisfaction with conventional medicine may also lead to increased intervention efficacy: those with greater dissatisfaction with conventional medicine might feel more comfortable with a CAM intervention. However, as studies have suggested that being dissatisfied with conventional medicine is not as strong a predictor of seeking CAM treatment as is having a positive attitude towards CAM (Astin, 1998), it was hypothesized that it would have less of an impact on treatment outcome than would positivity towards CAM.

Additionally, how attitudes towards CAM affected baseline measures (pre-intervention) in each group was explored, as well as measures during the intervention in the stress study. It was also thought that having a positive attitude towards CAM might also lead to lower baseline stress responses, improved baseline performance, as well as enhanced relaxation during the intervention (stress study only), given that participants knew they might be assigned to and soon receiving a CAM treatment. While being dissatisfied with conventional medicine might lead participants to be more comfortable with a CAM intervention, some aspects of both studies are

similar to conventional medicine, such as physiological recordings (e.g., ECG and EEG). As such, it could be that those more dissatisfied with conventional medicine might feel uncomfortable with these measurements and as such, show greater anxiety at baseline or during the intervention.

Results from this study will be helpful in determining the influence of attitudes towards CAM and conventional medicine on treatment outcome. This could be useful in predicting who might respond well to particular therapies, helping practitioners of both conventional medicine and CAM in prescribing appropriate treatments. This is also important to account for in clinical trials; the CACMAS could be used to match experimental groups for attitudes towards CAM and conventional medicine prior to randomization.

Together, these studies aim to accomplish a number of goals. First, to investigate whether stimulation of acupoints elicits unique effects, physiologically and behaviorally, compared to stimulation of non-acupoints, when all other aspects of treatment are controlled. Additionally, as our previous findings suggest that acupressure might exert its effects as least partially through stress reduction, the following chapters focus on two populations for which non-pharmacological stress reduction could be particularly beneficial, to assess effects of acupressure in these populations. Stress has been found to exacerbate or unmask cognitive deficits following TBI (Ewing et al., 1980; Hanna-Pladdy et al., 2001), and college students are a population that often experiences high levels of stress (Tosevski et al., 2010). As well as exploring improvements in cognitive function following acupressure treatments, the TBI study also includes measures to assess subjective stress levels. The stress study includes multiple physiological and subjective stress measures and more explicitly examines the effects of acupressure on stress reduction.

Dosing of acupressure is also investigated, in a couple of ways. First, as the stroke study found eight treatments over eight weeks to elicit treatment effects, the TBI study aimed to see if condensing that treatment schedule to eight treatments over four weeks would be as (or more) effective. The number of acupressure treatments necessary to elicit treatment effects was also explored. As previous studies have found a single active acupressure treatment to elicit treatment effects in healthy populations, the stress study examined the effects of a single acupressure treatment on the physiological and behavioral stress response to a math task stressor immediately preceding and following the intervention. It could be that multiple treatments are necessary in a population with chronic illness (e.g., stroke), as is recommended by acupressure practitioners (Burmeister, 1997), but that a single treatment could be sufficient to see acute effects of acupressure in a healthy population.

Another aim of the following chapters is to explore the nature of placebo effects in acupressure treatments. As discussed above, there is often a strong placebo component to CAM therapies, due to such things as atmosphere (e.g., soothing music, dim lighting, lack of conventional medical equipment), practitioner optimism and enthusiasm, and the patient/practitioner relationship. Such elements can enhance expectations and positive attitudes surrounding treatment, influencing outcome. Because the placebo control used in the following studies controls for all elements except for the points stimulated (non-acupoints rather than acupoints), it allows us to ask the basic question of whether acupoint stimulation is at the core of the effects elicited by acupressure. However, in treatments administered in regular practice, there are many additional components as well as acupoint stimulation, such as the aforementioned contributors to placebo effects. To determine for whom acupressure is most (or least) effective, it is important to assess the contribution of other variables to observed treatment

effects. To this end, both the stress study and the TBI study use a placebo acupressure control, and the stress study incorporated an additional control condition to establish how much of an impact there would be from simply laying down and relaxing for 40-minutes compared to therapies incorporating touch (active and placebo acupressure treatments). Additionally, further analyses were conducted to assess the impact of attitudes towards CAM on treatment outcome.

In sum, the following chapters investigate the efficacy of acupressure as a non-pharmacological intervention for TBI survivors and healthy college students, to assess the effects of treatment on cognitive function (TBI study) and the stress response (stress study). Using appropriate scientific rigor, including placebo-controls, randomization and blinding, this thesis aims to assess not only the effectiveness of acupressure for these populations, but also the specific aspects of treatment driving these effects, be it specific acupoint stimulation, placebo effects, or another aspect of the intervention.

CHAPTER 2

ACUPRESSURE AS A NON-PHARMACOLOGICAL INTERVENTION FOR TRAUMATIC BRAIN INJURY

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Abstract

Acupressure is a complementary and alternative medicine (CAM) treatment using fingertips to stimulate acupoints on the skin. While suggested to improve cognitive function, acupressure has not been previously investigated with a controlled design in traumatic brain injury (TBI) survivors, who could particularly benefit from a non-pharmacological intervention for cognitive impairment. A randomized, placebo-controlled, single-blind design assessed the effects of acupressure (8 treatments over 4 weeks) on cognitive impairment and state of being following TBI, including assessment of event-related potentials (ERPs) during Stroop and auditory oddball tasks. It was hypothesized that active acupressure treatments would confer greater cognitive improvement than placebo treatments, perhaps due to enhanced relaxation response induction and resulting stress reduction. Significant treatment effects were found comparing pre- to post-treatment change between groups. During the Stroop task, the active group showed greater reduction in both P300 latency ($p = 0.010$, partial $\eta^2 = 0.26$) and amplitude ($p = 0.011$, partial $\eta^2 = 0.26$), as well as a reduced Stroop effect on accuracy ($p = 0.008$, partial $\eta^2 = 0.21$). Additionally, the active group improved more than placebo on the Digit Span test ($p = 0.043$, Cohen's $d = 0.68$). Together, these results suggest an enhancement in working memory function associated with active treatments. Since acupressure emphasizes self-care and can be taught to novice individuals, it warrants further study as an adjunct treatment for TBI.

Introduction

Traumatic brain injury (TBI) is a prevalent problem, with estimates ranging from 1.4-3 million per year in the USA (Sosin et al., 1996; McCrea, 2008), and even those numbers likely underestimate the true incidence of TBI (McCrea, 2008). TBI is a major cause of disability, with at least 5.3 million estimated to have resulting long-term or lifelong disability (Thurman et al., 1999). Given that those between the ages of 15-24 are at a high risk for TBI (Thurman et al., 2007), the TBI survivor faces a potential lifetime of living with injury-associated deficits and disability. A common and frustrating consequence of TBI is cognitive impairment, including difficulties with memory, attention, arousal, and speed of information processing (Arciniegas and Silver, 2006; Eslinger et al., 2007; Dikmen et al., 2009).

Considering the prevalence of TBI and the associated disability, it is important to investigate treatments to assist TBI survivors with persistent impairments, and exploring non-pharmacological treatments could be especially beneficial. Acupressure is a complementary and alternative medicine (CAM) treatment administered by applying pressure with the fingertips to *acupoints*, points on the skin designated as such by Traditional Chinese Medicine. Although there is some evidence that acupressure may enhance cognitive function (Clancy et al., 1996; Krebs and Brown, 1998), there is a dearth of controlled studies. Acupressure has been found to modify alertness in healthy medical professionals (Harris et al., 2005) and fatigue in patients with renal disease (Tsay, 2004), but there is little research on the effects of acupressure on cognitive function in general, and none in the English-language literature on the efficacy of acupressure for TBI. Acupressure could be a particularly useful treatment for TBI survivors because it can be taught to novice users and as such, can be used independently of funds, insurance, or a practitioner.

Although the mechanism by which acupressure affects the body remains unknown, there is evidence that it may modulate the autonomic nervous system (Felhendler and Lisander, 1999; Sugiura et al., 2007; McFadden and Hernández, 2010), and elicit the "relaxation response", a physiological response that includes reduced respiration, heart rate, and blood pressure (Benson et al., 1974). A previous placebo-controlled, single-blind study in our laboratory in stroke survivors found active acupressure treatments to elicit a significantly faster and greater relaxation response compared to placebo acupressure treatments (McFadden and Hernández, 2010). Other studies have found induction of the relaxation response to improve cognitive function through methods such as yoga (Subramanya and Telles, 2009) and meditation (So and Orme-Johnson, 2001; Newberg et al., 2010), although not all studies of yoga or meditation have shown improvement (Canter and Ernst, 2003; Oken et al., 2006). Additionally, Hanna-Pladdy et al. found induction of the relaxation response through a deep-breathing relaxation session to decrease cognitive complaints in individuals with mild TBI (Hanna-Pladdy et al., 2001).

The current study aims to determine whether acupressure treatments (specifically, Jin Shin acupressure (Mines, 1982; Burmeister, 1997; Mines, 2003)) affect cognitive sequelae following TBI. Specifically, a randomized, placebo-controlled, single-blind design was used to test the hypothesis that active acupressure treatments would confer greater improvement in cognitive function compared to placebo acupressure treatments, as assessed by a neuropsychological test battery and event-related potentials (ERPs) during Stroop (Stroop, 1935) and auditory oddball tasks.

To our knowledge, there are no studies in the English-language literature that use ERPs to evaluate possible neural effects of acupressure. Indeed, the use of ERPs in the current study allows for a noninvasive neurophysiological measure of performance on cognitive tasks in real

time (Spikman et al., 2004). The Stroop Color and Word Test (Stoelting Co., Wood Dale, IL, 1994), a measure of working memory (Lesak et al., 2004) and attention (Bohnen et al., 1992) was used in the current study as it is a common assessment for cognitive impairment in TBI (Bohnen et al., 1992; Marsh and Smith, 1995; Potter et al., 2002; Bagiella et al., 2010) and is sensitive to effects of TBI even in those with apparently good recovery (Bagiella et al., 2010). Oddball paradigms are commonly used clinically and experimentally with ERP recording to assess working memory and attention (Hruby and Marsalek, 2003; Polich, 2004) and have also been used to assess cognitive dysfunction in individuals with TBI (Rugg et al., 1993; Potter and Barrett, 1999; Sivak et al., 2008).

The current study used a multi-level approach to assess the effects of acupressure on cognitive function, employing a large range of self-report, behavioral, and neural measures. In addition to the neurophysiological measures using ERPs, the neuropsychological test battery included a multitude of tests that have been found to measure the following cognitive functions: working memory (Digit Span test (Lesak et al., 2004)), attention (Digit Symbol and Digit Span tasks (Lesak et al., 2004), and the Comprehensive Trail-Making Test (CTMT) (Dikmen et al., 1995; Lesak et al., 2004; Wang et al., 2007)), processing speed (Digit Symbol test (Wang et al., 2007) and the CTMT (Dikmen et al., 1983; Dikmen et al., 1995)), tactual spatial problem solving (Tactual Performance Test (Dikmen et al., 1983)), motor functioning and speed (the Finger Tapping Test (Dikmen et al., 1983; Dikmen et al., 1995)), and health-related quality of life (Sickness Impact Profile (SIP) (Pagulayan et al., 2006)). Furthermore, state of being was assessed with the State Anxiety Inventory, the Center for Epidemiologic Studies Depression Scale (CES-D), the Perceived Stress Scale (PSS), and the UCLA Loneliness Scale.

It was hypothesized that active acupressure treatments (8 treatments over 4 weeks) would improve cognitive function above any improvements seen following placebo acupressure treatments in participants with mild to moderate TBI. As well as increased improvements on the neuropsychological test battery and state of being assessments, it was hypothesized that active acupressure would impact ERP measurements above that seen with placebo treatments.

Methods

Participants

Participants aged 18-44 were recruited from the Denver/Boulder (Colorado) community via newspaper/newsletter advertisement and flyers. Participants completed a series of eligibility questions in addition to the Brain Injury Screening Questionnaire (BISQ) (Research and Training Center, New York, NY) over the telephone to determine eligibility for the study. The BISQ has been shown to reliably distinguish between brain injury and other conditions (e.g., spinal cord injury) or those with no disability (Gordon et al., 2000; Cantor et al., 2004). Participants eligible for the current study must have experienced a mild to moderate TBI at least nine months and no more than five years prior to beginning the study and be experiencing lasting deficits as a result of the injury, as assessed by the BISQ. Results of the BISQ must have been "positive" for brain injury, including experiencing symptoms common to brain injury, supporting that the symptoms resulted from the injury (e.g., difficulty learning new skills and new information, being easily distracted) (Gordon et al., 2000). Participants were only eligible if the BISQ determined that there was sufficient probability that current symptoms were a result of their self-reported history of head injury. As acupressure has not previously been investigated in survivors of TBI, the current study sought to recruit those with mild to moderate TBI rather than severe TBI, although there were no anticipated side effects. Eligibility criteria required participants to have experienced an alteration of consciousness, either through loss of consciousness or being dazed and confused following a blow to the head, but not to have experienced loss of consciousness for longer than 24 hours, as per common guidelines for mild/moderate TBI classification (McCrea, 2008; Summers et al., 2009). Participants were deemed ineligible if they smoked, were taking any drugs for recreational, psychiatric or medical purposes (unrelated to the brain injury), or had

prior experience with acupressure. Participants gave informed consent and all aspects of the present study were in accordance with and approved by the University of Colorado Institutional Review Board.

Design

A randomized, placebo-controlled, single-blind design was used. The study involved three phases: pre-treatment assessment, acupressure treatments (active or placebo), and post-treatment assessment. After being stratified by gender, consented individuals were randomly assigned to receive active or placebo acupressure treatments; a random number generator was used to assign participants to condition in blocks of four. The acupressure practitioner was provided with a sealed envelope prior to each participant beginning their first treatment session, revealing the treatment she was to administer. As such, only the practitioner knew the type of treatment being administered. Acupressure treatments (40 minutes in length) were administered twice per week for 4 weeks, for a total of 8 treatments. Participants were blinded to which treatment condition they were assigned and all data collection, entry, and analyses were done by blinded individuals.

Phase One: Pre-treatment assessment

Participants first answered demographic questions, followed by an assessment of attitudes towards and use of complementary medicine using the CACMAS (McFadden et al., in press), and an assessment of past, present, and likely future use of 17 CAM modalities (McFadden et al., in press). A modified version of the revised Life Orientation Test (LOT-R) (Scheier et al., 1994) was also administered. These questionnaires were used to measure baseline CAM usage, attitudes, and optimism among participants, to ensure that there were no differences between the active and placebo groups at baseline.

Questionnaires to assess state of being were administered during both pre- and post-treatment assessment sessions to explore treatment effects. These were the PSS (Cohen et al., 1983), the CES-D (Radloff, 1977), the State Anxiety Inventory (State portion of the State-Trait Anxiety Inventory (Mind Garden, Inc., Menlo Park, CA)) (Spielberger et al., 1970) and the UCLA Loneliness Scale (Version 3) (Russell, 1996).

To assess cognitive function, participants next completed a battery of neuropsychological tests: the Digit Span and Digit Symbol subtests from the WAIS-R (Wechsler, 1981) and the CTMT (Reynolds, 2002), as well as the Finger Tapping Test (Psychological Assessment Resources, Inc., Lutz, FL) and Tactual Performance Test (Psychological Assessment Resources, Inc., Lutz, FL) from the Halstead-Reitan Neuropsychological Test Battery (Reitan, 1969). Additionally, health-related quality of life was assessed with the SIP (Gilson et al., 1975). All were administered and scored according to standard methods in the literature.

Following the neuropsychological test battery, ERP data were recorded from 28 tin electrodes sewn into a stretch-lycra cap (Electro-Cap International, Eaton, OH), positioned according to the 10-20 international system (Jasper, 1958). Electrodes were also placed on the supra- and sub-orbit of the right eye to assess vertical eye movements, on the outer canthi of both eyes to assess horizontal eye movements, and over the left and right mastoid bone. Active scalp sites were referenced on-line to the left mastoid. Impedances were below 10 KΩ at all sites. ERP recordings were amplified with a gain of 500 using Neuroscan SynAmps amplifiers (Neuroscan, Inc., Sterling, VA), with a filter bandpass of 0.15-30Hz and digitized at 1000 Hz. Offline, data were re-referenced to a computed average of the left and right mastoids and submitted to a regression procedure for correction of eyeblink artifact (Semlitsch et al., 1986 and Presslich, 1986). Epochs were created starting 100ms prior to stimulus onset and lasting for

1000ms following stimulus onset, and baseline corrected to the mean voltage of the pre-stimulus period. Each trial was visually inspected for remaining ocular or other artifact; any trials in which artifact was detected were deleted from further analyses (Kubota and Ito, 2007).

The Stroop Color and Word Test (Stoelting Co., Wood Dale, IL, 1994) was adapted for computer administration using PsyScope v. 1.2.5 (Cohen et al., 1993). Prior to beginning the task, participants were tested for color-blindness using Ishihara plates (Ishihara, 2007) and only completed the task if it was determined that they were able to distinguish between the colors used in the task. Responses during the task were made verbally, using a headphone/microphone set (Optimus PRO 50MX Stereo Headphones), connected to the computer via button box to record response times. Before task onset, microphone sensitivity was tested by having participants read aloud days of the week presented in the center of the computer screen.

Participants first completed the 96 trials in the congruent block, in which words ("RED", "BLUE", or "GREEN") were presented in the matching color (e.g., "RED" in red letters). Next, the 96 trials in the incongruent block were completed, in which words were presented in a non-matching color (e.g., "RED" presented in green letters). Participants were instructed to say aloud the color of the letters rather than reading the actual word. Lastly, participants completed the 96 trials in the neutral block, in which a row of four X's was presented in the center of the screen in red, blue, or green, and participants were asked to name aloud the color in which the X's were presented. Prior to each 96-trial block, participants completed a practice of 6 trials to ensure task comprehension. There was a 1500ms inter-stimulus interval between word presentation (beginning when a response was made) and all words were presented on a black background in a dimly lit room for easy visibility. Participants were instructed to give all responses as quickly and accurately as possible and to avoid making any additional sounds so the microphone would

not be triggered inappropriately. The task only advanced to the next trial after a response was made. Accuracy was recorded by a research assistant seated behind the participant.

A three-armed paradigm was used for the auditory oddball task (for review, see Polich, 2004), programmed with PsyScope Version 1.2.5 (Cohen et al., 1993). Participants were asked to discriminate between a frequently presented standard stimulus, an infrequently presented target stimulus (the "oddball"), and an infrequently presented non-target distracter stimulus (a white noise burst). They were instructed to respond by button press to only the target stimulus, and not to respond to the standard or distracter stimuli.

All participants reported normal hearing prior to this task. To ensure that participants were able to hear the tones presented during the task, a brief test was conducted in which participants indicated they could hear a 1000Hz tone administered both at and below the level at which stimuli would be presented. Stimuli were created with SoundStudio3 (Freeverse, Brooklyn, NY) and presented at 75 dB SPL (measured by Radioshack Digital-Display Sound-Level Meter) using Optimus PRO 50MX Stereo Headphones. The target stimulus was a 1000Hz tone and the standard stimulus was a 500Hz tone, both presented for 70ms (50ms with 10ms rise/fall time). The distracter stimulus used was a white noise burst, presented for 100ms (80ms with 10ms rise/fall time), which was slightly longer than the tones to make it distinguishable as white noise. During the task, 400 stimuli were presented, consisting of the standard, target, and distracter stimuli with probabilities of 0.75, 0.125 and 0.125, respectively (300 trials, 50 trials, 50 trials). The 400 stimuli were presented in pseudorandom order, such that target or distracter stimuli were never presented consecutively (i.e., there was always at least one standard tone separating them). There was an inter-stimulus interval of 1300ms between all stimuli.

Prior to beginning the task, participants listened to the three stimuli with the research assistant and were instructed to only respond to target stimuli. Following this, participants completed a practice of 30 stimuli and began the task after confirming they understood the procedure. After presentation of the first 200 stimuli, participants were given a chance to take a brief break before the remaining 200 stimuli, to help prevent drowsiness. Participants were notified of this break prior to task onset, and a message on the screen invited participants to rest briefly if desired and to push the button when ready to resume the task. To reduce eye movement, it was suggested that participants focus on a fixation point on the computer screen during the task.

Phase Two: Acupressure treatments

Within a week after completing the pre-treatment assessment, participants began the acupressure treatment sessions. During treatment sessions, participants lay face up on a massage table, fully clothed with shoes removed, as is common practice for acupressure treatments (Mines, 1982; Burmeister, 1997). A Jin Shin (acupressure) practitioner with over 20 years of clinical and educational experience and appropriate certification administered treatments (active or placebo) behind a closed curtain. The practitioner was also trained in use of the placebo acupoints, which were established by T.D.H. (Hernández et al., 2003) and are points not found on established acupressure point charts. The placebo acupoints were each assigned a number and, using a random number generator, put into a matching sequence for each customary Jin Shin (acupressure) treatment.

During treatment, the practitioner applied pressure with her fingertips to different sites on the body, in sequence (see McFadden and Hernández, 2010 and Chapter 1 for detail). The entire treatment, itself, lasted 40 minutes. The placebo control procedure was designed to be

indistinguishable from the active treatment session, to last the same duration, and contain the same amount of physical contact. To guarantee matching practitioner/participant interactions for both treatment types, only scripted dialogue was used. Eight treatments were administered (twice weekly for 4 weeks) as our previous studies have found eight to be an optimal number to elicit treatment effects (McFadden and Hernández, 2010). A research assistant seated on the other side of the curtain was present during all treatment sessions to monitor the interaction between participants and the practitioner.

As has been done previously (McFadden and Hernández, 2010), expectancy was assessed (Myers et al., 2008) before treatments. To see if expectancy levels changed throughout the series of treatments, expectancy was assessed prior to treatments one, three and six. Participants also rated treatment credibility (Shapiro, 1981) immediately following treatments two, five, and eight.

Phase Three: Post-Treatment Assessment

Approximately 48 hours after their last acupressure treatment, participants completed the post-treatment assessment. This assessment consisted of the same measures as the pre-treatment assessment except for demographic measures, the CACMAS, CAM usage, and the modified LOT-R. ERP data were again recorded while participants completed the Stroop and auditory oddball tasks (see procedure above).

Data Analyses

Data were analyzed using SPSS 17.0 (SPSS Inc., Chicago, IL). State of being, neuropsychological test battery, and SIP data were analyzed with independent samples t-tests to assess differences within groups (simple pre- to post-treatment changes in active and placebo groups) as well as the differences between those group changes (active vs. placebo). Cohen's *d* was found for t-tests using G*Power Version 3.2.1 (Faul et al., 2007). A composite score was

created for the neuropsychological test battery, by ranking the change scores for each participant from least to most improved on each test, then obtaining a mean rank across the tests (similar to (Dikmen et al., 2000). Group differences in composite change scores were analyzed using an independent samples t-test. Expectancy and credibility data were analyzed using repeated measures ANOVA, given that the questionnaires were administered multiple times throughout the experiment. Behavioral data from the Stroop and auditory oddball tasks (reaction time and accuracy) were also analyzed using repeated measures ANOVA, to assess main effects of group (placebo or active), stimulus (*Stroop*: congruent vs. incongruent vs. neutral; *auditory oddball*: target vs. standard vs. distracter), and session (pre- vs. post-treatment), as well as any interactions among variables, using the Greenhouse-Geisser correction. Potential confounding variables (age, gender, time since injury, number of injuries, number of TBI-sensitive symptoms reported on the BISQ, expectancy levels, and credibility levels) were controlled by adding them into the model using ANCOVA.

In the Stroop and auditory oddball tasks, we quantified the P300 ERP component because of its association with working memory (Kok, 2001; Polich, 2004; Spikman et al., 2004) and because it is commonly investigated in these tasks (Ilan and Polich, 2001; Hruby and Marsalek, 2003; Polich, 2004). P300 amplitude is thought to reflect the degree of working memory engagement, and latency the speed with which working memory operations occur (Hruby and Marsalek, 2003; Polich, 2004). The P300 component was defined as the largest positive-going deflection within 250-400ms post-stimulus onset in both the Stroop and auditory oddball tasks. Additionally, for the Stroop task, we quantified two components associated with cognitive control: N2 and N450 components were quantified because they have been consistently investigated in Stroop tasks and are thought to reflect cognitive control processes (Larson et al.,

2009; Vanderhasselt and De Raedt, 2009). The N2 component was defined as the largest negative-going deflection within 200-300ms post-stimulus onset, with the N450 component the largest negative-going deflection within 400-500ms post-stimulus onset. Before these peaks were quantified, data were filtered offline with a 9Hz low-pass zero-phase filter. Peak latency for all components was measured from the time of stimulus onset, with amplitude measured relative to pre-stimulus baseline. Grand average ERP waveforms were created for active and placebo groups by session (pre- or post-treatment assessment) and stimulus type for each task (Stroop and auditory oddball).

ERP latency and amplitude were analyzed using repeated measures ANOVA to assess main effects of group (active vs. placebo), stimulus (*Stroop*: congruent vs. incongruent vs. neutral; *auditory oddball*: target vs. standard vs. distracter), and session (pre- vs. post-treatment), as well as any interactions among variables, using the Greenhouse-Geisser correction. Potential confounding variables (age, gender, time since injury, number of injuries, number of TBI-sensitive symptoms reported on the BISQ, expectancy levels, and credibility levels) were controlled by adding them into the model using ANCOVA.

Results

Participants

Many screened for participation were ineligible due to such reasons as length of time since brain injury, age, or having no lasting TBI-related sequelae, among others (see Figure 2.1). Of the 42 participants completing the study, 21 were randomly assigned to active acupressure treatments, while the other 21 were randomly assigned to placebo acupressure treatments. Eleven participants completed all aspects of the study except for the ERP testing, due to initiation of neuropsychological data acquisition preceding ERP data acquisition for seven participants (four active, three placebo) and four participants declining to take part in the ERP portion of the study (one active, three placebo). Seven participants were excluded from analyses for various reasons (see Figure 2.1), resulting in analyses for 21 participants in the active group and 17 participants in the placebo group for the state of being, neuropsychological test battery and SIP analyses, with 14 participants in the active group and 10 participants in the placebo group for the ERP analyses.

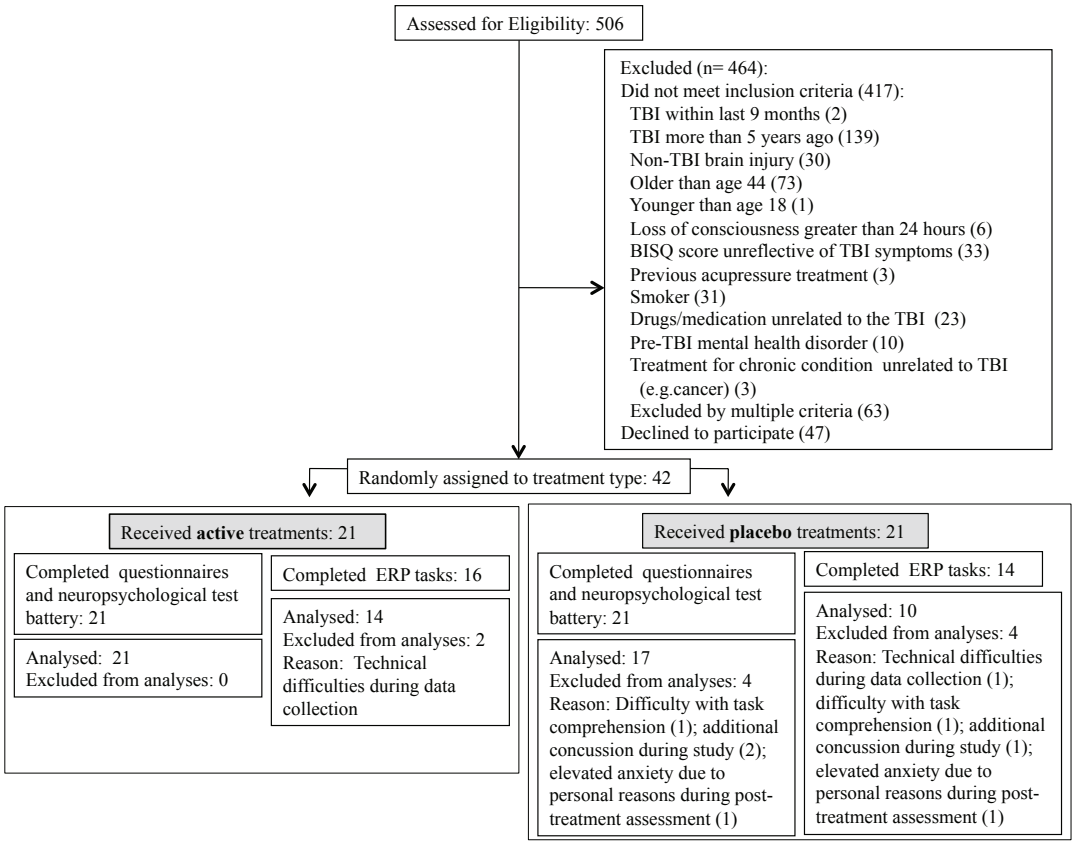

Figure 2.1. Participant flow through study.

There were no significant differences between the active and placebo groups in any of the demographical information collected (see Table 2.1), $p > 0.05$. Additionally, there were no significant differences between groups in terms of reported cause of injury (e.g., equal numbers reported due to motor vehicle accident, sports, etc.). Furthermore, there were no significant differences between the active and placebo groups on the modified LOT-R, the CACMAS, or in past, present, or likely future use of CAM (see Table 2.1), $p > 0.05$. Importantly, there were no significant main effects of treatment type on expectancy ratings (F (1, 36) = 1.64, $p = 0.21$) or credibility ratings (F (1, 36) = 2.26, $p = 0.14$), indicating that participants in both groups were equally expectant prior to treatments and also judged treatments to be equally credible. Interestingly, there was a significant linear effect of time on credibility rating, such that

credibility rating increased with each administration of the credibility questionnaire, but equally for both active and placebo groups, F (2, 72) = 5.07, p = 0.010, partial η^2 = 0.12. There was no effect of time on expectancy rating, $p > 0.05$.

	Active	Placebo
Sample size	21	17
Age (years)	24.24 ± 1.75	21.88 ± 1.29
Gender (% male)	57.1	64.7
Employment (% employed)	52.4	61.1
LOC (% less than 20 minutes)	61.9	52.9
BISQ TBI-sensitive symptoms (#)	10.71 ± 1.19	8.76 ± 1.14
Time since injury (months)	23.07 ± 3.41	25.83 ± 4.24
CACMAS		
Philosophical congruence with CAM	5.00 ± 0.16	5.00 ± 0.28
Dissatisfaction with conventional medicine	2.59 ± 0.23	2.84 ± 0.28
Holistic balance	4.45 ± 0.25	4.38 ± 0.34
CAM usage (# of types used)		
Past use	5.29 ± 0.59	5.41 ± 0.91
Present use	1.57 ± 0.36	1.76 ± 0.55
Would use in future	10.76 ± 0.95	11.29 ± 1.26
LOT-R (modified)	32.29 ± 1.13	31.12 ± 1.56
Expectancy ratings		
Treatment 1	4.81 ± 0.32	4.47 ± 0.43
Treatment 3	4.86 ± 0.31	4.00 ± 0.48
Treatment 6	4.88 ± 0.35	4.12 ± 0.50
Credibility rating		
Treatment 2	5.02 ± 0.31	4.12 ± 0.38
Treatment 5	5.25 ± 0.35	4.45 ± 0.46
Treatment 8	5.42 ± 0.39	4.64 ± 0.54

Table 2.1. Participant characteristics.
Mean ± SEM unless otherwise indicated.
LOC: Loss of consciousness (note: all were unconscious for less than 24 hours); *BISQ*: Brain Injury Screening Questionnaire; *CACMAS*: Complementary, Alternative and Conventional Medicine Attitudes Scale, mean score on a scale of 1-7, with 1 = strongly disagree to 7 = strongly agree; *CAM usage*: Complementary and alternative medicine usage, out of 17 listed types; *LOT-R*: modified version of the revised Life Orientation Test, sum, with a minimum

possible score of 0 (least optimistic) to 42 (most optimistic); *Expectancy rating*: mean score on a scale of 1-9, with 1 = least expectant to 9 = most expectant; *Credibility rating*: mean score on a scale of 1-9, with 1 = least credible to 9 = most credible.

State of being

There was a marginally significant treatment effect on the PSS, such that those in the active group indicated a larger reduction in subjective stress levels post-treatment than those in the placebo group, t (36) = 1.88, p = 0.069, Cohen's d = 0.59. Also, although the active group had a significantly lower score on the CES-D from pre- to post-treatment, the placebo group only showed a marginally significant reduction in CES-D score from pre- to post-treatment (see Table 2.2). However, this change from pre- to post-treatment was not significantly different between groups. There were also no significant group differences between pre- to post-treatment changes in score on the State Anxiety Inventory, or the UCLA Loneliness Scale, $p > 0.05$ (see Table 2.2).

	Active			Placebo			**Group Difference**
Measure	Pre	Post	*p*	Pre	Post	*p*	***p***
PSS	24.19 ± 1.45	20.19 ± 1.17	***	21.88 ± 2.09	21.47 ± 1.54	ns	†
CES-D	15.90 ± 1.42	12.05 ± 4.50	**	14.88 ± 2.12	11.59 ± 1.91	†	**ns**
State Anxiety Inventory	1.59 ± 0.08	1.59 ± 0.07	ns	1.70 ± 0.11	1.64 ± 0.13	ns	**ns**
UCLA Loneliness Scale	37.86 ± 2.29	35.67 ± 1.98	ns	39.12 ± 3.14	36.29 ± 3.15	ns	**ns**
Digit Span (WAIS-R)	12.05 ± 0.44	12.95 ± 0.48	*	12.47 ± 0.54	12.29 ± 0.58	ns	*
Digit Symbol (WAIS-R)	62.24 ± 2.08	69.05 ± 1.85	***	65.23 ± 3.04	70.88 ± 3.25	***	**ns**
CTMT composite	46.70 ± 2.40	56.70 ± 2.14	***	49.37 ± 2.20	59.37 ± 2.20	***	**ns**
FTT	46.84 ± 1.97	50.42 ± 1.71	**	47.64 ± 1.45	49.91 ± 1.24	*	**ns**
TPT	11.43 ± 0.98	8.43 ± 0.75	***	8.50 ± 0.51	6.54 ± 0.46	**	**ns**
SIP	6.31 ± 1.41	3.34 ± 1.32	***	6.12 ± 2.10	3.90 ± 2.28	**	**ns**

Table 2.2. Neuropsychological test battery, state of being, and health-related quality of life scores before and after the treatment series. All measures: mean ± SEM.
The first two p value columns reflect change from pre- to post-treatment *within* each group (active and placebo), while the last column reflects the difference in change (pre- to post-treatment) *between* groups (group difference: active vs. placebo): $p < 0.07$ = †, $p < 0.05$ = *, $p < 0.01$ = **, $p < 0.001$ = ***
State Anxiety Inventory: mean score on a scale of 1-4, with 1 = not at all anxious to 4 = very anxious; *CES-D: Center for Epidemiologic Studies Depression Scale*: sum score, with 0 = least depression and 60 = most depression; *PSS: Perceived Stress Scale*: sum, with a minimum possible score of 0 (never stressed) and maximum possible score of 56 (often stressed); *UCLA Loneliness Scale*: sum, with a minimum possible score of 20 (never lonely) and a maximum possible score of 80 (often lonely); *Digit Symbol*: number completed correctly (93 possible); *Digit Span*: sum of maximum number recalled correctly in Digits Forward plus maximum recalled correctly in Digits Backward (17 possible); *CTMT: Comprehensive Trail-Making Test:* composite index score; *FTT: Finger Tapping Test*: mean number of taps in 10 seconds using dominant hand; *TPT: Tactual Performance Test*: total minutes to complete test; *SIP: Sickness Impact Profile*: sickness score from 0 to 100.

Neuropsychological test battery and health-related quality of life

Those in the active acupressure group significantly improved from pre- to post-treatment on the Digit Span test (measured as the sum of the maximum number recalled in Digits Forward plus maximum recalled in Digits Backward) compared to those in the placebo group, t (36) =

2.09, $p = 0.043$, Cohen's $d = 0.68$ (see Table 2.2). This effect could not be accounted for by age, gender, time since injury, number of injuries, number of TBI-sensitive symptoms reported on the BISQ, expectancy levels, or credibility levels. While scores in both groups significantly improved from pre- to post-treatment assessment, there were no significant differences in improvement between the active and placebo acupressure groups on the Digit Symbol test, the CTMT, the Finger Tapping Test, the Tactual Performance Test, or the SIP, $p > 0.05$. However, there was a marginally significant effect seen in the neuropsychological test battery composite score, such that the active group improved overall more than the placebo group, $t(36) = 1.85$, $p = 0.073$, Cohen's $d = 0.59$.

Stroop Task

Data for the P300 component are reported at the Pz electrode, as analyses revealed that to be the electrode at which the greatest amplitude was found. Amplitude was greatest at the FCz electrode for the N450 component and at the Fz electrode for the N2 component, so data were analyzed accordingly at those electrodes. These scalp distributions are consistent with previous research (Ilan and Polich, 2001; Larson et al., 2009; Vanderhasselt and De Raedt, 2009).

ERP data showed a significant session by treatment group interaction in the Stroop task, such that those in the active group demonstrated a reduction in P300 latency and amplitude compared to those in the placebo group, $F(1, 22) = 7.90$, $p = 0.010$, partial $\eta^2 = 0.26$ and $F(1, 22) = 7.74$, $p = 0.011$, partial $\eta^2 = 0.26$, respectively (see Figure 2.2). These effects could not be accounted for by age, gender, time since injury, number of injuries, number of TBI-sensitive symptoms reported on the BISQ, expectancy levels, or credibility levels. There were no significant treatment effects found among the N2 or N450 components, $p > 0.05$.

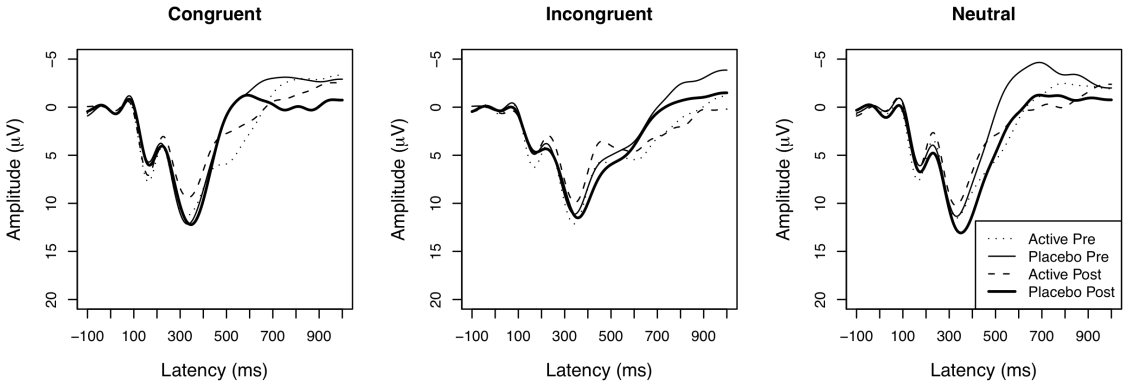

Figure 2.2. Grand average ERP waveforms at Pz during the Stroop Color and Word Test.

Looking at reaction times during the Stroop task, a significant main effect of stimulus was found, $F(2, 44) = 158.68$, $p < 0.001$, partial $\eta^2 = 0.88$. Reaction times were significantly different among all three stimuli, such that both active and placebo groups had longer reaction times to incongruent stimuli than to both congruent and neutral stimuli, and longer reaction times to neutral stimuli than to congruent stimuli (see Table 2.3). However, there were no significant effects of session (pre- or post-treatment) or treatment group (active or placebo), $p > 0.05$.

	Active		Placebo	
Stimulus	Pre	Post	Pre	Post
Congruent				
RT	514 ± 19	507 ± 19	488 ± 26	470 ± 17
% correct	99.85 ± 0.15	99.48 ± 0.38	99.90 ± 0.10	100.00 ± 0.00
Incongruent				
RT	717 ± 27	699 ± 25	681 ± 30	680 ± 30
% correct	98.36 ± 0.37	98.70 ± 0.36	98.95 ± 0.35	97.48 ± 0.65
Neutral				
RT	575 ± 18	588 ± 16	577 ± 28	595 ± 46
% correct	99.63 ± 0.18	99.31 ± 0.21	99.47 ± 0.29	99.27 ± 0.35

Table 2.3. Mean reaction times (ms) ± SEM and percent correct ± SEM during Stroop task.

In terms of accuracy, there was a significant interaction between treatment group, stimulus type, and session, F (2, 44) = 5.89, p = 0.008, partial η^2 = 0.21. To explain this interaction, analyses were broken down to investigate how the Stroop effect changed from pre- to post-treatment for each group. The Stroop effect states that incongruent trials will prove more difficult than congruent or neutral trials, because the automatic reading response interferes with naming the incongruent ink color (Bohnen et al., 1992; Potter et al., 2002). To investigate this, difference scores were calculated for incongruent vs. congruent accuracy as well as incongruent vs. neutral accuracy, for both pre- and post-treatment sessions. There were no significant differences between active and placebo groups in the incongruent/congruent Stroop effect or the incongruent/neutral Stroop effect pre-treatment. However, after the treatment series, the active group demonstrated a reduction in the incongruent/congruent Stroop effect compared to the change seen in the placebo group, t (22) = 3.20, p = 0.004, Cohen's d = 1.27, i.e., there was an active treatment-associated reduction in interference during the task. There was also a significant treatment effect seen in the incongruent/neutral Stroop effect, such that the active group again showed a reduced Stroop effect from pre- to post-treatment compared to the placebo group, t (22) = 2.35, p = 0.028, Cohen's d = 0.96 (see Table 2.4). Overall, active treatments reduced interference during the Stroop task as measured by accuracy.

	Active		Placebo	
	Pre	Post	Pre	Post
Congruent - incongruent (%)	1.49	0.78	0.95	2.52
Neutral - incongruent (%)	1.27	0.61	0.52	1.79

Table 2.4. Stroop accuracy (percent correct): Stroop effects as reflected in lower accuracy to incongruent trials as compared to congruent and neutral trials. Higher numbers indicate a larger Stroop effect.

In addition, there were significant main effects of session (F (1, 22) = 4.73, p = 0.041, partial η^2 = 0.18) and stimulus (F (2, 44) = 19.66, p < 0 .001, partial η^2 = 0.47) on accuracy. This was such that across treatment group and stimulus type, participants were more accurate during the pre-treatment assessment than the post-treatment assessment. Also, across treatment group and session (pre- or post-treatment), participants were correct on significantly fewer trials during the incongruent block than either the congruent or neutral blocks (see Table 2.3).

Auditory Oddball Task

During an oddball task, it is expected that both the target and distracter stimuli will elicit a P300 component, which will not be apparent in reaction to the standard stimuli (Polich, 2004). A classic oddball effect was seen during this task: there was a significant main effect of stimulus, such that P300 amplitude was increased for both the target (oddball) and the distracter (white noise) compared to the standard tone, F (2, 44) = 56.61, p < 0.001, partial η^2 = 0.72. There was also a significant main effect of stimulus for P300 latency, such that participants demonstrated decreased latency to the distracter (white noise) compared to the standard and target tones, perhaps due to the salience of the stimulus, F (2, 44) = 11.02, p = 0.002, partial η^2 = 0.33 (see Figure 2.3). There were no significant effects of treatment group, nor were there any interactions between treatment group and stimulus or session, p > 0.05.

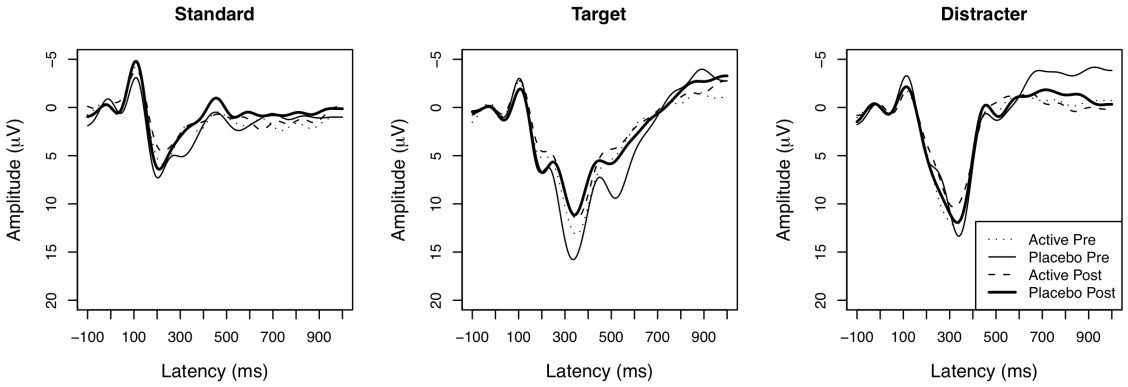

Figure 2.3. Grand average ERP waveforms at Pz during the auditory oddball task.

Similarly, there were no significant differences in reaction time or accuracy in responses to oddball stimuli from pre- to post-treatment assessment in either group, $p > 0.05$. Although there were no significant treatment effects, there was a significant main effect of stimulus when looking at the percentage of false positive responses (button press to either standard or distracter stimuli), such that participants made more false positive responses to distracter stimuli than standard stimuli, $F(1, 22) = 18.03$, $p < 0.001$, partial $\eta^2 = 0.45$, again perhaps due to stimulus salience (see Table 2.5).

	Active		Placebo	
	Pre	Post	Pre	Post
Reaction time (ms)	384 ± 16	398 ± 21	348 ± 21	353 ± 29
Target hits (%)	98.14 ± 0.90	98.86 ± 0.50	98.00 ± 1.1	97.80 ± 1.2
False positives (%)				
Standard	0.10 ± 0.05	0.12 ± 0.06	0.03 ± 0.03	0.03 ± 0.03
Distracter	1.6 ± 0.78	0.71 ± 0.34	2.4 ± 0.83	1.6 ± 0.78

Table 2.5. Mean reaction time ± SEM and percent correct ± SEM during the auditory oddball task.

Discussion

Significant treatment effects were found in the Stroop task, such that those in the active acupressure group demonstrated a reduction in both P300 latency and amplitude compared to those in the placebo acupressure group. The P300 component is thought to be a measure of working memory and selective attention (Hruby and Marsalek, 2003; Polich, 2004; Spikman et al., 2004). Specifically, P300 latency is said to reflect the speed of cognitive processing in working memory and P300 amplitude is hypothesized to represent the allocation of cognitive resources (Kok, 2001; Hruby and Marsalek, 2003; Polich, 2004). While there can be different interpretations of P300 amplitude reduction (Ilan and Polich, 2001; Kok, 2001), given that we also saw reduced P300 latency, we interpret these findings as an indication of reduced neural resources allocated to task completion, possibly suggesting an improvement in cognitive function. In support of this, recovery following TBI has also been associated with decreased demand for the additional "neural recruitment" indentified via neuroimaging during working memory tasks following TBI (Hillary et al., 2010; Nakamura et al., 2009). Furthermore, when looking at accuracy during the Stroop task, the active group demonstrated a reduction in interference after the treatment series that was not seen in the placebo group, suggesting treatment-associated improvement on the task even though there were no group differences in reaction time during the task. This reduced Stroop effect, in which there was less of a discrepancy between the more difficult incongruent trials and the easier congruent and neutral trials, suggests that the active acupressure treatment may have improved selective attention (Ilan and Polich, 2001). As such, it appears that although both groups were able to successfully complete the task, the active group may have required less processing time and fewer neural

resources than the placebo group post-treatment, suggesting an increase in function of working memory and attention.

A classic oddball effect was seen in both groups in the auditory oddball task, such that the P300 component was elicited to the target and distracter stimuli, but not to the standard stimuli. However, no significant treatment effects were found. One possible reason for this could be that the task was too easy for participants, as the oddball tone (1000Hz) was easily distinguishable from the standard tone (500Hz) (Katayama and Polich, 1998). Future studies can use a more difficult task (e.g., 950Hz compared to 1000Hz) to determine if there might be any treatment effects.

A significant treatment effect was found in the Digit Span test, such that participants in the active group improved compared to those in the placebo group. This is particularly interesting given the observed treatment-associated improvement on the Stroop task, as both tasks are measures of working memory and attention (Bohnen et al., 1992; Lesak et al., 2004). Although there were no significant treatment effects seen in the other tests given in the neuropsychological test battery, when looking at them together using a composite score, a marginally significant treatment effect was found: those in the active group improved more on the neuropsychological test battery overall compared to those in the placebo group, also suggesting enhanced cognitive function following active treatments. That they improved more than the placebo group also suggests that this enhanced performance was due to more than simply practice effects. Indeed, the active treatment-associated neural response seen during the Stroop task could be the mechanism underlying the functional improvement.

Those in the active group also reported a marginally significant greater reduction in subjective stress rating compared to the placebo group, as measured with the Perceived Stress

Scale. This reduction in subjective stress could be due to an increased relaxation response experienced by the active group. Following TBI, individuals may be particularly sensitive to anxiety and stress (Gouvier et al., 1992; Hanna-Pladdy et al., 2001; Bryant et al., 2010), which can exacerbate or unmask cognitive deficits (Ewing et al., 1980; Hanna-Pladdy et al., 2001). As such, a treatment that reduces stress and increases the relaxation response could be particularly beneficial to those experiencing cognitive impairments resulting from TBI. Furthermore, given that 86% of participants in the current study were college students, a population that often experiences high levels of stress (Tosevski et al., 2010), stress reduction would be particularly beneficial in this group with co-occurring TBI. Pilot data from a subset of TBI survivors in the present study showed that, similar to our prior study in stroke survivors (McFadden and Hernández, 2010), there was a greater and faster reduction in heart rate during active treatments compared to placebo treatments, although this difference was not statistically significant (unpublished data, available upon request). Future studies will include this measure to ascertain if the significant effects of acupressure on heart rate are replicated in a population other than stroke survivors.

There were no significant differences between the active and placebo groups in expectancy levels. This is important, as expectancy has been shown to influence treatment outcome (Shapiro, 1981; Price et al., 2008). Furthermore, there were no significant differences between the credibility ratings the participants in the active and placebo groups gave the treatments, which is important to establish that the placebo treatment was as credible as the active treatment. This suggests that participants were unaware of which treatment group they were in during the study. Interestingly, a questionnaire administered at the end of the study (after all data collection was complete) revealed that while only 42.9% of participants in the

active group correctly guessed which type of treatment they had received, 70.6% of those in the placebo group guessed correctly, but this difference was not statistically significant. It seems that this group difference only appeared after study completion, when participants were asked to retrospectively look back on the treatments as a whole, after the post-treatment assessment measures had been taken.

In a study of CAM, it is also necessary to establish that the participants in the placebo and active groups are not different in their attitudes towards and usage of CAM, as this could influence their receptivity towards the treatments they receive during the study. Importantly, there were no baseline differences between the active and placebo groups in their attitudes towards conventional and complementary medicine, or in the number of types of CAM they had used in the past, were currently using, or would be open to use in the future. The two groups also did not differ in their baseline level of optimism, which could affect treatment expectations and treatment effects (Scheier and Carver, 1992).

A potential limitation of the current study is that TBI status was determined using self-report rather than medical records or neuroimaging methods. However, given the stringent inclusion criteria and the reliability of the BISQ, which was used as a screening tool, in identifying brain injury (Gordon et al., 2000; Cantor et al., 2004), as well as the inability of some common imaging methods to ascertain mild TBI (Belanger et al., 2007), the current study sample should be representative of mild TBI survivors. As participants were not recruited from a medical center, but from the general population, future studies could involve participants with recently clinically diagnosed TBI recruited from a medical setting. Another potential limitation is that the current study focused on acute benefits of acupressure treatment, as post-treatment measures were taken approximately 48 hours after the last treatment administration. While

significant treatment effects were found, the enduring nature and long-term clinical significance of these effects remains to be determined. Future studies will assess enduring benefits of acupressure treatments, as well as whether the statistically significant enhancement of the relaxation response is replicated.

In conclusion, acupressure may confer a functional benefit in TBI survivors above and beyond that seen with placebo acupressure, specifically by improving cognitive, neurophysiological, and neuropsychological function. The mechanism underlying this improvement remains unknown, but could be due to an increased relaxation response, which has been suggested to break the stress-disease link (Esch et al., 2003). Given the adverse consequences of stress following TBI, it is valuable to show that an enhanced relaxation response in this population can lead to a reduction in stress and cognitive benefit. Additionally, since it is highly accessible, can be taught to the novice individual, and has no apparent side effects, acupressure warrants further study as an adjunct treatment following TBI.

CHAPTER 3

EFFICACY OF ACUPRESSURE AS A NON-PHARMACOLOGICAL INTERVENTION FOR STRESS REDUCTION IN COLLEGE STUDENTS

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Abstract

College students are a group often experiencing stress, which can be maladaptive and detrimental to health. Acupressure is a non-pharmacological complementary and alternative medicine therapy using fingertip pressure to stimulate acupoints and has been implicated as a potentially useful technique for stress reduction. To assess the efficacy of acupressure for stress reduction in healthy college students, a randomized, placebo-controlled, single-blind design was used. Students (n = 109) were randomly assigned to receive one of three interventions: active acupressure, placebo acupressure, or a relaxation CD control, all 40 minutes in length. A math task stressor was administered both before and after the intervention to assess effects of the interventions on stressor reactivity. Physiological measures (heart rate (HR), heart rate variability (HRV), skin conductance response (SCR)) and subjective stress measures (State Anxiety Inventory, nine-item Psychological Stress Measure (PSM-9)) were used to assess stressor responses. All interventions were associated with the following changes from the first stressor (pre-intervention) to the second stressor (post-intervention): reduced HR ($p < 0.001$), increased HRV (lnSDNN (log-transformed standard deviation of NN intervals): $p = 0.004$; lnLF power (log-transformed low frequency power): $p = 0.024$), reduced SCR ($p < 0.001$), reduced subjective stress scores ($p < 0.001$), and increased correct answers on the math task ($p < 0.001$). Although all three interventions significantly reduced the stress response, there were no group differences from pre- to post- intervention. Interestingly, HRV measures were greater in the active and placebo acupressure groups during the intervention itself compared to the relaxation group (lnSDNN: $p = 0.042$; lnLF power: $p = 0.054$). The lack of treatment effects may be due to insufficient dosing; recent studies in our laboratory have suggested more than one treatment may

be necessary for treatment effects. As such, this study is important for delineating optimal dosing for intervention efficacy.

Introduction

While stress is adaptive in some situations, chronic stress can be detrimental to physical health (Esch et al., 2003) and mental well-being (Ice and James, 2007). College students are a group that often experiences considerable stress (Tosevski et al., 2010), so finding a treatment to reduce the stress response could be particularly beneficial to this population. Acupressure is a complementary and alternative medicine (CAM) treatment in which fingertip pressure is applied to acupoints, points on the skin designated as such by Traditional Chinese Medicine. Previous studies have suggested that acupressure may reduce stress and anxiety in medical settings (Kober et al., 2003; Agarwal et al., 2005; Tsay et al., 2005). Studies with healthy participants have also found acupressure to reduce subjective stress levels in the absence of a stressor (Fassoulaki et al., 2003; Fassoulaki et al., 2007). Although the mechanisms underlying these effects are unknown, it has been hypothesized that acupressure may affect the autonomic nervous system (Felhendler and Lisander, 1999; Sugiura et al., 2007; McFadden and Hernández, 2010), since active acupressure treatments have been found to reduce heart rate significantly more and faster than placebo acupressure (McFadden and Hernández, 2010). As such, acupressure may be a promising treatment for stress as it is portable, non-pharmacological, and can be taught to the novice user.

The current study evaluates the effects of acupressure on the stress response (both physiologically and behaviorally) in healthy college students, induced in this case by a serial subtraction task. This stressor was administered both before and after participants experienced one of three interventions: active acupressure, placebo acupressure, or a relaxation CD control. The following markers of autonomic reactivity during a stressor (Acharya et al., 2006; Castro et al., 2008) were measured: heart rate (HR), skin conductance response (SCR), and heart rate

variability (HRV). A randomized, placebo-controlled, single-blind design tested the hypothesis that a single active acupressure treatment would result in a reduced stress response compared to both the placebo acupressure and relaxation control groups. Specifically, it was hypothesized that active acupressure would be associated with stress reduction as measured with subjective and physiological markers of the stress response and improved performance during the post-intervention stressor, above and beyond that seen in the other two groups and what might be expected from practice effects or habituation.

Methods

Participants

Undergraduate students at the University of Colorado at Boulder enrolled in an introductory psychology course received course credit for study participation. Inclusion criteria required participants to: be non-smokers; not be taking any drugs for medical or recreational purposes (including psychotropics); have no personal diagnosis of cardiovascular disease, respiratory disease, or diabetes; currently not be being treated for any medical conditions or receiving treatment from a mental health provider; and be naïve to acupressure treatment. Participants gave informed consent and all aspects of the present study were in accordance with and approved by the University of Colorado Institutional Review Board.

Procedure

A randomized, placebo-controlled, single-blind design was used. Participants were randomly assigned to receive one of the following interventions: active acupressure, placebo acupressure, or a relaxation CD session. Participants were blinded to which treatment condition they received if receiving active or placebo acupressure; if they were in the relaxation group, they would become aware of their assignment when the intervention (i.e., audio CD) began. During data collection, research assistants were blind to treatment condition if active or placebo acupressure, and all data entry and analyses were done by completely blinded individuals. Only the acupressure practitioner knew if an acupressure treatment was active or placebo. Research assistants remained in the room during treatments, but behind a curtain to ensure blinding to active or placebo acupressure conditions (due to the CD playing, they were aware of relaxation CD sessions). To control for diurnal biological variations in the stress response (Munck, 2010), all participants completed the experiment between 2-5pm.

After informed consent was obtained, electrodes (Vermed, Bellows Falls, VT) were affixed to participants' wrists and left ankle for ECG (electrocardiogram) data collection, with electrodes (ADInstruments, Colorado Springs, CO) affixed to the distal phalanges of the index and middle fingers of the non-dominant hand for SCR data collection, using a PowerLab 4/30 data acquisition system and stored with LabChart 7 software (ADInstruments). Data were continuously recorded at a sampling rate of 1000Hz for the duration of the experiment.

Pre-intervention Assessment

Following initiation of ECG and SCR data collection, participants answered demographic questions and completed the nine-item Psychological Stress Measure (PSM-9) (Lemyre and Lalande-Markon, 2009) to assess baseline subjective stress levels. Next, levels of expectancy about the intervention were assessed, as has been done previously (McFadden and Hernández, 2010). Baseline group differences in attitudes towards conventional and complementary medicine were assessed with the Complementary, Alternative, and Conventional Medicine Attitudes Scale (CACMAS) (McFadden et al., in press) and participants completed an assessment of past, present, and likely future use of 17 CAM modalities (McFadden et al., in press) to evaluate group differences in CAM usage. To assess general health and life attitudes, participants completed the Multidimensional Health Locus of Control (MHLC) scale (Wallston et al., 1978), the Satisfaction with Life Scale (SWLS) (Diener et al., 1985), and a modified version of the revised Life Orientation Test (LOT-R) (Scheier et al., 1994). Following this, participants completed the State Anxiety Inventory (State portion of the State-Trait Anxiety Inventory) (Spielberger et al., 1970), to assess anxiety levels prior to the first stressor. The PSM-9 was administered multiple times throughout the experiment to capture change in subjective stress levels (see Figure 3.1).

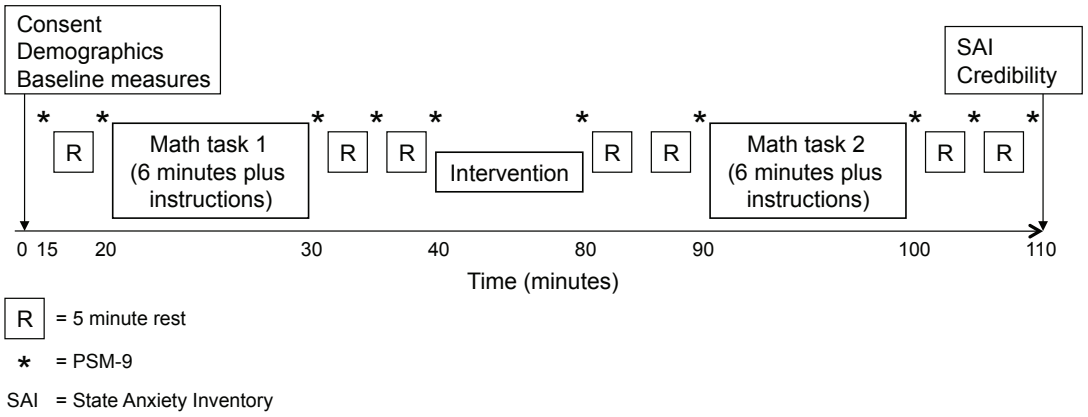

Figure 3.1. Experimental design.

Math Task 1

Following baseline measures, participants rested sitting in a chair quietly for 5 minutes, after which the PSM-9 was used to measure subjective stress levels prior to stressor administration. Instructions were then read for the math task, a task that reliably induces a stress response (Cacioppo et al., 1995; Burleson et al., 2003). Participants were asked to perform a series of serial subtractions, during which they continually subtracted backwards from a given number by another given number (e.g., subtract 3 from 298). If a mistake was made, the participant was corrected and continued subtracting from the correct answer. After each minute, new numbers were given. Difficulty of the task was adapted depending on performance; difficulty increased with better performance (i.e., the numbers to subtract by became more difficult) and vice versa. The task lasted 6 minutes, after which participants immediately completed the PSM-9 and rested for 5 minutes. Participants then completed one of the three interventions.

Intervention: Acupressure treatments

As has been done in prior work (McFadden and Hernández, 2010), participants lay face up on a massage table during treatment sessions, fully clothed with shoes removed, as is

common practice for acupressure treatments (Mines, 1982; Burmeister, 1997). Prior to treatment initiation, participants lay quietly on the massage table for 5 minutes, after which the PSM-9 was administered to evaluate pre-treatment subjective stress levels. An acupressure practitioner with over 20 years of clinical and educational experience and appropriate certification administered treatments (active or placebo). The practitioner was also trained in use of the placebo acupoints (Hernández et al., 2003). During treatment, the practitioner applied pressure with her fingertips to different sites on the body, in sequence (see Chapter 1 and McFadden and Hernández, 2010 for detail). The entire treatment, itself, lasted 40 minutes. The placebo control procedure was designed to be indistinguishable from the active treatment session, to last the same duration, and contain the same amount of physical contact. To guarantee matching practitioner/participant interactions for both treatment types, only scripted dialogue was used. A research assistant seated on the other side of a curtain was present during all treatment sessions to monitor the interaction between participants and the practitioner, as well as physiological data collection. After the treatment, participants again completed the PSM-9 and rested for 5 minutes.

Intervention: Relaxation CD

As with the acupressure treatments, those in the relaxation CD condition experienced the intervention laying face up on a massage table, fully clothed with shoes removed. Participants lay quietly on the massage table for 5 minutes, after which the PSM-9 was administered. A relaxation CD was then played, an adaptation of a commercially available relaxation CD ("Total Relaxation", Empowered Within, Salem, OR) adjusted to match the acupressure treatments in length. The CD had soothing background sounds (i.e., beach sounds, crickets) and calmly instructed participants to relax both mind and body. As with the acupressure treatments, the researchers remained in the room, behind a curtain, to monitor physiological data collection and

match researcher presence in the acupressure treatments. After the intervention, participants completed the PSM-9 and rested for 5 minutes.

Math Task 2

Participants moved from the massage table back to the chair and rested for 5 minutes. The PSM-9 was administered again to assess pre-stressor subjective stress levels. The instructions for the math task were re-read to the participant, after which the task began. The second math task was identical to the first, but different numbers were used. Following the task, participants immediately completed the PSM-9 and rested for 5 minutes.

Post-intervention Assessment

Following the rest after the second math task, participants rested for an additional 5 minutes, then completed post-treatment assessment measures. The PSM-9 was again completed, followed by the State Anxiety Inventory and credibility questionnaire (Myers et al., 2008; McFadden and Hernández, 2010).

Data Analyses

HR peaks were automatically detected and ectopic beats removed using LabChart 7. Ectopic beats were also manually inspected and removed as necessary. Mean HR was calculated for the intervention and for each minute during the math tasks.

Mean HRV measures were calculated using LabChart 7 for the intervention as well as each math task. Standard HRV measures were chosen (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). In the time domain, the standard deviation of the NN intervals was calculated (SDNN). In the frequency domain, low frequency power (0.04-0.15Hz), high frequency power (0.15-0.4Hz), and the LF/HF ratio were calculated. LF power is thought to be influenced mainly by the sympathetic nervous

system, with some input from the parasympathetic nervous system, while HF power is mediated by parasympathetic activity and the LF/HF ratio is a measure of balance between the two (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Acharya et al., 2006). HRV data were not normally distributed, so were log-transformed (ln) prior to analyses and will consequently be referred to as lnSDNN, lnLF power, lnHF power, and lnLF/lnHF ratio.

Average SCR was calculated with LabChart 7 for the intervention and each minute during the math tasks. Data were normalized using log transformation (ln), with an added constant to render all values above zero for transformation (ln(SCR + 20)), so data will be referred to as lnSCR.

Following calculation of HR, HRV, and SCR, data were imported into SPSS version 17.0 (SPSS, Inc., Chicago, IL) for analyses. Repeated measures ANOVA was used in analyses of all physiological data, with math task (task 1 vs. task 2) as a repeated factor and group (active vs. placebo vs. relaxation) as a between-subjects variable. Additional analyses assessed HR and SCR change across each math task with task minute (1 through 6) as a repeated factor and group as a between-subjects variable. Repeated measures ANOVA was also used to assess pre- to post-intervention changes in STAI score and number of correct subtractions during the math task. All repeated measures ANOVA analyses used Greenhouse-Geisser corrections.

Group differences in mean HR, HRV, and SCR during the intervention itself were assessed using one-way ANOVA. Group differences at baseline in the CACMAS, CAM usage, MHLC, the SWLS, the modified LOT-R, and age were also assessed with one-way ANOVA, as were group differences in PSM-9 scores, expectancy, and credibility. Bonferroni corrections

were used for post-hoc testing. To assess group differences in categorical demographic variables (gender and ethnicity), logistic regression was used (binomial and multinomial, respectively).

Results

Participants

The experiment was completed by 109 students, with no significant group (relaxation vs. active vs. placebo) differences in gender, ethnicity, the CACMAS, number of types of CAM used, the MHLC, the SWLS, or the modified LOT-R , $p > 0.05$ (see Table 3.1). There was, however, a significant group difference in age, F (2, 108) = 3.73, $p = 0.027$, partial $\eta^2 = 0.07$, with the placebo group being significantly older than the active group, $p = 0.043$. However, given that the difference was less than one year, it is unlikely that this age difference is relevant. Due to compatibility issues related to hardware and software interfacing and upgrades, data were available for fewer participants for SCR and HRV than other measures. However, demographic group comparisons remained the same regardless of group size. Sample size for each measure is 109 unless otherwise stated.

	Active	Placebo	Relaxation
Sample size	39	40	30
Age (mean ± SEM)*	18.97 ± 0.18	19.72 ± 0.27	19.03 ± 0.17
Gender (% male)	38.5	57.5	43.3
Ethnicity			
% Asian	5.1	12.5	3.3
% Black	2.6	0	3.3
% Latino	0	0	6.7
% White	87.2	82.5	86.7
% Other	5.1	5.0	0
Expectancy	5.87 ± 0.49	5.44 ± 0.47	5.03 ± 0.15
Baseline PSM-9 score	2.54 ± 0.26	2.40 ± 0.20	2.67 ± 0.18
CACMAS			
Philosophical congruence with CAM	4.22 ± 0.12	4.40 ± 0.15	4.42 ± 0.13
Dissatisfaction with conventional medicine	2.10 ± 0.14	2.42 ± 0.16	2.33 ± 0.14
Holistic balance	3.75 ± 0.14	4.11 ± 0.16	4.11 ± 0.18
CAM usage (# of types)			
Past use	3.15 ± 0.30	3.30 ± 0.38	3.03 ± 0.37
Current use	0.77 ± 0.19	0.95 ± 0.24	0.70 ± 0.19
Possible future use	9.51 ± 0.61	8.60 ± 0.90	8.23 ± 0.89
MHLC			
Internal	29.74 ± 0.59	30.89 ± 0.82	30.73 ± 0.86
Chance	19.23 ± 0.70	20.15 ± 0.81	20.40 ± 0.98
Powerful others	18.23 ± 0.91	17.55 ± 0.90	18.47 ± 0.88
SWLS	5.48 ± 0.16	5.48 ± 0.17	5.63 ± 0.12
LOT-R	31.74 ± 0.83	30.92 ± 0.98	31.97 ± 0.66
Credibility *	5.50 ± 0.28	4.87 ± 0.30	6.43 ± 0.26

Table 3.1. Participant characteristics and baseline measures.

Symbols reflect significant group difference (active vs. placebo vs. relaxation CD), * = $p < 0.05$
All measures: mean ± SEM (unless otherwise indicated)
Expectancy: mean score on a scale of 1-9, with 1 = least expectant to 9 = most expectant; *PSM-9: nine-item Psychological Stress Measure*: mean score on a scale of 1-8, with 1 = not at all stressed to 8 = extremely stressed; *CACMAS: Complementary, Alternative and Conventional Medicine Attitudes Scale*, mean score on a scale of 1-7, with 1 = strongly disagree to 7 = strongly agree; *CAM usage*: Complementary and alternative medicine usage, out of 17 listed types; *MHLC: Multiple Health Locus of Control scale*: sum, with a possible score of 6 to 42 for "internal" and "powerful others" locus of control and 7 to 49 for "chance"; *SWLS: Satisfaction with Life Scale*: mean score on a scale of 1-7, with 1 = strongly disagree to 7 = strongly agree; *LOT-R: modification of the revised Life Orientation Test*: sum, with a minimum possible score of 0 (least optimistic) to 42 (most optimistic); *Credibility rating*: mean score on a scale of 1-9, with 1 = least credible to 9 = most credible.

Heart Rate

Analysis of HR data during the tasks (n = 90) revealed a significant effect of task on HR, F (1, 87) = 36.97, $p < 0.001$, partial $\eta^2 = 0.30$, such that HR was lower during the second stressor (post-treatment) than the first (pre-treatment). However, there was no significant effect of group on HR and no interaction between task and group ($p > 0.05$), indicating that all interventions decreased stress reactivity to the stressor, but not differently (see Table 3.2). Additionally, there was no significant effect of time during the tasks, suggesting that HR did not habituate during each stressor, $p > 0.05$. Furthermore, there were no significant group differences during the intervention itself (n = 103), $p > 0.05$.

	Stressor 1	Intervention	Stressor 2
HR (BPM)			
Active	83.00 ± 2.22	65.73 ± 1.99	78.54 ± 1.90
Placebo	81.60 ± 2.08	61.84 ± 1.33	76.13 ± 1.78
Relaxation	84.45 ± 2.38	65.05 ± 1.67	78.79 ± 2.04
HRV: lnSDNN (ms^2)			
Active	4.28 ± 0.09	4.63 ± 0.09*[a]	4.36 ± 0.09
Placebo	4.19 ± 0.09	4.63 ± 0.09*[a]	4.29 ± 0.09
Relaxation	4.11 ± 0.09	4.36 ± 0.09*[a]	4.28 ± 0.09
HRV: lnLF (ms^2)			
Active	7.56 ± 0.19	7.73 ± 0.17*[b]	7.75 ± 0.18
Placebo	7.44 ± 0.19	7.83 ± 0.17*[b]	7.56 ± 0.17
Relaxation	7.32 ± 0.18	7.29 ± 0.16*[b]	7.63 ± 0.17
HRV: lnHF (ms^2)			
Active	6.91 ± 0.21	8.05 ± 0.26	6.85 ± 0.24
Placebo	6.51 ± 0.20	7.57 ± 0.25	6.50 ± 0.23
Relaxation	6.40 ± 0.20	7.47 ± 0.24	6.67 ± 0.23
HRV: lnLF/lnHF (ms^2)			
Active	0.65 ± 0.13	-0.32 ± 0.19	0.90 ± 0.18
Placebo	0.93 ± 0.12	0.26 ± 0.18	1.05 ± 0.18
Relaxation	0.92 ± 0.12	-0.18 ± 0.18	0.96 ± 0.17
lnSCR (μSiemens)			
Active	3.28 ± 0.05	2.48 ± 0.09	2.83 ± 0.11
Placebo	3.29 ± 0.06	2.46 ± 0.14	3.02 ± 0.09
Relaxation	3.31 ± 0.05	2.42 ± 0.16	3.06 ± 0.09

Table 3.2. Mean heart rate (HR), heart rate variability (HRV), and skin conductance response (SCR) measures during both math task stressors and the intervention (active acupressure, placebo acupressure, or relaxation CD).
All measures: mean ± SEM
*[a] = significant group difference within lnSDNN, $p = 0.042$
*[b] = marginally significant group difference within lnLF, $p = 0.054$

Heart Rate Variability

There was a significant effect of task on both lnSDNN and lnLF power (n = 51), such that lnSDNN (F (1, 48) = 9.17, $p = 0.004$, partial $\eta^2 = 0.16$) and lnLF power (F (1, 48) = 5.47, $p = 0.024$, partial $\eta^2 = 0.10$) were increased during the second task (post-treatment) compared to the first task (pre-treatment) (see Table 3.2). As with HR, however, there was no significant effect of group and no interaction between task and group ($p > 0.05$) suggesting decreased stress

reactivity following all interventions, although not differently. No significant effects of task or group, or significant interactions, were found for lnHF power or the lnLF/lnHF ratio, $p > 0.05$.

During the intervention, a significant group difference in lnSDNN was found (F (2, 50) = 3.38, $p = 0.042$, partial $\eta^2 = 0.12$), with a marginally significant group difference in lnLF power (F (2, 50) = 3.10, $p = 0.054$, partial $\eta^2 = 0.11$), such that both acupressure groups (active and placebo) showed an increased lnSDNN and lnLF power compared to the relaxation group (see Table 3.2). Post-hoc tests showed a marginal effect of both active ($p = 0.091$) and placebo ($p = 0.090$) groups having a higher lnSDNN than the relaxation group, but the two acupressure groups were not different from each other ($p = 1.00$). Post-hoc tests on lnLF power revealed a marginal difference between the relaxation group and placebo group ($p = 0.070$), but no significant differences between the active group and either the relaxation group ($p = 0.207$) or the placebo group ($p = 1.00$).

Skin Conductance

There was a significant effect of task on lnSCR (n = 49), F (1, 46) = 63.70, $p < 0.001$, partial $\eta^2 = 0.58$, showing a decrease from the first stressor (pre-intervention) to the second stressor (post-intervention) (see Table 3.2). A significant effect of minute during the math task was also found, F (5, 240) = 15.08, $p < 0.001$, partial $\eta^2 = 0.24$, such that lnSCR decreased across the minutes of the task, likely indicating habituation to the task. Although all groups showed a reduction in lnSCR, there were no effects of group or interactions between group, task, and minute, $p > 0.05$. During the intervention itself, there were also no significant group differences in lnSCR, $p > 0.05$ (see Figure 3.2).

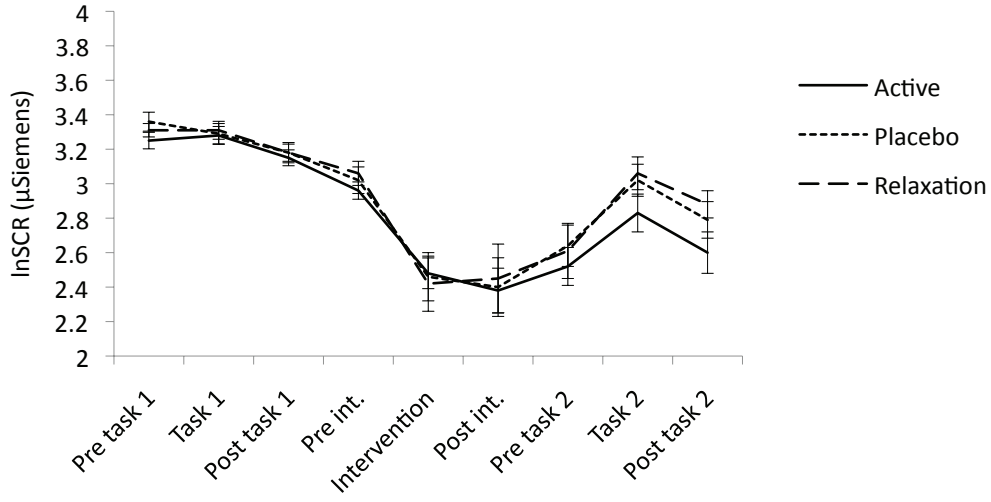

Figure 3.2. Physiological stress response throughout the experiment, as measured by lnSCR (µSiemens).

Math Task: Behavioral

There was a significant effect of task on the number of subtractions completed correctly during the math task, such that participants answered significantly more correctly during the second math task (post-intervention) ($M = 21.29$, $SEM \pm 0.40$) compared to the first (pre-intervention) ($M = 19.13$, $SEM \pm 0.42$), $F\ (1, 106) = 96.01$, $p < 0.001$, partial $\eta^2 = 0.47$. However, there was no significant effect of group, with all groups improving similarly from pre- to post-intervention, $p > 0.05$.

Subjective Stress Appraisal

There was a significant effect of time on State Anxiety Inventory score, $F\ (1, 106) = 14.81$, $p < 0.001$, partial $\eta^2 = 0.12$, showing that across group, participants reported reduced anxiety post-intervention ($M = 1.57$, $SEM = 0.05$) compared to baseline ($M = 1.69$, $SEM = 0.04$). However, there was no significant effect of group ($p > 0.05$): all groups reported reduced anxiety similarly. There were no significant differences in State Anxiety Inventory score among the three groups prior to the intervention, $p > 0.05$.

There were no significant group differences in PSM-9 score at any of the 10 measurement points, including baseline (see Table 3.1), $p > 0.05$. However, similar to the other measures, participants rated their subjective stress levels as being significantly lower following the second stressor (post-treatment) than they did the first (pre-treatment), F (1, 48) = 49.27, $p < 0.001$, partial $\eta^2 = 0.51$, suggesting that all interventions reduced subjective stress following the stressor (see Figure 3.3).

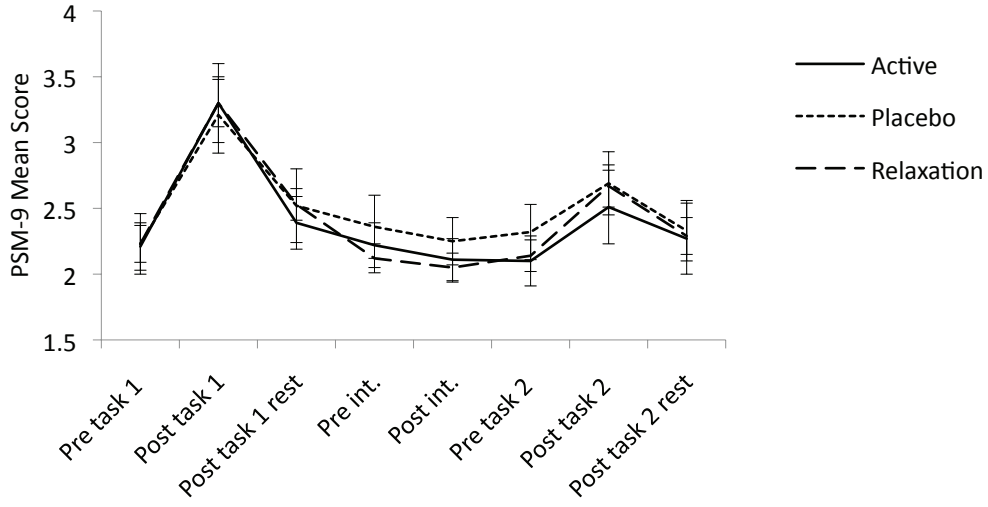

Figure 3.3. Subjective stress response throughout the experiment, as measured with the PSM-9.

Expectancy and Credibility

There was no significant group difference in mean expectancy prior to the intervention, $p > 0.05$. However, there was a significant group difference in mean credibility rating, F (2, 108) = 7.20, $p = 0.001$, partial $\eta^2 = 0.12$. Post-hoc tests revealed this difference to be between the relaxation ($M = 6.43$, $SEM = 0.26$) and placebo groups ($M = 4.87$, $SEM = 0.30$), $p = 0.001$, and marginally between the relaxation and active groups ($M = 5.50$, $SEM = 0.28$), $p = 0.078$. Importantly, the two acupressure treatments were not rated differently on credibility, $p = 0.315$ (see Table 3.1).

Discussion

All three interventions reduced physiological responses and subjective stress ratings to a math task stressor, although there were no significant differences in reduction among the groups (active acupressure, placebo acupressure, and relaxation CD). Interestingly, a significant group difference was found during the intervention itself. HRV (SDNN and LF power) was greater for the acupressure groups (both active and placebo) than for the relaxation group. As increased HRV can indicate better autonomic adaptation (Acharya et al., 2006; Vanderlei et al., 2009), this suggests an added benefit of touch treatment in comparison to the relaxation intervention, especially since HRV was not significantly different among the groups prior to the intervention. However, as there were no group differences in HRV during the post-treatment stressor, it remains to be seen if this increase in HRV during the intervention persists and whether there are any lasting benefits beyond the treatment period.

This study provides insight for optimal dosing of acupressure, which is important because it is as of yet unknown how many acupressure treatments are necessary to elicit an effect. Our laboratory recently reported 8 acupressure treatments were sufficient to observe treatment effects (active treatments were associated with a greater and faster heart rate reduction than placebo treatments) (McFadden and Hernández, 2010). The maximum treatment effect on heart rate was observed during treatments 5-8, but not before (i.e., during treatments 1-4). This could explain the lack of group differences seen in the current study, in which participants only received one treatment, suggesting that this may be an insufficient dosing. It is expected that lying down and relaxing (which occurs in all three interventions in the current study) would confer some stress-reduction benefit. However, it seems that more than one treatment may be necessary to experience an additional benefit from active acupressure treatments. As previous studies have

observed treatment effects in healthy participants following a single acupressure treatment (Felhendler and Lisander, 1999; Sugiura et al., 2007), it was surprising that a single treatment was not sufficient in the healthy population in the current study, especially given the acute timing of stress response assessment (immediately preceding and following the intervention). However, as this effect was not seen, future studies will examine the utility of acupressure for stress reduction when a series of treatments is administered rather than a single treatment.

Importantly, the three groups did not differ in expectations prior to the intervention, as expectancy can influence treatment effects (Shapiro, 1981; Price et al., 2008). Interestingly, participants rated the relaxation CD intervention as more credible than either the active or placebo acupressure treatments. A possible reason for this could be that participants knew they might have received a placebo treatment if they experienced acupressure, due to the informed consent process. Moreover, participants would become aware of group assignment once the relaxation CD began playing, but it was not distinguished as a control condition for comparison to the acupressure treatments in the consent form. As such, participants in the relaxation group likely assumed they were receiving a "real" treatment. It is important to note, however, that participants did not rate the placebo acupressure treatment as less credible than the active acupressure treatment, indicating that participants were unable to distinguish between placebo and active treatments, replicating prior work with the same placebo (McFadden and Hernández, 2010). That the placebo be credible as a treatment is crucial for its use as an acupressure control.

A potential confound of the current experiment is the possible habituation to the stressor participants may have experienced, as it was presented twice during the experiment. Task adaptability and the use of different numbers between tasks were employed to help minimize this and prevent practice effects. However, SCR is known to habituate with multiple task

administrations (Watts, 1975; Lykken et al., 1988). Indeed, it appears that SCR habituated with each additional minute within each math task, but this habituation was not seen for HR. Habituation of cardiovascular responses is less well-characterized (Jonsson et al., 2010), with some studies finding HR habituation (Szabo and Gauvin, 1992; Kelsey, 1993) and others finding little to no HR (Jonsson et al., 2010; Hamer et al., 2006; von Kanel et al., 2006) or HRV habituation (Jonsson et al., 2010). Similarly, habituation to the stressor and practice effects could account for improvements in the math task, but not all studies have shown this effect on performance in multiple administrations of an arithmetic stressor (Szabo and Gauvin, 1992). Had the originally hypothesized intervention differences been observed (i.e., greater effects seen in the active group compared to placebo and relaxation groups), this would have allowed practice effects and habituation to be teased apart from those of each intervention. Unfortunately, the present results make it difficult to determine the contribution of habituation and practice.

In conclusion, it was found that all three interventions were successful in reducing both physiological and behavioral markers of stress during a math task stressor. Since previous studies have suggested at least 5-8 acupressure treatments may be necessary to observe treatment effects above that of placebo, a possible explanation is that the single treatment administered during the current study was an insufficient dose. Interestingly, HRV measures during the intervention itself were increased for the active and placebo acupressure groups compared to the relaxation control group, suggesting a benefit of the treatments involving touch. Combined with the possibility for self-administration (and thus, portability and affordability), acupressure warrants further study as a treatment for stress reduction.

CHAPTER 4

THE IMPACT OF ATTITUDES TOWARDS COMPLEMENTARY AND CONVENTIONAL MEDICINE ON ACUPRESSURE INTERVENTION OUTCOME

Kristina L. McFadden, Tiffany A. Ito, and Theresa D. Hernández

Abstract

While studies have investigated the effect of attitudes towards complementary and alternative medicine (CAM) on the use of CAM, few have examined what impact these attitudes have on outcome following CAM treatment. The current study investigates this impact, analyzing data from two previous studies of acupressure. The first study was on the effects of acupressure on cognitive function in TBI survivors, while the second investigated acupressure-associated reduction in the stress response in healthy college students. To assess attitudes towards both CAM and conventional medicine in these studies, the Complementary, Alternative, and Conventional Medicine Attitudes Scale (CACMAS) was administered prior to the intervention. This measure is comprised of subscales measuring three factors: philosophical congruence with CAM, dissatisfaction with conventional medicine, and holistic balance. The current study performed correlational and multiple regression analyses to investigate the impact each of these factors had on outcome in each study, hypothesizing that positive attitudes towards CAM would contribute to placebo effects by increasing expectancy surrounding the upcoming CAM intervention. It was hypothesized that dissatisfaction with conventional medicine would similarly influence outcome, but to a lesser extent than attitudes towards CAM. Attitudes towards CAM and conventional medicine had less of an impact on treatment outcome than expected, although there were some interesting relationships found between attitudes and baseline measures, as well as measures taken during the intervention itself in the stress study. Surprisingly, having a higher holistic balance score predicted less improvement and/or stress reduction in both studies, suggesting that the holistic balance factor might be more complex than originally hypothesized. Although exerting less of an impact on outcome than hypothesized, it is still recommended that attitudes towards CAM be taken into account during experimental design

as attitudes may influence baseline measures and physiological reactions during the intervention itself.

Introduction

The use of complementary and alternative medicine (CAM) treatments is increasingly common in the United States, with an estimated 38% of American adults reporting use of a CAM therapy in the previous year (Barnes et al., 2009) and spending an estimated $33.9 billion on CAM therapies in 2007 (Nahin et al., 2009). This popularity has led many to speculate on the reasons for choosing CAM treatment in addition to or instead of conventional medicine. Attitudes towards CAM as well as towards conventional medicine have been found to influence the use of CAM treatments in the United States (McFadden et al., in press; O'Callaghan and Jordan, 2003; Testerman et al., 2004; Bishop et al., 2007). To assess these attitudes, as well as those towards conventional medicine, the Complementary, Alternative, and Conventional Medicine Attitudes Scale (CACMAS) was developed (see Appendix B; McFadden et al., in press).

The CACMAS was developed based on a review of the existing literature and modified from a scale assessing attitudes of medical students towards CAM (Lie and Boker, 2004), a survey investigating reasons for CAM use (Astin, 1998), and content analyses of interviews with CAM users regarding their reasons for seeking CAM treatment (Vincent and Furnham, 1996). While attitudes towards CAM have largely been explored in medical providers (Lie and Boker, 2004; Lie and Boker, 2006; Chaterji et al., 2007; Pettersen and Olsen, 2007; Desylvia et al., 2008), the CACMAS was designed to assess CAM attitudes in potential healthcare recipients, to address how attitudes influence those who might seek CAM treatments. Initially, two attitudinal dimensions that have been discussed as theoretically relevant to understanding CAM use were the focus of the questionnaire: the possession of a philosophical orientation congruent with CAM and dissatisfaction with conventional medicine.

Philosophical congruence with CAM describes the degree to which individuals perceive CAM to be consistent with their conceptualization of health and illness (Astin, 1998), theorizing that those with a philosophical orientation congruent with CAM would be more likely to pursue CAM treatments. In the CACMAS, philosophical congruence with CAM was measured with items such as "Most complementary therapies stimulate the body's natural therapeutic powers" and "I believe complementary medicine enables me to take a more active part in maintaining my health."

The second attitudinal dimension the CACMAS initially focused upon is dissatisfaction with conventional medicine. This has also been suggested as a reason for seeking CAM treatment, with patients citing such issues as poor doctor-patient communication and not enough time spent with the doctor (Furnham and Smith, 1988; Furnham and Bhagrath, 1993; Sirois and Gick, 2002). Although there has been some debate over the contribution of this attitude in seeking CAM treatment, it may be an influencing factor for some patients (Furnham and Forey, 1994; Furnham and Kirkcaldy, 1996; McGregor and Peay, 1996; Astin, 1998; Ruggie, 2004). Dissatisfaction with conventional medicine was measured in the CACMAS with items such as "I don't trust medical doctors and hospitals, so I use them as little as possible," and "I have a lot of confidence in the medical doctor I see most often" (reverse scored).

Although those are the two attitudinal elements initially focused upon in CACMAS development, a third factor emerged with factor analysis (see Appendix B), which was named "holistic balance". This attitudinal dimension represents the more holistic views associated with CAM and includes the questions "Physical and mental health are maintained by an underlying energy or vital force", "Health and disease are a reflection of balance between positive life-enhancing forces and negative destructive forces" and "The body is essentially self-healing and

the task of a health care provider is to assist in the healing process." Though it correlated with philosophical congruence with CAM and dissatisfaction with conventional medicine, holistic balance emerged as a unique factor. Distinct from the philosophical congruence element, which focuses on a broad array of concepts, including the mind-body relationship and the nature of the client-practitioner relationship, the holistic balance items are more narrowly focused on particular elements of the mind-body relationship (e.g., as self-healing, in balance, and maintained by an underlying energy). Due to the clear emergence of this factor, it was decided to pursue three subscales.

Previous analyses with the CAMCAS (McFadden et al., in press) found that all three dimensions (philosophical congruence with CAM, dissatisfaction with conventional medicine, and holistic balance) correlated with CAM usage. This was such that greater philosophical congruence and holistic balance were associated with increased use of CAM. Similar to previous studies (Furnham and Forey, 1994), dissatisfaction had a less clear relationship with CAM usage than the other two factors. This was consistent with other findings that while dissatisfaction with conventional medicine is frequently mentioned anecdotally as a reason for using CAM, it may account for relatively little variance in why people actually seek CAM (Astin, 1998), suggesting that CAM treatments are sought out primarily because of congruence with mind-body practices rather than a desire to avoid conventional medicine. Indeed, CAM is often used as a *complementary* therapy, an adjunct to conventional medical treatments, rather than as an *alternative* to conventional medicine (Ruggie, 2004).

Although studies have investigated how attitudes towards CAM affect use of CAM (McFadden et al., in press; Astin, 1998; Testerman et al., 2004; Lie and Boker, 2006) as well as acceptance of CAM in the medical community (Lie and Boker, 2006; Desylvia et al., 2008; Mak

et al., 2009), little is known about how these attitudes impact treatment *outcome*. Linde et al. (2007) found positive attitudes towards acupuncture to be associated with improved outcome following acupuncture treatment for chronic pain. However, Lewith et al. (2002) found attitudes towards CAM to have no significant effect on outcome in a study of a homeopathic allergen treatment. Determining the influence of attitudes towards CAM and conventional medicine on treatment outcome could help to parse out elements of the placebo effect in CAM treatments. Placebo effects are thought to be the result of the psychosocial component of any medical treatment (Benedetti et al., 2005; Koshi and Short, 2007), both active and inert, and consist of multiple factors, such as expectancy surrounding treatment (Frankenhaeuser et al., 1963) and previous experiences with medicine (Colloca and Benedetti, 2006). If attitudes towards CAM affect treatment efficacy, it would suggest that CAM attitudes are contributing to the placebo effects present in both active *and* "placebo" treatments. Additionally, knowing the influence of CAM attitudes on treatment efficacy could help determine for whom CAM treatments may be most (and least) effective (e.g., if CAM is likely to be more effective for those with a strong philosophical congruence with CAM).

The current study investigates the effects of attitudes towards CAM and conventional medicine on outcome following acupressure treatments. The relationships between CAM attitudes and acupressure outcome have not been previously evaluated. Data from two previous acupressure intervention studies were used to assess whether the three attitudinal dimensions assessed in the CACMAS influenced outcome measures. Both studies assessed effects of acupressure, but involved distinct populations and experimental designs. The first study, the "traumatic brain injury (TBI) study" investigated the effects of a series of 8 active acupressure treatments on cognitive function following TBI compared to placebo acupressure treatments (see

Chapter 2). The second study, the "stress study" evaluated the effects of a single active acupressure treatment on reactivity to a stressor, compared to two control treatments (placebo acupressure and a relaxation CD session) (see Chapter 3). The use of studies with two distinct populations and experimental designs in the current study allows for assessment of the generalizability of results.

Four hypotheses were tested in the current study. First, it was hypothesized that those with more positive attitudes towards CAM (i.e., greater philosophical congruence with CAM and holistic balance) would show greater improvement in outcome measures as positive attitudes can increase placebo effects (Thomas, 1987; Price et al., 2008) and have previously been suggested to affect outcome following a CAM treatment (Linde et al., 2007). Similarly, negative attitudes towards CAM may predict reduced improvement following intervention, as participants would not have positive attitudes enhancing placebo effects. It could also be argued that negative attitudes towards CAM may negatively impact any effects of active treatment above placebo effects, as strong negative attitudes can reduce the efficacy of a real treatment (Suedfeld, 1984). Second, it was thought that attitudes towards CAM might also influence baseline measures, prior to the intervention, as well as measures taken during the intervention itself (in the stress study). As such, it was hypothesized that positive attitudes towards CAM might lead to lower baseline anxiety and a reduced stress response during the first stressor and the intervention, as well as enhanced pre-intervention performance, as someone with a worldview congruent with CAM might be more comfortable during an experimental trial of a CAM intervention.

Third, as dissatisfaction with conventional medicine has been found to influence the use of CAM less than philosophical congruence with CAM and holistic balance, it was hypothesized that dissatisfaction with conventional medicine may also exert an influence on intervention

outcome, but less so than positive attitudes towards CAM. Since acupressure is not a conventional medical treatment, it could be that dissatisfaction with conventional medicine may lead to improved reception of a CAM treatment, leading to increased intervention efficacy. However, given that some measurements taken (e.g., ECG and EEG) are more fitting with conventional medicine than with CAM, it could be that those with greater dissatisfaction with conventional medicine might feel uncomfortable with those measurements and consequently be less relaxed during the experiment. As such, it is also possible that those with a greater dissatisfaction with conventional medicine might instead show a reduced treatment effect. Finally, for this same reason, dissatisfaction with conventional medicine was hypothesized to impact baseline anxiety measures in both studies, as well as the stress response during the first stressor (pre-intervention) and the intervention in the stress study. Again, as physiological measurements incorporated the use of equipment associated with conventional medicine, it was hypothesized that this could lead to increased stress and anxiety in those with greater dissatisfaction with conventional medicine.

Methods

Participants

To assess the effects of the three attitudinal dimensions of the CACMAS, data were analyzed from two studies investigating the effects of acupressure. Due to population and methodological differences between the studies, they were analyzed and will be discussed separately. Participants in the first study (the TBI study; see also Chapter 2) were recruited from the Denver/Boulder community via newspaper/newsletter advertisement and flyers. Eligible participants in the TBI study had experienced a mild to moderate TBI at least nine months and no more than five years prior to the start of the study, with lasting deficits as a result of the injury. To assess TBI, participants were screened using the Brain Injury Screening Questionnaire (BISQ) (Research and Training Center, New York, NY), which has been found to reliably distinguish brain injury from other conditions (e.g., spinal cord injury) and those with no disability (Gordon et al., 2000; Cantor et al., 2004) and also determines if lasting symptoms likely result from the TBI. Participants must have experienced an alteration of consciousness as a result of the TBI (loss of consciousness or being dazed and confused), but not to have lost consciousness for longer than 24 hours. The participants in the second study (the stress study; see also Chapter 3) were healthy college students enrolled in an introductory psychology class at the University of Colorado and received course credit for study participation. Participants in both studies gave informed consent and all aspects of both studies were in accordance with and approved by the University of Colorado Institutional Review Board.

Procedure

The procedure for each study is detailed elsewhere (see Chapter 2 for TBI study details and Chapter 3 for stress study details). The following is a brief overview of the procedure in

each study with portions relevant to the current study highlighted. The CACMAS was administered during pre-intervention assessment in both studies, with participants responding using a 7-point Likert scale, ranging from 1 ("strongly disagree") to 7 ("strongly agree").

The TBI study had a randomized, placebo-controlled, single-blind design. After completing the informed consent process and answering demographic questions, participants completed a series of questionnaires and a neuropsychological test battery during their initial visit. Additionally, in this first visit participants completed Stroop and auditory oddball tasks during electroencephalogram (EEG) recording, to obtain event-related potentials (ERPs) during both tasks. Participants were randomly assigned to receive either active or placebo acupressure treatments and were administered two 40-minute treatments per week for 4 weeks for a total of 8 treatments (see McFadden and Hernández, 2010 and Chapter 1 for details). In a final visit (post-treatment) to the laboratory, participants completed the same measures as they had in the first visit (pre-treatment), except for demographic measures and the CACMAS.

For the purposes of the current study, only outcome measures in which intervention effects were seen will be discussed. Specifically, any outcome measures in which significant pre- to post-intervention changes were seen *within* group (i.e., pre- to post-treatment change for each group), as well as any in which significant *between* group differences in those changes were seen (i.e., active group pre-to post-intervention change vs. placebo group pre- to post-intervention change). As such, the following TBI study measures will be discussed in the current study: the Perceived Stress Scale (PSS) (Cohen et al., 1983); the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977); the Digit Span and Digit Symbol subtests from the WAIS-R (Wechsler, 1981); the Comprehensive Trail-Making Test (CTMT) (Reynolds, 2002); the Finger Tapping Test and Tactual Performance Test (Psychological Assessment

Resources, Inc., Lutz, FL) from the Halstead-Reitan Neuropsychological Test Battery (Reitan, 1969); the Sickness Impact Profile (SIP) (Gilson et al., 1975); P300 (ERP component) amplitude and latency at Pz during the Stroop task (averaged across stimulus type--congruent, incongruent, and neutral--as the significant effects seen in the TBI study were interactions showing a significant reduction in both P300 amplitude and latency from pre- to post-intervention in the active group across stimulus type); and accuracy Stroop effect (incongruent/congruent and incongruent/neutral comparisons in percent correct during the task), as original analyses found active acupressure treatments were associated with a reduced Stroop effect post-treatment compared to placebo treatments (see Chapter 2).

Although the protocol for active and placebo acupressure treatments was the same (see McFadden and Hernández, 2010 and Chapter 1 for details) the stress study involved a different experimental design than the TBI study. Similarly to the TBI study, the stress study involved a randomized, placebo-controlled, single-blind design. However, the stress study involved a single experimental session and as such, a single administration of the intervention, whereas those in the TBI study experienced a series of treatments. Also, an additional control (a relaxation CD) was included in addition to the placebo acupressure treatment (see Chapter 3 for relaxation CD description). While the placebo acupressure procedure controlled for time, lying down, touch, and practitioner attention, the relaxation CD controlled only for time and lying down, to allow placebo effects to be further parsed out. Therefore, participants received *one* administration of either active acupressure, placebo acupressure, or a relaxation CD session.

In brief, after arriving for the stress study and completing the informed consent process, participants answered demographic questions and had electrodes affixed for skin conductance response (SCR) and electrocardiogram (ECG) data collection. Participants then completed

baseline measures (including the CACMAS) and, after a brief rest, were administered a math task stressor, which involved completing serial subtractions aloud while being monitored and corrected by a research assistant. This task lasted 6 minutes, with numbers changing each minute and the task adapting difficulty level throughout, such that numbers became harder the more successful participants were and vice versa. Following the stressor, the assigned intervention was administered (either active acupressure, placebo acupressure or the relaxation CD). As with the TBI study, each intervention lasted 40 minutes. Following the intervention, participants again completed the math task stressor, but different numbers were used in the second task. Following the second stressor, participants completed final outcome measures.

As with the TBI study, for the purposes of the current study, only outcome measures from the stress study in which intervention effects were seen will be discussed. Specifically, any outcome measures in which significant pre- to post-intervention changes were seen *within* group, as well as any in which significant *between* group differences in those changes were seen will be included in the current analyses. As such, measures from the stress study that will be discussed are as follows: the State Anxiety Inventory (State portion of the State-Trait Anxiety Inventory, Mind Garden, Inc., Menlo Park, CA (Spielberger et al., 1970)); the nine-item Psychological Stress Measure (PSM-9) (Lemyre and Lalande-Markon, 2009); the number of correct answers during each math task stressor; heart rate (HR) during the intervention and both stressors; SCR during the intervention and both stressors; and two specific heart rate variability (HRV) measures during the intervention and both stressors. The HRV measures that will be discussed are the standard deviation of the NN intervals (SDNN) and low frequency power (LF power; defined as 0.04-0.15Hz). Original analyses of the stress study data found that SCR and HRV data were not normally distributed, so data were log-transformed (ln) prior to analyses. Thus, the

log-transformed measures will also be used in the current study and will be referred to in results as lnSCR, lnSDNN, and lnLF power.

Data Analyses

Data were analyzed using SPSS version 17.0 (SPSS, Inc., Chicago, IL). The three CACMAS variables (mean philosophical congruence with CAM score, mean dissatisfaction with conventional medicine score, and mean holistic balance score) were used as predictor variables in both correlation and multiple regression analyses. Correlational analyses with these predictor variables were conducted on the aforementioned variables for which either *within* group pre- to post-intervention changes and/or *between* group (*TBI study*: active vs. placebo acupressure; *stress study*: active acupressure vs. placebo acupressure vs. relaxation CD) differences in pre-to post-intervention changes were seen in the original analyses. Additionally, multiple regression analyses were used with each outcome variable above to determine the contribution of each CACMAS predictor variable when controlling for the other CACMAS variables.

As described above, for the TBI study, correlations between the predictor variables and pre- to post-treatment changes in the following variables were conducted: PSS, CES-D, the Digit Span test, the Digit Symbol test, the Finger Tapping Test, the Tactual Performance Test, the CTMT, the SIP, as well as P300 amplitude and latency at Pz across stimulus type (i.e., averaged across congruent, incongruent, and neutral trials) and the Stroop effect on accuracy (percent correct) between both incongruent/congruent stimulus trials and incongruent/neutral stimulus trials. To assess how the predictor variables influenced baseline measures, analyses also included pre-treatment measures.

The following variables were included in analyses for the stress study: State Anxiety Inventory, PSM-9, number correct on the math tasks, HR, lnSCR, as well as lnSDNN and lnLF

(HRV measures). Analyses focused on the relationship between the CACMAS predictor variables and change scores (post-pre) for these variables. Additionally, to assess the influence of the CACMAS variables on baseline stress, anxiety, and performance, analyses also looked at the relationship with baseline State Anxiety Inventory and PSM-9 as well as performance and physiological responses during the first stressor. As we were also interested in how the CACMAS variables influenced physiology during the intervention, we also looked at HR, lnSCR, lnSDNN and lnLF during the intervention.

Results

Participants

In the TBI study, 42 participants completed the experiment, with 31 participants completing the ERP portion of the experiment (see Chapter 2). In the stress study, 109 participants completed the experiment. Due to compatibility issues related to hardware and software upgrades, there were fewer usable data for SCR (49 participants) and HRV (51 participants) measures, but analyses found demographic group comparisons with the full group to be equivalent to the smaller groups (see Chapter 3).

Philosophical congruence with CAM: TBI study

In the TBI study, there were no significant correlations between philosophical congruence with CAM and outcome following treatment. There were, however, some significant relationships with baseline measures. Higher philosophical congruence with CAM scores were negatively correlated with baseline PSS scores in the active group, such that they predicted lower subjective stress, $r = -0.43$, $p = 0.049$. Also in the placebo group, there was a significant association between higher philosophical congruence with CAM and higher baseline CES-D scores, $r = 0.50$, $p = 0.041$, indicating an increase in baseline depression in those with higher philosophical congruence with CAM (see Tables 4.1 and 4.2).

	Philosophical congruence with CAM		Dissatisfaction with conventional medicine		Holistic balance	
	r	*p*	*r*	*p*	*r*	*p*
PSS pre-tx	-0.43	**0.049**	0.11	0.630	-0.23	0.232
PSS change	0.26	0.252	-0.02	0.923	0.06	0.785
CES-D pre-tx	-0.08	0.735	0.48	**0.029**	0.08	0.739
CES-D change	-0.11	0.643	-0.13	0.575	0.04	0.875
Digit Span pre-tx	0.03	0.901	0.19	0.410	0.02	0.940
Digit Span change	-0.15	0.503	0.05	0.827	-0.12	0.599
Digit Symbol pre-tx	0.10	0.680	0.01	0.968	-0.02	0.920
Digit Symbol change	0.20	0.374	0.06	0.790	0.01	0.990
CTMT pre-tx	0.07	0.756	0.27	0.257	0.09	0.705
CTMT change	-0.07	0.777	-0.18	0.444	-0.02	0.947
FTT pre-tx	-0.09	0.712	0.23	0.336	0.10	0.686
FTT change	-0.01	0.983	-0.35	0.145	0.09	0.718
TPT pre-tx	-0.06	0.813	0.07	0.761	0.27	0.247
TPT change	0.18	0.458	0.27	0.246	-0.03	0.890
SIP pre-tx	0.26	0.247	0.35	0.115	0.26	0.261
SIP change	0.09	0.700	0.35	0.116	0.33	0.150
Stroop P300 amplitude pre-tx	0.47	0.087	-0.17	0.562	-0.31	0.276
Stroop P300 amplitude change	0.06	0.850	-0.20	0.484	0.18	0.544
Stroop P300 latency pre-tx	-0.14	0.628	0.03	0.922	-0.05	0.876
Stroop P300 latency change	0.07	0.798	0.15	0.603	0.13	0.668
Stroop accuracy (incon/con) pre-tx	0.04	0.893	-0.17	0.556	-0.13	0.659
Stroop accuracy (incon/con) change	0.12	0.670	-0.02	0.946	0.50	0.069
Stroop accuracy (incon/neutral) pre-tx	0.06	0.839	-0.29	0.308	-0.22	0.451
Stroop accuracy (incon/neutral) change	-0.34	0.240	0.14	0.629	0.14	0.643

Table 4.1. Correlational analyses for the TBI study: **active** group.
All significant p values (< 0.05) are in bold. *PSS*: Perceived Stress Scale; *CES-D*: Center for Epidemiologic Studies depression scale; *CTMT*: Comprehensive Trail-Making Test; *FTT*: Finger Tapping Test; *TPT*: Tactual Performance Test; *incon*: incongruent; *con*: congruent; *tx*: treatment; *change*: post-intervention – pre-intervention change.

	Philosophical congruence with CAM		Dissatisfaction with conventional medicine		Holistic balance	
	r	*p*	*r*	*p*	*r*	*p*
PSS pre-tx	0.45	0.070	0.66	**0.004**	0.42	0.091
PSS change	-0.21	0.418	-0.22	0.395	-0.19	0.466
CES-D pre-tx	0.50	**0.041**	0.65	**0.004**	0.47	0.060
CES-D change	-0.23	0.380	-0.34	0.187	-0.10	0.711
Digit Span pre-tx	-0.15	0.576	-0.22	0.402	-0.18	0.484
Digit Span change	0.16	0.539	-0.11	0.662	0.18	0.476
Digit Symbol pre-tx	0.01	0.964	-0.16	0.540	0.01	0.981
Digit Symbol change	0.03	0.915	-0.08	0.758	-0.31	0.223
CTMT pre-tx	0.06	0.821	-0.33	0.205	0.13	0.636
CTMT change	-0.26	0.335	0.19	0.471	-0.43	0.092
FTT pre-tx	0.36	0.161	0.02	0.943	0.06	0.811
FTT change	-0.14	0.613	-0.15	0.585	0.10	0.698
TPT pre-tx	0.01	0.980	-0.10	0.689	-0.10	0.710
TPT change	-0.07	0.795	0.32	0.214	0.11	0.667
SIP pre-tx	0.35	0.172	0.47	0.054	0.33	0.202
SIP change	0.14	0.588	-0.16	0.542	0.38	0.132
Stroop P300 amplitude pre-tx	-0.62	0.057	-0.58	0.077	-0.67	**0.033**
Stroop P300 amplitude change	-0.57	0.083	-0.01	0.980	-0.55	0.102
Stroop P300 latency pre-tx	-0.14	0.701	-0.55	0.100	-0.06	0.878
Stroop P300 latency change	0.15	0.673	0.29	0.413	0.12	0.747
Stroop accuracy (incon/con) pre-tx	0.25	0.485	0.19	0.592	0.06	0.880
Stroop accuracy (incon/con) change	-0.04	0.905	-0.01	0.987	-0.13	0.717
Stroop accuracy (incon/neutral) pre-tx	-0.16	0.655	-0.03	0.939	-0.20	0.569
Stroop accuracy (incon/neutral) change	0.22	0.535	0.25	0.481	0.12	0.745

Table 4.2. Correlational analyses for the TBI study: **placebo** group.
All significant p values (< 0.05) are in bold. *PSS*: Perceived Stress Scale; *CES-D*: Center for Epidemiologic Studies depression scale; *CTMT*: Comprehensive Trail-Making Test; *FTT*: Finger Tapping Test; *TPT*: Tactual Performance Test; *incon*: incongruent; *con*: congruent; *tx*: treatment; *change*: post-intervention – pre-intervention change.

After controlling for the other CACMAS variables, philosophical congruence was no longer a significant predictor of baseline CES-D in the placebo group, $p > 0.05$. Furthermore, after controlling for the other CACMAS variables, philosophical congruence with CAM was only a marginally significant predictor of baseline PSS score in the active group, $\beta = -4.35$, $t = -1.84$, $p = 0.084$. Additionally, multiple regression analyses found philosophical congruence with CAM to be a significant predictor of baseline P300 amplitude during the Stroop task in the active group, $\beta = 6.43$, $t = 3.03$, $p = 0.013$, such that greater philosophical congruence was associated with greater baseline P300 amplitude. Controlling for other CACMAS variables also showed philosophical congruence with CAM to emerge as a significant predictor for a number of variables in the placebo group. Higher philosophical congruence with CAM in the placebo group was found to significantly predict higher scores on the Finger Tapping Test (higher scores indicate improved performance) at baseline, after controlling for other CACMAS variables, $\beta = 7.36$, $t = 3.18$, $p = 0.007$. Philosophical congruence with CAM also became a significant predictor of outcome (post-intervention score – pre-intervention score) on both the Digit Symbol test and the Tactual Performance Test in the placebo group, $\beta = 5.61$, $t = 3.29$, $p = 0.006$ and $\beta = -2.23$, $t = -2.22$, $p = 0.044$, respectively. As higher scores indicate better performance on the Digit Symbol test and participants improved overall from pre- to post-intervention, this relationship indicates that higher philosophical congruence scores were associated with greater improvement in the Digit Symbol test. In the Tactual Performance Test, lower scores indicate better performance, as it is measured in time taken to complete the task. Overall, participants completed the task faster post-treatment compared to pre-treatment. As such, this relationship indicates that higher philosophical congruence scores were also associated with greater

improvement (shorter latency) in the Tactual Performance Test, again only in the placebo group (see Tables 4.3 and 4.4).

	Philosophical congruence with CAM		Dissatisfaction with conventional medicine		Holistic balance	
	β	*p*	β	*p*	β	*p*
PSS pre-tx	-4.35	0.084	1.71	0.254	-0.40	0.803
PSS change	1.98	0.246	-0.31	0.766	-0.37	0.741
CES-D pre-tx	-0.10	0.395	0.17	**0.028**	-0.01	0.939
CES-D change	-0.06	0.543	-0.04	0.536	0.05	0.506
Digit Span pre-tx	0.04	0.964	0.42	0.413	-0.14	0.797
Digit Span change	-0.45	0.647	0.29	0.629	-0.20	0.755
Digit Symbol pre-tx	2.13	0.590	0.12	0.959	-1.02	0.700
Digit Symbol change	1.90	0.314	0.25	0.829	-0.77	0.536
CTMT pre-tx	0.22	0.960	2.71	0.315	-0.26	0.928
CTMT change	-0.71	0.811	-1.37	0.456	0.68	0.736
FTT pre-tx	-2.16	0.548	1.86	0.424	0.92	0.688
FTT change	-0.43	0.820	-1.94	0.115	0.99	0.395
TPT pre-tx	-1.74	0.341	-0.13	0.910	1.66	0.163
TPT change	-2.23	0.306	1.16	0.195	1.50	0.332
SIP pre-tx	1.39	0.578	1.78	0.251	0.28	0.866
SIP change	-0.60	0.551	0.68	0.272	0.71	0.292
Stroop P300 amplitude pre-tx	6.43	**0.013**	-0.03	0.981	-3.18	**0.029**
Stroop P300 amplitude change	-0.15	0.841	-0.38	0.441	0.32	0.488
Stroop P300 latency pre-tx	-0.01	0.685	0.01	0.968	0.01	0.973
Stroop P300 latency change	0.01	0.876	0.01	0.659	0.01	0.823
Stroop accuracy (incon/con) pre-tx	0.01	0.809	-0.01	0.665	-0.01	0.689
Stroop accuracy (incon/con) change	-0.01	0.692	-0.01	0.674	0.01	0.090
Stroop accuracy (incon/neutral) pre-tx	0.01	0.690	-0.01	0.439	-0.01	0.490
Stroop accuracy (incon/neutral) change	-0.01	0.170	0.01	0.872	0.01	0.334

Table 4.3. Multiple regression analyses for the TBI study: **active** group.
All significant p values (< 0.05) are in bold. *PSS*: Perceived Stress Scale; *CES-D*: Center for Epidemiologic Studies depression scale; *CTMT*: Comprehensive Trail-Making Test; *FTT*: Finger Tapping Test; *TPT*: Tactual Performance Test; *incon*: incongruent; *con*: congruent; *tx*: treatment; *change*: post-intervention – pre-intervention change.

	Philosophical congruence with CAM		Dissatisfaction with conventional medicine		Holistic balance	
	β	*p*	β	*p*	β	*p*
PSS pre-tx	-1.08	0.741	4.63	**0.020**	2.17	0.404
PSS change	-0.35	0.928	-1.08	0.606	-0.47	0.874
CES-D pre-tx	-0.02	0.878	0.22	**0.025**	0.10	0.417
CES-D change	-0.10	0.529	-0.08	0.400	0.07	0.572
Digit Span pre-tx	0.43	0.709	-0.44	0.481	-0.48	0.589
Digit Span change	0.43	0.753	-0.56	0.456	0.20	0.853
Digit Symbol pre-tx	2.17	0.739	-2.48	0.488	-0.85	0.867
Digit Symbol change	5.61	**0.006**	-1.17	0.228	-4.83	**0.003**
CTMT pre-tx	-0.91	0.914	-3.00	0.224	2.00	0.706
CTMT change	4.96	0.144	0.63	0.496	-4.45	**0.045**
FTT pre-tx	7.36	**0.007**	-1.68	0.206	-4.65	**0.024**
FTT change	-3.35	0.124	0.13	0.909	2.81	0.108
TPT pre-tx	0.92	0.398	-0.36	0.542	-0.73	0.398
TPT change	-2.23	**0.044**	1.16	0.052	1.50	0.077
SIP pre-tx	-0.58	0.883	3.24	0.146	1.57	0.611
SIP change	-1.52	0.259	-0.49	0.499	2.06	0.062
Stroop P300 amplitude pre-tx	1.33	0.787	-1.93	0.398	-2.49	0.430
Stroop P300 amplitude change	-3.04	0.504	2.43	0.254	-0.57	0.837
Stroop P300 latency pre-tx	-0.02	0.542	-0.03	0.099	0.02	0.365
Stroop P300 latency change	0.01	0.804	0.01	0.525	-0.01	0.779
Stroop accuracy (incon/con) pre-tx	0.03	0.118	0.01	0.686	-0.02	0.130
Stroop accuracy (incon/con) change	0.02	0.569	0.01	0.889	-0.01	0.505
Stroop accuracy (incon/neutral) pre-tx	0.01	0.834	0.01	0.819	-0.01	0.683
Stroop accuracy (incon/neutral) change	0.03	0.427	0.01	0.625	-0.02	0.448

Table 4.4. Multiple regression analyses for the TBI study: **placebo** group.
All significant p values (< 0.05) are in bold. *PSS*: Perceived Stress Scale; *CES-D*: Center for Epidemiologic Studies depression scale; *CTMT*: Comprehensive Trail-Making Test; *FTT*: Finger Tapping Test; *TPT*: Tactual Performance Test; *incon*: incongruent; *con*: congruent; *tx*: treatment; *change*: post-intervention – pre-intervention change.

Philosophical congruence with CAM: stress study

In the stress study, greater philosophical congruence with CAM in the placebo group was negatively correlated with PSM-9 change (post-intervention – pre-intervention), $r = -0.52$, $p = 0.031$). As higher scores reflect greater perceived stress, this indicates that with higher

philosophical congruence scores, PSM-9 scores were further reduced following the intervention. In the active group, there were no significant correlations with outcome, but higher philosophical congruence with CAM was associated with lower HRV, specifically lnSDNN (r = -0.71, p = 0.002) and lnLF power (r = -0.79, $p < 0.001$) during the first stressor. There were no significant correlations between philosophical congruence and outcome variables in the relaxation group, $p > 0.05$ (see Tables 4.5, 4.6, and 4.7).

	Philosophical congruence with CAM		Dissatisfaction with conventional medicine		Holistic balance	
	r	*p*	*r*	*p*	*r*	*p*
State Anxiety Inventory baseline	0.01	0.966	0.47	**0.003**	-0.06	0.704
State Anxiety Inventory change	0.10	0.563	-0.13	0.437	0.03	**0.044**
PSM-9 baseline	0.26	0.321	0.75	**0.001**	0.31	0.238
PSM-9 change	0.04	0.868	-0.26	0.338	-0.37	0.156
Math task 1 number correct	-0.10	0.532	0.06	0.720	-0.20	0.225
Math task number correct change	-0.08	0.619	-0.04	0.814	-0.10	0.551
HR task 1	0.13	0.487	-0.09	0.626	-0.12	0.501
HR change	-0.13	0.507	-0.12	0.539	0.04	0.812
HR intervention	-0.01	0.939	0.04	0.783	-0.17	0.285
lnSCR task 1	0.12	0.665	-0.24	0.363	0.46	0.073
lnSCR change	0.13	0.637	-0.02	0.940	0.61	**0.012**
lnSCR intervention	0.05	0.843	0.09	0.732	0.52	**0.039**
HRV lnSDNN task 1	-0.71	**0.002**	0.23	0.384	-0.41	0.113
HRV lnSDNN change	0.40	0.121	0.19	0.485	0.56	**0.023**
HRV lnSDNN intervention	-0.37	0.160	0.10	0.719	-0.47	0.069
HRV lnLF task 1	-0.79	**0.000**	0.02	0.944	-0.43	0.092
HRV lnLF change	0.37	0.160	0.14	0.594	0.46	0.074
HRV lnLF intervention	-0.24	0.372	-0.05	0.846	-0.50	**0.047**

Table 4.5. Correlational analyses for the stress study: **active** group.
All significant p values (< 0.05) are in bold. *PSM-9*: nine-item Psychological Stress Measure; *HR*: heart rate; *lnSCR*: skin conductance response (log-transformed); *HRV*: heart rate variability; *lnSDNN*: standard deviation of the NN interval (log-transformed); *lnLF*: low-frequency power (log-transformed); *change*: post-intervention – pre-intervention change.

	Philosophical congruence with CAM		Dissatisfaction with conventional medicine		Holistic balance	
	r	*p*	*r*	*p*	*r*	*p*
State Anxiety Inventory baseline	-0.09	0.561	0.44	**0.004**	-0.33	**0.036**
State Anxiety Inventory change	0.13	0.406	0.31	0.052	0.06	0.701
PSM-9 baseline	0.18	0.500	0.51	**0.037**	-0.51	**0.036**
PSM-9 change	-0.52	**0.031**	0.01	0.964	0.31	0.220
Math task 1 number correct	-0.21	0.200	-0.38	**0.016**	-0.10	0.529
Math task number correct change	-0.09	0.573	0.16	0.327	-0.31	0.052
HR task 1	-0.26	0.137	-0.03	0.867	0.04	0.815
HR change	-0.14	0.435	-0.22	0.218	-0.20	0.266
HR intervention	-0.22	0.191	0.07	0.657	0.05	0.774
lnSCR task 1	-0.05	0.851	0.25	0.366	-0.50	0.060
lnSCR change	-0.03	0.912	-0.05	0.839	0.07	0.777
lnSCR intervention	-0.19	0.502	0.58	**0.025**	-0.54	**0.039**
HRV lnSDNN task 1	0.12	0.634	-0.06	0.819	0.10	0.696
HRV lnSDNN change	0.17	0.505	-0.03	0.893	0.24	0.342
HRV lnSDNN intervention	0.11	0.677	0.13	0.613	-0.06	0.811
HRV lnLF task 1	0.24	0.358	-0.05	0.839	0.07	0.777
HRV lnLF change	-0.07	0.791	-0.05	0.849	-0.08	0.755
HRV lnLF intervention	0.03	0.906	0.09	0.724	-0.03	0.895

Table 4.6. Correlational analyses for the stress study: **placebo** group.
All significant p values (< 0.05) are in bold. *PSM-9*: nine-item Psychological Stress Measure; *HR*: heart rate; *lnSCR*: skin conductance response (log-transformed); *HRV*: heart rate variability; *lnSDNN*: standard deviation of the NN interval (log-transformed); *lnLF*: low-frequency power (log-transformed); *change*: post-intervention – pre-intervention change.

	Philosophical congruence with CAM		Dissatisfaction with conventional medicine		Holistic balance	
	r	*p*	*r*	*p*	*r*	*p*
State Anxiety Inventory baseline	0.12	0.525	0.54	**0.002**	0.09	0.624
State Anxiety Inventory change	0.08	0.663	-0.20	0.299	-0.25	0.185
PSM-9 baseline	0.15	0.553	0.36	0.146	-0.12	0.951
PSM-9 change	0.09	0.723	0.10	0.682	0.25	0.312
Math task 1 number correct	-0.12	0.538	0.06	0.737	-0.01	0.939
Math task number correct change	0.05	0.788	-0.16	0.404	-0.04	0.827
HR task 1	-0.29	0.151	-0.13	0.540	-0.28	0.168
HR change	0.33	0.102	0.33	0.096	0.40	**0.044**
HR intervention	-0.14	0.514	-0.26	0.204	-0.22	0.300
lnSCR task 1	-0.12	0.642	-0.02	0.935	-0.18	0.463
lnSCR change	0.10	0.686	0.14	0.566	-0.41	0.093
lnSCR intervention	0.03	0.910	0.12	0.621	-0.59	**0.011**
HRV lnSDNN task 1	0.28	0.260	0.30	0.233	0.28	0.268
HRV lnSDNN change	-0.19	0.445	-0.21	0.407	-0.30	0.231
HRV lnSDNN intervention	-0.02	0.941	0.45	0.063	0.32	0.192
HRV lnLF task 1	0.16	0.520	0.16	0.531	0.22	0.373
HRV lnLF change	-0.19	0.444	-0.04	0.866	-0.11	0.665
HRV lnLF intervention	-0.04	0.879	0.32	0.190	0.16	0.528

Table 4.7. Correlational analyses for the stress study: **relaxation CD** group.
All significant p values (< 0.05) are in bold. *PSM-9*: nine-item Psychological Stress Measure; *HR*: heart rate; *lnSCR*: skin conductance response (log-transformed); *HRV*: heart rate variability; *lnSDNN*: standard deviation of the NN interval (log-transformed); *lnLF*: low-frequency power (log-transformed); *change*: post-intervention – pre-intervention change.

When controlling for the other CACMAS variables, philosophical congruence with CAM remained a significant predictor of greater perceived stress reduction (change in PSM-9 score) in the placebo group, $\beta = -0.40$, $t = -2.88$, $p = 0.013$. It also remained a significant predictor of lnSDNN ($\beta = -0.20$, $t = -3.15$, $p = 0.008$) and lnLF power ($\beta = -0.45$, $t = -3.85$, $p = 0.002$) during the first stressor for the active group. Additionally, when controlling for other CACMAS variables, philosophical congruence with CAM became a significant predictor of HR in the placebo group during the first stressor ($\beta = -5.20$, $t = -2.05$, $p = 0.049$) and the intervention ($\beta = -$

3.91, t = -2.15, p = 0.039), such that higher philosophical congruence was associated with lower HR (see Tables 4.8, 4.9, and 4.10).

	Philosophical congruence with CAM		Dissatisfaction with conventional medicine		Holistic balance	
	β	*p*	β	*p*	β	*p*
State Anxiety Inventory baseline	0.07	0.371	0.21	**0.002**	-0.07	0.320
State Anxiety Inventory change	-0.49	0.594	-0.76	0.295	1.71	**0.039**
PSM-9 baseline	0.22	0.442	0.83	**0.002**	0.09	0.718
PSM-9 change	0.32	0.333	-0.17	0.500	-0.45	0.133
Math task 1 number correct	-0.02	0.987	0.38	0.663	-1.05	0.283
Math task number correct change	-0.16	0.766	-0.10	0.810	-0.17	0.714
HR task 1	3.38	0.313	-0.71	0.777	-2.74	0.330
HR change	-1.62	0.424	-1.06	0.546	1.04	0.529
HR intervention	-0.59	0.847	0.04	0.988	0.86	0.748
lnSCR task 1	-0.04	0.593	-0.08	0.154	0.14	**0.044**
lnSCR change	-0.08	0.393	-0.05	0.481	0.24	**0.012**
lnSCR intervention	-0.12	0.359	-0.01	0.921	0.25	**0.037**
HRV lnSDNN task 1	-0.20	**0.008**	0.09	0.104	-0.04	0.448
HRV lnSDNN change	0.06	0.532	0.02	0.767	0.15	0.112
HRV lnSDNN intervention	-0.07	0.528	0.06	0.429	-0.13	0.164
HRV lnLF task 1	-0.45	**0.002**	0.05	0.560	-0.05	0.664
HRV lnLF change	0.15	0.514	0.03	0.846	0.24	0.252
HRV lnLF intervention	0.01	0.982	0.03	0.822	-0.26	0.100

Table 4.8. Multiple regression analyses for the stress study: **active** group.
All significant p values (< 0.05) are in bold. *PSM-9*: nine-item Psychological Stress Measure; *HR*: heart rate; *lnSCR*: skin conductance response (log-transformed); *HRV*: heart rate variability; *lnSDNN*: standard deviation of the NN interval (log-transformed); *lnLF*: low-frequency power (log-transformed); *change*: post-intervention – pre-intervention change.

	Philosophical congruence with CAM		Dissatisfaction with conventional medicine		Holistic balance	
	β	*p*	β	*p*	β	*p*
State Anxiety Inventory baseline	0.03	0.672	0.15	**0.006**	-0.14	0.051
State Anxiety Inventory change	0.20	0.709	0.70	0.072	0.06	0.912
PSM-9 baseline	0.18	0.424	0.34	0.083	-0.48	**0.047**
PSM-9 change	-0.40	**0.013**	0.10	0.395	0.28	0.066
Math task 1 number correct	-0.63	0.490	-1.45	**0.027**	-0.11	0.898
Math task number correct change	0.36	0.505	0.30	0.431	-0.95	0.061
HR task 1	-5.20	**0.049**	0.24	0.907	3.25	0.171
HR change	0.02	0.994	-2.24	0.245	-1.84	0.387
HR intervention	-3.91	**0.039**	1.18	0.355	2.67	0.114
lnSCR task 1	-0.01	0.967	0.03	0.673	-0.13	0.126
lnSCR change	-0.01	0.984	-0.01	0.826	-0.02	0.821
lnSCR intervention	-0.16	0.284	0.29	**0.038**	-0.22	0.138
HRV lnSDNN task 1	0.06	0.662	-0.02	0.821	0.03	0.797
HRV lnSDNN change	0.05	0.596	-0.01	0.955	0.07	0.429
HRV lnSDNN intervention	0.05	0.729	0.04	0.713	-0.03	0.849
HRV lnLF task 1	0.24	0.383	-0.07	0.759	0.03	0.925
HRV lnLF change	-0.05	0.864	-0.04	0.840	-0.08	0.765
HRV lnLF intervention	0.02	0.944	0.06	0.770	-0.02	0.942

Table 4.9. Multiple regression analyses for the stress study: **placebo** group.
All significant p values (< 0.05) are in bold. *PSM-9*: nine-item Psychological Stress Measure; *HR*: heart rate; *lnSCR*: skin conductance response (log-transformed); *HRV*: heart rate variability; *lnSDNN*: standard deviation of the NN interval (log-transformed); *lnLF*: low-frequency power (log-transformed); *change*: post-intervention – pre-intervention change.

	Philosophical congruence with CAM		Dissatisfaction with conventional medicine		Holistic balance	
	β	*p*	β	*p*	β	*p*
State Anxiety Inventory baseline	-0.02	0.832	0.27	**0.003**	0.01	0.935
State Anxiety Inventory change	1.12	0.449	-1.03	0.347	-1.40	0.179
PSM-9 baseline	0.11	0.772	0.37	0.221	-0.06	0.811
PSM-9 change	-0.07	0.800	0.09	0.674	0.18	0.347
Math task 1 number correct	-1.31	0.413	0.60	0.607	0.46	0.676
Math task number correct change	0.58	0.472	-0.54	0.358	-0.28	0.612
HR task 1	-3.08	0.509	-0.34	0.922	-2.03	0.558
HR change	0.44	0.827	1.77	0.258	1.82	0.237
HR intervention	1.08	0.748	-3.14	0.222	-1.39	0.597
lnSCR task 1	-0.01	0.907	-0.01	0.989	-0.04	0.587
lnSCR change	0.20	0.202	0.03	0.793	-0.23	**0.041**
lnSCR intervention	0.44	0.123	0.04	0.832	-0.63	**0.004**
HRV lnSDNN task 1	0.08	0.727	0.17	0.330	0.11	0.450
HRV lnSDNN change	0.01	0.993	-0.08	0.461	-0.09	0.325
HRV lnSDNN intervention	-0.27	0.115	0.32	**0.024**	0.23	0.052
HRV lnLF task 1	0.04	0.942	0.20	0.602	0.24	0.493
HRV lnLF change	-0.15	0.563	0.01	0.970	-0.01	0.943
HRV lnLF intervention	-0.38	0.341	0.47	0.142	0.27	0.328

Table 4.10. Multiple regression analyses for the stress study: **relaxation CD** group. All significant p values (< 0.05) are in bold. *PSM-9*: nine-item Psychological Stress Measure; *HR*: heart rate; *lnSCR*: skin conductance response (log-transformed); *HRV*: heart rate variability; *lnSDNN*: standard deviation of the NN interval (log-transformed); *lnLF*: low-frequency power (log-transformed); *change*: post-intervention – pre-intervention change.

Dissatisfaction with conventional medicine: TBI study

In the TBI study, greater dissatisfaction with conventional medicine predicted a higher baseline score on the CES-D (indicating greater depression) in both active and placebo groups, $r = 0.48$, $p = 0.029$ and $r = 0.65$, $p = 0.004$, respectively. In the placebo group, greater dissatisfaction with conventional medicine also predicted a higher baseline score on the PSS, indicating greater perceived stress, $r = 0.66$, $p = 0.004$ (see Tables 4.1 and 4.2).

After controlling for the other CACMAS variables, the same relationships remained. Greater dissatisfaction with conventional medicine was still a significant predictor of a higher baseline CES-D score in the active ($\beta = 0.17$, $t = 2.41$, $p = 0.028$) and placebo ($\beta = 0.22$, $t = 2.52$, $p = 0.025$) groups, and of a higher baseline score on the PSS in the placebo group, $\beta = 4.63$, $t = 2.65$, $p = 0.020$. Additionally, multiple regression analyses found dissatisfaction with conventional medicine to be a marginally significant predictor of outcome (post-intervention score – pre-intervention score) on the Tactual Performance Test in the placebo group, $\beta = 1.16$, $t = 2.13$, $p = 0.052$. As mentioned above, a lower score post-intervention compared to pre-intervention on the Tactual Performance Test indicates improvement (reduced time to complete the task). Therefore, this relationship finds greater dissatisfaction with conventional medicine to be associated with *less* improvement on the Tactual Performance Test (see Tables 4.3 and 4.4).

Dissatisfaction with conventional medicine: stress study

Baseline State Anxiety Inventory scores were significantly correlated with dissatisfaction with conventional medicine for the active ($r = 0.47$, $p = 0.003$), placebo ($r = 0.44$, $p = 0.004$), and relaxation ($r = 0.54$, $p = 0.002$) groups. This was such that higher levels of dissatisfaction predicted higher levels of pre-intervention anxiety for all three groups. Dissatisfaction with conventional medicine was also a marginally significant predictor of outcome (post-intervention – pre-intervention) on the State Anxiety Inventory in the placebo group, $r = 0.31$, $p = 0.052$. Higher scores on the State Anxiety Inventory indicate greater anxiety and since participants showed a reduction from pre- to post-intervention overall, this positive correlation indicates that higher dissatisfaction with conventional medicine scores were associated with *less* reduction in anxiety. Additionally, greater dissatisfaction with conventional medicine was a significant predictor of higher baseline PSM-9 scores in both the active and placebo groups, $r = 0.75$, $p =$

0.001 and $r = 0.51$, $p = 0.037$, respectively, indicating increased perceived stress with greater dissatisfaction with conventional medicine. Higher levels of dissatisfaction with conventional medicine in the placebo group also predicted higher lnSCR during the intervention, $r = 0.58$, $p = 0.025$, as well as fewer correct answers during the first stressor, $r = -0.38$, $p = 0.16$. In the relaxation group, dissatisfaction with conventional medicine was a marginally significant predictor of lnSDNN during the intervention, with greater dissatisfaction associated with higher lnSDNN, $r = 0.45$, $p = 0.063$ (see Tables 4.5, 4.6, and 4.7).

Multiple regression analyses (controlling for the other CACMAS variables) found dissatisfaction with conventional medicine to remain a significant predictor of baseline State Anxiety Inventory scores for all three groups (active: $\beta = 0.21$, $t = 3.32$, $p = 0.002$; placebo: $\beta = 0.15$, $t = 2.94$, $p = 0.006$; relaxation: $\beta = 0.27$, $t = 3.21$, $p = 0.003$). Additionally, when controlling for the other CACMAS variables, greater dissatisfaction with conventional medicine was still a significant predictor of higher baseline PSM-9 scores for the active group, $\beta = 0.83$, $t = 3.91$, $p = 0.002$ and marginally for the placebo group, $\beta = 0.34$, $t = 1.88$, $p = 0.083$. In the placebo group, dissatisfaction was also still a significant predictor of lnSCR during the intervention ($\beta = 0.29$, $t = 2.36$, $p = 0.038$) and of less correct answers during the first stressor ($\beta = -1.45$, $t = -2.30$, $p = 0.027$), after controlling for all other predictor variables. In the relaxation group, higher dissatisfaction with conventional medicine was still associated with higher lnSDNN during the intervention after controlling for the other CACMAS variables, $\beta = 0.32$, $t = 2.53$, $p = 0.024$ (see Tables 4.8, 4.9, and 4.10).

Holistic Balance: TBI study

The only significant correlation involving holistic balance in the TBI study was a significant relationship between holistic balance score and baseline P300 amplitude during the

Stroop task (averaged across congruent, incongruent, and neutral trials) in the placebo group. This was such that higher holistic balance predicted lower baseline P300 amplitude, $r = -0.67$, $p = 0.033$ (see Table 4.2). However, when controlling for the other CACMAS variables, this relationship was no longer significant for the placebo group ($p > 0.05$), but was for the active group, $\beta = -3.18$, $t = -2.54$, $p = 0.029$. Surprisingly, multiple regression analyses controlling for the other CACMAS variables found higher holistic balance scores in the placebo group to predict less improvement on both the Digit Symbol test ($\beta = -4.83$, $t = -3.62$, $p = 0.003$) and CTMT ($\beta = -4.45$, $t = -2.23$, $p = 0.045$) from pre- to post-treatment. Higher scores on the Digit Symbol test indicate better performance (more correct answers); this is the same for the CTMT, as results are reported with the manufacturer-recommended composite index score (a higher composite index score indicates better performance). Overall, participants showed pre- to post-intervention improvement on both tasks. As such, the negative correlations with holistic balance score indicate less post-intervention improvement on each task. Also surprisingly, higher holistic balance scores were associated with worse performance on the Finger Tapping Test at baseline in the placebo group, $\beta = -4.65$, $t = -2.56$, $p = 0.024$ (see Tables 4.3 and 4.4).

Holistic Balance IGP: stress study

There were multiple relationships with holistic balance score in the stress study. In the placebo group, a higher holistic balance score predicted a lower State Anxiety Inventory score at baseline, $r = -0.33$, $p = 0.036$, as well as a lower baseline PSM-9 score, $r = -0.51$, $p = 0.036$, indicating lower perceived stress and anxiety in those with higher holistic balance scores. Additionally, higher holistic balance predicted State Anxiety Inventory Score outcome (post-intervention score – pre-intervention score) in the active group, $r = 0.03$, $p = 0.044$. Lower State Anxiety Inventory scores indicate less anxiety, and as participants showed an overall reduction in

State Anxiety Inventory score following the intervention, this relationship indicates that with increased holistic balance scores, participants showed *less* reduction in anxiety from pre- to post-intervention. A similar relationship was seen between holistic balance and lnSCR. In the active group, holistic balance was positively correlated with change in lnSCR (post-intervention level – pre-intervention level), $r = 0.61$, $p = 0.012$. Higher lnSCR indicates greater anxiety, and overall, participants showed a reduction in lnSCR from the first (pre-intervention) to the second (post-intervention) stressor. As such, this relationship indicates that with higher holistic balance scores, there was *less* reduction in lnSCR from pre- to post-intervention. There was a less clear relationship in the active group between holistic balance score and lnSDNN, such that higher holistic balance scores were associated with greater change in lnSDNN (post-intervention – pre-intervention), $r = 0.56$, $p = 0.023$. However, in the active group, about one-half of the participants showed an increase in lnSDNN from pre- to post-intervention, while the other half showed a decrease, making interpretation difficult (see Tables 4.5, 4.6, and 4.7).

All groups showed significant correlations between holistic balance score and lnSCR during the intervention. However, while the relaxation ($r = -0.59$, $p = 0.011$) and placebo ($r = -0.54$, $p = 0.039$) groups demonstrated negative correlations (higher holistic balance scores predicted lower lnSCR during the intervention), the active group showed a positive correlation, such that higher holistic balance scores predicted higher lnSCR during the intervention ($r = 0.52$, $p = 0.039$). Additionally, both active and placebo groups showed marginally significant correlations between holistic balance and lnSCR during the first stressor ($r = 0.46$, $p = 0.073$ and $r = -0.50$, $p = 0.060$, respectively), but again in opposite directions: higher holistic balance scores predicted higher lnSCR during the first task for the active group, but lower lnSCR for the placebo group. Also in the active group, higher holistic balance scores predicted lower lnLF

power during the intervention, $r = -0.50$, $p = 0.047$. Additionally, in the relaxation group, higher holistic balance scores predicted a lesser effect of the intervention on HR reduction from the first to the second stressor (post-intervention HR – pre-intervention HR), $r = 0.40$, $p = 0.044$. Higher HR indicates greater anxiety and overall, a reduction in HR from the first (pre-intervention) to the second (post-intervention) stressor was seen. Given this, the relationship indicates that higher holistic balance scores were associated with *less* reduction in HR. Similarly, in the placebo group, holistic balance was a marginally significant predictor of change in the number of correct answers during the math task stressor following the intervention, $r = -0.31$, $p = 0.052$. Higher scores (more correct answers) indicate better performance, so given that participants improved overall in performance from the first (pre-intervention) to the second (post-intervention) stressor, this negative correlation suggests that higher holistic balance scores were associated with *less* improvement (see Tables 4.5, 4.6, and 4.7).

After controlling for all other predictor variables, higher holistic balance score remained a significant predictor of change in State Anxiety Inventory score from pre- to post-treatment in the active group ($\beta = 1.71$, $t = 2.15$, $p = 0.039$), such that it predicted *less* anxiety reduction. Holistic balance also remained a marginally significant predictor of baseline State Anxiety Inventory score in the placebo group ($\beta = -0.14$, $t = -2.02$, $p = 0.051$). Multiple regression analyses also found higher holistic balance scores to remain predictive of lower baseline PSM-9 scores in the placebo group after controlling for the other CACMAS variables, $\beta = -0.48$, $t = -2.19$, $p = 0.047$. Additionally, holistic balance was still a marginally significant predictor of *less* improvement in the number of correct answers during the math task from the first to the second stressor in the placebo group, $\beta = -0.95$, $t = -1.93$, $p = 0.061$. Holistic balance also remained a significant predictor of lnSCR during the intervention for the active ($\beta = 0.25$, $t = 2.36$, $p =$

0.037) and relaxation groups (β = -0.63, t = -3.45, p = 0.004) (but not the placebo group), as well as lnSCR during the first stressor in the active group (β = 0.14, t = 2.25, p = 0.044) and the change in lnSCR from the first to the second stressor in the active group (β = 0.24, t = 2.95, p = 0.012) (indicating *less* anxiety reduction). Controlling for other predictor variables also revealed higher holistic balance scores to have a marginally significant association with higher lnSDNN during the intervention for the relaxation group, β = 0.23, t = 2.12, p = 0.052 (see Tables 4.8, 4.9, and 4.10).

Discussion

Attitudes towards CAM and conventional medicine, as measured by the CACMAS, had less of an impact on intervention outcome than had been hypothesized. Although involving few variables, the impact holistic balance scores had on outcome was surprising, as it was the opposite impact predicted by original hypotheses. However, the CACMAS variables did appear to influence baseline measures in both studies, as well as physiological measures during the intervention itself in the stress study.

There was little effect of philosophical congruence on outcome in either study, and only in the control groups. Philosophical congruence with CAM in the TBI study predicted outcome on two measures in the placebo group, after controlling for the other CACMAS variables. In agreement with hypotheses, having a greater philosophical congruence predicted greater improvement on both the Digit Symbol test and the Tactual Performance Test. Since this was not seen in the active group, this may suggest that a positive attitude towards CAM mediated the improvement seen following placebo treatments, but not the improvement following active treatments.

In the TBI study, there was also a reduction in baseline stress in the active group seen with increased philosophical congruence with CAM, such that greater philosophical congruence was associated with a lower baseline PSM-9 score, which was still marginal when controlling for the other CACMAS variables. A reason for this could be that those more comfortable with CAM may feel less anxious when beginning a study of a CAM intervention. Similarly, when controlling for the other CACMAS variables in the placebo group, greater philosophical congruence with CAM was associated with a higher baseline Finger Tapping Test score, indicating having a greater philosophical congruence was associated with more taps (better

performance) in a 10-second period. Again, this could possibly be due to feeling more comfortable, and perhaps less anxious, if more comfortable with a study of a CAM intervention.

Also in agreement with hypotheses, results from the stress study showed greater philosophical congruence with CAM predicted greater stress reduction following the second stressor compared to the first (as measured by the PSM-9) in the placebo group, even when controlling for the other CACMAS variables. This could indicate that some of the stress reduction seen in the placebo group was driven by a positive attitude towards CAM.

While philosophical congruence with CAM in the stress study did not predict outcome for any variable in the active group, it did predict HRV during the first (pre-intervention) stressor, with higher philosophical congruence predicting lower SDNN and LF power during the first stressor. While the reason for this is uncertain, it could be that those with a higher philosophical congruence with CAM were more comfortable with the upcoming intervention. As LF power is thought to be mainly influenced by the sympathetic nervous system, with some parasympathetic input (Task Force of the European Society of Cardiolgy and the North American Society of Pacing and Electrophysiology, 1996; Acharya et al., 2006), this might indicate a reduction in sympathetic activation, perhaps suggesting reduced anxiety during the stressor. Similarly, in the placebo group, an increased philosophical congruence with CAM predicted lower HR during the first stressor, again perhaps suggesting increased comfort. Additionally, greater philosophical congruence in the placebo group predicted a greater reduction in HR during the intervention, indicating a reduced stress response during the placebo intervention with higher philosophical congruence with CAM. This makes sense, as it would be expected that those with a philosophy congruent with CAM might feel more comfortable during a treatment involving aspects of CAM. Since this effect wasn't seen for the active group, who

received a similar treatment, this suggests that heart rate reduction during the placebo treatments may have been influenced by attitudes towards CAM (i.e., a placebo effect), whereas attitudes did not have as much of an influence on heart rate during the active treatment. As a previous study in our laboratory found active acupressure to elicit a greater effect on heart rate than placebo (McFadden and Hernández, 2010), it could be that placebo effects are driving heart rate reduction during placebo treatments, but the acupoint stimulation may be driving the effects during the active treatments.

In the TBI study, there was a significant relationship between dissatisfaction with conventional medicine and baseline stress. In the placebo group, greater dissatisfaction was associated with higher baseline PSS scores (measuring perceived stress) even when controlling for the other CACMAS variables. Although acupressure is not a conventional medical treatment, a possible reason for this could be that participants with greater dissatisfaction with conventional medicine were less comfortable with the research setting, and knowing they were going to have EEG measurements taken shortly after the PSS was administered. It is uncertain why the same relationship was not seen in the active group, given that no treatments had been administered prior to baseline measurements. Scores on the CES-D at baseline were found to be associated with higher dissatisfaction with conventional medicine in both active and placebo groups, even when controlling for the other CACMAS variables. A possible reason for this could be that those with a higher depression score have more dissatisfaction in general, reflected by their higher dissatisfaction with conventional medicine score, or they may have had more negative experiences with doctors. Greater dissatisfaction with conventional medicine in the placebo group was also associated with *less* improvement on the Tactual Performance Test from pre- to post-intervention. Again, this could reflect a discomfort with the aspects of the study

similar to conventional medical procedures (e.g., in a research setting, anticipating EEG data collection). However, this relationship was not seen in any of the other neuropsychological tests or in the active group, so it is difficult to determine what is driving this effect.

In the stress study, levels of dissatisfaction with conventional medicine were associated with higher levels of anxiety at baseline for all groups, even when controlling for other CACMAS variables. Similarly, greater dissatisfaction with conventional medicine was associated with higher scores on the PSM-9, a measure of perceived stress, in both the active and placebo groups, even when controlling for the other CACMAS variables. Additionally, having a higher dissatisfaction score was a marginally significant predictor of less anxiety reduction from pre- to post-intervention in the placebo group. As with the TBI study, although acupressure is not a conventional medical treatment, perhaps being in a setting in which medical measures were being taken (HR, SCR, HRV) with researchers wearing lab coats increased stress and anxiety in those uncomfortable with medical settings. This could also be the reason why participants in the placebo group with greater dissatisfaction with conventional medicine showed fewer correct answers during the pre-intervention math task. Additionally, in the placebo group higher levels of dissatisfaction with conventional medicine predicted higher SCR during the intervention itself, also indicating increased anxiety. Again, this makes sense given that participants were still undergoing ECG and SCR data collection while having the intervention administered. However, it is surprising that this relationship was not also seen in the active group, as the procedure was the same for both interventions (the relaxation CD did not have a practitioner administering the intervention). It could be that the active acupressure in and of itself (i.e., stimulation of acupoints) may have acted as a buffer of sorts against anxiety related to dissatisfaction with conventional medicine; however, it is unlikely that this was a universal effect, as there were no

significant differences found amongst groups in SCR during the intervention in original analyses (see Chapter 3). In the relaxation group, greater dissatisfaction with conventional medicine was associated with increased SDNN during the intervention, suggesting increased HRV. Since increased HRV can indicate better autonomic adaptation (Acharya et al., 2006; Vanderlei et al., 2009), it could be that having a higher dissatisfaction with conventional medicine could lead to reduced anxiety when discovering that the relaxation CD was the assigned intervention, and not an intervention involving a practitioner or physical touch. As such, this reduced autonomic response (reduced anxiety) could lead to reduced HRV.

Agreement with a holistic balance viewpoint appeared to influence outcome more than either philosophical congruence with CAM or dissatisfaction with conventional medicine, in both studies. Surprisingly, the influence on outcome was the opposite of that predicted by hypotheses. In the TBI study, increased holistic balance scores in the placebo group were associated with *less* improvement on both the Digit Symbol test and the CTMT. Higher holistic balance scores were also associated with a lower score on the Finger Tapping Test (fewer taps in a 10-second period) in the placebo group pre-treatment. These results are surprising given the original hypothesis, as it would be expected that having a positive attitude towards CAM would lead to improved outcome rather than less improvement. As the holistic balance factor was discovered following factor analysis of the CACMAS, it could be that this factor is measuring something different than was hypothesized, likely something more complex than a positive attitude towards CAM. Given that the questions included in the holistic balance factor emphasize a natural underlying energy and the body's capacity for self-healing, it could be possible that those with a holistic balance viewpoint might view any type of intervention, conventional medicine *or* CAM, to be unnecessary or excessive.

Similar results were found in the stress study. Increased holistic balance scores in the active group were associated with *less* anxiety reduction from pre- to post-intervention, as measured by both the State Anxiety Inventory and SCR. Additionally, in the relaxation group, increased holistic balance scores were also associated with *less* anxiety reduction, as measured by HR. Furthermore, increased holistic balance scores in the placebo group were associated with *less* improvement in performance during the math task. Again, it was hypothesized that having an agreement with holistic balance would lead to higher expectations and therefore, enhanced placebo effects. This further suggests that the holistic balance factor may be capturing something more than originally thought.

Interestingly, holistic balance was a predictor of SCR during the intervention for all groups, but in different directions. While higher holistic balance was a predictor of increased SCR during the intervention for the active group, it predicted lower SCR for both the placebo and relaxation groups. A possible explanation for this could be that active treatments have an "active" element to them, perhaps engaging the autonomic nervous system (ANS) more than the other treatments (see Chapter 5), resulting in greater responsivity during the intervention itself. Those with a viewpoint in agreement with holistic balance may experience an additional placebo effect on top of any benefit of active acupressure, possibly due to a positive belief in the treatment. In the relaxation group only, higher holistic balance predicted increased HRV (SDNN and LF power) during the intervention. This result was interesting as original analyses found both acupressure groups (active and placebo) to have increased HRV during the intervention compared to the relaxation group (see Chapter 3). Perhaps having a higher holistic balance score added a placebo effect to the intervention so that those with higher scores in the relaxation group were more likely to have increased HRV, such that a high holistic balance score might have

shifted HRV in the direction of a treatment that involves touch. In the placebo group, those with higher holistic balance scores showed lower baseline subjective stress, as measured by both the State Anxiety Inventory and the PSM-9, even when controlling for the other CACMAS variables. This makes intuitive sense, as those with a viewpoint more in agreement with holistic balance might feel less anxious preceding a CAM intervention.

A potential limitation to the current study is that it is unknown how stable the CACMAS variables are, or if they might vary over time. The CACMAS was only administered at the beginning of each study, to assess group differences in attitudes towards CAM. In a study of acupuncture intervention for treatment of chronic pain, White found that while attitudes towards CAM did not influence outcome (decrease in pain), attitudes themselves changed from before to after the series of acupuncture treatments. This change was such that participants indicated an increased belief in CAM following the acupuncture treatments, regardless of their individual outcome (White et al., 2003). Since we have not investigated how experiencing acupressure treatments may influence CACMAS scores, future studies can see if attitudes towards CAM change following acupressure administration, by re-administering the CACMAS post-intervention.

Future studies could also recruit from more specific populations in an attempt to find groups that are widely different in their attitudes towards CAM. For example, comparing results from those recruited at a CAM clinic to the general population would be a way to incorporate additional diversity in attitudes. A potential limitation of the current analyses is that both studies were conducted in Boulder, CO, an area in which CAM treatment and education is prevalent. Boulder has 89 listed acupuncture practitioners (Acufinder.com, 2009), and houses two acupuncture colleges (Southwest Acupuncture College, 2009; Ruseto College, 2009), a massage

college (Boulder College of Massage Therapy, 2009), and a school devoted to the study of homeopathy (Homeopathy School International), which is considerable for a city with a population of only 103,650 (Community Data Report: Boulder, CO, 2009). As such, a next step would be to see if the effects of CAM attitudes on outcome in a geographic location less CAM-friendly would be similar to those seen in the current study.

In conclusion, of all the predictors, holistic balance score was most predictive of post-intervention outcome in both studies. However, this impact was not in the expected direction, with increased holistic balance predicting *less* improvement and/or *less* anxiety reduction post-intervention. Although relationships between holistic balance and baseline/intervention measures suggested holistic balance to measure a positive attitude towards CAM, the impact on outcome suggests that there is likely something more complex involved in this factor that remains to be determined. Also surprising, philosophical congruence with CAM had less of an impact on outcome than was hypothesized, although there were some interesting relationships at baseline in both studies and during the intervention itself in the stress study. Although CAM attitudes as a whole were not strong predictors of outcome, they were still significant predictors of change in some measures, and differently among groups. As such, care must be taken in experimental design to assure that these variables are systematically controlled for, perhaps by matching groups at the outset based on positive/negative attitudes towards CAM and conventional medicine prior to intervention.

CHAPTER 5

GENERAL DISCUSSION

Summary of findings

The studies detailed in the preceding chapters suggest that active acupressure elicits additional effects above and beyond those seen with placebo acupressure, but that more than a single treatment is necessary to elicit treatment effects. In the TBI study (Chapter 2), active acupressure was associated with cognitive improvements, above and beyond those seen following placebo acupressure. However, in the stress study (Chapter 3), a single active acupressure treatment was not found to reduce the stress response more than placebo acupressure or a relaxation CD.

Taken together with results from the stroke study (see Chapter 1), our results suggest that active acupressure may lead to an increased relaxation response compared to placebo acupressure, but it may be dose-dependent. This short-term induction of the relaxation response could lead to a reduction in stress, which could mediate the cognitive improvement seen in the TBI study. As stress can exacerbate or unmask cognitive deficits following TBI (Ewing et al., 1980; Hanna-Pladdy et al., 2001), a treatment that reduces stress could therefore lead to the observed improvements in cognitive function in the TBI study. As well as cognitive improvement (seen in neuropsychological tests and ERPs), a greater decrease in subjective stress was also observed following active acupressure compared to placebo acupressure in the TBI study. We hypothesized that the greater and faster reduction in HR seen during active acupressure compared to placebo acupressure in the stroke study indicated greater and faster induction of the relaxation response. Since the stress response has been linked to disease (Esch et al., 2002) and induction of the relaxation response may break the stress-disease link by reducing the response to stress (Esch et al., 2003), we suggest that the increase in the relaxation response could confer a functional benefit due to stress reduction. As stress reduction is

hypothesized to be a strong factor in the cognitive improvements seen in the TBI study, the two studies suggest a similar mechanism.

Contributions of the current research to the existing acupressure literature

While many acupressure studies in the literature focus on the use of acupressure for the relief of nausea, for which it has shown consistent and replicable efficacy (Alkaissi et al., 2002; Streitberger et al., 2006; Dibble et al., 2007), there is a dearth of research on the effects of acupressure for other conditions or in affecting other bodily systems. Previous studies have found acupressure to reduce heart rate, which is a reliable, non-invasive marker of autonomic nervous system (ANS) activity. Our results replicate and extend those finding acupressure to reduce heart rate (Felhendler and Lisander, 1999; Sugiura et al., 2007; Wu et al., 2007) by showing heart rate effects in a population with cardiovascular problems (e.g., stroke; see McFadden and Hernández, 2010 and Chapter 1). Additionally, the current studies use a more appropriate placebo control than previous studies of acupressure. Felhendler and Lisander (1999) compared cardiovascular effects of two types of acupoint stimulation (firm pressure on acupoints and stroking along meridians) with pressure on non-acupoints (light pressure). This non-acupoint control is not ideal as it uses a different type of pressure than the other two groups (light pressure on non-acupoints compared to firm pressure or stroking on acupoints), making it difficult to determine if differences between groups are due to acupoint stimulation or differences in pressure. Sugiura et al. (2007) did not utilize control points, but simply administered acupressure to the soles of both feet. As such, it is impossible to know if the resulting heart rate reduction was due to acupoint stimulation, touch itself (regardless of location), or from simply reclining. Wu et al. (2007) compared treatments with acupoints in patients with chronic obstructive pulmonary disease to treatments using sham points. For the

"real acupressure" group, they chose points that were designated in TCM to induce relaxation and to relieve dyspnea, as those were the study goals. However, for the "sham acupressure" group, they also used real acupoints, but chose points on different meridians that are thought to help intestinal function, since many of the participants were elderly and also had intestinal difficulties. While a nice way to attempt to elicit a health benefit even in the placebo group, using real acupoints as control points assumes that the actual physiological effects of stimulating each different point is known. That they saw improvements in the real acupressure group compared to the sham group (greater reduction in depression, blood pressure, and heart rate) may be good evidence of point specificity in acupressure. However, it doesn't take into account what the specific effects of stimulation on the "sham" acupoints might have been. As such, the inclusion of a group receiving acupressure on non-acupoints and/or a group receiving a control without touch would have been helpful to determine what specifically about the treatments was causing the observed effects.

The findings detailed in this thesis also add to the existing literature by examining the effects of acupressure on cognitive function in TBI survivors, another group experiencing neurological insult. There are few investigations of acupressure for cognitive function. Harris et al. found acupressure to modify alertness in the classroom, which could be expected to impact cognitive performance. Healthcare professionals enrolled in a research design course were taught to self-administer acupressure to 10 acupoints, 5 of which were thought to be stimulating points and 5 of which were thought to be relaxing points, according to TCM theory. Over the course of three days in the classroom, participants engaged in 15 minutes of either "stimulating" or "relaxing" acupoint pressure, without knowing which type they were self-administering each day. On the days participants were assigned to stimulation points, they reported a reduction in

sleepiness compared to days in which relaxation points were stimulated, suggesting that acupressure can change alertness in a classroom setting. However, the authors point out that this design makes it impossible to determine if pressure on stimulation points decreases fatigue, pressure on relaxation points increases fatigue, or a combination of the two. Additionally, it is uncertain if this reduction in fatigue would translate to better performance in the classroom (Harris et al., 2005).

Clancy et al. investigated the effects of Jin Shin acupressure in participants with HIV, reporting significant improvements in cognitive and physical (e.g., vomiting and sore throat) symptoms following 20 weeks of once-weekly acupressure treatments. However, as they didn't use a control group, it is difficult to attribute these improvements specifically to acupressure. They also did not specify what measures they used to assess cognitive function (Clancy et al., 1996). Furthermore, although some papers have examined waveform changes (Sugiura et al., 2007) and bispectral index changes (Agarwal et al., 2005; Fassoulaki et al., 2007) via EEG in acupressure, our study in TBI survivors was the first in the English-language literature that we know of to use ERPs in a study of acupressure, allowing us to assess neurophysiological correlates of cognitive function.

Another important contribution of this research is that of attempting to determine an appropriate number of acupressure treatments needed to elicit effects. Many acupressure studies in the literature utilize single treatment sessions in healthy participants and demonstrate significant effects of acupressure (Felhendler and Lisander, 1999; Sugiura et al., 2007). Consequently, in the stress study we were surprised not to see group differences in stress reduction between active acupressure, placebo acupressure, and the relaxation CD intervention following a single intervention administration. While a series of acupressure treatments is often

recommended for those with chronic health problems (e.g., stroke or TBI) (Burmeister, 1997), a single treatment could reasonably be expected to be sufficient in a population of healthy individuals without chronic pathology. A single treatment would also be expected to elicit a sufficient response in the simple measures used in the stress study (i.e., SCR, HR, HRV), given that we were looking at an acute response to a single event (a math task stressor). However, our findings that active acupressure-associated treatment effects were elicited with 8 treatments in the stroke study, added to our significant findings in the TBI study (which also utilized 8 treatments) and the lack of group differences in the stress study following a single treatment, suggest that a series of treatments may be more effective than a single treatment. Additionally, we found that the more condensed schedule of treatments in the TBI study (2 per week for 4 weeks) was just as effective as the more spread out treatment schedule in the stroke study (1 per week for 8 weeks). While active acupressure was associated with greater and faster heart rate reduction in the stroke study, no functional benefits (e.g., motor or speech function) were observed. Although there may have been functional benefits in the stroke study that the measurements used did not detect, a functional benefit (improved cognitive performance) of acupressure was seen in the TBI study. As such, administering 8 treatments over 4 weeks (rather than 8 weeks) was as successful, if not more, in eliciting treatment effects.

By looking at the impact attitudes towards CAM and conventional medicine had on baseline, intervention, and outcome measures in both the stress study and the TBI study (using the CACMAS; see Chapter 4), we also found that overall, having a philosophy congruent to that of CAM predicted lower stress and anxiety. This suggested that participants who had greater philosophical congruence with CAM felt less anxious and more comfortable during an experimental trial of a CAM treatment. We also saw greater improvements in outcome (i.e.,

greater improvement on neuropsychological tests and greater reduction in perceived stress) in those with greater philosophical congruence with CAM. This relationship was only seen in the control groups (placebo acupressure and/or relaxation CD intervention), suggesting that a positive attitude towards CAM may have been driving at least some of the improvement in the control groups, such that attitudes were contributing to placebo effects.

Additionally, those with greater dissatisfaction with conventional medicine demonstrated increased stress and anxiety at the start of the experiment, prior to intervention administration. Furthermore, increased dissatisfaction with conventional medicine predicted less improvement on some measures from pre- to post-intervention (i.e., less cognitive improvement, less anxiety reduction). A possible reason for this could be that elements of the experiment similar to conventional medicine (e.g., researchers wearing lab coats, equipment used for ECG, SCR, and EEG measurement) may have made participants uncomfortable with medical settings feel more anxious. Additionally, increased anxiety during the intervention itself in the stress study for those with increased dissatisfaction with conventional medicine could be due to the presence of a practitioner and the physical touch involved in the treatment, as this was only seen in the placebo group (the relaxation CD intervention involved neither a practitioner or physical touch). These findings can be applied to both CAM and conventional medicine. For one, measures such as the CACMAS could be used to predict which patients might response best, or least, to CAM therapies, by gauging their positivity towards CAM, as it seems positive attitudes towards CAM can enhance placebo effects (which occur in both "real" and "placebo" interventions). However, this could also be useful in conventional medicine. If a patient indicates a strong holistic balance viewpoint, or a philosophy congruent with that of CAM, it suggests what particular aspects of healthcare they might response best to. For instance, if a doctor is aware that their patient has a

philosophy congruent with CAM, that could suggest that the patient may respond better to having a more active role in their own treatment, or may benefit from a warmer doctor/patient interaction. Similarly, knowing if a patient has a strong dissatisfaction with conventional medicine is useful in both CAM and conventional medicine. If a conventional medical doctor is aware of a patient's dissatisfaction with conventional medicine, it could let them know to talk to the patient to determine what is driving their dissatisfaction (e.g., not enough time with the doctor, the doctor/patient relationship, previous medical experiences) and find ways to make their medical experience more comfortable and successful.

Possible physiological mechanisms of acupressure

As the TCM theory of acupressure does not fit well with modern Western medicine concepts, researchers have been investigating an explanation for acupressure that has a solid scientific basis in human physiology. Determining a physiological mechanism for the effects of acupressure would help to determine for which purposes and populations acupressure might be most useful. The studies discussed in the previous chapters suggest that active acupressure can elicit physiological changes (i.e., HR, ERP) as well providing additional functional (i.e., cognitive improvement) and subjective (i.e., reduced perceived stress and anxiety) benefits above and beyond those seen with placebo acupressure. In the rigorously controlled scientific studies described in this thesis, we eliminated the effects of practitioner time and attention, the research setting and procedure (e.g., physical contact), and atmosphere, leaving the only difference between active and placebo treatments to be the points stimulated by the practitioner. Although more research is necessary to determine additional benefits and lasting effects of acupressure, the obvious question is what it is about acupressure that might elicit these benefits above and beyond placebo effects.

As discussed in Chapter 1, acupoints are thought to be physiologically distinct from non-acupoints, perhaps having lower electrical resistance (Chen and Ma, 2005; Colbert et al., 2009; Kramer et al., 2009) or increased blood flow (Hsiu et al., 2010; Hsiu et al., 2007). It has also been suggested that there may be an increased number of nerve fibers at acupoints compared to surrounding areas (Chen and Ma, 2005). As well as what might be physiologically distinct about acupoints, how stimulation of these points physiologically affects the body remains uncertain, although there are a number of theories currently under research.

A theory that has been widely suggested and fits well with the cardiovascular changes we observed during active acupressure is that stimulation of acupoints impacts the ANS, which is subdivided into the parasympathetic and sympathetic nervous systems (PNS and SNS, respectively). Specifically, it has been suggested that somatosensory stimulation via acupoint stimulation elicits a reflex response from the ANS (Uchida et al., 2010; Sato, 1997). As mentioned previously, our lab and others have consistently found acupressure to reduce heart rate (Felhendler and Lisander, 1999; Sugiura et al., 2007; Wu et al., 2007; McFadden and Hernández, 2010). Clinical studies of acupuncture, which also involves stimulation of acupoints using needles rather than finger pressure, have also found acupuncture needle stimulation to reduce heart rate (Uchida et al., 2010; Nishijo et al., 1997; Sakai et al., 2007). A common theory is that acupuncture stimulates nerves of the PNS, resulting in this cardiovascular change (Mori et al., 2002; Huang et al., 2005). Supporting this, Nishijo et al. (1997) found injection of atropine (a muscarinic acetylcholine receptor antagonist that inhibits the actions of the vagus nerve on the heart) to attenuate the heart rate reduction seen following acupuncture needle stimulation in humans. This indicates that cardiovascular changes following acupuncture are at least partially due to activation of the PNS, via vagal activation.

Vagal stimulation via acupoint stimulation not only explains acupressure-mediated heart rate reduction (via vagal stimulation of the heart), but could also explain why acupressure has seen such success as a treatment for nausea and vomiting, as vagal stimulation also exerts gastrointestinal effects (Andrews and Lawes, 1992). Given the connection between vagal modulation and nausea/vomiting, as well as the efficacy of stimulation of a particular acupoint (P6) in the reduction of nausea and vomiting, Huang et al. investigated the contribution of vagal modulation in P6 stimulation using heart rate variability (HRV). HRV is a non-invasive way to explore the contribution of PNS and SNS activation/inhibition. Standard frequency domain measures of HRV derived from ECG recordings are low-frequency power (LF power), high-frequency power (HF power), and the low-frequency/high-frequency ratio (LF/HF ratio) (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). LF power is thought to be influenced mainly by the sympathetic nervous system, with some input from the parasympathetic nervous system, while HF power is mediated by parasympathetic activity and the LF/HF ratio is a measure of balance between the two (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996; Acharya et al., 2006). In their clinical study of P6 acupuncture, Huang et al. (2005) found acupuncture to increase HF power, indicating an increase in cardiac vagal activation. This effect was not seen in a sham acupuncture group (acupuncture at a non-acupoint) or in a group receiving no treatment (Huang et al., 2005).

As well as PNS activation, it has been hypothesized that SNS activity is suppressed as a result of acupoint stimulation. Uchida et al. (2010) have suggested that acupuncture stimulates afferent nerve fibers, leading to an ANS reflex response that causes heart rate reduction, but suggest a larger role for sympathetic inhibition rather than parasympathetic activation. Their

research has suggested that the reflex center for this response is located in the brain, as spinal cord transection in anesthetized rats at the 1st cervical level abolishes acupuncture-induced heart rate reduction (Uchida et al., 2010). They also suggest that $GABA_A$ receptors play a role in this response, as blocking $GABA_A$ receptors in the brainstem with bicuculline (a $GABA_A$ receptor antagonist) reduced the acupuncture-induced heart rate reduction (Uchida et al., 2010). Uchida et al. therefore suggest that acupuncture leads to activation of GABAergic neurons in the brainstem, which leads to heart rate reduction by inhibition of sympathetic outflow to the heart (Uchida et al., 2010). However they note that since the rats were anesthetized, vagal efferent activity would likely have been suppressed as a result of the anesthesia, impeding the ability to examine the contribution of the PNS to acupuncture-induced heart rate reduction. Also suggesting SNS involvement, Nishijo et al. found injection of propranolol (a β-adrenergic receptor antagonist, which inhibits effects of the SNS) to attenuate acupuncture-mediated heart rate reduction (Nishijo et al., 1997). Since propranolol reduces SNS activity and acupuncture did not reduce heart rate any further following propranolol injection, this indicates SNS involvement may also play a role alongside PSN involvement in acupuncture stimulation.

In a clinical study, Haker et al. (2000) found that acupuncture at an acupoint thought to be innervated mainly by parasympathetic fibers increased HF power, but not LF power, suggesting an increase in PNS activity. However, following stimulation of a different acupoint thought to be innervated mainly by sympathetic fibers, they observed an increase in both HF and LF power (Haker et al., 2000). This suggests that acupoint stimulation activates the ANS differently with stimulation of distinct acupoints. Supporting this, animal studies have found somatosensory stimulation of rats to affect ANS-driven responses differentially depending on where stimulation is administered. Sato et al. have shown that somatosensory stimulation of skin

on the rat stomach can decrease gastric motility, while hindpaw stimulation can increase gastric motility (Sato et al., 1993; Sato, 1997). Tada et al. (2003) found similar results when administering acupuncture to anesthetized rats: there were point-specific effects such that stimulation of the abdominal wall led to gastric relaxation, with stimulation of the right abdominal wall causing the greatest gastric relaxation. Acupuncture needle stimulation of the chest, face, back, or extremities produced either no effects on gastric motility or caused stomach contraction (Tada et al., 2003), further suggesting point-specificity.

The theory of acupoint stimulation exerting physiological effects via the ANS fits well with the studies presented in this thesis. Based on our findings, we have hypothesized that the treatment effects seen are likely due to ANS modulation. This is most clearly explained in the stroke study, in which we saw a direct cardiovascular effect of acupressure, which works well with the theory of vagal modulation. We have also proposed that the cognitive improvements observed in the TBI study are likely due to stress reduction caused by active acupressure treatments, resulting from greater and faster induction of the relaxation response (as seen in the stroke study). Benson, who first described and named the relaxation response, suggested that techniques used to elicit the relaxation response (e.g., meditation) stimulate the hypothalamus, leading to a decrease in SNS activity and a reduction in the stress response (Benson, 1975). Others have also postulated that the ANS modulation induced by acupuncture may have an impact on the hypothalamic-pituitary-adrenal (HPA) axis, via projections to the paraventricular nucleus (PVN) of the hypothalamus (Cho et al., 2006). This also fits well with the theory of acupressure-induced vagal modulation, as vagal efferents have an inhibitory influence on the HPA axis (Porges, 2010). This autonomic modulation could be the mechanism behind the relaxation response, and as such, behind the effects seen following acupressure.

Remaining questions and future directions of acupressure research

As well as suggesting potential candidates for conditions well-suited for acupressure treatment, the studies in this thesis also raise many important questions about acupressure treatment and directions for future research.

Additional populations

Since treatment effects above and beyond those seen with placebo treatment were only found in populations with neurological insult (stroke and TBI), the question remains if acupressure will prove to be beneficial in healthy populations. Studies have found acupressure to be useful for the prevention of nausea in healthy adults (Streitberger et al., 2006), but it would be useful to see if acupressure can convey additional benefits in a healthy population. For example, studies can address whether acupressure provides any cardiovascular benefits in populations not afflicted with cardiovascular disease, to see if there are protective cardiovascular benefits of acupressure.

Additionally, since positive cognitive benefits of acupressure were found in a population with TBI, a next step could be to investigate potential benefits in those with post-traumatic stress disorder (PTSD), especially if the effects of acupressure are mediated via stress reduction. PTSD is currently frequently seen comorbidly with TBI in veterans returning from Operations Iraqi Freedom (OIF) and Enduring Freedom (OEF) (Lew et al., 2008; Pietrzak et al., 2009), so a treatment that could target symptoms of both would be particularly helpful. Although no studies of acupressure following PTSD were found, there have been some investigations of the efficacy of acupuncture as a treatment for PTSD symptoms. Hollifield et al. found acupuncture to reduce symptoms of PTSD (as measured with the Posttraumatic Symptom Scale-Self Report (PSS-SR)), as well as depression and anxiety comparably to reductions seen with cognitive-behavioral

therapy (CBT) (Hollifield et al., 2007). Anecdotally, Pease et al. also found acupuncture to reduce PTSD symptoms (e.g., reduction in frequency of nightmares, reduction of anxiety) in 14 of 16 refugees treated (Pease et al., 2009). Given these initial promising findings in acupuncture, combined with our findings in TBI and the possible reduction of the stress response, acupressure may prove to be a useful adjunct treatment for PTSD, with or without comorbid TBI.

Given the evidence that acupressure may have an effect on vagal modulation, it could also be worthwhile to investigate the effects of acupressure in conditions for which vagus nerve stimulation (VNS) devices are currently used. Vagal stimulation has shown success for treatment of depression and epilepsy (Groves and Brown, 2005), so it would be interesting to see if acupressure would be a useful adjunct treatment in these conditions. Both the stroke study and the TBI study included a measure of depression (the CES-D). No change in CES-D score was found in the stroke study, likely due to participants indicating very low levels of depression at baseline. As such, it is likely that any effects that acupressure may have on depression would not have been observable due to these floor effects. In the TBI study, CES-D scores were similarly low at baseline, but showed significant improvement from pre- to post-treatment in the active group and marginal improvement in the placebo group, but with no group difference (active vs. placebo) in the amount of change in scores. This suggests that both treatments had an impact on depression scores, but more so in the active group. Previous studies have also suggested that acupressure can reduce depression indices, but the studies did not use appropriate controls (Cho and Tsay, 2004; Wu et al., 2007), so further controlled studies could examine the efficacy of acupressure as a treatment for depression. Studies specifically on a population with depression could examine the impact of acupressure while avoiding floor effects, and can use measures more sensitive to depression than the CES-D, which is a simple measure intended for research

use, not clinical diagnosis. Another measure that would be appropriate for assessment of depression in populations with neurological insult would be the Neurobehavioral Functioning Inventory (NFI) Depression Scale, which has been shown to reliably identify post-TBI depression (Seel and Kreutzer, 2003).

Also, there is some clinical evidence to suggest that increased stress levels can lead to an increase of seizures in those with epilepsy (Joels, 2009), and that depression might be a mediating factor in the effects of stress on epilepsy (Thapar et al., 2009). As such, acupressure could be a good candidate for an adjunct treatment for depression and epilepsy, given the possible vagal modulation and stress reduction. While there are no English-language investigations of acupressure as a treatment for epilepsy that we know of, there have been studies involving acupuncture. While Kloster et al. (1999) found seizure frequency to be reduced following a clinical trial of acupuncture, this reduction was not greater than that seen in control groups, so additional studies could determine if this effect is due to more than a placebo effect.

Studies have also suggested vagal stimulation may enhance cognitive performance. Clark et al. (1999) found epilepsy patients to show enhanced verbal recognition memory when vagal stimulation was administered after reading a paragraph, compared to a group that received sham stimulation. Additionally, Sackeim et al. (2001) found cognitive improvements (motor speed, language fluency, and executive function measures) following VNS given to a group of patients to treat depression. However, they acknowledged that these changes could be due to practice effects and/or relief of depression itself, so further research is needed. These studies further implicate vagal involvement following acupressure stimulation, given that cognitive improvements were seen in the TBI study, and suggest that acupressure might be an appropriate treatment for cognitive impairment in other populations, such as those with Alzheimer's disease.

Indeed, there is some evidence that VNS might improve cognitive performance in Alzheimer's patients. In a pilot study, Sjögren et al. (2002) found 7 of 10 Alzheimer's patients to show a positive cognitive response (via improvement or absence of impairment on the Alzheimer's Disease Assessment Scale-cognitive subscale) following three months of VNS. As such, if acupressure leads to vagal stimulation, it could be a promising adjunct treatment for symptoms of Alzheimer's disease.

Dosing and control groups

The findings in the stress study did not differentiate the effects of active acupressure from those of placebo acupressure or a relaxation CD control. However, this could have been due to the confounds of habituation and practice, or that a single treatment was not sufficient to elicit a treatment effect. This was surprising, given that other studies in healthy populations have observed treatment effects following a single acupressure administration (Felhendler and Lisander, 1999; Sugiura et al., 2007). However, both the stroke study and the TBI study found acupressure to elicit effects above and beyond those seen in placebo acupressure with a series of 8 treatments, with data from the stroke study suggesting that at least four treatments were necessary to start seeing effects. As such, a trial of acupressure for stress reduction may show a differential treatment effect for active acupressure compared to controls if a series of multiple treatments is used rather than a single treatment.

Addressing timing of treatment administration, treatment effects were seen in both the stroke study and the TBI study. Both studies involved administration of 8 treatments, but the treatment schedule was more condensed for the TBI study (2 treatments per week for 4 weeks) than for the stroke study (1 treatment per week for 8 weeks). It appears that condensing the treatment schedule did not adversely affect study design; indeed, the more concentrated "dose"

of treatments in the TBI study may have been beneficial, as improved functional outcome (cognitive performance) was associated with acupressure treatments compared to placebo treatments in the TBI study. While faster and increased heart rate reduction was seen during active acupressure treatments in the stroke study, no functional benefits (e.g., motor function or speech improvement) were observed. This could be due to a number of reasons (e.g., the measurements taken did not capture functional improvement), but it could be that giving a more condensed schedule of acupressure treatments (i.e., more than one per week) could elicit acupressure-associated functional benefits in a population of stroke survivors. Future studies can further investigate if multiple administrations of acupressure within a shorter time period elicit distinct effects from a treatment series that is more spread out (e.g., compare a group receiving once weekly treatments to a group receiving multiple treatments in a week). Along with continuing to investigate optimal dosing of acupressure, future studies can explore enduring benefits of treatment. The studies discussed in this thesis all evaluated acute effects of acupressure (within 48 hours of treatment), which is a necessary first step in the research. Subsequent studies can explore whether these effects have a lasting effect and if so, for how long.

Additionally, future studies can employ additional control groups. The placebo acupressure condition controls for atmosphere (i.e., dim lighting, massage table), researcher presence, time, touch, and practitioner attention, so that essentially the only difference between placebo and active procedures is the stimulation of non-acupoints vs. acupoints. The relaxation CD condition employed in the stress study aimed to determine not only if stimulation of acupoints was more effective than stimulation of non-acupoints, but also whether active acupressure (or placebo acupressure) was more effective than simply lying down and relaxing

for the same length of time. Unfortunately, the stress study did not find any differences among the three groups with a single administration of the intervention, making it difficult to determine if improvements following intervention were actually due to intervention-induced relaxation or were simply the result of a confound of habituation and practice effects. Also, participants responded positively to the relaxation CD intervention, which was shown both anecdotally (e.g., many participants expressed afterwards that it was relaxing and one participant asked if the CD could be purchased for repeated use) and by participants rating the relaxation as more credible than both the active and placebo acupressure treatments (see Chapter 3). As such, it may have been a more "active" control condition than would be optimal. Future studies could use a more inert control in addition to the relaxation and placebo conditions, in an attempt to tease apart placebo effects inherent in even an "active" treatment. One possibility could be a "waiting" control, in which participants experience the stressor, and are then asked to wait in another room for a comparable amount of time as the interventions. This could help to determine how much of the observed stress reduction and improvement in task performance is due simply to habituation and practice to investigate if there were additional benefits of the interventions above and beyond those factors.

Single vs. double-blind research design

Another potential limitation of the study design used in the experiments discussed here is that it only allows for single-blind intervention administration. Although participants and researchers were blind to condition assignment, it was necessary for the practitioner to be aware of the condition, as she administered both active and placebo acupressure treatments. All possible steps were taken to ensure that the practitioner administered treatments in as similar a manner as possible, including having the practitioner only use scripted dialogue when interacting

with participants and having her interact with them as little as possible while still making them feel comfortable. Additionally, research assistants monitored all practitioner/participant interactions. However, it is impossible to be completely sure that there were no subconscious differences in attitudes or subtle behaviors on the part of the practitioner, given that she would be aware of administering an active or placebo treatment. A way to solve this problem would be to train a naïve practitioner in both the active and placebo acupressure treatments, without being aware of which treatment was which, then assign a treatment type (A or B) for each participant. This would require training persons naïve to acupressure to ensure that they would be unaware of which treatment they were administering. The advantage of using an experienced acupressure practitioner, as was done in the current studies, is that there is no doubt that she knows to administer the correct amount of pressure and at the correct acupoints, according to Jin Shin (acupressure) teaching. Additionally, the design for the studies in this thesis called for individualized treatment. Due to the lack of quality scientific research in the field, it seemed premature to determine one or two potentially useful acupoints and use only those, as other studies have done (Bazarganipour et al., 2010; Dullenkopf et al., 2004; Sugiura et al., 2007). Alternately, the current studies were designed to more accurately reflect acupressure as would be received in actual practice, with the practitioner using "pulse diagnosis" to determine the points for stimulation during the session, as is done in acupressure treatment (see Chapter 1 for description). The practitioner administering acupressure in the studies presented here was extensively trained in Jin Shin acupressure and had over 20 years of experience administering acupressure, allowing for accurate use of pulse diagnosis, something that would be very difficult to teach to novice practitioners. A way to conduct a fully blinded experiment would be to train a novice practitioner as described above, but have an experienced acupressure practitioner perform

pulse diagnosis. The experienced practitioner could read the pulses, then inform the novice practitioner of which set of points to stimulate. This way, the novice practitioner would know only that they were administering treatment "A" or "B" without knowing which was active or placebo, and the experienced practitioner would leave the room during point stimulation so she would remain blinded to the type of acupressure administered. In another approach, with additional experiments, it may be possible to determine which acupoints could be most beneficial for certain purposes (e.g., nausea, headache, stress-reduction). At this point, a systematic set of points to use in a study could be decided upon and novice practitioners could be trained to administer pressure at those points rather than using pulse diagnosis, also allowing for double-blind administration of placebo and active acupressure treatments.

Self-care

Another interesting direction to take this research in would be to expand upon the potential benefits of self-care. One of the most appealing aspects of acupressure (particularly Jin Shin acupressure) is that it can be taught to the novice user, given that it only involves 26 acupoints. Anecdotally, our laboratory has found that teaching acupressure to individuals for self-care can lead to successful home implementation. Two pilot studies have explored the feasibility of teaching self-care to a group of participants for self-administration, in stroke survivors and individuals with mild TBI. These studies involved an 8-class course taught by the same practitioner who administered acupressure treatments in our experiments. Participants attended an hour-long class either once or twice weekly, and kept diaries of their acupressure use in between class attendance. Over the course of the classes, they were taught the locations of the 26 Jin Shin acupressure points, as well as how to "hold" the points and for what purposes Jin Shin teachings recommend each point be used (e.g., headache, anxiety, etc.). These feasibility

studies found participants to anecdotally enjoy the classes and enjoy practicing the points at home, and found self-reported use of Jin Shin to be consistent throughout the 8-class course. Additionally, no adverse effects of self-care were encountered, showing that it was well-tolerated and safe.

However, as the focus was to determine how successful teaching a self-care course would be, there were no controls employed, so the next step would be to run a more controlled study to determine the potential benefits of acupressure self-care. For example, a possible control could be to have a group of stroke survivors meet once or twice weekly to discuss stroke-related issues (e.g., coping strategies learned post-stroke, such as new ways to tackle a task following hemiplegia). Since many in the classes seemed to enjoy and benefit from the camaraderie of being in a group facing similar challenges, this would control for the social benefits of being in the class itself. Measures obtained during the pilot studies found that quality of life significantly improved following the class (unpublished data, available upon request). Including a condition to control for the social aspect of the class would allow us to determine if such benefits were from positive social interaction or from regular practice of acupressure. Alternately (or additionally), two separate self-care classes could be taught, with one class learning the real acupoints and the other class learning placebo points (non-acupoints). This would control for all aspects of the class other than the actual points stimulated and is a design that has previously shown some success. Maa et al. (2007) incorporated a self-care group learning sham points as a control group in a study with those learning real acupoints in an investigation of the effects of acupressure on bronchiectasis, finding symptoms (sputum self-assessment, health-related quality of life) in both self-care groups to improve following eight weeks of self-administered acupressure more than a group with no acupressure self-care.

Self-care is an important component of Jin Shin acupressure, as it makes the treatment portable and affordable, allowing patients to self-administer a treatment without insurance, funds, or a practitioner. Additionally, a common reason for seeking CAM is to gain a sense of control over one's own health, and self-care enables patients to feel a sense of independence in their healthcare plan. This could be of particular benefit to such patients as stroke survivors or those with TBI, who may have lost elements of independence in their lives (e.g., driving, living alone, taking care of personal finances).

Future directions of CAM research

The studies presented in this thesis are examples of the direction that CAM research could continue. Rigorous scientific research remains critical, employing high scientific standards such as randomization, appropriate control conditions and blinding practices as well as examination of the contribution of such variables as attitudes towards CAM. This is especially important given that CAM can be particularly susceptible to placebo effects (see Chapter 1). As more patients turn to CAM (Barnes et al., 2009), the need for meticulous scientific investigation of CAM modalities increases. There are many important questions to be answered. First, it would be useful to discover which CAM modalities are appropriate for certain conditions and populations. In addition to discovering which treatments are helpful, it is also imperative to explore potential harmful effects of CAM, and under which conditions. For example, administration of a type of Ayurvedic remedy along with phenytoin can lead to a reduction in phenytoin-mediated seizure control, and a coagulation abnormality was observed after combining Chinese herbal drugs with warfarin (Ernst, 1998). Additionally, there are risks of infection or nerve damage involved in acupuncture needling and possible risks of injury or paralysis from chiropractic treatment (Pham and Primack, 2003). Rigorously conducted

scientific research could help both doctors and patients make informed treatment choices regarding CAM therapies to minimize these risks (Spencer, 2003). Also, having more in-depth knowledge of CAM modalities is a necessary first step in establishing appropriate practitioner training requirements, to ensure that patients will receive safe and quality care from CAM practitioners.

Some say that standardizing CAM in such a way that it can be scientifically researched takes away many of the appealing (and perhaps effective) aspects of the treatment, such as the atmosphere (e.g., calming music, waterfalls, dim lighting) and optimism of the practitioner. If these non-specific aspects of treatment are removed, with the basic elements of the treatment left (e.g., stimulation of acupoints without the usual atmosphere and practitioner interaction) and no treatment effects are seen, this suggests that any efficacy of the treatment is merely due to placebo effects. Some wonder if this might not be enough, though; if a treatment produces positive results, some question if the patient benefits from the knowledge that these are simply placebo effects (Jonas et al., 2002). From a scientific viewpoint, it is not enough to simply have anecdotal evidence of efficacy, but treatment efficacy above and beyond placebo effects should be determined and, optimally, a physiological mechanism for observed treatment effects should be established. However, even if treatment efficacy is only due to placebo effects, this information is still useful, even if it suggests there is no additional benefit from the treatment. If the particular aspects of treatment driving these placebo effects can be determined, this could be used to enhance the effectiveness of proven treatments. For example, if it is found that a certain CAM modality only provides a benefit due to the practitioner-patient relationship, this evidence could be used to enhance conventional medical therapies, perhaps by training medical students to spend more time with patients. Measures such as the CACMAS can also be incorporated into

healthcare, to help determine what type of CAM might be most appropriate for a patient (e.g., therapies with a stronger mind/body element to it, such as meditation vs. therapies that feel closer to conventional medicine, such as chiropractic intervention). Eliciting a placebo effect is not necessarily a negative thing, given that the therapy itself is actually effective; purposely inducing a favorable environment for placebo effects could simply give proven therapies a "boost".

Conclusions

In conclusion, the studies presented in the previous chapters have found acupressure to show promise as an adjunct treatment for stroke survivors and following TBI. These effects may be due to active acupressure inducing a relaxation response to a greater extent than placebo acupressure, perhaps through ANS stimulation. We hypothesize that this short-term relaxation response induction can lead to a reduction in the stress response. Given that the stress response has been linked to disease (Esch et al., 2002), the relaxation response could help to break this stress-disease link by reducing the response to stress (Esch et al., 2003). The functional benefits of this need further investigation, but could include improved cognitive function (if cognitive function is impaired as a result of stress, as is common in TBI) and reduced subjective feelings of stress and anxiety. As well as being beneficial to those with neurological insult (e.g., stroke or TBI), acupressure could prove to be a useful treatment for healthy adults experiencing stress, be it chronic or acute. While we did not find acupressure to have an additional impact on stress reduction above and beyond control interventions, this could be due to an inadequate "dosing" or confounds of task habituation and practice. Future studies can examine the effects of a series of acupressure treatments on the stress response. Given that acupressure can be taught to novice

individuals, it warrants further study as a portable and affordable adjunct treatment method in any conditions for which stress reduction could prove beneficial.

Ernst (2009) makes the excellent point that while conventional medical treatments are held to specific and mandated standards of research prior to approval for use, many studies of CAM are sorely lacking important aspects of rigorous scientific research. Indeed, he proposes that all types of healthcare should be held to the same standards, regardless of what category they fall under, be that conventional medicine or CAM (Ernst, 2009). Our research on acupressure is a solid contribution towards reaching this goal.

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APPENDIX A:

LIST OF ACRONYMS

7D-PAR: Stanford Seven-Day Physical Activity Recall

ANCOVA: Analysis of covariance

ANOVA: Analysis of variance

ANS: Autonomic nervous system

BISQ: Brain Injury Screening Questionnaire

CACMAS: Complementary, Alternative, and Conventional Medicine Attitudes Scale

CAM: Complementary and Alternative Medicine

CES-D: Center for Epidemiologic Studies Depression Scale

CTMT: Comprehensive Trail-Making Test

ECG: Electrocardiogram

ERP: Event-related potential

GABA: γ-Aminobutyric acid

HF: High Frequency Power

HR: Heart Rate

HRV: Heart Rate Variability

HPA-axis: Hypothalamic-pituitary-adrenal axis

LF: Low Frequency Power

LF/HF: Low frequency power/high frequency power ratio

lnHF: Log-transformed high frequency power

lnLF: Log-transformed low frequency Power

lnLF/lnHF: Log-transformed low frequency power/ high frequency power ratio

lnSCR: Log-transformed skin conductance response

lnSDNN: Log-transformed standard deviation of NN intervals

LOT-R: Life Orientation Test-Revised

MHLC: Multidimensional Health Locus of Control scale

PNS: Parasympathetic nervous system

PSM-9: Nine-item Psychological Stress Measure

PSS: Perceived Stress Scale

PTSD: Post-Traumatic Stress Disorder

PVN: Paraventricular nucleus

SCR: Skin conductance response

SDNN: Standard deviation of NN intervals

SIP: Sickness Impact Profile

SNS: Sympathetic nervous system

STAI: State-Trait Anxiety Inventory

SWLS: Satisfaction with Life Scale

TBI: Traumatic brain injury

TCM: Traditional Chinese Medicine

VNS: Vagus nerve stimulation

WAIS-R: Wechsler Adult Intelligence Scale-Revised

APPENDIX B:

COMPLEMENTARY, ALTERNATIVE, AND CONVENTIONAL MEDICINE ATTITUDES SCALE (CACMAS) WITH FACTOR ANALYSIS

	Subscale Factor Loading		
Questions (answered on a scale of 1-7, with 1 = strongly disagree and 7 = strongly agree)	P	H	D
1. The health of my body, mind, and spirit are related, and whoever cares for my health should take them into account. (3)	**.435**	.010	.272
2. I have a more equal relationship with my complementary practitioner than with my doctor. (5)	**.579**	.160	.368
3. Effects of complementary therapies are usually the result of a placebo effect. (Reverse scored) (6)	**-.517**	-.003	-.010
4. I feel that complementary treatment is a more natural form of healing than orthodox medicine. (7)	**.595**	.468	-.005
5. Complementary therapies are a threat to public health. (Reverse scored) (9)	**-.716**	.036	.090
6. I feel so relaxed after complementary treatment sessions. (17)	**.575**	.122	-.013
7. I believe that complementary medicine enables me to take a more active part in maintaining my health. (18)	**.588**	.384	.046
8. Most complementary therapies stimulate the body's natural therapeutic powers. (19)	**.639**	.403	.241
9. Complementary therapies include ideas and methods from which conventional medicine could benefit. (20)	**.658**	.132	.082
10. Treatments not tested in a scientifically recognized manner should be discouraged. (Reverse scored) (21)	**-.521**	-.079	.018
11. I believe that complementary therapy will be more effective for my problem than orthodox medicine. (22)	**.538**	.213	.325
12. The explanation of my illness that I was given by my complementary practitioner made sense. (23)	**.631**	.210	-.175

13. I value the emphasis on treating the whole person. (24)	**.681**	.037	.078
14. The body is essentially self-healing and the task of a health care provider is to assist the healing process. (2)	.096	**.605**	.265
15. Physical and mental health are maintained by an underlying energy or vital force. (10)	.220	**.538**	.214
16. A patient's symptoms should be regarded as a manifestation of a general imbalance or dysfunction affecting the whole body. (12)	.249	**.482**	.095
17. Health and disease are a reflection of balance between positive life-enhancing forces and negative destructive forces. (13)	-.038	**.993**	.109
18. The last time I went to see a medical doctor, I was very satisfied with the care I received. (Reverse scored) (1)	-.144	.061	**-.748**
19. The last time I had important questions about my health care and I asked a medical doctor about them, I understood the answer. (Reverse scored) (4)	-.018	-.076	**-.357**
20. I have a lot of confidence in the medical doctor I see most often for my health care. (Reverse scored) (8)	.099	-.134	**-.807**
21. I don't trust doctors and hospitals, so I use them as little as possible. (11)	.210	.283	**.474**
22. The last time I saw a medical doctor, he or she did not understand my problem. (14)	.040	.177	**.700**
23. The last time I saw a medical doctor, he or she did not give me enough time. (25)	.030	.107	**.574**
24. I found it difficult to talk to my doctor. *(16)	.065	.076	**.523**
25. A patient's expectations, health beliefs, and values should be integrated into the health care process. ** (15)	.304	.203	-.010

P = Philosophical congruence with CAM
D = Dissatisfaction with conventional medicine
H = Holistic balance
Number in parenthesis indicates question order.
* Question not included in analyses due to low reliability
** Question not included in analyses due to low factor loading