The Use of Strong Personal Media in the Context of Chronic Disease Treatment: Music as a Mediator of Depression and Pain Experience

by

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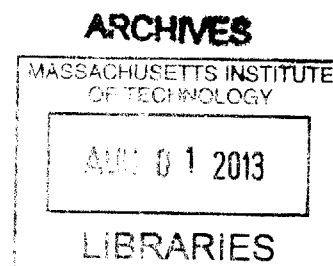Submitted to the Division of Health Sciences and Technology

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I. Introduction

It is postulated that music has been part of society for at least 50,000 years, since the time that humans lived in one location of the world before dispersing across the globe (44). Over the eras it evolved in its manifestation, from classical performances enjoyed only by the elite, to soulful songs sung in the fields, to myriad forms of expression to be used by anyone. Today, its prominence has even evolved into being used as a tool for cognitive therapy, such as for aphasia patients (41), or to heal those who no longer have the ability to move their bodies (40). Given its incredible, seemingly endless potential, it is fruitful to explore new innovations in its usage – with treatment for chronic diseases such as depression, anxiety, and other mental disorders being ideal candidates. These diseases are high in their cost on resources, both human and monetary, and have weighty long-term impacts on patients' lives as well as their families', with depression being the leading cause of disability worldwide according to the World Health Organization (43). Music is positioned as a potent remedy, as its attributes are almost the mirror negative of the effects from chronic disease: it is low cost, pleasurably pervasive, and socially connecting.

Thus, the intention behind the design of study 1 in this thesis was to create a pilot, self-driven, wellness-enhancing music treatment that could be used as the basis for a future treatment for depression. It was meant to be a relatively brief longitudinal study examining adherence and feasibility for a personal music augmented mindfulness practice in a small group of healthy subjects. From the insights gleaned during this study, it was determined that the choice of strongly emotional, personal music could be potentially powerful in another disease context. In study 2, the design contracted from a longitudinal one to an acute, nuanced observation of enhanced music analgesia during experimental heat pain with healthy subjects. The clinical tool of interest was a proven analgesia boosting conditioning paradigm, which was combined in this study with personal music. Together, the two studies provide a revealing glimpse of humankind's ability to harness the best attributes it can for self-care from a medium it itself created.

II. Study 1: Effects of a 6 week, integrated audio and mindfulness intervention on mood and rumination

Introduction

Generally, depressive relapse has been linked to mood-induced reactivation of negative cognitive patterns and maladaptive response strategies such as rumination, thought suppression, and experiential avoidance (1). Mindfulness therapies seek to address these types

of thought patterns and often incorporate physical components as well, including slow, deep breathing exercises that may help balance sympathetic and parasympathetic responses disrupted by excessive stressors (2). Through addressing mood and mental issues, mindfulness appears to be a prime method for prevention of relapse. Mindfulness Based Cognitive Therapy (MBCT) is a more formal treatment developed to combat depression by combining mindfulness with cognitive therapy strategies. Thus far, at least a small handful of randomized controlled trials have found MBCT to cut relapse rates by approximately half in patients with three or more previous episodes, with the follow up often conducted 12 months after the treatment was delivered (3, 4). MBCT may also successfully reduce symptoms in currently depressed patients including those resistant to other forms of treatment (5).

Taking another approach to reducing relapse are practitioners of music therapy, though this field has not had a strong, quantitative research base thus far. Part of this stems from the fact that the methodology is not standardized and often is tailored to specific, highly subjective interpretations of patients' symptoms. Recently, there has been a surge in medical adjunctive use of music therapy, such as during procedures (6, 7), to reduce everything from anxiety, fear, and depression to length of hospital stay, pain, and need for analgesic medications. In a comprehensive meta-analysis of the effects of music therapy added to standard care on adults with serious mental disorders, Gold et al. (8) found significant salubrious effects on global state, general symptoms, negative symptoms, depression, anxiety, and general functioning. Music therapy may play an important role that more traditional talk therapies cannot because of their purely verbal interaction style, but evidence for music therapy's specific efficacy is still in its infancy, though the clinical findings indicate that it is promising for many patient populations.

More generally, music as a therapeutic modality has a number of advantages over more traditional therapies. Pathologies like depression often manifest with different symptoms across cultures(9), making it difficult to address ethnically and demographically diverse groups with psychotherapy. Music has the power to be understood universally: even a culture that has never heard a note of Western music can understand its basic emotionality (10). It is also widely accessible through services like Pandora Radio and YouTube (both free with Internet access), or through now nearly ubiquitous mp3 players and phone music players. We know that it can have a strong effect across a variety of people, as even musically untrained (experienced only through everyday exposure) listeners can still have strong emotional responses (11). Music is also highly socially accepted, whereas psychotherapy and medication carry much stigma, leading to decreased adherence. This may be especially important in countries like the United States, with its individualistically-oriented culture (12) where work and success are often the focus more than community strength. A self-regulatory yet socially minded intervention may help increase the amount of perceived community connection and acceptance towards illness.

Perhaps most importantly, in contrast to many medications, using music is low risk and has general health benefits (13-15), is of lower cost, and is safe, with no drug interactions. It is used in both hospitals and recreationally to such an extent that it would be difficult to feel danger from it given its pervasiveness in daily life. With the availability of music players, private

vs. public ways of listening, sources of music, and customizability of music collections, this medium is ripe for further development into clinically effective treatments.

In this pilot study we combined personally chosen music with mindfulness techniques in a six week wellness intervention targeting depressive symptoms. Though both music and mindfulness still require more evidence to have greater confidence in their efficacy and specific mechanisms, the significance of this current work arises from the power of combining healing elements from the two therapies in a synergistic way such that some of the factors that may detract from efficacy for each are taken away. The idea of combining therapies is common, such as the dual delivery of antidepressants + MBCT for depression, or music therapy added to standard care. In general, the need for more integrated, holistic treatments and medical services that account for factors such as adherence, prevention, and well-being maintenance is now being recognized (16). The intervention here differs slightly from other previous therapeutic combinations in that it explores an "enhanced music" regimen with a "light mindfulness" treatment. This study specifically used personal choice of music over active music therapy so that the intervention felt like it resonated more with the subject, and was possible to carry out without a therapist actively providing the "dosage". We added in a mindfulness component in a subtler way than it is taught in more traditional mindfulness-based therapies so that the practice component was more likely to be naturally integrated into the subject's lifestyle. This was based on our conjecture that those with mental health needs may not find it easy to take on the nuance and depth of mindfulness meditation when they are already burdened by significant mental and emotional issues. We also added mindfulness because music listening on its own has not been shown to reduce depressive symptoms like rumination in many studies. On the other hand, music informs and influences identity during youth, is used by people for their moods and expression, and choice reflects individual-specific factors such as personality, age, and gender (17-19). We postulated that mindfulness techniques may be better learned, adhered to, and implemented in daily life by using a highly personal musical stimulus as part of the training. The complete design included a six session, six week training protocol with home practices, and also compared three audio types – personal music choice, music chosen from a provided classical set, and a no choice, well-being oriented audiobook control. We measured the effects of this training on various psychological factors relevant to depression in healthy subjects.

Methods

Participants

      Participants in this study were recruited from the community through flyers, the Massachusetts General Hospital Clinical Trials listings website and email broadcasts, and the MIT Behavioral Research Lab experiment management system. Each participant completed an online pre-screening questionnaire before coming to session 1. The final total enrollment was 24 subjects. Subjects were healthy, included both genders, and were 18-65 years old, with no current diagnoses of emotional disorders and a BDI-II (Beck Depression Inventory) score less than 20. The BDI-II cut off was set to preclude undiagnosed yet possibly clinically depressed individuals. Additionally, 16 of the original 24 subjects completed a follow up questionnaire 6-10 months post-intervention. All participants provided written informed consent, and ethical approval was obtained from both the MGH Institutional Review Board (protocol #2010P002894) and the MIT Committee on the Use of Human Experimental Subjects (COUHES) (protocol # 1009004034).

Study Design and Procedure

      The study was conducted between September 2010 and October 2011. This was an eight week, eight session design with one pre- and one post-assessment session, six weekly training sessions, and assigned daily 30-minute home practices with online survey logs (Fig. 1). Each subject received a randomly assigned order of three audio conditions during their six weeks of training. After providing written informed consent, subjects completed baseline surveys of the Profile of Mood States (POMS), the Perceived Stress Scale (PSS) and the Rumination Reflection Questionnaire (RRQ) (descriptions all below), previous music education, training, and habits survey, an expectancy scale, and ratings of their emotional reactions to the music sets. They were then instructed briefly in music appreciation methods.
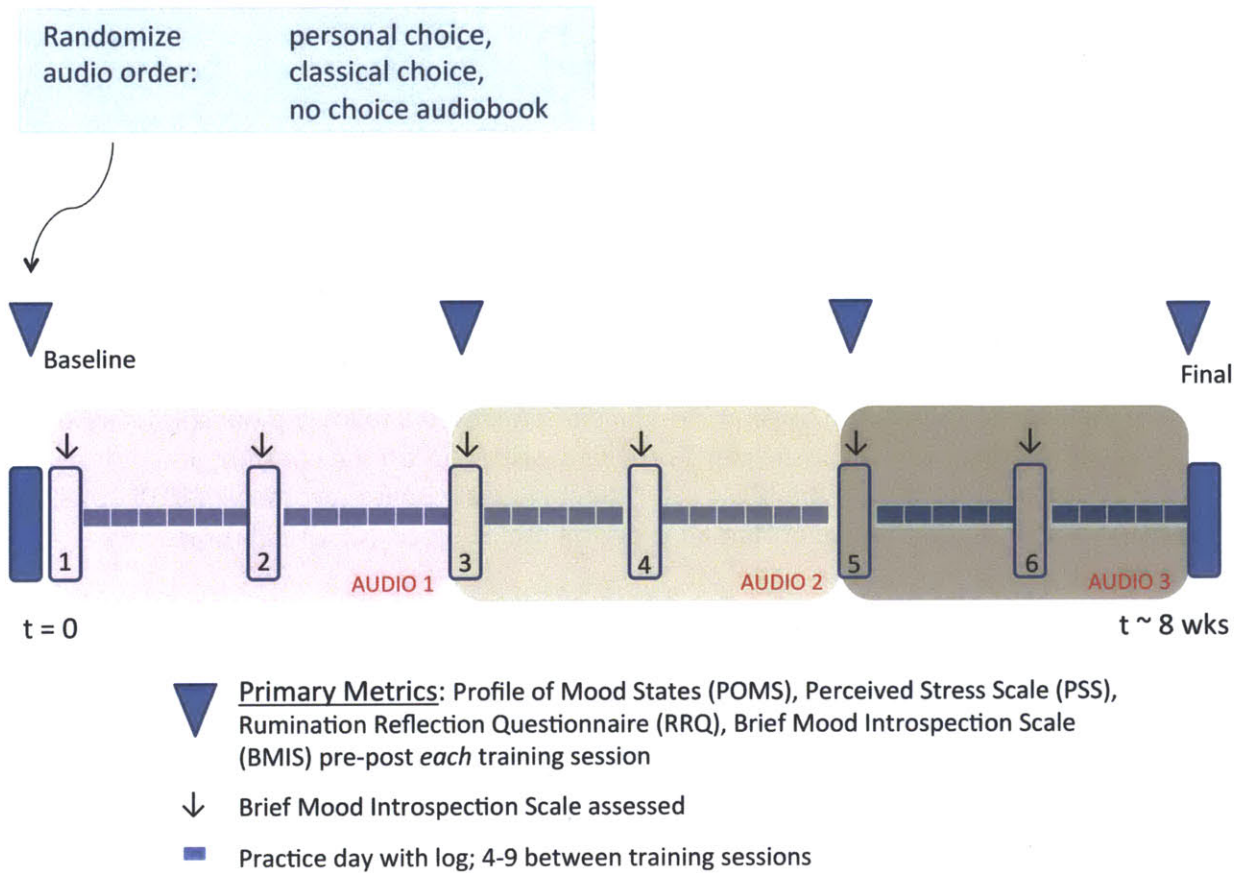
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Randomize audio order: personal choice, classical choice, no choice audiobook

Baseline

Final

1 2 AUDIO 1 3 4 AUDIO 2 5 6 AUDIO 3

t = 0

t ~ 8 wks

▼ Primary Metrics: Profile of Mood States (POMS), Perceived Stress Scale (PSS), Rumination Reflection Questionnaire (RRQ), Brief Mood Introspection Scale (BMIS) pre-post *each* training session

↓ Brief Mood Introspection Scale assessed

▪ Practice day with log; 4-9 between training sessions

Figure 1: Schematic of overall study design. Prior to beginning the training, all subjects receive a randomized audio order of the three types including full choice personal music, partial choice classical music, and no choice audiobook stories. Colored unnumbered vertical blocks at the ends of the schematic show the initial and final assessment sessions, during which no training occurred. Triangles indicate where primary outcome assessments were taken. The arrow shows assessment points for the Brief Mood Introspection Scale, which was taken both before and after each training session. Numbered unfilled vertical blocks depict the training sessions, where subjects practiced a breathing exercise, learned mindfulness principles, and carried out the audio practice jointly with the study moderator. Finally, subjects had 4-9 days between training sessions to practice and complete logs. All subjects had two weeks of audio 1, 2, and 3 each.

During the study, the primary outcome measures of the POMS, PSS, and RRQ were assessed after each two week audio block, that is, at the beginning of sessions 3 and 5 before the lesson was introduced that day. At the end of six weeks, subjects again completed the POMS, PSS, and RRQ, expectancy scale, and ratings of their emotional reactions to the music sets. They were also given a feedback survey. After 6-10 months, they were asked to complete

an e-mailed online follow up survey assessing the extent that they still used the practice methods or principles in their daily lives.

Intervention

During weekly 60 minute one-on-one sessions, subjects first completed the appropriate psychometric surveys (as outlined in the procedure section), then were taught interactively about stress and mood management from mindfulness principles. These brief lessons changed weekly and were roughly based on sequences from mindfulness based therapies (20). This was followed by a moderator-guided breath meditation for about 5 minutes and a discussion of the subject's progress with the practice and its integration into daily life. The session finished by listening to their relevant audio jointly and discussing *how* the subject was attending to the stimuli, until the hour had elapsed.

For the audio component, we varied both amount of choice and audio type between two-week blocks, including three categories: music of complete personal choice (order and track); choices from a classical set we provided (order and track); and no-choice non-musical audio tracks from the "Best of a 4th course" edition of the "Chicken Soup for the Soul" series. Each subject used one type of audio in his/her practice for a two-week block, and then repeated this for each of the other audio types, with order of presentation of the three audio options randomized between subjects.

For their personal set, subjects were asked to provide 30-35 minutes of songs that were "particularly meaningful or evoke strong/deep emotion for you, and you are willing to listen to a few times a week within two weeks", based on the theory that music's rewarding effects are thought to be related to the degree of emotional arousal evoked (21). A set of matching songs from our specific list of classical songs was chosen by the subject during the baseline session. The classical songs provided were selected for their ability to induce strong emotion according to the literature (22, 23); they were all classical because of the greater number of studies examining music and emotion within that genre (22-27).

Within a music block, subjects could choose to listen to whatever songs they liked, however many times (within the 30 minutes allotted), each time they did the home practice. For the audiobook story block, subjects had no choice in the order or tracks that they listened to from the set of 60 minutes (14 tracks) we provided. Story orders were randomized across subjects. Subjects were asked to take a three minute break between songs, during which they could either sit at rest being mindfully present, or focus on their breathing. The number of minutes of audio provided for each block was chosen by considering how many times a particular track would be heard; for music, we estimated that each song would be heard a few times a week, with each set being used for two weeks. For the stories, we doubled the amount of minutes they received to prevent excess boredom from listening to the same stories repeatedly. We chose to assign 30 minutes of practice because it was judged to be short

enough to plausibly be done daily, yet long enough to achieve some measure of well-being and/or mood change. This is in line with studies that look at practice times for mindfulness based interventions, such as by Carmody and Baer (28), who found that each mindfulness exercise was practiced for at most about 30 minutes daily, and among all practices the result was an average of about 30 minutes a day as well.

Subjects were also asked to complete daily practices and online logs at home in between sessions. The logs were forms created to capture quantitative ratings of their enjoyment, ease with, feeling of difference from regular audio listening, and worth of the daily practice. They were also a record of what audio was listened to on what days, the duration of practice, and any other observations subjects had. Thus the number of logs, minutes of practice, and their quantified as well as qualitative reactions could serve as indicators of adherence and implementation of the intervention.

Metrics

For the following metrics, refer to Figure 1 for what time points each one was assessed.

- POMS: Profile of Mood States. This scale includes 65 adjectives with a 5 point Likert scale for each and is designed to assess transient, fluctuating mood states over the *last week*. It has been validated in adult nonpsychiatric populations (29, 30).

- PSS: Perceived Stress Scale. This scale includes 10 questions of how often a stressor was felt with a 5 point Likert scale for each, and is assessed over the last *month*. It is validated in adult, nonpsychiatric populations (31).

- RRQ: Rumination Reflection Questionnaire. This consists of 24 questions, 12 assessing agreement with reflection statements, 12 on rumination statements, each also with a 5 point Likert scale. There is no specific timescale requested for answers (i.e subjects are told to answer it generally), and it is validated in adult, nonpsychiatric populations (32).

- BMIS: Brief Mood Introspection Scale. This scale includes 16 adjectives with a 7 point Likert scale for each, and assesses *present* mood. It is validated in adult, nonpsychiatric populations. The Pleasant-Unpleasant (PU) subscale is defined by adjectives such as *happy* and *content* vs. *grouchy, sad*; the Positive-Tired (PT) subscale is defined by adjectives like *excited, peppy* vs. *sleepy, tired;* and the Negative-Relaxed subscale is defined by adjectives like *fearful, jittery* vs. *relaxed, calm* (33).

- Daily log entries – These served to capture the recorded time of practice, duration, audio tracks used, and other qualitative reactions and free response comments each day subjects practiced (see Results section for specific questions asked).

Statistical Analysis

We used SPSS 18.0.0 to run ANOVA repeated measures analyses to test the main and interaction effects of time, group, and amount of practice (measured by practice minutes and number of practices logged) on the primary outcome measures. We also ran Pearson's correlation analyses in SPSS, and limited number of correlations run such that we did not find results due to chance. Significance was set at the 0.05 level.

Additional Analyses

Following recommendations from Yin (42), qualitative case study methods were also applied to examine the wealth of data contained in the logs completed by subjects throughout the course of the study. These analyses complemented the cross-sectional statistical analyses with in-depth exploration of potential explanations of the main effects as well as additional insights into differential effects from the audio types and the temporal evolution of the practice. A subset of the qualitative data is presented alongside quantitative finding of interest to further elucidate potential causal factors.

Results

The 24 subjects were healthy and ranged in age from 18-61 years old, with a mean and standard deviation of 29.5 ± 11.7 years, and included 8 males and 16 females. About 80% had obtained a 4-year educational degree or more and just over 70% of the group was Caucasian.
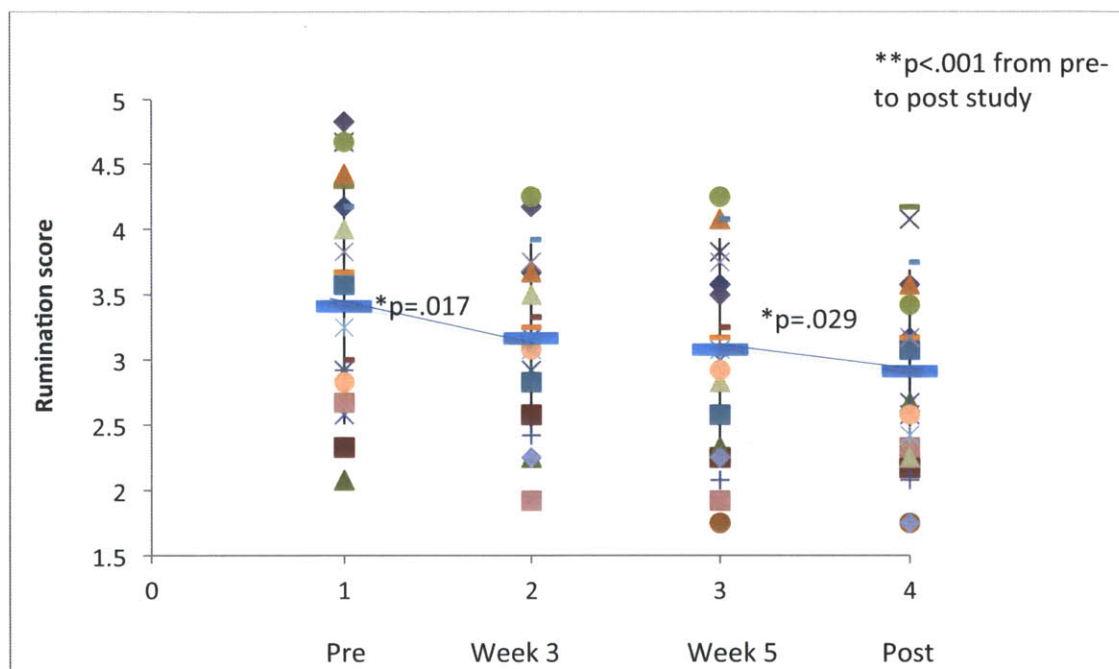
Main Effect of Intervention

Figure 2: Rumination change over study period. The variability of the subject responses (each subject indicated by a unique marker on the Y-scale at each of 4 time points) is shown with means represented as longer blue bars and standard deviations marked as vertical lines beneath individual subject symbols. The data indicate a significant group decrease in rumination over the entire treatment period, despite the high variance typical of psychological data. Due to the largely healthy population recruited for the study, a floor effect limiting magnitude of rumination decrease likely influences the result above.
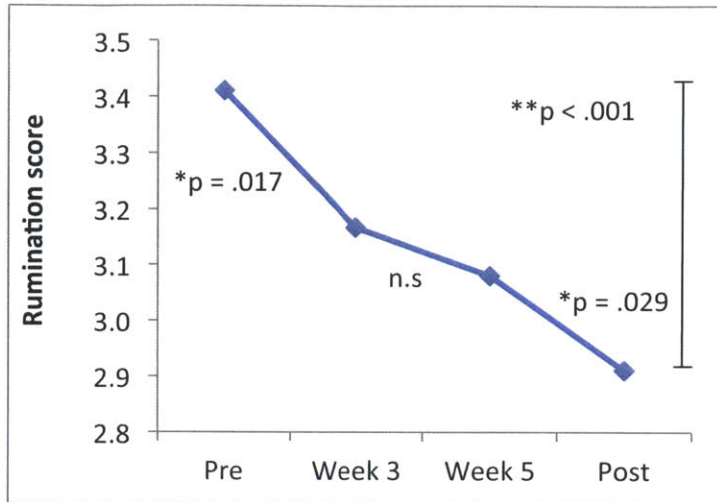
Figure 3: Average rumination change over study period. Decreases were significant from the innitial assessment to the beginning of the second block, and then from the beginning of the third block to the end.
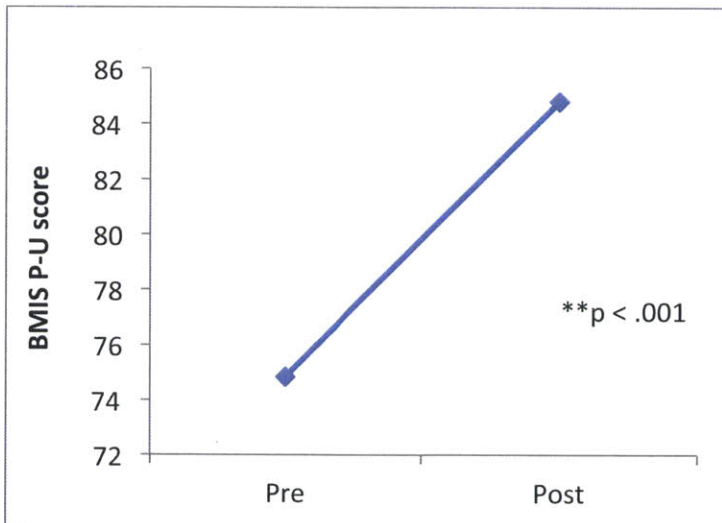

Figure 4: Average session mood change on the Brief Mood Introspection Scale (BMIS), Pleasant-Unpleasant subscale.

Figures 3-6 summarize the main significant results of the intervention. Figure 3 shows the average decrease in rumination (RRQ scale) from pre- to post-study, with N=24. Signficant decreases were seen from the initial assessment to the beginning of week 3, and from the start of week 5 to the end of the study. The main effect of time on rumination was significant with $F_{(df=3, err=54)} = 9.576$, **$p < .001$. Figures 4-6 depict the improvement in mood (BMIS Pleasant-Unpleasant subscale, Positive-Tired subscale, and Negative-Relaxed subscale) *within*

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sessions, for N=22 (two missing subjects).   The first is commonly held to be a more overall metric of mood, whereas the second and third subscales tend to reflect subtler sides of positive and negative moods (i.e. are also not as illustrative of total mood).   These main effects of time *within sessions* on mood were significant with F(df=**1**, err=**11**) = 67.532, **p < .001, F(df=**1**, err=**14**) = 48.948, **p < .001, and df=**1**, err=**14**) = 59.348, **p < .001 respectively. The Positive-Tired and Negative-Relaxed subscales also showed slightly significant improvements over the entire intervention period, with F(df=**6**, err=**96**) = 2.383, *p = .034 and F(df=**6**, err=**96**) =2.631, *p = .021. This latter set of ANOVAs was computed using the pre-session BMIS scores during the intervention. This indicates that as time went on, with successive sessions these aspects of positive and negative mood at session start improved.
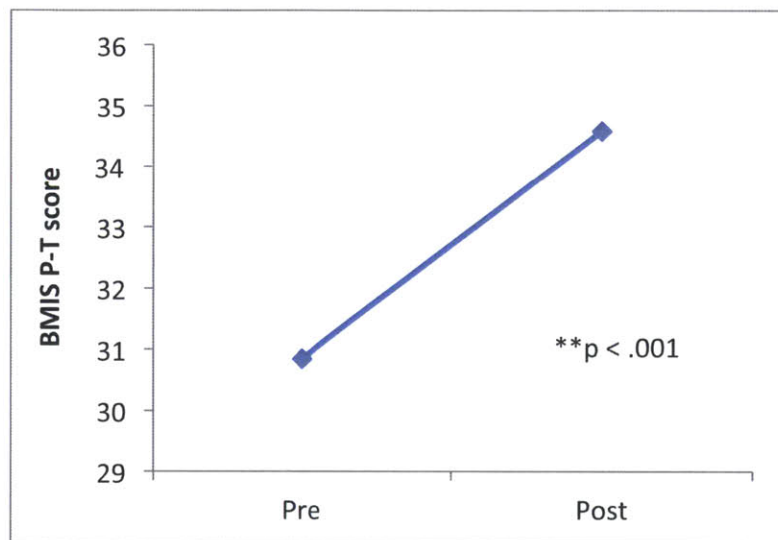

Figure 5: Average session mood change on the BMIS, Positive-Tired subscale.
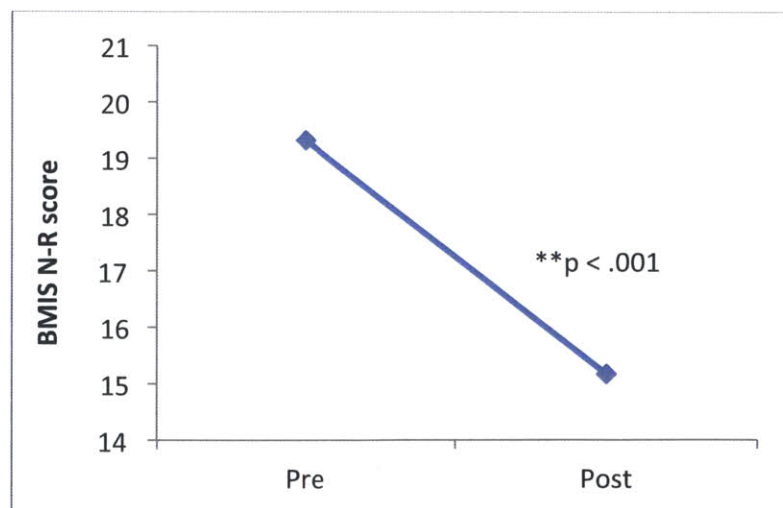

Figure 6: Average session mood change on the BMIS, Negative-Relaxed subscale.

In all analyses, there was no significant effect of order on changes – the six audio orders (e.g., personal/classical/story, classical/personal/story, etc.) were equal in their effects, as assessed by using order as a between-subjects factor in our ANOVA models.

When testing for whether these main effects interacted with different audio types listened to (group), we did not find significance: for rumination by group, $F(1.798, 36) = .181$, $p = .81$; or for mood (P-U subscale) by group, $F(1.661, 23.26) = .492$, $p = .583$ (Fig. 7-8). Thus the three audio types appeared no different in their effects on rumination and mood. We analyzed group measures by subtracting pre-post scores for each two week block for the RRQ, then comparing the three resulting sets of scores in an ANOVA between audio types. Neither did we find significance when testing for interaction with practice amount, as measured by number of logs or minutes of practice self-reported: for rumination by logged minutes, $F(19, 1) = .916$, $p =.691$; or for rumination by number of logs, $F(19, 1) = 1.526$, $p = .572$. This indicates that the change in rumination was not influenced by the amount of practice subjects reported doing. For these analyses we used number of logs and minutes of practice as between-subjects factors in our ANOVA model, as well as by summing logs and minutes within each two week block and comparing between audio types.
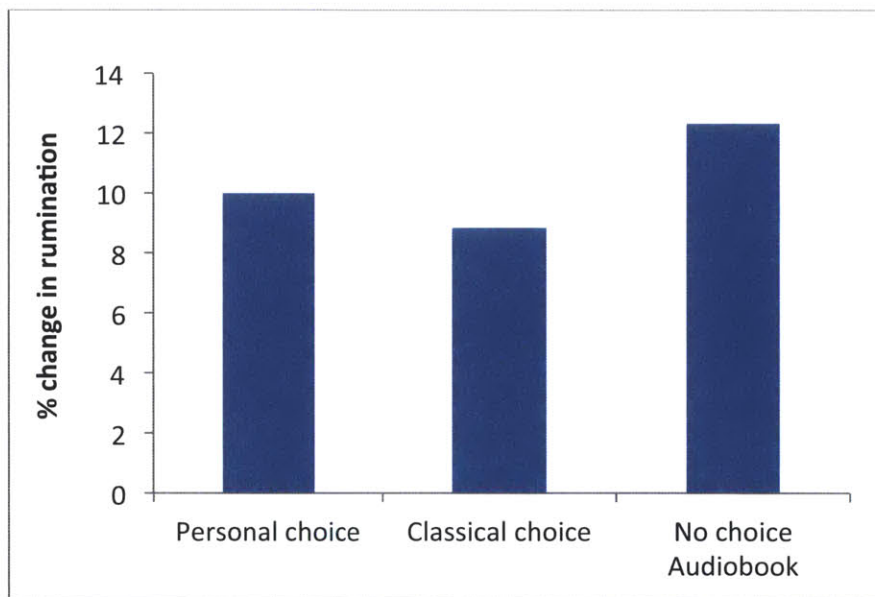

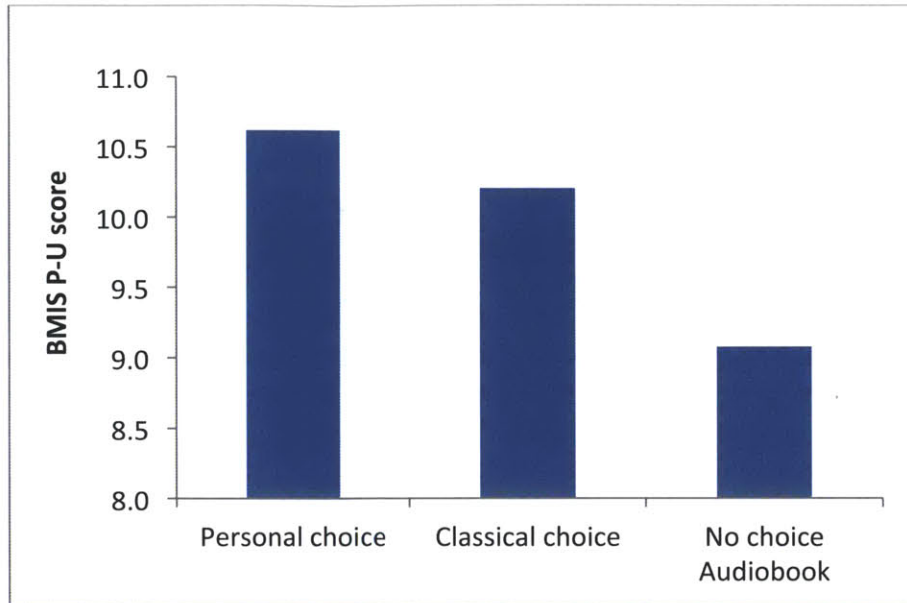Figure 7: Percent change in rumination by audio type.

Figure 8: Average session mood change, BMIS Pleasant-Unpleasant subscale, by audio type.

Figures 9-10 show the percentages of possible (assigned) practices logs and self-reported minutes completed during each two week audio type, for N=19. Again, these groups did not statistically differ in the amounts of practices completed, though as with session mood change as seen in Figure 8, there was a downward trend from personal choice to classical choice to no choice audiobook.
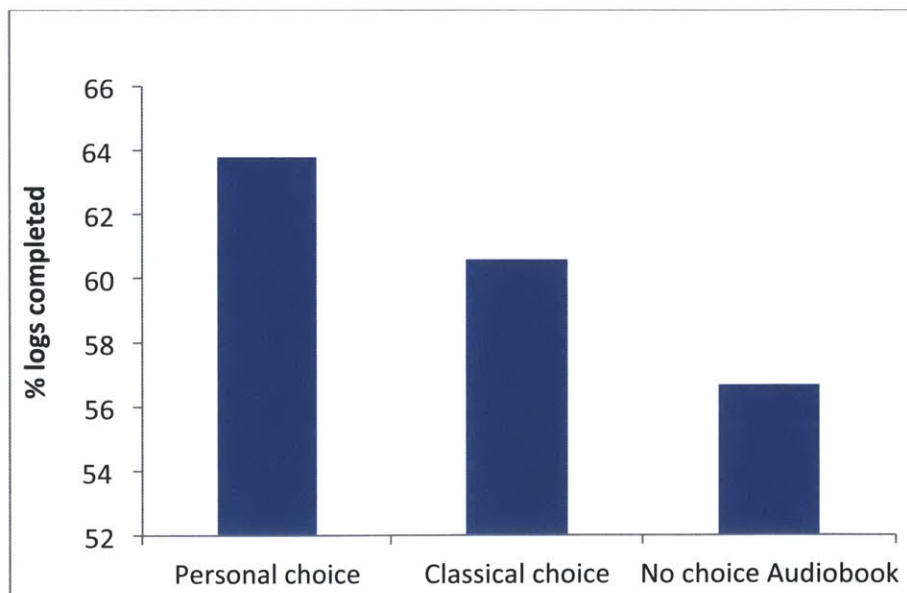

Figure 9: Percent of possible logs completed during each audio block. Percentages were calculated by dividing logs reported by actual number of days between training sessions.
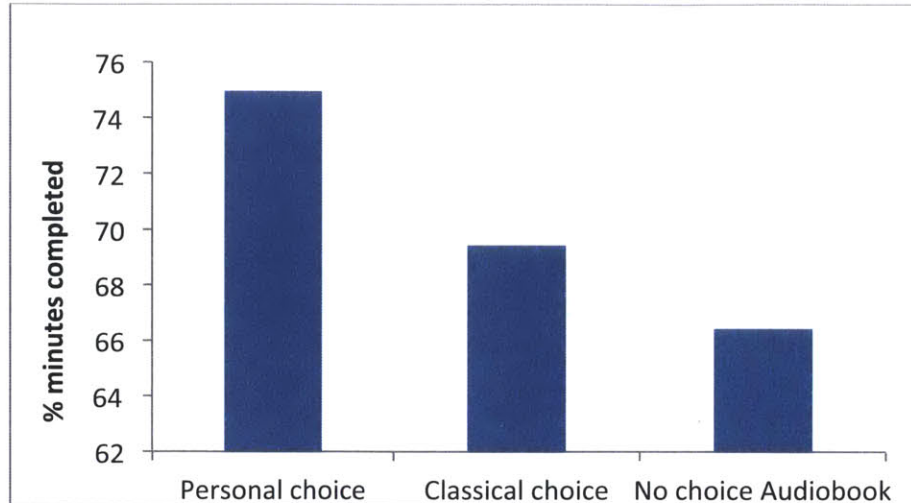
Figure 10: Percent minutes of practice completed during each audio block. Percentages were calculated from the practice durations subjects reported on completed logs.

Correlations

Baseline :	BDI	RRQ Rumination	BMIS PU (session 1 change)	PSS	POMS Total Mood
BMIS PU increase	.51, p=.021*	.45, p=.049*	n.s.	n.s.	n.s.
Rumination change	n.s.	.51, *p=.01	.452, p=.03*	n.s.	n.s.

* significance at the p < .05 level.

Table 1: Correlations between baseline psychometrics and main primary outcomes. Baseline metrics include the Beck Depression Inventory (BDI), RRQ rumination score, Brief Mood Introspection Scale Pleasant-Unpleasant (BMIS PU) post-pre score from session 1, Perceived Stress Scale (PSS), and the Profile of Mood States (POMS) Total Mood Score.

Table 1 shows the correlations between the main primary outcomes of rumination decrease and within session mood improvement (BMIS Pleasant-Unpleasant subscale) with baseline psychometric values. Other significant correlations included the BMIS Negative-Relaxed subscale with initial RRQ rumination: corr coeff = .514, *p=.021; and initial expectation scores with initial RRQ rumination: corr coeff = .61, **p=.002. Initial rumination was not correlated with initial session mood improvement (BMIS PU subscale, session 1), nor were the two scores correlated in their overall averages. Rumination change was correlated with subjects' initial rumination scores: corr coeff = .51, *p = .01, and to initial expectation: corr coeff = .39, though not quite significant at p = .056.

Additional analyses of rumination improvements by various subgroups were carried out, including male vs. female, amateur musician vs. musically naïve, and music holding extreme importance vs. not. Amateur musician was defined as those who had greater than 5 years of instrument experience, possibly formal education in music, and may have also played recreationally for greater than 3 years (n=9). Musically naïve included all other subjects (n=15). Music importance to subjects was divided between those who endorsed "extremely important" (n=8), vs. all other lesser categories (n=16). Rumination decrease for males vs. females was .39 ± .38 vs. .56 ± .64; for amateur musician vs. naïve the decrease was .79 ± .52 vs. .33 ± .54; and for extreme music importance vs. not the decrease was .88 ± .55 vs. .31 ± .48.

No other primary outcomes (POMS, PSS) showed significant changes over the course of the intervention or between audio types.
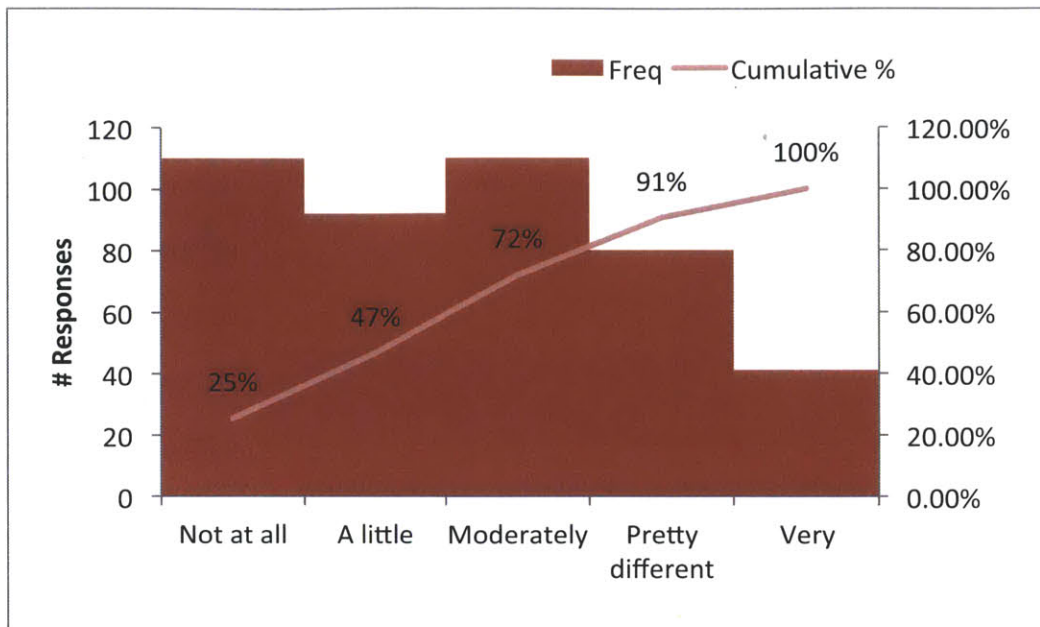
Figure 11: Histogram of all subject responses to daily log question "Was your experience of the audio made different by trying to shift away from 'doing' thoughts when they came up?"

In figure 11 is a histogram of the overall differences in subject experience with the audio, with a cumulative percentage line marking the relative proportions of answers. Below is an overlapped histogram marking the time course of this distribution change between blocks.
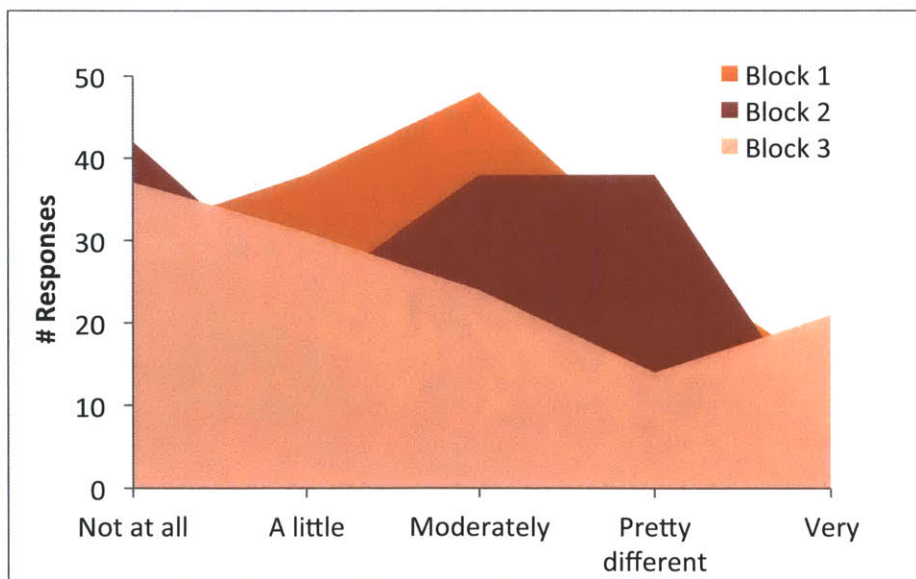

Figure 12: Time course of all subject responses to daily log question "Was your experience of the audio made different by trying to shift away from 'doing' thoughts when they came up?"
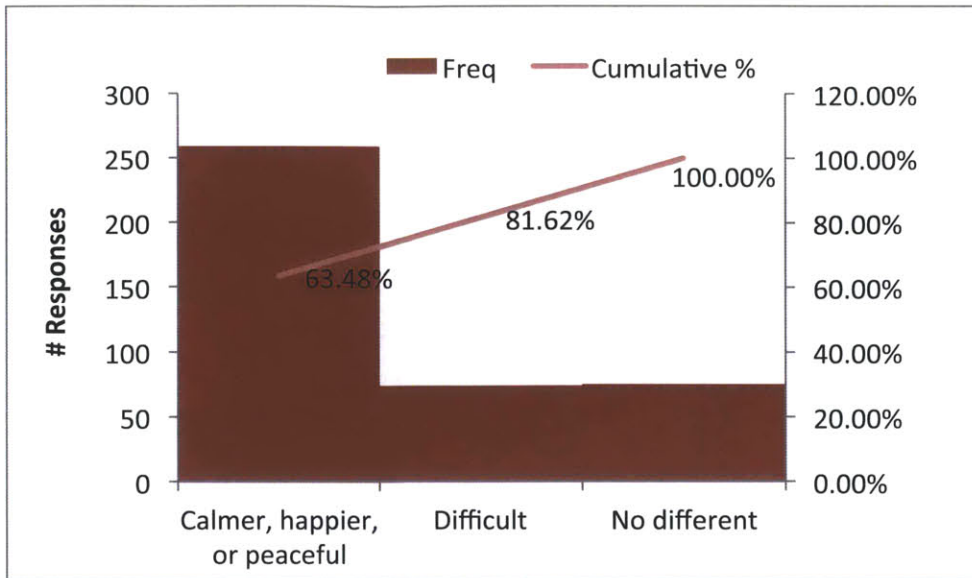
Figure 13: Histogram of all subject responses to daily log question "How did it feel to listen 'actively' to each choice?"

Figure 13 shows subjects' responses to a query about their evaluation of the practice, restricted to three categories. The relative distributions did not change from the average distribution over the study course – subjects most frequently felt the active mindful listening was a calm and peaceful experience.
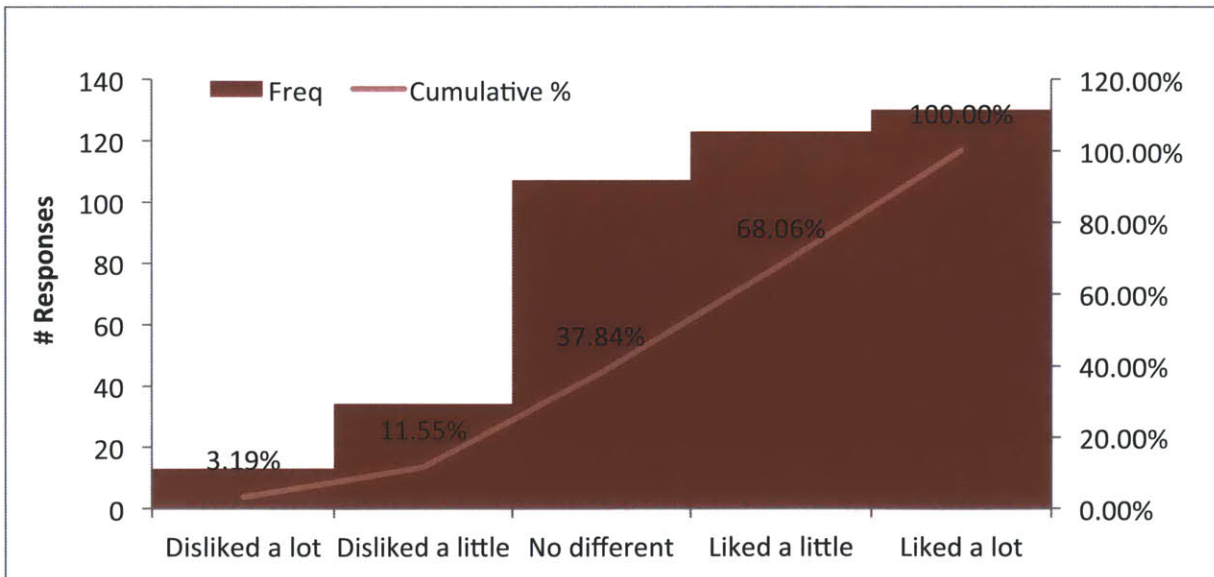

Figure 14: Histogram of all subject responses to daily log question "How did you feel about sitting and only listening to the audio rather than using it as a background to another activity?"

Figure 14 shows the overall subject evaluation of mindful listening as compared to using audio as a background to other activities. A high proportion (>50%) consistently marked that they either liked this method a little or a lot. Following are the distributions over time:
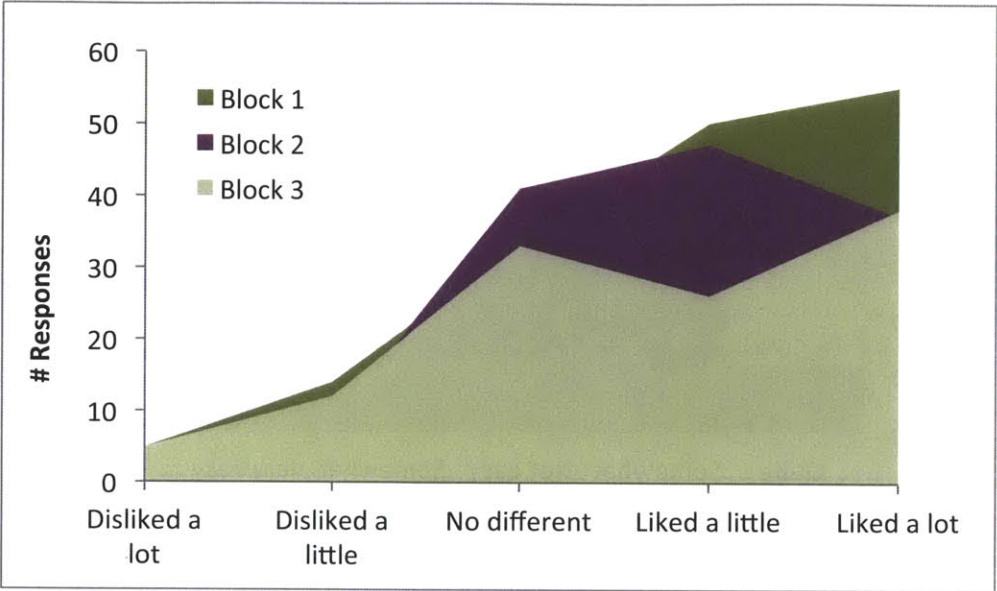

Figure 15: Time course of all subject responses to the daily log question "How did you feel about sitting and only listening to the audio rather than using it as a background to another activity?"

Subjects' responses remained fairly consistent over the study course, with a good proportion enjoying solely listening to the music as a daily practice.
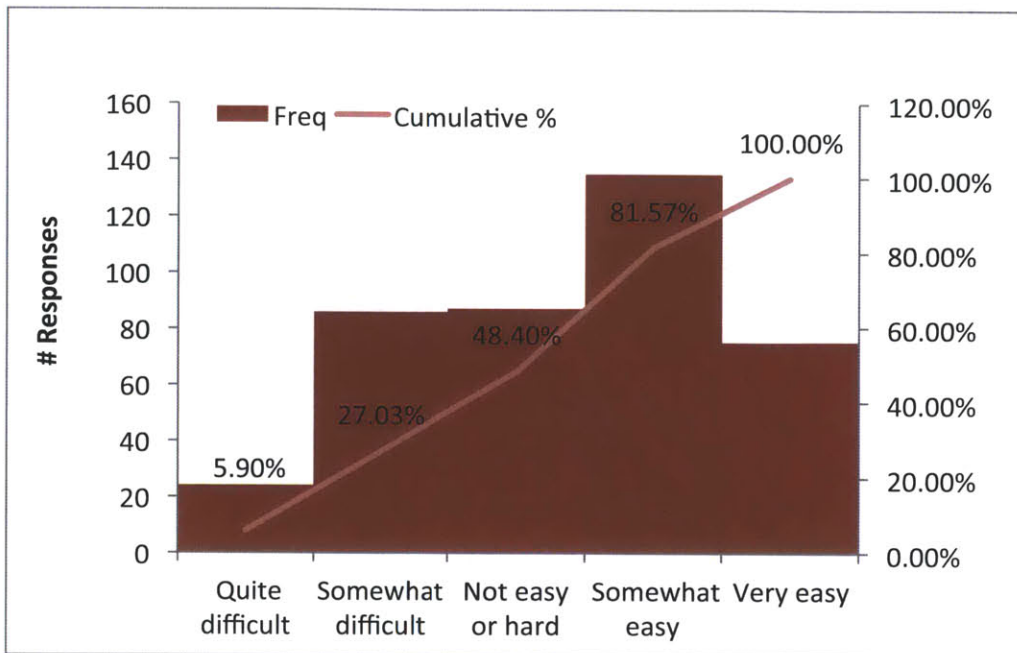
Figure 16: Histogram of all subject responses to daily log question "Today, how easy did you feel this practice was for you?"
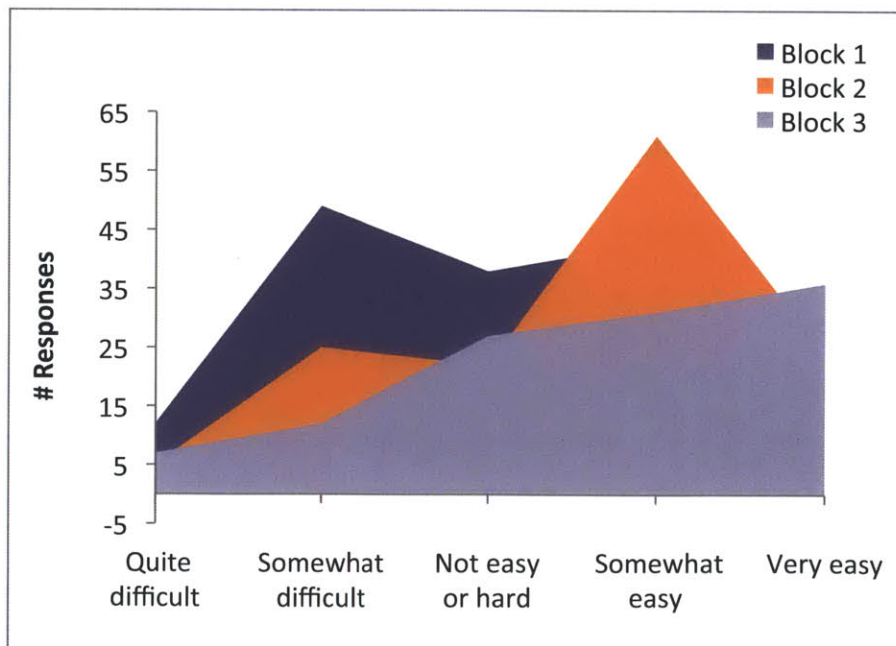

Figure 17: Time course of all subject responses to the daily log question "Today, how easy did you feel this practice was for you?"

Notably, here we do see a shift in distribution towards the practice becoming easier over time.

Finally, below is the overall subject evaluation of whether they felt the practice was worth doing, with total responses over the course of the study.
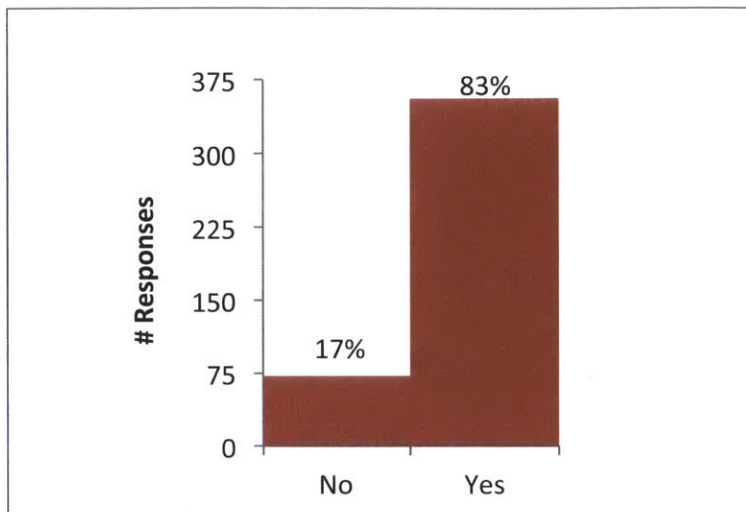

Figure 18: Histogram of all subject responses to daily log question "Today, do you feel this practice is worth doing?"

This did not shift much over the course of the study, as with the trend of the practice being consistently calming or peaceful.

In general, participants were excited about starting, and went to surprising lengths to keep practicing (e.g., on vacation, while sick) though they were not receiving compensation, suggesting that they were motivated and engaged with the task. The logs in particular allowed us to gain a more nuanced understanding of an individual's response to maintaining well being using this method. There was also evidence of how the three audio types differed in their effects on experience of the practice, though these differences were not reflected in the metrics and analyses described already.
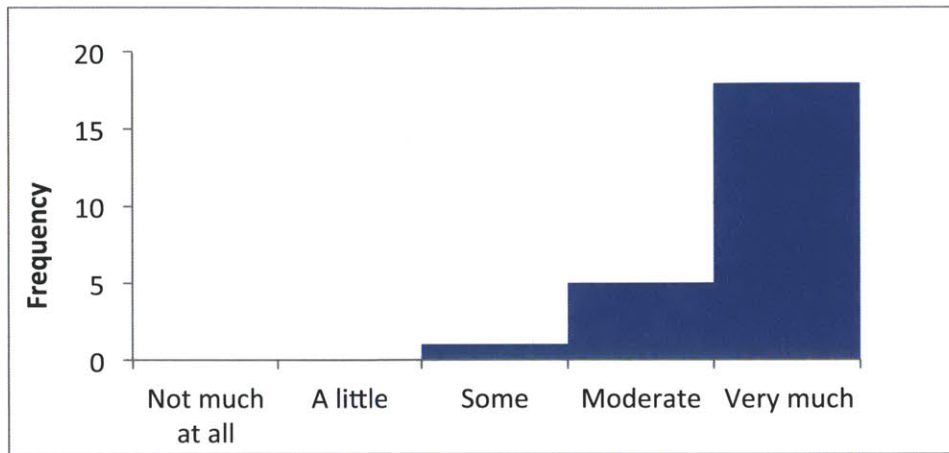
Figure 19: Histogram of survey question "How much rapport did you feel you had with the session moderator?"

At the end of the study, a high proportion of subjects marked that they felt they had very much rapport with the moderator who gave the sessions (the study author).
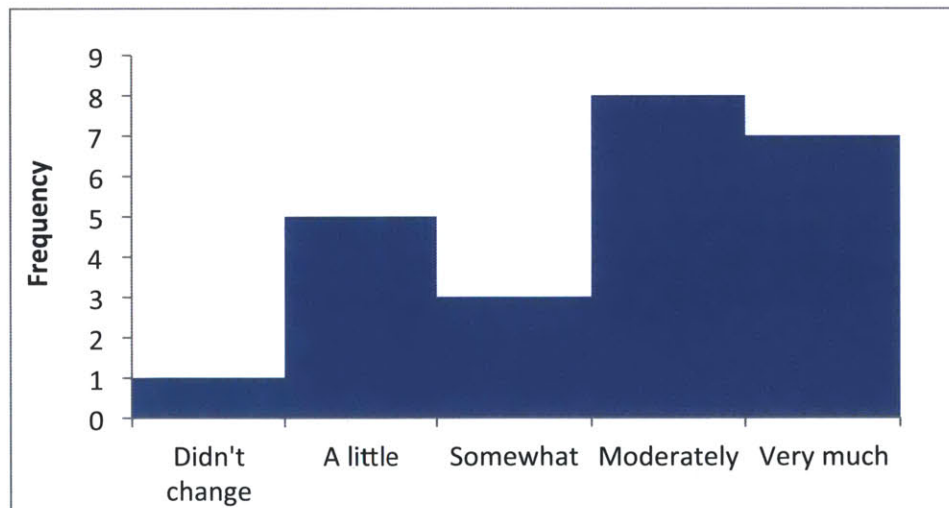
Figure 20: Histogram of question "How much did this training change your ability to deal with (accept or respond to) your reactions and patterns of thinking?"

Greater than 50% of the subjects felt that their reactivity and ability to handle it had been changed moderately or very much by the end of the study.

Figure 21: Subject answers to questions "Was this practice useful in your life?" and "Would you tell friends to try this method of listening?"

Overall, almost all subjects found the practice to be useful and were willing to recommend it to friends as well.

Figure 22: Histogram of question "How much do you expect the active listening training will help you reduce your stress and improve your mood from now on?"

Expectations of the training's effects for the future were very positive.

Figure 23: Final survey expectation to continue using practice aspects.

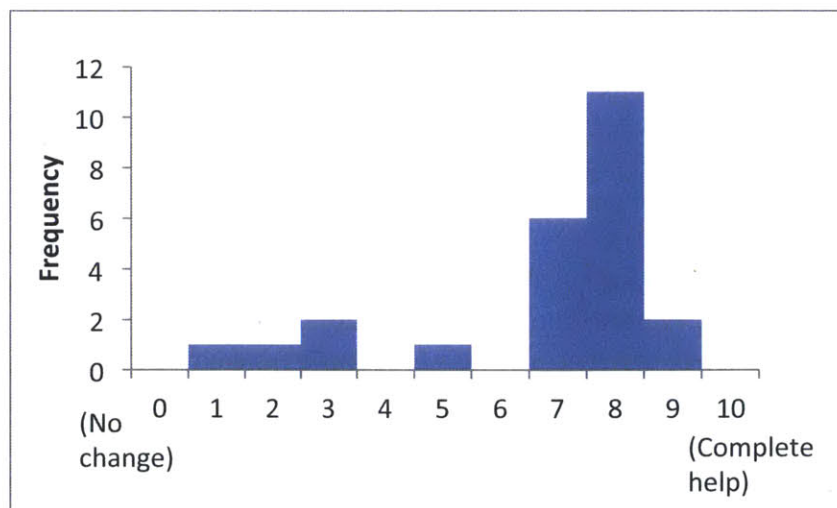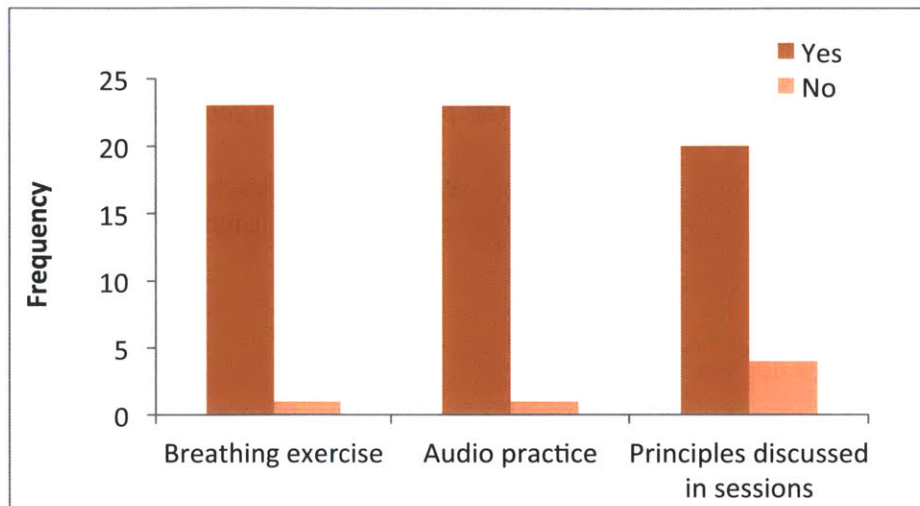When asked if they expected to continue using various practice components, most subjects endorsed high likelihoods of continuing, with slightly less answering positively for the mindfulness principles discussed. This slightly higher negative rate reflected the response of a couple of subjects who quite obviously had much cognitive conflict with the intent of the training to shift their patterns of thought – they felt that their original style of thinking was more useful to them than the new method taught. In the figure below, these included subjects 32815 and 37636.

Using case study methods to combine qualitative and quantitative analyses, we looked at initial expectations for the study to improve stress and mood (assessed from 0 – 10, with 0 representing "no change" and 10 representing "complete help"), a qualitative content analysis of subject responses to the study within their log free responses, a distribution of final expectations of the practice improving stress and/or mood with continued usage, subjects' assessments of how much the training changed their ability to cope with stressful thoughts and change their reactivity patterns (also shown in Figure 20), individual changes in rumination, and the post-study follow up study responses. This served as a time course analysis of subject experience throughout the study, including primary outcome measures. The greatest improvements in rumination were not necessarily those who reacted positively in the other ways we look at as stated above. Those who negatively reacted to the study tended to do the worst across multiple facets and stayed that way 6-10 months later, though.
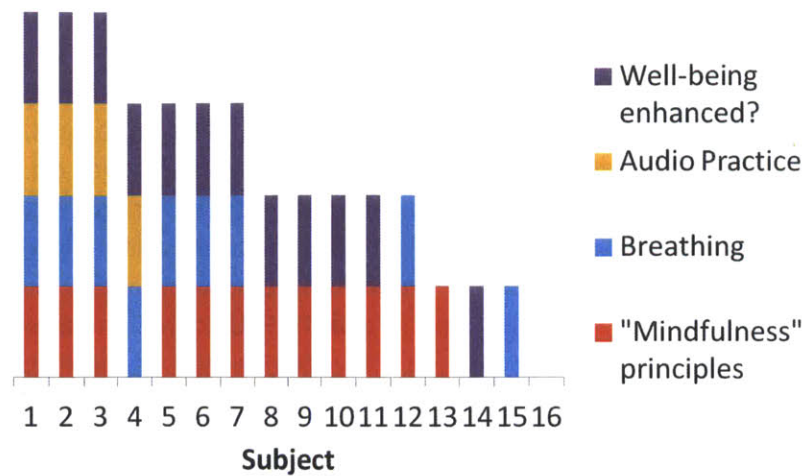
Figure 25: Components of taught practice still present at the 6-10 month follow up survey.

Figure 25 shows the response to the 6-10 month follow up online survey, which 16 of the original 24 subjects completed. Respondents mostly indicated that the principles they were taught during the study were still being used, equally that their well-being was indeed enhanced, followed by the breathing exercise and the audio practice. Five of 16 respondents also stated that they picked up other wellness enhancing practices. During the study, the number of subjects logging practices progressed from 21/24 in block 1, to 20/24 in block 2, to 17/24 in block 3. 12 of the 16 subjects who responded in the follow up survey were subjects who had logged practices during the entire study.

Discussion

Overall, the results of this study indicate that the mindfulness-based audio intervention acted to decrease rumination scores, as measured on the Rumination-Reflection Questionnaire, and increased within-session mood scores, as measured on the Brief Mood Introspection Scale, Pleasant-Unpleasant Subscale. For comparison, the magnitude of decrease in rumination is about 0.7 * one standard deviation of the normative sample in the study by Trapnell and Campbell (32). The improvement in mood subscales are about 1.35, .93, and 1.17 * one standard deviation of the BMIS PU, PT, and NR subscales of the normative sample in Mayer and Gaschke (33). These changes did not vary by audio types used or amount of practice logged. The results are consistent with numerous studies measuring the effects of mindfulness-based therapies on symptoms of mood disorders like rumination (34, 35). It is possible that the high amounts of rapport subjects felt with the moderator (the author) (Fig. 19) contributed to the

consistently improved mood within sessions. At the moment, it is not clear what long-term impact an increased mood within sessions has, though mood regulation over time has been linked to depression outcomes (1). However, the decrease in rumination is of great interest because this cognitive state is a symptom and predictor for depressive episodes (35). Given that residual symptoms can predict higher rates of relapse (36), it is important to find a practice or intervention that continues to motivate individuals to maintain an "eye" on their mental well-being, and to attend to themselves with care when they detect an increase in residual symptoms. Correlations indicated slightly statistically significant relationships between initial BDI and rumination scores with average session mood improvement on the Pleasant-Unpleasant subscale of the BMIS, and between initial BMIS P-U scores and average rumination decrease. These results seem to indicate that initially more depressed individuals, though subthreshold for clinical depression, could have more consistent mood increases from the intervention, and that initial session mood increase might predict rumination decrease over the study. There was also a significant correlation between initial rumination and rumination improvement, possibly indicating again that initially more troubled subjects benefited more from the intervention. Another significant correlation was between initial expectation of improving well being during the study, and initial rumination scores. It seems likely that the relationship there is in the direction of having higher expectations of improvement if rumination is greater; one hypothesis is that the higher expectation scores reflects a greater hope in the ruminators of achieving well being through seeking help from the study. Finally, analyses of mean rumination change between subgroups indicates that females could have a small advantage over males with this kind of intervention, and that increased musical training or music having extreme importance may be factors that lead to increased benefit from this intervention. Greater power with a larger subject cohort and even subgroup numbers would allow more advanced statistics to determine whether these subgroup differences are statistically significant.

This appears to be the first study to combine mindfulness and audio explicitly for self-practice. In contrast to formal music therapy that is guided by a trained music therapist, here we used a simple moderator to run sessions. Similarly, other mindfulness-based treatments are formally manualized to standardize the treatment and also involve well-trained therapists disseminating the principles and practice (2). In contrast, the intervention designed in this study removes a formally trained therapist (though retains a teacher), but utilizes a simple mindfulness framework and combines this with individuals' audio choices. We were surprised to find that a decrease in rumination did not vary with amount of practice logged, since practice is a fundamental tenet of mindfulness interventions. However, the specific effects of practice amount on outcomes in mindfulness studies have not received that much attention. In one of the few studies looking explicitly at this relationship, Carmody and Baer (28) found formal practice amounts to be related to beneficial psychological outcomes, but did not find a correlation between the informal practice component and well being. It is conceivable that the intervention in this study was more closely related to informal practice – it did not include a body scan, yoga, or formal sitting meditation. Amongst the practice components it did include (mindful music listening, 3-5 minute breathing exercise), the breathing exercise could be considered more formal but is also much shorter than typical of those found in mindfulness

interventions, and the music listening is certainly an informal practice of applying mindfulness to an everyday activity.

Because of the process-oriented nature of this kind of practice, it is likely that it must be studied for a long time to develop a deep and effective understanding. It has been said that Buddhist meditation must be practiced for at least 10,000 hours to attain mastery. Similar to other studies requiring daily or frequent self-practice, this intervention saw a successive decrease in reported practices over the three blocks. As this study was not only shorter in overall duration and with less contact hours than standardized mindfulness interventions (6 training sessions vs. 8, 45 minutes therapeutic time per session vs. 2.5 hours, and no day long retreat), these factors may explain why a comparable improvement in perceived stress and on the POMS scale was not seen. Indeed a recent study by Baer, Carmody, and Hunsinger (37) found that significant changes in perceived stress did not occur until week 4 of an MBSR program, and that these improvements were predicted by change in mindfulness skills, which did not occur until the second week of the program. Another review of MBSR class contact hours did not find a correlation between class hours and effect sizes for variables of psychological distress, but noted that "session time may be important to the development of other kinds of program outcomes" (38). Interestingly, a review including laboratory based studies on the mechanisms of change from mindfulness training found that brief mindfulness training as short, guided meditation practices or simply mindfulness instructions could have immediate positive effects on dysphoria and emotional reactivity to aversive stimuli (35). This may explain the improvement in BMIS and rumination scores in the current study.

Anecdotally, subjects had many things to share about their experiences, and their responses overall revealed a favorable reaction. With respect to the audio stories used, the specificity of plot details/voices seemed to make them less compatible with repeat usage, as there were often complaints about the repetition of content or tone of voice. For example, one subject noted: "When you hear the stories for multiple times it's harder to focus on them (at least for me)." The overall consensus was that the stories were not ideal for use in this context due to emotionally sensitive topics and religious overtones, despite the intention of the series creators to be heart-warming. On the other hand, it seemed that mindfully listening to strongly emotional, personal songs was sometimes too much to work with for a daily practice. Though subjects were encouraged to take on the challenge of being with the emotion, and many did in fact do this, it could also have added stress. For the classical songs, the main limiting factor seemed to be the difference in character from the subjects' normal listening genres (as was intended to make it a different condition than the personal choice). Still, a few subjects echoed the sentiment of one who benefited from the change in music: "Overall, I enjoy having music that my mind can fade into a little more. The lack of lyrics helps a lot in this."

This feedback is interesting to consider in conjunction with the non-statistically significant trends in effects between audio types in figures 8-10. The difference between audio blocks within the main outcomes could have been washed out by subject efforts to try to do the practice anyway, as many actually used their displeasure with the audio as another focus *upon which* to practice mindfulness! Unfortunately, it is not possible to know from this study whether improvement in rumination could have been greater without using the least favored

story block, a limitation in the design of this exploratory pilot. All together, the results indicate that given more time spent with each audio type or a greater number of subjects to power the study, differences between audio types may become statistically significant.

It was also apparent that the practice did progress in nature even over just the six weeks of the study. This, and other factors in the subjects' comments yielded some potential insight into what may have contributed to rumination improving. Frequently comments on the log were of the following nature:

> "I felt upset about some feedback and decided to start doing this. I feel much calmer now, and I think I've gained some perspective. Thanks for giving me an excuse to step back and relax."

Figures 13-15 show that subjects truly enjoyed concentrating on the audio listening only, and that the experience was consistently calming or happy on a daily basis over the six weeks. A great percentage of the subjects believed that the training had truly helped them respond better to their reactivity patterns (Fig. 20), which was also echoed in many comments that they felt a difference. Strikingly, even with difficult practices at times, subjects almost always marked that the practice was worth doing, again testifying to the potential reason the difficult audio stories and songs may not have influenced results as much as the intent to practice. It may be that a true potential strength of mindfulness is showcased in this study, with subjects being exposed to various emotional circumstances in a "simulated" way (rather than working directly on personal life situations) and learning to overcome them. Figure 17 even shows the practice becoming progressively easier over time, and in Figure 12 the progressively lower difference they felt in the practice may be an indication that they were already closer to "being" mode to start at each practice. From this evidence, it could be postulated that the audio acts only as a medium upon which mindfulness can be practiced and built. It could be argued though that the addition of audio to a mindfulness practice can act to breakdown the barriers to initiating what could otherwise be perceived as a foreign and difficult practice. Indeed, the majority of respondents did mark in their initial and final survey that they were seeking a new way to improve their well being, and that music was important enough to them that they were intrigued and excited to try the study.

Lastly, the follow up survey seemed to show that subjects had more effectively integrated the mindfulness principles into their lives than the breathing or music listening practices. Additionally, a high percentage of participants indicated that at the 6-10 month follow up point, they did believe the study had enhanced their well-being. For comparison, a study by Bondolfi et al. (4) assessed the survival of practice components 7-12 months following MBCT, and found that the percentage of participants practicing once per week for the informal practice, 3 minute breathing, sitting meditation, and body scan ran from 61.5%, to 60%, to 46.2%, to 11.5%, respectively. In light of these results, it would be interesting to see if there were a consistent drop off of practice components proportional to the number originally introduced during the intervention, with the most formal always dropping out most. Whether the differential survival of intervention components here speaks to which pieces were most effective during the training weeks would also have to be investigated in additional mechanism-

focused studies. The time course analyses combining qualitative and quantitative metrics that gave a summary of subject experience and outcome from the study showed that those who improved in rumination were not necessarily those who reacted positively in many other ways to the study. This seems to indicate that there can be a group of responding subjects who have conscious, positive reactions, and a group of responders who have subconscious positive primary outcomes, even if they did not self-report positive reactions. These results underscore the importance of including both quantitative and qualitative social science measures in clinically oriented studies that have a large psychological component. Those who negatively reacted to the study tended to do the worst across multiple facets and stayed that way 6-10 months later, although surprisingly, one subject actually continued the practice despite disliking it so much during the study. This subject seemed to drop the mindfulness principles of thought change and continued instead with the active listening and breathing. As the old adage goes: "It was a good idea in theory, but *in practice...*" – the picture is not always so clear or as expected!

This study is unique to the author's knowledge in its specific combination of music and mindfulness components. Future iterations of this type might utilize more formalized adherence measures and a better way to measure engagement, so that these components may be further explored. There were also a number of potential limitations of this study. We do not know how strong any placebo effect (i.e., expectation of benefit from treatment) is here, since there was no non-specific control arm in which no intervention of any sort took place. With respect to the intervention design, we cannot definitively distinguish whether it was the active audio practice, the breathing, or the mindfulness framework that helped, as these components were present in all audio treatments. In a similar vein, we do not know whether it is the content of the intervention or the therapist-like element of a person listening and talking, that helped - given that a high level of attention was given to each subject, it remains to be tested whether a less intense moderator role can still be effective. Future studies should also examine the effects of a scaled up design including a larger cohort and longer timeline of study, more comparable to evaluations of other mindfulness based interventions. A larger cohort followed for a longer period could allow us to test for subtle effects of each audio type and effects from a greater amount of time to learn the practice. It is possible that due to the design of the study, which involves a switch in audio type every two weeks, subjects may have had more difficulty learning the practice. As stated previously, in other studies mindfulness is usually disseminated as a practice for at least 8 weeks and often shows decreases in perceived stress, contrary to what was found in this study.

Overall, the effects on rumination and mood change, relevant to depression, are important to consider in the context of the holistic and naturalistic character of the intervention. Currently the long term psychopathologies associated with medical problems such as depression often cannot be adequately managed without clinician support and medication. Yet, medication and professional services can become costly over time, thus necessitating effective alternative strategies. For depression, there has been evidence that antidepressants may not be as effective as other therapies for the long term prevention of relapse of depressive episodes (36). There may even be problems with prolonged

antidepressant usage; Leykin et al. (39) showed that drug resistance increased as a function of the prior number of exposures to antidepressants. Other possibilities for support and enhanced well-being are potentially powerful because of their lower cost, alignment with individuals' values, less stigma, greater enjoyment, and social support and reinforcement. It is especially imperative to help patients find a way of coping that is balanced such that it can be maintained independently of too much clinician or hospital support – only in this way may they feel that they have regained control and reclaimed their lives from disease again.

Conclusion

This study tests novel therapeutic methods and contributes to research on the increasingly urgent issue of maintaining wellness with lower costs and labor. In sum, in response to a brief intervention combining mindfulness and daily exposure to music/audio, rumination improved over the course of 6 weeks, and mood consistently improved each session. There was also a sense of positive valuing of the study by subjects, as observed in their comments and in the follow-up questionnaire. More importantly, the study shows the potential impact on depressive symptoms of a mindfulness-based intervention that is less formal, has less session training time, less homework, and is shorter in weeks than other mindfulness interventions. Because holistic health is moving into an age of electronic records and mobile devices, the design invoked here looks toward a future of remote practictioner-supported, personal health management. This research helps establish a next step toward lasting, creative self-practices based on proven psychological treatments that improve lives and are able to grow with people over time.

References for Intro and Study 1

Study data were collected and managed using REDCap electronic data capture tools hosted at MGH.[1] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

[1]Paul A. Harris, Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, Jose G. Conde, Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform. 2009 Apr;42(2):377-81.

1. Kovacs M, Rottenberg J, George C. Maladaptive mood repair responses distinguish young adults with early-onset depressive disorders and predict future depression outcomes. Psychol Med. 2009; 39: 1841-1854.

2. Hofmann SG, Sawyer AT, Witt AA, Oh D. The Effect of Mindfulness-Based Therapy on Anxiety and Depression: A Meta-Analytic Review. J Consult Clin Psychol. 2010; 78(2): 169–183.

3. van Aalderen JR, Donders ART, Giommi F, Spinhoven P, Barendregt HP, Speckens AEM. The efficacy of mindfulness-based cognitive therapy in recurrent depressed patients with and without a current depressive episode: a randomized controlled trial. Psychological Medicine. 2012; 42: 989-1001.

4. Bondolfi G, et al. Depression relapse prophylaxis with Mindfulness-Based Cognitive Therapy: replication and extension in the Swiss health care system. J Affect Disord. 2010; 122(3): 224-31.

5. Barnhofer T, Crane C, Hargus E, Amarasinghe M, Winder R, Williams JM. Mindfulness-based cognitive therapy as a treatment for chronic depression: A preliminary study. Behav Res Ther. 2009; 47(5): 366-373.

6. Pothoulaki M, Macdonald RA, Flowers P, Stamataki E, Filiopoulos V, Stamatiadis D, et al. An investigation of the effects of music on anxiety and pain perception in patients undergoing haemodialysis treatment. J Health Psychol. 2008; 13(7):912-20.

7. Voss JA et al. Sedative music reduces anxiety and pain during chair rest after open-heart surgery. Pain. 2004; 112(1-2):197-203

8. Gold C, Solli HP, Krüger V, Lie SA. Dose-response relationship in music therapy for people with serious mental disorders: systematic review and meta-analysis. Clin Psychol Rev. 2009; 29(3):193-207.

9. Gotlib IH and Hammen CL. Handbook of Depression. New York, NY; 2009.

10. Fritz T, Jentschke S, Gosselin N, Sammler D, Peretz I, Turner R, et al. Universal recognition of three basic emotions in music. Current biology. 2009; 19(7), 573-6.

11. Bigand E, Poulin-Charronnat B. Are we "experienced listeners"? A review of the musical capacities that do not depend on formal musical training. Cognition.2006; 100(1),100-30.

12. Mesquita B, Walker R. Cultural differences in emotions: A context for interpreting emotional disturbances. Behaviour Research and Therapy. 2003; 41 (7), 777-793.
13. Forsblom A, Laitinen S, Särkämö T, Tervaniemi M. Therapeutic role of music listening in stroke rehabilitation. Ann N Y Acad Sci. 2009; 1169: 426-30.
14. Maratos AS et al. Music therapy for depression. 2008; Cochrane Database Syst. Rev.
15. Thaut MH, Gardiner JC, Holmberg D, Horwitz J, Kent L, Andrews G, Donelan B, et al. Neurologic music therapy improves executive function and emotional adjustment in traumatic brain injury rehabilitation. Ann N Y Acad Sci. 2009; 1169: 406-16.
16. Narayan VA, Mohwinckel M, Pisano G, Yang M, Manji HK. Beyond magic bullets: true innovation in health care. Nat Rev Drug Discov. 2013; 12(2):85-6.
17. Hargreaves DJ, Miell D, Macdonald RA. "What are Musical Identities, and Why are They Important?"
18. Kaemmer JE. "Uses and Functions of Music."
19. Rentfrow PJ, Gosling SD. The do re mi's of everyday life: the structure and personality correlates of music preferences. Journal of Personality and Social Psychology. 2003; 84(6), 1236-1256.
20. Williams M, Teasdale J, Segal Z, Kabat-Zinn J. The Mindful Way through Depression. New York: Guilford Press; 2007.
21. Salimpoor VN, Benovoy M, Longo G, Cooperstock JR, Zatorre RJ. The rewarding aspects of music listening are related to degree of emotional arousal. PloS one. 2009; 4(10)
22. Mitterschiffthaler MT, Fu CH, Dalton JA et al. A functional MRI study of happy and sad affective states induced by classical music. Hum Brain Mapp. 2007; 28: 1150–1162.
23. Jallais C, Gilet AL. Inducing changes in arousal and valence: comparison of two mood induction procedures. Behav Res Methods. 2010; 42(1):318-25.
24. Koelsch S, Fritz T, V Cramon DY, Müller K, Friederici AD. Investigating emotion with music: an fMRI study. Hum Brain Mapp. 2006; 27(3):239-50.
25. Gomez P, Danuser B. Relationships between musical structure and psychophysiological measures of emotion. Emotion. 2007; 7(2):377-87.
26. Krumhansl CL. An exploratory study of musical emotions and psychophysiology. Can J Exp Psychol. 1997; 51(4):336-53.
27. Peretz I, Gagnon L, Bouchard B. Music and emotion: perceptual determinants, immediacy, and isolation after brain damage. Cognition. 1998; 68(2):111-41.
28. Carmody J, Baer RA. Relationships between mindfulness practice and levels of mindfulness, medical and psychological symptoms and well-being in a mindfulness-based stress reduction program. J Behav Med. 2008; 31(1):23-33
29. McNair D, Lorr M, Droppleman LF. (1981). EITS manual for the profile of mood states. San Diego, CA: Educational and Industrial Testing Service.

30. Nyenhuis DL, Yamamoto C, Luchetta T, Terrien A, Parmentier A. Adult and geriatric normative data and validation of the profile of mood states. J Clin Psychol. 1999; 55(1):79-86.

31. Cohen S, Kamarck T, Mermelstein R. A global measure of perceived stress. J Health and Social Behavior. 1983; 24(4): 385-396.

32. Trapnell, PD, Campbell, JD. Private self-consciousness and the five-factor model of personality: Distinguishing rumination from reflection. Journal of Personality and Social Psychology. 1999; 76(2), 284-304.

33. Mayer JD, Gaschke YN. The experience and meta-experience of mood. J Pers Soc Psychol. 1988; 55(1):102-11.

34. Edenfield TM, Saeed SA. An update on mindfulness meditation as a self-help treatment for anxiety and depression. Psychol Res Behav Manag. 2012; 5:131-41.

35. Keng SL, Smoski MJ, Robins CJ. Effects of mindfulness on psychological health: a review of empirical studies. Clin Psychol Rev. 2011; 31(6):1041-56.

36. Dobson KS et al. Randomized trial of behavioral activation, cognitive therapy, and antidepressant medication in the prevention of relapse and recurrence in major depression. Journal of Consulting and Clinical Psychology. 2008; 76(3): 468-477.

37. Baer RA, Carmody J, Hunsinger M. Weekly Change in Mindfulness and Perceived Stress in a Mindfulness-Based Stress Reduction Program. J Clin Psychol. 2012 Epub.

38. Carmody J, Baer RA. How long does a mindfulness-based stress reduction program need to be? A review of class contact hours and effect sizes for psychological distress. J Clin Psychol. 2009; 65(6):627-38.

39. Leykin Y, Amsterdam JD, DeRubeis RJ, Gallop R, Shelton RC, Hollon SD. Progressive Resistance to a Selective Serotonin Reuptake Inhibitor but Not to Cognitive Therapy in the Treatment of Major Depression. Journal of Consulting and Clinical Psychology. 2007; 75 (2): 267–276.

40. Boulanger, A. "Music, Mind and Health: How Community Change, Diagnosis, and Neuro-rehabilitation can be Targeted During Creative Tasks." Ph.D. Thesis. MIT Media Laboratory, 2010.

41. Norton A, Zipse L, Marchina S, Schlaug G. Melodic intonation therapy: shared insights on how it is done and why it might help. Ann N Y Acad Sci. 2009 Jul;1169:431-6.

42. Yin, RK (2009). "Ch. 5: Analyzing Case Study Evidence". Case Study Research: Design and Methods. Sage Publications.

43. Sixty-fifth World Health Assembly, WHO: "The global burden of mental disorders and the need for a comprehensive, coordinated response from health and social sectors at the country level". 25 May 2012.

44. Wallin, Nils Lennart; Steven Brown, Björn Merker (2001). The Origins of Music. Cambridge: MIT Press.

A Shift in Context: From Study 1 to Study 2

Just as the allure of music drew subjects to try a new method of enhancing their well-being in study 1, this same power naturally led to the trial of using strong, personal music in another chronic disease context. Study 2 moved personal music into an acute analgesia setting, again with a proven psychological paradigm that held potential clinical applications. Music was joined with expectancy-boosting conditioning to attempt to elucidate further the cognitive and emotional mechanisms behind the phenomenon, and to possibly further boost the analgesic effects through the combination.

III. Study 2: Effects of a personal music-enhanced conditioning paradigm on heat pain analgesia

Introduction

The experience of pain has both sensory and affective elements, and can be modulated with cognitive distractions as well as emotional manipulation. The neural network involved in analgesia includes both the dopaminergic reward system and a descending pain inhibitory opiodergic system that begins in the cerebral cortex and extends downwards to the spinal cord, with some evidence of additional mediators that antagonize the opiodergic circuit through factors such as anxiety (59). Placebo analgesia studies have shown an effect from verbal expectancy manipulation, which can be additionally boosted through covert conditioning (32). More recently, there have been a number of demonstrations of music's analgesic capabilities in experimental settings (14-16, 19, 21, 22, 25). Music has been shown to both reduce anxiety and activate reward circuitry (2, 7, 10); because both factors are part of the neural pathways modulating pain perception, it is conceivable that music could access one or both pathways as an analgesic vehicle.

In this study, we attempted to control or measure all previously successful elements of music analgesia. Following the success and feasibility of the personal music choice paradigm in study 1 of this thesis, the design of this study examined the effects of specific personal music alone (i.e. without mindfulness) on pain perception. We sought to harness the benefit of familiarity to enhance music analgesia, and also to further the clinical promise of the intervention by using conditioning to augment any effects that music could have on pain perception.

The use of personal music choice in music induced analgesia

Applied to pain-related disorders, music as a therapeutic modality has a number of advantages over more traditional therapies. Pathologies like depression, often associated with long term illnesses like chronic pain, tend to manifest with different symptoms across cultures, making it difficult to address ethnically and demographically diverse groups with psychotherapy. As mentioned for study 1, music has the power to be universally understood, is highly accessible, can have a strong effect across a variety of people, and has general health benefits (2-4, 9, 11).

The scientific complexity of personal music choice is great in the context of analgesia. From the effects of choice (15, 21, 27), expectation of relief, and potential conditioning from previous exposure, to music specific elements including valence/arousal (14, 18, 19, 22), mood dependent preferences, specific memories (41, 42), and induced chills (7), the mechanisms operating behind this potentially powerful clinical tool are many. The neural basis of music and emotions is a nascent yet fast growing area of research, and many overlapping regions between nociceptive and music affective circuitry have been found, including limbic, paralimbic, dopaminergic, and hippocampal networks (5, 8, 24). The history of audioanalgesia itself stretches back to 1959, when Gardner (43) treated 1000 dental patients and found that using music and noise, ¼ of them did not need any other analgesia during a dental procedure. Through the research completed in this study, we hoped to further increase mechanistic understanding of personal music's role as a potential analgesic by controlling many of the above factors and testing personal music's effects in combination with conditioning. Perhaps one of the key aspects of our specially selected personal music was that it was designed to be shrouded in all the expectations built up from each individual's life – in a sense, maximized for baseline expectations of pain relief. Comparing this with a relatively innocuous sound sample that still served as a control auditory stimulus allowed us to test the effects on analgesia from the combination of a powerful, personally and culturally conditioned cue and our own expectancy conditioning procedure.

Balancing carefully between clinical utility and scientific integrity, we chose to exclude music choices that invoke specific autobiographical memories and chills as best we could, and included a set of individually-selected and characterized songs that were perceived to be highly pleasurable over a range of arousal levels. We allowed individuals to choose their preferred song from that set during the experiment. By requesting that subjects provide songs that cover a range in arousal, we could further explore the uncertainty behind music's role as a mediator of anxiety or agent of reward (16, 19-22), as higher arousal is generally correlated with anxiety but higher *music*-induced arousal to strongly pleasurable music is correlated with reward. Roy et al (2012) specifically tested arousal to pleasant music for pain modulation, but their samples were not personally chosen by the subjects, and other studies have shown familiarity to mediate reward in the context of arousal (10, 13, 25, 28). Thus, because we are using strongly familiar music here, we will likely tap maximally into the rewarding aspects of music that could temper pain experience. We also attempted to assess levels of attention and focus on the audio using both scales and interview methods.

Experimental manipulations of expectancy

Positive expectation of pain relief is likely a critical component of context effects in pain treatments, but one that is challenging to tease out from other context effects and manipulate experimentally. Additionally, a problem with studying analgesia using healthy volunteers in experimentally-induced pain studies is that the analgesic effects can be fewer and of lower magnitude than in genuine clinical pain studies. This study took advantage of the fact that positive expectation of treatment related to pain relief can be robustly manipulated in an acute experimental setting using a well-studied conditioning- expectancy paradigm (32, 47-50). We used an experimental manipulation based on the method originally developed by Voudoris and colleagues (46), who applied a placebo cream as a local analgesic and surreptitiously reduced the pain stimulus. This manipulation successfully produced heightened analgesia to subsequent noxious stimuli. Here, instead of pairing pain reduction with a physical, inert "analgesic" agent, we paired it with an emotional and cognitive stimulus (music) that has already shown some analgesic effects on its own (see above). As shown before (32, 50), expectancy and conditioning each have separate importance in the context of analgesia, and we expected to be able to partially differentiate those effects between our conditioning groups and our non-conditioning group. In all published attempts this conditioning paradigm has been effective in creating robust placebo analgesia sufficient to allow quantitative behavioral measurements; in this study we predicted the paradigm would robustly boost whatever analgesic effects the personal music stimulus already had.

Potential clinical applications

Though music and conditioning have been studied separately as potential mediators of pain relief, they had not to date been combined in a rigorous, controlled study to test their efficacy together. The studies mentioned thus far have found mostly modest effect sizes, but together these two analgesic methods may be able to more substantially reduce pain. In the case that the effects are not linearly additive, the addition of music into the conditioning-expectancy paradigm links a clinically effective, analgesic perceptual modulation with a modality that is already well integrated into most patient's lives. Additionally, as music is already a medium that induces associative conditioning of socio-cultural cues, emotions, memories, and identity, it may be an ideal candidate for a surreptitiously conditioned analgesic therapy. Piloting of this dual analgesic helps pave the way to future longitudinal studies of a personal music treatment that is low cost, patient-centered and driven, and can potentially be a lasting, effective relief. This could reduce medication needed and number of medical visits, outcomes that would impact analgesic quantities used post-surgery and by chronic pain patients, and generally decrease the lifestyle impacts that the experience of pain carries with it.

<u>Strategic approach</u>

To assess both the magnitude and specific advantages of music both as an agent of analgesia and a potential partner with conditioning, we included conditioned chosen noise, non-conditioned chosen noise, and silence as controls in our experiment. In providing a chosen noise control, our aim was to match the psychological advantages of perceived control, and more strictly test personal music against a relatively innocuous, personally chosen sound. It also served the important role of controlling for the auditory stimulus modality of music. As an added element of interest, the noise was a similar low frequency filtered (low pass) sound sample to that used by Gardner et al. (43) in their dental procedures, where they had used music and noise concurrently to completely block pain experience. Upon completion of the primary cohort, we added a second experiment consisting of only a music conditioning group that operated under an *explicit* conditioning paradigm, as opposed to the more implicit protocol used in the first music conditioning group. Explicit conditioning more directly increases the probability that subjects believe they are receiving analgesia by adding in a reminder that they are receiving equivalent heat levels, while simultaneously still turning the heat level down during conditioning. Our purpose was to compare the effects on analgesia between the two subtly different modes of conditioning when used in the context of personal music.

Specific Aim

Music and conditioning to simple cues (e.g light) have each separately shown analgesic effects in experimental pain settings. This study combined, separately, specific personal music and chosen sound with conditioning to test whether there were increased conditioning benefits for music vs. sound analgesia on experimental pain in healthy subjects.

Hypothesis 1: Highly pleasurable, personally chosen music will reduce pain compared to sound and silence in healthy subjects.

Hypothesis 2: Conditioning will enhance pain reduction when sound or music is on, compared to non-conditioned sound and music.

Hypothesis 3: Conditioning will enhance pain reduction when highly pleasurable, personally chosen music is on, compared to conditioned sound.

Subject Selection

All study procedures were carried out with Institutional Review Board approval from MIT COUHES (protocol # 1206005109) and MGH (protocol # 2012P000969).

Subjects included met the following criteria, or were screened out by the qualities below:

Inclusion Criteria:
a) Healthy male and female adults aged 18-50: Within this age range, subjects are likely old enough to understand the instructions and rating scales, yet young enough that their pain perception faculties have not changed dramatically.
b) Body Mass Index < 30: Obese individuals potentially respond differently to pain stimuli given the difference in body composition under their skin, thus they were not included.

Exclusion Criteria:
a) Current major medical, neurological, or psychiatric disease
b) Pregnancy
c) Advanced music training
d) Instability of responses to experimental pain (see Study Procedures Section)
e) Non-fluent speaker of English
f) BDI-II (Beck Depression Inventory) score greater than 13
g) Previous experience in pain experiments
h) Current or previous ear/nose/throat or hearing issues compromising ability to listen to audio stimuli

Subject Recruitment

Normal adult volunteers were recruited by advertising for this study by email, web, and bulletin board announcements. In addition, the online recruitment system of the MIT Behavioral Research Lab was used. We recruited 58 subjects to have a total of 48 completing the study, as we anticipated up to an approximately 25% attrition rate for subjects due to inability to meet all continuation requirements (primarily the requirement of stable and reliable responses to pain stimuli necessary to perform the quantitative experiments, as observed in past studies using these methods).

Study Procedures

Overview of Experimental Design

To accomplish the original Specific Aims, a single two-session experiment was performed with 36 healthy, pain experiment-naïve subjects who were randomized into 3 treatment groups. The three treatment groups were music conditioning, sound conditioning, and no-treatment routine pain calibration. Primary outcome measures included the difference (pre- minus post-treatment) in subjective pain rating to calibrated experimental noxious heat stimuli. We also collected treatment expectations using an Expectancy of Relief Scale (ERS, below) and ratings of subjective responses to treatments assessed through various psychometric scales and surveys for all groups.

The two behavioral sessions were separated by a minimum of 2 days and a maximum of 10 days. Subjects were asked to hold common daily activities constant on experiment days (i.e. duration of sleep, eating habits, caffeine intake). Prior to coming to the experimental site, all

subjects were asked to acquire/choose a set of personal music that satisfied certain criteria for the study (see following section). During both sessions, subjects received sets of calibrated noxious thermal stimuli and after each stimulus used 0-100 visual analog scales to rate the pain sensation and unpleasantness. In the *first session*, subjects underwent the consent process and screening questions, and we also determined whether subjects could report consistent, appropriate responses to the application of the calibrated noxious thermal stimuli. This session lasted about 90-110 minutes. In the *second session* we repeated testing for appropriate responses to the thermal stimuli – only subjects that performed consistently on the pain rating task (could reliably rate mild intensity pain stimuli as less painful than moderate intensity stimuli and have comparable ratings across sessions - within about 1 STD) would continue to further testing during the second session. Subjects who were eligible to continue were randomized into one of the three treatment groups (N=12/group) (Fig. 26). Subjects in conditioning groups then received a modification of a well-characterized conditioning-expectancy manipulation procedure designed to enhance a subject's expectation of pain relief in response to their assigned treatment. This second session lasted about 115-120 minutes. At the end of the study all subjects completed a final questionnaire assessing their belief in the treatment efficacy.
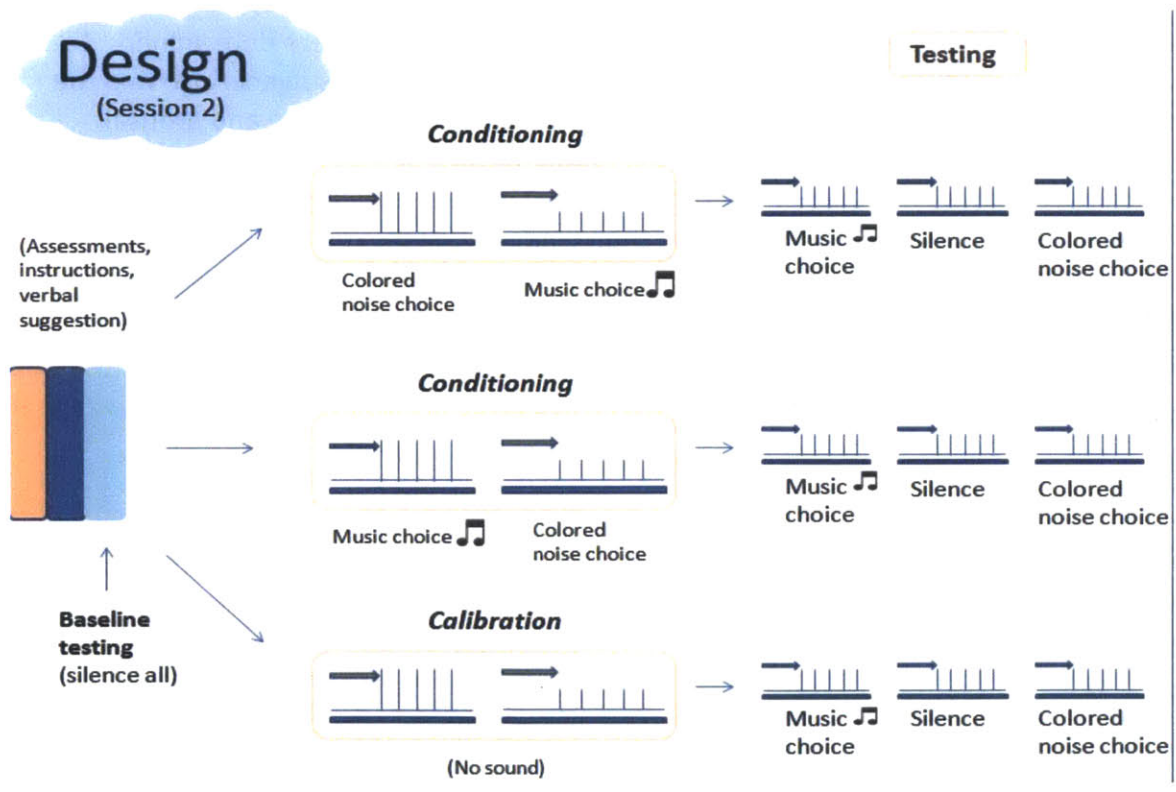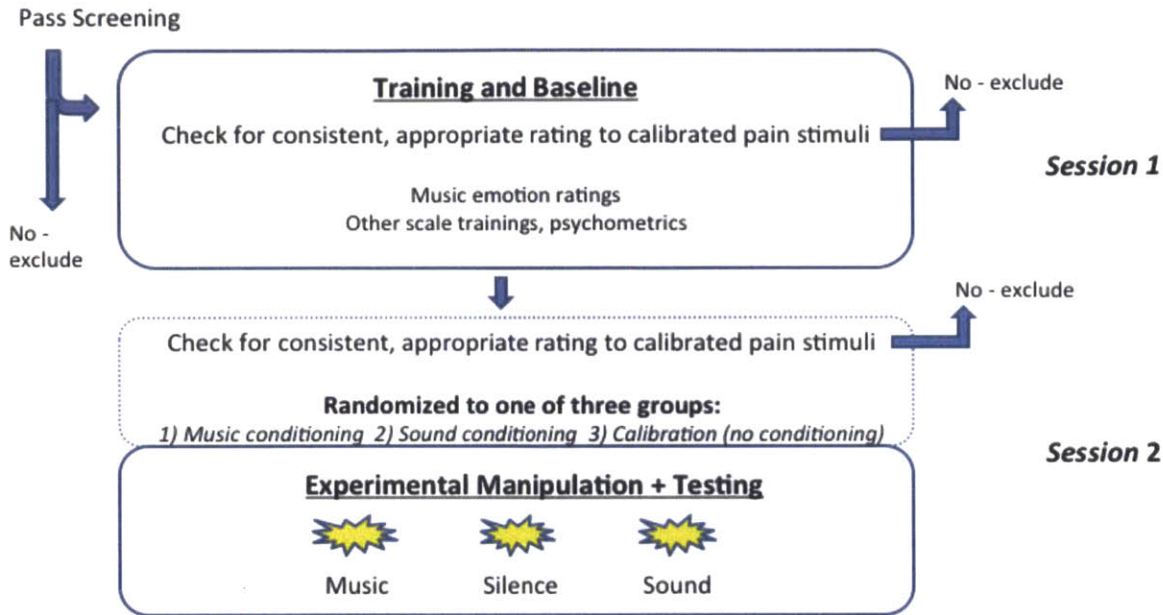

Figure 26: Schematic of study design. The colored blocks at left represent, respectively, assessments, instructions, and baseline testing. Following baseline testing, all subjects were randomized to one of three groups, where they received heat pain trials at two levels. Conditioning groups received lower heat levels when the conditioned audio stimulus was on

(here colored noise is the sound sample), while the calibration group received stimuli with silence. All groups were then tested with three audio conditions: music, sound, and silence, in randomized order across subjects. Within each set of trials, lead-in arrows represent the 1 minute of audio or silence that preceded pain stimuli beginning. Each stimuli was 12 seconds long (2.5 second ramps with 7 second plateaus).

Music and sound sample criteria and choices

Prior to coming to the experimental site, all subjects were asked to provide a set of songs (each at least 4 minutes long) that they love, had been familiar with for at least a few years but did not tend to get tired of, varied across a range from very relaxing to very energizing, did not evoke specific memories or chills, and that they had not seen the music video for. This list of criteria was designed to maximize our ability to discern the specific effects of subjects' personal music choices for analgesia. Subjects were asked to answer a variety of music usage questions prior to starting the study procedures. During Session 1, all subjects rated their songs in terms of valence and arousal on Self Assessment Manikin (SAM) scales (Bradley and Lang, 1994) and were again asked if specific memories or chills occurred while listening, to screen for these potentially confounding factors. Song excerpts centered on the most favored part of each piece and of length appropriate for the intended pain stimulation were determined. To somewhat match the element of choice present in their personal music, subjects also had the option of choosing one of two sound samples, both neutrally rated in valence and arousal (validated separately by lab members naive to the nature of the control). The sound samples were colored noise that was frequency filtered to remove higher frequencies and had previously been perceived to be less distressing than white noise (14, 25). Subjects were exposed to the two sound samples during Session 1 to familiarize them with the stimuli. Then, during Session 2, before the conditioning trials began all subjects first chose the song and sound sample they wanted to listen to during the pain trials.

Subject Flow

Pass Screening

Training and Baseline

Check for consistent, appropriate rating to calibrated pain stimuli

No - exclude

Session 1

Music emotion ratings
Other scale trainings, psychometrics

No - exclude

No - exclude

Check for consistent, appropriate rating to calibrated pain stimuli

Randomized to one of three groups:
1) Music conditioning 2) Sound conditioning 3) Calibration (no conditioning)

Session 2

Experimental Manipulation + Testing

Music   Silence   Sound

Session 1: Subject screening, pain response characterization, and training

After giving consent, all subjects completed self-report baseline assessments (BDI-II, TAS, STAI-State, GSES, RRQ; see descriptions below). Session 1 was made up of *threshold/tolerance acquisition, screening/calibration*, and *rating stability testing*.

Before beginning heat testing, to ensure that sensitization and habituation of the same area of skin were avoided in successive stimulation sets, lines were drawn to divide the skin on the palmar surface of the right forearm into four discrete regions (labeled 1-4 in Figure 27). Noxious heat stimuli were delivered using a Thermal Sensory Analyzer (TSA-II) or the Pathway CHEPS model (Contact Heat-Evoked Potential Stimulator) with a 3 cm x 3 cm probe (Medoc Advanced Medical Systems, Rimat Yishai, Israel) running proprietary computerized visual analog scale software (COVAS).

The purpose of Session 1 was primarily to train subjects to rate their pain using the 0-100 sensory and unpleasantness visual analog scales (VAS, description below), and to determine individually calibrated stimuli temperatures that would elicit certain intensity ratings for each subject. The first block of stimuli was part of threshold/tolerance acquisition, during which subjects were instructed on how to use the 0-100 VAS to rate the heat stimuli applied to the skin on the back of their right hand. Each subject used a button press to start and stop the CHEPS device, running a slowly ascending (.5ºC/sec) series, to indicate both their pain threshold

("as soon as you feel pain") and their pain tolerance ("as much pain as you can tolerate"). We ran 2-3 series for each of their threshold and tolerance levels, switching to adjacent areas of skin on the back of the hand, for a total of 4-6 series that yielded reliable average values for threshold and tolerance. Then, we performed up to two ascending series of calibrated heat stimuli on region 1 on the palmar surface of the right forearm (Fig. 27). The first stimulus of each ascending series was initiated from a resting temperature of 32°C and increased to a target temperature of 38°C. The stimulus was presented for 12 seconds, including 2.5 seconds each for ramp up and ramp down from resting.

Figure 27: Session 1 right arm spots and order for stimuli application. On spot 1 a continuously ascending sequence was applied, on spots 2 and 3 were random sequences, and on spot 4 a series of identical stimuli.

Subsequent stimuli, separated by a minimum of 30 seconds, were increased by 1°C until reaching 52°C or the subject's self-reported limit. Temperatures that elicited subjective intensity ratings of Moderate/low = 30-50 and Strong/high = 55-75 were selected for each subject for use in Session 2, when subjects were able to meet these ranges. Once the Moderate and Strong heat pain intensities for a subject had determined, we initiated screening/calibration.

In the screening/calibration block, random sequences of Moderate and Strong intensity noxious stimuli were administered to regions 2 and 3. If the subjects could reliably rate the Strong stimuli as more intense than the Moderate stimuli, they were still eligible to continue.

Finally, during rating stability testing, we administered 5 stimuli on region 4, all at one temperature that elicited the subject's Strong intensity ratings to test whether the subject could consistently rate the same noxious heat stimulation. This was the final test during Session 1 for whether subjects could proceed to Session 2.

During Session 1, subjects also learned to use the SAM scales by rating one block of pain stimuli and their chosen music. They also described how they were attending to the audio and their anxiety during one set of pain stimuli. We also asked them whether any specific memories or autonomic chills responses occurred during their music, and asked for a different song sample to be used if this were the case as these were music exclusion criteria in this study

(as previously stated). Lastly, subjects were introduced to both the sound samples that they could use during Session 2, and were asked to not listen to their music samples until the study had concluded. For the second music conditioning group, an additional assessment of expectancy was done at the end of session 1, as a baseline before verbal induction in the second session.

Session 2: Expectancy manipulation and testing

Sessions 1 and 2 were separated by at least two days (but no more than 10 days) to avoid sensitization to repeated application of the noxious stimuli. Before any pain testing began in Session 2, subjects completed the STAI-State and BMIS (descriptions below). The rest of Session 2 was made up of *screening/calibration, pre-test/baseline, conditioning manipulation* and *post-manipulation testing.*

The screening/calibration block was the same as that completed in Session 1 to determine eligibility to continue participation in the experiment, with this second pass included to thoroughly check for rating consistency (this procedure significantly improves the quality of the data and interpretability of results in experimental analgesia studies). The two sets of random stimuli were applied to regions labeled 'RS' in Figure 2. If they passed this screening, they completed a set of pre-test/baseline stimuli of the same procedure as the rating stability testing from Session 1, though this time in each of regions 1-3 (Figure 28). Ratings for the first set of baseline stimuli during Session 2 were required to be within roughly 20% of ratings given during rating stability testing during Session 1 to minimize instability of subject rating across sessions. Throughout the administration of noxious pain sequences, subjects rated each stimulus using the 0-100 scales immediately after they were presented. After each set of noxious stimuli, subjects additionally rated their perceived control and valence/arousal (SAM scales), attention, and anxiety.
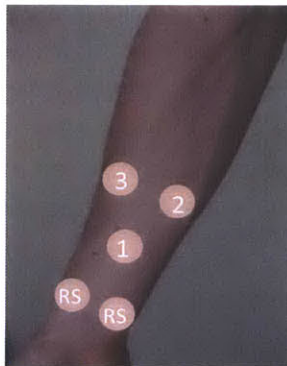

Figure 28: Session 2 right arm spots and order for stimuli application. Following application of random sequences on the 'RS' spots, baseline testing (all identical stimuli) was carried out on spots 1, 2, and 3.

Before the experimental manipulation, all subjects chose the music and sound samples they wished to proceed with. The two emotionally equivalent samples of sound presented in

Session 1 were re-presented for subjects to choose from. Subjects did not listen to their music samples to determine their choice, but rather visually picked from their list. Subjects were then randomized to one of three groups (N=12/group), with the groups characterized by conditioning type (music, sound, or none/calibration), for the manipulation block. After choosing their sound and music samples, subjects in conditioning groups were told that during the intended conditioned stimuli they could experience less pain. The script consisted of the following: "Today we're testing a treatment for pain that is not yet in clinical use. The reason we're using _____ (this special frequency-filtered sound, your specially selected music) is because previous studies have shown them to have pain relieving properties. This is what we're testing today, and we're just comparing it to _____ (the sound, the music), and silence." In the calibration group, we stated that *either* their music or the sound could have analgesic effects. Subjects then filled out the ERS indicating the degree to which they anticipated the "treatment" would work as an analgesic. Importantly, in the second music conditioning group, after this ERS we additionally included the following line: "Now we're going to do some tests where you'll be introduced to the audio along with the stimuli. You will receive four sets total that are the same as the ones you just received before, only now you will have them with alternating music, then sound, music and sound." This served as an explicit reminder that they would be receiving identical stimuli during the conditioning block; in the original conditioning groups, subjects were not reminded of this fact before the manipulation.

Within conditioning groups, we randomly assigned subjects to receive either the conditioned stimuli first, or the non-conditioned stimuli. The conditioned stimuli consisted of lower heat stimuli (the subject's Moderately rated heat level) paired with either music or sound, and non-conditioned stimuli consisted of the same temperature stimuli used in pre-test/baseline paired with the other audio, sound or music. This conditioning procedure was designed to induce a positive expectancy manipulation in addition to the verbal expectancy introduced earlier. In the calibration group, subjects experienced both heat levels, with either the Moderate or Strong pain stimulus first but without any paired auditory stimuli or specific verbal suggestions. Stimuli during the manipulation block were applied to regions 1-4 on the *left* arm, as seen in Figure 29, to avoid over-stimulation of regions on the right arm. After each block of stimuli, subjects in conditioning groups were also asked to indicate whether any specific memories or autonomic chills responses occurred to their music samples, and all subjects rated their perceived control, valence, and arousal (SAM scales) to the audio or silence, and attention and anxiety.

Figure 29: Session 2 left arm spots and order for stimuli application. Pink spots represent one heat level, red, the second. Order of starting with high or low stimuli was randomized across subjects.

After manipulation they again filled out the ERS, and then continued to the post-manipulation test. This was the same as pre-test/baseline, except that stimuli were now presented in three contexts: their chosen music, their chosen sound, and silence, with order of presentation randomized across subjects. Stimuli were again applied to regions 1-3 on the right arm (Fig. 28). After each set of audio/silence + noxious stimuli, subjects again rated their perceived control, valence/arousal to the audio or silence, attention, anxiety, and indicate whether any specific memories or autonomic chills responses occurred.

Subjects answered a final ERS indicating their anticipation of their assigned treatment's analgesic capacity in future treatments, and completed final questionnaires. After completion of Session 2 testing procedures, subjects were allowed to ask questions.

Psychological assessments

Beck Depression Inventory (BDI): The 21-item BDI has shown good sensitivity and specificity for major depression in chronic pain patients (52, 53). A score greater than 18 was considered high, and less than 13, low for depression symptoms.
Expectations for Relief Scale (ERS): The ERS is a 0-10 scale (with 0 indicating a very negative expectation of "does not work at all" and 10 indicating a very positive expectation of "complete pain relief") used to measure the expectation of treatment pain relief (32). See figure below for assessment points during the study.
Tellegen Absorption Scale (TAS): TAS measures individual differences in absorption, a trait that involves an openness to experience emotional and cognitive alterations across a range of situations (34). It is a 34-item true-false scales that asks participants to rate the degree to which they become absorbed in everyday imaginative experiences (e.g., viewing a sunset). It has been widely used in personality research.
Spielberger State-Trait Anxiety Inventory (STAI): STAI consists of two 20-item self-report inventories. It is a rapid but detailed assessment that can distinguish between basal and

reactive anxiety. Scores range from 20 to 80 and the higher the score the greater the level of anxiety (40). Part 1 (trait) measures basal anxiety and was administered during Session 1 and Part 2 (state) which measures reactive anxiety was administered pre-post-Session 2. Normative data are available (40).

General Self Efficacy Scale (GSES): This is a 10-item psychometric scale that is designed to assess optimistic self-beliefs to cope with a variety of difficult demands in life. In contrast to other scales that were designed to assess optimism, this one explicitly refers to personal agency, i.e., the belief that one's actions are responsible for successful outcomes (33).

Rumination Reflection Questionnaire (RRQ): Trapnell and Campbell (38) originally developed the RRQ to distinguish between the maladaptive and adaptive components of rumination. Rumination items are based on research findings related to metacognitions and evaluations associated with both anxiety and depression. Items on the reflection subscale are from research associated with the cognitive and motivational tendencies typically linked to openness to experience, curiosity, and interest in abstract or philosophical thinking. Each subscale consists of 12 statements to endorse agreement of.

Brief Mood Introspection Scale (BMIS): Consisting of 16 adjectives, two from each of 8 mood categories, it assesses present mood and has been shown to have good factor validity and reliability (39). We measured this pre-post-Session 2.

Sensory and Unpleasantness Visual Analog Scale (VAS): This is a simple 0-100 visual scale representing the magnitude of either pain intensity or pain unpleasantness. It has been widely validated and used in studies taking behavioral pain ratings, and instructions are given to subjects on how to distinguish between intensity vs. affective unpleasantness.

Self Assessment Manikin (SAM): A set of three visual scales that were always shown in succession, representing valence, arousal, and perceived control used widely in emotion rating studies (see end of section).

Final Questionnaire: To determine the success of our procedures, we administered a final questionnaire asking patients whether they believed they had received genuine treatment, how certain they were of their answer, why the treatment might or might not have worked for them, and their final attitudes toward the treatment. We also asked them various questions about their experience during the procedures.
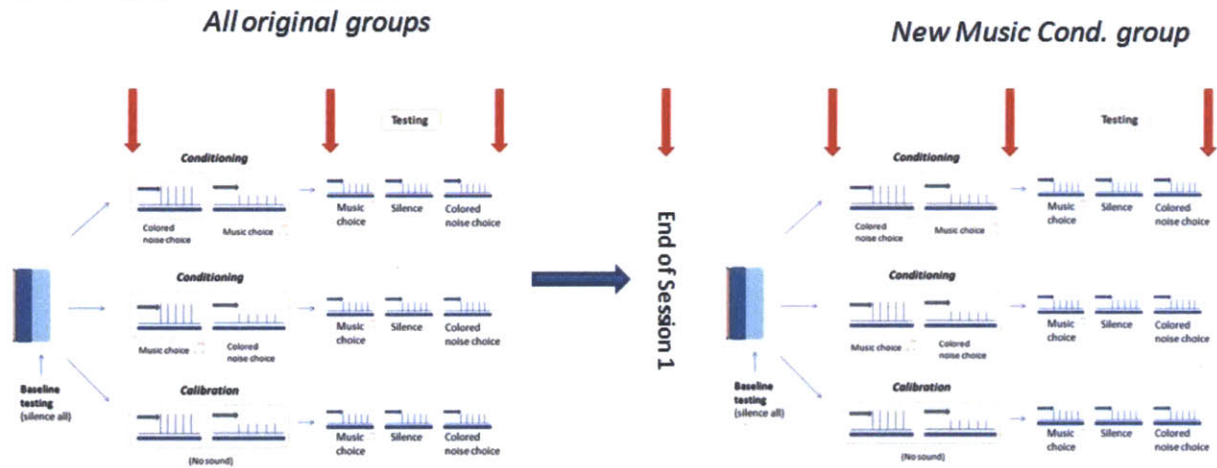
Figure 30: Schematic of ERS assessment points, and addition of one more baseline ERS assessment within the new music conditioning group. In all groups ERS was assessed right after verbal induction, then following conditioning/left arm stimulations, and finally after testing, all within session 2. The additional assessment point for the new group occurs at the end of session 1.
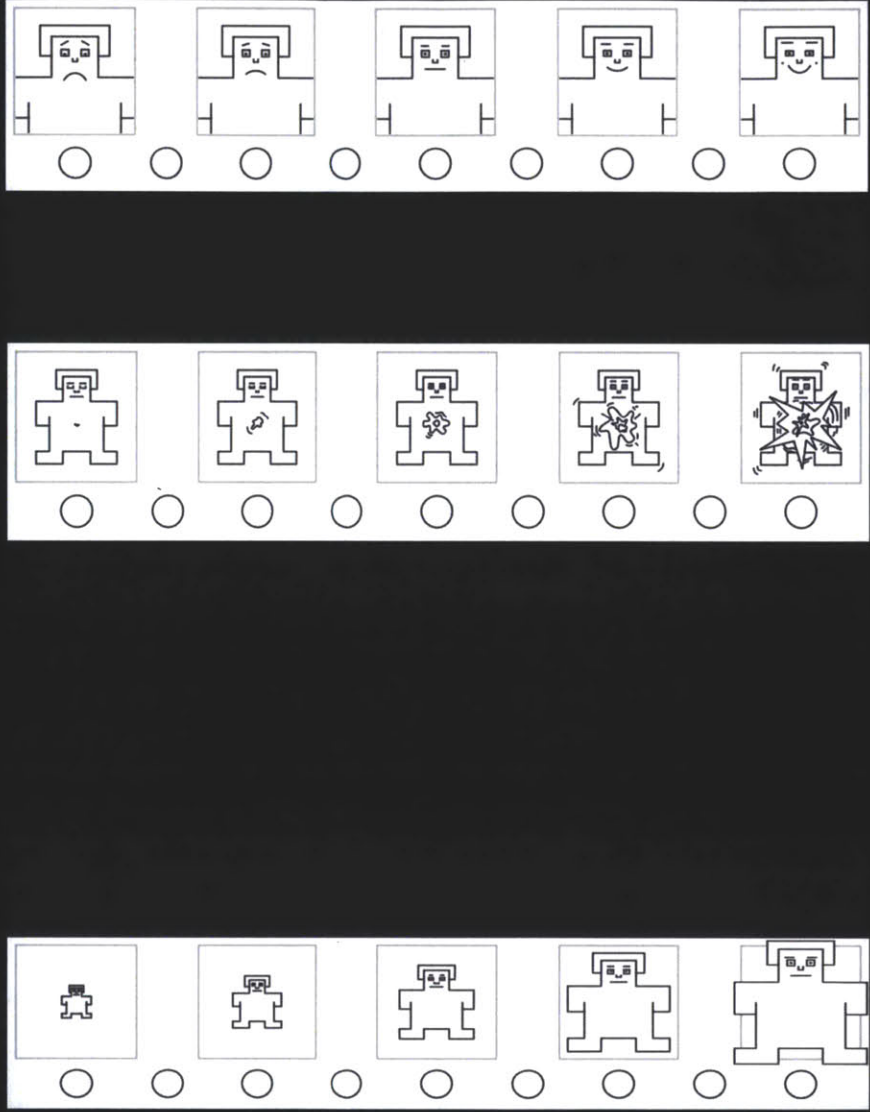
Figure 31: Self Assessment Manikin scales (in order of valence, arousal, and control). Subjects were presented with all three scales in succession after each block of stimuli had ended during baseline, left arm stimulation, and testing.

Statistical Analysis

We studied 12 subjects in four groups for a total of 48 subjects; the primary end points were differences between the music/sound conditioning groups and the no conditioning (calibration) group. In our previous studies for placebo analgesia using a similar model (32, 54-56), we observed a SD for pain rating difference of 1.7, on a scale from 0-20. Converting this value to a 0-100 scale, we anticipated requiring a minimum of n=12 subjects for each group.

The main outcome was the pain rating differences in different conditions. The data was analyzed using repeated measures analysis of covariance (ANCOVA) with group as the covariate, and audio modality (music, sound or silence) as the factor of interest. Post-hoc and pairwise t-tests were also used for direct comparisons. We also assessed expectancy to check for conditioning effects, as is usually done with placebo conditioning studies.

Results

Baseline

Expectancy
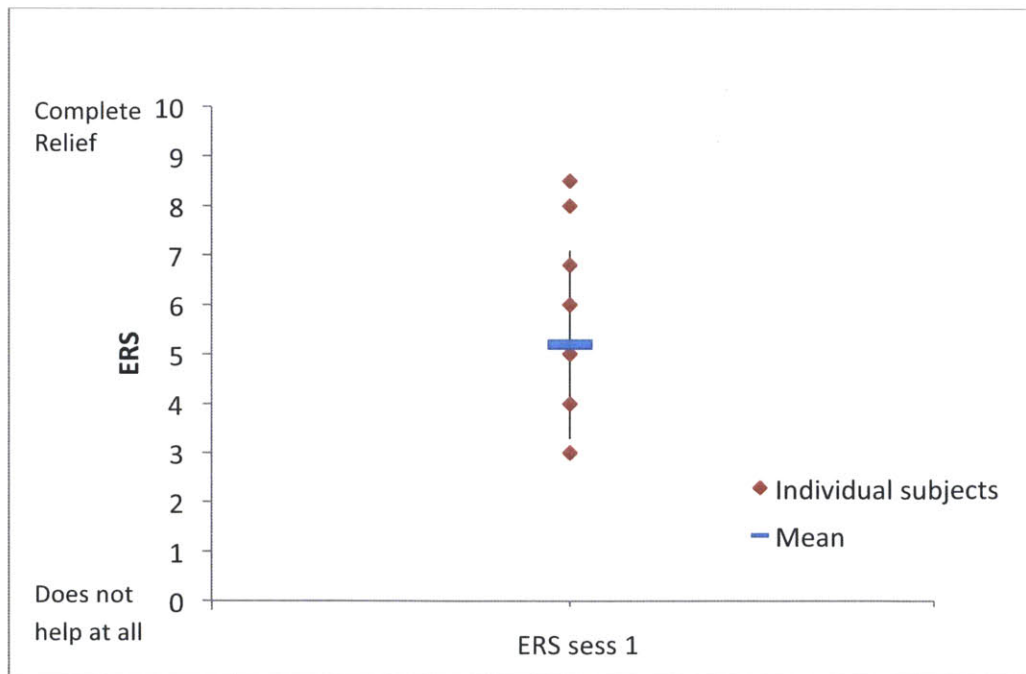
Figure 32: Naive expectations for all subjects in the Music New group, measured at the end of session 1 before verbal induction took place in session 2.

In this figure we see the initial expectations on the ERS from the added music group (n=12) when asked at the end of session 1, before they have been given the verbal induction of

expectation. The mean is shown as a blue bar, with a vertical standard deviation line. There are already a number of fairly high expectations, in the 7-9 range, when subjects have not been explicitly told why the music was being used yet in the experiment.

Presented here are pre-post difference scores of all baseline tests (Strong/High pain level) averaged, by group, with standard deviations.

Calibration group:
      Average Pain Intensity score: 56 ± 13.7
      Average Pain Unpleasantness score: 47 ± 21.2
Music Conditioning group:
      Average Pain Intensity score: 60 ± 18
      Average Pain Unpleasantness score: 50 ± 16
Music Conditioning New group:
      Average Pain Intensity score: 56 ± 15.8
      Average Pain Unpleasantness score: 44 ± 22.9
Sound Conditioning group:
      Average Pain Intensity score: 50 ± 14.9
      Average Pain Unpleasantness score: 45 ± 21.5

Expectancy changes
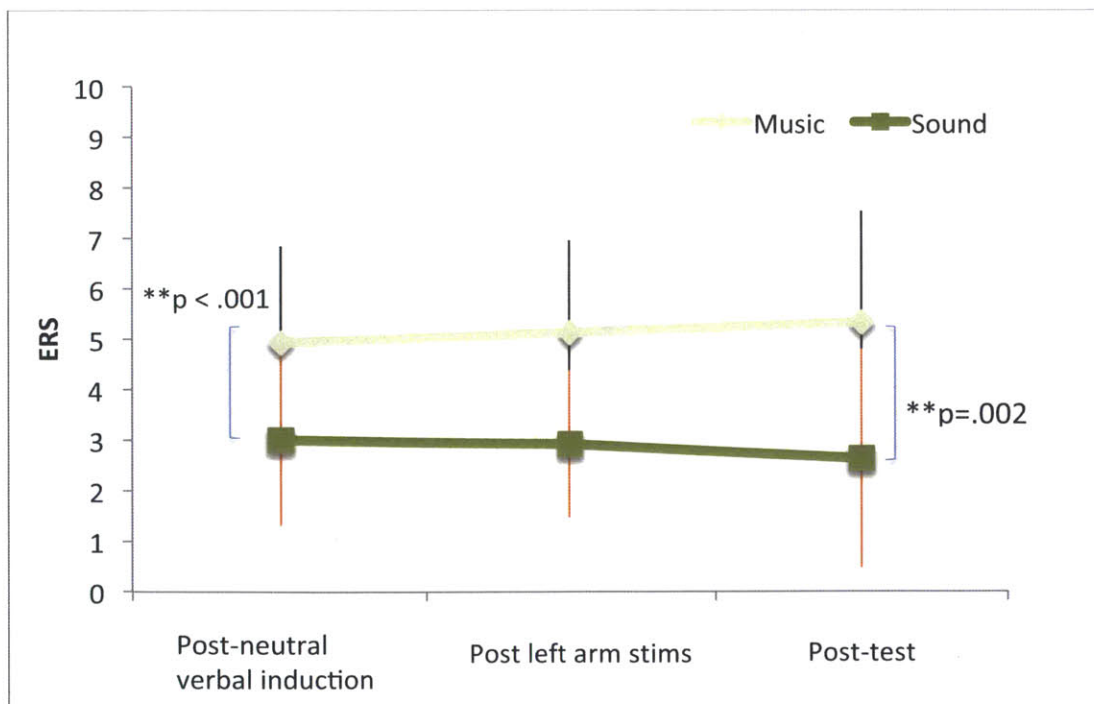
Figure 33: Average expectancy scores in the Calibration Group across all ERS assessments. ERS 1 was taken after an equal verbal induction for both sound and music, ERS 2 after the block

with two heat levels used, during which conditioning occurs for the other groups, and ERS 3 occurred after the testing block. A significant difference between music and sound was found at ERS 1 (p < .001) and remained at ERS 3 (p = .002).
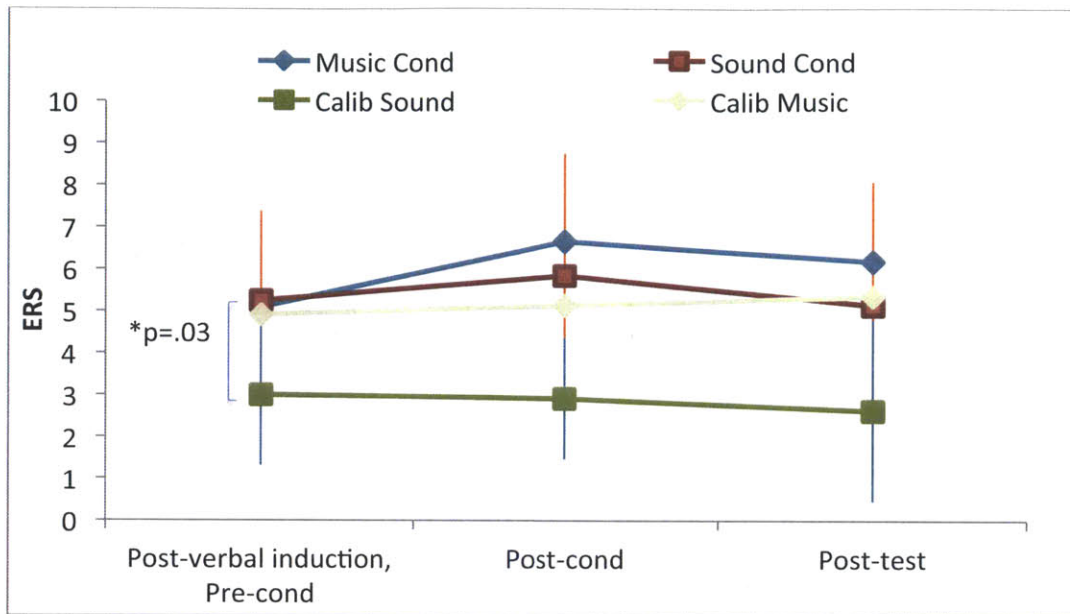
Figure 34: Average expectancy scores in all original groups across all ERS assessments. There was a significant difference at the post-verbal induction, pre-conditioning ERS between scores for calibration sound and conditioned sound, p = .03.
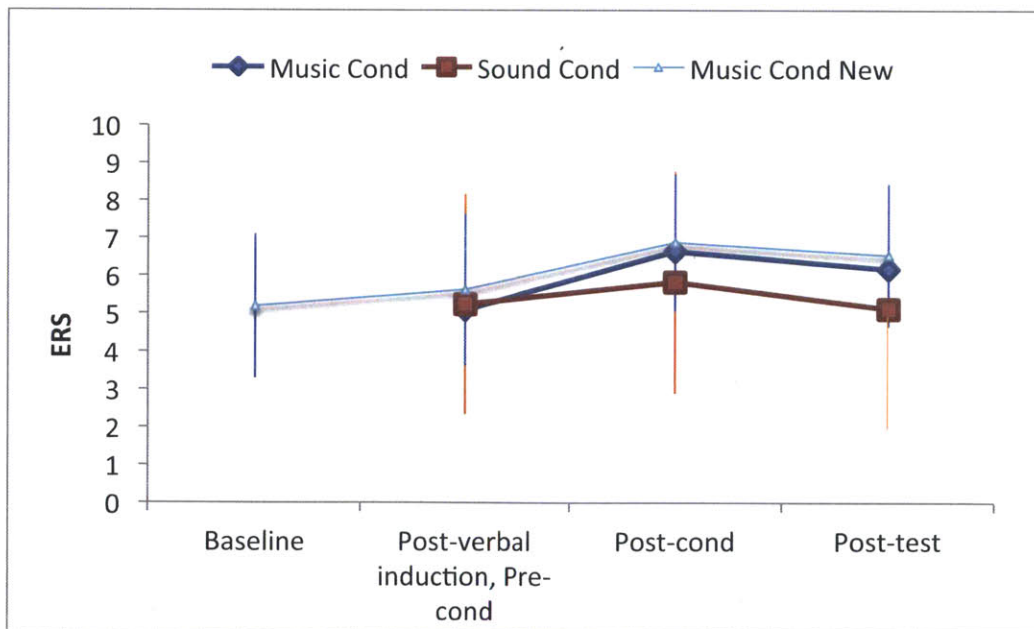
Figure 35: Average expectancy scores in all conditioning groups, across all ERS assessments (including added baseline ERS). Adding the additional assessment of ERS at a completely naive

baseline in the new music group confirms that verbal induction did not significantly raise expectations for music from what subjects already felt for it (I.e. the difference between baseline and post-verbal induction ERS was not significant in the new music conditioning group).
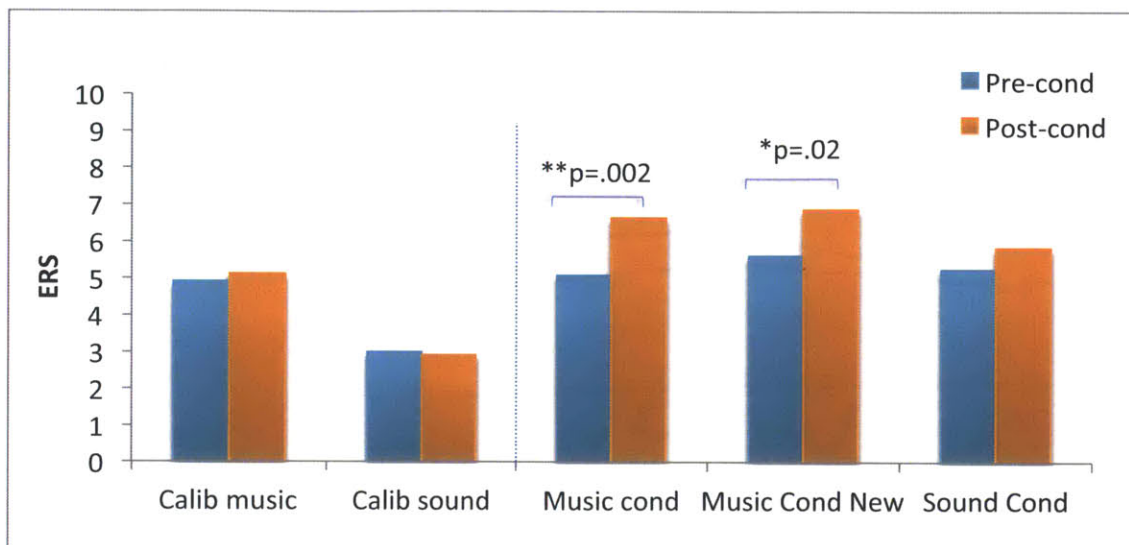
Figure 36: Effects of conditioning on expectancy. Within the control Calibration group, as expected ERS scores did not increase across the same time interval as the conditioning block, when both low and high heat levels, not paired with any audio, were used. In the Music conditioning group, conditioning significantly increased ERS scores (p = .002). Scores also increased, slightly less significantly, in the new music group (p = .02). ERS scores did not rise significantly for the sound conditioning group.
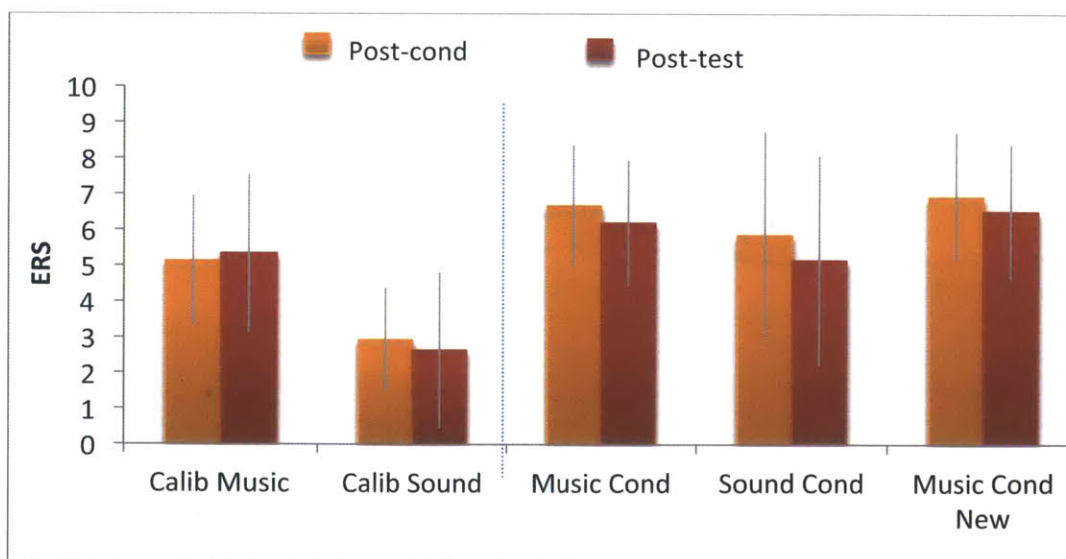
Figure 37: Effects of testing on ERS. ERS scores did not decrease significantly after testing for any of the groups, indicating that the conditioning boost received did not "extinguish" after returning to high heat levels during testing for the music conditioning groups.

Pain Ratings – Pain Intensity
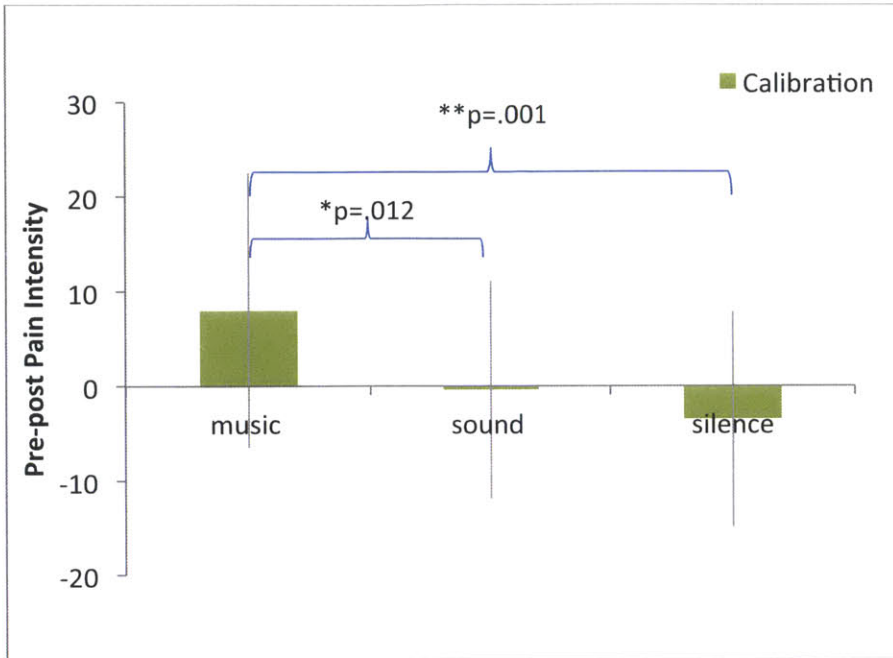
Figure 38: Pain Intensity analgesia, calibration group. Shown here and in all following analgesia graphs are pre (baseline) minus post (testing) pain difference scores; positive values indicate analgesic effects from a decrease in pain. In the calibration group, music significantly reduced pain intensity more than silence, and somewhat more significantly than sound.
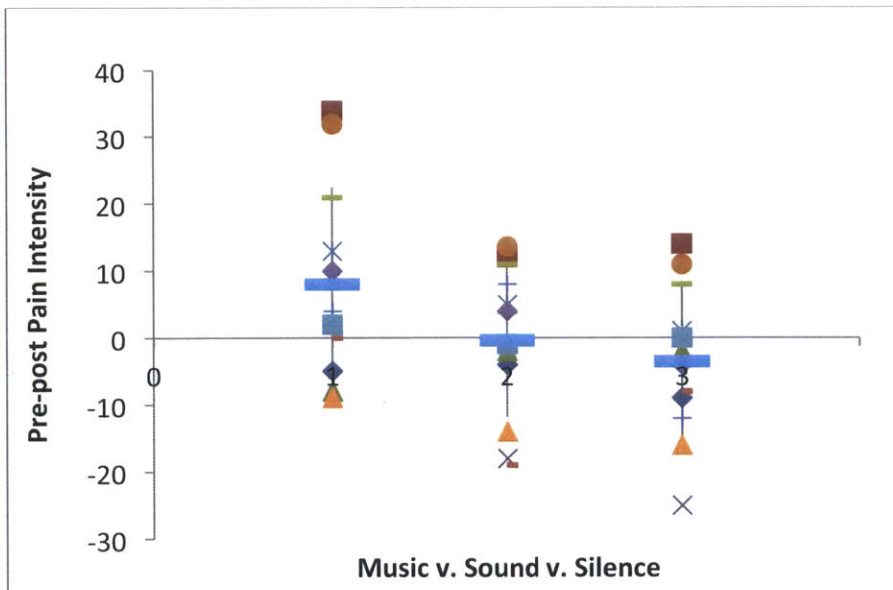

Figure 39: Individual scores in the calibration group, Pain Intensity analgesia. In this and all following charts of this type, the large blue bar indicates the average, with a vertical line underneath showing standard deviation.
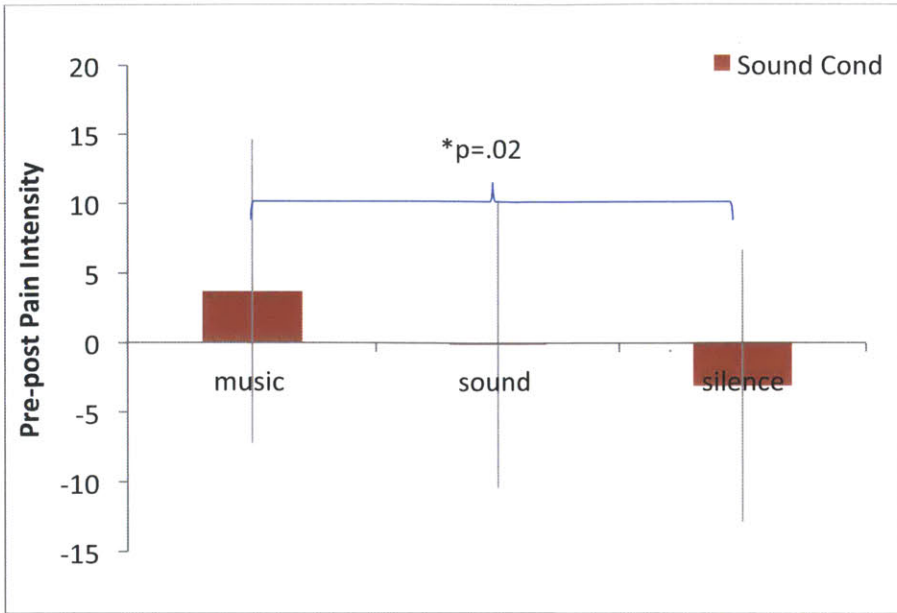
Figure 40: Average pain intensity analgesia, sound conditioning group. Only music (the unconditioned stimulus) reduced pain intensity significantly more than silence. Conditioned sound did not reduce pain compared to silence. Music also did not have a significantly different effect than conditioned sound.
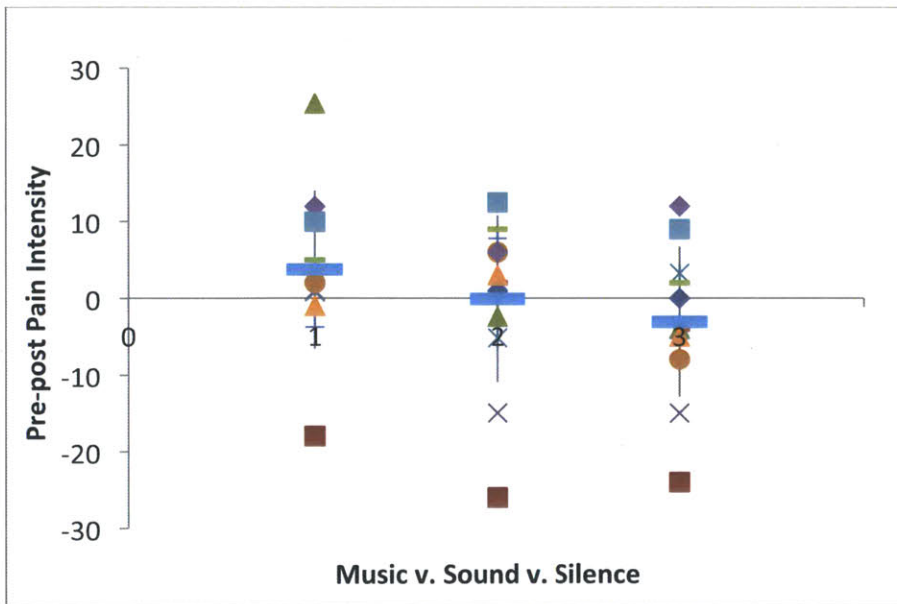

Figure 41: Individual subjects' pain intensity analgesia, sound conditioning group.

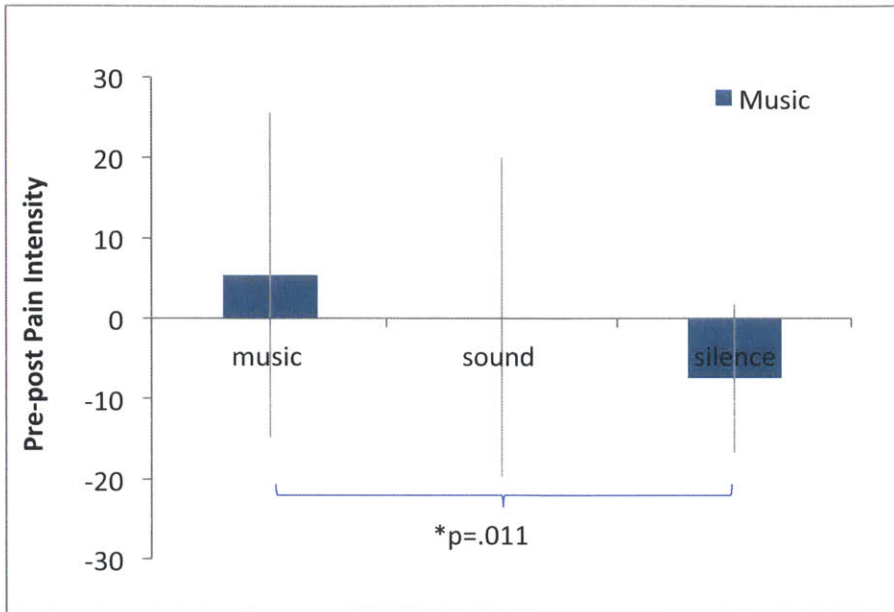Additional analyses removing outlier subjects are shown later in the results section.

Figure 42: Average pain intensity analgesia, music conditioning group. Conditioned music reduced pain intensity somewhat significantly more than silence, but not as compared to sound.
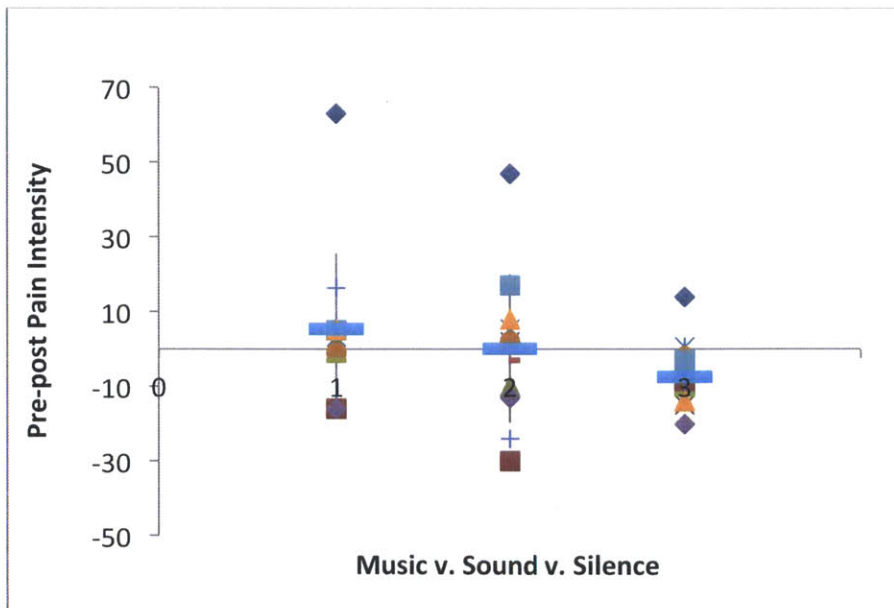

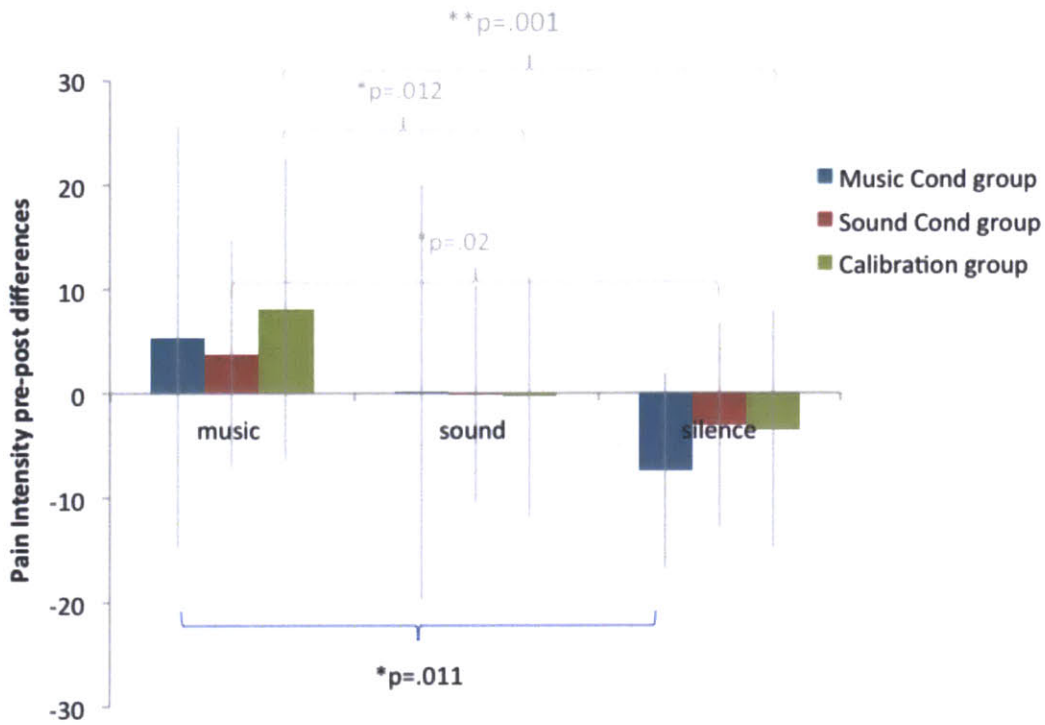Figure 43: Individual subjects' pain intensity analgesia, music conditioning group.

Figure 44: Summary of average pain intensity analgesia ratings in original cohort.
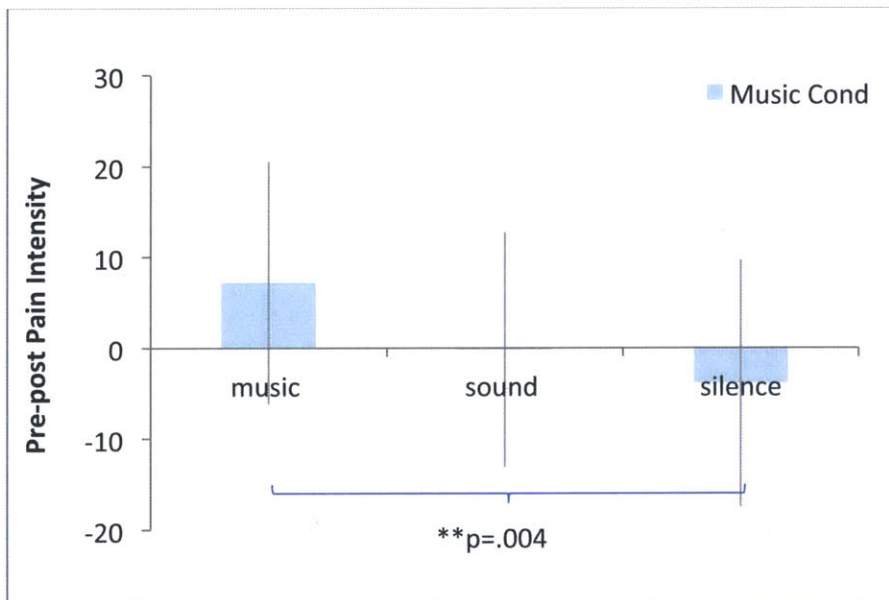

Figure 45: Pain intensity analgesia, new music conditioning group. In this group, which used an explicit conditioning paradigm, conditioned music reduced pain significantly more than silence, but not as compared to sound. The result is similar to that found in the original music conditioning group, with a slight increase in significance.
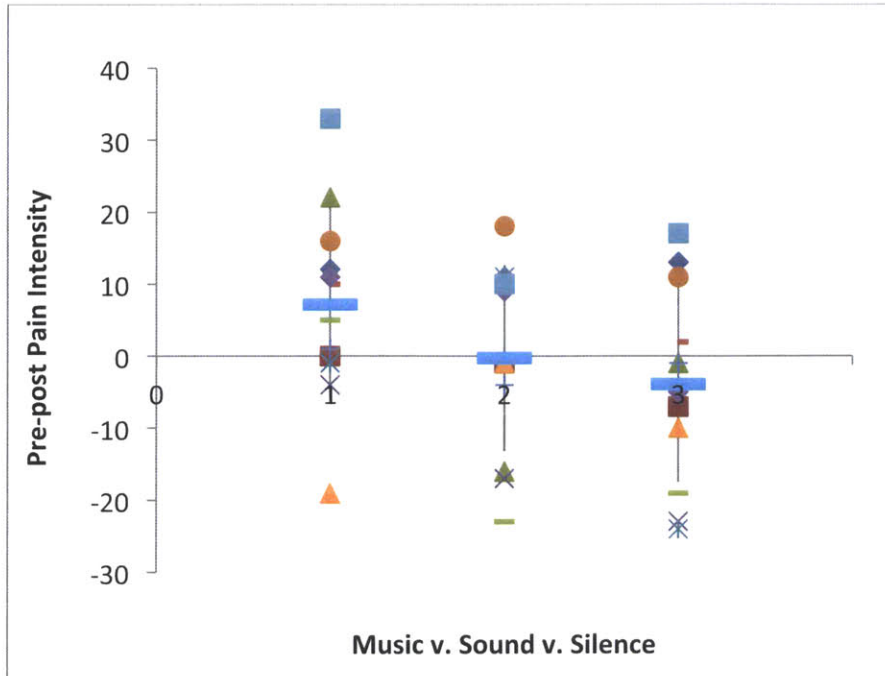
Figure 46: Individual subjects' pain intensity analgesia, new music conditioning group.
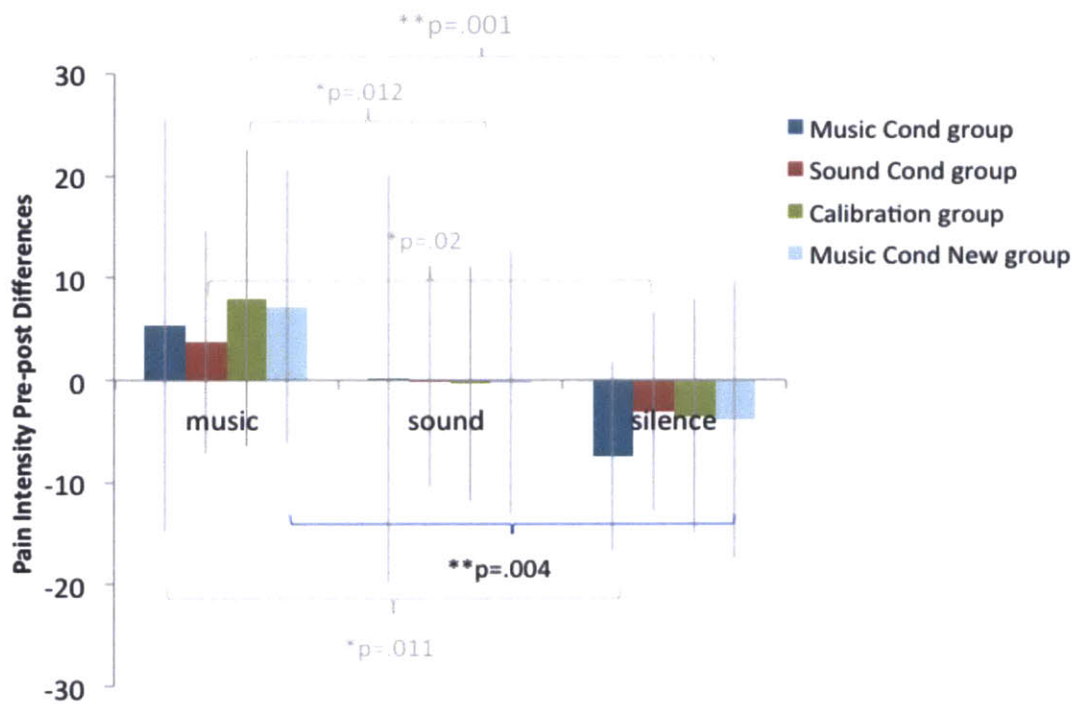

Figure 47: Summary of average pain intensity analgesia ratings, all groups.
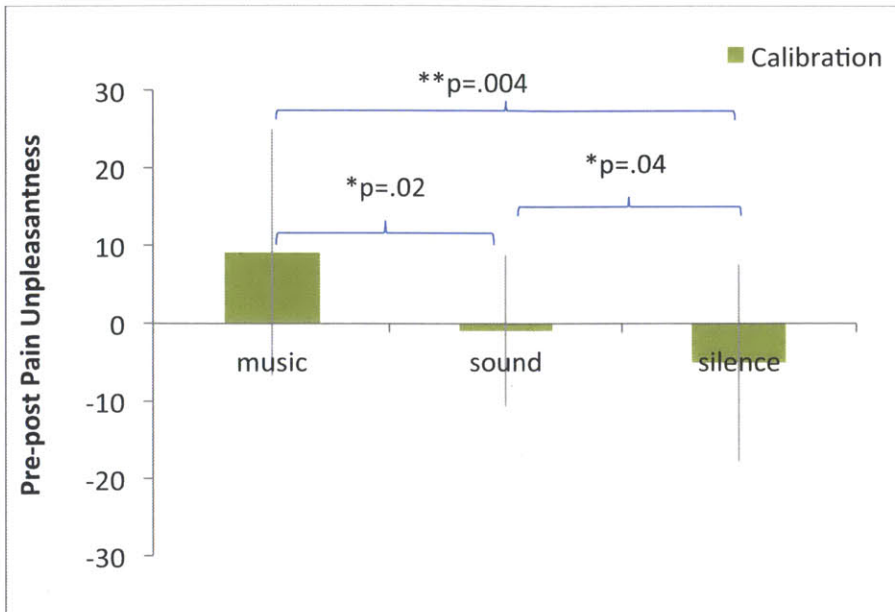
Pain Ratings – Pain Unpleasantness

Figure 48: Average pain unpleasantness analgesia, calibration group. Pain unpleasantness was reduced significantly by music as compared to silence, and somewhat significantly by music compared to sound, and sound compared to silence.
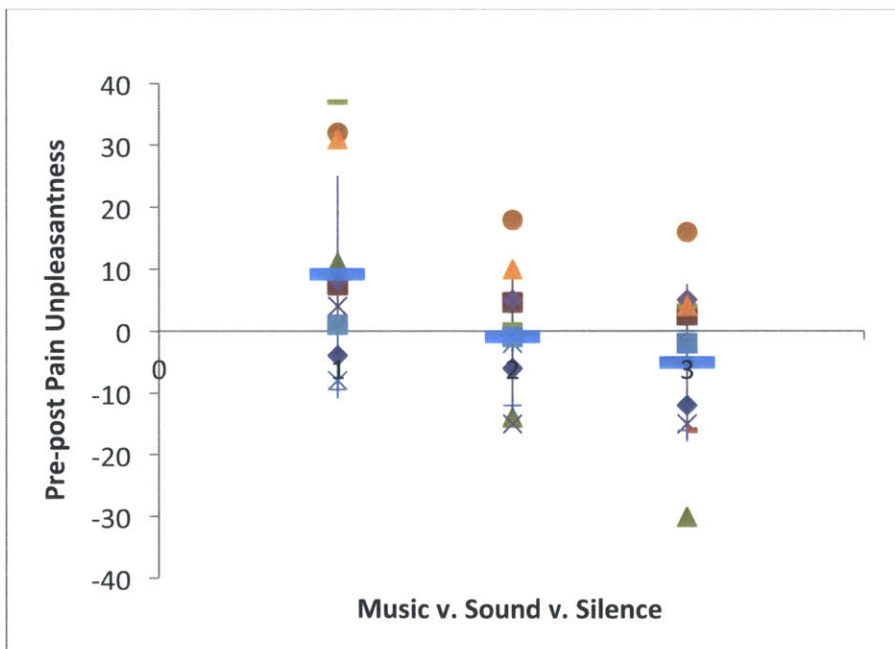

Figure 49: Individual subjects' pain unpleasantness analgesia, calibration group.
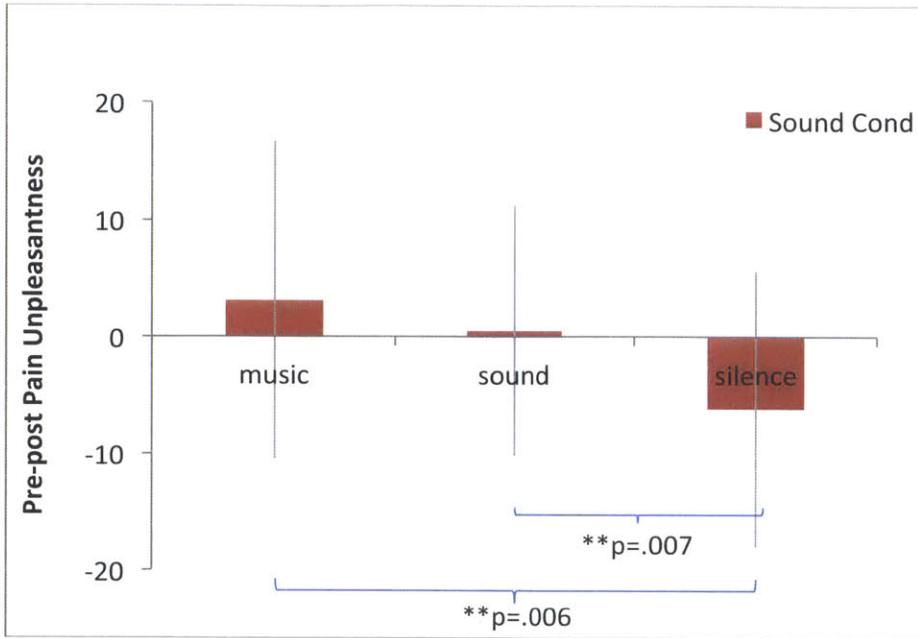
Figure 50: Average pain unpleasantness analgesia, sound conditioning group. Pain unpleasantness was significantly reduced by both music and conditioned sound as compared to silence.
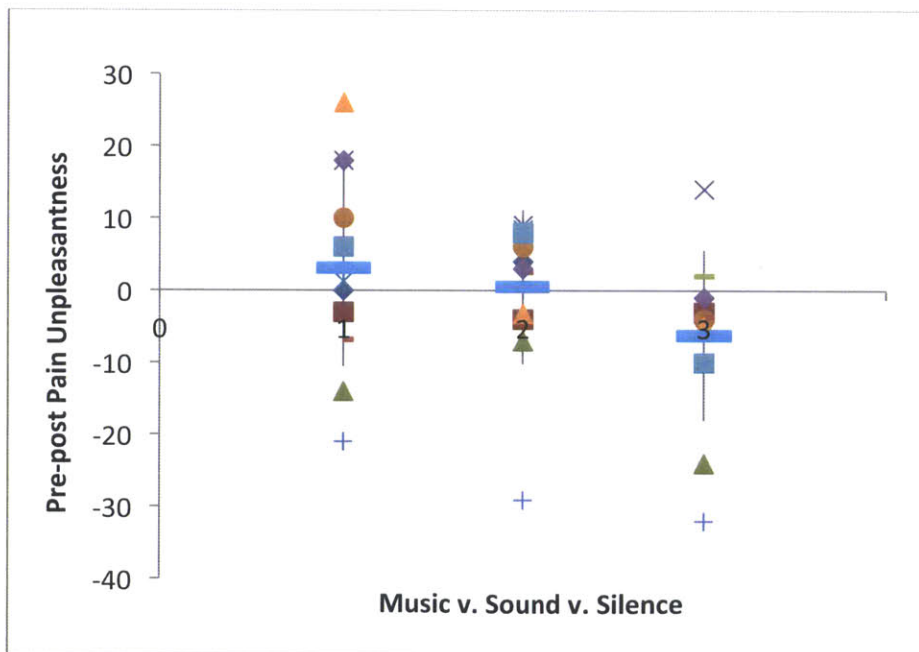

Figure 51: Individual subjects' pain unpleasantness analgesia, sound conditioning group.
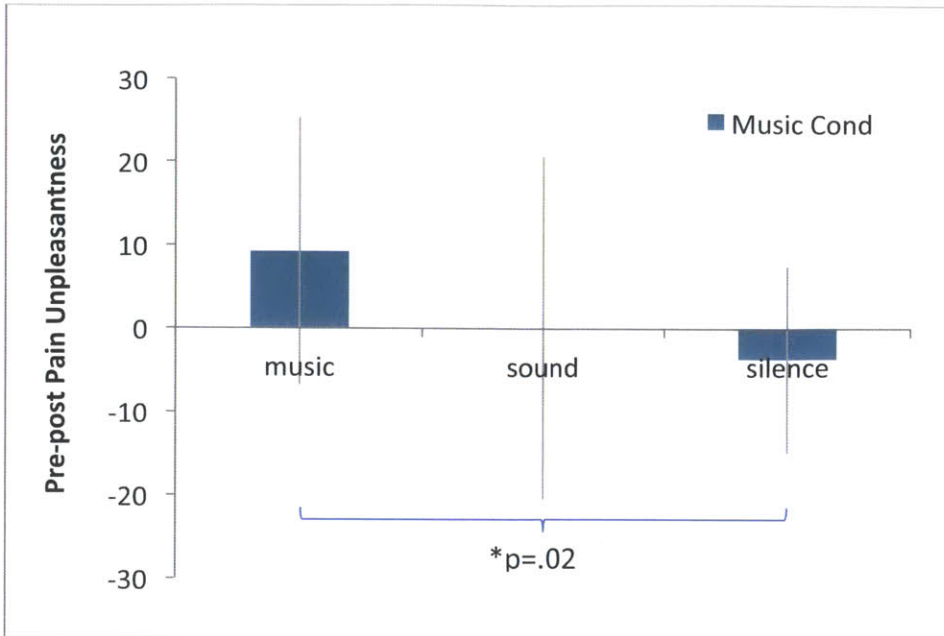
Figure 52: Average pain unpleasantness analgesia, music conditioning group. Conditioned music reduced pain somewhat significantly more than silence, but not as compared to sound.
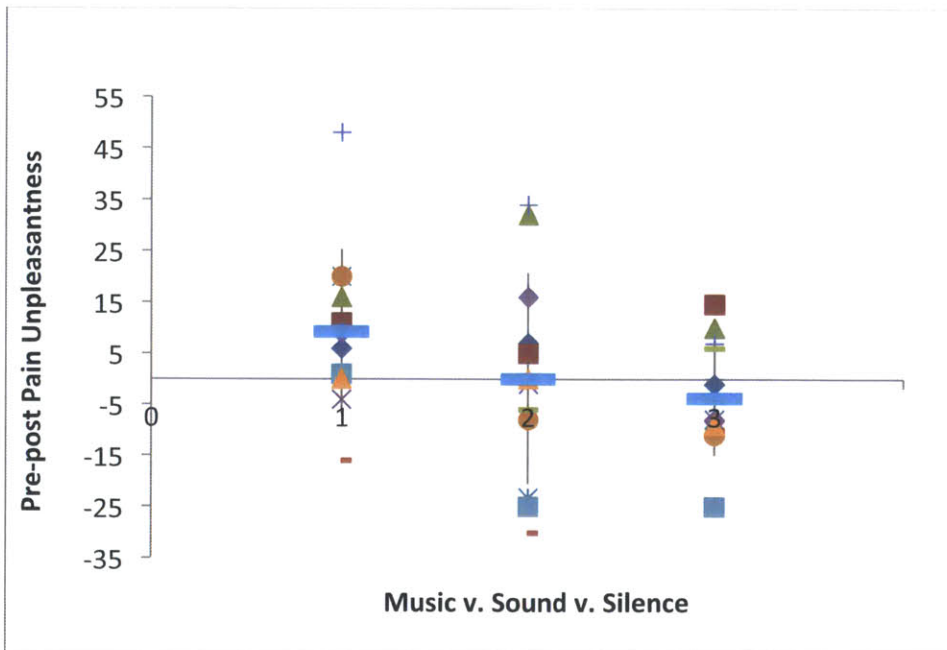
Figure 53: Individual subjects' pain unpleasantness analgesia, music conditioning group.
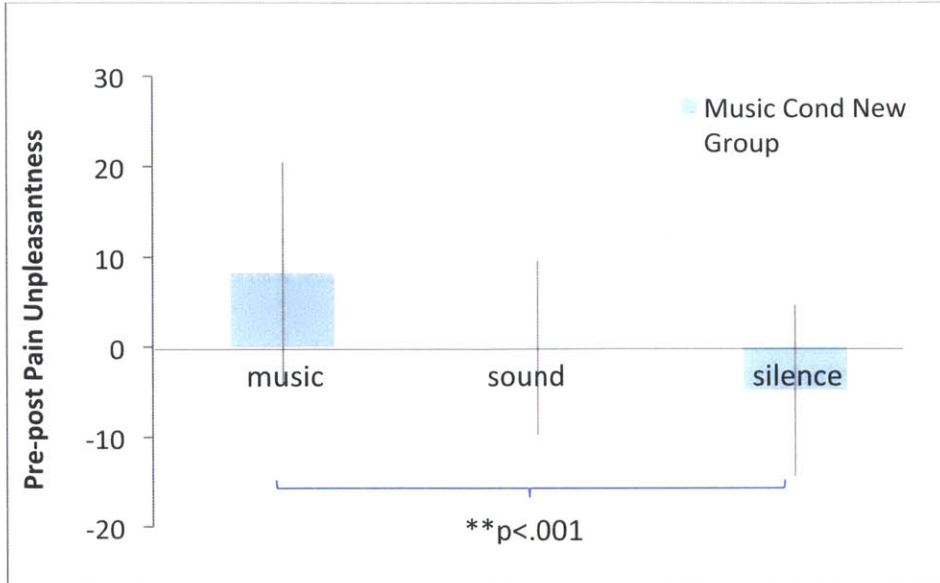
Figure 54: Average pain unpleasantness analgesia, new music conditioning group. In the new music conditioning group, which used an explicit conditioning paradigm, the pain reduction by conditioned music as compared to silence was highly significant, but not as compared to sound.
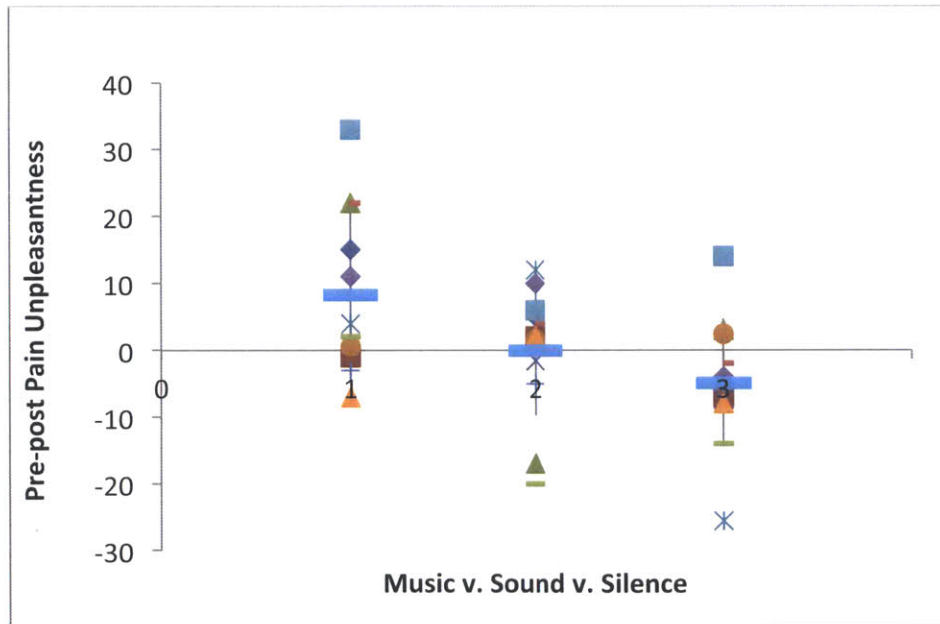
Figure 55: Individual subjects' pain unpleasantness analgesia, new music conditioning group.

For both pain intensity and pain unpleasantness, the two music conditioning groups did not differ significantly in their magnitudes of analgesia. All analgesic effects were also verified in repeated measures analyses using SPSS; audio was still found to be the main factor of significance ($p < .001$), with group a nonsignificant factor.

Additional analyses on pain ratings with outliers removed

To address the large standard deviation in the original music conditioning group, additional analyses were completed by removing subjects who gave ratings that were greater than two standard deviations from the mean (i.e. outliers). An analysis of variance did not show significant differences in analgesia for music, sound, or silence between the two music conditioning groups. Generally the same between-audio significant effects were seen, with p-values for changed groups now at:

**p = .008 for the music conditioning group, between music and silence for Pain Intensity; *p = .03 between music and silence for Pain Unpleasantness

*p = .01 for the second music conditioning group, between music and silence for Pain Unpleasantness

*p = .04 for the sound conditioning group, between music and silence for Pain Intensity; *p=.01 between music and silence, **p = .008 between sound and silence for Pain Unpleasantness

The greatest change appeared to be a reduction in significance in the second music conditioning group, in the Pain Unpleasantness ratings between music and silence, from ***p<.001 to *p=.01, rendering it essentially equivalent to the effect in the original music conditioning group. Three outliers were removed from this second music group.

Relationship between Analgesia and Expectancy
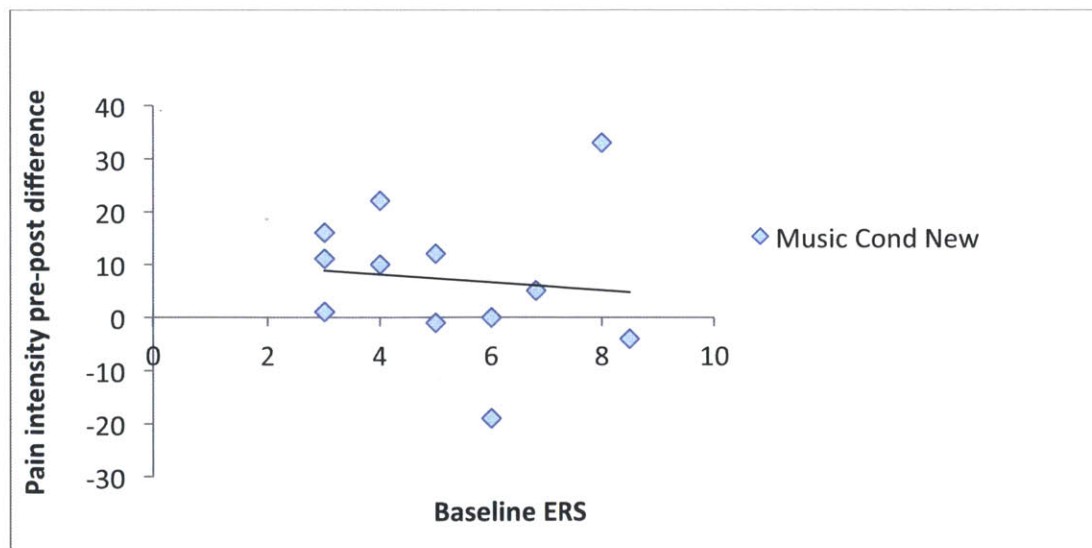
Figure 56: Average pain intensity analgesia in the new music conditioning group, as a function of baseline ERS. There appears to be no relationship between music analgesia and the completely naive ERS baseline score, before verbal induction.
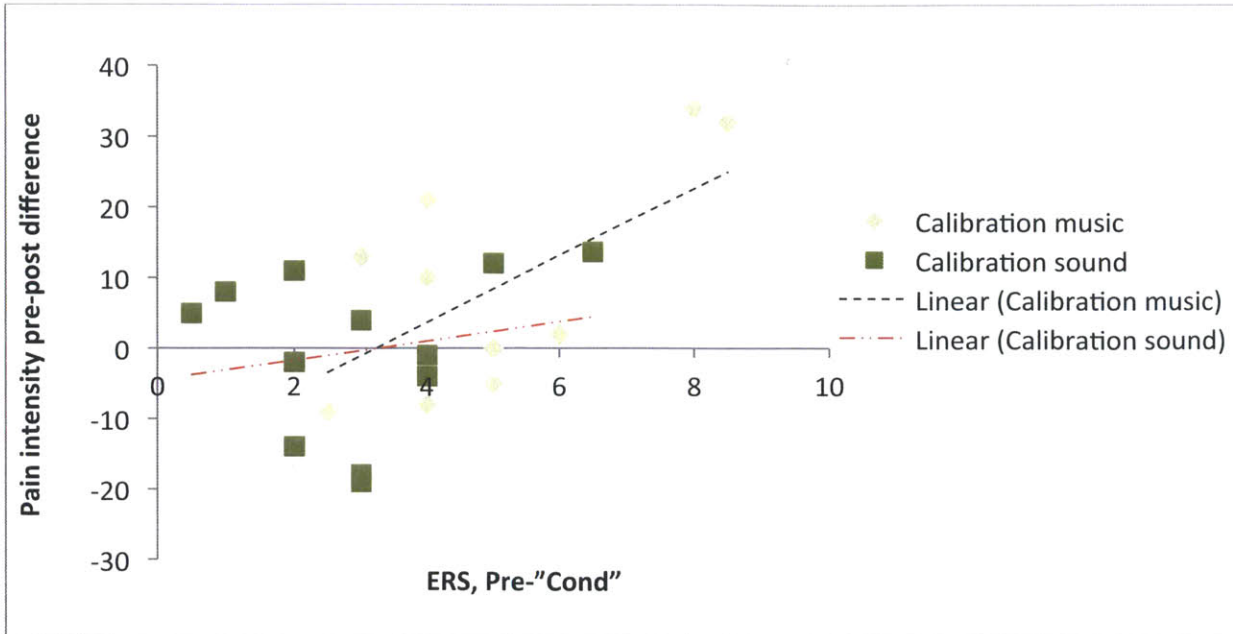
Figure 57: Average pain intensity analgesia in the calibration group, as a function of ERS assessed after neutral verbal induction and before the left arm stimulation (equivalent of conditioning in conditioning groups). Linear regression trendlines show there is a fairly strong relationship between analgesia and ERS assessed after "neutral" verbal induction for music. There is a much smaller, perhaps insignificant relationship for sound.
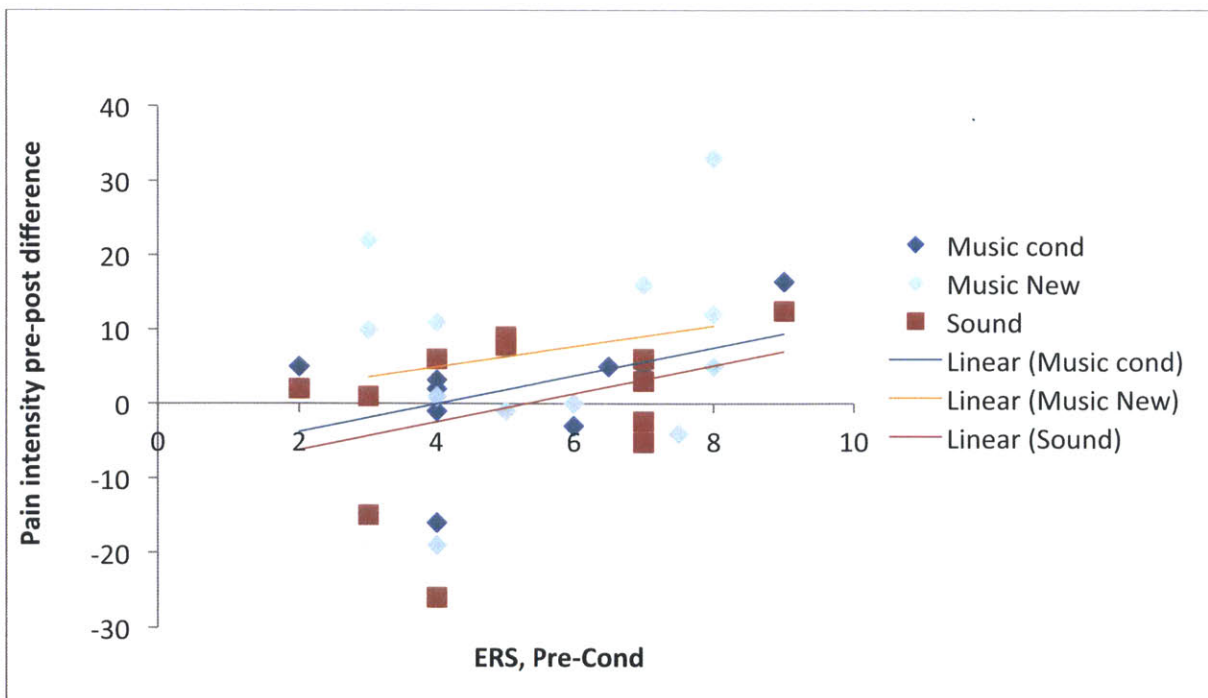
Figure 58: Average conditioned stimuli pain intensity analgesia in the conditioning groups, as a function of ERS assessed after specific verbal inductions. A similar relationship holds for the

conditioning groups, compared to music in the calibration group, for ERS at the post-verbal induction/pre-conditioning point. Explicit music conditioning appears to achieve more analgesia than the original music conditioning. In this and the following plot, one subject with outlier scores was removed from the music conditioning group.
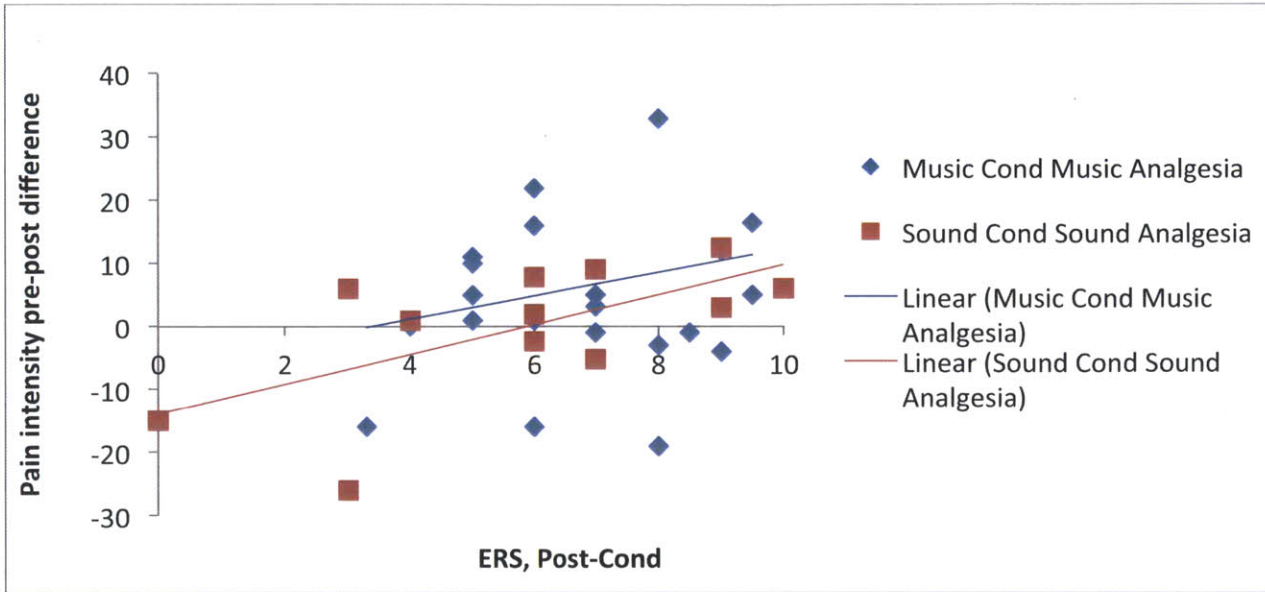
Figure 59: Average conditioned stimuli pain intensity analgesia in the original conditioning groups, as a function of ERS assessed after conditioning. The data show that the two conditioned stimuli had similar relationships to their ERS scores post-conditioning, with the music conditioning achieving more analgesia than the sound conditioning.

Variability of Pain Ratings
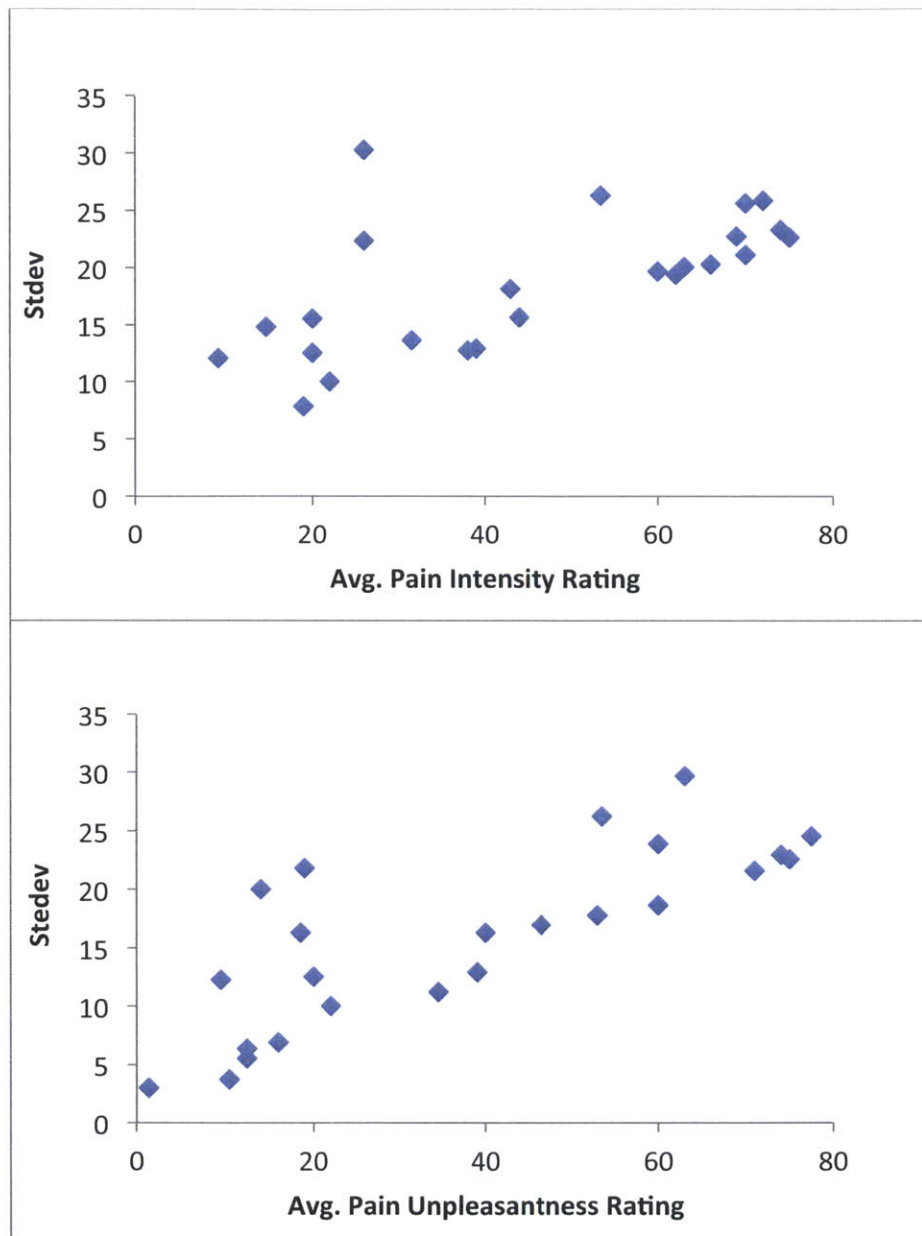
Figure 60: Calibration group - Stdevs of individual trials, Pain Intensity (upper panel), Stdevs of individual trials, Pain Unpleasantness (lower panel). Shown here is the variability of subjects' pain ratings, with standard deviation plotted as a function of the average pain rating each subject gave during low and high heat trials in the calibration group.

Additional Analyses
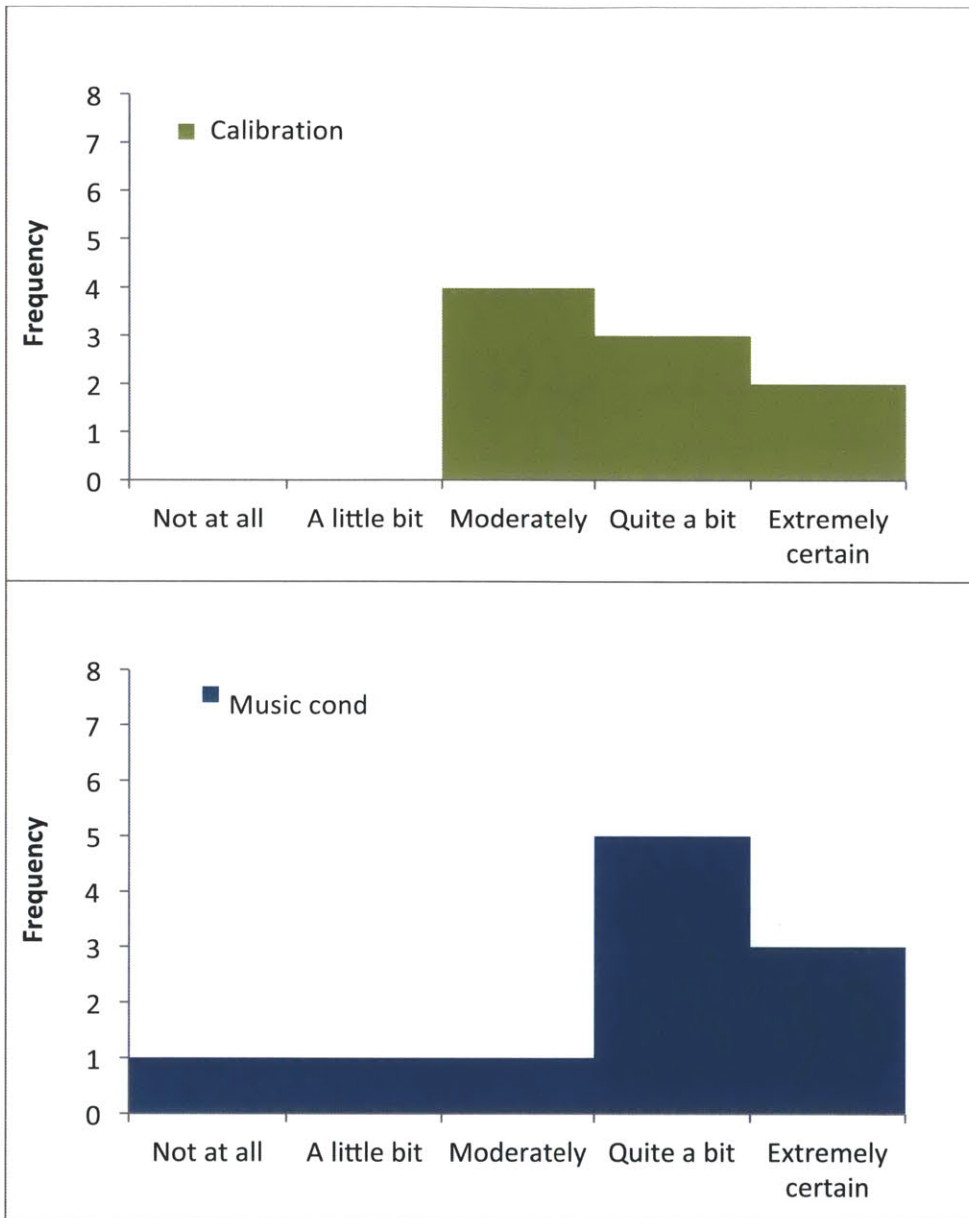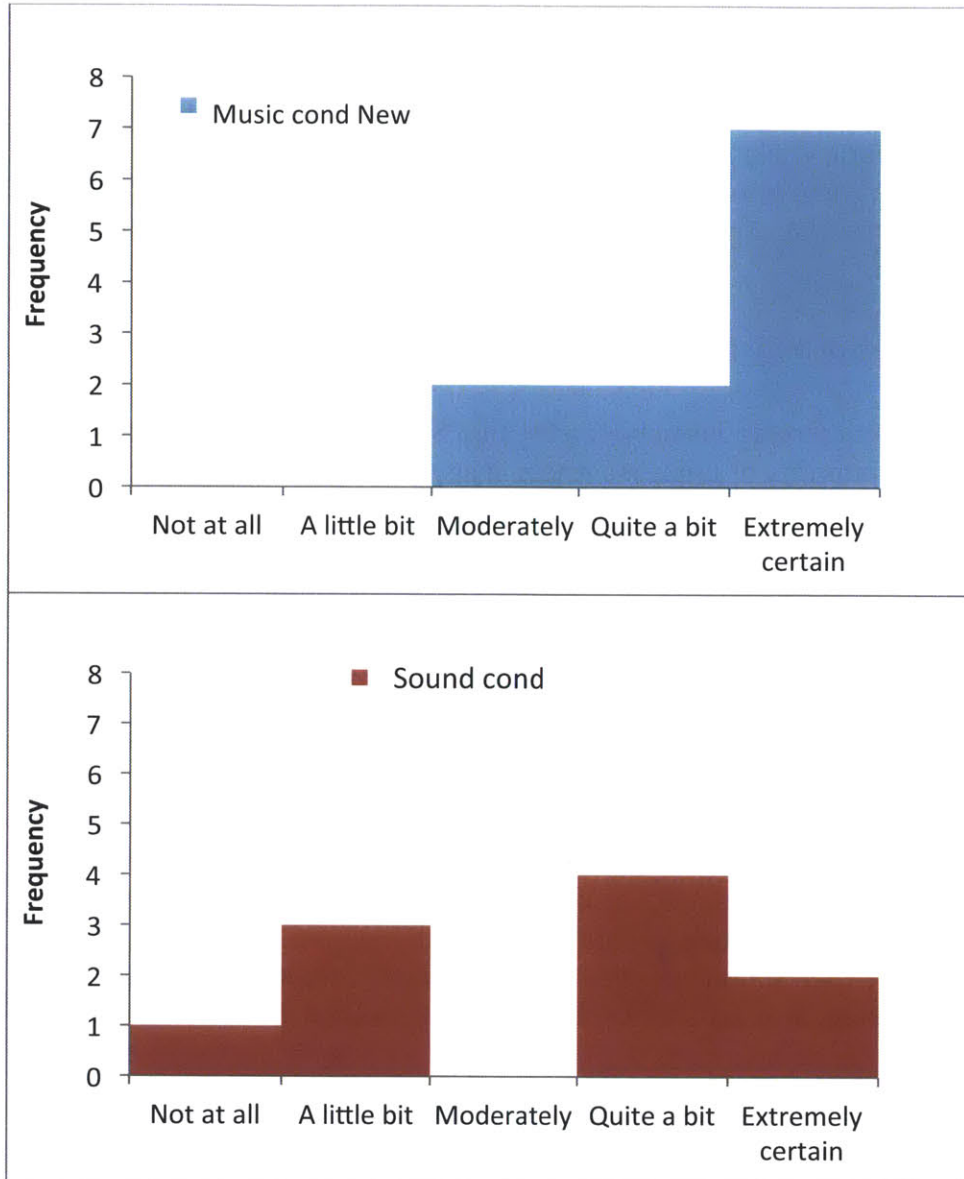
Figure 61: Histograms of certainty of pain relief, as assessed on the final survey. Shown are answers from subjects who answered "yes" first to the question "Are you certain you felt relief with your treatment?", and then answered how certain they were of their answer. For the calibration group, certainty is only shown for subjects' thoughts about the music, not the sound sample.

Comparing the two music conditioning groups to the calibration group, conditioning appears to skew subjects' impression that they are certainly feeling less pain when listening to the music, as assessed in the final survey after testing. The explicit conditioning shifts subjects' certainty to be even more certain than the implicit music conditioning. Those in the sound conditioning group seemed to feel most ambivalent, with roughly half being fairly uncertain and half being fairly certain.

Self Assessment Manikin (SAM) – Calibration group

T-tests show that a comparison of perceived control, the last visual scale of the SAM, between music v. sound and music v. silence are significant at *p = 0.012 and **0.005, respectively. For valence, differences between music v. sound and music v. silence are quite significant at **p=.002 and ***p<.001. There were no significant differences between audio conditions for the arousal scale.

Correlations with baseline personality factors

There were no significant correlations between the BDI, STAI-T, rumination (RRQ), TAS, or GSES and analgesia for pain intensity or unpleasantness in any groups.

Discussion

Overall, expectancy differed significantly within the calibration group between expectations for music and that for the sound sample (**p<.001). This difference was seen at all time points the ERS was assessed, with a slightly less significant difference after testing. The verbal induction boosts expectations significantly higher (*p=.03) in the sound conditioning group, to the level of music expectations. In the new music conditioning group, an additional assessment of ERS at a completely naive baseline in this group shows that verbal induction did not significantly raise expectations for music. We also see a replication of pre-conditioning ERS scores for music conditioning. For pain ratings, within the calibration group, music reduced pain intensity significantly more than sound and silence. In the sound conditioning group, only unconditioned music reduced pain, as compared to silence. In the original music conditioning group, only music reduced pain as compared to silence, with neither magnitude or significance greater than that seen in the calibration group. In the second music conditioning group, music again reduced pain as compared to silence, with a slight increase in significance compared to the original music conditioning group.

Expectations

Prior to beginning the study, subjects have already had years of experience with the song they would choose for the testing phase. Thus these songs were already powerful emotionally, with depth and richness in their associations to each individual's life. Even though efforts were made to exclude songs with conscious specific memories and autonomic chill reactions associated with them, it is likely that at the subconscious level the music's history with each person influenced its role in the analgesia. This is probably a factor contributing to the fairly high expectations for music seen in the second music conditioning group even at baseline (Fig. 32), before the verbal induction had occurred. Thus one could argue that there may not be much more potential for subject's expectations for music to be increased further when already starting at such a high level. In fact, this is seen in Figure 35 where verbal

induction, a technique that frequently successfully boosts expectations of analgesia in placebo studies (32, 54-56), does little to further enhance expectations in the two music groups. Music on its own was consistently rated higher than the sound sample as seen in Figure 33 in the calibration group. The initial ratings for the sound sample were slightly low yet comparable to initial expectations seen in other placebo analgesia studies with relatively neutral cues (55). Presumably, though expectations for the sound sample were not assessed before the verbal induction in the sound conditioning group, subjects had a low starting expectation similar to that seen in the calibration group (with no reason to expect otherwise, as the two groups did not differ until the verbal induction point) where there was only neutral verbal introduction of the audio analgesia. Following verbal induction, expectations in the sound conditioning group rose to the same pre-conditioning level as for the music groups and for music in the calibration group. This would indicate that verbal induction on its own can successfully boost expectations for a stimuli like the sound sample used.

However, attempting to further boost expectations with the conditioning block failed in the sound conditioning group, whereas the procedure was modestly successful in the music conditioning groups (Fig. 36). Levels of expectancy enhancement achieved were comparable to those seen in other conditioned analgesia studies (32, 55). The lack of significant boost to expectation for sound seems consistent with the responses to the question in the final survey of how certain subjects were that they felt relief with their treatment. Within the sound conditioning group there was a split in certainty of analgesia (Fig. 61); this seemed to correspond with the qualitative feedback received on the nature of the sound sample – soothing to some, annoying to others. It is possible that the negative evaluations some subjects made of the sound sample interfered with the conditioning of the sound such that these subjects became uncertain of relief even when part of them had experienced the conditioned analgesia, a kind of emotional destructive interference for the conditioning. This may have also influenced the expectations of the subjects.

Pain Ratings

Within pain ratings, the pattern was more nuanced than simply a dichotomy between music and sound. In the calibration group, music significantly reduced pain intensity ratings more than silence, and somewhat significantly more than sound (Fig. 38). For the affective evaluation of pain unpleasantness, the same pain reductions held (Fig. 48), but sound was also able to reduce pain unpleasantness somewhat significantly as compared to silence. This indicates that for pain intensity, a rating subjects were told represented more of the physical sensation of the stimuli, music was the most effective; for the evaluation of how much the stimulus bothered them, the proportion of subjects finding sound to be effective over silence was comparable to the difference in proportion feeling that music was better than sound. Thus sound was able to serve some sort of role in changing the affective experience of the pain.

In the sound conditioning group, only music was able to reduce pain intensity somewhat significantly more than silence. Conditioned sound was not effective, nor was music more pain-relieving than sound in this group. However, the ratings for pain unpleasantness indicated a different pattern. Both conditioned sound and unconditioned music significantly reduced pain unpleasantness more than silence. Once again, as for the calibration group, sound was able to

reduce the emotional impact from the pain, but even with a boost from conditioning it was unable to shift the pain intensity ratings significantly away from those for silence. It is striking that music, even when it is the unconditioned stimulus juxtaposed with conditioned sound, still has potent pain relieving effects. This is often not the case in other conditioning studies, where the unconditioned cue can actually have a hyperalgesic, nocebo effect (54). Here, music actually remains analgesic, though it is apparent that its magnitude of analgesia is lower in the sound conditioning group than it is in the other three groups. This lowering of music's analgesic effect is most likely also responsible for the lack of significant difference in analgesia between music and sound in the sound conditioning group, whereas the calibration group displayed a significantly greater pain reduction from music over sound.

For the original music conditioning group, conditioned music reduced both pain intensity and unpleasantness significantly more than silence, but not more than sound. Sound was not an effective pain reliever for either pain sensation or the affective component. Presumably the lack of analgesia from sound as compared to silence (an effect that was present in the calibration group for pain unpleasantness) is due to it being in the unconditioned stimulus position within this group. Similar to the situation in the sound conditioning group, the conditioned music could have reduced the efficacy of the sound sample in reducing pain unpleasantness. Interestingly, music was not more effective than sound for either intensity or unpleasantness, contrary to the situation in the calibration group. One possible explanation for this observation is the difference in timing of when music and sound occur in the context of the pain stimuli between the calibration and conditioning groups. Whereas the calibration group hears the two types of audio for the first time during the testing block, the conditioning groups (necessarily to invoke conditioning) have already heard each audio type twice by the time they enter testing. It is possible that this introduces ambiguity or variance into subject ratings of pain in the testing block for the conditioning groups, as they may have additional cognitive load from their previous experience of having heard the audio samples already a couple times in association with the pain, whereas subjects in the calibration group may have a more uniform reaction to their music the first time they hear it with the pain stimuli. In study 1 of this thesis, difficulty was also seen with repeat usage of the same songs on successive days – repetition may actually be a negative factor when using a cue like music in the context of cognitive and perceptual modulation.

Shifting to the second music conditioning group, where an explicit conditioning paradigm was used, the only significant effect also appears to be for music relieving pain intensity and unpleasantness more than silence. In comparing the two music conditioning groups, the most apparent difference is between significance levels of the effects, with the original group achieving lower levels of significance. This implies that the second conditioning paradigm was able to achieve a greater distinction in subject evaluation of pain in the context of music, versus silence. The difference between conditioning procedures was not reflected in a direct, pairwise comparison of analgesia magnitudes. However, from the final survey question of certainty of analgesia, again we may be able to draw clues. In the calibration group, despite there being a spread in certainty of relief, the skew is towards moderate to very certain belief in analgesia with music (Fig. 61). While the implicitly conditioned music group shifts responses to "quite" or "extremely" certain of pain relief, a couple subjects also end up being very much or fairly uncertain, indicating that there was some cognitive conflict in experiencing

analgesia with the conditioned music in this group. The explicitly conditioned music group appears to be similar to the calibration group in distribution on the certain side, but with the majority of responses being extremely certain. This seems to indicate that whatever ambiguity was generated in the first music conditioning group was eliminated in the second music group – possibly a result of less subconscious cognitive dissonance. Thus, the difference in levels of significance within pain ratings between the groups could be associated with the difference in distribution of certainty ratings marked by subjects after the testing block. When considering the analyses undertaken with outliers removed, the fact that the two groups become equivalent with respect to this effect means that the explicit conditioning procedure does not consistently change the percept of all subjects in the group, but rather it affected 3 of the 12 subjects strongly (these three were removed as outliers). The change in result with the removal of outliers is taken cautiously here, as 3 out of 12 of the subjects is a quarter of the group, a sizeable proportion to take out. Given larger group sizes, the influence of the outliers may actually be the same as the effect of explicit conditioning on the majority of the group.

Analgesia as a Function of Expectancy

A deeper look at the relationship between pain intensity analgesia and expectation between the different groups reveals an interesting pattern of changes between different ERS assessment times. The second music conditioning group shows the relationship between naïve expectations, taken at the first assessment before verbal induction, and conditioned music analgesia (Fig. 56). It appears that subjects' native expectations of their music were not actually related to their music-induced analgesia. Conceptually, this relationship could look the same as that in the calibration group between music expectation after neutral verbal induction and music analgesia, given that the two ERS conditions are functionally equivalent (neutral verbal induction should not in theory boost expectations for music given the presented context). However, Figure 57 shows that for the calibration group there is in fact a positive relationship between music analgesia and expectation. The difference may mean that even though music was presented neutrally to the calibration group prior to testing with it, simply reminding subjects explicitly that music (and the sound sample) has been found to have analgesic effects could subtly shift their focus to thinking about their expectations in the specific context of actually relieving their pain. The difference is essentially only in the words surrounding the queries for expectation – for the naïve expectation, it is simply asked without a priming statement about music and the sound sample having analgesic effects, so subjects at that time could have marked a more general expectation of their music to be positive. In the calibration group, after verbal induction for both music and sound, subjects could be focused more specifically on the idea of their music relieving pain and marked their expectation of relief *for the next set of pain stimuli with their music*. If this were the case, it would be important to be aware of the statements surrounding the timing of the ERS scale assessment in future analgesia studies involving expectancy manipulation.

Expectations for the sound sample did not appear to be related to sound-induced analgesia in the calibration group. Given that expectations for sound remained significantly lower throughout the session in this group, it is possible that without a specific verbal induction (i.e. without mentioning that music may also relieve pain) and without conditioning, influence

from this sound sample remained minimal in that subjects had no reason to attend to or believe specifically in it, and hence was unrelated to any analgesic effects.

For the conditioning groups, expectations before and after the conditioning block were positively related to analgesia from the conditioned stimulus (Fig. 58, 59), with the relationship being similar in both cases. These results are consistent with previous studies designed to boost analgesia through expectancy manipulation (32). It is interesting that conditioned sound-induced analgesia was still related to post-conditioning expectations for sound, even though conditioning did not significantly boost expectations for sound. This seems to indicate that despite boosts in expectancy being small, wherever subject expectations ended up in that group they still played a role in sound-induced analgesia. It is also of merit to note that ERS scores did not decrease significantly after the post-test for any of the conditioning groups (Fig. 37). This implies that there is a robust analgesic expectation of both the music and sound, even after testing at the high pain level again. Thus, there is likely an interaction with expectation from the audio samples themselves beyond what something like a placebo analgesia cream could achieve – again this is probably due to the affective nature of the audio leading subjects to have a more complex relationship to the cues than they could to a cream. In fact, there has been strong evidence that the nature of the cue in placebo studies significantly changes the potential for analgesia. Specifically, the more ritual surrounding the treatment of interest, whether it is placebo or not, the more often it is able to elicit multiple kinds of salubrious effects on the subjects. On the other hand, this also introduces a factor of cognitive load (57), which could complicate intended conditioning effects. Still, these kinds of subconscious factors have been seen to have extraordinary effects in a placebo study completed recently (58). In the study at hand, personal music is undoubtedly laden with symbolism for subjects, and even the sound sample probably invoked a cognitive concept of related past experiences. In fact, many subjects mentioned that it reminded them of either "the noise machine [they] use to sleep", or ocean waves. Thus there could be an ongoing capacity for these audio cues to carry analgesic effects over repeated pain stimulations, almost as if the rich emotional and cognitive associations acted as protective gates while pain stimulations battered against the doors. Future experiments could test whether music or the sound sample could hold pain relieving effects over a longer time course than even a conditioned placebo cream could.

Potential Analgesic Features of Personal Music

An important and well-debated alternative explanation for the results seen here could be that the complex emotional and cognitive effects from the music and sound sample acted as potent forms of distraction. From the differences between ratings for pain intensity and unpleasantness, it is apparent that they are differentially affected by audio. Pain unpleasantness seems to be more vulnerable to modulation by both music and sound than pain intensity. This is in some contrast to most audio analgesia studies, and in fact many other experimental pain studies, where pain intensity and unpleasantness ratings are usually modulated similarly (14, 19, 32), or pain intensity not at all in the case of some audio analgesia studies. Certain specific studies that aimed to modulate emotion were able to differentially change pain unpleasantness over pain intensity; it has been hypothesized that distractions

reduce pain intensity, whereas emotional stimuli affect pain unpleasantness more (18). Still, the results here are unique: not only did music and sound on their own reduce pain unpleasantness ratings, but music was able to also reduce pain intensity without conditioning. Most likely this is a testament to the specific criteria that music in this study fulfilled – all strongly pleasurable, highly familiar pieces. Framed in the theory behind these studies, it could be that the music we requested is essentially a strongly emotional distraction, able to modulate both pain intensity and unpleasantness effectively. Strongly pleasurable music is known to engage brain regions central to reward, arousal, and personality (7, 10, 26). Strong negative experiences often have a "magnetic" effect, where individuals find it difficult to disengage from attending to the negative cue. This is very related to rumination, the construct that was modulated by the treatment in study 1 of this thesis. It is very difficult to imagine a highly emotional stimulus that is *not* distracting. Accordingly, that the music was able to both attenuate pain unpleasantness *and* intensity indicates that not only was it emotionally modulating and rewarding but that the strength of the emotion was strong enough to shift attention away from the percept of the pain sensations.

Within the Self Assessment Manikin (SAM) ratings, a pattern supporting this line of reasoning was seen. Music did not appear to act as a modulator of SAM arousal either in a relaxing way or to energize – instead, the lack of difference in arousal between music, sound, and silence most likely reflects subject reactions to the arousing nature of the pain stimuli rather than any audio. However, music significantly increased ratings for valence and control over sound and silence during testing. It is likely that the increase in control from music was linked to the way that many subjects used it, as reflected in their comments during the study and in the final survey. Many times the song was used purposefully as a distractor to focus attention upon, almost as an anchor of comfort and control during the trials of pain. It was consistently stated that the music worked because it was either soothing or a good distraction.

Limitations

A few caveats and directions for future studies are worth mentioning. First, the use of the left arm for the conditioning block may have made it more difficult for the conditioning to be effective, as indicated by some subjects' comments in the final survey. Those respondents stated that they felt the left arm may have been different than the right – in essence, subjects have more reason to be sensitive to changes in pain levels due to the large location switch. It may be that staying on the same arm would minimize attention to shifts in heat levels during the covert conditioning. Secondly, a large standard deviation of pain ratings was seen at the higher heat levels (Fig. 60); this may have made results less significant within the relatively small group sizes here. Finally, future work could explore other comparison audio conditions that are more complex and potentially more magnetic for attention than the sound sample used here.

Conclusion

The results of this study demonstrate that individuals inherently know how to use their music to calm, distract, or regulate themselves even in the context of intense pain. Thus, this

kind of music has strong clinical potential, as it is an effective analgesic even without adding in conditioning. Music was seen to have analgesic potential beyond simply distraction or emotional soothing, as subjects *actively* worked with it to enhance its analgesic power. Future explorations should aim to discover how a sustainable course of pain management could be charted through the inclusion of dynamic, personal music usage.

IV. Closing

The studies in this thesis work explore the potential of music to augment treatments for chronic diseases. In study 1, it was seen that music could be used successfully as an anchor to teach people mindfulness practice. The practice became easier over time, and it was calming and enjoyable to many who participated. It even proved to be better than the three minute breaks that originated from the ideals of other more formal mindfulness practices, possibly indicating that music could be effective in helping people cross a threshold of decision to initiate the practice. In study 2, subjects demonstrated their ability to use personal music effectively to regulate their pain experience, even without the intended boost from conditioning. This is in line with previous research showing the inherent capability most individuals have in harnessing music even without training, to change their mood, calm anxiety, regulate themselves, and enrich their lives. Overall, the results of both works inform and encourage the design of future studies that could push the boundaries of what can be achieved with the rich complexity of music. The promise inherent in our deep relationship with music will foster connections to health and new innovative developments for decades to come.

References for Study 2

Study data were collected and managed using REDCap electronic data capture tools hosted at MGH.[1] REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.

[1]Paul A. Harris, Robert Taylor, Robert Thielke, Jonathon Payne, Nathaniel Gonzalez, Jose G. Conde, Research electronic data capture (REDCap) - A metadata-driven methodology and workflow process for providing translational research informatics support, J Biomed Inform. 2009 Apr;42(2):377-81.

1. Bufalini A (2009). Role of interactive music in oncological pediatric patients undergoing painful procedures. *Minerva Pediatr*. 61(4):379-389.
2. Moradipanah F, Mohammadi E, Mohammadil AZ (2009). Effect of music on anxiety, stress, and depression levels in patients undergoing coronary angiography. *East Mediterr Health J*. 15(3):639-47.
3. Park H, Pringle Specht JK (2009). Effect of individualized music on agitation in individuals with dementia who live at home. *J Gerontol Nurs*. 35(8):47-55.
4. Forsblom A, Laitinen S, Särkämö T, Tervaniemi M (2009). Therapeutic role of music listening in stroke rehabilitation. *Ann N Y Acad Sci*. 1169: 426-30.
5. Mitterschiffthaler MT, Fu CH and Dalton JA *et al.* (2007). A functional MRI study of happy and sad affective states induced by classical music, *Hum Brain Mapp* 28: 1150–1162.
6. Peretz *et al* (1998). Music and emotion: Perceptual determinants, immediacy, and isolation after brain damage. Cognition. 68: 111-141.
7. Blood A and Zatorre RJ (2001). Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. Proc. Natl. Acad. Sci. USA 98 : 11818–11823.
8. Osuch EA, Bluhm RL, Williamson PC, Théberge J, Densmore M, Neufeld RW (2009). Brain activation to favorite music in healthy controls and depressed patients. *Neuroreport*. 20(13):1204-8.
9. Fritz T, Jentschke S, Gosselin N, Sammler D, Peretz I, Turner R, et al. (2009). Universal recognition of three basic emotions in music. *Current biology : CB*, *19*(7), 573-6.
10. Salimpoor, V. N., Benovoy, M., Longo, G., Cooperstock, J. R., & Zatorre, R. J. (2009). The rewarding aspects of music listening are related to degree of emotional arousal. *PloS one*, *4*(10)
11. Bigand, E., & Poulin-Charronnat, B. (2006). Are we "experienced listeners"? A review of the musical capacities that do not depend on formal musical training. *Cognition, 100*(1), 100-30.
12. Rentfrow, P. J., & Gosling, S. D. (2003). The do re mi's of everyday life: the structure and personality correlates of music preferences. *Journal of Personality and Social Psychology*, *84*(6), 1236-1256

13. Osuch EA, Bluhm RL, Williamson PC, Theberge J, Densmore M, Neufeld RW (2009). Brain activation to favorite music in healthy controls and depressed patients. *Neuroreport* 20(13): 1204-1208.

14. Villarreal EA, Brattico E, Vase L, Østergaard L, Vuust P. Superior analgesic effect of an active distraction versus pleasant unfamiliar sounds and music: the influence of emotion and cognitive style. PLoS One. 2012;7(1). Epub 2012 Jan 5.

15. Bradshaw DH, Donaldson GW, Jacobson RC, Nakamura Y, Chapman CR. Individual differences in the effects of music engagement on responses to painful stimulation. J Pain. 2011 Dec;12(12):1262-73.

16. Knox D, Beveridge S, Mitchell LA, MacDonald RA. Acoustic analysis and mood classification of pain-relieving music. J Acoust Soc Am. 2011 Sep;130(3):1673-82.

17. Colloca L, Petrovic P, Wager TD, Ingvar M, Benedetti F. How the number of learning trials affects placebo and nocebo responses. Pain. 2010 Nov;151(2):430-9.

18. Villemure C, Schweinhardt P. Supraspinal pain processing: distinct roles of emotion and attention. Neuroscientist. 2010 Jun;16(3):276-84.

19. Roy M, Peretz I, Rainville P. Emotional valence contributes to music-induced analgesia. Pain. 2008 Jan;134(1-2):140-7.

20. Colloca L, Benedetti F. Nocebo hyperalgesia: how anxiety is turned into pain. Curr Opin Anaesthesiol. 2007 Oct;20(5):435-9

21. Mitchell LA, MacDonald RA, Brodie EE. A comparison of the effects of preferred music, arithmetic and humour on cold pressor pain. Eur J Pain. 2006 May;10(4):343-51.

22. Mitchell LA, MacDonald RA. An experimental investigation of the effects of preferred and relaxing music listening on pain perception. J Music Ther. 2006 Winter;43(4):295-316.

23. Perlini AH, Viita KA. Audioanalgesia in the control of experimental pain. Canadian Journal of Behavioural Science/Revue canadienne des sciences du comportement, Vol 28(4), Oct 1996, 292-301.

24. Koelsch S. Towards a neural basis of music-evoked emotions. Trends in Cognitive Sciences. 1 March 2010. 14(3), 131-137.

25. Roy M, Lebuis A, Hugueville L, Peretz I, Rainville P. Spinal modulation of nociception by music. Eur J Pain. 2012 Jan 31.

26. Montag C, Reuter M, Axmacher N. How one's favorite song activates the reward circuitry of the brain: personality matters! Behav Brain Res. 2011 Dec 1;225(2):511-4.

27. Rose JP, Geers AL, Rasinski HM, Fowler SL. Choice and placebo expectation effects in the context of pain analgesia. J Behav Med. 2011 Aug 18.

28. Pereira CS, Teixeira J, Figueiredo P, Xavier J, Castro SL, Brattico E. Music and emotions in the brain: familiarity matters. PLoS One. 2011;6(11):e27241.

29. Gracely, R.H., R. Dubner, and P.A. McGrath, *Narcotic analgesia: fentanyl reduces the intensity but not the unpleasantness of painful tooth pulp sensations.* Science, 1979. 203: p. 1261-1263.

30. Gracely, R.H., P.A. McGrath, and R. Dubner, *Ratio scales of sensory and affective verbal pain descriptors.* Pain, 1978. 5: p. 5-18.

31. Gracely, R.H., P.A. McGrath, and R. Dubner, *Validity and sensitivity of ratio scales of sensory and affective verbal pain descriptors: manipulation of affect by diazepam.* Pain, 1978. 5: p. 19-29.

32. Kong, J., et al., *Brain activity associated with expectancy-enhanced placebo analgesia as measured by functional magnetic resonance imaging.* J Neurosci, 2006. 26(2): p. 381-8.

33. Schwarzer R, Jerusalem M. Generalized Self-Efficacy scale. Windsor, England.: NFER-NELSON, 1995.

34. Tellegen, A. and G. Atkinson, *Openness to absorbing and self-altering experiences ("absorption"), a trait related to hypnotic susceptibility.* J Abnorm Psychol, 1974. 83(3): p. 268-77.

35. Neff, D.F., E.B. Blanchard, and F. Andrasik, *The relationship between capacity for absorption and chronic headache patients' response to relaxation and biofeedback treatment.* Biofeedback Self Regul, 1983. 8(1): p. 177-83.

36. Owens, J.E., A.G. Taylor, and D. Degood, *Complementary and alternative medicine and psychologic factors: toward an individual differences model of complementary and alternative medicine use and outcomes.* Journal of Alternative & Complementary Medicine, 1999. 5: p. 529-41.

37. Bell, I.R., D.A. Lewis, 2nd, A.J. Brooks, et al., *Individual differences in response to randomly assigned active individualized homeopathic and placebo treatment in fibromyalgia: implications of a double-blinded optional crossover design.* J Altern Complement Med, 2004. 10(2): p. 269-83.

38. Private self-consciousness and the five-factor model of personality: Distinguishing rumination from reflection. Trapnell, Paul D.;Campbell, Jennifer D. Journal of Personality and Social Psychology, Vol 76(2), Feb 1999, 284-304

39. Mayer, J. D., & Gaschke, Y. N. (1988). The experience and meta-experience of mood. *Journal of Personality and Social Psychology, 55,* 102-111.

40. Spielberger, C.D., R.L. Gorsuch, and R.E. Lushene, *Manual for the State-Trait Anxiety Inventory.* 1970, Palo Alto, CA: Consulting Psychology Press.

41. Szpunar KK, Schellenberg EG, Pliner P. Liking and memory for musical stimuli as a function of exposure. J Exp Psychol Learn Mem Cogn. 2004 Mar;30(2):370-81.

42. Janata P. The neural architecture of music-evoked autobiographical memories. Cereb Cortex. 2009 Nov;19(11):2579-94. Erratum in: Cereb Cortex. 2010 Jan;20(1):254-5

43. Gardner, W., Licklider, J. & Weisz, A. (1960). Suppression of pain by sound, *Science, 132,* 32.

44. Pothoulaki M, Macdonald RA, Flowers P, Stamataki E, Filiopoulos V, Stamatiadis D, Stathakis ChP. An investigation of the effects of music on anxiety and pain perception in patients undergoing haemodialysis treatment. J Health Psychol. 2008 Oct;13(7):912-20.

45. Voss JA, Good M, Yates B, Baun MM, Thompson A, Hertzog M. Sedative music reduces anxiety and pain during chair rest after open-heart surgery. Pain. 2004 Nov;112(1-2):197-203.

46. Voudouris, NJ, Peck, CL, Coleman, G. The role of conditioning and verbal expectancy in the placebo response. Pain 1990. 43(1), 121-128.

47. Watson, A., et al., Placebo conditioning and placebo analgesia modulate a common brain network during pain anticipation and perception. Pain, 2009. 145(1-2): p. 24-30.

48. Montgomery, G.H. and I. Kirsch, Classical conditioning and the placebo effect. Pain, 1997. 72: p. 107-113.

49. Price, D.D. and J. Barber, An analysis of factors that contribute to the efficacy of hypnotic analgesia. J Abnorm Psychol, 1987. 96(1): p. 46-51.

50. De Pascalis, V., C. Chiaradia, and E. Carotenuto, The contribution of suggestibility and expectation to placebo analgesia phenomenon in an experimental setting. Pain, 2002. 96(3): p. 393-402.

51. Price, D.D., et al., An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. Pain, 1999. 83: p. 147-156.

52. Geisser, M.E., R.S. Roth, and M.E. Robinson, Assessing Depression Among Persons with Chronic Pain Using the Center for Epidemiological Studies Depression Scale and the Beck Depression Inventory: A Comparative Analysis. Clin J Pain, 1997. 13: p. 163-170.

53. Turner, J.A. and J.M. Romano, Self-Report Screening Measures for Depression in Chronic Pain Patients. J Clin Psychol, 1984. 40: p. 909-913.

54. Kong J, Gollub RL, Polich G, Kirsch I, Laviolette P, Vangel M, Rosen B, Kaptchuk TJ. A functional magnetic resonance imaging study on the neural mechanisms of hyperalgesic nocebo effect. Journal of Neuroscience 2008; 28: 13354-13362. PMID: 19052227 PMCID: PMC2649754.

55. Kong J, Kaptchuk TJ, Polich G, Kirsch I, Vangel M, Zyloney C, Rosen B, Gollub R: Expectancy and treatment interactions. A dissociation between acupuncture analgesia and expectancy evoked placebo analgesia. Neuroimage 2008; 45: 940-9. Epub 2008 Dec 29. PMID: 19159691

56. Kong J, Kaptchuk TJ, Polich G, Kirsch I, Vangel M, Zyloney C, Rosen B, Gollub RL: An fMRI study on the interaction and dissociation between expectation of pain relief and acupuncture treatment. Neuroimage 2009; 47: 1066-76. Epub 2009 Jun 6. PMID: 19501656

57. Kaptchuk TJ, Shaw J, Kerr CE, Conboy LA, Kelley JM, Csordas TJ, Lembo AJ, Jacobson EE. "Maybe I made up the whole thing": placebos and patients' experiences in a randomized controlled trial. Cult Med Psychiatry. 2009 Sep;33(3):382-411.

58. Jensen KB, Kaptchuk TJ, Kirsch I, Raicek J, Lindstrom KM, Berna C, Gollub RL, Ingvar M, Kong J. Nonconscious activation of placebo and nocebo pain responses. Proc Natl Acad Sci U S A. 2012 Sep 25;109(39):15959-64. Epub 2012 Sep 10.

59. Garland EL. Pain processing in the human nervous system: a selective review of nociceptive and biobehavioral pathways. Prim Care. 2012 Sep;39(3):561-71. doi: 10.1016/j.pop.2012.06.013. Epub 2012 Jul 24. Review. PubMed PMID: 22958566