RESEARCH PROPOSAL

STUDY: A Study of the Effect of Rhythmic Sensory Stimulation and Music on Fibromyalgia

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STUDY SUMMARY: Fibromyalgia is a chronic pain disorder associated with widespread pain that dramatically impacts patient's quality of life. Its exact cause has not yet been identified, however recent studies have indicated that fibromyalgia is associated with significant imbalance of the connectivity within brain networks associated with pain (Cifre *et al.,* 2012), decreased functional connectivity in the descending pain-modulating system, and increased activity in the pain matrix related to central sensitization (Cagnie *et al.,* 2014). It has been suggested, therefore, that treatments that stimulate or induce coherent neuronal activity, and synchronize dysregulated brain circuitry, have significant benefits, improving pain management and enhancing patient's quality of life.

An example of a non-invasive treatment that is thought to indirectly stimulate neuronal coherence is Rhythmic Sensory Stimulation (RSS) in gamma frequencies. RSS stimulates the mechanoreceptors in the body using low-frequency sound (e.g., 40 Hz) by means of speakers in a chair (Lehikoinen, 1997). Previous research has demonstrated significant results on pain management in several pain conditions (e.g., rheumatoid arthritis, low-back pain, sports injuries); however, little is known about the effect of Rhythmic Sensory Stimulation with low-frequency sound on fibromyalgia. The use of RSS to treat fibromyalgia was first explored by Naghdi and colleagues (2015) at Mount Sinai Hospital (Toronto/Canada), suggesting that this treatment could be an effective treatment to fibromyalgia given that 40 Hz low-frequency sound stimulation indirectly stimulates neuronal coherence. The present research proposal aims to expand Naghdi's study in order to determine the effectiveness of Rhythmic Sensory Stimulation with 40 Hz sound on the treatment of fibromyalgia.

Aim: The present study aims to examine and determine the effectiveness of Rhythmic Sensory Stimulation at 40 Hz with sound on improvement of pain management and quality of life of patients with fibromyalgia.

Intervention: The proposed treatment involves 30 minutes of daily rhythmic vibroacoustic stimulation at 40Hz, 5 days per week, for 5 weeks. The treatment is self-administered by the patients at home with the Sound Oasis VTS 1000 portable device. Measures of pain severity, fibromyalgia symptoms, sleep quality, and depression, will be compared before and after treatment between the treatment and control groups.

Outcomes: It is expected that patients undergoing RSS at 40 Hz will have significantly different scores after treatment in all outcome measures examined in comparison to the control group. The results of the present study will help to better understand the effectiveness of Rhythmic Sensory Stimulation to the treatment of chronic pain disorders, such as fibromyalgia, and contribute to the development of future studies to investigate the neural driving effects of therapies based on Rhythmic Sensory Stimulation.

Keywords: Fibromyalgia, Rhythmic Sensory Stimulation, Gamma Stimulation

A Study of the Effect of Rhythmic Sensory Stimulation and Music on Fibromyalgia

Introduction

Fibromyalgia is characterized by complex chronic widespread pain for which no alternative cause (e.g., tissue damage or inflammation) can be identified (Sommer, 2010; Clauw, 2009; Wolfe *et al*., 2011). Fibromyalgia is also associated with chronic fatigue, sleep disturbance, anxiety, headaches, gastrointestinal symptoms, depression, and others. It is estimated that 2% to 4% of the population is affected by fibromyalgia, of whom 80% are women between 30 to 50 years of age (Wolfe *et al*., 1995). Studies suggest that 5 million people in the United States are affected by fibromyalgia (Lawrence *et al*., 2008), and approximately 393,000 in Canada. Currently, there is no cure for fibromyalgia, and most effective treatments involve multi-disciplinary approaches including medications, physical therapy, psychologically based therapies, and complementary/alternative treatments (Arnold, 2009).

The probable causes of fibromyalgia have not yet been clearly determined, however, recent studies have suggested that this chronic condition is associated to a disorder of central pain processing that results in heightened responses to painful stimuli (hyperalgesia), and painful responses to nonpainful stimuli (allodynia) (Clauw, 2009). More specifically, it has been demonstrated that fibromyalgia is associated with significant imbalance of the connectivity within brain networks associated with pain (Cifre *et al.,* 2012), decreased functional connectivity in the descending pain-modulating system, and increased activity in the pain matrix related to central sensitization (Cagnie *et al.,* 2014).

Dysregulation of Connectivity within Brain Circuits

Using a musical metaphor, the healthy brain function depends on a "harmonious symphony" of neuronal groups oscillating in rhythmic coherence at particular frequencies, which leads to the supposition, that when one group plays out of tune, too fast or too slow, or too high or too low, the "symphony" quickly turns to "cacophony." Current evidence from studies using Deep Brain Stimulation suggests that circuitry dysfunction is commonly observed in many neurological and psychiatric conditions (Lozano & Lipsman, 2013; Llinás *et al.,* 2001). Essentially, the circuit dysregulations underlying these conditions are either caused by (a) lack of coherence due to inadequate excitation or disturbances to that coherence, or (b) an overly strong coherence in inappropriate neural populations.

Llinás was first to identify and define dysregulation of rhythmic neuronal coherence in thalamocortical loops (Llinás & Ribary, 1993; Ribary *et al.,* 1991; Llinás *et al.,* 1999; Llinás *et al.,* 2001; Llinás *et al.,* 2005). According to Llinás, brain function depends on a rich interconnectivity of thalamocortical loops and their rhythmic oscillatory coherence. Optimally functioning thalamocortical loops show strong rhythmic activity in the alpha band (~ 10 Hz) with uninhibited gamma activity around 40 Hz. Thalamocortial dysrhythmia (TCD) is characterized by a general shift in the lower frequency oscillatory activity toward theta at 4 – 7 Hz, and a reduction in 40 Hz activity. TCD has been revealed in various conditions including neurological and psychiatric conditions related to motor, mood, auditory, and cognitive functions and has been linked to conditions including Parkinson's, depression, neurogenic pain, schizophrenia, and tinnitus (Llinás *et al.,* 1999). TCD is the putative mechanism underlying several of these dysfunctions, however, other circuits/systems likely contribute to these dysfunctions including, globus pallidus internus over-activity, beta and theta oscillation disturbance, subthalmic nucleus over-activity, orbitofrontal cortex hyperactivity, and default mode network dysfunction (Lozano & Lipsman, 2013).

The etiologies of circuit disturbances are varied and include damage to neural pathways, loss of neural elements and populations, as well as disturbances in the functional activity of neural circuits, through disordered firing and pathological oscillatory activity in neuron ensembles (Lozano & Lipsman, 2013, p. 406). According to Lozano and Lipsman (2013), the best approaches to treat circuitry dysregulation entails either driving coherent neuronal activity in under-activated circuits or reducing activity in over-activated circuits.

Brain Stimulation: current approaches

If we accept that a healthy brain requires an array of optimally functioning neuronal circuits that exist primarily through coherent rhythmic brain oscillation and that pathological conditions arise related to a dysfunction of these neural circuits, then brain stimulation to regulate these dysfunctional circuits becomes a crucial part of a neurorehabilitation strategy. Electro-stimulation of the brain is the dominant form of stimulation being pursued within medical research and clinical treatment at present (Kellner, 2012). Examples of invasive therapies include Electroconvulsive therapy and Deep Brain Stimulation, which require surgery to insert electrodes energized with an electric pulse precisely targeting a specific area of the brain (Wagner *et al.,* 2007). These treatments are able to address specific dysregulated neurological circuits to either inhibit excessive destructive neural coherence or to excite greater positive coherence (Lozano & Lipsman, 2013).

Less invasive therapies include Transcranial Magnetic Stimulation (TMS) and repetitive TMS (rTMS), which use an electromagnetic coil to stimulate specific areas of the brain. Transcranial Direct-Current Stimulation (tDCS) uses electrodes placed on specific parts of the sculp to stimulate the brain with a constant low amplitude direct current (Priori, Hallett & Rothwell, 2009). This can be positive "anodal" stimulation that increases neuron excitability and negative "cathodal" stimulation which decreases neuron excitability.

Explanations of the mechanisms by which electric stimulation produces beneficial effects on symptoms include: (1) blocking depolarization, (2) inhibiting or depressing synapse activity, and (3) inducing modulation of dysregulated networks with stimulation (McIntyre *et al.,* 2004). Robert Chen and his associates found significant gamma effects from rTMS, and speculate that such stimulation is useful as a cognitive enhancing strategy (Barr *et al.,* 2009). The latter possibility offers most potential for sound stimulation.

Although there is an existing literature demonstrating the positive effects of electro-stimulation to treat conditions associated with significant imbalance of the connectivity within brain networks, such as Parkinson's, depression, and tinnitus (Llinás *et al.,* 1999), treatments involving the current methodologies tend to present important limitations including equipment/setting access, cost and invasiveness associated, to varying degrees, with such techniques (Zaghi *et al*., 2009). Recent studies have demonstrated, nevertheless, that when auditory, sensory or visual stimulation is presented in a periodic and repetitive manner, neural activity responds at the same frequency and develops increased neural coherence at the frequency of the stimulation. This synchronization between the stimulus and brain activity can be observed at frequencies as low as 2Hz into the gamma frequencies of 30 to 120Hz, which means that the brain responds to a slow musical pulse (e.g., piano notes played like footsteps at a walking pace), as well as to individual sound waves like those produced by the lowest "E" note on the piano at 40Hz. Although we may hear sound waves as a continuous pitch, the brain is still stimulated by individual sound wave pulses and their attendant neural firing. Treatments that explore the effect of rhythmic auditory or visual stimulation include Rhythmic Sensory Stimulation (RSS) (Russel & Turow, 2011). Skille (1997) focused on somatosensory stimulation with low-frequency sound. In this proposed project, RSS will refer to sound-activated auditory and somatosensory stimulation.

Music/Sound Stimulation Therapies

It is crucial to differentiate between "music" and "sound." First, what we count as "music" is constructed through human cognition within cultural contexts. This means music is sound heard by the human mind "as" music and as such has learned conventional characteristics and a host of associations with humans' experience that develop over time. However, physically music is sound and vibration. As such music has distinct properties related to the frequency of compression and decompression of air molecules that act on our auditory system and somatosensory systems, which serve as "input channels" to neural activity. In this way, sound and music can be viewed as brain stimulation which can be observed in terms of how its rhythmicity interacts with neural coherence and activates particular brain circuits.

Examples of treatment approaches that use music stimulation are Thaut's Neurologic Music Therapy (NMT) (2005) and Altenmüller's Music Supported Rehabilitation (MSR) (Altenmüller *et al.,* 2009; Fujioka *et al.,* 2012; Raglio *et al.,* 2013). These treatments use specific music making tasks to engage a muscular and neural response. Both NMT and MSR cross over into sound-based stimulation.

A direct sound stimulation approach is Rhythmic Sensory Stimulation (RSS) (also referred as Rhythmic Auditory Stimulation) which uses rhythmic sensory cues to induce entrainment (Thaut et al., 2007; Thaut & Abiru, 2010). This therapeutic approach is often used to facilitate movement in Parkinson's or as rehabilitation with stroke. In this case the sounds consist merely of rhythmic clicks or claps.

Another example of therapeutic approach that uses rhythmic sound stimulation is Low Frequency Sound Stimulation (LFSS), variously known as vibroacoustic or physioacoustic therapy. Olav Skille and Petri Lehikoinen performed pioneering work in sound stimulation. Lehikoinen developed a system called Physioacoustic Therapy (PAT) using low-frequency sound (LFS) to stimulate the body by means of speakers in a chair (see Bartel, 2013). He assumed that LFS in the range of 27 – 110 Hz would resonate with muscle fibers, as well as massage the lymphatic system (Lehikoinen, 1997). A feature of PAT is frequency "scanning", that is, continuously varying the pitch through a spectrum, along with slow pulsation in amplitude, designed to avoid adaptation of the mechanoreceptors. PAT and Lehikoinen's chair device was FDA approved in 1996 for three claims: increased circulation, decreased pain, increased mobility. Although Lehikoinen never connected the whole-body somatosensory stimulation of PAT to an effect on neural coherence, it may well contribute to such an effect, despite the continuous pitch change. Recent research by Bernhard Ross demonstrates a driving effect in the auditory modality from a continuously moving binaurally detuned pitch pulsation (Miyazakia *et al.,* 2013). Olav Skille developed Vibroacoustic Therapy (VAT), using a similar approach as PAT, but instead of continuously varying pitches used static low frequency pitches, commonly at 40, 52, 68 and 86 Hz (Skille, 1997; Wigram, 1996; Bartel, 2013b).

Low Frequency Sound Stimulation (LFSS) has demonstrated significant impact on pain management. LFSS usually delivered through chairs or beds specially fitted with low frequency transducers, has been found to improve mobility (Wigram, 1997), increase circulation (Karkkainen & Mitsui, 2006), decrease low-density lipoprotein and blood pressure (Zheng *et al.,* 2009), help decrease pain (Karkkainen & Mitsui, 2006; Zheng *et al.,* 2009) and to reduce muscle strain and stiffness (Karkkainen & Mitsui, 2006). Studies with LFSS have examined specific pain conditions: rheumatoid arthritis with 40Hz (Chesky, Rubin & Frische, 1992), polyarthritis in hands and chest with 40Hz (Skille, 1989; Skille & Wigram, 1995), low-back pain with 52Hz (Skille, 1989; Skille & Wigram, 1995), knee replacement pain (Burke & Thomas, 1997), post-operative gynecological pain (Burke, 1997), menstrual pain and dysmenhorea 52Hz (Skille, 1989; Skille & Wigram, 1995), and sports injuries (Skille, Wigram & Weeks, 1989; Skille, 1989; Skille & Wigram, 1995). Although significant results have been demonstrated in several chronic pain conditions, very little is known about the effectiveness of the use of low-frequency sound stimulation on the treatment of fibromyalgia (Naghdi et al., 2015).

Research and clinical efforts primarily assumed that the effects of vibroacoustic and physioacoustic therapy were due to physiologic effects, given that these treatments stimulate mechanoreceptors and cellular structures in the body, resonating with muscle fibers and the lymphatic system, thereby serving potentially to block pain transmission (see GCT discussion below) (Lehikoinen, 1997). However, more recently, it has been suggested that the effect of rhythmic sensory stimulation can be due to its indirect stimulation of brain coherence in areas associated with pain, therefore, to a neural driven effect (Karkkainen & Mitsui, 2006; Lehikoinen, 1998).

Music/Sound Stimulation and Pain

Advances in medical technology, including imaging and non-invasive recording of brain activity, have opened new windows on the structural and physiological dimensions of pain, and have elucidated a network of brain regions linked to pain in a "pain matrix" (Chen, 2002; Schweinhardt & Bushnell, 2010). Pain pathways are not simple "one-way streets" carrying traffic to consciousness; pain is subject to modulation by the central nervous system. Emotional state, anxiety, distraction, past experiences and memories, are among the factors influencing the experience of pain (Ossipov, Dussor & Porreca, 2010).

Although there have been numerous studies of music and pain (Dileo & Bradt, 2005), few have been adequately theorized to explain why music/sound reduces pain. Gate Control Theory (GCT) (Melzack, 1965) postulated that affective and cognitive responses, such as music-responsive attention and psychological states, influenced the gate through efferent descending fibers. Although research has shown that GCT oversimplified neural systems (Moayedi & Davis, 2013), GCT does explain why stimulation of touch fibers can reduce pain perception as is demonstrated with certain applications of low frequency sound stimulation that induces mechanical vibrotactile stimulation of mechanoreceptors and spinal cord functioning (Meyerson & Linderoth, 2000).

Melzack (2001) proposed another pain theory that would explain the effects of music as a unified brain mechanism-based body-self neuromatrix (NM). Sensory, cognitive, and affective dimensions are fully credited with affecting pain perception and these dimensions are subject to cognitive-evaluative (attention, expectation, anxiety, valence) and motivational-affective (neurotransmitter, hormonal, limbic) inputs. Although exact mechanisms are not yet understood, NM offers explanation why functions of music such as distraction, stress and anxiety reduction, and aesthetic pleasure reduce pain perception. Neither GCT or NM explain pain associated with rhythmic oscillatory coherence (Fries, 2005; Ward, 2003). The correlation of thalamocortical oscillatory dysrhythmia (TCD) with pain has been demonstrated (Llinás *et al.,* 1999; Walton & Llinás, 2010) but no definitive theory has been established.

Given the role that neurotransmitters, hormones and the limbic system play in pain according to the Neuromatrix theory, it is relevant to mention the interaction between music and the limbic and endocrine systems. For instance, it has been shown that music affect the release of endorphins (Bahatara *et al.,* 2011; Menon & Levitin, 2005; Levitin, 2009; McKinney *et al.,* 1997; Kuhn, 2012; Liégeois-Chauvel *et al.,* 1998; Peretz & Zatorre, 2005; Blood *et al.,* 1999; Salimpoor *et al.,* 2009), dopamine (Salimpoor *et al.,* 2011; Gangrade, 2012), serotonin (Brandes *et al.,* 2010, Erkkilä *et al.,* 2011), and decrease in cortisol (Khalfa *et al.,* 2003; Fukui & Yamashita, 2003; Levitin, 2007; Chanda & Levitin, 2013; Möckel, Röcker & Störk, 1994; Möckel *et al.,*1995). A recent review of 400 published scientific papers on music as medicine found strong evidence that music has effects on brain chemistry, as well as mental and physical health benefits on management of mood and stress reduction and that it is the rhythmic stimulation of music, rather than the melody, that has the greatest effect in the brain coherence (Koelsch, 2014). Specific brain correlates can now also be identified with strong emotional response to music. Brain imaging shows that "music can modulate activity in brain structures that are known to be crucially involved in emotion, such as the amygdala, nucleus accumbens, hypothalamus, hippocampus, insula, cingulate cortex and orbitofrontal cortex. The potential of music to modulate activity in these structures has important implications for the use of music in the treatment of psychiatric and neurological disorders" (Koelsch, 2014, p.170).

A few studies have also examined the effect of music/sound stimulation on brain coherence and EEG asymmetry. Field *et al*. (1998) used frontal EEG asymmetry as an observable outcome in a study with 28 depressed adolescent females. One group listened for 23 minutes to pop/rock music selected for the study by similar aged girls and the other group was asked to sit and relax their mind and muscles. Three minute EEG readings were done before, during, and after the sessions. No changes were observed in behaviour or mood as a result of the treatment, but the music group showed decreased frontal asymmetry and decreased cortisol levels. A rating of preference for the music was done and the basic finding supported greater shift to symmetry with preferred music. Petchkovsky *et al*. (2013) used QEEG data to examine the effects of depressed adults participating in a choir (1wk/ 8 weeks) as well as practicing with a prepared practice CD that included physical and singing exercises, meditation dialogue, and accompaniments. QEEG results are based on a random sample (9 from group of 21) that was tested before and after the intervention. Data comparison between scores before and after intervention showed significant improvement. The resting QEEG data revealed greater left right hemispheric activity symmetry, reduced hyperactivity in the right prefrontal area, and reduced hypercoherence.

Recent research has recognized the potential of low frequency stimulation on brain response. Koike *et al*. (2012) studied 15 elderly subjects who had symptoms of depression, assessed with the Dementia Mood Assessment Scale (DMAS). Participants were given 30 minutes (5 days/wk, 2 wks) of unspecified classical music while resting on a lounge with 2 speakers by the head and frequency crossover at 150 Hz sending the low frequency component of the sound to transducers in the body area. A cognitive assessment was done with the Mini-Mental State Exam, and results showed a significant improvement in the DMAS with significance in the mood and depression scales but not in the overall dementia severity scales when comparing the scores before and after treatment.

Music/Sound Stimulation and Fibromyalgia

Little research has focused specifically on the effects of music or low frequency sound stimulation on fibromyalgia. Chesky and colleagues (1997) studied the effects of music and musically fluctuating vibration (60-300 Hz) on tender point pain in patients with fibromyalgia, however the study demonstrated that musically fluctuating vibration failed to alter pain perception in fibromyalgia. Onieva-Zafra and associates (2013) studied the effect of four weeks daily music listening to unspecified classical music mixed with salsa music. The music listening group showed significant reduction in pain measured by the McGill Pain scale, whereas the control that received no treatment showed no significant change. Müller-Busch and Hoffmann (1997) studied chronic pain patients including fibromyalgia with a treatment of active music therapy using unspecified performed music. Results found significant reduction in reported pain intensity, but no change in depression and anxiety scores. Leão and Da Silva (2004) found that women with chronic pain had less pain after listening to classical music.

The few studies of sound and fibromyalgia that exist primarily draw on cognitive and affective effects of music. However, rhythmic sensory stimulation with low-frequency sound has not been systematically studied in fibromyalgia. A recent study conducted at the Music and Health Research Collaboratory at University of Toronto in collaboration with the Wasser Pain Management Centre at Mount Sinai Hospital demonstrated that fibromyalgia treated with auditory Rhythmic Sensory Stimulation embedded in music resulted in significant improvement in fibromyalgia symptoms, as assessed by the Fibromyalgia Impact Questionnaire (Picard *et al.,* 2014). Another subsequent study also demonstrated that fibromyalgia treated with 23 minutes of rhythmic sensory stimulation twice a week for five weeks resulted in significant improvement in Fibromyalgia symptoms as measured by the Fibromyalgia Impact Questionnaire (Naghdi *et al.,* 2015). These studies revealed an important potential to the use of Rhythmic Sensory Stimulation with low-frequency sounds to support the treatment of fibromyalgia. This innovative, low-cost and self-administered alternative treatment for chronic pain requires further investigations in order to gather consistent results across different research studies, and further the understanding of its underlying mechanisms.

Proposed Study and Hypothesis

Aim and Hypothesis:

This study aims to investigate the effect of Rhythmic Sensory Stimulation on symptoms related to fibromyalgia. More specifically, the proposed clinical trial examines the effectiveness of Rhythmic Sensory Stimulation at 40 Hz sound on improvement of pain management and quality of life of patients with fibromyalgia.

Past research and clinical studies were premised on the assumption that the effectiveness of Rhythmic Sensory Stimulation (RSS) with low-frequency sound on the treatment of chronic pain was associated to its direct stimulation of muscle fibers and the lymphatic system, thereby serving potentially to block pain transmission as proposed by the Gate Control Theory (Lehikoinen, 1997). However, more recently, it has been suggested that the effect of rhythmic sensory stimulation is given its indirect stimulation of brain coherence in areas associated with pain, that is, to a neural driven effect (Karkkainen & Mitsui, 2006; Lehikoinen, 1998). Naghdi and colleagues (2015) particularly suggested that Rhythmic Sensory Stimulation can potentially reset thalamocortical dysregulated oscillations when using 40 Hz stimulation. This hypothesis was based on previous research demonstrating the significant effect of 40 Hz auditory stimulation (Llinás & Ribary, 1993), and 40 Hz steady-state vibratory stimulation (Ross *et al*., 2013) to reset incoherent thalamocortical oscillation.

Therefore, based on recent findings that fibromyalgia is associated with significant imbalance of the connectivity within brain networks associated with pain (Cifre *et al*., 2012), and that Rhythmic Sensory Stimulation (RSS) can drive neural rhythmic oscillatory activity, it is hypothesized that RSS with 40 Hz low-frequency sounds will be significantly effective in treating fibromyalgia. To test this hypothesis, the intervention group will receive low-frequency sound stimulation of a sustained single pitch of 40Hz sound of regular temporal intervals. On the other hand, the control group will receive a sham stimulation of a diffused and non-specific pitch in the 30-100Hz frequency range and irregular temporal interval. Low frequency sound played by the special subwoofer speakers (transducers) built in to the treatment device is experienced as somatosensory vibration rather than audible sound. With that, participants of both groups will experience a mild vibrotactile sensation on their back and hear a low-level hum. However, according to Skille (1997) and Lehikoinen (1997), only stimuli of specific sustained pitch (e.g., 40 Hz) may interact with brain circuits and stimulate neuronal coherence. Therefore, it is not expected that stimuli delivered in the sham stimulation will lead to improvements in any of the outcome measures examined. If the control group presents improved results after the intervention, these results would suggest that the effect of Rhythmic Sound Stimulation with low frequency sound is associated with its direct stimulation of muscle fibers, as suggested by the Gate Control Theory. However, if only the treatment group presents significantly improved scores after the treatment, it is hypothesized that the effect is associated with an indirect brain stimulation inducing brain coherence in areas associated with pain, as suggested in the literature. No measures of brain coherence will be recorded in the present study, but may be pursued in future studies.

Subject Selection:

A total of 50 outpatients with fibromyalgia are to be recruited for this study. Inclusion criteria include: patients with clinical diagnosis of fibromyalgia conducted by the clinical staff at Wasser Pain Management Centre; able to read and write English adequately; that have satisfactory hearing bilaterally (self-reported); and that have the ability to operate the supplied device;

Patients with the following conditions will not be included in this study: 1) acute and active inflammatory conditions (e.g., rheumatoid arthritis, osteoarthritis, autoimmune disease) 2) unstable medical or psychiatric illness 3) history of psychosis, epilepsy, seizures 4) pregnancy or breast feeding 5) hemorrhaging or active bleeding 6) thrombosis, angina pectoris 7) heart disease, such as hypotension, arrhythmia, pacemaker 8) substance abuse in the last year 9) suffering from a recently prolapsed vertebral disc or 10) recovering from a recent accident with back or neck injury.

Of the 50 patients recruited, participants will be randomly allocated to one of the study groups, with equal probability of being allocated to the treatment or control group. The allocation process will be done with Random Allocation software.

Intervention:

The treatment consists of 30 minutes daily low-frequency sound stimulation, 5 days per week, for five weeks of treatment, for a total of 25 sessions. The treatment sessions will be conducted at the patient's home, for which they will be given a portable sound unit device. Participants are instructed to place the device on a comfortable chair or bed, turn ON the device and the MP3 player, select the treatment sound file stored on the MP3 player (only the assigned treatment sound file will be available on the MP3 player), and adjust the sound volume to Level 15, and the vibration intensity to Level 15. The subjects will be instructed to expect a low frequency vibrotactile sensation on their lower-back and shoulders, and hear a low-level hum. Once the stimulation starts, participants will be asked to start timing their session. There are no restrictions on the type of activity performed during the sessions (e.g., reading, watching television, using the computer). The volume of the sound track and the intensity of the vibration can be adjusted if the participant feels any discomfort.

The stimulation received by participants in the treatment group consists of low-frequency sound stimulation of a sustained single pitch of 40Hz sound of regular temporal intervals. The stimulation is given through low frequency speakers built in to the device. Low frequency sounds played by these special subwoofer speakers are experienced as somatosensory vibration rather than audible sound. The control group will receive sham vibroacoustic stimulation, that is, low frequency sounds of non-specific pitch in the 30-100Hz frequency range and irregular temporal interval. The sham stimulation will also produce somatosensory vibration; however the asynchrony of the stimulus is not expected to stimulate rhythmic neuronal coherence.

Assessments and Outcome Measures:

Baseline assessment will be conducted one week prior to initiating treatment. Initial assessment will include the following questionnaires: Participant Demographic Information and Medication Information, Revised Fibromyalgia Impact Questionnaire (Bennett *et al*., 2009), Brief Pain Inventory – Short Form (Cleeland & Ryan, 1994), Pittsburgh Sleep Quality Index (PSQI) (Buysse *et al*., 1989), Patient Health Questionnaire-9 (PHQ-9) (Kroenke & Spitzer, 2002), and Quality of Life Enjoyment and Satisfaction (Endicott *et al*., 1993). Pain data will also be collected on a daily basis through the treatment diary that participants will be asked to complete immediately after each treatment session. This diary includes two questions assessing pain severity on a scale from 0 (no pain) to 10 (extreme pain) right after the treatment, and on average in the last 24 hours.

Outcome assessment will be conducted one week after the end of treatment, when participants will be reassessed on the same measures as in the initial assessment, and also on a global impression of change with: Patient Global Improvement Impression (PGI-I) (Guy, 1976), and a modified version of Glasgow Benefit Inventory (Robinson *et al*., 1996).

Data Analysis:

A comparison of scores for each outcome measure will be done using a 2-way between-within ANOVA with Group as the between subjects factor, and Assessment Time as within subjects factor. Clinical and demographic variables will be described with means and standard deviations for continuous data, and frequencies and percentages for categorical data and compared between the groups with t-tests and chi-squared tests, respectively. Post-treatment scores will be compared between groups using analysis of covariance with baseline scores as covariates.

Equipment:

The stimuli will be delivered with a portable device called Sound Oasis VTS-1000 Vibroacoustic Therapy System unit. This is a low-voltage consumer product device that has three built in subwoofer low frequency speakers. The sound device is connected to one MP3 player that contains one sound track that will be defined according to the study group in which the participant is allocated. The Music and Health Research Collaboratory owns this portable device, and participants will receive the equipment at the first assessment session, and will be asked to return the equipment at the end of the treatment. It is possible that the same device will be used by more than one person. Cleaning, disinfection and sterilization of the study equipment will be conducted as necessary.

Risks:

Rhythmic Sensory Stimulation therapy has contra-indications, and participants with any of the following conditions will not be included in this study: 1) acute and active inflammatory conditions (e.g., rheumatoid arthritis, osteoarthritis, autoimmune disease) 2) unstable medical or psychiatric illness 3) history of psychosis, epilepsy, seizures 4) pregnancy or breast feeding 5) hemorrhaging or active bleeding 6) thrombosis, angina pectoris 7) heart disease, such as hypotension, arrhythmia, pacemaker 8) substance abuse in the last year 9) suffering from a recently prolapsed vertebral disc or recovering from a recent accident with back or neck injury. Patients with fibromyalgia may find it uncomfortable to remain seated for 30 minutes. In this case, participants are advised to place the device on the bed and lay down while administering the treatment. Patients can also adjust the settings of the device to change sound loudness and the intensity of the vibration in case of discomfort. Other risks that can be associated with this treatment include: feeling tingling sensation, urgency to relieve bowel, neck discomfort due to vibration in shoulder area. Risks associated with completing the questionnaires may include sadness, embarrassment, fatigue and boredom.

Project timeline:

Project Timeline

2015	March	Apr	May	June	July	Aug.	Sept.	Oct.	Nov.	Dec.
Clinical Trials	Proposal	Proposal	*REB submission (MSH)	*Recruit	**Clinical Trials**	**Clinical Trials**	**Clinical Trials**	**Clinical Trials**	**Clinical Trials**	**Clinical Trials**
2016	Jan.	Feb.	March	Apr	May	June	July	Aug.	Sept.	Oct.
Clinical Trials	**Clinical Trials**	**Clinical Trials**	**Clinical Trials**	*Data analysis	*Data analysis	*Data analysis *Study evaluation	*Paper writing	*Paper writing	*Paper writing	*Paper writing

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