Full-Length Article

Vibroacoustic Stimulation and Brain Oscillation: *From Basic Research to Clinical Application*

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Abstract

This paper addresses the importance of steady-state brain oscillation for brain connectivity and cognition. Given that a healthy brain maintains particular levels of oscillatory activity, we argue that disturbances or dysrhythmias of this oscillatory activity coincide with common health conditions including Alzheimer's disease (AD), Parkinson's disease (PD), pain, and depression. This review shows that electric brain stimulation contributes to regulation of neural oscillatory activity and the alleviation of related health conditions. It is then argued that specific sound frequencies in their vibratory nature can serve as a means to brain stimulation through auditory and vibrotactile means and as such can entrain and regulate oscillatory activity. The frequencies employed and found effective in electric stimulation are reviewed with the intent of guiding the selection of sound frequencies for vibroacoustic stimulation in the treatment of AD, PD, pain, and depression.

Keywords: *neural oscillation, vibroacoustic therapy, brain stimulation, music medicine, thalamocortical dysrhythmia*

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Rhythmic Oscillatory Coherence and Connectivity

The origin and function of neural rhythmic oscillatory activity in the brain remains a central research question in neuroscience. Although several explanations have been proposed [1], recent work has raised important issues related to clinical application of oscillatory brain activity in neurodegenerative diseases and neurorehabilitation [2]. Can oscillatory brain activity be used as diagnostic biomarker for conditions like Parkinson's disease (PD), Alzheimer's disease (AD), and depression? And can oscillatory brain activity be modulated in support of therapeutic interventions?

The healthy human brain has intrinsic and constant rhythmic oscillation. Popular psychology explained the oscillatory rhythms of "brain waves" as neural indices of specific mental states, e.g., delta with sleep (0.1–4Hz), theta with deep relaxation and creative insight (4–8Hz), alpha with relaxation (8–12Hz), and beta with problem solving (12–20Hz). Although generally true, scientific interest is moving toward understanding the role that oscillatory rhythms may play in coordinating neural activity supporting perceptual, cognitive, and motor functions [3]. Oscillatory activity may index local neural networks from modality-specific brain areas as well as long-range neural systems that engage sensory and supra-modal brain regions (e.g., prefrontal and parietal cortices) [4]. Ward [5] proposed that consciousness is related to synchronous neural rhythms in general, but that memory processes are related to gamma (30–50Hz) and theta oscillatory rhythms, whereas attention is dependent on alpha and gamma activity. His review of the literature points toward an increased connectivity between frontal and parietal cortex during memory recall from larger spectral power in gamma and theta frequency bands, with the magnitude of gamma activity modulated by the theta rhythm. This intra-brain communication through neuronal oscillatory coherence is thought to index healthy functioning of specific circuits – like memory, or movement. Although it is well accepted that brain activity related to perceptual, cognitive, and motor functions depends on widely distributed neural networks, the functional connectivity between the nodes of the networks is less well understood. Fries [6] proposed that the mechanism of neuronal communication depends on similar neuronal oscillatory activity and that communication within a local network (e.g., sensory cortex) happens mainly with coherent oscillation in the gamma frequency range (30–100 Hz). For communication between distant brain areas, the amount of local gamma oscillations is controlled by slower rhythm in the theta frequency range (4–8 Hz) [7].

Dysregulation of Connectivity within Brain Circuits

Using a musical metaphor, we premise that the healthy brain function depends on a "harmonious symphony" of neuronal groups oscillating 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." Evidence from using Deep Brain Stimulation (DBS – see Electro-stimulation section that follows) as a probe or as a treatment suggests that "circuit" dysfunction is common to many neurological and psychiatric conditions [8,9]. Essentially, the circuit dysregulations underlying these conditions are either (1) a lack of coherence due to inadequate excitation or disturbances to that coherence, or (2) overly strong coherence in inappropriate neural populations.

Llinas was among the first to identify that recurrent connections between the cortex and the thalamus serve as a mechanism for interconnecting cortical areas and controlling the flow of information [9,10,11,12,13]. Using a technical metaphor, thalamocortical loops provide a mechanism for communication within the brain like a major hub does for the internet. According to Llinas, the interconnectivity of thalamocortical loops depends strongly on their rhythmic oscillatory activity. Optimally functioning thalamocortical loops show rhythmic activity in the alpha (~10 Hz) and gamma (~40 Hz) bands. Thalamocortical dysrhythmia (TCD) is characterized by slowing of alpha oscillatory activity toward the theta band at 4–8 Hz and a reduction in gamma band activity. TCD has been revealed in neurological and psychiatric conditions related to motor, mood, auditory, and cognitive functions, and has been linked to conditions including PD, depression, neurogenic pain, schizophrenia, and tinnitus [10].

With the development of DBS, Lozano and others identified neural circuits that are dysfunctional and include the wide range of motor, limbic, auditory, executive function, cognitive, reward, memory, sensory, mood, and interoceptive awareness [8]. TCD is thought to be one of the putative mechanisms underlying several of these dysfunctions. However, other circuits/systems likely play a role in these dysfunctions including, but not limited to, globus pallidus internus over-activity, beta and theta oscillation disturbance, subthalmic nucleus over-activity, orbitofrontal cortex hyperactivity, and default mode network dysfunction [8]. The etiologies of "circuit disturbances vary widely 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" [8, p. 406]. According to Lozano and Lipsman [8], circuit dysregulation and its treatment is best illustrated with the "prototypical conditions" affecting motor, mood, and cognitive circuits: PD, major depressive disorder, and AD. The approach to treatment entails regulation of neural oscillations to their normal level by either entraining coherent neuronal activity in under-activated circuits or attenuating activity in over-activated circuits.

Electric Stimulation of the Brain

If we accept that the healthy brain requires an array of optimally functioning neuronal circuits that exist through coherent rhythmic brain oscillation and that disease conditions arise related to a dysfunction of these neural circuits, then brain stimulation that regulates these dysfunctional circuits could become a crucial part of neurorehabilitation strategies. Electrostimulation is currently the dominant approach being pursued within medical research and clinical treatment [14].

Principles of Electric Stimulation

Electroconvulsive therapy (ECT) involves passing an electrical current through the brain, is applied under anesthesia, and often triggers a seizure. Magnetic Seizure Therapy (MST) is an experimental treatment that can also induce seizures through stimulation with magnetic fields. Two other types of electrical stimulation include Vagus Nerve Stimulation used for treatment of seizures and depression, and Transcutaneous Electrical Nerve Stimulation (TENS) used to control nerve pain. Recently developed brain stimulation methods are more focal by limiting the stimulation to a specific target area. For instance, Transcranial Magnetic Stimulation (TMS) and repetitive TMS (rTMS) use an electromagnetic coil to stimulate specific areas of the brain such as the motor cortex. Transcranial Direct-Current Stimulation (tDCS) [15] uses electrodes placed on specific scalp locations to stimulate the brain with a constant low amplitude direct current. tDCS modulates the neuron's membrane potential. It is divided into positive "anodal" stimulation that increases neural excitability and negative "cathodal" stimulation, which decreases excitability. Deep Brain Stimulation (DBS) requires surgery and the insertion of electrodes, but offers precise targeting of a brain area, which is a limitation of the non-invasive methods [16]. These electrodes deliver electric pulses from a surgically implanted device. Because of this precise targeting DBS is able to address specific dysregulated neurological circuits to either inhibit excessive destructive neural coherence or to excite greater positive coherence [8], although the specific mechanisms of DBS are not known [17]. See Table 1 for references for the positive effects of electric stimulation.

	ECT	TMS/rTMS	tDCS	DBS
Parkinson's	Popeo & Kellner 2009 [18]	Zanjani et al. 2015 [19] Gonzalez-Garcıa et al 2011[20]	Benninger et al. 2010 [21]	Lozano & Lipsman 2013 [8], Mehanna & Lai 2013 [22]
Alzheimer's	Burgut & Popeo 2010 [23]	Cotelli et al. 2011 [24]	Hansen 2012 [25]	Lozano & Lipsman 2013 [8], Kaplan 2012 [26]
Depression	Kellner et al. 2012 [27]	Weiduschat & Dubin 2013 [28]	Ferrucci et al. 2009 [29]	Lozano & Lipsman 2013 [8]
Pain	Mowla et al. 2007 [30]	Short et al. 2011 [31]	Lefaucheur et al. 2008 [32]	Lozano & Lipsman 2013 [8], Kaplan 2012 [26]

Table 1. *Positive Effects of Electric Stimulation*

Underlying Mechanism

Electric brain stimulation does not interact directly with neural activity in the sense of eliciting neural firing. Instead, brain stimulation modulates excitability in neural networks through a variety of interactions, including (1) blocking depolarization, (2) inhibiting synaptic responses, (3) depressing synaptic activity, (4) stimulus-induced modulation of pathological network activity [33], (5) modulation of plasticity, and (6) activation of remote but connected areas [1,33]. For rTMS at rates between 10 and 20 Hz, an increase of gamma oscillations in the 30 to 50 Hz range has been found, which is interpreted as indexing perceptual and cognitive function. Chen and his associates found significant gamma effects from rTMS and speculated that such stimulation is useful as a cognitive enhancing strategy [34]. The stimulant effect in the 30–50Hz gamma range offers most potential for sound stimulation because low frequency sound reaches to that level but is ineffective for the 10–20Hz range.

Music/Sound Stimulation of the Brain

Music, as a multi-faceted cultural product, can be seen as a brain stimulant as it engages several cognitive functions, including associative memory. The importance of music in memory functions has been highlighted by social worker Dan Cohen's "Music & Memory" organization and their "iPod Project" (musicandmemory.org) which provides access to recorded music for the elderly. Treatment approaches that are accompanied by scientific validation include Thaut's Neurologic Music Therapy (NMT) [35] and Altenmüller's Music Supported Rehabilitation (MSR) [36,37, 38] that use specific music-making tasks to engage a muscular and neural response. The distinction between music and sound is highly relevant for differentiating the approaches of music

stimulation, either using more global features of music, for example for inducing mood changes, or employing specific rhythms of music at various scales. Both NMT and MSR cross over into sound-based stimulation when employing musical rhythm for interaction between sound and movement. A direct sound stimulation approach is Rhythmic Auditory Stimulation (RAS) [39,40,41], which is used to facilitate movement in Parkinson's or as rehabilitation with stroke. In this case, the sounds consist merely of rhythmic clicks or claps.

Auditory stimulation, that is not musical, includes Peripheral Ultrasonic Neurostimulation (PUNS), using pulsed low frequency ultrasound [42,43,44], and its related application of Transcranial focused ultrasound (tFUS) [45]. The latter employs beams of ultrasound most often pulsed at 70–100 Hz to target specific areas in the brain with "mechanical" stimulation of the brain tissue. One application is to stimulate brain activity while another is to change brain function by causing a focal lesion. tFUS has the ability to target specific areas deep in the brain, similar to DBS. Our interest here is in the stimulation aspect, for which beneficial effects have been shown with psychiatric disorders including depression, chronic pain, and PD.

A reset is a brief interaction with the dynamics of ongoing oscillation, which effectively reduces the magnitude of the oscillation. Acoustic Coordinated Reset (ACR) is a neuromodulation of dysregulated brain circuits, which is based on the concept of Coordinated Reset (CR) in DBS, to reset the firing phase of those neurons that are assumed to create the dysregulation [46]. As an intervention for tinnitus, Tass developed ACR for emulating the effect of CR on the auditory cortex, and possibly the thalamocortical circuit, using audible sounds at the frequency of sound perceived in tinnitus [47]. The approach was based on the assumption that tinnitus is a dysregulation of brain circuitry, possibly a thalamocortical dysrhythmia [9,10] also implicated in PD, depression, and pain. In tinnitus, ACR was used to "reset" a circuit assumed to be too rhythmically synchronized in its firing. Further research is required for testing the possibly easier task of using pulsed audible sound or reinforcement of rhythmic coherence at a particular frequency.

Thaut [35] proposed at least 4 mechanisms at work with sound and music: (1) affective-aesthetic response focused on arousal, motivation, and emotion; (2) patterned information processing – essentially "thinking music" – music engaging the brain as a language on its own; (3) differential neural processing, e.g., language with music and language alone use different brain pathways; and (4) rhythmic stimulation and entrainment. Thaut applied the latter to the rhythm of walking [35]. We argue that rhythmic sound stimulation and entrainment can be extended to an even wider frequency range with steady-state brain stimulation at the rate of targeted brain activity, ranging from sleep states at delta to the whole sweep of gamma frequencies. We are proposing, therefore, that music/sound is a potential analog to electro-

stimulation of the brain in the way that sound stimulates neural activity and contributes to rhythmic neuronal coherence at particular frequencies.

Olav Skille in Norway and Petri Lehikoinen in Finland performed pioneering work in sound stimulation. Lehikoinen [48] developed Physio Acoustic Therapy (PAT) using low frequency sound to stimulate the body by means of loudspeakers mounted inside a chair. The underlying concept is that sound in the range of 27–113 Hz resonates with muscle fibers, and massages the lymphatic system [49]. The stimulus frequency in PAT is continuously varied through the spectral range, along with slow pulsation in amplitude, to avoid adaptation of the mechanoreceptors. PAT and Lehikoinen's chair device was FDA approved in 1996 for three claims: increased circulation, decreased pain, and 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 continuously changing stimulus frequency. Recent research demonstrated a driving effect in the auditory modality using binaurally detuned pitch pulsation with continuous variation over a frequency range similar to PAT [50].

Olav Skille [51] developed Vibroacoustic Therapy (VAT) using an approach similar to PAT but stimulating with static low frequency (e.g., at 40, 52, 68 or 86 Hz) instead of continuously varying the stimulus frequency [52,53]. Although a possible interaction with brain activity had been considered [54,55], research and clinical efforts primarily assumed an effect on muscle and tissue. The devices designed for VAT and PAT can be used potentially to deliver stimuli at gamma rhythms to the brain through the somatosensory system. A recent pilot study by Clements-Cortes et al. [56] used a VAT device to deliver 40 Hz brain stimulation to Alzheimer's patients through vibrotactile and auditory means.

Since both PAT and VAT as low frequency sound stimulation (LFSS) generated by special subwoofer-type loudspeakers or vibrotactile transducers [57] is experienced through mechanoreceptors as somatosensory vibration rather than – or in addition to – through hearing as audible sound, research on the effects of tactile stimulation applies. Research of Rhythmic Sensory Stimulation (RSS) in somatosensory, auditory, and potentially visual modality, currently being pursued by the authors, builds on recent research showing that vibrotactile stimulation has a strong neural driving effect [58,59,60]. In this previous research we induced effects observed in magnetoencephalography (MEG) from localized mechanical stimulation, using a pneumatic stimulator, because current sound-driven stimulation on the whole body involves the use of magnetic transducers, which are incompatible with MEG sensors. From previous studies it is known that stimulation of a finger, the hand, or the median nerve results in an oscillatory response in primary and secondary sensorimotor cortices [57,61,62] and depends only little on attention [63].

Compared to the research using vibrotactile stimulation, considerably more research has used auditory stimulation for eliciting steady-state or spontaneous oscillatory responses. Steady-state response to rhythmic auditory stimuli can be elicited using clicks, amplitude-modulated isochronous sounds [64], or pure tones; for example, a 40 Hz amplitude modulated tone [65,66], or even the rhythms of binaural beats, that are created through binaurally detuned tones [50]. Common to those methods is that vibrotactile stimulation with sound, as well as auditory stimulation, can be used to drive a neural response.

Parkinson's Disease - Music/Sound Stimulation

Considerable research investigated the concept of rhythmic pulses to stimulate a brain response and to initiate movement in PD. Results showed significant improvement in gait performance with rhythmic auditory stimulation (RAS) [39,40,41,67,68]. This applied even when medication had been withdrawn [69,70]. Rhythmic auditory stimulation produced greater improvement in cadence and stride length compared to visual cueing [71]. Improvements through rhythmic cuing have also been observed for arm movements [72,73].

The effect of whole body vibration on PD symptoms has been considered since Charcot's 19th century discovery that PD symptoms subsided during a carriage ride [74]. In two recent reviews, Pinto et al. [75] and Lau et al. [76] reported that vibration at 6–25 Hz or vibrotactile sound at 30 Hz consistently provided the most positive results.

Three studies have used RSS to address PD symptoms beyond gait: San Vicente et al. [77] studied 60 PD patients; 30 received 25 sessions each 25 minutes long over six months of "relaxing" music plus 40 Hz sine waves applied simultaneously through a bed with integrated vibrotactile stimulation; 30 patients received only the music. Both groups showed significant improvements on the Unified Parkinson's Disease Rating Scale (UPDRS), while the 40 Hz group showed a larger gain in the "activities of daily living" scale. The researcher acknowledged that the music-only treatment also resulted in a vibration effect since it was played through the bed speakers. King et al. [78] studied 40 PD patients (20 slow/rigid, 20 tremor dominant) not withdrawn from their medication. All participants received RSS stimulation at 30 Hz in five series lasting one minute each separated by one-minute rest periods. UPDRS scores improved significantly in all major symptom categories. Kapur et al. [74] studied 20 patients treated with recordings of nature sounds and the inherent low frequency sounds ranging from 30–500 Hz. One group of ten participants listened to the recording through headphones only, and ten listened to the same headphone sounds but also received the low frequency sound through a set of transducers in the reclining lounge. Participants received 30 minute treatments each day for four weeks in their home with self-reported compliance (93.5%). Results showed significant

improvement in both groups on the UPDRS Part 1 and Part 3. While the stimulation targeted the somatosensory system, partial transmission of the 30–500 Hz content through the earphones cannot be excluded.

Finding the Optimum RSS Frequency for Parkinson's Disease.
The oscillation model of PD places great attention on the subthalmic nucleus (STN) and related motor circuit. Normal motor functions are associated with rhythmic STN activity in the 31–100 Hz range with activity between 60–80 Hz being associated with improved motor performance [79]. The typical DBS stimulation frequency that improves symptoms in PD is 130–185 Hz, and the frequency that decreases motor function is below 30 Hz [79,80]. Some research showed DBS in the 30–90 Hz range as effective at improving motor performance as in the 130–185 Hz range [79]. Given that stimulation at one frequency also produces a resonant stimulant response at mathematical multiples (e.g., stimulation at 20 Hz increases response at 40, 60, and 80 Hz [58]), a good frequency to emulate DBS stimulation would be about 70–80 Hz, with its first partial resonance being 140–160 Hz [81]. This is also a frequency used by pulsed low frequency ultrasound [82]. The 160 Hz resonance would be close to 167 Hz, identified as having a crucial role in restoring thalamic relay function [80].

An STN rhythm detected in conjunction with dopamine and apomorphine (peak at about 319 Hz plus or minus 33 Hz) is believed to support the basal ganglia circuit's information transmission [83,84]. Other research points to 235 Hz [85]. Activity in the 300 Hz range seems also to be correlated with activity in 60–90 Hz. A reduction of oscillatory activity near 300 Hz may be a potential biomarker for PD [83,84]. The concern that this effect may be related to advanced state of PD and medication is countered by research showing that 300 Hz is also observed in other conditions [86].

If 300 Hz is an essential oscillatory frequency, and DBS at 130 Hz proves effective with PD, the question is whether the DBS stimulus is only inhibitory, disrupting activity in the <30Hz area, or is also excitatory, driving activity in the 300 Hz range through resonance. This is debated with positive argument for a direct driving effect [83,84,87] and counter evidence of no overtone effect [88]. One issue is that the currently approved DBS devices cannot stimulate above 185 Hz but sound-based RSS can do so easily, and so may have a potent role in treatment. Another good frequency for brain stimulation with PD then may be 300 Hz.

Three other types of stimulation are worth including. Electrical Stimulation of the motor cortex [89] is another form of brain stimulation, however less effective than DBS. The stimulus frequencies ranged between 10–30 Hz in one study and 130 Hz in another and were typically varied across a range instead of using a single constant frequency. Although the whole body vibration research does not seem to monitor brain response and so is not developed based on the oscillatory

model of PD, body vibration has considerable history as treatment. There is a known effect from muscular movement on gamma activity and so potentially might act as a stimulant. Two reviews of whole body vibration research recently show 6 Hz as the most common stimulus with only one using 25 Hz [75,76]. Studies with rTMS on patients with PD [20,60] use a range of frequencies below 25 Hz because of technical limitations and safety considerations, but the mechanism is not generally considered one of excitation and neural driving.

Low frequency sound stimulation through vibrotactile devices is limited to above 27 Hz because transducers are less efficient at lower rate. Two previous RSS studies with PD used 30 Hz [78] and 40 Hz [77]. Assuming neural resonance response up to four multiples, the stimulus frequency [58] for optimal sound stimulation of PD could be 40 Hz, eliciting responses at 40, 80, 120, and 160 Hz, or 80 Hz with responses at 80, 160, 240, and 320 Hz. Because a reduction of STN activity in the 300 Hz range has been observed, and because 320 Hz specifically may be a potential biomarker for PD [83,84], sound stimulation at 320 Hz could be a possible target.

Music and Sound Stimulation in Alzheimer's Disease

The effects of music on AD patients have been observed for years and inspired a broad range of research. Thaut's postulated mechanisms for the effect of music [35] are in essence all forms of brain stimulation: (1) arousal, motivation, and emotion (2) information processing, and (3) differential neural processing. Although in one systematic review of music therapy studies authors determined there was inadequate scientific quality [91], other studies have shown the effectiveness of music therapy in AD [92,93,94] but possible brain mechanisms or even neurophysiological changes have rarely been shown. Neuroimaging studies found that older adults with AD were able to learn new and unfamiliar music and that music memory training and familiar melodies enhanced long-term memory for unconnected texts [95,96]. There appears to be a shift in the functional neuroanatomical network activated for memory with dementia, i.e., greater use of prefrontal-amygdala connections instead of prefrontal-hippocampal networks [97,98]. That may make music-based encoding more resilient in people with AD [35].

However, little research has attempted to use vibratory sound frequency as a means to stimulate the oscillatory rhythm of the brain or neural cells. Koike et al. [99] postulated that music may have a role in AD as a catalyst to neural regeneration, although they admitted that the mechanisms are not well understood and proposed that stimulating neural outgrowth with sound may point to a mechanism. The study used PC12m3 cells cultured in single-cell suspension and stimulated with nerve growth factor. These cells were then subjected to direct contact vibration with speakers or at a distance of 12 cm from the speaker. Cells were treated to a

range of frequencies from 10 Hz to 200 Hz for seven days. Results showed that all frequencies produced greater outgrowth than the non-vibration control but the greatest outgrowth occurred when treated with direct vibratory sound at 40 Hz.

Clements-Cortes et al. [56] premised their study on evidence that cognitive deficits in AD are related to reduced gamma power around 40 Hz and that vibrotactile and auditory stimulation can drive oscillatory power and potentially improve cognitive function [12]. The treatment was 40 Hz vibrotactile and auditory stimulation two times a week for three weeks. Results showed that there was an average effect size of .58 for each session and qualitative results that showed some improvements in cognitive clarity and memory.

RSS Frequency for Alzheimer's Disease
A scientific foundation for oscillatory mechanisms in AD is not as well developed as that for PD. Also, less research with brain stimulation including electro-stimulation has been done and work with DBS is just beginning. Potential stimulation frequencies will be inferred from possible dysrhythmias.

Findings of thalamocortical dysrhythmia in AD included increased power at delta and theta frequencies [100] and a power decrease at alpha, beta, and gamma frequencies [100,101,102,103]. Research points to a relationship between gamma oscillatory activity and cognitive functions [104]. Specifically, research in AD showed decreased spectral power around 40 Hz [12,105], although brain activity in this frequency range seems to decrease generally with cognitive decline and aging [106,107]. Other research reported an increase in 30–100 Hz gamma band power in AD [101,108] without specifically studying 40 Hz activity, yet considering only evoked instead of studying spontaneous activity. The research supported the potential role of theta and gamma rhythms for biomarkers of early stages of AD [109].

Brain stimulation for AD is at an early exploratory stage. High frequency of 130 Hz has been used in DBS [8] and 20 Hz in an rTMS study [24]. Gamma-band oscillation can be modulated with low frequency sound or vibrotactile sensory stimulation [104]. 40 Hz, which is decreased in AD, appears to be a critical frequency for brain stimulation in AD since 40 Hz seems generally implicated in brain communication [5,6]. It appears to stimulate neural outgrowth [99], and the potential to drive gamma response with auditory or somatosensory stimulation has been demonstrated [58,60,64].

Pain - Music/Sound Stimulation

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, i.e., a network of brain regions linked to pain in a "pain matrix" [110,111]. 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 [112].

A meta-analysis of 48 studies involving music and pain found that in studies where patients were allowed to select preferred music, the effect size was slightly higher (r=.20) than in studies where they were not (r=.18) [94]. Particularly noteworthy, the effect in patients with cancer/terminal illness/AIDS was considerably higher (r=.45) than in those post-surgery (r=.15). This points to different effects based on the nature of the pain.

Although there have been numerous studies of music and pain [94], few have been adequately theorized to explain why music reduces pain. Gate Control Theory (GCT) [113] postulated that pain receptors send information along a pathway of interconnected nerves to the brain and that at the point where the nerve enters the spinal cord a "gateway" exists that can be open to let the signal through or closed. The gate can be closed by sensory stimulation, like massaging the area of the pain, or possibly by vibration along the spine. GCT also maintained 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 [114] and the efferent system is not effective, GCT does help explain why stimulation of touch fibers can reduce pain perception as is demonstrated with certain applications of low frequency sound stimulation (LFSS) that induces mechanical vibrotactile stimulation of mechanoreceptors and spinal cord functioning not unlike electrical skin and spinal cord stimulation [115]. Melzack [116] proposed a more adequate 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 provides a framework to understand why functions of music such as distraction, stress, and anxiety reduction, and aesthetic pleasure reduce pain perception. Neither GCT nor NM explains pain associated with rhythmic oscillatory coherence [117,118]. The correlation of thalamocortical oscillatory dysrhythmia (TCD) with pain has been demonstrated [10,119] but no definitive theory has been established.

Effects of Music on Pain
Given the role that neurotransmitters, hormones, and the limbic system play in pain according to the Neuromatrix theory, it is highly relevant that music has been shown to affect the release of endorphins [120,121,122,123,124, 125,126,127,128], dopamine [129,130], serotonin [131, 132],

and decrease in cortisol [130,133,134,135,136,137,138]. A recent review of 400 published scientific papers found strong evidence that music has effects on brain chemistry and has 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 anti-pain effect in the brain [136]. Specific brain correlates can now also be identified with strong emotional response to music [139]. 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" [139, p.170].

Effects of Sound Stimulation on Pain
LFSS stimulates the mechanoreceptors in the body and cellular structures, thereby serving to potentially block pain transmission according to the GCT. In addition to the general effects of LFSS, which include improved mobility [140], increased circulation [141], decreased low-density lipoprotein and blood pressure [142], and reduced muscle strain and stiffness [141], LFSS helps decrease pain [141,142]. Studies with LFSS have examined specific pain conditions: rheumatoid arthritis [143] and polyarthritis in hands and chest with 40 Hz [144,145], low-back pain, menstrual pain, and dysmenorrhea with 52 Hz [144,145], knee replacement pain [146], post-operative gynecological pain [147], and sports injuries [144,145,148]. Despite this research on specific pain, the assumption has primarily been that the effect is mechanical cell stimulation and not neurological rhythmic driving of oscillatory coherence to affect pain circuits.

Music and Fibromyalgia
Few studies have focused specifically on music or LFSS on fibromyalgia (FM). Chesky et al. [149] found that musically fluctuating vibration (60–300 Hz) failed to alter pain perception in patients with fibromyalgia. Onieva-Zafra et al. [150] examined the effect of 4 weeks daily music listening to unspecified "classical" music mixed with salsa music. The music listening group showed significant reduction in pain as measured by the McGill Pain scale. The control group received no treatment and showed no significant change. Müller-Busch and Hoffmann [151] studied chronic pain patients including fibromyalgia with a treatment of active MT using unspecified performed music. The results showed significant reduction in reported pain intensity but no change in depression and anxiety scores. Leão and da Silva [152] showed that women with chronic pain had less pain (p<.001) after listening to classical music. The few studies of sound and fibromyalgia that exist primarily draw on cognitive and affective effects of music. LFSS and fibromyalgia research has

not been previously theorized and conducted as in the present study.

Deriving an RSS Frequency for Pain
There is relatively little research that looks at pain as an oscillatory dysregulation except for TCD research and for electro-stimulation research that, to some extent, is premised on dysregulated sensory system circuits [8]. TCD is implicated in chronic and neuropathic pain with the typical shift of oscillatory power toward lower frequencies [153,154] and the edge effect as increased beta activity instead of the more usual gamma activity. In the case of neuropathic pain the thalamus appears to be more seriously affected to the point of atrophy [155]. DBS addresses this with stimulation at the typical 130 Hz frequency. The change in alpha power identified in TCD research is consistent with observations of alpha power related to placebo analgesia [156]. The hypothesis is that changes in alpha activity may be related to expectation of pain relief, with the change in alpha resulting from either the generation of expectation, maintenance of expectation, or expression of it. Since this is assumed to be a top-down process, manipulation of alpha activity with stimulation might then be a way to control pain [156]. Since alpha stimulation is possible with music and sound, this would be a possible direction for treatment. Although not placed in conjunction with TCD or alpha power, research on "mind wandering away" [157] may involve the same mechanism by changing coherence and alpha power.

Considerable research has been conducted on the application of rTMS in relation to pain. One assumption about rTMS is that stimulation above 5 Hz is excitatory and stimulation below 1 Hz is inhibitory. In relation to chronic pain, studies have found 10 Hz and 20 Hz to relieve pain but not 0.5, 1, or 5 Hz [87]. This is in agreement with a meta-analysis of rTMS pain studies showing that, with repeated sessions, treatment around 10 Hz was more effective than using low frequency stimulation (<1 Hz) or higher frequency stimulation >10 Hz [158]. An evidence-based guideline considered that high frequency rTMS applied to the motor cortex is effective in the treatment of pain [159]. Specifically with fibromyalgia, 10 Hz was found to be effective [160]. Both rTMS and TCD research point to theta and low beta over-activations that can be ameliorated with stimulation of high alpha (10 Hz) [161]. Moreover, motor cortex stimulation (MCS) shows some effect at reducing chronic pain (phantom pain) with stimulation in the 15–25 Hz range [162].

Sound stimulation for pain was applied in several noteworthy studies. Chesky and colleagues [149] used a range of frequencies with fibromyalgia in a moving manner rather than at fixed frequency and found little effect. Barnes et al. [163] reported decreased pain in a single case with fibromyalgia using 25 Hz stimulation with whole body sound vibration. Naghdi et al. [164] found significant pain reduction (Fibromyalgia Impact Questionnaire p<.0001) using 40 Hz

stimulation and pointing to TCD as the probable mechanism underlying the effect. Given the findings of oscillatory states with pain, effects from electro-stimulation, and assuming downward oscillatory resonance [165], sound stimulation at 10, 20, or 40 Hz should target the frequencies with greatest treatment potential.

Depression - Music/Sound Stimulation

Music has for many years been regarded as a means to both engage emotions and to "cheer up." A classic story in the Old Testament has King Saul bothered by "an evil spirit" and requests David to play his harp and when David plays, the "evil spirit" leaves him. Recently neuroscience is revealing the hormonal basis for some of these positive affective correlations with music [121,128,129,130,136,139], as well as detailing specific brain components involved in processing emotion with music [139]. Greater detail was already described in the section on "Pain."

Music Therapy and Listening
Scientific studies examining the clinical effect of music on depression are rare. A 2008 Cochrane Review [166] only found five studies that met inclusion criteria requiring therapist-mediated "music therapy" and were too varied to allow a meta-analysis. Findings in four of those studies showed a greater reduction in depression symptoms in participants treated with music therapy than those receiving standard care. What "music" was used in the therapy was not detailed. Since 2008, a number of studies in both music therapy and music medicine have been done with important findings [131,132,167,168,169]. Of these, Brandes et al. [131,169] used specifically prepared music that may have featured an entrainment device for brain stimulation, but details of the proprietary music have not been published.

Sound Stimulation of the Brain
A few music studies have addressed the extensive EEG asymmetry research [170]. This research observed alpha level coherent rhythmic oscillatory brain activity and compared left frontal with right frontal activity or activation. There is considerable evidence that this asymmetry is related to mood disorders and may even have a role as a biomarker for depression [171]. Field et al. [172] 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 behavior or mood as a result of the treatment, but the music group showed decreased frontal asymmetry (p=.05) and decreased cortisol levels (p=.02). A rating of preference for the music was done and the basic finding supported

greater shift to symmetry with preferred music. Jones and Field [173] looked at the effect of massage therapy and 23 minutes of rock/pop music listening on frontal EEG asymmetry. Except for the addition of massage, this study was a basic replication of Field et al. [172]. Results showed a similar effect of reduced asymmetry. Im [174] studied frontal EEG asymmetry in postpartum depressed mothers (n=9) compared to non-depressed mothers who recently gave birth (n=9) and 10 non-depressed women who had not given birth. EEG was recorded for 5 minutes before and after the treatment. The length and content of the music session were not reported. All three groups showed a shift to greater symmetry after the music session but only for the postpartum depressed group was the shift significant (p=.021). Petchkovsky et al. [175] used QEEG data to examine the effects of depressed adults participating in a choir (1week 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 a group of 21), who were tested before and after the intervention. Pre- and post-intervention data from the BDI and a mental state examination showed significant improvement (p<.001). The resting QEEG data revealed greater left-right hemispheric activity symmetry, reduced hyperactivity in the right prefrontal area, and reduced hypercoherence.

The only study that recognizes the potential of low frequency stimulation on brain response is Koike et al. [176]. In this study 15 elderly adults, who had symptoms of depression assessed with the Dementia Mood Assessment Scale (DMAS), were given 30 minutes (five days/week, two weeks) of unspecified "classical" music while resting on a lounge chair with two speakers close to 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. The before and after results showed significant improvement (p<.05) in the DMAS with significance in the mood and depression scales but not in the overall dementia severity scales. No brain imaging was done.

Deriving an RSS Frequency for Depression
Research about oscillatory mechanisms underlying depression found extensive frontal hemispheric asymmetry in EEG [177]. Typically this involves a comparison of frontal alpha power in left side versus right side. Although the phenomenon had been described extensively, underlying mechanisms are not clear [171], and research on whether frontal asymmetry is a mediator or moderator of emotions is not clear [170]. If there were a "causal" role for alpha asymmetry to depression, then regulation of the asymmetry would be a treatment, and that might be done by stimulating at 10 Hz. Drug treatments for depression do seem to restore greater symmetry [177], but without knowledge of specific mechanisms it cannot be a firm

biomarker. Music therapy has been shown to have a positive effect on frontal asymmetry in several studies [172,173,174,175,178]. However, vibratory-based rhythmic stimulation was not a variable in any study.

Another oscillatory theory that applies to depression is TCD [9,10]. Not unlike the asymmetry theory, it identifies a dysregulation of alpha and theta bands (increasing power in lower frequencies) accompanied by gamma frequency effects [179,180]. No regulatory stimulation frequency is commonly identified but speculation might point to 10–14 Hz and 40 Hz as a possible starting point. Since music in general has a regulatory effect on frontal asymmetry, higher alpha seems to deteriorate with TCD, and gamma dysregulation is reset with auditory stimulation [104], a potential brain stimulation for depression could be 10–14 Hz within music and low frequency stimulation in the 30–70 Hz range. A possible experimental response to the lack of research precedent and evidence could be to use a series of progressive frequencies between 10–130 Hz, as has been done in DBS research [181].

Summary

This paper has presented a discussion premised on the importance of steady-state brain oscillation for brain connectivity and cognition. Given that a healthy brain maintains particular levels of oscillatory activity, it was argued that disturbances or dysrhythmia of this oscillatory activity can be implicated in several health conditions including AD, PD, pain, and depression. Literature was reviewed that shows that electro-stimulation can contribute to oscillatory regulation and the alleviation of certain health conditions. It was then argued that specific frequencies of sound in its vibratory nature can serve as a means to brain stimulation through auditory and vibrotactile means and as such can contribute to regulation of oscillatory activity. The frequencies employed and found effective in electric stimulation were reviewed with the intent of guiding the selection of sound frequencies for vibroacoustic stimulation in the treatment of AD, PD, pain, and depression.

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