BENEFITS OF MUSIC THERAPY FOR INDIVIDUALS
WITH PARKINSON'S DISEASE OR ALZHEIMER'S DISEASE

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PREFACE

The musicians in the bands associated with Music Mends Minds, Inc. and their families and caregivers have wonderful testimonials as to the power of music to improve their quality of life. The purpose of this section is to summarize the current research into the effects of Music Therapy (also called Neurologic Music Therapy or NMT for neurological conditions) on people with Parkinson's disease and Alzheimer's disease. We also suggest directions for future research. If you would like to add a relevant study published in a medical journal to our summary or references, please email info@musicmendsminds.org.

BRAIN CHANGES AND SYMPTOMS

Understanding the changes that occur to the brain of a person with Parkinson's disease (PD) or Alzheimer's disease (AD) and the resulting symptoms is essential before reviewing the current research into NMT. Although the causes of PD and AD are out of the scope of this article, it should be noted that chronic inflammation leading to over-activation of the microglia (immune cells in the brain) and subsequent release of cytokines may be part of the cascade of events which leads to damaged neurons (Kim & Joh, 2006, Solito & Sastre, 2012, and Tang & Le, 2014). The substantia nigra cells in the basal ganglia, which are involved in motor control, appear to be particularly sensitive to such glial over-activation.

Inflammation also may prevent the microglia from performing their function of removing protein and other debris. Abnormal deposits of proteins in the form of neurofibrillary tangles can be found in neurons in PD and AD, with extracellular plaques also seen in AD. Proteins identified thus far include tau, alpha-synuclein and beta-amyloid. The beta-amyloid also may be present in a soluble, non-tangled form (Haass & Selkoe, 2007). Beta-synuclein is being studied for its possible role in axonal pathology (Sekigawa, et al., 2015).

In Parkinson's disease, the protein deposits are called "Lewy bodies", which consist mainly of alpha-synuclein. This protein, found normally at presynaptic nerve terminals, appears to be involved in inhibiting the release of dopamine, a brain chemical that controls the start and stop of voluntary and involuntary movements (Perez, et al., 2002). The Lewy bodies may damage the neuron and interfere with dopamine processing (Wakabayashi, et al., 2007), although more recent studies indicate a possible protective role of the Lewy bodies for injured neurons in PD (Wakabayashi, et al., 2013).

In Alzheimer's disease, beta-amyloid protein and tau appear to predominate, but alpha-synuclein is being called the "[t]hird Musketeer in AD [p]athophysiology" (Rogers, 2012). Thus, Parkinson's disease and Alzheimer's disease appear to be different ways in which abnormal proteins cause diverse symptoms, depending on the location of the protein aggregates in the brain.

The symptoms of Parkinson's may include motor changes, including tremors, "freezing" of gait, inability to initiate movement and difficulty in regulating step rate and stride length, muscle rigidity, postural control, balance problems, speech difficulties and dementia. The initial motor changes are due to decreased dopamine levels in the substantia nigra, but eventually other neurotransmitters and brain areas are affected (Yanagisawa, 2006).

Estimates of the percentage of Parkinson's patients who develop dementia (dementia now is classified under "Neurocognitive Disorder", according to the DSM-V) range from 50% to 80%.[52] Dementia includes such symptoms as "changes in memory, concentration and judgement [sic], trouble interpreting visual information, muffled speech, visual hallucinations, delusions, especially paranoid ideas, depression, irritability, anxiety, and sleep disturbances…"[52] Some symptoms seen in PD, such as dyskinesia, also may be due to dopaminergic medication (Kimber, Thompson & Kiley, 2008; Lee, et al., 2008).

In Alzheimer's disease, memory loss is one of the first symptoms due to damage to the neurons in the hippocampus, an area of the brain which controls memory. Cell death in the rest of the brain occurs in a predictable pattern.[53] Other areas of the cortex involved include the frontal lobe, which controls intelligence and executive functioning; the temporal lobe, which also is involved in memory, and the parietal lobe, which is involved in language processing. Serotonin, norepinephrine and acetylcholine are the neurotransmitters most studied as losing function in Alzheimer's, but recent studies have started to find a role for dopaminergic dysfunction in cognitive decline in Alzheimer's (Martorana & Koch, 2014).

BENEFITS OF MUSIC THERAPY

Now that we have a basic knowledge of the parts of the brain and brain chemistry which are affected by PD and AD, let's look at the research which shows that music positively impacts brain structure and function.

1. Music Induces Neuroplasticity and Bypasses Damaged Circuits

Listening to music, singing and making music contribute to neuroplasticity—the development of axonal sprouting and formation of new synaptic connections. Areas of the brain related to music share pathways with other functions, such as those involved in motor control (Chen, Penhune & Zatorre, 2008), memory, attention, higher executive functioning and language (Thaut & McIntosh, 2010) —all of which may be affected by

neurodegenerative diseases. For example, music affects sensory and motor regions in the frontal, parietal and temporo-occipital regions, the cerebellum, cingulate gyrus, midbrain, amygdala and hippocampus. For a detailed description, read "Apollo's gift: new aspects of neurologic music therapy" by Altenmüller and Schlaug (2015). The areas of the brain affected by a particular piece of music may vary, depending on whether the music is perceived as harmonious or dissonant, or creates a positive or negative emotional experience (Ueda, et al., 2013).

Music can bypass injured brain circuits and support the development of new neuronal connections. In "How Music Helps to Heal the Injured Brain" (2010), Thaut and McIntosh give examples of the way in which music bypasses damaged brain regions. Music tends either to activate the right side of the brain more than the left or both sides of the brain at the same time. The article authors state that "For injuries on one side of the brain, music may create more flexible neural resources to train or relearn functions."[40]

The frontal lobe is involved in working memory, mood and judgment, and the temporal lobe is involved in the formation of memories. Thaut, Peterson and McIntosh (2005) found that bilateral temporal and frontal brain activation occurs when subjects learn word lists using a song. When the study volunteers used only spoken-word learning, the left side of the brain alone is activated. Music may help to overcome unilateral neural deficits that affect memory and cognitive function by activating the uninjured side of the brain.

2. Music Affects Neurochemistry

Listening to music increases dopamine & serotonin. Using PET scans and measures of autonomic nervous system activity in humans, Salimpoor and her colleagues (2011) found that dopamine was released in the striatum during the peak of emotional feeling while listening to music. Listening to music that causes an intensely pleasurable emotional experience also increases regional cerebral blood flow (rCBF) in the ventral striatum, midbrain, anterior insula, anterior cingulate cortex and the orbitofrontal cortex (Blood and Zatorre, 2001). Increased rCBF means more oxygen, more glucose for energy and more nutrients into the brain region.

Sutoo and Akiyama (2004) found that hearing music increases dopamine levels in the neostriatum and nucleus accumbens in rats. Since the striatum is one region in which dopamine dysfunction occurs in PD, the study authors theorize that music can increase the production of dopamine in the undamaged dopaminergic nerve cells in the neostriatum and reduce the symptoms of PD.

Arkadir and colleagues (2014) demonstrated that "Collateral axonal sprouting of dopaminergic terminals [occurs] into the denervated striatum" in rodents with PD. Unfortunately, the collateral sprouting "leads to aberrant neuronal networks" (p. 1093). Perhaps music can increase the formation of a healthy compensatory dopaminergic network in the damaged brains of humans.

An excellent review of the research on the neurochemistry of music was done by Chanda and Levitin (2014). Although the research is not discussed in terms of the effect of music on the neurochemistry of patients with PD or AD, it provides a baseline for the known effects of music on brain opioids, immune function markers and stress markers. Chronic over-activation of stress chemicals, such as cortisol, has been implicated in the development of inflammation, dementia, PD and AD (de Pablos et al., 2014). Music has been shown to reduce these stress markers.[5]

Suzuki and colleagues (2005) performed a study of elderly patients with senile dementia before and after three months of MT. Among the measurements they took was saliva chromogranin A, a stress marker. After the three-month trial, saliva chromogranin A was significantly decreased, indicating a reduction in physiological stress.

Studies have shown that 17-beta estradiol and testosterone may have protective effects on the brain to delay or prevent Alzheimer's disease (Simpkins, et al., 2009; Xu, et al., 1998). In addition, testosterone and estrogen have been shown to reduce amyloid-beta (Gouras, et al., 2000; Xu, et al., 1998). However, hormonal replacement therapy can have negative side effects. A study was performed on patients with Alzheimer's disease to determine if receptive music therapy could endogenously increase these protective hormones. Indeed, after one month of MT, the levels of both testosterone and 17-beta estradiol increased significantly (Fukui, Arai & Toyoshima 2012).

3. Music Therapy Improves Motor Function in Parkinson's Disease

In PD, the death of dopamine-producing neurons in the substantia nigra pars compacta means the direct pathway for motor control cannot properly initiate movement. Dopamine also inhibits the neurons of the indirect pathway, which inhibits movement. Therefore, in PD, the inhibitory pathway over-functions, producing the symptoms of freezing gait and difficulty initiating movement. Dopamine agonists are used to reduce these symptoms in PD, but they can lead to dopamine dysregulation syndrome. (Kimber, et al., 2008; Lee, et al., 2008) What if the brain could be encouraged to increase dopamine levels naturally and without causing dysregulation? Music might be one way to achieve this outcome.

Thaut, McIntosh and Hoemberg (2014) delineated the neurobiological basis for neurologic music therapy. This basis is called entrainment. Entrainment is the ability of a higher energy oscillator to "entrain" the weaker oscillator to its repeating pattern. Music, with its repetitive beat pattern, provides a temporal cue that changes the timing of movement in patients with PD. The researchers say that music causes "priming" of the motor system so that it creates a state of readiness which makes movement occur more easily. In addition, a quality of "anticipation" occurs with music, which contributes to modulation of muscle activation and control (p. 2)—useful in mitigating the problems in PD of inability to initiate movement and freezing during movement.

Numerous studies have been performed on the effects of an external rhythm and cuing on PD symptoms, particularly gait. Nombela and her colleagues (2013) published a detailed review of this research. They found via neuroimaging studies that the perception of rhythm activates structures that are compromised in PD, such as the premotor area, the supplementary motor area, the basal ganglia and the cerebellum. The researchers state that the "automatic engagement of motor areas during rhythm perception may be the connecting link between music and motor improvements in Parkinson's disease" (p. 2564).

Hayashi, Nagaoka and Yoshikuni (2006) performed a study which involved Parkinson's patients who listened to rhythmic auditory stimulation (RAS) embedded in music at home for at least one hour per day for 3-4 weeks. The patients did not receive gait training. After four weeks, the gait speed and stride length of the patients improved significantly as well as their self-assessment of depression. The experimenters found that "external stimulation may have enabled parkinsonian patients to reproduce the internal rhythmic generation of gait…allowing them to walk faster and more smoothly." [17]

Another study on RAS and gait training in Parkinson's patients was performed by Thaut and colleagues (1996). As with the Hayashi, et al. study described above, the patients increased their gait velocity and stride length, as well as step cadence. After the RAS was discontinued, the patients could reproduce the RAS speed, indicating that entrainment of their gait patterns had occurred.[42]

Grahn (2009) evaluated the role of the basal ganglia in beat perception using fMRI. She found that "the basal ganglia are strongly linked to the generation of beat, particularly where internal generation of the beat is required, as opposed to rhythms with strongly externally cued beats". "Functional connectivity between part of the BG, specifically the putamen, and cortical motor areas "premotor and supplementary motor areas" is higher during perception of beat rhythms compared to non-beat rhythms. "Increased connectivity is found between cortical motor and auditory areas in those with musical training."[12] One could theorize that playing music would be even more beneficial to the brain than simply tapping to a beat.

Grahn and Brett (2007), using fMRI, demonstrated that the putamen (one component of the striatum) is activated by a rhythmic beat, and the putamen is one of the areas most involved in PD. Since the internal timing clock is affected in PD and self-initiated movements are adversely affected, external rhythmic cues can bypass the affected neurologic loops and allow for improvements in gait.[13] It should be noted that each patient must be assessed for their normal gait, as RAS can have negative effects when the beat is too fast or too slow relative to that person's current gait (Pachetti et al., 2000).

Slachtova and her colleagues (2014) did a pilot study to 1) assess the specific changes in gait in PD patients compared with non-PD controls and 2) ascertain if music or a

metronome of the same tempo was better at improving gait parameters. They found that listening to music significantly improved the gait over a metronome of the same beat. Improvement occurred only at the tempo of 90 or 120 beats per minute, not at 75 bpm.

Pachetti et al. (2000) performed a randomized, controlled study comparing the effects of active MT and physical therapy on patients with Parkinson's disease. MT clearly improved bradykinesia compared to PT, but did not appear to have an effect on rigidity or tremor. The patients who participated in active MT showed significant improvement in activities of daily living, such as cutting food, dressing, and decreased freezing and falling.

4. Music Therapy Positively Impacts Behavioral and Psychological Symptoms of Dementia (BPSD).

Ueda and his colleagues (2013) did a meta-analysis of 20 studies and found that MT had "moderate effects" on anxiety, 'large effects" if the duration of the study was greater than 3 months, and "small effects" on behavioral symptoms.

Vasionyté and Madison (2013) performed a meta-analysis of nineteen studies on the effectiveness of music therapy for patients with dementia. Although they did note that many studies they analyzed had poor methodology, they were able to conclude that "Many of these indicate large positive effects on behavioural, cognitive and physiological outcome measures, and medium effects on affective measures." (p.1203)

Conway, Pisoni and Kronenberger (2009) put forth the auditory scaffolding hypothesis to explain how music can aid in cognitive improvement, such as in acquisition and retrieval in memory. Although this research was not discussed in relation to patients with dementia, the hypothesis may have applications in future research using music to improve cognition in these patients.

Svansdottir and Snaedal (2006) performed a single-blind study on elderly Icelanders with moderate or severe Alzheimer's dementia. Active participation in music therapy over a 6-week period produced statistically significant improvements in agitation and anxiety over a control group.

Janata (2012) enlisted 38 patients in an assisted living facility with moderate-to-severe Alzheimer's dementia, determined their musical preferences, and piped in their preferred music to their rooms three hours daily for twelve weeks. This exposure to music was much greater than that seen in other studies. Improvements in agitation, anxiety and depression over the duration of the study were noted in the direct exposure to music group. The control group, afterwards called the "indirect group", also showed some improvement in these markers. Some of them may have accidentally been exposed to the music playing in the rooms of the direct group. However, a slight increase in Sundowner Syndrome, in which patients with advanced Alzheimer's

dementia become more agitated towards sunset, occurred in some of the patients over the course of the study.

In the Suzuki et al. (2005) study discussed previously, rating scales, such as the Mini-Mental State Exam, Gottfries-Brane-Steen Scale, and Behavioral Pathology in Alzheimer's Disease Rating Scale were used to evaluate behavioral changes after three months of MT. The study found that specific symptoms of dementia, including "paranoid and delusional ideation" (p.74) improved significantly, in addition to the reduction in the saliva chromogranin A stress marker.

Guétin and his colleagues (2009) treated patients with mild-to-moderate Alzheimer-type dementia using receptive MT. Significant improvements were demonstrated in anxiety and depression for the MT group compared to the control group.

Holmes and colleagues (2006) compared the effectiveness of music therapy in BPSD in patients with dementia. Pre-recorded music resulted in 25% of the patients showing improvement, but live interactive music was found to improve apathy in 69% of the patients.[18]

5. Music Therapy Reduces Speech and Language Deficits

The principle of entrainment has been shown to be effective in speech and language rehabilitation. Thaut, McIntosh, McIntosh and Hoemberg (2001) and others have applied principles of RAS to Parkinson's-related speech deficits with strongly positive results. Wan and her colleagues (2010), in "The Therapeutic Effects of Singing in Neurological Disorders", cited several studies (di Benedetto, et al., 2009, Haneishi, 2001, Ramig, et al., 2001) which used singing with Parkinson's patients, and all of them demonstrated improvement in the speech deficits seen in PD. One pilot study, however, did not find that group singing therapy resulted in significant improvement in speech and voice impairment in Parkinson's patients (Shih, et. al, 2012).

Summary and Suggestions for Future Research

It is clear that music can improve motor functioning, cognition and quality of life in Parkinson's and Alzheimer's patients. Music encourages neuroplasticity, helping to grow new connections around damaged neuronal axons and synapses. Music can improve neurochemistry by raising dopamine, estrogen and testosterone levels and decreasing stress markers such as cortisol and saliva chromogranin A. Music can bypass damaged neural circuits to improve motor and speech functioning. Music improves symptoms of dementia, including apathy, agitation, anxiety, depression, paranoia and delusions.

Some studies, however, have suffered from small sample size and methodology problems. Only a few studies retested weeks or months after completion of the trial to

determine if the benefits of MT were long-lasting. More research needs to be done delineating the relative effects of passive listening vs. active participation. Individuals respond differently to different genres of music, and not all songs from a single genre of music, e.g., classical, may have the same positive effect on an individual (Bodner, et al., 2001). A methodology should be developed to account for these differences.

Additional studies should look at the effects of music on axonal sprouting and on microglial and neuronal restoration in the PD and AD brain. Studies that demonstrate increased rCBF and activation of brain regions in healthy subjects listening to or playing music should be repeated with patients with PD and AD. And of course, the extent to which MT can prevent neurodegeneration is a crucial topic for study. Advances in functional diagnostic imaging, such as fMRI, MEG, DaT/SPECT and PET scans, will lead the way to greater understanding of the specific ways in which music is medicine for the injured brain and can prevent disease in the healthy brain.

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