Facts and figures: Results of a randomized placebo controlled double blind clinical trial on personalized music-focused auditory stimulation therapy – a novel approach for the treatment of depression, dystyhmia and stress-related disorders

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Abstract

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The application of therapeutic music interventions enjoy a growing interest from clinical practice and neurobiological research. Commonly, people listen to music to positively alter mental states and to encourage relaxation, support resilience and to help control anxiety. The therapeutic application of music is generally not associated with negative side effects and can be easily implemented. These factors contribute to high adherence and favorable treatment outcomes. Neuroimaging studies have demonstrated that processing of music activates particular pathways in the brain, in areas associated with emotional behavior (e.g. the insular and cingulate cortex, hypothalamus, hippocampus, amygdala, and prefrontal cortex). Neurochemical studies have also shown that biochemical mediators of emotional behavior (e.g. endorphins, endocannabinoids, dopamine and nitric oxide) may be triggered by music [1]. Compared to healthy controls, diminished activation of reward-processing neurocircuitry in depressed patients is associated with the loss of the experience of pleasure from listening to music [2]. Anhedonia is a key symptom of depression. Prior studies of different music interventions for depression provided evidence, but were not placebo-controlled and did not compare the specific effects of different stimuli. Part of depression's negative effect involves decreased heart rate variability [3,4]. We evaluated a new receptive music therapy method which was specifically developed for the treatment of depression on the basis of experiments which confirmed positive effects of specific music composition on heart rate variability (HRV) [5].

Methods: Recruited through media and by contacting doctors, potential subjects were screened online using the Goldberg Depression Questionnaire (GDQ) [6] to determine eligibility. All subjects provided written informed consent before participation in the study. The study was reviewed and approved by the local ethics commission and

registered with the National Institute of Health's clinical trial registry (www.clinicaltrials.gov, # NCT00644527). The first 204 respondents who completed the GDQ and met the inclusion criteria (aged 18+ and a GDQ score between 15 and 65) underwent more comprehensive baseline assessments. Respondents were not accepted if they had changed in the six month prior to study initiation: (a) therapists, (b) therapeutic session frequency, (c) antidepressants, or (d) antidepressant dosage. Further, individuals were only included if the agreed not to make any such changes during the course of the study period. 203 subjects (average age 49.6 ± 13.1 years, 28.1% male) entered the study protocol. The study design included four arms: Music Therapy 1 (MT1), Music Therapy 2 (MT2), Placebo (nature sounds) and waiting-list Control. The subjects were followed over four consecutive, five-week study periods (T1, T2, T3 and T4). During the T1 period, control arm subjects did not listen to study-provided music. (T2, T3 and T4) were employed to explore the effects of extended treatment duration.

MT1 and MT2 were personalized music-focused auditory stimulation therapies (I-MATs) developed by the study investigators as receptive music interventions for depression treatment. Both programs were developed and refined through a series of case studies and included two specific programs for different times of the day. Subjects listened twice daily for 30 minutes following am individualized treatment protocol. Depression status was assessed at the beginning of T1 and T2 using the Hamilton Rating Scale for Depression (HAM-D) [7], the Beck Depression Inventory (BDI) [8] and the Hospital Anxiety and Depression Scale (HADS-D) [9]. HAM-D was administered by trained psychologists blinded to the subjects' arm assignment. A composite (COMP) depression scale was constructed based on the HAM-D (double weighted), BDI and HADS-D z-scores. Utilizing multivariate linear regression models, Changes in depressive symptoms between the beginning of T1 and T2 were assessed based on a composite scale (COMP) and the Hamilton Rating Scale for Depression (HAM-D), Beck Depression Inventory (BDI) and Hospital Anxiety and Depression Scale-Depression Subscale (HADS-D) alone. At the beginning of T1, each subject also completed an extensive questionnaire covering various potential confounders. Separate multivariate linear regression models were constructed for each of the depression change variables with stepwise, backward elimination of possible confounders. Analyses were carried out based on an intention-to-treat approach with significance assessed both at the $p \leq 0.05$ and $p \leq 0.0125$ level [10].

Results: Compared to the control arm, a significant, positive effect in COMP was observed for MT1 in T1 (b=1.44, p=0.030), but not for MT2 (b=1.14, p=0.059) or Placebo b=0.57, p=0.397). No significant change in any depression score was detected in the placebo arm. After T2 to T3, the treatment was associated with a mean HAM-D score reduction of 60%. HAM-D, BDI and HADS-D score changes correlated only

moderately, with the highest correlation observed between BDI and HADS-D (ρ=0.59). In bivariate analysis, a "worries" scale was the only possible confounder significantly associated with all four depression scores, suggesting that the HAM-D, BDI and HADS-D scales may focus on different aspects of the construct of depression (e.g. cognitive and emotional factors).

Conclusions: The study included both subjects treated with personalized music-focused auditory stimulation therapy alone, or in combination with pharmacological and/or psychotherapy treatment approaches. Subjects in both patient groups benefited from the treatment. Based on possible neurophysiologic and neuro-chemical effects, personalized music-focused auditory therapy, as explored in this trial, is associated with reduced depressive symptoms and high treatment compliance, and may therefore potentially represent an effective depression treatment alternative, alone or in combination with psychosocial and pharmacological approaches. Further study is needed to explain the neurophysiological mechanisms. The author can be reached at vera.brandes@pmu.ac.at