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Audio Therapy Significantly Attenuates Aberrant Mood in Residential Patient Addiction Treatment: Putative Activation of Dopaminergic Pathways in the Meso-Limbic Reward Circuitry of Humans

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Abstract

Using fMRI, Menon and Levitin and Salimpoor et al. clearly show that listening to music strongly modulates activity in a network of mesolimbic structures involved in reward processing including the nucleus accumbens (NAc) and the ventral tegmental area (VTA), as well as the hypothalamus, and insula, which are thought to be involved in regulating autonomic and physiological responses to rewarding and emotional stimuli. We hypothesized that patients exposed to Stress & Deep Relaxation using Audio Therapy (music & sound) would show significant improvements in ten withdrawal symptoms systematically assessed supporting a role for this modality in recovery of patients with co-occurring mental illness and addiction. Thus our laboratory embarked on the evaluation of pleasant audio therapy in addicted patients undergoing recovery in our in-patient facility. We found significant pre to post Stress & Deep Relaxation using Audio Therapy (music & sound) in 76 drug dependent patients. Significant (at least p <.00002) improvements from pre-treatment to post-treatment were found for all ten of the withdrawal symptoms assessed, including the following behaviors and physical ailments: cravings; stress; depression; mood swing; anxious; resentful; anger; fearful; body aches and headaches. This analysis was obtained one-hour –half after the audio therapy and was compared to the initial Pre- five -point score. We believe that this form of therapy, and specifically the Prescription Audio, is an excellent adjunct to treatment. Audio therapy, and specifically music, has been shown in the literature to potentiate the effects of dopamine. Listening to music elicits a response in centers of the brain associated with the experience of pleasure and the mitigation of stress. Our work is in agreement with Ross et al. who found that music therapy appears to be a novel motivational tool in a severely impaired inpatient sample of patients with co-occurring mental illness and addiction.

Introduction

Using fMRI, Menon and Levitin [1] clearly found for the first time that listening to music strongly modulates activity in a network of mesolimbic structures involved in reward processing including the nucleus accumbens (NAc) and the ventral tegmental area (VTA), as well as the hypothalamus, and insula, which are thought to be involved in regulating autonomic and physiological responses to rewarding and emotional stimuli. Importantly, responses in the NAc and VTA were strongly correlated pointing to an association between dopamine release and NAc response to music. Listing to pleasant music induced a strong response and significant activation of the VTA-mediated interaction of the NAc with the hypothalamus, insula, and orbitofrontal cortex.

The enhanced functional and effective connectivity between brain regions mediating reward, autonomic, and cognitive processing provides insight into understanding why listening to music is one of the most rewarding and pleasurable human experiences. However, little is known about why some people have a more or less powerful mesolimbic experience when they are listening to music. This difference may reside in genetic deficits associated with many reward dependence behaviors including but not limited to addictive behaviors. Blum et al. [2] provided the first evidence that the dopamine D2 receptor gene (DRD2) Taq 1 A1 allele significantly associated with severe alcoholism whereby the authors suggested that they found the first "reward gene" located in the mesolimbic system.

Moreover, it is well-known that music may induce an endorphinergic response that is blocked by naloxone, a known opioid antagonist (Goldstein [3]). Opioid transmission in the NAc is associated with dopamine release in the VTA. Moreover, dopamine release in the VTA is linked to polymorphisms of the DRD2 gene whereby carriers of the DRD2 A1 allele show a reduced NAc release of dopamine (DA) [4].

It is noteworthy that music has no functional resemblance to other rewarding stimuli, and has no demonstrated biological value, yet individuals continue listening to music for pleasure. It has been

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suggested that the pleasurable aspects of music listening are related to a change in emotional arousal, although this link has not been directly investigated. Salimpoor et al [5] using methods of high temporal sensitivity investigated whether there is a systematic relationship between dynamic increases in pleasure states and physiological indicators of emotional arousal, including changes in heart rate, respiration, electrodermal activity, body temperature, and blood volume pulse. Results revealed a strong positive correlation between ratings of pleasure and emotional arousal. Importantly, a dissociation was revealed as individuals who did not experience pleasure also showed no significant increases in emotional arousal. Moreover, the same investigators using the neurochemical specificity of [(11)C] raclopride positron emission tomography scanning, combined with psychophysiological measures of autonomic nervous system activity found that intense pleasure in response to music can lead to dopamine release in the striatal system. The anticipation of an abstract reward can result in dopamine release in an anatomical pathway distinct from that associated with the peak pleasure itself [6].

It is well –known that drug seeking behavior is related to low Dopamine D2 receptors due to carrying the Dopamine D2 receptor A1 allele [7-10] and listening to music strongly modulates activity in a network of mesolimbic structures involved in reward processing including the nucleus accumbens (NAc) and the ventral tegmental area (VTA), as well as the hypothalamus, and insula, which are thought to be involved in regulating autonomic and physiological responses to rewarding and emotional stimuli.

A program known as Prescription Audio Chill uses vibrational sounds to gradually guide brainwave states to deeper levels of relaxation, where the neural chemicals that help heal stress-related damage are released, and the mind can enter a meditative state. Specifically, by denying us the ability to experience deep, restful relaxation, stress can inhibit many of our natural healing responses. Regular meditation has been shown to lower blood pressure and heart rate, enhance immune system response, promote greater cohesion between brain hemispheres, and sharpen memory [11-12]. The therapies employed in Chill may affect brain processes related to stress specifically as it relates to dopaminergic activity.

The EEG in Figure 1 is only shown to demonstrate the brain wave response to the Chill program and is not part of the results of the current study. The EEGs of a subject using the Prescription Audio Chill program over a 30 day period, the subjects alert state (Alpha and Beta waves, Green and Yellow respectively) is lowered by the treatments and replaced by a restorative, restive or sleep state (Theta and Delta waves Purple and Pink respectively) during the session and in progressively longer periods in subsequent EEGs. The treatment started at the 10 minute mark. The 10 minute control period prior to the start of each session clearly shows an alert subject. The difference between day 1 and day 60 demonstrates the entrainment of the subject's brain over time (Figure 1).

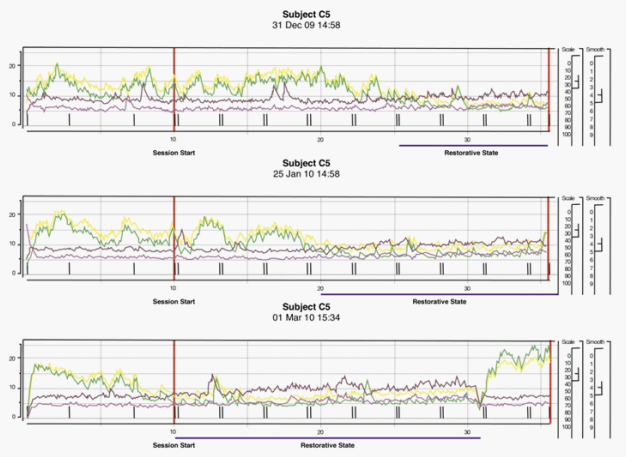
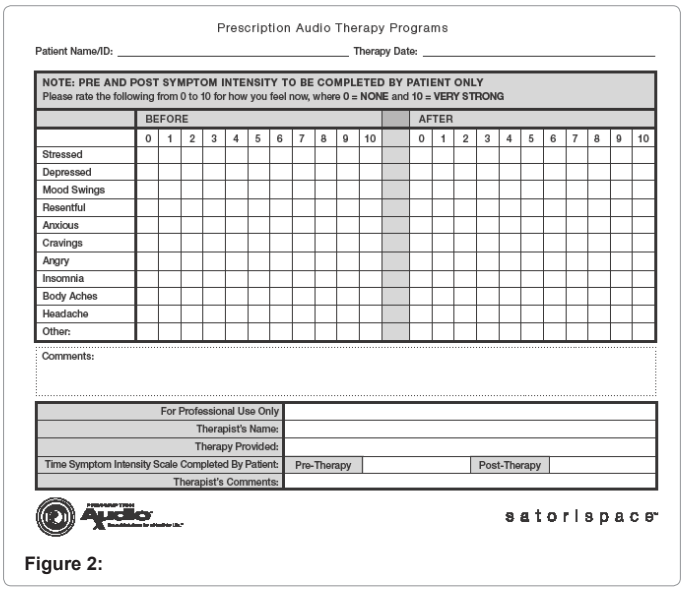


Figure 1:


Prescription Audio Therapy Programs

Patient Name/ID: _____ Therapy Date: _____

NOTE: PRE AND POST SYMPTOM INTENSITY TO BE COMPLETED BY PATIENT ONLY
Please rate the following from 0 to 10 for how you feel now, where 0 = NONE and 10 = VERY STRONG

	BEFORE											AFTER									
	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
Stressed																						
Depressed																						
Mood Swings																						
Resentful																						
Anxious																						
Cravings																						
Angry																						
Insomnia																						
Body Aches																						
Headache																						
Other:																						

Comments:

For Professional Use Only	
Therapist's Name:	
Therapy Provided:	
Time Symptom Intensity Scale Completed By Patient:	Pre-Therapy / Post-Therapy
Therapist's Comments:	

satorispace

Figure 2:

Methods

Program description

A description of the product used, "Chill Relaxation and Meditation Program" was retrieved from http://www.prescriptionaudio.com/sound-therapy-products/chill-stress-relief-solution and was utilized in this study." Chill is a natural, drug-free solution for stress relief. This vibrational sound program combines the principles of Quantum Harmonics TM with the benefits of meditation to help achieve deeper responses that once took years to achieve. The program quickly guides a subjects brainwave patterns from relaxing alpha frequencies to deeply meditation theta states. Quantum Harmonics uses a unique application of sound frequencies to achieve hemispheric

The EEG study used to demonstrate the brain wave response to the Prescription Audio Chill program was conducted at the clinical offices of Life Transformations in San Luis Obispo, CA between January 1, 2010 and March 31, 2010. Subjects were recruited to participate in the study and agreed to self-administer the Chill program daily for 30 days and to present themselves at the Life Transformation offices receive an EEG on Day 1, approximately Day 15 and Day 30. The program was provided free of charge to each subject. The EEG sessions were conducted in a darkened exam room. Figure 1 is the EEG of a single, representative female subject.

Based on this earlier unpublished work and other known literature, we hypothesized that patients exposed to Stress & Deep Relaxation using Audio Therapy (music & sound) would show significant improvements in ten withdrawal symptoms systematically assessed supporting a role for this modality in recovery of patients with co-occurring mental illness and addiction in the in-patient facility.

synchronization through brainwave entrainment. As such, repeated use of the program builds entrainment." (Figure1)

Each session is 24-minutes in duration and is delivered by stereo headphones or earbuds. Subjects received the sessions in darkened or dim, quiet rooms.

Subjects

The Chill Relaxation and Meditation Program offered to the clients free of charge as part of the group therapy treatment process at G & G Holistic Addiction Treatment, Inc. North Miami Beach, Florida resulted in a total of 76 subjects for participation in this open label study. The participants in this study agreed to utilize this therapy during their stay at the center. These 76 clients were all enrolled in residential treatment for a minimum of 28 days, had met American Society of Addiction Medicine [ASAM] criteria and were all diagnosed with a substance abuse disorder. Men comprised 70% of the sample, and women 30% of the sample. The racial breakdown was as follows: White – 80%; Black – 8%; Hispanic 7%; other – 5%. All subjects entered into the study meeting the Diagnostic and Statistical Manual of Mental Disorders, revision 4 (DSM IV) inclusion criteria and all subjects signed an informed consent statement developed by G&G Holistic Addiction Treatment Center and approved by PATH Foundation NY, New York, New York. The PATH Research Foundation approved the study (National Institute of Health [NIH] registration # 00002334) as a part of a systematic investigation related to holistic approaches in the treatment of Reward Deficiency Syndrome (RDS).

		Value	*Percentage (%)*
Gender	Male	52	68.4
	Female	24	31.6
Age	Median	34	
	Mean (+/-sd)	36 (11.4)	
Race	White	55	72.3
	Black	2	2.6
	Hispanic	1	1.3
	Native American	3	3.8
	No response	15	20

Table 1: DEMOGRAPHICS FOR AUDIO Rx *(N=76)*

		Mean	SD	p=
Cravings	Before	1.91	2.43	.00001
	After	.66	1.09	
Depression	Before	2.01	2.31	.00001
	After	.89	1.22	
Mood Swings	Before	2.26	2.52	.00001
	After	.70	1.17	
Resentful	Before	1.74	2.10	.00001
	After	.58	1.06	
Anxious	Before	3.59	2.82	.00001
	After	1.21	1.58	
Body Aches	Before	2.58	2.71	.00001
	After	1.09	1.76	
Headaches	Before	1.45	2.22	.00001
	After	.45	0.99	
Anger	Before	1.48	2.11	.00001
	After	.44	0.79	
Stress	Before	3.03	2.82	.00001
	After	.79	1.28	
Fearful	Before	2.58	2.69	.00001
	After	.72	1.26	

Table 2: Means and Standard Deviations of Symptoms Before and After Music Therapy.

Symptom	Cravings	Stress	Depression	Mood	Anxious	Resentful	Anger	Fearful	Body Aches	Headaches
Improvement (%)	66%	74%	56%	69%	66%	67%	70%	72%	58%	69%

Table 3: Percent Change.

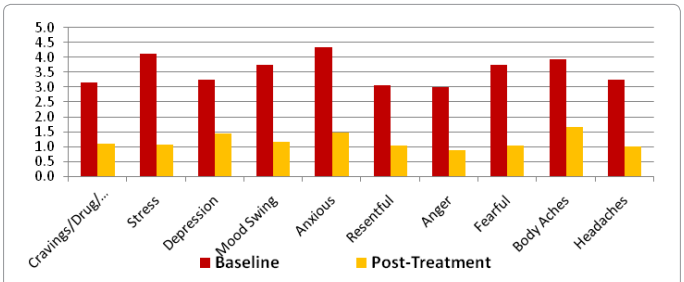


Figure 3: Mean Symptom Values at Baseline and Post-Treatment - Single Session.

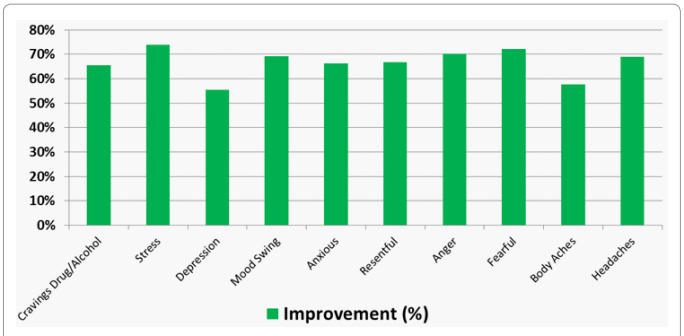


Figure 4: Percent Improvement.

Additionally, thirty-three (33) of the 76 subjects were tracked over multiple sessions, three sessions in total, to determine retention of symptom severity reduction. As all subjects were participants in a 28-day residential program, more than half of the participants were not available for the multiple session portion of the study as some subjects graduated from the program.

Procedure

Prescription Audio Chill Program (Voorhess, NJ) was evaluated in 76 clients [see demographic table 1] from group therapy sessions conducted in January 2010 and March 2010. Each group session consisted of a 25 minute audio listening portion. Seventy–six clients were asked to score the intensity of their symptoms immediately prior to the session and then asked to score them again immediately after treatment. Client scored the following symptoms: cravings, stress, depression, mood swings, anxiety, resentments, anger, fear, body aches and headache from 0 to 10 (where 0 = none and 10 = Very Strong) using the Symptom Intensity Scale (Table3). Each participant underwent a single session of the Prescription Audio Chill Program. This analysis was obtained within one-half hour after the audio therapy and was compared to the initial Pre-ten-point score.

Like any of the scales used for symptoms, such as pain, that are difficult to quantify by biometrics or observation, the Symptom

Intensity Scale (SI) is used to measure how intensely individuals are feeling a particular symptom and to monitor the effectiveness of treatments. The 'before' section of the SI scale is completed by the subject prior to the session. As stated previously, the 'after' section of the SI scale is finalized by the subject within a half-hour after the completion of the session. The values for before, after and the comparative differences between the before and after intensity levels were averaged for all subjects by symptom. Not tracked as part of the study, but anecdotally, clinicians using the SI scale indicate, that many times, discussing an individual's session results allows for a more open dialog with a patient.

Statistical analysis

Mean post-treatment scores were calculated and compared to pre-treatment means for each of the ten withdrawal symptoms in the single session study. Wilcoxon signed rank tests were calculated for each of the ten withdrawal symptoms. A Bonferroni correction for multiple comparisons required $p<.005$ to attain an experiment-wise significance level of $p<.05$.

Results

Wilcoxon signed rank tests performed on the 10 symptoms from before to after music and sound therapy were significant for 10 symptoms in the single session study ($Z = -9.53$ to -7.34, all $p <.00001$). All results remained significant after applying a Bonferroni correction. Examination of the changes in means showed a significant decrease from pre-treatment to post-treatment for all 10 symptoms (Table 2). The average change for each symptom ranged from 56% decrease to 72% decrease (Figure 3).

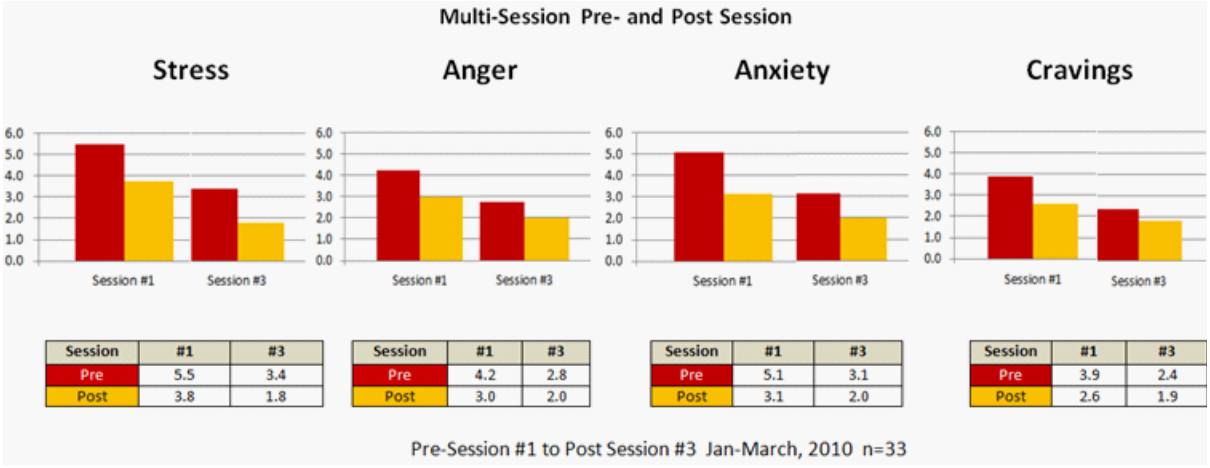
The 33 participants in the multi-session Figure 5 part of the study underwent two additional sessions of the Prescription Audio Chill program. In the key symptoms of cravings, anger, anxiety and stress, symptom severity was constantly reduced between pre-session #1 and pre-session #3 indicating retention of a portion of the improvement over multiple sessions. SI scale averages indicate symptoms were reduced 22% to 58% per session and between 52% and 67% from before session #1 to the end of session #3 (Table 4).

Discussion

The results obtained here using Chill inducing meditative states is not so surprising considering that other positive behavioral actions including video gaming another dopaminergic (carriers with the DRD2 A1 allele highly addicted to video gaming) based behavior also causes dopamine release. In fact it was previously found that during Yoga Nidra meditation, 11C-raclopride binding in ventral striatum decreased by 7.9%. This corresponds to a 65% increase in endogenous dopamine release [13]. It is suggested that being in the conscious state of meditation causes a suppression of cortico-striatal glutamatergic transmission which provides for increase dopamine release at the reward site of the brain (N.Accumbens). Previous work by others [1,5,14,15] indicate that intense pleasure in response to music can lead to DA release in the striatal system at approximately 9% over rest.

It is of interest that food increase DA release in the NAc at 6% whereas cocaine increases DA release at approximately 22% [5]. It is well-known from the work of Goldstein [3] that music may induce an endorphinergic response that is blocked by naloxone, a known opioid antagonist. Opioid transmission in the NAc is associated with DA release in the VTA. Based on the literature [16] coupled with the present findings Chill induces acute positive behavioral outcomes overcoming aberrant maladaptive behaviors associated with recovery potentially by activation of mesolimbic dopaminergic pathways.

Thus it is conjectured that similar mechanisms in terms of adequate dopamine release and subsequent activation of reward circuitry by listening to music might also be affected by an individual's D2 density in the VTA mediated interaction of the NAc [14]. It is therefore hypothesized for future consideration that carriers of DRD2 A1 allele may respond significantly differently to carriers of the DRD2 A2 genotype. In this regard, carriers of the D2 A1 allele have a blunted response to glucose and monetary rewards [17]. In contrast powerful D2 agonists like bromocryptine show a heightened activation of the reward circuitry only in DRD2 A1 allele carriers [18]. If music causes a powerful activation in spite of the DRD2 A1 allele due to a strong DA neuronal release which subsequently impinges on existing D2 receptors, then it is reasonable to assume that music is a strong indirect D2 agonist (by virtue of DA neuronal release in the NAc) and may have important therapeutic applicability in Reward Deficiency Syndrome (RDS) related behaviors including Substance Use Disorder (SUD)[14]. Ross et al [19] found that music therapy appears to be a novel motivational tool in a severely impaired inpatient sample of patients with co-occurring mental illness and addiction. There is also



Session	#1	#3
Pre	5.5	3.4
Post	3.8	1.8

Session	#1	#3
Pre	4.2	2.8
Post	3.0	2.0

Session	#1	#3
Pre	5.1	3.1
Post	3.1	2.0

Session	#1	#3
Pre	3.9	2.4
Post	2.6	1.9

Figure 5: Multi-Session.

Symptom Improvement (%)	Stress	Anger	Anxiety	Cravings
Session #1	31.3%	29.2%	38.9%	33.1%
Session #3	46.8%	27.3%	36.0%	22.1%
Session #1 to #3	67.2%	52.8%	60.9%	52.5%

Table 4: Percent Change.

emerging evidence that music therapy linked certain dopaminergic receptors (e.g.DRD4) in Autistic individuals may have benefits [20].

We are cognizant that there are a number of important limitations in this open label study. We have not identified the different response between males and females. Our study did measure other variables such as age, depression, psychosis, type of addiction (e.g. alcohol compared to other drugs). We did not carry out any multivariate analyses to elucidate if the relationship was independent from other variables. Based on this and the fact that we did not carry out a randomized –double-blind –placebo controlled large population study any interpretation must await further testing.

Conclusion

This clinical study shows that Audio Therapy significantly attenuates aberrant mood in residential addicted patients by putative activation of dopaminergic pathways in the meso-limbic reward circuitry of humans. It is parsimonious following a larger confirmatory study to cautiously suggest that Audio Therapy becomes "Standard of Care" especially in an holistic addiction treatment program.

Conflict of Interest

Monty D. Moeller is employed by Prescription Audio, Inc., Voorhees, New Jersey, USA the distributors of Audio RX therapy. No other authors claim a conflict of interest.

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