Music and Sound Interventions for Post-Traumatic Stress Disorder

Subjects: Health Care Sciences & Services
Contributor: Usha Pant

Post Traumatic Stress Disorder (PTSD) is characterized by symptoms including: intrusive memories, hyper-arousal, avoidance of trauma-related stimuli, and negative alterations in mood or cognition that develop following exposure to traumatic life events.

Keywords: music ; post traumatic stress disorder ; critical illness ; neurobiology ; autonomic nervous system ; limbic system

1. Pathophysiology of PTSD

1.1. The Hypothalamus-Pituitary-Adrenal Axis

The HPA axis involves a complex set of interactions among the hypothalamus, the pituitary gland, and the adrenal gland that determines the level of circulating cortisol. Stress triggers an HPA and sympathetic nervous system (SNS) response. Upon perception of a stressful stimulus, norepinephrine and indirect limbic inputs from the hippocampus, prefrontal cortex, and amygdala stimulate neurons in the paraventricular nucleus (PVN) of the hypothalamus that contain a corticotropin releasing factor (CRF), leading to the activation of the HPA axis and the release of adrenocorticotropic hormone (ACTH) into the systemic circulation. ACTH then binds to melanocortin 2 receptors in the zona fasciculata of the adrenal cortex and stimulates the release of glucocorticoids (specifically cortisol). Activation of the HPA axis is modulated by pituitary adenylate cyclase-activating polypeptide (PACAP), which appears to mediate the production of CRH. PACAP is also involved in the modulation of the sympathetic nervous system (SNS) response [1].

The SNS contributes to the flight or fight response by signaling the adrenal medulla to release catecholamines (epinephrine and norepinephrine) and enkephalins. Cortisol, catecholamines and enkephalins together stimulate a series of effects such as enhancing glucose availability, regulating the immune system and brain function, and impacting electrolyte balance to manage stressors [2]. Simultaneously, several brain structures control the HPA axis activity. Specifically, both the hippocampus and prefrontal cortex (PFC) impede the CRF neurons in the PVN of the hypothalamus. In contrast, the amygdala triggers CRF neurons in the PVN. Cortisol regulates HPA-axis activity by generating negative feedback to both the hypothalamus and the anterior pituitary.

Cortisol acts as the primary molecule to enable the stress response, as well as prevent ongoing HPA axis activity. The function of the HPA axis is controlled by two factors: (a) the effectiveness and (b) number of glucocorticoid receptors in the pituitary and hypothalamus [3][4], which regulate both CRF and ACTH release. However, if the negative feedback cycle of the HPA axis is disrupted, either due to the overactivity of CRF or due to hypersensitivity to glucocorticoids, the production of cortisol continues. This negative feedback system appears to be compromised in patients with PTSD. A metanalysis of 24 studies examining six HPA-axis genes in PTSD patients demonstrated involvement of two genes: (a) NR3C1 associated with the encoding of the glucocorticoid receptor, and (b) FKBP5 linked with regulating the affinity of the glucocorticoid receptor [5]. Moreover, persistent exposure to stressful events leads to multiple such cycles in a single day, preventing the HPA axis from returning to the baseline [6]. The aberrant stress response resulting from an overactive and prolonged HPA axis response increases stress-like symptoms in people with PTSD [7]. Moreover, the over-production of cortisol generates a state of toxic stress that changes the physical structure and function of the amygdala, hippocampus, and PFC.

1.2. The Amygdalae

The amygdalae are a subcortical collection of nuclei situated in the anterior temporal lobe of each hemisphere, projecting to the brainstem and hypothalamic regions. The amygdalae play a critical role in emotional processing and generation of fear responses. In particular, amygdalae are associated with the execution of the physical, autonomic, and musculoskeletal components of the emotional response. Moreover, they have connections with other emotional centers in the brain. The amygdalae process the stressful events resulting in the release of cortisol through HPA-axis activation. In the case of an aberrant HPA axis feedback cycle, the continuous cortisol release enhances the amygdala's ability to communicate within and with other brain structures [7][8]. This makes the amygdalae more receptive to perceived threat. A metanalysis of fifteen functional imaging studies investigating PTSD patients demonstrated significant hyperactivation of the amygdalae [9].

1.3. The Hippocampus

The hippocampus is an extension of the cerebral cortex situated deep within the temporal lobe. The hippocampus plays a crucial role in the consolidation of information from short-term memory to long-term memory. It is also involved in the neuroendocrine regulation of stress hormones. Alterations in the structure and function of the hippocampus are observed in several neurological and psychiatric disorders [7][10]. Boccia et al., (2016) through functional magnetic resonance imaging, observed a hypoactive hippocampus among participants with PTSD [11]. The hippocampus has projections to the hypothalamus and is involved in the regulation of adrenocorticotropic hormones. Therefore, hypo-activity of the hippocampus may result in increased HPA axis activity [12].

Traumatic stressors have also been shown to alter hippocampal dendritic morphology and inhibit neurogenesis in the hippocampus [10][13][14][15]. Chronic stress rapidly reduces the number of dendritic spines and branches of pyramidal neurons in the Cornu Ammonis subfield 3 (CA3) and compromises the integrity of CA1, which is involved in the persistence and re-experiencing of traumatic memories [16][17]. For example, early magnetic resonance imaging studies demonstrated smaller hippocampal volumes in Vietnam Veterans with PTSD compared with controls [18][19][20][21][22]. Small hippocampal volumes were associated with the severity of trauma and memory impairments in these studies. Stress also suppresses the production of new granule neurons in the dentate gyrus regions of the hippocampus [23]. Evidence also shows that small hippocampal volumes are involved in increased susceptibility to stress and trauma [24]. Moreover, prolonged HPA axis activation generates various neurobiological changes in the hippocampus that influence the hippocampal functions, such as learning and memory functioning [13].

1.4. The Pre-Frontal Cortex

PFC is vitally involved in executive functions, such as concentration, organization, judgement, reasoning, problem solving, decision making, creativity, emotional regulation, and abstract thinking. Chronic exposure to stress impairs prefrontal cortex functioning, which leads to aberrant stress responses and maladaptive coping. Decreased volumes of the frontal cortex are associated with significant hypoactivation of the PFC in individuals with PTSD [9][25]. There are dense white matter connections between the ventral region of PFC and the amygdalae that facilitate bi-directional communication between these two areas. Amygdalic activity is inhibited through the PFC [26][27][28][29][30]. Therefore, a hypoactive PFC in individuals with PTSD may impair regulation of emotional processing in the amygdalae [31]. Besides this, prefrontal dysfunction also results in a reduced ability to concentrate and regulate executive functions [7][32]. Thus, the hypoactivity of the prefrontal cortex can explain some of the symptoms of PTSD such as the inability to focus, solve problems and guide thoughts or emotions using working memory [33][34].

2. Music Therapy

2.1. Effect of Music in Neuropsychiatric Conditions and PTSD

Various music and sound interventions have been used to improve health outcomes in a broad spectrum of psychological and neurological disorders [35][36][37][38]. Music therapy has demonstrated significant effectiveness for the reduction of depression in people with dementia [36][39] and improvement of mobility in people with stroke [40]. Music therapy delivered by a professional music therapist revealed the efficiency of music to improve social interaction and communication skills in children with autism spectrum disorder [41]. Moreover, there is evidence that music therapy in addition to standard care improved mental state and social functioning in schizophrenia patients [36][42].

A meta-ethnography of 46 qualitative studies found that participatory music engagement, music actively made by the participant, including singing, and not limited by musical genre such as classical or jazz, improved well-being by facilitating self-development, providing respite from problems, and fostering social connections [43]. There is growing evidence that music therapy can abate the stress response, decrease anxiety, and induce an overall relaxation response by reducing stress-inducing stimuli. A recent meta-analytic study by Witte et al. (2020) revealed the effectiveness of music interventions to relieve stress in a variety of settings, including mental health, polyclinic medical settings, medical surgery, and everyday life. The study's findings demonstrated that pre-recorded relaxation music without lyrics could reduce physiological stress symptoms such as heart rate, blood pressure, and stress-related hormones, as well as psychological stress symptoms such as anxiety, nervousness, restlessness, and feelings of worry [44]. McKinney & Honig (2017), examined effects from randomized and non-randomized controlled trials and found a medium to large effect of guided imagery and western classical music on various psychological measures including anxiety, and mood disturbance [45]. Bradt et al. (2013) demonstrated the beneficial effect of patient-selected music from different styles of music such as jazz, easy listening, country and western, or classical music on preoperative anxiety and recommended its use as an alternative to sedative drugs [46]. Hole et al. (2015) confirmed that Chinese classical music reduced postoperative pain, anxiety, and analgesia use and increased patient satisfaction [47].

The effect of music and sound interventions has also been explored in ICU patients [48]. Various forms of music interventions in ICU populations are found beneficial in reducing ICU-related anxiety and in-hospital stress [48][49]. In mechanically ventilated patients, patient-directed music therapy is associated with lower anxiety scores, sedation frequency, and sedation intensity when compared to usual care [50][51][52][53]. A majority of included studies used music that contains simple repetitive rhythms, low pitch, slow tempos, harmony and lack percussive instruments and vocals. Hetland et al. (2015) indicated that relaxing music, such as nature-based sounds, classical, and easy listening, can help manage pain, agitation, delirium, post-traumatic stress disorder (PTSD), anxiety, and depression in ICU patients by reducing the need for sedatives during mechanical ventilation, length of stay, and physiologic signs of anxiety and biomarkers of the stress response [54]. Moreover, implementing music interventions in usual care is free of adverse side effects and can also reduce ICU costs. A recent study by Chlan et al. (2018) demonstrated that patient-directed music interventions can save about $2000/patient and concurrently better manage anxiety with less sedative medication than usual care [55]. However, to date, the effect of music and sound interventions have not been explored in relation to the psychiatric disorders and PTSD after discharge from the ICU.

Despite this gap in evidence, music appears to be a promising adjunct in the treatment of PTSD [35]. Evidence from various studies shows a significant effect of individual and group music therapy in the reduction of core PTSD symptoms and the increase in social function among PTSD patients. Creative art therapy also pointed out the potential of relaxation music therapy to creatively process, cope, and recover from PTSD [56]. A mixed method study by Story and Beck (2017) reported experiencing classical music as a tool for coping with PTSD symptoms, particularly to regulate emotions, decrease arousal, express repressed feelings, and connect with others [57]. Moreover, group music therapy in adult psychiatric patients with persistent PTSD, who had been unable to benefit from cognitive behavioral therapy CBT, showed a significant decrease of all dimensions of PTSD symptoms [58]. The study explored therapist guided music improvisation technique using a variety of musical instruments such as xylophones, maracas, Indian bells, gato drums, djembe, tone bars, guitar, piano and cabassas.

Empirical evidence suggests that music therapy may reduce prominent symptoms of post-traumatic stress, including emotionally dysregulating intrusions, avoidance, negative alterations in mood, and arousal. A study by Zergani & Naderi (2016) demonstrated beneficial effects of Iranian traditional music on quality of life and anxiety symptoms among hospitalized veterans with PTSD [59]. A double blinded randomized control trial, conducted by Pourmovahed et al., (2021) demonstrated that listening to non-verbal music can significantly reduce the severity of PTSD in mothers of premature infants hospitalized in NICU and promote emotional bonding between the mother and baby [60]. The music included the sound of rain, sea, and nature with a slow, gentle, and soothing rhythm. Another randomized controlled trial that examined the effects of music therapy on symptoms of PTSD among prison inmates demonstrated a significant decrease in PTSD-symptoms [61]. A mixed method study examining the efficacy of group drumming therapy in military veterans with PTSD indicated a significant reduction of specific symptoms such as isolation, lack of connectedness, avoidance of traumatic memories, rage, and anxiety [62]. A mixed method study on the feasibility of group music therapy for women with PTSD and complex PTSD found significant changes in the PTSD, dissociation, anxiety, and depression scales, indicating symptom reduction [63]. The qualitative analysis of participant experiences revealed that music assisted in establishing contact with feelings and bodily sensations, as well as providing an experience of expansion, relaxation, and new energy. Furthermore, six participants no longer had a PTSD diagnosis after treatment as shown by the PCL-5 cut-off values, which was sustained even at follow-up.

Music guided relaxation has also shown a positive impact in reducing depression, PTSD and increasing sleep quality in veterans [35]. In a naturalistic study of 102 women with complex PTSD, guided imaginary and classical music significantly reduced symptoms of extreme stress, dissociation, interpersonal problems, and a sense of coherence [64]. Another study demonstrated similar results of guided imaginary and classical music in refugees with PTSD. After sixteen GIM sessions, adult refugees showed positive improvements in PTSD symptoms, sleep quality, well-being, and social functioning [65]. A recent randomized control trial with 74 refugees with PTSD, employing western classical music, New Age music, and music from the participants’ own national culture showed improvements in quality of life and fewer symptoms of psychological dissociation after music therapy [66]. In addition, unlike the standard treatment, the positive effects of music and imagery were manifested even at the 6 month follow-up.

2.2. Mechanisms Underlying the Effects of Music in PTSD

Musical stimuli stimulate neural networks associated with various functional domains, such as movement, cognition, communication, emotion, and social responses [67]. Studies clearly demonstrate that instrumental music without lyrics, Chinese and Western music can evoke changes in emotion and stimulate the brain structures involved with motivation, reward, and emotion [68][69][70][71][72]. There is evidence that music can provoke changes in individual emotions, hormone arousal, emotional motor expression, and action movements [69]. The studies included in this analysis used various experimental approaches, such as investigating music-evoked experiences of intense pleasure, emotional responses to consonant or dissonant music, happy or sad music, joy- or fear-evoking music, musical expectancy violations and music-evoked tension. Listening to joyful dance-tunes has been shown to reduce stress and enhance emotional responses, such as joy and peace [72][73]. In particular, music is observed to stimulate increase in blood–oxygen level dependent (BOLD) signals in the amygdala, and the hippocampus [72]. A meta-analysis of functional neuroimaging studies [70] found that the amygdalae, hypothalamus, and hippocampus, which are vital parts of the brain in producing emotion and in experiencing PTSD symptoms, are stimulated by music. None of the included studies used music with lyrics. The ventral tegmental area (VTA), involved in dopamine production and release within the reward system, is also significantly activated by both unfamiliar musical pieces and the participant’s favorite music, in contrast, PFC activity was positively correlated with pleasure scores associated with music [74][75]. However, favorite versus neutral music listening contrasts showed a greater activation in healthy participants than depressed patients [74].

PTSD is characterized by hypervigilance associated with altered connectivity between the amygdalae and the hippocampus [76]. Communication between these brain areas is vital in the symptomatology of PTSD. There is evidence that participant’s own favorite music to which they usually had a chill experience, can enhance the connection between the amygdalae, PFC, and the hippocampus [77]. Moreover, contrast analysis of joy, fear and neutral musical stimuli revealed strongest BOLD signals in the superficial amygdala during joyful music, such as classical music, Irish jigs, jazz, reggae, South American and Balkan music [78]. Thus, music could potentially play a role in balancing the processing of stimuli and in reducing the amygdala’s startle response so they can revert to the premorbid state. Moreover, attentive listening to musical clips played with the piano or violin can also stimulate PFC [79], and therefore, can possibly recruit PFC to exert inhibitory control over amygdalic stress responses. Initiating communication between the amygdalae, PFC and hippocampus through music can, therefore, not only mitigate the hypervigilance of PTSD, but can also enhance cognitive processing of emotions.

Attentive listening to or playing music can stimulate neurogenesis and neuroplasticity in the brain [67][73][80] which is relevant for individuals with PTSD who experience neuronal loss and impaired neurogenesis in parts of the limbic system. The increased hippocampal communication with the hypothalamus can also help balance the HPA axis [80]. There is evidence suggesting that musical training in healthy participants can stimulate the hippocampus, induce neurogenesis, and produce a larger hippocampus [81][82][83]. Altering the hippocampal volume can consequently increase positive emotions and regulate negative affect. Koelsch and Skouras (2014) reported increased functional connectivity between the hippocampus and hypothalamus, and amygdalae and nucleus accumbens during exposure to joyful music in healthy adults [84]. The study used non-vocal joyful instrumental music from various epochs and styles. In addition, several studies on music-evoked emotions have reported activity changes in the hippocampus associated with a reduction of emotional stress associated with a lowering of the cortisol level [73][85][86][87]. Overall, 75% of these studies involved experimenter-selected music (classical, new age or easy listening, and world), while the other 25% involved self-selected music, either “entirely self-selected” or “quasi-self-selected”. Clinical studies, which included a majority of the ICU population, demonstrated a stress-reducing effect of music listening irrespective of genre, self-selection of the music, or duration of listening [85]. Classical music demonstrated a significant reduction in cortisol levels among mechanically ventilated ICU survivors [86].

Evidence suggests that active vs. passive music therapy may have differential effects on patient engagement and receptivity. According to fMRI and PET scan studies, active music participation engages more parts of the brain than just listening to music [88]. In a qualitative study, passive music therapy participants reported an immediate therapeutic effect, such as a reduction in anxiety [89]. Active music therapy participants, on the other hand, described interactive session elements as stimulating, alleviating anxiety through pleasant social interaction. Music improvisation (drum based) has been found to be effective in expressing and managing emotions among veterans with PTSD [62]. Moreover, a systematic review showed that passive listening to relaxing music didn’t seem to have any significant effects on PTSD symptoms, suggesting the importance of active music therapy to evoke change in PTSD patients [56]. The researchers posited that specialist skills and an ongoing therapeutic relationship is vital in reducing symptoms of PTSD.

However, music selection needs careful consideration. Music that the participant does not enjoy may result in a stress rather than a relaxation response. Moreover, music can trigger strong memories, which influence the affective response to music and can, therefore, modulate the therapeutic effects of music [90]. In the acute phase of critical illness, despite some controversy around the role of patients' music preferences, it appears that patient-directed music selection associates with better outcomes [91]. Several studies allowed participants to choose music from a variety of musical genres. However, participants' choices were restricted within the range of selections offered by the researchers. Music interventions for mechanically ventilated patients reported participant dropout rates to be higher in researcher-selected music compared to patient-selected [92]. Instead, studies involving a music therapist to assess patient music preferences have reported no dropouts and a high degree of participant satisfaction [35][65][66]. Therefore, self-selected music appears to be associated with both the effectiveness of music interventions and participant retention.

Basic psychoacoustic properties of music, such as pitch (high or low tone of sounds), rate (fast or slow speed of sounds), loudness (loud or soft intensity of sounds), mode (major or minor key), timbre, and rhythm have been shown to be important factors in the perception and induction of positive as well as negative emotional states. The music therapy research supports music containing a slower tempo, low pitch, containing primarily string composition, regular rhythmic patterns, no extreme changes in dynamics, and no lyrics are associated with relaxation, joy, or peace [93]. The tempo of 60–80 beats per minutes can help induce a state of relaxation and regulate emotions [94]. A study by Beck et al., 2021, used predictable slow-tempo music to decrease arousal and induce relaxation in PTSD patients [66]. In addition, the harmonic complexity of relaxing music should be consonant and remain within the diatonic key with a clear tonal center [93][94]. Predictable music leads to positive responses, such as reward, appraisal, and pleasantness, thus it may support the relaxation response, while dissonant and unexpected harmonies with frequent chord changes activate the amygdala and defeat the purpose of emotion regulation [95]. Research has stated that music with less sharp timbres has been proven to induce relaxation [93]. Possible instrumental arrangements include piano, cello, flute and marimba [94]. In addition, the use of instrumental music over nature sounds can effectively induce relaxation.

References

1. Chu, B.; Marwaha, K.; Sanvictores, T.; Ayers, D. Physiology, Stress Reaction. In StatPearls; StatPearls Publishing: Treasure Island, FL, USA, 2021. Available online: https://www.ncbi.nlm.nih.gov/books/NBK541120/ (accessed on 13 November 2021).
2. Myers, B.; McKlveen, J.M.; Herman, J.P. Glucocorticoid actions on synapses, circuits, and behavior: Implications for the energetics of stress. Front. Neuroendocrinol. 2014, 35, 180–196.
3. Dunlop, B.W.; Wong, A. The hypothalamic-pituitary-adrenal axis in PTSD: Pathophysiology and treatment interventions. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 2019, 89, 361–379.
4. Ehlert, U.; Gaab, J.; Heinrichs, M. Psychoneuroendocrinological contributions to the etiology of depression, posttraumatic stress disorder, and stress-related bodily disorders: The role of the hypothalamus-pituitary-adrenal axis. Biol. Psychol. 2001, 57, 141–152.
5. Sheerin, C.M.; Lind, M.J.; Bountress, K.E.; Marraccini, M.E.; Amstadter, A.B.; Bacanu, S.A.; Nugent, N.R. Meta-Analysis of Associations Between Hypothalamic-Pituitary-Adrenal Axis Genes and Risk of Posttraumatic Stress Disorder. J. Trauma Stress 2020, 33, 688–698.
6. Nickel, T. Trauma: HPA Axis . 2011. Available online: https://www.youtube.com/watch?v=otLHMbNyUx0 (accessed on 13 November 2021).
7. Sherin, J.E.; Nemeroff, C.B. Post-traumatic stress disorder: The neurobiological impact of psychological trauma. Dialogues Clin. Neurosci. 2011, 13, 263–278.
8. Fuchs, E.; Flügge, G. Adult neuroplasticity: More than 40 years of research. Neural Plast. 2014, 2014, 541870.
9. Etkin, A.; Wager, T.D. Functional neuroimaging of anxiety: A meta-analysis of emotional processing in PTSD, social anxiety disorder, and specific phobia. Am. J. Psychiatry 2007, 164, 1476–1488.
10. Coburn, D. Using MR to View PTSD's Effect on the Amygdala and Hippocampus. Radiol. Technol. 2018, 89, 501–504.
11. Boccia, M.; D'Amico, S.; Bianchini, F.; Marano, A.; Giannini, A.M.; Piccardi, L. Different neural modifications underpin PTSD after different traumatic events: An fMRI meta-analytic study. Brain Imaging Behav. 2016, 10, 226–237.
12. McNerney, M.W.; Sheng, T.; Nechvatal, J.M.; Lee, A.G.; Lyons, D.M.; Soman, S.; Liao, C.P.; O'Hara, R.; Hallmayer, J.; Taylor, J.; et al. Integration of neural and epigenetic contributions to posttraumatic stress symptoms: The role of hippocampal volume and glucocorticoid receptor gene methylation. PLoS ONE 2018, 13, e0192222.

13. Kim, E.J.; Pellman, B.; Kim, J.J. Stress effects on the hippocampus: A critical review. Learn. Mem. (Cold Spring Harb. N.Y.) 2015, 22, 411–416.
14. Kim, J.J.; Yoon, K.S. Stress: Metaplastic effects in the hippocampus. Trends Neurosci. 1998, 21, 505–509.
15. Anand, K.S.; Dhikav, V. Hippocampus in health and disease: An overview. Ann. Indian Acad. Neurol. 2012, 15, 239–246.
16. Postel, C.; Mary, A.; Dayan, J.; Fraisse, F.; Vallée, T.; Guillery-Girard, B.; Viader, F.; Sayette, V.; Peschanski, D.; Eustache, F.; et al. Variations in response to trauma and hippocampal subfield changes. Neurobiol. Stress 2021, 15, 100346.
17. Warner-Schmidt, J.L.; Duman, R.S. Hippocampal neurogenesis: Opposing effects of stress and antidepressant treatment. Hippocampus 2006, 16, 239–249.
18. Gilbertson, M.W.; Shenton, M.E.; Ciszewski, A.; Kasai, K.; Lasko, N.B.; Orr, S.P.; Pitman, R.K. Smaller hippocampal volume predicts pathologic vulnerability to psychological trauma. Nat. Neurosci. 2002, 5, 1242–1247.
19. Gilbertson, M.W.; Williston, S.K.; Paulus, L.A.; Lasko, N.B.; Gurvits, T.V.; Shenton, M.E.; Pitman, R.K.; Orr, S.P. Configural cue performance in identical twins discordant for posttraumatic stress disorder: Theoretical implications for the role of hippocampal function. Biol. Psychiatry 2007, 62, 513–520.
20. Smith, M.E. Bilateral hippocampal volume reduction in adults with post-traumatic stress disorder: A meta-analysis of structural MRI studies. Hippocampus 2005, 15, 798–807.
21. Van Rooij, S.J.H.; Kennis, M.; Sjouwerman, R.; van den Heuvel, M.P.; Kahn, R.S.; Geuze, E. Smaller hippocampal volume as a vulnerability factor for the persistence of post-traumatic stress disorder. Psychol. Med. 2015, 45, 2737–2746.
22. Wang, Z.; Neylan, T.C.; Mueller, S.G.; Lenoci, M.; Truran, D.; Marmar, C.R.; Weiner, M.W.; Schuff, N. Magnetic resonance imaging of hippocampal subfields in posttraumatic stress disorder. Arch. Gen. Psychiatry 2010, 67, 296–303.
23. Schoenfeld, T.J.; Gould, E. Stress, stress hormones, and adult neurogenesis. Exp. Neurol. 2012, 233, 12–21.
24. Grupe, D.W.; Hushek, B.A.; Davis, K.; Schoen, A.J.; Wielgosz, J.; Nitschke, J.B.; Davidson, R.J. Elevated perceived threat is associated with reduced hippocampal volume in combat veterans. Sci. Rep. 2019, 9, 14888.
25. Selemon, L.D.; Young, K.A.; Cruz, D.A.; Williamson, D.E. Frontal Lobe Circuitry in Posttraumatic Stress Disorder. Chronic Stress 2019, 3, 2470547019850166.
26. Stevens, J.S.; Jovanovic, T.; Fani, N.; Ely, T.D.; Glover, E.M.; Bradley, B.; Ressler, K.J. Disrupted amygdala-prefrontal functional connectivity in civilian women with posttraumatic stress disorder. J. Psychiatr. Res. 2013, 47, 1469–1478.
27. Liu, T.; Ke, J.; Qi, R.; Zhang, L.; Zhang, Z.; Xu, Q.; Zhong, Y.; Lu, G.; Chen, F. Altered functional connectivity of the amygdala and its subregions in typhoon-related post-traumatic stress disorder. Brain Behav. 2021, 11, 1–15.
28. Delgado, M.R.; Nearing, K.I.; Ledoux, J.E.; Phelps, E.A. Neural circuitry underlying the regulation of conditioned fear and its relation to extinction. Neuron 2008, 59, 829–838.
29. Johnstone, T.; van Reekum, C.M.; Urry, H.L.; Kalin, N.H.; Davidson, R.J. Failure to regulate: Counterproductive recruitment of top-down prefrontal-subcortical circuitry in major depression. J. Neurosci. Off. J. Soc. Neurosci. 2007, 27, 8877–8884.
30. Urry, H.L.; van Reekum, C.M.; Johnstone, T.; Kalin, N.H.; Thurow, M.E.; Schaefer, H.S.; Jackson, C.A.; Frye, C.J.; Greischar, L.L.; Alexander, A.L.; et al. Amygdala, and ventromedial prefrontal cortex are inversely coupled during regulation of negative affect and predict the diurnal pattern of cortisol secretion among older adults. J. Neurosci. Off. J. Soc. Neurosci. 2006, 26, 4415–4425.
31. Xiong, K.; Zhang, Y.; Qiu, M.; Zhang, J.; Sang, L.; Wang, L.; Xie, B.; Wang, J.; Li, M. Negative emotion regulation in patients with posttraumatic stress disorder. PLoS ONE 2013, 8, e81957.
32. Matsuo, K.; Taneichi, K.; Matsumoto, A.; Ohtani, T.; Yamasue, H.; Sakano, Y.; Sasaki, T.; Sadamatsu, M.; Kasai, K.; Iwanami, A.; et al. Hypoactivation of the prefrontal cortex during verbal fluency test in PTSD: A near-infrared spectroscopy study. Psychiatry Res. 2003, 124, 1–10.
33. Arnsten, A.F. Stress signalling pathways that impair prefrontal cortex structure and function. Nat. Rev. Neurosci. 2009, 10, 410–422.
34. Mary, A.; Dayan, J.; Leone, G.; Postel, C.; Fraisse, F.; Malle, C.; Vallée, T.; Klein-Peschanski, C.; Viader, F.; de la Sayette, V.; et al. Resilience after trauma: The role of memory suppression. Science 2020, 367, eaay8477.
35. Blanaru, M.; Bloch, B.; Vadas, L.; Arnon, Z.; Ziv, N.; Kremer, I.; Haimov, I. The effects of music relaxation and muscle relaxation techniques on sleep quality and emotional measures among individuals with posttraumatic stress disorder.

Ment. Illn. 2012, 4, e13.

36. Wang, S.; Agius, M. The use of Music Therapy in the treatment of Mental Illness and the enhancement of Societal Wellbeing. Psychiatr. Danub. 2018, 30 (Suppl. 7), 595–600.
37. Xu, B.; Sui, Y.; Zhu, C.; Yang, X.; Zhou, J.; Li, L.; Ren, L.; Wang, X. Music intervention on cognitive dysfunction in healthy older adults: A systematic review and meta-analysis. Neurol. Sci. Off. J. Ital. Neurol. Soc. Ital. Soc. Clin. Neurophysiol. 2017, 38, 983–992.
38. Golden, T.L.; Springs, S.; Kimmel, H.J.; Gupta, S.; Tiedemann, A.; Sandu, C.C.; Magsamen, S. The Use of Music in the Treatment and Management of Serious Mental Illness: A Global Scoping Review of the Literature. Front. Psychol. 2021, 12, 649840.
39. Van der Steen, J.T.; van Soest-Poortvliet, M.C.; van der Wouden, J.C.; Bruinsma, M.S.; Scholten, R.J.; Vink, A.C. Music-based therapeutic interventions for people with dementia. Cochrane Database Syst. Rev. 2017, 5, CD003477.
40. Magee, W.L.; Clark, I.; Tamplin, J.; Bradt, J. Music interventions for acquired brain injury. Cochrane Database Syst. Rev. 2017, 1, CD006787.
41. Geretsegger, M.; Elefant, C.; Mössler, K.A.; Gold, C. Music therapy for people with autism spectrum disorder. Cochrane Database Syst. Rev. 2014, 6, CD004381.
42. Geretsegger, M.; Mössler, K.A.; Bieleninik, Ł.; Chen, X.J.; Heldal, T.O.; Gold, C. Music therapy for people with schizophrenia and schizophrenia-like disorders. Cochrane Database Syst. Rev. 2017, 5, CD004025.
43. Perkins, R.; Mason-Bertrand, A.; Fancourt, D.; Baxter, L.; Williamon, A. How Participatory Music Engagement Supports Mental Well-being: A Meta-Ethnography. Qual. Health Res. 2020, 30, 1924–1940.
44. De Witte, M.; Spruit, A.; van Hooren, S.; Moonen, X.; Stams, G.J. Effects of music interventions on stress-related outcomes: A systematic review and two meta-analyses. Health Psychol. Rev. 2020, 14, 294–324.
45. McKinney, C.H.; Honig, T.J. Health Outcomes of a Series of Bonny Method of Guided Imagery and Music Sessions: A Systematic Review. J. Music Ther. 2017, 54, 1–34.
46. Bradt, J.; Dileo, C.; Shim, M. Music interventions for preoperative anxiety. Cochrane Database Syst. Rev. 2013, 6, CD006908.
47. Hole, J.; Hirsch, M.; Ball, E.; Meads, C. Music as an aid for postoperative recovery in adults: A systematic review and meta-analysis. Lancet (Lond. Engl.) 2015, 386, 1659–1671.
48. Umbrello, M.; Sorrenti, T.; Mistraletti, G.; Formenti, P.; Chiumello, D.; Terzoni, S. Music therapy reduces stress and anxiety in critically ill patients: A systematic review of randomized clinical trials. Minerva Anestesiol. 2019, 85, 886–898.
49. Wade, D.F.; Moon, Z.; Windgassen, S.S.; Harrison, A.M.; Morris, L.; Weinman, J.A. Non-pharmacological interventions to reduce ICU-related psychological distress: A systematic review. Minerva Anestesiol. 2016, 82, 465–478.
50. Chariyawong, P.; Copeland, S.; Mulkey, Z. What is the role of music in the intensive care unit? Southwest Respir. Crit. Care Chron. 2016, 4, 40–44.
51. DellaVolpe, J.D.; Huang, D.T. Is there a role for music in the ICU? Crit. Care 2015, 2016, 19.
52. Gullick, J.G.; Kwan, X.X. Patient-directed music therapy reduces anxiety and sedation exposure in mechanically ventilated patients: A research critique. Aust. Crit. Care Off. J. Confed. Aust. Crit. Care Nurses 2015, 28, 103–105.
53. Mofredj, A.; Alaya, S.; Tassaioust, K.; Bahloul, H.; Mrabet, A. Music therapy, a review of the potential therapeutic benefits for the critically ill. J. Crit. Care 2016, 35, 195–199.
54. Hetland, B.; Lindquist, R.; Chlan, L.L. The influence of music during mechanical ventilation and weaning from mechanical ventilation: A review. Heart Lung J. Crit. Care 2015, 44, 416–425.
55. Chlan, L.L.; Heiderscheit, A.; Skaar, D.J.; Neidecker, M.V. Economic Evaluation of a Patient-Directed Music Intervention for ICU Patients Receiving Mechanical Ventilatory Support. Crit. Care Med. 2018, 46, 1430–1435.
56. Baker, F.A.; Metcalf, O.; Varker, T.; O'Donnell, M. A systematic review of the efficacy of creative arts therapies in the treatment of adults with PTSD. Psychol. Trauma Theory Res. Pract. Policy 2018, 10, 643–651.
57. Story, K.M.; Beck, B.D. Guided Imagery and Music with female military veterans: An intervention development study. Arts Psychother. 2017, 55, 93–102.
58. Carr, C.; d′Ardenne, P.; Sloboda, A.; Scott, C.; Wang, D.; Priebe, S. Group music therapy for patients with persistent post-traumatic stress disorder--an exploratory randomized controlled trial with mixed methods evaluation. Psychol. Psychother. 2012, 85, 179–202.
59. Zergani, E.J.; Naderi, F. The Effectiveness of Music on Quality of Life and Anxiety Symptoms in the Post Traumatic Stress Disorder in Bustan Hospital of Ahvaz City. Rev. Eur. Stud. 2016, 8, 237–243.

60. Pourmovahed, Z.; Yassini Ardekani, S.M.; Roozbeh, B.; Ezabad, A.R. The Effect of Non-verbal Music on Posttraumatic Stress Disorder in Mothers of Premature Neonates. Iran. J. Nurs. Midwifery Res. 2021, 26, 150–153.

61. Macfarlane, C.; Masthoff, E.; Hakvoort, L. Short-Term Music Therapy Attention and Arousal Regulation Treatment (SMAART) for Prisoners with Posttraumatic Stress Disorder: A Feasibility Study. J. Forensic Psychol. Res. Pract. 2019, 19, 376–392.

62. Bensimon, M.; Amir, D.; Wolf, Y. Drumming through trauma: Music therapy with post-traumatic soldiers. Arts Psychother. 2008, 35, 34–48.

63. Rudstam, G.; Elofsson, U.; Søndergaard, H.P.; Beck, B.D. Trauma-focused group music and imagery with women suffering from PTSD/complex PTSD: A feasibility study. Approaches. Music Ther. Spec. Educ. 2017, 9, 202–216.

64. Maack, C. Outcomes and Processes of the Bonny Method of Guided Imagery and Music (GIM) and Its Adaptations and Psychodynamic Imaginative Trauma Therapy (PITT) for Women with Complex PTSD. Ph.D. Thesis, Aalborg University, Aalborg, Denmark, 2012. Available online: https://vbn.aau.dk/ws/portalfiles/portal/68395912/Carola_Maack_12.pdf (accessed on 13 November 2021).

65. Beck, B.D.; Messel, C.; Meyer, S.L.; Cordtz, T.O.; Søgaard, U.; Simonsen, E.; Moe, T. Feasibility of trauma-focused Guided Imagery and Music with adult refugees diagnosed with PTSD: A pilot study. Nord. J. Music Ther. 2017, 27, 67–86.

66. Beck, B.D.; Meyer, S.L.; Simonsen, E.; Søgaard, U.; Petersen, I.; Arnfred, S.; Tellier, T.; Moe, T. Music therapy was noninferior to verbal standard treatment of traumatized refugees in mental health care: Results from a randomized clinical trial. Eur. J. Psychotraumatol. 2021, 12, 1930960.

67. Mclntosh, G.; Thaut, M. How Music Helps to Heal the Injured Brain: Therapeutic Use Crescendos Thanks to Advances in Brain Science. The Dana Foundation. 2010. Available online: http://www.dana.org/Cerebrum/Default.aspx?id=39437 (accessed on 13 November 2021).

68. Ding, Y.; Zhang, Y.; Zhou, W.; Ling, Z.; Huang, J.; Hong, B.; Wang, X. Neural Correlates of Music Listening and Recall in the Human Brain. J. Neurosci. Off. J. Soc. Neurosci. 2019, 39, 8112–8123.

69. Koelsch, S. Brain correlates of music-evoked emotions. Nat. Rev. Neurosci. 2014, 15, 170–180.

70. Koelsch, S. A coordinate-based meta-analysis of music-evoked emotions. NeuroImage 2020, 223, 117350.

71. Schaefer, H.E. Music-Evoked Emotions-Current Studies. Front. Neurosci. 2017, 11, 600.

72. Koelsch, S. Emotion and Music. In The Cambridge Handbook of Human Affective Neuroscience; Armony, J., Vuilleumier, P., Eds.; Cambridge University Press: Cambridge, UK, 2013; pp. 286–303.

73. Fukui, H.; Toyoshima, K. Music facilitates the neurogenesis, regeneration, and repair of neurons. Med. Hypothes. 2008, 71, 765–769.

74. Mavridis, I.N. Music and the nucleus accumbens. Surg. Radiol. Anat. SRA 2015, 37, 121–125.

75. Zatorre, R.J. Musical pleasure and reward: Mechanisms and dysfunction. Ann. N. Y. Acad. Sci. 2015, 1337, 202–211.

76. Chetty, S.; Friedman, A.R.; Taravosh-Lahn, K.; Kirby, E.D.; Mirescu, C.; Guo, F.; Krupik, D.; Nicholas, A.; Geraghty, A.; Krishnamurthy, A.; et al. Stress and glucocorticoids promote oligodendrogenesis in the adult hippocampus. Mol. Psychiatry 2014, 19, 1275–1283.

77. Koelsch, S. Towards a neural basis of music-evoked emotions. Trends Cogn. Sci. 2010, 14, 131–137.

78. Koelsch, S.; Skouras, S.; Fritz, T.; Herrera, P.; Bonhage, C.; Küssner, M.B.; Jacobs, A.M. The roles of superficial amygdala and auditory cortex in music-evoked fear and joy. NeuroImage 2013, 81, 49–60.

79. Armony, J.L.; Aubé, W.; Angulo-Perkins, A.; Peretz, I.; Concha, L. The specificity of neural responses to music and their relation to voice processing: An fMRI-adaptation study. Neurosci. Lett. 2015, 593, 35–39.

80. Reybrouck, M.; Vuust, P.; Brattico, E. Music and brain plasticity: How sounds trigger neurogenerative adaptations. Neuroplast. Insights Neural Reorganization 2018, 85, 74318.

81. Groussard, M.; Viader, F.; Landeau, B.; Desgranges, B.; Eustache, F.; Platel, H. The effects of musical practice on structural plasticity: The dynamics of grey matter changes. Brain Cogn. 2014, 90, 174–180.

82. Olszewska, A.M.; Gaca, M.; Herman, A.M.; Jednoróg, K.; Marchewka, A. How Musical Training Shapes the Adult Brain: Predispositions and Neuroplasticity. Front. Neurosci. 2021, 15, 630829.

83. Guo, P.; Li, Q.; Wang, X.; Li, X.; Wang, S.; Xie, Y.; Xie, Y.; Fu, Z.; Zhang, X.; Li, S. Structural Covariance Changes of Anterior and Posterior Hippocampus During Musical Training in Young Adults. Front. Neuroanat. 2020, 14, 20.

84. Koelsch, S.; Skouras, S. Functional centrality of amygdala, striatum, and hypothalamus in a “small-world” network underlying joy: An fMRI study with music. Hum. Brain Mapp. 2014, 35, 3485–3498.

85. Finn, S.; Fancourt, D. The biological impact of listening to music in clinical and nonclinical settings: A systematic review. Prog. Brain Res. 2018, 237, 173–200.
86. Khan, S.H.; Kitsis, M.; Golovyan, D.; Wang, S.; Chlan, L.L.; Boustani, M.; Khan, B.A. Effects of music intervention on inflammatory markers in critically ill and post-operative patients: A systematic review of the literature. Heart Lung J. Crit. Care 2018, 47, 489–496.
87. Koelsch, S.; Fuermetz, J.; Sack, U.; Bauer, K.; Hohenadel, M.; Wiegel, M.; Kaisers, U.X.; Heinke, W. Effects of Music Listening on Cortisol Levels and Propofol Consumption during Spinal Anesthesia. Front. Psychol. 2011, 2, 58.
88. Yinger, O.S.; Gooding, L.F. A systematic review of music-based interventions for procedural support. J. Music Ther. 2015, 52, 1–77.
89. Lynch, K.A.; Emard, N.; Liou, K.T.; Popkin, K.; Borten, M.; Nwodim, O.; Atkinson, T.M.; Mao, J.J. Patient Perspectives on Active vs. Passive Music Therapy for Cancer in the Inpatient Setting: A Qualitative Analysis. J. Pain Symptom Manag. 2021, 62, 58–65.
90. Sakka, L.S.; Saarikallio, S. Spontaneous Music-Evoked Autobiographical Memories in Individuals Experiencing Depression. Music Sci. 2020, 3, 2059204320960575.
91. Heiderscheit, A.; Breckenridge, S.J.; Chlan, L.L.; Savik, K. Music preferences of mechanically ventilated patients participating in a randomized controlled trial. Music Med. 2014, 6, 29–38.
92. Bradt, J.; Dileo, C. Music interventions for mechanically ventilated patients. Cochrane Database Syst. Rev. 2014, 2014, CD006902.
93. Parada-Cabaleiro, E.; Batliner, A.; Schedl, M. An Exploratory Study on the Acoustic Musical Properties to Decrease Self-Perceived Anxiety. Int. J. Environ. Res. Public Health 2022, 19, 994.
94. Tan, X.; Yowler, C.J.; Super, D.M.; Fratianne, R.B. The interplay of preference, familiarity and psychophysical properties in defining relaxation music. J. Music Ther. 2012, 49, 150–179.
95. Moore, K.S. A systematic review on the neural effects of music on emotion regulation: Implications for music therapy practice. J. Music Ther. 2013, 50, 198–242.