HHS Public Access
Author manuscript
Mol Neurobiol. Author manuscript; available in PMC 2017 July 01.

Published in final edited form as:
Mol Neurobiol. 2017 July ; 54(5): 3753–3758. doi:10.1007/s12035-016-9934-y.

Hypothesizing Music Intervention Enhances Brain Functional Connectivity Involving Dopaminergic Recruitment: Common Neuro-correlates to Abusable Drugs

Kenneth Blum[1,2,3,4,5,6,7,8,9], **Thomas Simpatico**[2], **Marcelo Febo**[1], **Chris Rodriquez**[6], **Kristina Dushaj**[5], **Mona Li**[5], **Eric R. Braverman**[5], **Zsolt Demetrovics**[8], **Marlene Oscar-Berman**[10], and **Rajendra D. Badgaiyan**[11,12,13]

[1]Department of Psychiatry & McKnight Brain Institute, University of Florida, College of Medicine, Box 100183, Gainesville, FL 32610-0183, USA

[2]Department of Psychiatry and Human Global Mental Health Institute, Center for Clinical & Translational Science, University of Vermont, Burlington, VT, USA

[3]Division of Neuroscience –Based Therapy, Summit Estate Recovery Center, Las Gatos, CA, USA

[4]Division of Addition Services, Dominion Diagnostics, LLC, North Kingstown, RI, USA

[5]PATH Foundation NY, New York, NY, USA

[6]IGENE, LLC, Austin, TX, USA

[7]Division of Applied Clinical Research, Dominion Diagnostics, LLC, North Kingstown, RI, USA

[8]Department of Clinical Psychology and Addiction, Institute of Psychology, Eötvös Loránd University, Budapest, Hungary

[9]Division of Neuroscience Research & Addiction Therapy, Shores Treatment & Recovery Center, Port Saint Lucie, FL, USA

[10]Departments of Psychiatry and Anatomy & Neurobiology, Boston University School of Medicine and Boston VA Healthcare System, Boston, MA, USA

[11]Department of Psychiatry, University of Minnesota, Minneapolis, MN, USA

[12]Neuromodulation Program, University of Minnesota Twin City Campus, Minneapolis, MN, USA

[13]Laboratory of Advanced Radiochemistry, University of Minnesota Twin City Campus, Minneapolis, MN, USA

Correspondence to: Kenneth Blum.

Compliance with Ethical Standards

Conflict of Interest Kenneth Blum holds the US and Foreign nutrigenomic patents to treat Reward Deficiency Syndrome (RDS) with dopaminergic agonists. Dr. Blum is a member of the scientific advisory board of Dominion Diagnostics, LLC.

Author Contributions KB wrote the basic manuscript. TS is a psychiatrist and musician who provided the impetus and design for the hypothesis. KD reviewed and developed the second draft of the manuscript. ZD, MOB added important comments and clinical interpretations. CR provided information related to the practice of music from a perspective of a musician. ERB, RDB and ML provided manuscript edits and comments concerning clinical applications and psychiatry.

Abstract

The goal of this review is to explore the clinical significance of music listening on neuroplasticity and dopaminergic activation by understanding the role of music therapy in addictive behavior treatment. fMRI data has shown that music listening intensely modifies mesolimbic structural changes responsible for reward processing (e.g., nucleus accumbens [NAc]) and may control the emotional stimuli's effect on autonomic and physiological responses (e.g., hypothalamus). Music listening has been proven to induce the endorphinergic response blocked by naloxone, a common opioid antagonist. NAc opioid transmission is linked to the ventral tegmental area (VTA) dopamine release. There are remarkable commonalities between listening to music and the effect of drugs on mesolimbic dopaminergic activation. It has been found that musical training before the age of 7 results in changes in white-matter connectivity, protecting carriers with low dopaminergic function (DRD2A1 allele, etc.) from poor decision-making, reward dependence, and impulsivity. In this article, we briefly review a few studies on the neurochemical effects of music and propose that these findings are relevant to the positive clinical findings observed in the literature. We hypothesize that music intervention enhances brain white matter plasticity through dopaminergic recruitment and that more research is needed to explore the efficacy of these therapies.

Keywords

Music therapy; Brain white matter; Dopaminergic recruitment; Cognition; Impulsivity

Introduction

Systematic analysis of the role of music in the brain reward circuitry has been explored by many investigators utilizing sophisticated neuroimaging tools to dissect specific loci of music activation in the brain [1]. Our laboratory has been involved in studying the role of neurotransmitters, especially dopamine in all drug and non-drug related addictive behaviors [2]. We have subsequently published on positive outcomes of stress and deep relaxation using audio therapy (music and sound) in highly drug dependent patients attending an inpatient treatment program in North Miami Beach, Florida [3]. We have also hypothesized that the activation of the mesolimbic reward system, which causes music listening responses, can be affected by dopaminergic polymorphisms. [4] However, much more work is required to unravel the connections related to reward gene polymorphisms including those that impinge on dopaminergic function.

The neuroscience field is very familiar with the work of others using functional magnetic resonance imaging (fMRI), such as Menon and Levitin [5], who initially observed that music listening intensely modifies mesolimbic structural changes responsible for reward processing (e.g., nucleus accumbens [NAc], ventral tegmental area [VTA]) and may very well control the emotional stimuli's effect on autonomic and physiological responses (e.g., hypothalamus, insula). There is additional work from Salimpoor et al. [6] citing the use of autonomic nervous system psychophysiological measures along with positron emission tomography (PET) scanning that identifies the neurochemical specificity of [(11)C]raclopride in pinpointing striatum endogenous dopamine release during music listening evoking peak emotional feelings. Anticipation is activated by the caudate, while peak emotional responses are activated by the nucleus accumbens. Significantly, NAc and VTA responses were positively correlated to a connection between dopamine release and NAc music response. Based on previous work from around the world, it is well established that neurogenetics plays a significant role in how we as *Homo sapiens* experience music and provides information as to the high value of music throughout the origins of human societies. Interestingly, even our archaic ancestors over 63,000 years ago developed musical instruments (www.pbs.org/wgbh/nova/ancient/pioneers-of-easter-island.html).

What We Have Learned from Neuroimaging

It is scientifically known and proven that the endorphinergic response impeded by naloxone, a common opioid antagonist, is induced by music listening [7]. VTA dopamine release is related to NAc opioid transmission. Furthermore, VTA dopamine release is associated with DRD2 gene polymorphisms and perhaps attention-deficit hyperactivity disorder (ADHD), where decreased dopamine (DA) release in the NAc is evident in DRD2 A1 allele carriers. This takes on even more significance in terms of reward deficiency or substance seeking/non-substance seeking behavior knowing that resting state functional connectivity is hijacked by drugs [8], food [9], and aberrant pathological internet gaming [10]. Along these lines, Alluri et al. [11] utilized two musical medleys during continuous fMRI response subject models, showing that auditory, limbic, and motor activations in the brain could be predicted. Remarkably, both the medial orbitofrontal region and anterior cingulate cortex activations, responsible for self-referential appraisal and esthetic judgments, could effectively be anticipated. Moreover, Wu et al. [12] found experimental evidence to establish rises in functional connectivity as well as increases in random network structure in the alpha2 during music perception. The networks included commonly found resting-state networks, including the default mode network, the core network, primary motor and visual network, and two lateralized parietal-frontal networks. In addition, Keller et al. [13], using fMRI with musical stimuli, examined brain responses and potential effective connectivity in relation to anhedonia. They found that anhedonia, a genetic trait, was negatively correlated with satisfaction music stimuli ratings and in regards to reward processing activation, in particular brain structures (e.g., NAc, basal forebrain, hypothalamus), the medial forebrain bundle was linked to the VTA. Brain regions, important for processing salient emotional stimuli, including anterior insula and orbitofrontal cortex were also negatively correlated with anhedonic traits.

Common Features of Brain Connectivity

In the addiction medicine scientific literature, it has been shown that chronic cocaine use reduces brain white matter [14], which dynamically changes during withdrawal from the drug. Lim et al. [15] found using diffusion tensor imaging (DTI) analysis that cocaine users had lower fractional anisotropy (FA) than controls, specifically in inferior frontal white matter. FA is a measure used in DTI to indicate areas of fiber density, axonal diameter, as well as white matter myelination. Our ability to measure the cognitive components of complex decision-making across species has greatly facilitated our understanding of its neurobiological mechanisms. Vulnerability could be indexed by reversal learning, particularly for disorders categorized by impulsive behaviors, including tendencies for substance abuse and also compulsiveness associated with dependence [16]. Dopamine in the striatum is known to be important for reversal learning. van der Schaaf et al. [17] suggested two interconnected mechanisms that are postulated for neuroadaptations in addiction, often associated with poor reversal learning; the dysregulation of frontocorticostriatal circuitry as well as the changes in poor dopamine (D2 receptor) of this specific circuitry. By using a fiber-based approach, they show that dopaminergic drug effects on striatal BOLD signal varied as a function of FA in a pathway connecting the OFC with the amygdala. There are many studies showing the role of music therapy as an adjunct to addiction therapy as espoused by Ross et al. [18]. In an attempt to understanding the mechanisms by which listening to music affects neurological processes, we are struck by the work of Steele et al. [19], who found that early trained musicians had greater connectivity in the posterior mid-body/isthmus of the corpus callosum and that the beginning age of training and sensorimotor synchronization performance is linked to FA in this area. They proposed that training before the age of 7 years results in changes in the white-matter connectivity that could protect carriers with low circuitry as well as reduced dopamine function (DRD2 A1 allele, etc.) from poor decision-making, reward dependence, and impulsivity.

Luhar et al. [20] reported that compared to non-smoking non-alcoholics, alcoholics who smoke had volumetric abnormalities in pre- and para-central frontal cortical areas and rostral middle frontal white matter, the amygdala, parahippocampal and temporal pole regions, the pallidum, the lateral ventricle, and the ventral diencephalic region. They also found that the comorbid group performed worse than non-smoking non-alcoholics on tests of executive functioning and on visually based memory tests. This would suggest that these impairments could be attenuated by chronic music therapy for smoking alcoholics and warrants further testing. On another note, psychiatrists in London, England are embracing hip-hop therapy for schizophrenics such as the popular tune “Happy” (http://www.theguardian.com/society/2014/oct/11/hip-hop-rap-therapy-mental-health-psychiatrists-pharrell-happy).

In addition, other work reveals very specific changes following musical training. More et al. [21] reviewed the current literature and revealed that modifications in cross-hemispheric networks can be induced by musical training, evident with substantial distinctions in several corpus callosum regions of musicians when compared with non-musicians. Neuroplasticity in musicians have been found by a number of investigators [22–24]. Specifically, Imfeld et al. [22] evaluated fiber tractography and subsequent voxelwise analysis, region of interest (ROI) analysis, and detailed slicewise analysis of diffusion parameters in the corticospinal tract (CST) on 26 professional musicians and a control group of 13 participants. They found that training-induced changes in diffusion characteristics of the axonal membrane lead to increased radial diffusivity as reflected in decreased fractional anisotropy (FA) values. Han et al. [23] found that voxel-based analysis of the DT-MRI data showed that pianists had higher FA (indicating higher white matter integrity [WMI]) in the right posterior limb of the internal capsule. The sMRI and DT-MRI results indicate that both the gray matter density (GMD) and WMI of pianists may exhibit movement-related increases during adolescence or even early adulthood compared with non-musicians. Schmithorst and Wilke [24] found that musicians, compared to controls, displayed significantly greater FA in the genu of the corpus callosum, while significantly less FA was found in the corona radiata and the internal capsule bilaterally.

Neurogenetics of Musical Aptitude

While there is paucity with regard to the neurogenetics of music and how it plays out in the addiction field, there have been some clues. Firstly, it is important to realize that composing and interpreting music by singing, playing an instrument, or dancing are very complex, but creative functions based on still unknown reward circuitry of the human brain [25]. Certainly, the ability to think creatively has been considered to be based on genetics [26]. In terms of gifted children, Winner [27] proposed that the well-known child prodigy phenomenon in the music field supports genetic differences in musical creativity at an early age. Winner [27] correctly espoused that environmental factors (e.g., parental guidance), practice, or random occurrences are not sufficient to describe the remarkable creative accomplishments of great artists at very young ages such as Mozart, Yehudi Menuhin, or Jacqueline du Pré, and jazz artists like Kevin Lovejoy, Ephraim Owens, and Stanley Clark.

Creativity is a biological activity that requires decreased levels of cortical activation, relatively higher right than left-hemisphere activation and decreased levels of frontal-lobe activation [28]. Bengtsson et al. [29] found that a pianist's cortical regions—right dorsolateral prefrontal cortex, pre-supplementary motor area, rostral part of the dorsal premotor cortex, and the left posterior portion of the superior temporal gyrus—were triggered during improvisation. Limb and Braun [30] reported that prefrontal activity accompanied by widespread activation of neocortical sensory-motor areas was demonstrated in fMRI experiments of improvising professional jazz pianists. These studies taken together provide evidence that improvising jazz requires distributed neural pattern to provide a cognitive context that enables the emergence of spontaneous creative activity.

Certainly, most agree that music perception and musical aptitude are cognitive functions of the human brain. While there are many genes involved in cognitive function in both animals and humans, arginine vasopressin (AVP) is a hormone that plays a significant role in regulating higher cognitive activities, such as memory and learning [31]. Wassink et al. [32] suggested that the AVP receptor 1A that is coded by the AVPR receptor 1A gene, affects the AVP hormone in neural circuits of the brain. Moreover, AVP has been observed to affect many social, emotional, and behavioral traits, especially pair bonding and aggression in males [33], parenting [34], sibling relationships [35], love [36], and altruism [37].

While the dopaminergic and serotoninergic systems and related genes have been observed to affect cognitive and motor functions in human and animal studies, little is known about the relationship of polymorphisms of these genes and musical aptitude [38, 39]. It is known that the human serotonin transporter (SLC6A4; 5-HTT) is expressed in the brain, particularly in areas involved with emotions in the cortex and limbic systems. The role of the SLC6A4 polymorphism 5-HTTLPR has been linked to reward-seeking behaviors [39] by influencing the release of dopamine at the VTA. Interestingly, the SLC6A4 with the arginine vasopressin receptor gene (AVPR1A) polymorphisms has been shown to associate with artistic creativity in professional dancers [40] and with short-term musical memory [41]. Furthermore, tryptophan hydroxylase (TPH), the rate-limiting enzyme in the biosynthesis of serotonin (5-HT), regulates the quantitative amount of serotonin in the synaptic cleft [42]. In fact, the tryptophan hydroxylase gene 1 (TPH1) polymorphism A779C A-allele is associated with figural and numeric creativities [26]. Moreover, TPH1 A779C has been associated with addiction, specifically nicotine dependence [43].

Catechol-O-methyltransferase (COMT) inactivates dopamine in the synaptic cleft, and the Val158Met polymorphism of the COMT gene has shown up to a 40 % increased COMT activity than those who have the Met allele [44]. Those who are carriers of the Met allele may have a cognitive advantage [45, 46]. Val158Met polymorphism has been associated with basal cognitive processes. While the Met carriers have a better memory and cognition [47], the Val carriers have emotional difficulties and addiction liability [48]. In fact, when a number of gene polymorphisms including the arginine vasopressin receptor 1A (AVPR1A), serotonin transporter (SLC6A4), catecol-O-methyltranferase (COMT), dopamine receptor D2 (DRD2), and tyrosine hydroxylase 1 (TPH1) were tested in a Finnish population of musicians and amateurs, it was found for the very first time that creative music behaviors have a substantial genetic element in these Finnish multigenerational families [49].

While there may be many genes involved in a musical performance, it is interesting that Kanduri et al. [50] showed that following a 2-h concert performed by professional musicians, their upregulated genes affected dopaminergic neurotransmission, motor actions, neuronal plasticity, and neurocognitive activities such as learning and memory. Specifically, candidate genes including SNCA, FOS, and DUSP1 were identified, which are known to be involved in song perception and production in songbirds. Thus, showing evolutionary need for musical events in both animals and humans alike provides the never-ending importance of music in societies now and then.

Conclusion

A PubMed search using the terms “Music Therapy and Addiction” resulted in only 16 published articles [4–16–15]. Based on this brief medical hypothesis and the advent of neuroimaging and genetic tools, we are beginning to understand the potential of music therapy in the treatment and potential prevention of RDS. In fact, Parkinson and Wheatley [51] correctly pointed out the importance of why white matter microstructure predicts emotional empathy. They found that empathic concern was positively correlated with FA in tracts providing communicative pathways within the limbic system. These effects may have relevance in terms of enhancing functional connectivity, especially during resting state, following drug abuse and obesity [52].

Finally and importantly, we know that long–term exposure to listening to music, especially by trained musicians results in neural adaptations dependent on the period of interaction, the initial age, the role of attention, the extent of motor practice, and the musical genre played [53]. This notation may be relevant for exposure to pleasurable music in addicts to assist in the recovery process. We encourage more neuroimaging and genetic studies including the role of epigenetics to assess the effect of listening to music in not only professional musicians, but also ordinary non-musicians, especially addicts [54]. In the future, genetic and epigenetic testing for specific polymorphic and DNA methylation of reward genes like the DRD2, DAT1, and COMT, may help provide further evidence of the importance of music and even music therapy. The reason being this modality may play a significant role in reducing relapse to RDS behaviors [55].

Acknowledgments

Marlene Oscar Berman is the recipient of grants from the National Institutes of Health, NIAAA (RO1-AA07112 and K05-AA00219). Marcelo Febo is the recipient of R01DA019946. Kenneth Blum is the recipient of the Life Extension Foundation grant awarded to PATH Foundation NY. We also thank Margaret A. Madigan for her expert editorial work.

Funding This work was supported by the National Institutes of Health grants 1R01NS073884 and 1R21MH073624, awarded to Dr. Rajendra D Badgaiyan. Dr. Marcelo Febo is the recipient of R01DA019946 and R21DA038009. The writing of this paper was supported in part by funds from the National Institutes of Health, NIAAA (RO1-AA07112 and K05-AA00219), and the Medical Research Service of the US Department of Veterans Affairs (MOB). KB and ERB are the recipients of a grant to PATH FOUNDATION NY, by Life Extension Foundation, Ft/Lauderdale, Florida.

References

1. Pinho AL, de Manzano O, Fransson P, Eriksson H, Ullén F. Connecting to create: expertise in musical improvisation is associated with increased functional connectivity between premotor and prefrontal areas. J Neurosci. 2014; 34(18):6156–6163. DOI: 10.1523/JNEUROSCI.4769-13.2014 [PubMed: 24790186]
2. Gold MS, Blum K, Oscar-Berman M, Braverman ER. Low dopamine function in attention deficit/ hyperactivity disorder: should genotyping signify early diagnosis in children? Postgrad Med. 2014; 126(1):153–177. DOI: 10.3810/pgm.2014.01.2735 [PubMed: 24393762]
3. Morse S, Giordano J, Perrine K, Downs BW, Waite RL, et al. Audio Therapy Significantly Attenuates Aberrant Mood in Residential Patient Addiction Treatment: Putative Activation of Dopaminergic Pathways in the Meso-Limbic Reward Circuitry of Humans. J Addict Res Ther. 2011; S3:001.doi: 10.4172/2155-6105.S3-001
4. Blum K, Chen TJ, Chen AL, Madigan M, Downs BW, et al. Do dopaminergic gene polymorphisms affect mesolimbic reward activation of music listening response? Therapeutic impact on Reward Deficiency Syndrome (RDS). Med Hypotheses. 2010; 74(3):513–520. DOI: 10.1016/j.mehy. 2009.10.008 [PubMed: 19914781]
5. Menon V, Levitin DJ. The rewards of music listening: response and physiological connectivity of the mesolimbic system. Neuroimage. 2005; 28(1):175–184. Epub 2005 Jul 14. [PubMed: 16023376]
6. Salimpoor VN, Benovoy M, Larcher K, Dagher A, Zatorre RJ. Anatomically distinct dopamine release during anticipation and experience of peak emotion to music. Nat Neurosci. 2011; 14(2): 257–262. DOI: 10.1038/nn.2726 [PubMed: 21217764]
7. Goldstein A. Thrills in response to music and other stimuli. Physiol Psych. 1980; 8(1):126–129. DOI: 10.3758/BF03326460
8. McHugh MJ, Demers CH, Braud J, Briggs R, Adinoff B, Stein EA. Striatal-insula circuits in cocaine addiction: implications for impulsivity and relapse risk. Am J Drug Alcohol Abuse. 2013; 39(6): 424–432. DOI: 10.3109/00952990.2013.847446 [PubMed: 24200212]
9. García-García I, Jurado MÁ, Garolera M, Segura B, Sala-Llonch R, et al. Alterations of the salience network in obesity: a resting-state fMRI study. Hum Brain Mapp. 2013; 34(11):2786–2797. DOI: 10.1002/hbm.22104 [PubMed: 22522963]
10. Ding WN, Sun JH, Sun YW, Zhou Y, Li L, Xu JR, Du YS. Altered default network resting-state functional connectivity in adolescents with Internet gaming addiction. PLoS One. 2013; 8(3):e59902.doi: 10.1371/journal.pone.0059902 [PubMed: 23555827]
11. Alluri V, Toiviainen P, Lund TE, Wallentin M, Vuust P, et al. From Vivaldi to Beatles and back: predicting lateralized brain responses to music. Neuroimage. 2013; 83:627–636. DOI: 10.1016/ j.neuroimage.2013.06.064 [PubMed: 23810975]

12. Wu J, Zhang J, Ding X, Li R, Zhou C. The effects of music on brain functional networks: a network analysis. Neuroscience. 2013; 250:49–59. DOI: 10.1016/j.neuroscience.2013.06.021 [PubMed: 23806719]
13. Keller J, Young CB, Kelley E, Prater K, Levitin DJ, Menon V. Trait anhedonia is associated with reduced reactivity and connectivity of mesolimbic and paralimbic reward pathways. J Psychiatr Res. 2013; 47(10):1319–1328. DOI: 10.1016/j.jpsychires.2013.05.015 [PubMed: 23791396]
14. Bell RP, Foxe JJ, Nierenberg J, Hoptman MJ, Garavan H. Assessing white matter integrity as a function of abstinence duration in former cocaine-dependent individuals. Drug Alcohol Depend. 2011; 114(2–3):159–168. DOI: 10.1016/j.drugalcdep.2010.10.001 [PubMed: 21075564]
15. Lim KO, Wozniak JR, Mueller BA, Franc DT, Specker SM, et al. Brain macrostructural and microstructural abnormalities in cocaine dependence. Drug Alcohol Depend. 2008; 92(1–3):164–172. Epub 2007 Sep 29. [PubMed: 17904770]
16. Izquierdo A, Jentsch JD. Reversal learning as a measure of impulsive and compulsive behavior in addictions. Psychopharmacology (Berl). 2012; 219(2):607–620. DOI: 10.1007/s00213-011-2579-7 [PubMed: 22134477]
17. van der Schaaf ME, Zwiers MP, van Schouwenburg MR, Geurts DE, Schellekens AF, et al. Dopaminergic drug effects during reversal learning depend on anatomical connections between the orbitofrontal cortex and the amygdala. Front Neurosci. 2013; 7:142.doi: 10.3389/fnins.2013.00142 [PubMed: 23966907]
18. Ross S, Cidambi I, Dermatis H, Weinstein J, Ziedonis D, et al. Music therapy: a novel motivational approach for dually diagnosed patients. J Addict Dis. 2008; 27(1):41–53. DOI: 10.1300/J069v27n01_05 [PubMed: 18551887]
19. Steele CJ, Bailey JA, Zatorre RJ, Penhune VB. Early musical training and white-matter plasticity in the corpus callosum: evidence for a sensitive period. J Neurosci. 2013; 33(3):1282–1290. DOI: 10.1523/JNEUROSCI.3578-12 [PubMed: 23325263]
20. Luhar RB, Sawyer KS, Gravitz Z, Ruiz SM, Oscar-Berman M. Brain volumes and neuropsychological performance are related to current smoking and alcoholism history. Neuropsychiatr Dis Treat. 2013; 9:1767–1784. DOI: 10.2147/NDT.S52298 [PubMed: 24273408]
21. Moore E, Schaefer RS, Bastin ME, Roberts N, Overy K. Can musical training influence brain connectivity? Evidence from diffusion tensor MRI. Brain Sci. 2014; 4(2):405–427. DOI: 10.3390/brainsci4020405 [PubMed: 24961769]
22. Imfeld A, Oechslin MS, Meyer M, Loenneker T, Jancke L. White matter plasticity in the corticospinal tract of musicians: a diffusion tensor imaging study. Neuroimage. 2009; 46(3):600–6007. DOI: 10.1016/j.neuroimage.2009.02.025 [PubMed: 19264144]
23. Han Y, Yang H, Lv YT, Zhu CZ, He Y, et al. Gray matter density and white matter integrity in pianists' brain: a combined structural and diffusion tensor MRI study. Neurosci Lett. 2009; 459(1):3–6. DOI: 10.1016/j.neulet.2008.07.056 [PubMed: 18672026]
24. Schmithorst VJ, Wilke M. Differences in white matter architecture between musicians and non-musicians: a diffusion tensor imaging study. Neurosci Lett. 2002; 321(1–2):57–60. [PubMed: 11872256]
25. Zatorre R, McGill J. Music, the food of neuroscience? Nature. 2005; 434(7031):312–315. DOI: 10.1038/434312a [PubMed: 15772648]
26. Reuter M, Roth S, Holve K, Hennig J. Identification of first candidate genes for creativity: a pilot study. Brain Res. 2006; 1069:190–197. Epub 2006 Jan 3. [PubMed: 16403463]
27. Winner, E. Gifted Children: Myths and Realities. Basic Books; New York: 1996.
28. Martindale, C. The concept of creativity: prospects and paradigms. In: Sternberg, RJ., Lubart, TI., editors. Handbook of creativity. Cambridge University Press; New York: 2006. p. 137-152.
29. Bengtsson S, Csíkszentmihályi M, Ullén F. Cortical regions involved in the generation of musical structures during improvisation in pianists. J Cogn Neurosci. 2007; 19(5):830–842. [PubMed: 17488207]
30. Limb CJ, Braun AR. Neural substrates of spontaneous musical performance: an fMRI study of jazz improvisation. PLoS One. 2008; 3(2):e1679.doi: 10.1371/journal.pone.0001679 [PubMed: 18301756]

31. Fink S, Excoffier L, Heckel G. High variability and non-neural evolution of the mammalian avpr1a gene. BMC Evol Biol. 2007; 7:176.doi: 10.1186/1471-2148-7-176 [PubMed: 17900345]
32. Wassink TH, Piven J, Vieland VJ, Pietila J, Goedken RJ, et al. Examination of AVPR1a as an autism susceptibility gene. Mol Psychiatry. 2004; 9:968–972. [PubMed: 15098001]
33. Thompson R, Gupta S, Mills S, Orr S. The effects of vasopressin on human facial responses related to social communication. Psychoneuroendrocrinology. 2004; 29(1):35–48.
34. Hammock EAD, Young LJ. Oxytocin, vasopressin and pair bonding: implications for autism. Philos Trans R Soc Lond B Biol Sci. 2006; 361(1476):2187–2198. DOI: 10.1098/rstb.2006.1939 [PubMed: 17118932]
35. Bachner-Melman R, Zohar AH, Bacon-Shnoor N, Elizur Y, Nemanov L, et al. Link between vasopressin receptor AVPR1A promoter region microsatellites and measures of social behavior in humans. J Individ Differ. 2005; 26:2–10. DOI: 10.1027/1614-0001.26.1.2
36. Zeki S. The neurobiology of love. FEBS Lett. 2007; 581:2575–2579. [PubMed: 17531984]
37. Knafo A, Israel S, Darvasi A, Bachner-Melmann R, Uzefovsky F, et al. Individual differences in allocation of funds in the dictator game associated with length of the arginine vasopressin 1a receptor RS3 promoter region and correlation between RS3 length and hippocampal mRNA. Genes Brain Behav. 2008; 7:266–275. [PubMed: 17696996]
38. Barnett JH, Heron J, Ring SM, Golding J, Goldman D, et al. Gender-specific effects of the catechol-O-methyltransferase Val108/158Met polymorphism on cognitive function in children. Am J Psychiatry. 2007; 164:142–149. [PubMed: 17202556]
39. Kremer I, Bachner-Melman R, Reshef A, Broude L, Nemanov L, et al. Association of serotonin transporter gene with smoking behavior. Am J Psychiatry. 2005; 162:924–930. [PubMed: 15863794]
40. Bachner-Melman R, Dina C, Zohar AH, Constantini N, Lerer E, et al. AVPR1a and SLC6A4 gene polymorphisms Are associated with creative dance performance. PLoS Genet. 2005; 1(3):e42.doi: 10.1371/journal.pgen.0010042 [PubMed: 16205790]
41. Granot R, Frankel Y, Gritsenko V, Lerer E, Gritsenko I, et al. Provisional evidence that the arginine vasopressin 1a receptor gene is associated with musical memory. Evol Human Behav. 2007; 28:313–318. 2007.05.003.
42. Cooper MI. The enzymic oxidation of tryptophan to 5-hydroxytryptophan in the biosynthesis of serotonin. J Pharmacol Exp Ther. 1961; 132:265–268. [PubMed: 13695323]
43. Reuter M, Hennig J. Pleiotropic effect of the TPH A779C polymorphism on nicotine dependence and personality. Am J Med Genet B Neuropsychiatr Genet. 2005; 134B(1):20–24. [PubMed: 15635702]
44. Gosso MF, de Geus EJ, Polderman TJ, Boomsma DI, Heutink P, et al. Catechol O-methyl transferase and dopamine D2 receptor gene polymorphisms: evidence of positive heterosis and gene–gene interaction on working memory functioning. Eur J Hum Genet. 2008; 16:1075–1082. DOI: 10.1038/ejhg.2008.57 [PubMed: 18382477]
45. Aleman A, Swart M, van Rijn S. Brain imaging, genetics and emotion. Biol Psychol. 2008; 79(1): 58–69. DOI: 10.1016/j.biopsycho.2008.01.009 [PubMed: 18329779]
46. Zhang X, Li J, Qin W, Yu C, Liu B, Jiang T. The catechol-o-methyltransferase Val(158)Met polymorphism modulates the intrinsic functional network centrality of the parahippocampal cortex in healthy subjects. Sci Rep. 2015; 5:10105.doi: 10.1038/srep10105 [PubMed: 26054510]
47. Hill SY, Lichenstein S, Wang S, Carter H, McDermott M. Caudate Volume in Offspring at Ultra High Risk for Alcohol Dependence: COMT Val158Met, DRD2, Externalizing Disorders, and Working Memory. Adv J Mol Imaging. 2013; 3(4):43–54. [PubMed: 25364629]
48. Lohoff FW, Weller AE, Bloch PJ, Nall AH, Ferraro TN, et al. Association between the catechol-O-methyltransferase Val158Met polymorphism and cocaine dependence. Neuropsychopharmacology. 2008; 33(13):3078–3084. DOI: 10.1038/npp.2008.126 [PubMed: 18704099]
49. Ukkola LT, Onkamo P, Raijas P, Karma K, Järvelä I. Musical aptitude is associated with AVPR1A-haplotypes. PLoS One. 2009; 4(5):e5534.doi: 10.1371/journal.pone.0005534 [PubMed: 19461995]
50. Kanduri C, Kuusi T, Ahvenainen M, Philips AK, Lähdesmäki H, et al. The effect of music performance on the transcriptome of professional musicians. Sci Rep. 2015; 5:9506.doi: 10.1038/srep09506 [PubMed: 25806429]

51. Parkinson C, Wheatley T. Relating anatomical and social connectivity: white matter microstructure predicts emotional empathy. Cereb Cortex. 2014; 24(3):614–625. DOI: 10.1093/cercor/bhs347 [PubMed: 23162046]

52. Hu Y, Salmeron BJ, Gu H, Stein EA, Yang Y. Impaired functional connectivity within and between frontostriatal circuits and its association with compulsive drug use and trait impulsivity in cocaine addiction. JAMA Psychiatry. 2015; 72(6):584–592. DOI: 10.1001/jamapsychiatry.2015.1 [PubMed: 25853901]

53. Wijngaarden MA, Veer IM, Rombouts SA, van Buchem MA, Willems van Dijk K, et al. Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience. Behav Brain Res. 2015; 287:127–134. DOI: 10.1016/j.bbr.2015.03.016 [PubMed: 25779924]

54. Reybrouck M, Brattico E. Neuroplasticity beyond sounds: neural adaptations following long-term musical aesthetic experiences. Brain Sci. 2015; 5(1):69–91. DOI: 10.3390/brainsci5010069 [PubMed: 25807006]

55. Fritz TH, Vogt M, Lederer A, Schneider L, Fomicheva E, et al. Benefits of listening to a recording of euphoric joint music making in polydrug abusers. Front Hum Neurosci. 2015; 9:300.doi: 10.3389/fnhum.2015.00300 [PubMed: 26124713]