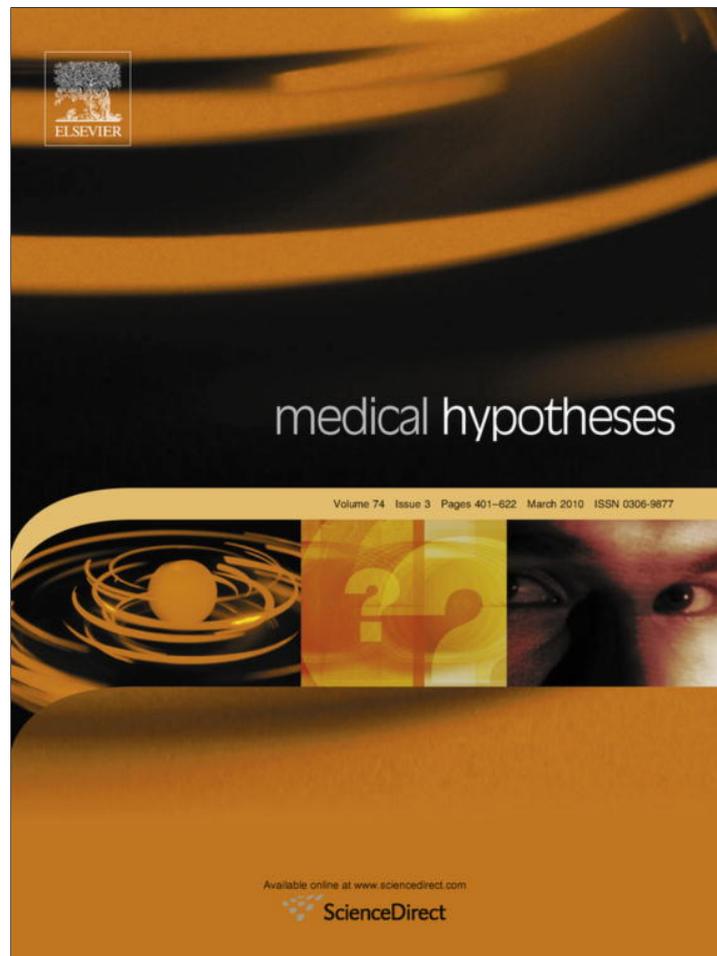


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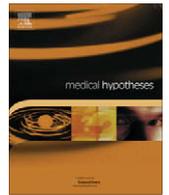
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# Do dopaminergic gene polymorphisms affect mesolimbic reward activation of music listening response? Therapeutic impact on Reward Deficiency Syndrome (RDS)

Kenneth Blum<sup>a,d,f,h,\*</sup>, Thomas J.H. Chen<sup>b,\*</sup>, Amanda L.H. Chen<sup>c</sup>, Margaret Madigan<sup>d</sup>, B. William Downs<sup>d</sup>, Roger L. Waite<sup>d</sup>, Eric R. Braverman<sup>e,f</sup>, Mallory Kerner<sup>f</sup>, Abdalla Bowirrat<sup>g</sup>, John Giordano<sup>h</sup>, Harry Henshaw<sup>h</sup>, Mark S. Gold<sup>a</sup>

<sup>a</sup> Department of Psychiatry, University of Florida, College of Medicine and McKnight Brain Institute, Gainesville, Florida, USA

<sup>b</sup> Department of Occupational Safety and Health, Chang Jung Christian University, Taiwan, ROC

<sup>c</sup> Department of Engineering and Management of Advanced Technology, Tainan, Taiwan, ROC

<sup>d</sup> Department of Nutrigenomics, LifeGen Inc., San Diego, California, USA

<sup>e</sup> Department of Neurological Surgery, Weill Cornell College of Medicine, New York, USA

<sup>f</sup> Department of Clinical Neurology, Path Research and Medical Foundation, New York, USA

<sup>g</sup> Clinical Neuroscience and Population Genetics, Ziv Government Medical Center, Safed, Israel

<sup>h</sup> Department of Holistic Medicine, G&G Holistic Treatment Center, North Miami Beach, FL, USA

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### SUMMARY

Using fMRI, Menon and Levitin [9] 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. Listening 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. Blum et al. [10] provided the first evidence that the dopamine D2 receptor gene (DRD2) *Taq 1 A1* allele significantly associated with severe alcoholism whereby the author's suggested that they found the first "reward gene" located in the mesolimbic system. 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. It is well-known that music may induce an endorphinergic response that is blocked by naloxone, a known opioid antagonist (Goldstein [19]). 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 and even attention-deficit hyperactivity disorder (ADHD), whereby carriers of the DRD2 A1 allele show a reduced NAc release of dopamine (DA). 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. It is therefore hypothesized 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. In contrast powerful D2 agonists like bromocriptine show a heightened activation of the reward circuitry only in DRD2 A1 allele carriers. 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). Ross et al. [18] 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.

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\* Corresponding authors. Address: Department of Psychiatry, University of Florida, College of Medicine and McKnight Brain Institute, Gainesville, Florida, USA. Tel.: +1 619 890 2167; fax: +1 619 236 3316 (K. Blum).

E-mail addresses: [drd2gene@aol.com](mailto:drd2gene@aol.com) (K. Blum), [tjchen@yahoo.com.tw](mailto:tjchen@yahoo.com.tw) (T.J.H. Chen).

## Introduction

### Background

Music is one of the most pleasurable experiences known to the human race being an essential part of most people's lives independent of age. Through well documented archeological evidence and records we know that music has been with *Homo sapiens* for a very long time – and according to Cross [1] as long as anything else for which we have evidence. Its ubiquity and its antiquity demonstrate its importance and no known culture now or in the past lacks music in some form [2,3]. Trehub [4] suggests that mothers in every culture sing songs to their infants, making music one of the newborn's first experience. Music, like speech, is a product of both our biologies (e.g. gene polymorphic expressions) and our social interaction (e.g. environment). It has been correctly suggested that music is a necessary and integral dimension of human development; and that music may have played a central role in the evolution of the modern human mind.

Over the last decade, a number of studies demonstrated that music listening (and even more so music production) activates a multitude of brain structures involved in cognitive, sensorimotor, and emotional processing [5–7]. For example, music engages sensory processes, attention, memory-related processes, perception-action mediation (“mirror neuron system” activity), multisensory integration, activity changes in core areas of emotional processing, processing of musical syntax and musical meaning, and social cognition. Presently, although the mechanisms underlying such effects are currently not well understood, it is likely that the engagement of these processes by music can have beneficial effects on the psychological and physiological health of individuals and even as a therapeutic modality to treat Substance Use Disorders (SUD) [8]. Moreover in the literature, no consensus exists regarding the efficacy of music therapy as treatment for patients with addictions. The solution to this controversy may reside in an individual's genotype especially with regard to polymorphisms in at least the DRD2 gene.

### Hypothesis

Listening 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 [9]. Blum et al. [10] provided the first evidence that the dopamine D2 receptor gene (DRD2) *Taq 1 A1* allele significantly associated with severe alcoholism. The author's suggested that they found the first “reward gene” (DRD2) located in the mesolimbic system. 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. Moreover, dopamine release in the VTA is linked to polymorphisms of the DRD2 gene and even attention-deficit hyperactivity disorder (ADHD), whereby carriers of the DRD2 polymorphisms (*Taq 1 A1*) show a reduced neuronal accumbens release of dopamine (DA) [11]. The lack of neuronal release is also seen with polymorphisms of Parkin, causal gene of autosomal recessive juvenile Parkinsonism (AR-JP) [12]. Thus it is conjectured that similar confounds 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. It is therefore hypothesized that carriers of DRD2 A1 allele may respond significantly differently than carriers of the DRD2 A2 genotype.

### Proposal

The authors propose that genotyping individuals for the DRD2 alleles coupled with fMRI response to listening to music may be very informative in dissecting the therapeutic use of music to treat SUD. It is well-known that carriers of the D2 A1 allele have a blunted response to glucose [13] and monetary [14] rewards. Moreover Schott et al. [15] observed correlations of reward-related mesolimbic fMRI activation from monetary rewards and dopamine release provide evidence that dopaminergic neurotransmission plays a quantitative role in human mesolimbic reward processing. In contrast, powerful D2 agonists like bromocryptine show a heightened activation of the reward circuitry only in DRD2 A1 allele carriers. 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) [16]. The DRD2 A1 allele has also been shown to associate with enhanced sensitivity to negative feelings in children which could link to future SUD especially with stressful events [17]. Ross et al. [18] 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.

### Music listening and connectivity of the mesolimbic system

It is of physiological interest that listening to for example classical music is known to evoke strong emotions including feelings of pleasure accompanied by physical responses such as thrills, chills, shivers, and even heart rate changes. These effects can be blocked by the narcotic antagonist naloxone [19]. Narcotic antagonism also blocks ethanol induced dependence in animals [20]. Kelly and Berridge [21] have reported that opioid transmission in the NAc is associated with dopamine release in the VTA and as such are involved in mediating the brain's responses to reward (pleasure). Menon and Levitin [9] found that passive listening to music resulted in significant activation of a network of subcortical structures including the NAc, the VTA, and the hypothalamus. In a related positron emission tomography (PET) study, activation in the ventral striatum was correlated with intensity of pleasurable responses to music [5]. A major importance in the Menon and Levitin study [9] is the demonstration for the first time of the involvement of the NAc itself. Previous studies of the NAc activation in humans have focused on its role in processing monetary reward [22] and recreational and addictive drugs [23]. It is noteworthy that music [9] like humor [24] both similarly activate the NAc. In fact, Mobbs et al. [24] reported on a fMRI study that demonstrated that humor engages a network of subcortical regions including the nucleus accumbens. Similar to music, humor has also been considered as a therapeutic modality to treat addiction suggesting the importance of commonality of the mesolimbic activation as having therapeutic impact on RDS [25].

### Neurochemical mechanisms: music and substance seeking behavior

In the late 80s neuroscientists agreed that brain reward involved the interaction of multiple neurotransmitters (e.g. serotonin, enkephalins, GABA and dopamine) in mesolimbic VTA and NAc sites with the net release of dopamine as the final common pathway to pleasure [26]. It is well established that substance

seeking behavior is related to genetic deficits in the mesolimbic system of the brain.

The role of specific candidate genes have been the subject of much debate and to date there is no consensus of a unique gene panel for addiction. There are many candidate genes representing the neurochemical mechanisms involved in reward dependence behaviors linked to mesolimbic circuitry. Most recently Hodgkinson et al. [27] developed a panel of markers able to extract full haplotype information for candidate genes in alcoholism, other addictions and disorders of mood and anxiety. A total of 130 genes were haplotype tagged and genotyped in 7 case/control populations and 51 reference populations using Illumina GoldenGate SNP genotyping technology, determining haplotype coverage. The following schematic shows the 130 candidate genes involved (Fig. 1).

Other array work has been accomplished by Li et al. [28] who integrated 2343 items of evidence from peer-reviewed publications between 1976 and 2006 linking genes and chromosome regions to addiction by single-gene strategies, microarray, proteomics, or genetic studies. They identified 1500 human addiction-related genes and developed KARG (<http://karg.cbi.pku.edu.cn>), the first molecular database for addiction-related genes with extensive annotations and a friendly Web interface. Li et al. [28] then performed a meta-analysis of 396 genes that were supported by two or more independent items of evidence to identify 18 molecular pathways that were statistically significantly enriched, covering both upstream signaling events and downstream effects. Five molecular pathways significantly enriched for all four different types of addictive drugs were identified as common pathways which may underlie shared rewarding and addictive actions,

including two new ones, GnRH signaling pathway and gap junction. They connected the common pathways into a hypothetical common molecular network for addiction. Interestingly two final pathways emerged that included the glutamate pathway and the dopaminergic pathway.

The relationship between dopamine and subjective pleasure has been the subject of intensive research for many decades. The anhedonia (opposite of pleasure) hypothesis – that brain dopamine plays a critical role in the subjective pleasure associated with positive rewards – was intended to draw the attention of psychiatrists to the growing evidence that dopamine plays a critical role in the objective reinforcement and incentive motivation associated with food and water, brain stimulation reward, and psychomotor stimulant and opiate reward. Despite its limited heuristic value for the understanding of psychosis, however, the anhedonia hypothesis has had major impact on biological theories of reinforcement, motivation, and addiction. Brain dopamine plays a very important role in reinforcement of response habits, conditioned preferences, and synaptic plasticity in cellular models of learning and memory. The notion that dopamine plays a dominant role in reinforcement is fundamental to the psychomotor stimulant theory of addiction, to most neuroadaptation theories of addiction, and to current theories of conditioned reinforcement and reward prediction. Properly understood, it is also fundamental to recent theories of incentive motivation [29]. Simply put, the analyses of anhedonic non-clinical subjects, nonanhedonic depressed patients, and depressed patients with various levels of anhedonia seem to favor the hypothesis that the severity of anhedonia is associated with a deficit of activity of the ventral striatum (including the nucleus accumbens) and an excess of activity in the ventral region of the prefrontal cortex

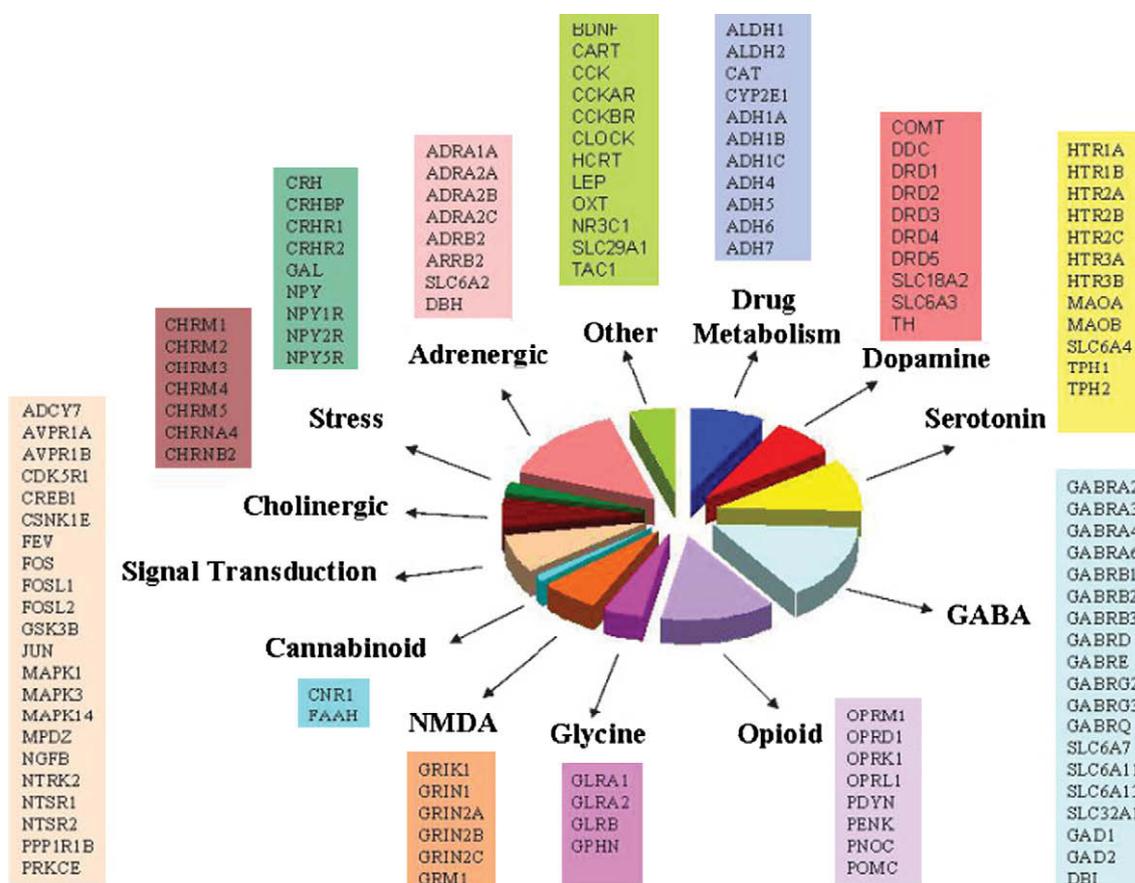


Fig. 1. Addictions biology: haplotype-based analysis for 130 candidate genes on a single array (with permission Hodgkinson et al. [27]).

(including the ventromedial prefrontal cortex and the orbitofrontal cortex), with a pivotal, but not exclusive, role of dopamine.

There is also the relationship between opiates, dopamine and food addiction, and pleasure states [30]. If this is the case, can we extend this hedonic hypothesis to the relationship between opiates, dopamine and music? It is remarkable that Menon and Levitin [9] found that NAc and VTA activation were significantly correlated suggesting an association between dopamine release and NAc response to pleasant music. There may be a common mechanism between music and drugs of abuse similar to earlier concepts related to common brain mechanisms between opiates and alcohol [31,32]. While there are dopamine independent processes that contribute significantly to the reinforcing effects of many drugs of abuse, increased dopamine transmission is clearly both necessary and sufficient to promote psychostimulant reinforcement. For the other four classes of abused substances, self-administration experiments suggest that although increasing mesolimbic dopamine transmission plays an important role in the reinforcing effects of opiates, ethanol, cannabinoids, nicotine other neurotransmitters are involved. Thus it is possible that more natural rewards like music also stimulate the NAc due to positive affect causing dopamine release [33]. It is likely that the rewarding and reinforcing aspects of listening to music are mediated by increased dopamine levels in the VTA and NAc. It is noteworthy that withdrawal from drugs of abuse (e.g. heroin, alcohol, psychostimulants) is painful, and pleasure and pain anchor opposing ends [34]. Taylor et al. [35] reasoned that VTA-NAc responses are related to suppression of aversive stimuli, which would be of a “rewarding nature.” It is further conjectured that these music listening response induces suppression of aversive stimuli. Certainly it is worthwhile exploring the role of music as a therapeutic modality in the treatment and possibly even prevention tactics in SUD (a clinical subtype of RDS).

### Dopaminergic genes and addiction

In 1996, our laboratory first described Reward Deficiency Syndrome (RDS) to define common genetic variants involving dopamine D2 receptor gene (DRD2) polymorphisms [36] as a putative predictor of impulsive and addictive behaviors. The D2 receptor has been associated with pleasure, and the DRD2 A1 allele has been referred to as a reward gene [37]. The DRD2 gene has been one of the most widely studied in neuropsychiatric disorders in general and in alcoholism, other addictions (carbohydrate), and reward behaviors. The DRD2 gene, and especially its *Taq 1 A1* allele, may also be involved in co-morbid antisocial personality disorder symptoms, and high novelty seeking. Addiction is increasingly recognized to be one disease sharing a common neuroanatomy and neurobiology. The meso-cortico-limbic dopaminergic pathway plays an especially important role in mediating the reinforcement of natural rewards like food and sex, as well as by drugs of abuse. As such, there may be a common neurocircuitry for multiple addictions and for a number of psychiatric disorders.

When there is a dysfunction in the reactivity of the meso-cortico-limbic dopamine reward system (potentially caused by certain genetic variants), the end result is RDS, which tends to increase the risk for subsequent drug-seeking behavior. RDS refers to the breakdown of the reward cascade and resultant destructive behaviors and possibly aberrant conduct, due to specific genetic and environmental influences. It is well-known that alcohol and other drugs of abuse, as well as most positive reinforcers (i.e. sex food, gambling, aggressive thrills) cause activation and neuronal release of brain dopamine, which can decrease negative feelings and satisfy abnormal cravings for alcohol, cocaine, heroin, and nicotine, which among others, are linked to low dopa-

mine function. A deficiency of the D2 receptors then predisposes individuals to a high risk for multiple addictive, impulsive, and compulsive behaviors [38]. Although other neurotransmitters (e.g. glutamate, gamma-aminobutyric acid (GABA), serotonin, and enkephalins) may be important in determining the rewarding and stimulating effects of methamphetamine, dopamine may be critical for initiating drug use and for reinstating drug use during protracted abstinence [39].

Following the initial findings of a positive association of the *Taq 1 A1* of the DRD2 gene and severe alcoholism, substance dependence, and related behaviors [10], there have been many replication studies (including linkage to ANKK1 gene and other markers) [40] as well as some that have failed to find this relationship [41]. It has been observed that the *Taq 1 A1* allele is associated with low dopamine D2 receptor density in alcoholics [42]. Moreover, other studies have confirmed that the striatal post-synaptic D2 receptor densities are low among alcoholics [43].

Even in the first paper by Blum et al. [10], the concept of the dopamine D2 receptor gene as a specific target for alcohol, was dismissed by the authors, who suggested that they have found a non-specific “reward” gene. Moreover, the DRD2 *Taq 1 A* as well as the 957C < T polymorphism have been also associated with stress and anxiety [44], and both symptoms have been related to heightened sensitivity of pre-synaptic D2 receptors to dopamine.

Grasping the mechanism of motivated behavior requires an understanding of the neural circuitry of rewards, otherwise called positive reinforcers. This is operationally defined as an event that increases the probability of a subsequent response. Drugs of abuse are considered to be stronger positive reinforcers than natural reinforcers (e.g. food and sex). The distinction between “natural rewards” and “unnatural rewards” is an important one. Natural rewards include satisfaction of physiological drives (e.g. hunger and reproduction), and unnatural rewards are learned and involve satisfaction of acquired pleasures such as hedonic sensations derived from alcohol and other drugs, as well as from gambling and other risk-taking behaviors [45]. One wonders about the power of music listening in terms of D2 activation.

In discussing RDS, we refer specifically to an insensitivity and inefficiency in the reward system [36]. When dopamine D2 receptors are low due to genetic antecedents then it is likely that these individuals will be more attracted to more powerful dopamine activators such as drugs because they give the powerful dopamine surge that the person with compromised D2 receptors needs. RDS also encompasses the acquired need to escape or avoid negative effects created by repeated cycles of alcohol and drug abuse or repetitive bouts of overeating. As stated earlier, dopamine has been associated with pleasure, and it has been called the “anti-stress molecule” and/or the “pleasure molecule”. When dopamine is released into the synapse, it stimulates a number of receptors (D<sub>1</sub>–D<sub>5</sub>) which results in increased feelings of well-being and stress reduction. The neural circuitry for positive reinforcement involves multiple brain regions. Core regions constituting the brain reward pathway are located in the limbic system. Functions of the limbic system include monitoring of internal homeostasis, mediating memory and learning, and contributing to emotions [46]. The limbic system also drives important aspects of sexual behavior, motivation, and feeding behaviors. Primary areas of the limbic system include the hypothalamus, amygdala, sub-lenticular amygdala, hippocampus, septal nuclei, and anterior cingulate gyrus. Also important in the function of the limbic system are the nucleus accumbens (NAc), ventral caudate nucleus, and the putamen. Other structures important in the brain reward system include the prefrontal cortex, substantia nigra, periaqueductal gray matter, and the ventral tegmental area (VTA). The genes regulating this region of the brain are involved in the feelings of happiness (well-being) [47].

As cited above, persons carrying an A1 allele have a lower D2 receptor density and a higher risk of substance abuse. One study was designed to investigate the influence of the DRD2 Taq IA polymorphism and the selective D2 receptor agonist bromocriptine on the activation of the reward system by means of functional magnetic resonance imaging (fMRI). In a double-blind crossover study with 24 participants, Kirsch et al. [14] found an increase of reward system activation from placebo to bromocriptine only in subjects carrying the A1 allele. Further, only A1 carriers showed an increase of performance under bromocriptine. The results are interpreted as reflecting a specific sensitivity for dopamine agonists in persons carrying an A1 allele and may complement actual data and theories of the development of addiction disorders postulating a higher genetic risk for substance abuse in carrier of the A1 allele [48,49]. It is well-known that after prolonged abstinence, individuals who use their drug of choice experience a powerful euphoria [less for cigarette and glucose relative to other powerful drugs] that often precipitates relapse. While a biological explanation for this phenomenon has remained elusive, we hypothesize that this clinically observed “super sensitivity” might be tied to genetic dopaminergic polymorphisms. Another important phenomenon relates to the paradoxical finding that the dopaminergic agonist bromocriptine induces stronger activation of brain reward circuitry in individuals who carry the DRD2 A1 allele compared to DRD2 A2 allele carriers. Based upon the fact that carriers of the A1 allele relative to the A2 allele of the DRD2 gene have significantly lower D2 receptor density, a reduced sensitivity to dopamine agonist activity would be expected in the former. Thus, it is perplexing that with low D2 density there is an increase in reward sensitivity with the dopamine

agonist bromocriptine [14]. Moreover, under chronic or long-term therapy, the potential proliferation of D2 receptors with bromocriptine has been shown *in vitro*. One explanation for this relates to the demonstration that the A1 allele of the DRD2 gene is associated with increased striatal activity of l-amino acid decarboxylase, the final step in the biosynthesis of dopamine. This appears to be a protective mechanism in that it compensates for low DA receptor numbers by favoring the utilization of amino-acid neurotransmitter precursor for preferential synthesis of dopamine. This seems to lead to a positive outcome and significantly better treatment compliance only in A1 carriers [50].

It is noteworthy that Cohen et al. [49] found that cabergoline (a D2 agonist) increased neural reward responses in the medial orbitofrontal cortex, cingulate cortex, and striatum for A1+ subjects but decreased reward responses in these regions for A1– subjects. In contrast, cabergoline decreased task performance and fronto-striatal connectivity in A1+ subjects but had the opposite effect in A1– subjects. Further, the drug’s effect on functional connectivity predicted the drug effect on feedback-guided learning. Thus, individual variability in how dopaminergic drugs affect the brain reflects genetic disposition. These findings may help to explain the link between genetic disposition and risk for addictive disorders. The same findings may occur with A1+ carriers with response to listening to pleasant music.

We propose herein that low D2 receptor density and polymorphisms of the D2 gene are associated with risk for relapse of substance abuse including alcohol dependence, heroin craving, cocaine dependence, methamphetamine abuse, nicotine sensitization, and glucose craving. This being the case, would pleasant

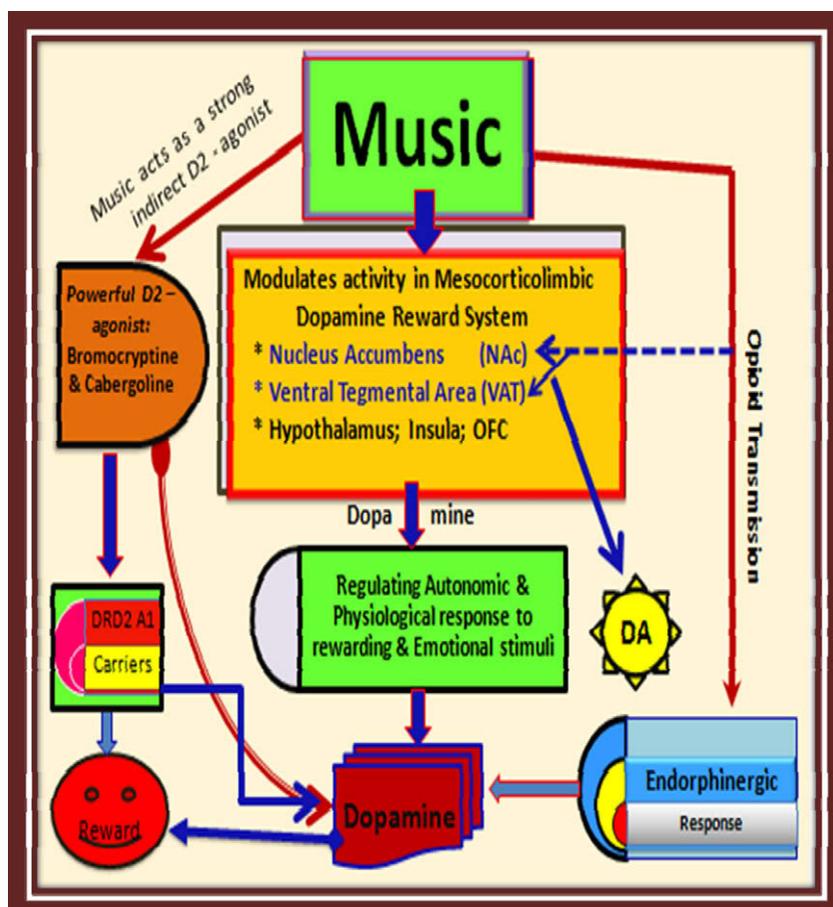


Fig. 2. Schematic illustration potential powerful D2 agonistic activity of music.

music provide a strong dopamine D2 activation especially in D2 A1 allele carriers similar to bromocriptine [14] or cabergoline? Or would it act as glucose [13] or monetary rewards [22] showing a blunted response in DRD2 A1 carriers in the VTA-NAc brain region?

### Music as a therapeutic modality in addiction

A review of the literature reveals that the earliest paper that addresses the issue between music and addiction dates back to the late 50s whereby successful musicians having addiction problems were treated with psychotherapy [51]. Successful treatment of addicted musicians using psychotherapy was first reported by Winick and Nyswander [52].

Jazz music and jazz musicians have often been linked for better or worse to the world of addictive substances. Many talented jazz musicians either had their careers sidetracked or prematurely ended due to their addiction to drugs and/or alcohol. The rigors of nightly performances, travel, and for many musicians a disapproving society exacted a toll that impacted the creativity of many artists of the genre. The fact that drug and alcohol use had a significant impact on the performance levels of numerous jazz musicians in the 1940s and 1950s has been much discussed, but more study of that impact is warranted. While recent research has provided new information regarding this challenging topic, there is still much to learn. Indeed, a number of questions for inquiry may be posed. Among those questions are the following: Was the work of these jazz artists truly inspired? Would their creative output have been enhanced had they not been addicted to substances? What was the impact of the addictive substances on their ability to function as creative artists and is there evidence to refute or verify that impact? Are there identifiable traits in certain artists that allowed them to be creative in spite of their addictions? What is the role of genetics as a predisposing factor in this group of musicians?

Music therapy is the use of musical interventions in a therapeutic setting to accomplish health-related goals. Descriptions of music therapy exist in the peer-reviewed literature and indicate potential use of music therapy in treatment of patients with addiction disorders. Few studies quantitatively assess the use of music therapy in the treatment of patients with addictions. Music listening provided by music therapists is commonly studied. Music therapy sessions reported were at best additive, not independent, treatment modalities. In the literature, no consensus exists regarding the efficacy of music therapy as treatment for patients with addictions. Is the efficacy of music therapy linked to dopaminergic polymorphisms?

Another important question relates to how music may influence drug-seeking behavior especially in adolescents? It is now known that the average adolescent is exposed to approximately 84 references to explicit substance use daily in popular songs, and this exposure varies widely by musical genre. The substance use depicted in popular music, which is frequently motivated by peer acceptance and sexuality, has highly positive associations and consequences [53].

In a recent study as cited earlier, Ross et al. [18] carried out a prospective naturalistic non-randomized pilot study without a control group that sought to evaluate how participation in a music therapy program affected treatment outcomes for individuals with co-occurring mental illness and addiction. In summary, music therapy appears to be a novel motivational tool in a severely impaired inpatient sample of patients with co-occurring disorders. More specifically certain types of music may have differential effects on the addicted patient. For example even the preference to certain substances (e.g. tobacco) may be predicted by music preferences [54]. In addition there is relationship between rap music and alcohol consumption in African-Americans [55]. Moreover, Beatty and

Borrell [56] performed a study using sixty-three clients from a local methadone clinic and a comparison group of 24 non-abusing subjects with knowledge about drugs who listened to a song about cocaine addiction. In the study the subjects were asked to identify the title, artist, year the song was first popular and the meaning of the song. The authors found no significant differences between the groups in identifying the song title, artist, or year, but the drug-abusers were significantly more likely to state that the song was about cocaine or drug addiction.

In addition differences in pitch, timbre, rhythm may have impact on the success or failure of music therapy. A review by Winkelmann [57] found drumming produces pleasurable experiences, enhanced awareness of preconscious dynamics, release of emotional trauma, and reintegration of self. Drumming alleviates self-centeredness, isolation, and alienation, creating a sense of connectedness with self and others. Drumming provides a secular approach to accessing a higher power and applying spiritual perspectives. Thus drumming circles have applications as complementary addiction therapy, particularly for repeated relapse and when other counseling modalities have failed. Moreover dance therapy has been shown to improve self-esteem in woman prisoners [58].

### Conclusion

Finally music appears to mimic some of the features of language and to convey some of the same emotions that vocal communication does, but in a nonreferential and non-specific way. It also invokes some of the same neural regions that language does, but far more than language, music taps into primitive brain structures (mesolimbic system) involved with emotion, motivation and reward [59]. There may even be a similarity in using language tools and music therapy in influencing motivational change in addicts [60].

Confirmation of our hypothesis showing that unlike glucose and monetary rewards but similar to strong D2 agonists like bromocriptine and cabergoline, music powerfully activates mesolimbic reward circuitry especially in DRD2 A1 allele carriers compared to A2 allele carriers of the DRD2 gene. This could ultimately provide the rationale for systematically utilizing pleasant music to treat addiction (RDS behaviors) and prevent relapse in high risk addiction prone genetically compromised low D2 density subjects. The concept low of DA levels and or a low number of DA receptors associating with anhedonia and substance seeking behavior, relapse and withdrawal symptomology has been known for some time as well as popular music acting as a stimulus for drug abuse [61–64].

It would be of interest to couple pleasant music, albeit being very subjective (for those addicts that love Jazz) such as Stan Getz's famous scores including his work with Gilberto, Cal Jader, and a tune like Desifando during a fMRI session in both DRD2 A1+ and A1– genotypes and determine the differential outcome in terms of the connectivity and magnitude of activation of music listening response at the VTA-mediated NAc reward circuitry.

Whether or not music is simple pleasure inducing only or it has adaptation of the species properties leading to the passage of genes from one generation to another by promoting human propagation of the species is still questionable. However, we argue that music is not an evolutionary accident, it is indeed fundamental to our species, perhaps even more so than language.

If music causes a powerful activation in spite of the DRD2 A1 allele due to a strong DA neuronal release that 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 includ-

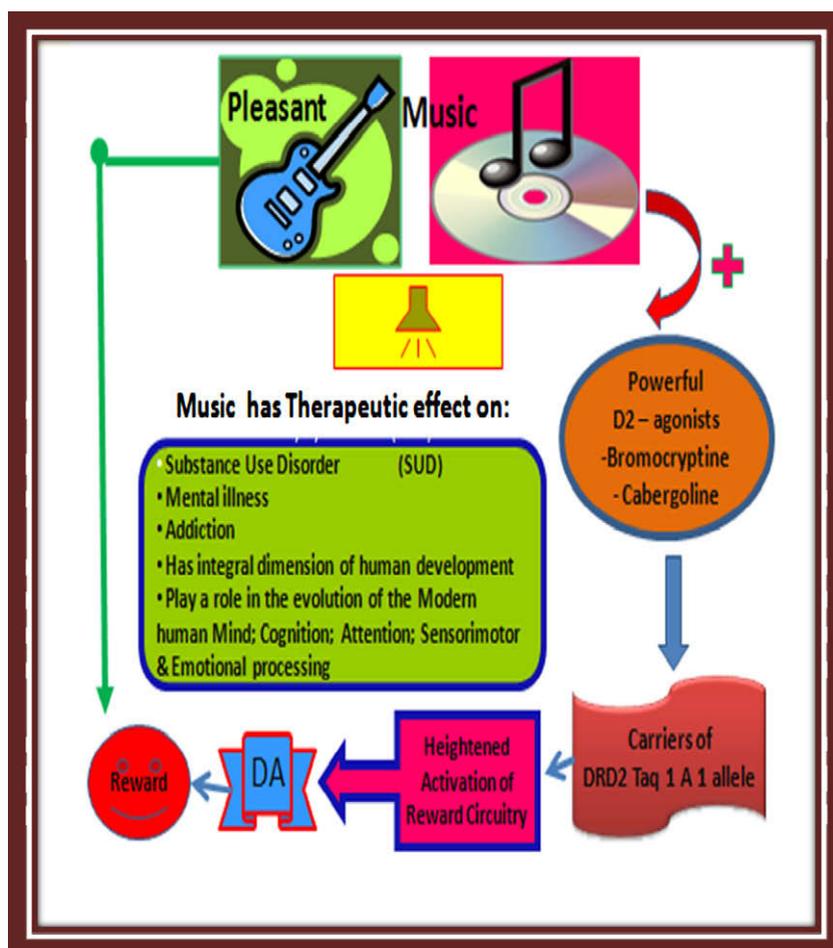


Fig. 3. Schematic illustrating music activation of reward center in the brain as function of dopamine D2 genotypes.

ing Substance Use Disorder (SUD). If our hypothesis is born out genotyping the individual for dopaminergic polymorphisms might help explain and direct who should get music therapy. Is your brain on music D2 A1 or not D2 A1? (see Figs. 2 and 3). That is the question.

In closing Levitin [59] suggests “music breathes, speeds up, and slows down just as the real world does, and our cerebellum finds pleasure in adjusting itself to stay synchronized”.

#### Conflict of interest

Kenneth Blum, B. William Downs, Roger L. Waite and Margaret Madigan own stock in LifeGen, Inc., the exclusive distributors of patents related to an addictive gene panel. There are no other conflicts of interest.

#### Special dedication

This article is dedicated to the legendary Stan Getz who unfortunately succumbed to alcoholism but whose music lives on generationally. We also dedicate this article to our friend Joseph L. Marillo, a resident Jazz musician of San Diego, California who is honored to have known Stan and his family and continues to showcase his music through Getz’s personal saxophone mouth piece. This article is also dedicated to Monica Getz who’s continued work for the development of Al Anon worldwide has brought strength and hope for friends and families of problem drinkers. One of us (KB) had the unique experience to be with Monica in 1989 and a

team of USA delegates to initiate and develop the first Al-Anon meeting in Moscow.

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