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Dopamine Genetics and Function in Food and Substance Abuse

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Abstract

Having entered the genomics era with confidence in the future of medicine, including psychiatry, identifying the role of DNA and polymorphic associations with brain reward circuitry has led to a new understanding of all addictive behaviors. It is noteworthy that this strategy may provide treatment for the millions who are the victims of “Reward Deficiency Syndrome” (RDS) a genetic disorder of brain reward circuitry. This article will focus on drugs and food being mutually addictive, and the role of dopamine genetics and function in addictions, including the interaction of the dopamine transporter, and sodium food. We will briefly review our concept that concerns the genetic antecedents of multiple-addictions (RDS). Studies have also shown that evaluating a panel of established reward genes and polymorphisms enables the stratification of genetic risk to RDS. The panel is called the “Genetic Addiction Risk Score (GARS)”, and is a tool for the diagnosis of a genetic predisposition for RDS. The use of this test, as pointed out by others, would benefit the medical community by identifying at risk individuals at a very early age. We encourage, in depth work in both animal and human models of addiction. We encourage further exploration of the neurogenetic correlates of the commonalities between food and drug addiction and endorse forward thinking hypotheses like “The Salted Food Addiction Hypothesis”.

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Conflict of Interest Kenneth Blum, PhD., holds a number of US and foreign patents related to diagnosis and treatment of RDS, which has been exclusively licensed to LifeGen, Inc. Lederach, PA. Dominion Diagnostics, LLC, North Kingstown, Rhode Island along with LifeGen, Inc., are actively involved in the commercial development of GARS. John Giordano is also a partner in LifeGen, Inc. There are no other conflicts of interest and all authors read & approved the manuscript.

Keywords

Food addiction; Substance Use Disorder (SUD); Reward Deficiency Syndrome (RDS); Dopaminergic gene polymorphisms; Neurogenetics

Introduction

Dopamine (DA) is a neurotransmitter in the brain, which controls feelings of wellbeing. This sense of wellbeing results from the interaction of DA and neurotransmitters such as serotonin, the opioids, and other brain chemicals. Low serotonin levels are associated with depression. High levels of the opioids (the brain's opium) are also associated with a sense of wellbeing [1]. Moreover, DA receptors, a class of G-protein coupled receptors (GPCRs), have been targeted for drug development for the treatment of neurological, psychiatric and ocular disorders [2]. DA has been called the "anti-stress" and/or "pleasure" molecule, but this has been recently debated by Salamone and Correa [3] and Sinha [4].

Accordingly, we have argued [5-8] that Nucleus accumbens (NAc) DA has a role in motivational processes, and that mesolimbic DA dysfunction may contribute to motivational symptoms of depression, features of substance abuse and other disorders [3]. Although it has become traditional to label DA neurons as reward neurons, this is an over generalization, and it is necessary to consider how different aspects of motivation are affected by dopaminergic manipulations. For example, NAc DA is involved in Pavlovian processes, and instrumental learning appetitive-approach behavior, aversive motivation, behavioral activation processes sustained task engagement and exertion of effort although it does not mediate initial hunger, motivation to eat or appetite [3,5-7].

While it is true that NAc DA is involved in appetitive and aversive motivational processes we argue that DA is also involved as an important mediator in primary food motivation or appetite similar to drugs of abuse. A review of the literature provides a number of papers that show the importance of DA in food craving behavior and appetite mediation [6,7]. Gold has pioneered the concept of food addiction [5-8]. Avena et al. [9] correctly argue that because addictive drugs activate the same neurological pathways that evolved to respond to natural rewards, addiction to food seems plausible. Moreover, sugar per se is noteworthy as a substance that releases opioids and DA and thus might be expected to have addictive potential. Specifically, neural adaptations include changes in DA and opioid receptor binding, enkephalin mRNA expression and DA and acetylcholine release in the NAc. The evidence supports the hypothesis that under certain circumstances rats can become sugar dependent.

The work of Wang et al. [10] involving brain imaging studies in humans has implicated DA-modulated circuits in pathologic eating behavior(s). Their studies suggest that the DA in the extracellular space of the striatum is increased by food cues, this is evidence that DA is potentially involved in the non-hedonic motivational properties of food. They also found that orbitofrontal cortex metabolism is increased by food cues indicating that this region is associated with motivation for the mediation of food consumption. There is an observed reduction in striatal DA D2 receptor availability in obese subjects, similar to the reduction in drug-addicted subjects, thus obese subjects may be predisposed to use food to compensate temporarily for under stimulated reward circuits [11]. In essence, the powerful reinforcing effects of both food and drugs are in part mediated by abrupt DA increases in the mesolimbic brain reward centers. Volkow et al. [11] point out that abrupt DA increases can override homeostatic control mechanisms in the brain's of vulnerable individuals. Brain imaging studies have delineated the neurological dysfunction that generates the shared

features of food and drug addictions. The cornerstone of the commonality, of the root causes of addiction are impairments in the dopaminergic pathways that regulate the neuronal systems associated also with self-control, conditioning, stress reactivity, reward sensitivity and incentive motivation [11]. Metabolism in prefrontal regions is involved in inhibitory control, in obese subjects the inability to limit food intake involves ghrelin and may be the result of decreased DA D2 receptors which are associated with decreased prefrontal metabolism [12]. The limbic and cortical regions involved with motivation, memory and self-control, are activated by gastric stimulation in obese subjects [10] and during drug craving in drug-addicted subjects. An enhanced sensitivity to the sensory properties of food is suggested by increased metabolism in the somatosensory cortex of obese subjects. This enhanced sensitivity to food palatability coupled with reduced DA D2 receptors could make food the salient reinforcer for compulsive eating and obesity risk [10]. These research results indicate that numerous brain circuits are disrupted in obesity and drug addiction and that the prevention and treatment of obesity may benefit from strategies that target improved DA function.

Lindblom et al. [13] reported that dieting as a strategy to reduce body weight often fails as it causes food cravings leading to bingeing and weight regain. They also agree that evidence from several lines of research suggests the presence of shared elements in the neural regulation of food and drug craving. Lindblom et al. [13] quantified the expression of eight genes involved in DA signaling in brain regions related to the mesolimbic and nigrostriatal DA system in male rats subjected to chronic food restriction using quantitative real-time polymerase chain reaction. They found that mRNA levels of tyrosine hydroxylase, and the dopamine transporter in the ventral tegmental area were strongly increased by food restriction and concurrent DAT up-regulation at the protein level in the shell of the NAc was also observed via quantitative autoradiography. That these effects were observed after chronic rather than acute food restriction suggests that sensitization of the mesolimbic dopamine pathway may have occurred. Thus, sensitization possibly due to increased clearance of extracellular dopamine from the NAc shell may be one of the underlying causes for the food cravings that hinder dietary compliance. These findings are in agreement with earlier findings by Patterson et al. [14]. They demonstrated that direct intracerebroventricular infusion of insulin results in an increase in mRNA levels for the DA reuptake transporter DAT. In a 24- to 36-hour food deprivation study hybridization was used *in situ* to assess DAT mRNA levels in food-deprived (hypoinsulinemic) rats. Levels were in the ventral tegmental area/substantia nigra pars compacta significantly decreased suggesting that moderation of striatal DAT function can be effected by nutritional status, fasting and insulin. Ifland et al. [15] advanced the hypothesis that processed foods with high concentrations of sugar and other refined sweeteners, refined carbohydrates, fat, salt, and caffeine are addictive substances. Other studies have evaluated salt as important factor in food seeking behavior. Roitman et al. [16] points out that increased DA transmission in the NAc is correlated with motivated behaviors, including Na appetite. DA transmission is modulated by DAT and may play a role in motivated behaviors. In their studies *in vivo*, robust decreases in DA uptake via DAT in the rat NAc were correlated with and Na appetite induced by Na depletion. Decreased DAT activity in the NAc was observed after *in vitro* Aldosterone treatment. Thus, a reduction in DAT activity, in the NAc, may be the consequence of a direct action of Aldosterone and may be a mechanism by which Na depletion induces generation of increased NAc DA transmission during Na appetite. Increased NAc DA may be the motivating property for the Na-depleted rat. Further support for the role of salted food as possible substance (food) of abuse has resulted in the “The Salted Food Addiction Hypothesis” as proposed by Cocores and Gold [17]. In a pilot study, to determine if salted foods act like a mild opiate agonist which drives overeating and weight gain, they found that an opiate dependent group developed a 6.6% increase in weight during opiate withdrawal showing a strong preference for salted food. Based on this and

other literature [18] they suggest that Salted Food may be an addictive substance that stimulates opiate and DA receptors in the reward and pleasure center of the brain. Alternately, preference, hunger, urge, and craving for “tasty” salted food may be symptoms of opiate withdrawal and the opiate like effect of salty food. Both salty foods and opiate withdrawal stimulate the Na appetite, result in increased calorie intake, overeating and disease related to obesity.

Brain Dopaminergic Function

Dopamine D2 receptor gene (DRD2)

When synaptic, DA stimulates DA receptors (D1–D5), individuals experience stress reduction and feelings of wellbeing [19]. As mentioned earlier, the mesocorticolimbic dopaminergic pathway mediates reinforcement of both unnatural rewards and natural rewards. Natural drives are reinforced physiological drives such as hunger and reproduction while unnatural rewards involve satisfaction of acquired learned pleasures, hedonic sensations like those derived from drugs, alcohol, gambling and other risk-taking behaviors [8,20,21].

One notable DA gene is the DRD2 gene which is responsible for the synthesis of DA D2 receptors [22]. The allelic form of the DRD2 gene (A1 versus A2) dictates the number of receptors at post-junctional sites and hypodopaminergic function [23,24]. A paucity of DA receptors predisposes individuals to seek any substance or behavior that stimulates the dopaminergic system [25-27].

The DRD2 gene and DA have long been associated with reward [28] in spite of controversy [3,4]. Although the Taq1 A1 allele of the DRD2 gene, has been associated with many neuropsychiatric disorders and initially with severe alcoholism, it is also associated with other substance and process addictions, as well as, Tourette’s Syndrome, high novelty seeking behaviors, Attention Deficit Hyperactivity Disorder (ADHD), and in children and adults, with co-morbid antisocial personality disorder symptoms [28].

While this article will focus on drugs and food being mutually addictive, and the role of DA genetics and function in addictions, for completeness, we will briefly review our concept that concerns the genetic antecedents of multiple-addictions. “Reward Deficiency Syndrome” (RDS) was first described in 1996 as a theoretical genetic predictor of compulsive, addictive and impulsive behaviors with the realization that the DRD2 A1 genetic variant is associated with these behaviors [29-32]. RDS involves the pleasure or reward mechanisms that rely on DA. Behaviors or conditions that are the consequence of DA resistance or depletion are manifestations of RDS [30]. An individual’s biochemical reward deficiency can be mild, the result of overindulgence or stress or more severe, the result of a DA deficiency based on genetic makeup. RDS or anti-reward pathways help to explain how certain genetic anomalies can give rise to complex aberrant behavior. There may be a common neurobiology, neuro-circuitry and neuroanatomy, for a number of psychiatric disorders and multiple addictions. It is well known that drugs of abuse, alcohol, sex, food, gambling and aggressive thrills, indeed, most positive reinforcers, cause activation and neuronal release of brain DA and can decrease negative feelings. Abnormal cravings are linked to low DA function [33]. Here is an example of how complex behaviors can be produced by specific genetic antecedents. A deficiency of, for example, the D2 receptors a consequence of having the A1 variant of the DRD2 gene [34] may predispose individuals to a high risk for cravings that can be satisfied by multiple addictive, impulsive, and compulsive behaviors. This deficiency could be compounded if the individual had another polymorphism in for example the DAT gene that resulted in excessive removal of DA from the synapse. In addition, the use of substances and aberrant behaviors also deplete

DA. Thus, RDS can be manifest in severe or mild forms that are a consequence a biochemical inability to derive reward from ordinary, everyday activities. Although many genes and polymorphisms predispose individuals to abnormal DA function, carriers of the Taq1 A1 allele of the DRD2 gene lack enough DA receptor sites to achieve adequate DA sensitivity. This DA deficit in the reward site of the brain can results in unhealthy appetites and craving. In essence, they seek substances like alcohol, opiates, cocaine, nicotine, glucose and behaviors; even abnormally aggressive behaviors that are known to activate dopaminergic pathways and cause preferential release of DA at the NAc. There is now evidence that rather than the NAc, the anterior cingulate cortex may be involved in operant, effort-based decision making [35-37] and a site of relapse.

Impairment of the DRD2 gene or in other DA receptor genes, such as the DRD1 involved in homeostasis and so called normal brain function, could ultimately lead to neuropsychiatric disorders including aberrant drug and food seeking behavior. Prenatal drug abuse in the pregnant female has been shown to have profound effects of the neurochemical state of offspring. These include ethanol [38]; cannabis [39]; heroin [40]; cocaine [41]; and drug abuse in general [42]. Most recently Novak et al. [43] provided strong evidence showing that abnormal development of striatal neurons are part of the pathology underlying major psychiatric illnesses. The authors identified an underdeveloped gene network (early) in rat that lacks important striatal receptor pathways (signaling). At two postnatal weeks the network is down regulated and replaced by a network of mature genes expressing striatal-specific genes including the DA D1 and D2 receptors and providing these neurons with their functional identity and phenotypic characteristics. Thus, this developmental switch in both the rat and human, has the potential to be a point of susceptibility to disruption of growth by environmental factors such as an overindulgence in foods, like salt, and drug abuse.

Dopamine transporter (DAT)

The DA transporter (also DA active transporter, DAT, SLC6A3) is a membrane-spanning protein that pumps the neurotransmitter DA out of the synapse back into cytosol from which other known transporters sequester DA and norepinephrine into neuronal vesicles for later storage and subsequent release [44].

The DAT protein is encoded by a gene located on human chromosome 5 it is about 64 kbp long and consists of 15 coding exon. Specifically, the DAT gene (SLC6A3 or DAT1) is localized to chromosome 5p15.3. Moreover, there is a VNTR polymorphism within the 3' non-coding region of DAT1. A genetic polymorphism in the DAT gene which effects the amount of protein expressed is evidence for an association between and DA related disorders and DAT [45]. It is well established that DAT is the primary mechanism which clears DA from synapses, except in the prefrontal cortex where DA reuptake involves norepinephrine [46,47]. DAT terminates the DA signal by removing the DA from the synaptic cleft and depositing it into surrounding cells. Importantly, several aspects of reward and cognition are functions of DA and DAT facilitates regulation of DA signaling [48].

It is noteworthy that DAT is an integral membrane protein and is considered a symporter and a co-transporter moving DA from the synaptic cleft across the phospholipid cell membrane by coupling its movement to the movement of Na ions down the electrochemical gradient (facilitated diffusion) and into the cell.

Moreover, DAT function requires the sequential binding and co-transport of two Na ions and one chloride ion with the DA substrate. The driving force for DAT-mediated DA reuptake is the ion concentration gradient generated by the plasma membrane Na⁺/K⁺ ATPase [49].

Sonders et al. [50] evaluated the role of the widely-accepted model for monoamine transporter function. They found that normal monoamine transporter function requires set rules. For example, Na ions must bind to the extracellular domain of the transporter before DA can bind. Once DA binds, the protein undergoes a conformational change, which allows both Na and DA to unbind on the intracellular side of the membrane. A number of electrophysiological studies have confirmed that DAT transports one molecule of neurotransmitter across the membrane with one or two Na ions like other monoamine transporters. Negatively charged chloride ions are required to prevent a buildup of positive charge. These studies used radioactive-labeled DA and have also shown that the transport rate and direction are totally dependent on the Na gradient [51].

Since it is well known that many drugs of abuse cause the release of neuronal DA [52], DAT may have a role in this effect. Because of the tight coupling of the membrane potential and the Na gradient, activity-induced changes in membrane polarity can dramatically influence transport rates. In addition, the transporter may contribute to DA release when the neuron depolarizes [53]. In essence, as pointed out by Vandenberg et al. [54] the DAT protein regulates DA-mediated neurotransmission by rapidly accumulating DA that has been released into the synapse.

The DAT membrane topology was initially theoretical, determined based on hydrophobic sequence analysis and similarity to the GABA transporter. The initial prediction of Kilty et al. [55] of a large extracellular loop between the third and fourth of twelve transmembrane domains was confirmed by Vaughan and Kuhar [56] when they used proteases, to digest proteins into smaller fragments, and glycosylation, which occurs only on extracellular loops, to verify most aspects of DAT structure.

DAT has been found in regions of the brain where there is dopaminergic circuitry, these areas include mesocortical, mesolimbic, and nigrostriatal pathways [57]. The nuclei that make up these pathways have distinct patterns of expression. DAT was not detected within any synaptic cleft which suggests that striatal DA reuptake occurs outside of the synaptic active zones after DA has diffused from the synaptic cleft.

Two alleles, the 9 repeat (9R) and 10 repeat (10R) VNTR can increase the risk for RDS behaviors. The presence of the 9R VNTR has associated with alcoholism and Substance Use Disorder. It has been shown to augment transcription of the DAT protein resulting in an enhanced clearance of synaptic DA, resulting in a reduction in DA, and DA activation of postsynaptic neurons [58]. The tandem repeats of the DAT have been associated with reward sensitivity and high risk for Attention Deficit Hyperactivity Disorder (ADHD) in both children and adults [59,60]. The 10-repeat allele has a small but significant association with hyperactivity-impulsivity (HI) symptoms [61].

Mapping Reward Genes and RDS

Support for the impulsive nature of individuals possessing dopaminergic gene variants and other neurotransmitters (e.g. DRD2, DRD3, DRD4, DAT1, COMT, MOA-A, SLC6A4, Mu, GABA_B) is derived from a number of important studies illustrating the genetic risk for drug-seeking behaviors based on association and linkage studies implicating these alleles as risk antecedents that have an impact in the mesocorticolimbic system (Table 1). Our laboratory in conjunction with LifeGen, Inc. and Dominion Diagnostics, Inc. is carrying out research involving twelve select centers across the United States to validate the first ever patented genetic test to determine a patient's genetic risk for RDS called Genetic Addiction risk Score™ (GARS).

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Table 1

Candidate Reward Genes and RDS - (A sampling).

Gene	Polymorphism(s)	Study Findings	Reference	Comment
D2 dopamine receptor gene (DRD2)	SNP rs: 1800497	Taq A1 allele associates with sever alcoholism	Blum et al. [24]	First study to associate with alcoholism (called reward gene)
	ANKKI -p.Glu713Lys	DRD2 Taq1A RFLP is a single nucleotide polymorphism (SNP) that causes an amino acid substitution within the 11 th ankyrin repeat of ANKK1	Neville et al. [62]	The ANKKI gene is a reflection of DRD2 A ₁ allele.
	SNP rs: 1800497	This SNP has been found to predict future RDS behaviors as high as 74%.	Blum et al. [63]	using Bayesian analysis
	SNP rs: 1800497	Presence of the A1 ⁺ genotype (A1/A1, A1 / A2) compared to the A ⁻ genotype (A2/A2), is associated with reduced density	Noble et al. [25]	This reduction causes hypodopaminergic functioning in the dopamine reward pathway.
	SNP rs: 6277 at exon 7	T ⁺ allele associates with alcohol dependence.	Hoffman et al. [64]	Associates with drug seeking behavior and other RDS behaviors
	SNP rs: 1800497	10 year follow up that carriers of the DRD2 A1 allele have a higher rate of mortality compared to carriers of the A2 allele in alcohol dependent individuals	Dahlgren et al. [65]	Taq I A1 allele and a substantially increased relapse rate
	DRD2-haplotypes I-C-G-A2 and I-C-A-A1	Confirmed the hypothesis that haplotypes, which are supposed to induce a low DRD2 expression, are associated with alcohol dependence.	Kraschewski et al. [66]	High frequency of haplotype was associated with Cloninger Type 2 and family history of alcoholism.
D4 dopamine receptor gene (DRD4)	SNP rs: 1800497	Genotype analysis showed a significantly higher frequency for the TaqIA polymorphism among the addicts (69.9%) compared to control subjects (42.6%; Fisher's exact χ^2 , $p < .05$).	Teh et al. [67]	The addicts had higher scores for novelty seeking (NS) and harm avoidance (HA) personality traits
	DRD4 - The 7 repeat (7R) VNTR	The length of the D4 dopamine receptor (DRD4) exon 3 variable number of tandem repeats (VNTR) affects DRD4 functioning by modulating the expression and efficiency of maturation of the receptor.	Van Tol [68]	The 7 repeat (7R) VNTR requires significantly higher amounts of dopamine to produce a response of the same magnitude as other size VNTRs
	120bp duplication, -616C/G, and -521C/T	Strong finding of -120 bp duplication allele frequencies with schizophrenia ($p = 0.008$); -521 C/T polymorphism is associated with heroin addiction.	Lai et al. [69]	This reduced sensitivity or "dopamine resistance" leads to hypodopaminergic functioning. Thus 7R VNTR has been associated with substance - seeking behavior

Gene	Polymorphism(s)	Study Findings	Reference	Comment
	DRD4 7-repeat allele	A number of putative risk alleles using survival analysis revealed that by 25 years of age 76% of subjects with a DRD4 7-repeat allele were estimated to have significantly more persistent ADHD compared with 66% of Subjects without the risk allele.	Biederman et al. [70]	Findings suggest that the DRD4 7-repeat allele is associated with a more persistent course of ADHD
	7-repeat allele of the dopamine D(4) receptor gene (DRD4)	Although the association between ADHD and DRD4 is small, these results suggest that it is real.	Faraone et al. [71]	For both the case-control and family-based studies, the authors found 1) support for the association between ADHD and DRD4, 2) no evidence that this association was accounted for by any one study, and 3) no evidence for publication bias.
	dopamine D4 receptor (DRD4) exon 3 polymorphisms (48 bp VNTR)	Found significant differences in the short alleles (2-5 VNTR) frequencies between controls and patients with a history of delirium tremens and/or alcohol seizures ($p = 0.043$).	Grzywacz et al. [72]	A trend was also observed in the higher frequency of short alleles amongst individuals with an early age of onset of alcoholism ($p = 0.063$).
	dopamine D4 receptor (DRD4) -7 repeat allele	Show that the 7-repeat allele is significantly over-represented in the opioid-dependent cohort and confers a relative risk of 2.46	Kotler et al. [73]	This is the first report of an association between a specific genetic polymorphism and opioid addiction.
Dopamine Transporter gene (DAT1)	Localized to chromosome 5p15.3. Moreover, within 3 noncoding region of DAT1 lies a VNTR polymorphism -9 repeat (9R) VNTR	The 9 repeat (9R) VNTR has been shown to influence gene expression and to augment transcription of the dopamine transporter protein	Byerley et al. [74]	Having this variant results in an enhanced clearance of synaptic dopamine, yielding reduced levels of dopamine to activate postsynaptic neurons
	R9 repeat (9R) VNT	DAT1, genotype 9/9 was associated with early opiate addiction	Galeeva et al. [75]	The combination of SERT genotype 10/10 with DAT1 genotype 10/10 was shown to be a risk factor of opiate abuse under 16 years of age.
	exon 15 rs27072 and VNTR (DAT), promoter VNTR and rs25531	The haplogenotypes 6-A-10/6-G-10 and 5-G-9/5-G-9 were more often present in type 2 alcoholics as compared with type 1 alcoholics [odds ratio (OR): 2.8], and controls (OR: 5.8), respectively.	Reese et al. [76]	In a typology proposed by Cloninger on the basis of adoption studies, a subgroup has been classified as type 2 with patients having high genetic loading for alcoholism, an early onset of alcoholism, a severe course, and coexisting psychiatric problems consisting of aggressive tendencies or criminality
	VNTR polymorphism at the dopamine transporter locus (DAT1) 480-bp DAT1 allele	Using the haplotype-based haplotype relative risk (HHRR) method revealed significant	Cook et al. [77]	While there have been some inconsistencies associated with the earlier results the evidence

Gene	Polymorphism(s)	Study Findings	Reference	Comment
		association between ADHD/ UADD and the 480-bp DAT1 allele (chi 2 7.51, 1 df, p = 0.006).		is mounting in favor of the view that the 10R allele of DAT is associated with high risk for ADHD in children and in adults alike
	dopamine transporter (DAT1) variable number tandem repeats (VNTR), genotypes- both 9 and 10-repeat alleles	The non-additive association for the 10-repeat allele was significant for hyperactivity/impulsivity (HI) symptoms. However, consistent with other studies, exploratory analyses of the non-additive association of the 9-repeat allele of DAT1 with HI and oppositional defiant disorder (ODD) symptoms also were significant.	Lee et al. [78]	The inconsistent association between DAT1 and child behavior problems in this and other samples may reflect joint influence of the 10-repeat and 9-repeat alleles.
Catechol-O-methyltransferase (COMT)	COMT Val158Met and DRD2 Taq1A genotypes	COMT Val158Met and DRD2 Taq1A may affect the intermediate phenotype of central dopamine receptor sensitivity.	Schellekens et al. [79]	COMT Val158Met and DRD2 Taq1A may confer their risk of alcohol dependence through reduced dopamine receptor sensitivity in the prefrontal cortex and hindbrain, respectively.
	The functional polymorphism (COMT Val108/158Met) affects COMT activity, with the valine (Val) variant associated with higher and the methionine (Met) variant with lower COMT activity	Male alcoholic suicide attempters, compared to male non-attempters, had the higher frequency of Met/Met genotype or Met allele, and significantly (Kruskal-Wallis ANOVA on ranks and Mann-Whitney test) higher aggression and depression scores.	Nedic et al. [80]	These results confirmed the associations between Met allele and aggressive behaviour or violent suicide attempts in various psychiatric diagnoses, and suggested that Met allele of the COMT Val108/158 Met might be used as an independent biomarker of suicidal behaviour across different psychopathologies.
	COMT Val(158)Met variation	Both controls and opiate users with Met/ Met genotypes showed higher NS scores compared to those with the Val allele.	Demetrovics et al. [81]	Association of the COMT polymorphism and NS temperament scale has been shown for heroin-dependent patients and controls regardless of group status.
	A functional polymorphism (COMT Val158Met) resulting in increased enzyme activity has been associated with polysubstance abuse and addiction to heroin and methamphetamine	These results suggest a significant association between COMT Val158Met polymorphism and susceptibility to cannabis dependence.	Baransel et al. [82]	Cannabis stimulates dopamine release and activates dopaminergic reward neurons in central pathways that lead to enhanced dependence. Catechol-O-methyl transferase (COMT) inactivates amplified extraneuronally released dopamine.
Serotonin transporter gene	serotonin transporter promoter polymorphism [5-HT transporter gene-linked polymorphic region (5-HTTLPR)]	5-HTTLPR had age-dependent effects on alcohol, tobacco and drug use: substance use did not differ by genotype at age 9, but at age 15, the participants with the short (s)/s	Merenäkk et al. [83]	Results reveal that expression of genetic vulnerability for substance use in children and adolescents may depend on age, gender, interaction of genes, and type of substance

Gene	Polymorphism(s)	Study Findings	Reference	Comment
	The short (s), low activity allele of a polymorphism (5-HTTLPR) in the serotonin transporter gene (SLC6A4) has been related to alcohol dependence	genotype had higher tobacco use, and at age 18, they were more active alcohol, drug and tobacco users. The 5-HTTLPR short allele predicted adolescent's growth (slope) in alcohol use over time. Adolescents with the 5-HTTLPR short allele showed larger increase in alcohol consumption than those without the 5-HTTLPR short allele.	van der Zwaluw et al. [84]	5-HTTLPR genotype was not related to the initial level (intercept) of alcohol consumption.
	triallelic 5-HTTLPR genotype : SA/SA and SA/LG compared to LA/LA	Remifentanil and opioid drug had a significantly better analgesic effect in individuals with a genotype coding for low 5-HTT expression (SA/SA and SA/LG) as compared to those with high expression (LA/LA), $p < 0.02$.	Kosek et al [85]	Previously the 5-HTTLPR s-allele has been associated with higher risk of developing chronic pain conditions but in this study we show that the genotype coding for low 5-HTT expression is associated with a better analgesic effect of an opioid. The s-allele has been associated with down regulation of 5-HT1 receptors and we suggest that individuals with a desensitization of 5-HT1 receptors have an increased analgesic response to opioids during acute pain stimuli, but may still be at increased risk of developing chronic pain conditions.
Mu Opiate Receptor (MOR)	A single nucleotide polymorphism (SNP) in the human MOR gene (OPRM1 A118G) has been shown to alter receptor protein level in preclinical models and smoking behavior in humans	Independent of session, smokers homozygous for the wild-type OPRM1 A allele exhibited significantly higher levels of MOR BP (ND) than smokers carrying the G allele in bilateral amygdala, left thalamus, and left anterior cingulate cortex.	Ray et al. [86]	Among G allele carriers, the extent of subjective reward difference (denicotinized versus nicotine cigarette) was associated significantly with MOR BP(ND) difference in right amygdala, caudate, anterior cingulate cortex, and thalamus.
	Polymorphism in A118G in exon 1 and C1031G in intron 2 of the MOR gene	Results showed a significant association for both A118G and C1031G polymorphisms and opioid dependence. The G allele is more common in the heroin-dependent group (39.5% and 30.8% for A118G and C1031G polymorphisms, respectively) when compared to the controls (29.4% and 21.1% for A118G and C1031G polymorphisms, respectively).	Szeto et al. [87]	This study suggests that the variant G allele of both A118G and C1031G polymorphisms may contribute to the vulnerability to heroin dependence.
	A118G single-nucleotide polymorphism (SNP) in exon 1 of the MOR gene (OPRM1), which encodes an aminoacid	There was a significant overall association between genotypes with an 118G allele and alcohol dependence ($p = 0.0074$). The	Bart et al. [88]	There was no difference in A118G genotype between type 1 and type 2 alcoholics. In central Sweden, the functional

Gene	Polymorphism(s)	Study Findings	Reference	Comment
	substitution, is functional and receptors encoded by the variant 118G allele bind the endogenous opioid peptide beta-endorphin with three-fold greater affinity than prototype receptors. Other groups subsequently reported that this variant alters stress-responsivity in normal volunteers and also increases the therapeutic response to naltrexone (a mu-preferring opioid antagonist) in the treatment of alcohol dependence	attributable risk for alcohol dependence in subjects with an 118G allele was 11.1%		variant 118G allele in exon 1 of OPRM1 is associated with an increased attributable risk for alcohol dependence.
	MOR gene knockout (KO) were examined in wild-type (+/+), heterozygote MOR KO (+/-), and homozygote MOR KO (-/-) mice on voluntary ethanol consumption	Heterozygous and homozygous MOR KO mice consumed less ethanol than wild-type mice. These effects appeared to be greater in female KO mice than in male KO mice. MOR KO mice, especially females, exhibited less ethanol reward in a conditioned place preference paradigm.	Hall et al. [89]	These data fit with the reported therapeutic efficacy of MOR antagonists in the treatment of human alcoholism. Allelic variants that confer differing levels of MOR expression could provide different degrees of risk for alcoholism.
GABA Beta subunit 3	GABA A receptor beta3 subunit gene (GABRB3)	The G1- alleles of the GABRB3 in COAs were significantly higher than non COAs.	Namkoong et al. [90]	In the same study the frequency of the A1+ allele at DRD2 in the COAs was significantly higher than non COAs
	Beta 3 subunit mRNAs	The levels of the beta 2 and beta 3 subunit mRNAs remains elevated at 24 hr. withdrawal from chronic ethanol. Chronic ethanol treatment increased the levels of both of these polypeptides in cerebral cortex	Mhatre and Ticku [91]	Chronic ethanol administration produced an up-regulation of the beta-subunit mRNA and the polypeptide expression of these subunits in rat cerebral cortex.
	A1+ (A1A1 and A1A2 genotypes) and A1- (A2A2 genotype) alleles of the DRD2 and G1+ (G1G1 and G1 non-G1 genotypes) and G1- (non-G1 non-G1 genotype) alleles of the GABRB3 gene. Study involved Mood-related alcohol expectancy (AE) and drinking refusal self-efficacy (DRSE) were assessed using the Drinking Expectancy Profile	Patients with the DRD2 A1+ allele, compared with those with the DRD2 A1- allele, reported significantly lower DRSE in situations of social pressure. Similarly, lower DRSE was reported under social pressure by patients with the GABRB3 G1+ allele when compared to those with the GABRB3 G1- alleles. Patients with the GABRB3 G1+ allele also revealed reduced DRSE in situations characterized by negative affect than those with the GABRB3 G1- alleles. Patients carrying the GABRB3 G1+ allele showed stronger AE relating to	Young et al. [92]	Molecular genetic research has identified promising markers of alcohol dependence, including alleles of the D2 dopamine receptor (DRD2) and the GABAA receptor beta3 subunit (GABRB3) genes.

Gene	Polymorphism(s)	Study Findings	Reference	Comment
	Dinucleotide repeat polymorphisms of the GABA(A) receptor beta 3 subunit gene were compared to scores on the General Health Questionnaire-28 (GHQ)	<p>negative affective change (for example, increased depression) than their GABRB3 G1-counterparts.</p> <p>Analysis of GHQ subscale scores showed that heterozygotes compared to the combined homozygotes had higher scores on the somatic symptoms ($p = 0.006$), anxiety/insomnia ($p = 0.003$), social dysfunction ($p = 0.054$) and depression ($p = 0.004$) subscales.</p> <p>A significant progressive increase was observed in DRD2 A1 allelic prevalence ($p = 3.1 \times 10^{-6}$) and frequency ($p = 2.7 \times 10^{-6}$) in the order of non-alcoholics, less severe and severe alcoholics. In severe alcoholics, compared to non-alcoholics, a significant decrease was found in the prevalence ($p = 4.5 \times 10^{-3}$) and frequency ($p = 2.7 \times 10^{-2}$) of the GABRB3 major (G1) allele. Furthermore, a significant progressive decrease was noted in G1 allelic prevalence ($p = 2.4 \times 10^{-3}$) and frequency ($p = 1.9 \times 10^{-2}$) in nonalcoholics, less severe and severe alcoholics, respectively.</p> <p>Significant three-way interactions, MAOA genotype by abuse by sex, predicted dysthymic symptoms. Low-activity MAOA genotype buffered against symptoms of dysthymia in physically abused and multiply-maltreated women. Significant three-way interactions, MAOA genotype by sexual abuse by race, predicted all outcomes. Low-activity MAOA genotype buffered against symptoms of dysthymia, major depressive disorder, and alcohol abuse for sexually abused white participants. The high-activity genotype was protective in the nonwhite sexually abused group.</p>	Feusner et al. [93]	<p>The present study indicates that in a population of PTSD patients, heterozygosity of the GABRB3 major (G1) allele confers higher levels of somatic symptoms, anxiety/insomnia, social dysfunction and depression than found in homozygosity.</p> <p>In sum, in the same population of non-alcoholics and alcoholics studied, variants of both the DRD2 and GABRB3 genes independently contribute to the risk for alcoholism, with the DRD2 variants revealing a stronger effect than the GABRB3 variants. However, when the DRD2 and the GABRB3 variants are combined, the risk for alcoholism is more robust than when these variants are considered separately.</p>
MOA-A	MAOA genotype	<p>Individuals with CUD had reductions in GMV</p>	Alia-Klein et al. [96]	<p>This prospective study provides evidence that MAOA interacts with child maltreatment to predict mental health outcomes.</p> <p>Long-term cocaine users with the low-repeat MAOA allele</p>

Gene	Polymorphism(s)	Study Findings	Reference	Comment
		in the orbitofrontal, dorsolateral prefrontal and temporal cortex and the hippocampus compared with controls. (2) The orbitofrontal cortex reductions were uniquely driven by CUD with low- MAOA genotype and by lifetime cocaine use.		have enhanced sensitivity to gray matter loss, specifically in the orbitofrontal cortex, indicating that this genotype may exacerbate the deleterious effects of cocaine in the brain.
	MAOA u-VNTR	Girls, carrying the long MAOA u-VNTR variant showed a higher risk of being high alcohol consumers, whereas among boys, the short allele was related to higher alcohol consumption	Nilsson et al. [97]	The present study supports the hypothesis that there is a relation between MAOA u-VNTR and alcohol consumption and that this relation is modulated by environmental factors.
	30-bp repeat in the promoter region of the monoamine oxidase-A gene (MAO-A)	Significant associations between cold pain tolerance and DAT-1 ($p = 0.008$) and MAO-A ($p = 0.024$) polymorphisms were found. Specifically, tolerance was shorter for carriers of allele 10 and the rarer allele 11, as compared to homozygous for allele 9, and for carriers of allele 4 (MOA) as compared to homozygous for allele 3, respectively.	Treister et al. [98]	These results, together with the known function of the investigated candidate gene polymorphisms, suggest that low dopaminergic activity can be associated with high pain sensitivity and vice versa.
	The Revised Psychopathy Checklist (PCL-R) has shown a moderate association with violence and as such studied with MAOA genotyped alcoholic offenders	The PCL-R total score predicts impulsive reconviations among high-activity MAOA offenders (6.8% risk increase for every one-point increase in PCL-R total score, $p = 0.015$), but not among low-activity MAOA offenders, whereas antisocial behavior and attitudes predicted reconviations in both genotypes (17% risk increase among high-activity MAOA offenders and 12.8% increase among low-activity MAOA offenders for every one-point increase in factor 2 score)	Tikkanen et al. [99]	Results suggest that the efficacy of PCL-R is altered by MAOA genotype, alcohol exposure, and age, which seems important to note when PCL-R is used for risk assessments that will have legal or costly preventive work consequences
	Genotyping of two functional polymorphisms in the promoter region of the serotonin transporter and monoamine oxidase-A, respectively, (5-HTT-LPR and MAOA-VNTR), was performed in a group of women with severe alcohol addiction	Within the group of alcoholics, when the patients with known co-morbid psychiatric disorders were excluded, aggressive anti-social behavior was significantly linked to the presence of the high activity MAOA allele	Gokturk et al. [100]	The pattern of associations between genotypes of 5-HTT-LPR and MAOA VNTR in women with severe alcoholism differs from most corresponding studies on males.
	The MAOA gene presents	The results suggest that the 3-repeat allele	Contini et al. [101]	Results confirmed previous reports showing an

Gene	Polymorphism(s)	Study Findings	Reference	Comment
	several polymorphisms, including a 30-bp VNTR in the promoter region (MAOA-uVNTR). Alleles with 3.5 and 4 repeats are 2-10 times more efficient than the 3-repeat allele	is associated to: (1) alcohol dependence ($p < 0.05$); (2) an earlier onset of alcoholism ($p < 0.01$); (3) comorbid drug abuse among alcoholics ($p < 0.05$); and (4) a higher number of antisocial symptoms ($p < 0.02$).		association of the low activity 3-repeat allele of MAOAuVNTR polymorphism with substance dependence and impulsive/antisocial behaviors. These findings in a different culture further support the influence of the MAOA-uVNTR in psychiatric disorders
Dopamine D3	The genotypes of the BDNF Val66Met and DRD3 Ser9Gly polymorphisms. BDNF regulates expression of D3	Logistic regression analysis showed a significant main effect for the Val/Val genotype of the BDNF Val66Met polymorphism ($p = 0.020$), which predicted bipolar-II patients. Significant interaction effects for the BDNF Val66Met Val/Val genotype and both DRD3 Ser9Gly Ser/Ser and Ser/Gly genotypes were found only in bipolar-II patients ($p = 0.027$ and 0.006 , respectively)	Lee et al. [102]	Evidence that the BDNF Val66Met and DRD3 Ser9Gly genotypes interact only in bipolar-II disorder (hypomania) and that bipolar-I (Mania) and bipolar-II may be genetically distinct.
	D3R KO mice	The possible interaction between morphine-induced tolerance and D3 receptors has not been investigated. Compared with wildtype (WT) mice, the dopamine D3 receptor knockout (D3R KO) mice showed pronounced hypoalgesia. The D3R KO mice clearly developed lower morphine-induced tolerance and showed attenuated withdrawal signs compared with the WT mice.	Li et al. [103]	These results suggest that D3 receptors regulate basal nociception and are involved in the development of morphine-induced tolerance and withdrawal.
	DNA microarrays of two different alcohol-preferring rat lines (HAD and P) and D3 receptors	Data revealed an up-regulation of the dopamine D3 receptor (D3R) after 1 yr of voluntary alcohol consumption in the striatum of alcohol preferring rats that was confirmed by qRT-polymerase chain reaction.	Vengeliene et al. [104]	Long-term alcohol consumption leads to an up-regulation of the dopamine D3R that may contribute to alcoholseeking and relapse. We therefore suggest that selective antagonists of this pharmacological target provide a specific treatment approach to reduce alcohol craving and relapse behavior.
	Gly9 homozygotes in comparison to Ser9 carriers of D3 receptor gene	German descent and have found diminished parietal and increased frontal P300 amplitudes in Gly9 homozygotes in comparison to Ser9 carriers. Further studies should address the direct role of the DRD3 Ser9Gly polymorphism	Mulert et al. [105]	An important reason for the interest in P300 eventrelated potentials are findings in patients with psychiatric disorders like schizophrenia or alcoholism in which attenuations of the P300 amplitude are common findings.

Gene	Polymorphism(s)	Study Findings	Reference	Comment
	Dopamine receptor D3 gene Ball polymorphism	<p>in attenuated P300 amplitudes in psychiatric disorders like schizophrenia or alcoholism.</p> <p>Patients above the median value for cognitive impulsiveness (one of the three dimensions of the Barratt scale) were more frequently heterozygous than both alcohol-dependent patients with lower impulsiveness (OR = 2.51, $p = 0.019$) and than 71 healthy controls (OR = 2.32, $p = 0.025$).</p>	Limosin et al. [106]	The D3 Receptor gene has been associated with addictive behaviors especially impulsiveness.
	Bal I polymorphism at the DRD3 gen	<p>Patients with a sensation-seeking score above 24 were more frequently homozygotes for both alleles than patients with a sensation-seeking score under 24 ($p = 0.038$) or controls ($p = 0.034$).</p>	Duaux et al. [107]	These results suggest that the DRD3 gene may have a role in drug dependence susceptibility in individuals with high sensation-seeking scores
	mRNA of both DRD2 and DRD3 gene expression	<p>After a chronic schedule of intermittent bingeing on a sucrose solution, mRNA levels for the D2 dopamine receptor, and the preproenkephalin and preprotachykinin genes were decreased in dopamine-receptive regions of the forebrain, while D3 dopamine receptor mRNA was increased. The effects of sugar on mRNA levels were of greater magnitude in the nucleus accumbens than in the caudateputamen.</p>	Spangler et al. [108]	DRD3 gene accounted for 1.64% of the variance of cocaine dependence.
	MscI/BalI polymorphism of the DRD3 gene	<p>Significant decrease in the frequency of 12 heterozygotes (increase homozygosity) in subjects with cocaine dependence (29.8%) vs. controls (46.9%) ($p = 0.028$). This percentage was still lower in those who had chronically used cocaine for more than 10 years (25%), or more than 15 years (21.5%).</p>	Comings et al. [109]	The DRD2 gene had an independent and additive effect on cocaine dependence. These findings support a modest role of the DRD3 gene in susceptibility to cocaine dependence.

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