

Neurobiology and Genetics of Behavioral Addictions: A Brief Review

Davranışsal Bağımlılıkların Nörobiyolojisi ve Genetiği: Kısa Bir Gözden Geçirme

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Abstract

Among behavioral addictions gambling disorder, sex, digital game, exercise, food, shopping and work addictions are similar to substance addictions at many points, including disruption in functionality, tolerance and withdrawal, comorbid diseases, genetic background and neuronal mechanisms. While neurobiological studies of behavioral addictions are very recent, research on biochemical, radiologic, genetic and treatment related features of behavioral addictions have revealed strong neurobiological associations with alcohol and substance addictions. Most of the studies in the literature focused on gambling addiction and internet addiction, but it is shown that beside their differences, there is also similar neurobiological and structural alterations exist in other behavioral addictions. It is important to recognize and understand behavioral addictions with their genetic and neurobiological aspects, to increase awareness of these disorders, to handle the process better and to develop prevention and treatment strategies. In this article, we reviewed data on the neurobiological and genetic manifestations and associated neurobiological pathways of behavioral addictions that are beginning to gain more attention from clinicians and researchers.

Keywords: Gambling disorder, Internet addiction, Food addiction, Sex addiction, Exercise addiction, Compulsive buying

Öz

Kumar oynama bozukluğu, seks bağımlılığı, dijital oyun bağımlılığı, egzersiz bağımlılığı, internet bağımlılığı, yeme bağımlılığı, alışveriş bağımlılığı ve iş bağımlılığı gibi davranışsal bağımlılıklar, işlevsellikte bozulma, tolerans ve çekilme, eşlik eden hastalıklar, nöronal yollar ve genetik arka plan dahil olmak üzere birçok noktada madde bağımlılıklarına benzemektedir. Bu alandaki nörobiyolojik araştırmalar henüz yeni olmakla birlikte, davranışsal bağımlılıklar biyokimyasal, radyolojik ve genetik özellikler açısından ele alındığında, madde kullanım bozuklukları ile güçlü nörobiyolojik ilişkiler ortaya çıkarmıştır. Literatürdeki çalışmaların çoğu kumar bağımlılığı ve internet bağımlılığı üzerine odaklanmış ancak diğer davranışsal bağımlılıkların da farklılıklarının yanı sıra benzer bazı yapısal değişikliklere de sahip oldukları gösterilmiştir. Davranışsal bağımlılıkları genetik ve nörobiyolojik yönleriyle tanımak ve anlamak, bu bozukluklara ilişkin farkındalığı artırmak, süreci daha iyi ele almak, önleme ve tedavi stratejileri geliştirmek açısından önemlidir. Bu yazıda, klinisyenler ve araştırmacılar tarafından son yıllarda daha fazla ilgi görmeye başlayan davranışsal bağımlılıkların nörobiyolojik ve genetik özellikleri ve ilişkili nörobiyolojik yollara ilişkin verileri gözden geçirmeyi amaçladık.

Anahtar kelimeler: Kumar oynama bozukluğu, internet bağımlılığı, yeme bağımlılığı, seks bağımlılığı, egzersiz bağımlılığı, kompulsif satın alma

Introduction

Addiction is defined as a “habitual impulse” to engage in a specific activity or drug abuse, which has undesirable results on an individual’s psychologic and physical health, social and financial status (1). The concept of behavioral addiction, on the other hand, includes an uncontrollable desire to exhibit a certain behavior and repeated pleasurable behavioral patterns, although

it harms the individual’s life (2,3). Behavioral addictions such as gambling disorder (GD), sex, digital game, exercise, internet, food, work and shopping addictions (compulsive buying) have become important public health problems. Among these disorders, only GD is classified in DSM -5, but other behavioral addictions have started to be encountered frequently in the psychiatric practice (4).



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Addictive drugs that are rewarding in nature reinforce dopamine (DA) system in the brain and increase DA release in the nucleus accumbens (NAc) which is an important part of reward neurocircuits along with the extended amygdala, hippocampus, ventral tegmental area (VTA), ventral striatum, mesolimbic dopaminergic pathway, and prefrontal cortex (5,6). DA is the most important neurotransmitter of this reward system. According to the reward deficiency hypothesis individuals who do not acquire enough satiety with natural rewards (water, food, sexuality) gravitate towards substances and behaviors to activate the reward pathway. DA receptor insufficiency creates a marked predisposition to impulsive and compulsive behaviors, alcohol and substance addiction, pathological gambling and addictive behaviors. Also, increased sensitivity to rewarding and reward seeking behaviors occurs. For example; internet use mimics the stimulation caused by alcohol and other substances with becoming a rapid reward with a short delay and providing more reward seeking and behavioral motivation (7).

Although neurobiological studies of behavioral addictions are relatively more recent than substance addiction researches, strong neurobiological associations has been demonstrated by biochemical, radioimaging, genetic and treatment studies between these disorders (8). Compulsive repetition of a problematic behavior, an appetizing impulse or urge before engaging in this act, diminished self-control, and a hedonic feature during the behavior are common key clinical features of behavioral and substance addictions (9). In addition, substance use disorders may often coexist with behavioral addictions. Comorbidity rates of gambling disorder with nicotine addiction have been reported as 70%, with alcohol addiction as 50-75% and with other substances this rate approaches 40% (10-13). In this review, we aimed to address the neurobiological and genetic aspects of behavioral addictions.

Gambling Disorder

Gambling disorder (GD) can be described as insistent, repetitive and uncontrolled gambling in a way that impairs psychosocial functionality (4). While the pathophysiology of GD has not been completely understood, there is broad concurrence that several phenotypes are involved such as; increased impulsivity, risky decision making, sensory seeking, compulsivity and reward sensitivity and also cognitive distortions (14,15).

Neurotransmitters

Stimulation of the DA transmission by drugs is a core feature of the reward system (16). While DA seems to be important in learning, motivation, emphasis and reward and lost processes, its role in GD continues to be investigated (17,18). Recent data assert that the differentiation of stimuli from D2, D3 and D4 receptors may explain the role of DA in the pathophysiology of

GD (19,20). 5-HT metabolite levels (5-hydroxyindolacetic acid (5-HIAA)) in cerebrospinal fluid was found to be decreased in GD, and dysregulation in serotonergic functions in gamblers may be associated with impulsivity and inhibition of behavior (21-23). The decrease in platelet monoamine oxidase (MAO) activity, which is an indicator of biological susceptibility for impulsivity, is another evidence for serotonergic dysfunction in GD (24-26). Serotonin 1B receptor is also related with GD severity (27,28).

Neuroimaging

Neuroimaging studies have shown dysfunctionalities in different areas of the brain in GD, although they focus especially on frontal and striatal zones (29-31). Among GDs both an increase and a decrease in ventromedial prefrontal cortex (vmPFC) activity have been reported during gambling and decision-making tasks compared to control group (32-36). Deterioration in frontal lobe function has been reported in patients with GD, and gambling behavior can be seen in patients with bilateral vmPFC lesions. (37, 38). Steady diversions in key node in neural circuit, including striatum, medial prefrontal cortex, amygdala, and insula have observed shown by functional magnetic resonance imaging (fMRI) during reward processing and decision-making tasks in patients with GD. Nevertheless, several studies have shown hypoactivity of this system while others have shown hyperactivity (32,39-41).

Genetics

In twin studies, it has been shown that genetic factors contribute more than environmental factors in the development of GD, and the prevalence of GD in first-degree relatives of individuals with GD was found to be 20% (42-45). These studies also revealed common genetic risk factors for GD and alcohol abuse (46).

An increase in A1 allele at the D2 receptor of DA (DRD2) locus was found in gamblers (47). Genetic polymorphisms related to DA transmission was shown to be related with irregular gambling (48, 49). Other studies highlights allelic variants such as; 5HTTLPR and MAO-A in 5-HT transmission genes in GD (50,51). Also, polymorphisms in several genes, including DRD3, DRD4, HTR2A, and COMT have been shown in patients with GD (25,50,52-55).

Internet Addiction

Internet addiction is defined as having difficulty to control the use of the internet, spending more time on the internet, the loss of importance of time spent without using the internet, the emergence of excessive irritability, tension, anxiety when couldn't access internet and deterioration in the individual's work, social and family life (56).

Neurotransmitters

In internet addiction disorder (IAD) autonomic nervous system

(ANS) is activated, heart rate and breathing accelerate and peripheral temperature decreases (57). Serum cortisol levels were found to be considerably high in adolescents with IAD (58). A decrease in plasma catecholamine levels such as; adrenaline and noradrenaline can be seen in adolescents with online game addiction at resting state (59). The peripheral blood DA levels are related to IAD in adolescents. (60). Increased anxiety and low peripheral blood norepinephrine levels was found to be associated with IAD (61).

Neuroimaging

Many imaging studies have shown some important changes in neural structure in IAD, mainly reduction in gray matter volume and changes in white-matter density (62). IAD was also found to be associated with thickening of the left anterior central cortex, middle frontal cortex, middle temporal cortex, infratemporal cortex, as well as slimming of the left lateral orbitofrontal cortex, insular cortex and entorhinal cortex (63,64). Strengthening functional connections between the bilateral posterior lobes of the cerebellum and the middle temporal gyrus, but also, weakening of the connections between the bilateral lower parietal lobes and the right lower temporal gyrus have been reported (65).

Glucose metabolism decreases in the prefrontal and temporal cortices and limbic systems, and also dysregulation of D2 receptors in the striatum have been observed in digital gamers as a result of overuse for many years (66). Money making activates orbitofrontal cortex and losses decrease the activation of cingulate cortex in internet addicts (67).

In a PET study by Kim et al., researchers have shown a decrease in DA D2 receptor levels in the caudate nucleus and putamen regions, in adult males with internet addiction (68). Likewise, reduced dopamine transporter levels in the striatum have been demonstrated in a single photon emission computed tomography (SPECT) study in internet addicts (69). In fMRI studies, activation of right prefrontal cortex, right NAc, medial frontal cortex and right caudate nucleus was observed while showing game pictures and paired images to individuals with internet gaming addiction (70-73). Resting state cerebral perfusion in parahippocampal gyrus, amygdala and insula is also found substantially high (74).

In conclusion, structural and functional alterations mainly in the orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, and posterior cingulate cortex were observed IAD (75). These brain regions are especially associated with reward, motivation, memory, and cognitive control.

Genetics

There are a few studies on the genetics of IAD. It has been shown that the genetic transition of internet addiction is around 48-66% when unshared environmental factors are excluded (76).

In a Korean study, excessive internet users was found to have a higher frequency of homozygous short allelic variant of the 5-HT transporter gene as in patients with major depression and also genetic and personality traits were found similar (77). Polymorphism in the nicotinic acetylcholine receptor gene is significantly frequent in internet addicts (78).

Food Addiction

Food addiction (FA) is defined as the frequent and abnormal consumption of some "extremely tasty" foods rich in high calories and glucose and the difficulty of controlling eating behavior (79). Repeated binge eating periods, increased binge eating after relative restriction of eating, loss of control overeating, consuming high-calorie foods, negative affect, and emotional lability are recommended criteria for FA, although there is no consensus (80).

Neurotransmitters

Natural rewarding stimuli such as water and food are also associated with significant synaptic changes in the mesolimbic DA system, as similar with the rewarding effects of psychostimulants and other abusive drugs (81,82). Recent evidence suggests that compulsive eating behaviors and obesity influence the brain's reward circuit, particularly circuits of dopaminergic neural substrates as in substance use disorder. Increasing genetic and imaging data on addiction has indicated that obese individuals and substance addicts can show alterations in expression of DA D2 receptors in certain brain regions which can be stimulated by food and drugs (83).

In a study showing that striatal DA D2 receptors were significantly low in obese individuals compared to healthy controls, and body mass index (BMI) and D2 receptors were negatively correlated, it has been suggested that obese individuals continue pathological eating to compensate for DA deficiency and decrease in activation of motivation and reward circuits (84).

In obese mice down-regulation of striatal DA D2 receptors has been found similar to individuals with substance use disorder. Moreover, in rats with access to delicious high-fat foods, lentivirus-mediated destruction of striatal DA D2 receptors was found to accelerate compulsive foraging and the development of reward deficits as in addiction disorders. These data assert that excessive consumption of tasty food triggers neuroadaptive reactions as in addiction and compulsive eating, FA and substance addiction may share common hedonic mechanisms (85).

Neuroimaging

The ventromedial prefrontal cortex, ventral striatum, amygdala, anterior insula, and mediodorsal thalamus are responsible for monetary, sexual and eating habits (86). Hippocampus which is found to be associated with obesity is stimulated by craving,

hunger, and tasting (87,88). Reduced DA D2 receptor activity in ventral striatum have identified in PET studies and also food addiction is found to be partially associated with ventral striatum activity (5) (89).

Genetics

Reduced DA D2 receptor density have been found in individuals with A1 allele as in addiction disorders and obesity and a relatively high degree of reward sensitivity has been detected in obese patients carrying the A1 allele (90). In a study showing multilocus polymorphism of the DA D2 receptor gene and the mu-opioid receptor (OPRM1) gene, it was emphasized that individuals with binge eating disorder had higher scores in hedonic eating scales, and binge eating disorder is a biologically based obesity subtype (91).

Sex Addiction/Compulsive Sexual Behaviour

Sexual addiction (SA), that is also named as sexual impulsivity or hypersexuality, is expressed by abnormal sexual desire, urge or behaviors and having difficulty to control these drives and behaviors. (92,93). The major symptoms are compulsive masturbation, excessive use of pornography or sexual webcam, repetitive seeking behavior of different sexual partner, and/or compulsive sex with a constant partner (94,95).

Although there is no consensus on the conceptualization of SA, extensive criteria used to identify the disorder includes (a) increased time and effort devoted to sexual activity; (b) destruction of self-control; (c) spending less time on responsibilities; and (d) persistence in these sexual acts despite the negative outcomes. Tolerance, withdrawal and craving are common symptoms for SA and other addiction disorders (96,97).

Neurotransmitters

Preliminary results show that dopamine might contribute to the pathogenesis of compulsive sexual behavior (CSB). Dopamine agonists and other DA replacement therapies that used in Parkinson's disease (PD), increase the risk of having CSB (98). Naltrexone as an opioid antagonist has been found to be effective in alleviating excessive sexual impulses and behaviors, which is consistent with potential opioidergic alterations of mesolimbic DA function (99). Results of a study in which citalopram was superior to placebo in the treatment of CSB in homosexual men supports serotonergic dysfunction in CSB (91).

Neuroimaging

In a diffusion tensor imaging study mean diffusivity of superior frontal region was found considerably high in patients with CSB compared to controls (100). Activation of the dorsal anterior cingulate, amygdala, and also ventral striatum have shown by fMRI in CSB patients by sexual stimuli (101). Exposure to

pornographic cues has been found to increase the sexual desire in PD patients with hypersexuality, and activate the ventral striatum, cingulate cortex and orbitofrontal cortex (102). Increased time spent watching pornography among healthy men has been associated with left putaminal activity (103).

Subjects with CSB have shown higher amplitudes of the P300 response in attention control when subjected to sexual images compared to neutral images. (104). In a study evaluating responses to sexually stimuli, sexual desire was found to be associated with dorsal anterior cingulate activity, and substantia nigra activity increased in patients with CSB as a result of dopaminergic activity (101).

While erotic rewards and food have been associated with the anterior insular activity, amygdala activity was found to be more specifically related to erotic rewards. A recent study showed that the longer consumption of pornography was associated with left putaminal activity in healthy men (103). When hypersexuality is observed in behavioral variant frontotemporal dementia, the right ventral putamen and pallidum atrophy can be seen in correlation with reward seeking scores (105). In addition, in a case report of CSB, a partial increase in blood flow in the mesial temporal regions was observed on SPECT images (106).

Genetics

Limited evidence suggests that the majority of subjects with CSB had first-degree relatives with CSB or substance use disorder (107). It has been found that DA D2 receptor allele was found to be associated with first sexual intercourse age, and a stronger relationship observed when the DA D2 receptor interacted with the DA D1 receptor. (108). Specifically, across all ethnicities, polymorphism analyzes in DA D4 receptor have shown that age of first sexual intercourse is higher in those with any - 3R genotype than any other (109). Human leukocyte antigen (HLA) alleles were analyzed in Klein level syndrome, which is often accompanied by hypersexuality, and a significant amount of immunoresponsive HLA-DQB1, DQB1 * 0602, was detected (110).

Compulsive Buying/Shopping Addiction

People often turn to compulsive purchases in order to cope with daily stresses and create a positive impact. Compulsive buying or shopping addiction is described as the repetitive and excessive purchase of unnecessary consumer products. Compulsive buyers often describe short-term satisfaction and mood alterations. But this behavior can often causes large debts, negative comments from social environment, guilt and psychological stress, resulting in negative effects on self-esteem and comfort of life (111,112).

Neurotransmitters

There is an imbalance between overstimulated urge state and deterioration of frontal inhibition, and impairment in reward

system. An exaggerated state of craving and urge is observed due to changes in DA systems which is related with reward and reinforcement. Endogenous opioids lead to alterations in impulse control through working on reward, pleasure, and pain. There is also a decrease in peripheral 5-HT markers due to insufficiency of 5-HT system, that results in disinhibition (8).

Addiction-like behaviors such as hoarding or compulsive buying may be associated with high stress levels and the cumulative effects of neurotransmitters genetic variants, particularly DA. Therefore, when outcomes of dopaminergic activation are unsatisfying with agonist therapy, DA homeostasis can be targetted in treating these undesirable behaviors (113). Some reports suggest that hyperdopaminergic states are observed in impulsive hoarding behavior, such as shopping addiction, and the blockage of D2 receptors may improve the condition (114). In a study by Kelley and Stinus, it was shown that when 6-hydroxydopamine lesions were seen in mesolimbic DA neurons, the hoarding behavior disappeared in rats, and was restored when L-Dopa was administered (115). In compulsive shopping neurotransmitter activity was found to be low and positive results were obtained with citalopram treatment. These results suggested possible serotonergic dysfunction in compulsive shopping (116,117).

Neuroimaging

Remarkable differences were found in fMRI in the activity of cortical and subcortical areas related to decision-making between compulsive buyers and the healthy controls (118). Evidence from neuroimaging studies shows that gain and loss are determined by different brain circuits; while the insula is activated by high prices before the decision of purchase, the mesial prefrontal cortex is deactivated, and product preference is related with the NAc (119).

Several different cognitive domains were shown to support a possible neurobiological overlap between other behavioral and substance addictions to shopping addiction. Compared to healthy controls, individuals with compulsive buying appear to have deterioration in spatial working memory, response inhibition and risk assessment during decision-making (120). In a case report with substance use disorder, the addition of a pro-dopamine compound KB200z to the treatment regimen significantly reduced stacking and shopping behaviors (113).

Genetics

There is not much data in the literature regarding the genetic basis of compulsive buying. The psychiatric disease comorbidity is high in compulsive buyers and their first degree relatives than healthy controls (121). In a study consist of 21 patients diagnosed with compulsive buying, deletion of 44-base pair (bp) was found in the promoter region of 5-HT transporter gene (122).

Exercise Addiction/Compulsive Exercise

Exercise addiction is defined as having difficulty in controlling exercise habits, spending more time for exercising and increasing frequency and intensity of exercise, inability to fulfill responsibilities due to exercise and exercising instead of spending time with family and friends and having troubles in planning the social life, other interests due to daily exercise routine (123,124).

Neurotransmitters

Dopamine release increases in the hypothalamus with continuous aerobic exercise and in the dorsal striatum with running, and exercise also increases norepinephrine in the hypothalamus (125,126). It is known that endogenous opioid system is one of the key factors in addictive disorders. Desire to increase β -endorphin levels through excessive exercise might be a potential mechanism leading to exercise addiction (127). Human and animal tests have pointed that aerobic exercise can improve many aspects of cognition and performance (128). It has been claimed that physical activity improves brain functions and cognition, and thus have protective effects against the neurodegenerative diseases (129). Physical activity has constructive effects on learning and memory by increasing advanced adult hippocampal neurogenesis and synaptic plasticity (130). It was shown that the effect of voluntary exercise reduced the exploratory and aggressive behavior in the spontaneously hypertensive rats and a sudden break on exercise leads to withdrawal reaction (131). The frequently mentioned molecular mechanism underlying structural and functional recovery of the brain in exercising animals is stimulation of hippocampal neurogenesis and BDNF expression (132,133). In addition, a dramatic increase in cell proliferation and cognitive functions has been detected (134,135). Another study assert that glutamatergic system modulates hippocampal volume and function through physical activity, but the mechanisms underlying this condition have not been clearly identified (136).

Neuroimaging

Running was shown to mediate the expression of ionotropic glutamate receptors in the subdivisions of rat hippocampus and it was considered to alter synaptic activity of hippocampus and thus have behavioral consequences (137). The exercising rats had 18% lower DA D1 receptor binding levels in the olfactory tubercle and 21% lower in the nucleus accumulators, compared to sedentary rats. In line with these findings, it can be claimed that aerobic exercise may cause alterations in the mesolimbic pathway and so drug-seeking behavior will decrease (138). Apart from these studies, cell proliferation in the hippocampus, which was low in 'depressed' rats, increased after 5 weeks of running. Therefore, it has been stated that repression of cell proliferation in the hippocampus may predispose to depression and exercise

can be an effective in treatment (139).

Genetics

It has been suggested that some rodents with a predisposition to addictive drugs may show different preferences in running wheel exercise in crossbreds (140). It was observed that Lewis rats prone to addiction, developed a higher running activity than Fischer rats when given free access to running wheels, and were able to run up to 10 km / day after two weeks (141). Genetic studies suggest that naturally rewarding stimuli such as exercise are also controlled by genes that control drug preference, and moreover, considering the antidepressant efficacy of running, genes are assumed to be responsible for the neurochemical effects of running. (142).

Conclusion

Neurobiological similarities between substance addiction and behavioral addictions are well known. In this paper, we reviewed both the structural and biological changes in the brain and genetic studies with current studies in behavioral addictions. The effects of 5-HT, DA, NA and opioid systems and especially the reward system is emphasized on pathophysiology of behavioral addictions in literature. Similar to substance addiction, cortical and subcortical areas such as prefrontal cortex, nucleus accumbens, ventral tegmental area, amygdala, and hippocampus are also affected in behavioral addictions. In addition, genetic studies show that behavioral addictions are associated with some similar gene regions, although there are not many. Although only pathological gambling is included in the DSM-5 among behavioral addictions, we think that understanding the neurobiology of behavioral addictions will be important to develop prevention and treatment strategies.

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