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New Developments on the Neurobiological and Pharmaco-Genetic Mechanisms Underlying Internet and Videogame Addiction

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Background: There is emerging evidence that the psychobiological mechanisms underlying behavioral addictions such as internet and videogame addiction resemble those of addiction for substances of abuse.
Objectives: Review of brain imaging, treatment and genetic studies on videogame and internet addiction.
Methods: Literature search of published articles between 2009 and 2013 in Pubmed using "internet addiction" and "videogame addiction" as the search word. Twenty-nine studies have been selected and evaluated under the criteria of brain imaging, treatment, and genetics.
Results: Brain imaging studies of the resting state have shown that long-term internet game playing affected brain regions responsible for reward, impulse control and sensory-motor coordination. Brain activation studies have shown that videogame playing involved changes in reward and loss of control and that gaming pictures have activated regions similarly to those activated by cue-exposure to drugs. Structural studies have shown alterations in the volume of the ventral striatum possible as result of changes in reward. Furthermore, videogame playing was associated with dopamine release similar in magnitude to those of drugs of abuse and that there were faulty inhibitory control and reward mechanisms videogame addicted individuals. Finally, treatment studies using fMRI have shown reduction in craving for videogames and reduced associated brain activity.
Conclusions and Scientific Significance: Videogame playing may be supported by similar neural mechanisms underlying drug abuse. Similar to drug and alcohol abuse, internet addiction results in sub-sensitivity of dopamine reward mechanisms. Given the fact that this research is in its early stage it is premature to conclude that internet addiction is equivalent to substance addictions. (Am J Addict 2015;24:117–125)

INTRODUCTION

Problematic internet use (PIU) or excessive internet use is characterized by excessive or poorly controlled preoccupations, urges or behaviors regarding computer use and internet access that lead to impairment or distress. There is no diagnosis of internet addiction although it has been proposed for inclusion in the next version of the diagnostic and statistical manual of mental disorder (DSM-V) that has been recently released[1] (see Ref.[2] for review). Surveys in the US and Europe have indicated prevalence of between 1.5% and 8.2%, with varying diagnosis methods between countries (see also Ref.[3]). Cross-sectional studies on samples of patients report high co-morbidity of internet addiction with psychiatric disorders, especially affective disorders (including depression), anxiety disorders (generalized anxiety disorder, social anxiety disorder), and attention deficit hyperactivity disorder (ADHD).[2,4–8] Several factors are predictive of PIU, including personality traits, parenting and familial factors, alcohol use, and social anxiety. The few published treatment studies for internet addiction are based on interventions and strategies used in the treatment of substance use disorders. Limitations include problems in diagnosis, lack of randomization and blinding techniques, lack of adequate control, insufficient information on treatment procedures (see Refs.[9,10]). Thus, it is premature to recommend any evidence-based treatment of internet addiction although preliminary results of psychological and pharmacological interventions seem promising.

Recently, several reviews have described the resemblance between the neural mechanisms underlying drug and alcohol abuse and internet and videogame addiction.[11,12] This review will describe new developments in the psychobiology of internet and videogame addiction in particular the association between brain imaging, mechanisms of addiction, treatment, and pharmaco-genetic studies. It will first describe the different types of imaging studies (resting state, structural and activation studies, dopamine receptor and transporter imaging). Secondly, it will describe how brain imaging studies are related to specific neuropsychological mechanisms of addiction (reward, decision making loss of control). Finally, it will address issues such as pharmaco-genetic studies[13,14] and brain imaging

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studies that assess pharmacological treatment[15,16] of internet addiction (Fig. 1).

There are different questionnaires assessing internet addiction and different terminologies are being used to describe internet addiction, videogame addiction and videogame users (for review see Ref.[2]). In this review we rely on measures used in each study to define internet and videogame addiction. PIU or addiction is characterized by excessive or poorly controlled preoccupations, urges or behaviors regarding internet use that lead to impairment or distress. Internet addiction includes three major components: communication (email, texting) gaming, and cybersex. Videogame and computer game addiction are regarded as a component of internet addiction.

The terms “internet-addicted,” “dependent individuals,” or “internet addiction disorder” refer to internet addiction. The term videogame addiction is excessive or compulsive use of computer and video games that may interfere with daily life. The terms “videogame-addicted,” “videogame-dependent subjects,” “excessive videogame users” are utilized to describe individuals with video-game addiction. The terms “excessive Internet game use” and “internet gaming addiction” refer to videogame addiction that is played online on the internet.

Literature search of published articles between 2009 and 2013 was performed in Pubmed using “internet addiction” and “videogame addiction” as search words. Twenty-nine studies have been selected and evaluated under the criteria of brain imaging, treatment, and genetics. The choice of the dates (2009–2013) was made since this review is an update of our previous review in 2010.[2]

BRAIN IMAGING STUDIES OF THE RESTING STATE

Excessive internet game use was shown to be associated with abnormal neurobiological mechanisms in the orbitofrontal cortex (OFC), striatum, and sensory regions, which are implicated in impulse control, reward processing, and somatic representation of previous experiences in a study measuring regional cerebral metabolic rates of glucose in positron emission tomography (PET) in normal and excessive internet game users.[17] Excessive internet game users also showed greater impulsiveness than control users and there was a positive correlation between the severity of excessive Internet game use and impulsiveness. Internet game overuse seems to share psychological and neural mechanisms with other types of impulse control disorders and substance-related addiction suggesting an impulse control disorder.[17] Internet game addicted (IGA) subjects also showed enhanced regional homogeneity (ReHo) in the brainstem, inferior parietal lobule, left posterior cerebellum, and left middle frontal gyrus that are related with sensory-motor coordination in a functional magnetic resonance (fMRI) study.[18] In addition, IGA subjects showed decreased ReHo in temporal, occipital and parietal brain regions that are responsible for visual and auditory functions. It was suggested that long-time online game playing

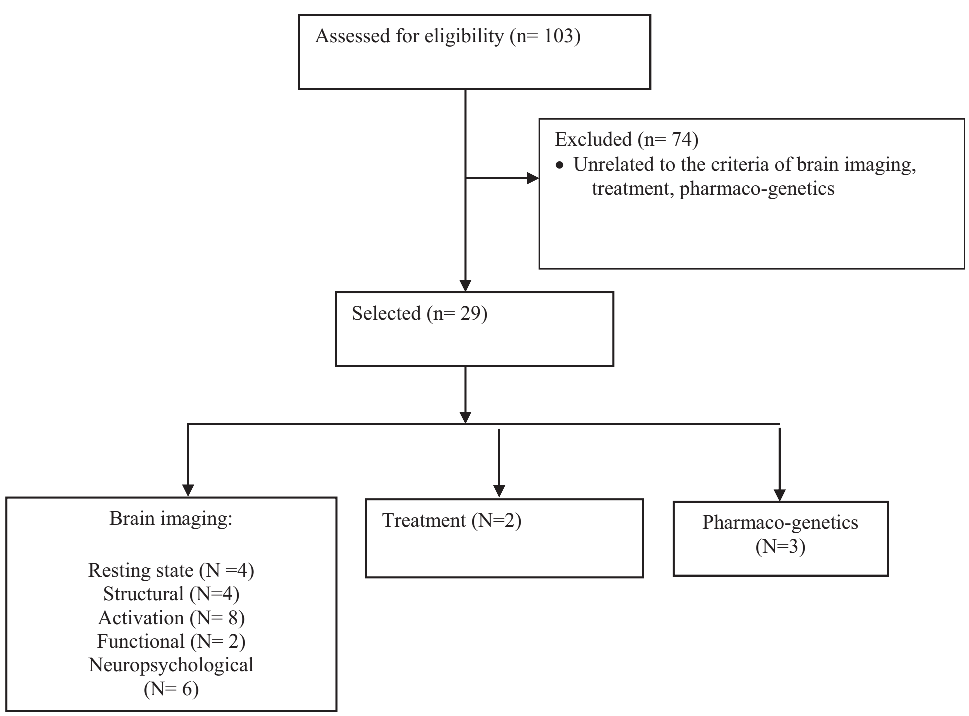

FIGURE 1. A flowchart.

enhanced the brain synchronization in sensory-motor coordination related brain regions and decreased the excitability in visual and auditory related brain regions. Finally, l ReHo was increased in several brain regions in internet-addiction disorder (IAD) subjects in an fMRI study.[19] Increased activity has been shown in areas including the cerebellum, brainstem, right cingulate gyrus, bilateral parahippocampus, right frontal lobe (rectal gyrus, inferior frontal gyrus, and middle frontal gyrus), left superior frontal gyrus, left precuneus, right postcentral gyrus, right middle occipital gyrus, right inferior temporal gyrus, left superior temporal gyrus and middle temporal gyrus, possibly reflecting the functional change of brain in internet-dependent users. The connections between the enhancement of synchronization among cerebellum, brainstem, limbic lobe and the frontal lobe may be relative to reward pathways. This evidence is consistent with activation studies in drug and alcohol addiction[20–27] and may have clinical implications for the brain's reward mechanisms.

Finally, functional connectivity among adolescents with internet addiction using fMRI was reported.[28] Functional magnetic resonance images were taken in adolescents with internet addiction and control subjects in a resting state. Adolescents with internet addiction showed reduced functional connectivity in a network of cortico-subcortical circuits including the prefrontal and parietal cortex. Bilateral putamen was the most extensively involved subcortical brain region. The results imply that internet addiction is associated with a widespread and significant decrease of functional connectivity in cortico-striatal circuits, in the absence of global changes in brain functional network topology which may impair cognitive function in adolescents with internet addiction. Taken altogether studies of the resting state in PET and fMRI have shown increased connectivity in areas associated with reward and sensory-motor coordination whereas the study of functional connectivity in adolescents shows a reduction in functional connectivity in cortco-striatal circuits.[28] The inconsistency between the results of adult IAD subjects who showed enhanced frontal-limbic connectivity in adults IAD subjects and reduced functional connectivity in cortico-striatal regions may be due to difference between the two subject populations.

STRUCTURAL STUDIES ON THE NEURAL BASIS OF VIDEOGAME PLAYING

A comparison of changes in gray matter density (GMD) in an adolescent internet addicted group and control subjects showed lower GMD in the left anterior cingulate cortex, left posterior cingulate cortex, left insula, and left lingual gyrus in the addicted group.[29] Furthermore, participants with on-line internet game addiction showed increased impulsiveness and perseverative errors, and volume in left thalamus gray matter, but decreased gray matter volume in inferior temporal gyri, right middle occipital gyrus, and left inferior occipital gyrus compared with control subjects in an fMRI study.[30] A third group of pro-gamers (frequent game players) showed increased gray matter volume in left cingulate gyrus, but decreased gray matter volume in left middle occipital gyrus and right inferior temporal gyrus compared with healthy control subjects. Additionally, pro-gamers showed increased gray matter volume in left cingulate gyrus and decreased left thalamus gray matter volume compared with the patients with online-game addiction. Increased gray matter volumes of the left cingulate gyrus in pro-gamers and of the left thalamus in subjects with online game addiction may contribute to the different clinical characteristics of pro-gamers and online game addicted individuals namely increased impulsiveness and making preservative errors which are also typical of drug and alcohol dependent individuals.[31] The brain areas of the cingulate gyrus and thalamus are also associated with long-term effects of drug abuse.[32] It should be noted that the authors used the term pro-gamers which refers to extensive on-line game playing, professional gamers (pro-gamers), who do not meet criteria for addiction.

Alterations in gray matter which is a major component of the central nervous system may affect motor control, perception, memory and emotions. The regions reported in videogame addiction namely the dorsolateral prefrontal cortex (DLPFC), the orbito-frontal cortex, the cerebellum and anterior cingulate have been previously associated with brain responses to drug-related cues[20–27] thus supporting the notion that videogame addiction may affect similar regions to drug addiction.

Brain white matter integrity was investigated using diffusion tensor imaging (DTI) in adolescents with IAD.[33] Whole brain voxel-wise analysis of fractional anisotropy (FA) was performed by tract-based spatial statistics (TBSS) to localize abnormal white matter regions between IAD and healthy control subjects. TBSS demonstrated that IAD had significantly lower FA than control subjects throughout the brain, including the orbito-frontal white matter, corpus callosum, cingulum, inferior fronto-occipital fasciculus, and corona radiation, internal and external capsules, while exhibiting no areas of higher FA. Volume-of-interest (VOI) analysis was used to detect changes of diffusion in the regions showing FA abnormalities. Negative correlations were found between FA values in the left genu of the corpus callosum and the Screen for Child Anxiety Related Emotional Disorders,[34] and between FA values in the left external capsule and the Young's Internet addiction scale. The findings suggest widespread reductions of FA in major white matter pathways and such abnormal white matter structure may be linked to the clinical characteristics of anxiety and internet addiction. Brain regions such as the orbito-frontal region and the cingulate have been associated with drug addiction[32] whereas other regions reported in this study such as the corpus callosum were not previously associated with drug addiction.

Finally, a single study investigated the effects of internet addiction on the microstructural integrity of major neuronal fiber pathways.[35] An optimized voxel-based morphometry (VBM) technique used to measure white matter FA changes using the DTI method, linking these brain structural measures to the duration of internet addiction. Multiple structural changes of the brain were found such as decreased gray matter volume in the bilateral DLPFC, the supplementary motor area (SMA), the OFC, the cerebellum and the left rostral ACC (rACC) in internet addicted subjects. DTI analysis revealed the enhanced FA value of the left posterior limb of the internal capsule (PLIC) and reduced FA value in the white matter within the right parahippocampal gyrus (PHG). Gray matter volumes of the DLPFC, rACC, SMA, and white matter FA changes of the PLIC were significantly correlated with the duration of internet addiction in the adolescents with IAD. The regions reported in this study namely the DLPFC, the orbito-frontal cortex, the cerebellum and anterior cingulate have been enhanced in the resting state and were previously associated with activation of drug-related cues,[20–27] thus supporting the notion that videogame addiction may be associated with similar regions related to drug addiction. Other regions are not altered in the resting state or by prolonged drug use and these are presumably changed as result of cognitive-motor function which is specific to playing videogames such as sensory-motor areas (SMA and thalamus), vision (occipital lobe), memory (temporal lobe) and attention (cingulate cortex).

Structural changes of gray and white matter integrity assess different structures than those assessed by studies of the resting state. This may explain why some of the areas that showed decreased volume were also associated with changes in the resting or active state of the brain in videogame users whereas other areas were not. The discrepancy in the findings possibly reflects long-term structural changes in areas that are associated with cognitive-motor function in videogame addiction for example sensory-motor areas (SMA and thalamus), vision (occipital lobe), memory (temporal lobe) and attention (cingulate cortex).

It is interesting to note that unlike the findings of gray matter differences found in internet addiction, pathological gamblers have been shown to have no changes in regional gray matter volumes[36] whereas GMD differences have been shown in internet addiction.

BRAIN IMAGING STUDIES—ACTIVATION STUDIES OF VIDEOGAME URGES

The first activation study in videogame dependent subjects has used an fMRI procedure to measure brain activation contrasting a space-infringement game with a control task.[37] Males showed greater activation and functional connectivity compared to females in the meso-cortico-limbic system. These findings may be attributable to higher motivational states in males, as well as gender differences in reward prediction, learning reward values, and cognitive state during computer video game playing. These gender differences may help explain why males are more attracted to, and more likely to become "hooked" on video games.[37] The following study[38] has shown gaming pictures and neutral pictures to 10 participants with internet gaming addiction and 10 control subjects without internet gaming addiction together with fMRI scanning. The right OFC, right nucleus accumbens, bilateral anterior cingulate and medial frontal cortex, right DLPFC, and right caudate nucleus were activated in the dependent group. The activation of the region-of-interest (ROI) defined by the above brain areas was positively correlated with self-reported gaming urges and recalling of gaming experience provoked by the gaming pictures. The neural substrate of cue-induced gaming urge/craving in online gaming addiction (namely the nucleus accumbens, caudate, anterior cingulate, medial frontal cortex and dorso-lateral prefrontal cortex) is therefore similar to that of the cue-induced craving in substance dependence.[20–27]

Since then, several studies have followed changes in cue-induced brain activity in internet videogame players. Responses to Internet video-game cues in brain activity particularly within the orbitofrontal and cingulate cortices with videogame play were measured.[39] They have followed changes in brain activity between baseline and following 6 weeks of Internet video-game play using 3T blood oxygen level dependent fMRI imaging. During a standardized 6-week video-game play period, brain activity in the anterior cingulate and OFC of the excessive Internet game-playing group but not in the control group, increased in response to Internet video-game cues. In addition, the change of craving for Internet video games was positively correlated with the change in activity of the anterior cingulate in all subjects. These changes in frontal-lobe activity with extended video-game play may be similar to those observed during the early stages of addiction.[40] Brain activity correlated with craving during cue exposure in subjects with internet gaming addiction.[41] Bilateral DLPFC, precuneus, left parahippocampus, posterior cingulate and right anterior cingulate were activated in response to gaming cues in the Internet Game addiction group. These regions were previously activated in drug dependent users in response to drug cues.[20–27] Their ROI was also positively correlated with subjective gaming urge during cue exposure. Furthermore, the IGA group had stronger activation over right DLPFC and left parahippocampus than did the remission group. The novelty of this study is the use of remitted former internet addicted-individuals as control subjects showing that areas that were activated in the current users were no longer activated in the remitted group.

Positive motivational implicit response to Internet gaming cues (ie, screenshots of popular online games) was measured using an implicit association task to test their reaction to congruent pairing and incongruent pairing.[42] The internet dependent group reacted faster to congruent pairing possibly due to implicit response to screenshots of internet game dependent group. The brain correlates of cue-induced gaming urge or smoking craving in subjects with both IGA group and nicotine dependence were compared.[43] All subjects underwent 3-T fMRIs scans while viewing images associated with online games, smoking, and neutral images, which were arranged according to an event-related design. The anterior cingulate and the parahippocampus were activated in both cue-induced gaming urge and smoking craving among the comorbid group in comparison to the control group. Both IGA and nicotine dependence seem to share similar mechanisms of cue-induced reactivity of the fronto-limbic network, particularly for the parahippocampus.[44–46]

A study that investigated desire for videogame playing cues compared participants who are non-video-game-addicts to frequent videogame players.[47] The non-addicted players played a novel internet videogame for 10 days and were scanned in fMRI. They showed greater activity in the left inferior frontal gyrus, left PHG, right and left parietal lobe, right and left thalamus, and right cerebellum. Self-reported desire for playing was positively correlated with activity in the left inferior frontal gyrus, left PHG, and right and left thalamus. Frequent internet video game players showed greater activity in right medial frontal lobe, right and left frontal pre-central gyrus, right parietal post-central gyrus, right PHG, and left parietal precuneus gyrus. Controlling for total game time, reported desire for the internet video game in frequent players was positively correlated with activation in right medial frontal lobe and right PHG. It is being suggested that cue-induced activation to internet video game stimuli may be similar to that observed during cue presentation in persons with substance dependence or pathological gambling.[20–27] In particular, cues appear to commonly elicit activity in the dorsolateral prefrontal, OFC, PHG, and the thalamus. Finally, an activation study used the World of Warcraft game figures with fMRI in internet game addicts.[48] The study showed that the DLPFC, bilateral temporal cortex, cerebellum, right inferior parietal lobule, right cuneus, right hippocampus, PHG and the left caudate nucleus were activated in online game addicts. Craving measures were positively associated with activity in the bilateral prefrontal cortex, anterior cingulate cortex and right inferior parietal lobe. These brain regions were shown to be mediating cognitive, emotion and motivation-related function associated with drug addiction and craving.[20–27]

STUDIES ON DOPAMINE BRAIN MECHANISMS IN INTERNET ADDICTION

Consistent with the evidence that internet and videogame addiction would be associated with deficient dopamine reward activity, it was investigated whether internet addiction would be associated with reduced levels of dopaminergic receptor availability in the striatum.[49] They have used the radiolabeled ligand [^{11}C] raclopride and PET to assess dopamine D_2 receptor binding potential in men with and without Internet addiction. Reduced levels of dopamine D_2 receptor availability in subdivisions of the striatum including the bilateral dorsal caudate and right putamen was found in the addicted subjects, thus contributing to the hypothesis of deficient dopamine reward mechanisms in internet addiction. To test whether there is dopamine deficiency at the pre-synaptic level, another study measured striatal dopamine transporter (DAT) levels by (99m) Tc-TRODAT-1 single photon emission computed tomography (SPECT) in individuals with IAD.[50] DAT expression level of the striatum was significantly decreased and the volume, weight and whole brain were greatly reduced in individuals with IAD compared with control subjects. Taken together, these results suggest that IAD is associated with dysfunctions in the dopaminergic brain systems. These findings also support the claim that IAD may share similar neurobiological abnormalities with other addictive disorders.[32]

NEUROPSYCHOLOGICAL IMAGING STUDIES ON REWARD, INHIBITORY CONTROL, AND DECISION MAKING

Drug addiction is characterized with dysfunctional reward mechanisms, inhibitory control mechanisms and faulty decision making processes.[51,52] Several studies have investigated these processes together with brain-imaging in videogame dependent individuals.[53–55] A structural study using fMRI with the monetary incentive delay (MID) task and the Cambridge gambling task (CGT) showed higher left striatal gray matter volume in frequent compared with non-frequent video game players. The left striatal gray matter volume was negatively correlated with deliberation time in CGT.[53] Within the same region, activity on the MID task was enhanced in frequent compared with infrequent video game players during feedback of loss compared with no loss. This activity was also negatively correlated with deliberation time on the task. An association of video game playing with higher left ventral striatum volume could therefore reflect altered reward processing and represent adaptive neural plasticity similar to the alterations seen in drug dependence. It should be noted that the authors did not attempt to distinguish whether their participants played their games online or offline. Therefore, many of the participants are likely to be offline game players and are not related to Internet use or addiction.

It has been suggested that similarly to substance and alcohol abuse, internet, and videogame addicted individuals may display faulty inhibitory control mechanisms. Response inhibition on a Go/No Go task was measured in people with Internet addiction together with recording of event-related brain potentials (ERPs).[56] The IAD group exhibited lower NoGo-N2 amplitude, higher NoGo-P3 amplitude, and longer NoGo-P3 peak latency than the normal group. The results also suggested that the internet addiction group had lower activation in the conflict detection stage than the normal group; thus, they had to engage in more cognitive endeavors to complete the inhibition task in the late stage. In addition, the internet addiction group showed less efficiency in information processing and lower impulse control than their normal peers. The executive control ability of male students with Internet addiction was investigated by recording ERP during a color-word Stroop task.[57] Longer reaction time and more response errors in incongruent conditions were shown in the addicted group. Participants with IAD also showed reduced medial frontal negativity (MFN) deflection in incongruent conditions than the control group. Taken altogether, people with internet addiction showed impaired executive control ability compared with the control group. Finally, the neural correlates of response inhibition in males with and without internet addiction were measured using an event-related fMRI and the Stroop task.[54] Greater "Stroop effect"-related activity in the anterior and posterior cingulate cortices was shown in the addicted group. Diminished efficiency of response-inhibition processes in the IAD group was shown relative to healthy controls.

Behavioral addictions such as excessive internet videogame playing similarly to drug abusers are presumed to be associated with faulty decision making and preference for immediate reward to long-term gains (for review on impulsivity frontal lobe and drug addiction see Ref.[58]). Excessive World of Warcraft players and non-players who performed on the game of dice task (GDT) showed reduced decision making ability and higher psychological-psychiatric symptoms compared with control subjects.[55] Secondly, reward and punishment processing were measured in Internet addicted individuals while they subjectively experienced monetary gain and loss during the performance of a guessing task by Dong et al.[59] Increased activation in OFC in gain trials and decreased anterior cingulate activation in loss trials was shown in the addicted subjects, implicating enhanced reward sensitivity and decreased loss sensitivity. In conclusion, videogame dependent individuals manifest faulty reward, inhibitory control mechanisms and decision making which are associated with changes in neural mechanisms that are similar to drug dependent individuals.

PHARMACO-GENETIC STUDIES

There is plenty of research on the pharmaco-genetic mechanisms responsible for alcohol and drug abuse and several genes and polymorphisms have been suggested to be involved in the process.[60] However, there is little research on the pharmaco-genetic mechanisms responsible for behavioral addictions such as internet and videogame addiction. Cloninger's reward dependence and the Taq1A1 allele of the dopamine D_2 receptor (DRD_2 Taq1A1) and Val[158]Met in the catecholamine-O-methyltransferase (COMT) genes were studied among excessive internet game players in Korea.[15] The Taq1A1 variation of dopamine D_2 receptor and low activity MET (COMT) alleles were significantly more prevalent in the excessive internet player group. Within this group, the presence of the Taq1A1 allele correlated with higher reward-dependence scores. Excessive internet game players may have high reward dependency and higher prevalence of associated dopamine genes. Due to its association with reward deficiency, it has been suggested that internet addiction similarly to ADHD may be classified as a reward deficiency syndrome.[61,62] A second Korean study has found that excessive internet users had higher frequencies of the long-arm allele (SS-5HTTLPR), greater harm avoidance (On Cloninger's Personality Questionnaire TPQ), and higher Beck Depression Inventory[63] scores.[16] SS-5HTTLPR frequency was closely related to harm avoidance in excessive internet users. Subjects with excessive internet use may have therefore genetic and personality traits similar to depressed patients. A possible link of the T-variant (CC genotype) of the rs1044396 polymorphism on the CHRNA4 with internet addiction was shown.[64] This gene may have an effect on a vast range of behaviors, including cognition, emotion, nicotine and internet and addiction. In conclusion, it seems that similar to drug dependence the variations of dopaminergic and serotonergic genes and their associations with reward dependence and harm avoidance respectively may play an important role in videogame and internet addiction. Further studies on the pharmaco-genetics of behavioral addictions are required especially due to the similarity of reward activation in both types of disorders that should point out to the role of dopamine in behavioral addiction.

RECENT TREATMENT STUDIES USING BRAIN IMAGING WITH fMRI

The few published treatment studies for internet addiction are based on interventions and strategies used in the treatment of substance use disorders and are limited due to problems in diagnosis, lack of randomization and blinding techniques, lack of adequate control, insufficient information on treatment procedures (see Refs.[9,10] for review). Relatively few studies have investigated the effects of pharmacological treatment on videogame cue reactivity. Bupropion, a dopamine and norepinephrine inhibitor which was used for treatment of nicotine and substance dependence[65,66] was tested for treatment of internet videogame addiction.[13] Eleven subjects who met criteria for IAG playing StarCraft and eight healthy comparison subjects who had experienced playing StarCraft underwent 6 weeks of bupropion sustained release (SR) treatment and measurement of internet game cue-induced brain activity using fMRI. Higher brain activation in left occipital lobe cuneus, left DLPFC, and left PHG were shown in internet addicted gamers. After a 6-week period of bupropion SR, craving for Internet video game play, total game play time, and cue-induced brain activity in DLPFC were decreased in the Internet videogame addiction players. It was concluded that Bupropion SR may change craving and brain activity in ways that are similar to those observed in individuals with substance abuse or dependence. A following study has evaluated the effects of bupropion treatment on the severity of excessive online videogame play as well as depressive symptoms.[14] A 12-week, prospective, randomized, double-blind clinical trial, including an 8-week active treatment phase and a 4-week post-treatment follow-up period was done in male subjects treated with Bupropion and education compared with male subjects treated with placebo and education. During the active treatment period, Young Internet Addiction Scale scores and the mean time of online game playing in the bupropion group were greatly reduced compared with those of the placebo group. The Beck Depression Inventory scores in the bupropion group were also greatly reduced compared with those of the placebo group. During the 4-week post-treatment follow-up period, bupropion-associated reductions in online game play persisted, while depressive symptoms recurred. Bupropion may improve depressive mood as well as reduce the severity of excessive online videogame play in patients with comorbid major depressive disorder and online game addiction.

DISCUSSION

The studies reviewed so far show consistent findings demonstrating the resemblance between the neural mechanisms underlying drug and alcohol abuse and the behavioral addictions. Addiction predominantly involves reward processes and dopamine release and this activity is mediated by limbic circuits and other brain regions such as the frontal cortex and the anterior cingulate gyrus.[51] These regions are involved in cognitive and motivational functions such as regulation, control and inhibition of responses as well as emotional processes. The brain areas that are activated by drug and alcohol cues include the amygdala, dorsolateral and orbitofrontal cortex, anterior cingulate.[20–27] Studies of videogame addiction of the resting state, functional and structural studies provide evidence that the brain's reward system and other related systems mediating loss of control and inhibition are undergoing changes as result of prolonged videogame addiction. Furthermore, studies on gaming cue-induced reactivity have shown an activation pattern that is similar to drug-dependent patients who were exposed to drug cues. There is also some evidence that pharmacological treatment with medication such as bupropion can alter this activity and attenuate cue-induced brain activity in excessive video-game users, similar to the attenuation that occurs in nicotine-dependent users.[67] Finally, regular or chronic videogame playing was associated with reduced brain's dopamine indicated by lower DAT density and lower dopamine D_2 receptor occupancy in the brains of excessive videogame players. There is already evidence for reduced dopamine D_2 receptor occupancy in cocaine, methamphetamine, heroin and alcohol abusers.[68–71] It seems that prolonged use of the brain's dopamine reward system as result of videogame playing resembles the down-regulation seen in case of drug and alcohol abuse.

Previous brain imaging studies on videogame playing showed an involvement of dopamine-release in the ventral striatum.[72,73] These striatum-associated findings in healthy subjects playing videogames not necessarily online are in line with the clinical observation that dopaminergic medication in Parkinson's patients can lead to pathological gambling and other addictive behavior such as binge eating and hypersexuality.[74] Greater dopamine release in the ventral striatum has been shown in Parkinson's patients with addiction, obsession and gambling compared with Parkinson's patients without these symptoms.[75] These findings identify striatal function driven by dopamine as a core candidate promoting addictive behavior. It has also been demonstrated that pathological gamblers have an increased striatal dopamine release while losing money, a biological signal that may hinder the termination of gambling and excessive gambling in Parkinson's patients due to dopaminergic medication.[76] These studies raise important questions regarding the difference between endogenous dopamine that is being released in the brain by naturally occurring activities compared with exogenous dopamine that is being released in the brain due to external activity of psychostimulants drugs of abuse. Although videogame playing has been shown to release dopamine to a similar extent as drugs such as cocaine, the two processes are entirely different pharmacologically, one is endogenous dopamine whereas the other is exogenous dopamine.

Furthermore, the question is whether any stimuli can be considered as highly addictive and consequently as having the power to release dopamine in the brain? It is already shown that drugs such as alcohol released a significant amount of dopamine in the brain in healthy volunteers in a study using [^{11}C] raclopride in PET.[77] Food stimulation has also shown small release of dopamine in obese patients by using this method of brain imaging with methylphenidate.[78] Although monetary gains[79] as well as playing gambling games[74] were effective in releasing dopamine in the brain it is not clear whether watching sexually implicit videogames or watching hedonic food stimulation videos in sex-addicts and people with eating disorders are effective releasers of dopamine in the brain. So question remains, can anything be considered addictive and hence as a potent-dopamine releaser in the brain?

Finally, there is growing evidence for the importance of dopamine reward mechanisms in internet addiction. Consistent with the evidence that internet and videogame addiction would be associated with deficient dopamine reward activity, it was shown that internet addiction is associated with reduced levels of dopaminergic receptor availability in the striatum[49] and with reduced level of DAT occupancy in the striatum.[50] This evidence seems to suggest that IAD is associated with dysfunction of the dopaminergic brain systems. Consistent with this finding, there are pharmacological and brain imaging studies showing that pharmacological treatment with bupropion which affects dopamine neurotransmission can reduce craving for videogame addiction and activity in related brain areas. There is further pharmaco-genetic evidence pointing to the role of dopamine, in internet addiction. These studies support the suggestion that dopamine has an important role in the pharmaco-genetic vulnerability for internet addiction. Secondly, excessive internet use may result in deficient dopamine reward mechanisms in the brain. Finally, medications that stimulate dopamine and noradrenaline activity may have potential clinical usefulness in treatment of internet addiction.

In conclusion, further clinical and research studies should be developed investigating the cognitive and bio-psychological aspects of internet and videogame addiction should be carried out and its association with brain activity and pharmacogenetic mechanisms could provide a fruitful direction for research in this area. Given the fact that this research is in its early stage it is premature to conclude that internet addiction is equivalent to substance addictions.

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Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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