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Genetic and Molecular Basis of Internet Addiction: An Overview

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Abstract

Evidences from psychological and neurological studies have depicted similarity between substance use disorders such as alcoholism and excessive internet use, as both are characterized as a behavioural addiction. Moreover, neuro-imaging has helped to determine some alterations, including decreased gray matter volume and density in the anterior cingulate cortex as well as exaggerated reactivity of the striatum. However, little is known about the molecular basis of the underlying brain dysfunctions. A few studies have demonstrated some associations with molecular genetic markers. Dopamine and serotonin have been implicated as in many other addictions. In addition, a genetic variation on the CHRNA4 gene (a constituent of the cholinergic pathways of the brain), which has been associated with trait anxiety and smoking, is also found to be relevant to Internet addiction. The neuronal circuit for sadness is known to be down regulated by the hormone oxytocin and sadness has been linked with the overall general and problematic internet use and its manifestations such as mood regulation. Low empathy, with possible links to oxytocin, has also been found to be associated with higher Internet addiction. The present overview aims to demonstrate and understand individual differences in Internet addiction and focus on potential genetic and molecular mechanisms underlying the development and maintenance of Internet addiction.

Keywords:

Internet Addiction;
Norepinephrine;
Dopamine;
Serotonin;
CHRNA4
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1. Introduction

According to the data provided by Internet worldstats 49.2% population of the world had access to internet by June 2016. [1] However, concern over the potential harmful effects of excessive Internet usage on our

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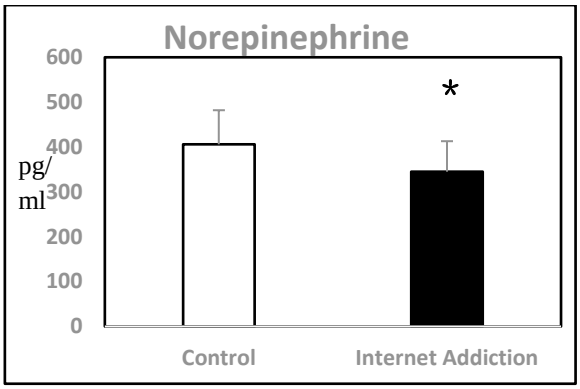
mental health is rising day by day [2]. The term Internet addiction was coined 20 years ago by Young [3]-[4]. The term problematic Internet use is also used sometime. The symptoms include preoccupation with the Internet, withdrawal when not being online and also negative repercussions in one's own life due to excessive usage such as may eventually result in marked distress and functional impairments of general life such as academic performance, social interaction, occupational interest and behavioral problems [5]. It has been classified into three major subtypes: Internet gaming disorder (IGD), sexual preoccupations, and email/text messaging [6]. Excessive internet use has been characterised as a behavioural addiction and similarities with substance abuse disorders such as alcoholism has been found like low self directedness and high neuroticism [7]-[10].Common neurological alterations have also been noticed, including decreased gray matter volume/density in the anterior cingulate cortex (ACC) or exaggerated reactivity of the striatum [11]-[12], [2]. In addition to associations between Internet addiction and problematic alcohol consumption[13]-[14], associations with other neuronal disorders; particularly depression and attention deficit hyperactivity disorder (ADHD) have also been reported [15]-[18]. Davis (2001) suggests that at the core of this problem is a potential delusional thought of being a champion in the online world and a nobody in the offline world [19]. This thought is often strengthened by plentiful online interactions, achievements in online computer games or getting liked and followed because of funny or kind or messages on burning issues via online social networking sites/apps. This repeat mechanism can result either in a generalized form of Internet addiction or in distinct forms of excessive Internet usage in areas such as online social networks, Internet gaming, online shopping, online gambling or online pornography [20]. Alarmingly, Diagnostic and Statistical Manual of Mental Disorders, fifth edition has included the term Internet Gaming Disorder as an emerging disorder [21].

Brand et al. (2014) have studied the dysfunctions in the fronto striatal limbic circuit in Internet addiction, which might help to understand the biological basis of excessive Internet usage. Internet addicts when offered with internet related cues, release strong dopaminergic bursts originating from striatal regions along with diminished enforcement functions in the dorsolateral prefrontal cortex. This may gradually lead to a loss of control over internet use [22]. Moreover, the mechanisms leading to the development and maintenance of Internet addiction have common aspect of sharing subcortical systems of dopamine mediated mesolimbic pathway [23].Another important structure showing reduction in Internet Addiction Disorder is the corpus callosum [24]. Compromised fiber connectivity within the corpus callosum is common in subjects with substance dependence [25]. Reduced bilateral genu and body of the corpus callosum have been reported in Internet Addiction Disorder subjects suggesting that heavy internet overuse, similar to substance abuse, may damage white matter of the corpus callosum [25]. The brain structure changes and cognitive control deficits were observed in Internet Gaming Disorder adolescents.Cognitive control refers to the ability to control one's own actions, behavior, and even thoughts. Reduced cognitive control ability in terms of longer reaction time and more response errors along with abnormal brain Gray Matter Volume were observed compared with the control group. [26]. However,less is known about the molecular basis of the underlying brain dysfunctions involved in internet addiction disorder and this overview attempts to delineate individual differences in Internet addiction and focus on potential biological mechanisms.

2. Research Method

The assessment was done by as per preferred reporting items for systematic review. Pubmed search was performed using the key words "internet addiction" problematic internet use" internet addiction disorder" "excessive internet use". Only those records were selected which had studied any gene or molecule related to the key words.

3. Results and Analysis



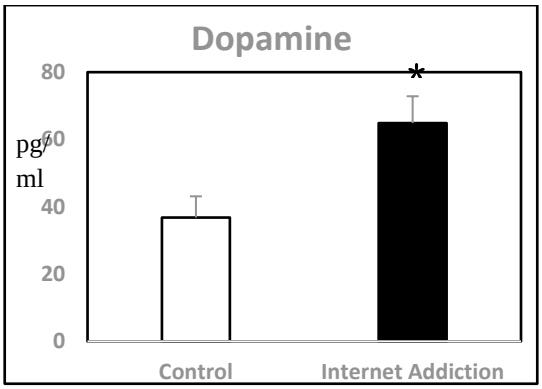


Figure 1 **Figure 2**

Neurotransmitters and hormones: Zhang et al (2013) performed a study on participants consisting of 15 adolescents without IAD and 20 who had been diagnosed with IAD. The participants completed self-reports on anxiety and depression and their blood levels of serotonin, dopamine, and norepinephrine were tested [27]. The imbalance in the levels of dopamine (DA), serotonin, and/or norepinephrine (NE), has been found to be associated with the onset of mood and anxiety disorders [28]-[31]. Hence, it was hypothesized that people with IAD with higher rates of self reported anxiety and depressive symptoms would have altered levels of peripheral blood dopamine, norepinephrine and serotonin. It was found that the participants with IAD indeed had much lower levels of norepinephrine than the control participants, although the dopamine and serotonin levels were similar (Figure 1). However, it is to be noted that, as NE is a metabolic product of Dopamine, it may be deduced that IAD may be associated with altered monoamine functional activity as a whole. However, as the sample size is small, further rigorous studies are required in this field. In another study by Liu and Leo (2015) on 33 Adolesecents with IAD against 33 gender and age matched controls significant rise in peripheral dopamine levels were observed (Figure 2). A significant positive correlation between the plasma dopamine level and the weekly online time ($r = 0.380$, $P < 0.01$) was observed [32]. It indicates that more the online time is spent by an individual, more is the plasma level of dopamine. Addictive drugs are known to increase the release of dopamine in the brain and when dopamine is released in certain areas of the brain it gives the feeling of pleasure or satisfaction. The addicted person grows a desire for this satisfaction. To satisfy the desire, the person repeats the behaviors that cause the release of dopamine [32]-[33]. That is how any addiction emerges and the increase in online time spent can be related to the increase in plasma dopamine levels in IAD patients .

Genetic basis: Several studies have provided evidence for involvement of serotonergic system along with dopaminergic system in internet addiction. Atmaca in 2007 reported that administration of selective serotonin reuptake inhibitors (SSRIs) may help in the treatment of Internet addiction [34]. The serotonin reuptake transporter gene (5HTT) has been studied in detail by several groups. It is located on chromosome 17q11.1-q12 and has a functional polymorphism in the variable repeat sequence in the promoter region (5HTTLPR) [35]-[36]. 5HTTLPR has been pointed out to be an important candidate in the regulation of serotonergic neuro-transmission. The homozygous long allelic variant (L) is found to be associated with higher concentrations of 5HTT messenger RNA and a greater rate of reuptake than variants containing the short allelic variant (S) [36]-[37]. These findings have led to the proposition that this 5HTTLPR polymorphism (specially, the presence of the S allele of 5HTTLPR) may play a key role in the cause behind internet addiction [38] just as in depression [39]-[40] and substance dependence [36]. In the case control study involving 16 age and educational background matched participants performed by (Lee et al., 2008) on korean adolescents, it was found that the internet addicted group had a score of more than double on the internet addiction scale as compared to control ones [38]. The homozygous short allelic variant of the serotonin transporter gene (SS-5HTTLPR) was more prevalent in the internet addicted group ($\chi 2=4.38$, df=1, pb0.05). The presence of the short 5HTTLPR allele has been linked to various forms of drug addiction as well as depression [40]-[41]. Hence, Internet addiction subjects demonstrate characteristics of depression and anxiety

in terms of serotonin transporter polymorphism. Another candidate gene found involved in internet addiction is the one coding for nicotinic acetylcholine receptor subunit alpha 4 (CHRNA4). This gene has been found to be involved in anxiety and addiction [42]. In addition to this , study by Tsai et al. (2012) has shown that elderly males who are carriers of the T-allele variant are less depressed and lonely [43]. It can be proposed that a anxious phenotype of this gene has the risk of becoming internet addictive along with other addictions as internet addiction is highly associated with anxiety and low self esteem[8]-[9]. in a case control study on 132 sex and age matched participants each, it was hypothesized that CC variant of this gene rs1044396 was associated with Internet addiction and it was found that the association between Internet addiction and genetic variation on CHRNA4 is driven by females ($\chi 2 = 6.37$, df = 1, P = 0.01, $\phi = 0.25$) and not males ($\chi 2 = 0.34$, df = 1,P = 0.56) [44]. As discussed till now , a major cause of any addiction is sadness and neuropeptide oxytocin is known to down regulate sadness [45]. Hence, low oxytocin levels could be a factor which makes an individual predisposed to sadness and addiction. Genetic association between variation of the OXTR gene and Internet addiction has been studied by Sariyska et al. (2016) [46]. From a large study over parts of Europe and Asia , they reported that only male carriers of the TT genotype for OXTR polymorphism (rs2268498), showed significantly lower Problematic Internet Use values ($p<05$) than C allele carriers [46].

All, these reports suggest that dopaminergic system might be the common pathway for internet addiction like many other addictions as it is involved in the reward pathway. Internet addiction primarily arises from. emotional distress like sadness, low self esteem and neuroticism and hence the basic and initial impetus is to increase dopamine release in brain. However, other than the last [46], all these studies suffer from the lacunae of small sample size. Hence, future studies are needed on the genetic epistasis effects between the dopaminergic and the cholinergic systems to get a better understanding of the underlying biological mechanism of Internet addiction on a larger cohort.

4. Conclusion

This overview in its preliminary capacity would like to conclude that individual differences in arousal and maintenance of Internet addiction may be credited to the genetic differences in dopaminergic and cholinergic pathways in brain.

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