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Brief report

# Depression like characteristics of 5HTTLPR polymorphism and temperament in excessive internet users

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**Abstract**

*Introduction:* Excessive internet use (EIU) has been reported to be comorbid with depression and the manifestation of its symptoms. This study examines the characteristics of excessive internet users that are similar to those of patients with depressive disorders in terms of serotonin transporter gene expression and harm avoidance.
*Methods:* 91 male adolescents with EIU and 75 healthy comparison subjects were recruited. Between group comparisons were made on genetic polymorphisms of the serotonin transport gene and with respect to novelty seeking and harm avoidance (HA) of Cloninger's Temperament Character Inventory.
*Results:* The homozygous short allelic variant of the serotonin transporter gene (SS-5HTTLPR) is more frequent in the EIU group ($\chi^2=4.38$, $df=1$, $p<0.05$). The HA and Beck Depression Inventory (BDI) scores were significantly higher in the EIU group than in the healthy comparison group ($t=7.03$, $df=164$, $p<0.01$; $t=2.12$, $df=164$, $p=0.04$). EIU subjects expressing SS-5HTTLPR also showed higher HA (HA1, HA2, HA4, and total HA) and Young's internet addiction scale scores than EIU subjects expressing the other serotonin transporter gene allele variants ($t=2.47$, $df=89$, $p=0.01$; $t=2.33$, $df=89$, $p=0.02$; $t=2.17$, $df=89$, $p=0.03$; $t=2.25$, $df=89$, $p=0.03$; $t=2.93$, $df=89$, $p<0.01$ respectively).
*Conclusions:* The EIU group had higher SS-5HTTLPR frequencies, harm avoidance, and BDI scores. SS-5HTTLPR expression was closely related to harm avoidance in EIU. The results of this study suggest that EIU subjects may have genetic and personality traits similar to depressed patients.


*Keywords:* Depression; Excessive internet use; 5HHTLPR polymorphism; Harm avoidance

## 1. Introduction

The phenomenon of excessive internet use as a distinct entity within the addictive disorders continues to be the subject of debate (Kraut et al., 1998; Mitchell, 2000; Campbell et al., 2006). However, studies have shown that the addiction-like qualities of EIU may be responsible for behavioral problems including social isolation, depressed mood, and unstable impulsivity (Young, 1998; Reirdan, 1999). These symptoms are similar to those found in depression and anxiety disorders (Kraut et al., 1998; Shapira et al., 2000; Moody, 2001). In an association study between excessive internet use and depression, Kraut et al.

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(1998) showed that subjects with excessive internet use demonstrated loneliness, decline in communication with household family members and social withdrawal. Major depression is known to be one of the most common comorbid psychiatric disorders in Korean adolescents with EIU (Ha et al., 2006). Ha et al. (2007) also reported that adolescents with excessive internet use had high harm avoidance, low self-directedness, low cooperativeness and high self-transcendence, which are all seen in depression.

The serotonin reuptake transporter gene (5HTT) located on chromosome 17q11.1-q12 has a functional polymorphism in the variable repeat sequence in the promoter region (5HTTLPR) (Ramamoorthy et al., 1993; Lesch et al., 1996). 5HTTLPR may be important in the fine-regulation of serotonergic neurotransmission; the homozygous long allelic variant (L) is associated with higher concentrations of 5HTT messenger RNA and a greater rate of reuptake than variants containing the short allelic variant (S) (Lesch et al., 1996; Greenberg et al., 1999). These findings have led to suggestions that this 5HTTLPR polymorphism (specially, the presence of the S allele of 5HTTLPR) may play a key role in the etiology of depression (Blier and de Montigny, 1999; Wrase et al., 2006) and substance dependence (Lesch, 2005).

The Temperament and Character Inventory (TCI), developed by Cloninger and colleagues, has been widely used in research on psychobiological human behavior (Cloninger, 1987). Among the four dimensions of temperament, novelty seeking and harm avoidance are thought to be correlated with depression (Serretti et al., 2006; Jylha and Isometsa, 2006). Serretti et al. (2006) reported that S allele homozygote of 5HTTLPR was associated with low novelty seeking scores in mood disorder patients. Jylha and Isometsa (2006) demonstrated that harm avoidance is associated with depressive and anxiety symptoms in a normal population. Recently, Ha et al. (2007) also reported the association of harm avoidance and excessive internet use in adolescents with excessive internet use.

Based on these studies, we hypothesized that the EIU group will have characteristics similar to those of patients with depressive disorder in terms of genetic distribution and the harm avoidance dimension of TCI. To the best of our knowledge this is the first genetic polymorphism study of the serotonin and norepinephrine systems in EIU subjects.

## 2. Materials and methods

The design of this study was carried out in two phases. Subjects were first screened using self-report questionnaires and the Internet Addiction Scale (IAS)(Young, 1998). Two psychiatrists then conducted the interview with the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Health Disorders-IV (SCID) (with emphasis on the pathological gambling criteria) and assess subjects for the presence of other psychiatric disorders (D.H.H and Y.S.L; inter rater reliability ($n=20$)= 0.95).

For this study, male subjects were recruited from two high schools in Seoul and Kang-won, South Korea between the period of February, 2004 to March, 2005. Subjects were screened using the Korea manual of Symptom Checklist-90-Revision (Kim et al., 1984) for mental disorders and substance abuse. All subjects were given Young's Internet Addiction Scale (IAS), Beck Depression inventory (BDI) (Han et al., 1986), and a questionnaires targeted at disclosing the amount of time spent on the internet and the nature of internet use. In Korean child and adolescent population, Yoo et al. (2004) and Ha et al. (2006) already suggested the threshold of internet addiction as IAS score $\geq 50$. Lee et al. (2001) reported that 70% of Korean high school students used internet less than 1 h. Written informed consent was obtained from all participant and their parents. All aspects of the clinical protocol were reviewed and approved by Institutional Review Boards in Chun-Cheon National Hospital.

Of the 613 subjects initially surveyed, 125 subjects who, on average, used the internet over 1 h/day and had an IAS score above 50 were recruited to the EIU group. An 102 additional subjects who, on average, used the internet, less than 1 h/day and had an IAS score below 49 were recruited to the control group.

In the interview with psychiatrists, 8 subjects met the criteria for major depression, 6 subjects for conduct disorder, 3 subjects for social phobia, and 3 subjects for obsessive–compulsive disorders. An additional 41 EIU subjects withdrew from the study based on concerns regarding blood draw, genetic analysis, and/or absence from school. After screening, a total 91 EIU and 75 control subjects completed the study.

DNA was extracted from the blood leukocytes using a commercial DNA extraction kit (Gentra Systems, Minneapols, Minn.). The samples from subjects were analyzed for short 484 base pair, -S allele- and long 528 base pair and -L allele.

For the purpose of our research, we selected novelty seeking and harm avoidance subscales in the Korean version of the Temperament and Character Inventory which consists of a 240-item of true and false questionnaire (Cloninger, 1987; Sung et al., 2002). It proved to be reliable and valid by internal consistency (Cronbach $\alpha=.77$), test re-test reliability ($r=.81$), and a factor analysis (Sung et al., 2002).

Table 1
Demographic characteristics and serotonin transporter gene polymorphism

| | EIU | Controls | *t, p* |
|---|---|---|---|
| Age | 16.1±0.7 | 16.1±0.7 | 0.11, 0.91 |
| Education | 10.7±0.5 | 10.8±0.4 | 0.92, 0.35 |
| Time_internet | 2.2±1.7 | 0.8±0.4 | 7.41, <0.01 |
| YIAS | 68.8±10.5 | 27.0±4.1 | 32.02, <0.01 |
| BDI | 9.0±3.0 | 6.2±2.2 | 7.02, <0.01 |
| 5-HTTLPR | | | SS vs SL+LL |
| SS | 39 | 21 | $\chi^2$=4.38, *df*=1, |
| SL | 43 | 44 | *p*<0.05 |
| LL | 9 | 10 | |
| Allele frequency | S: 0.681, L: 0.319 | S: 0.573, L: 0.427 | |

*: Statistically significant, EIU: Excessive internet user, Time_internet: internet using time, YIAS: Young's internet addiction scale, BDI: Beck Depression inventory, 5HTTLPR: Serotonin transporter gene, S: short allele of 5HTTLPR, L: long allele of 5HTTLPR.

The BDI is a self-reported questionnaire for the assessing of the presence and severity of depressive symptoms. It consists of 21 items with the total range of scores from 0 to 62. It has been translated and standardized in Korea (Han et al., 1986).

Statistical analysis was performed by using parametric, independent tests to compare the mean difference of the TCI scale between the EIU and control groups. Chi-square tests were carried out to check Hardy-Weinberg genetic equilibrium and analyze the genetic polymorphisms, including the genotypes and allelic frequencies, between the two groups. All the statistical analyses were performed by using the software program STATISTICA version 6.0 (Stat Soft).

## 3. Results

There was no significant difference with regard to age and education years between the EIU and control groups (Table 1). The mean time of internet use, the mean Young's internet addiction scale score and the mean BDI score of the EIU group were 2.2±1.7 h/day, 68.8±10.5, and 9.0±3.0, respectively. The mean time of internet use, the mean Young's internet addiction scale score, and BDI score of the control group were 0.8±0.39 h/day, 27.00±4.13, and 6.2±2.16, respectively.

The homozygous short allelic variant of the serotonin transporter gene (SS-5HTTLPR) was more prevalent in the EIU group ($\chi^2$=4.38, *df*=1, *p*<0.05). Both EIU and control groups were in Hardy-Weinberg equilibrium (EIU: $\chi^2$=1.17, *df*=1, *p*=0.28; Controls: $\chi^2$=2.97, *df*=1, *p*=0.08).

There was no significant difference in terms of novelty seeking between EIU (23.5±5.7) and controls (22.1±5.5) (*t*=1.54, *df*=164, *p*=0.12). The scores of HA1, HA4, and total HA in the EIU group were higher than in the control group (*t*=2.27, *df*=164, *p*=0.02; *t*=3.20, *df*=164, *p*<0.01; *t*=2.12, *df*=164, *p*=0.04, respectively). EIU with the SS-5HTTLPR variant showed higher scores of HA (HA1, HA2, HA4, and total HA) and IAS than EIU with other allelic variants (*t*=2.47, *df*=89, *p*=0.01; *t*=2.33, *df*=89, *p*=0.02; *t*=2.17, *df*=89, *p*=0.03; *t*=2.25, *df*=89, *p*=0.03; *t*=2.93, *df*=89, *p*<0.01, respectively) (Fig. 1). There was a positive correlation between internet use time and IAS and BDI scores in the EIU group (*r*=0.75, *p*<0.01; *r*=0.55, *p*<0.01).

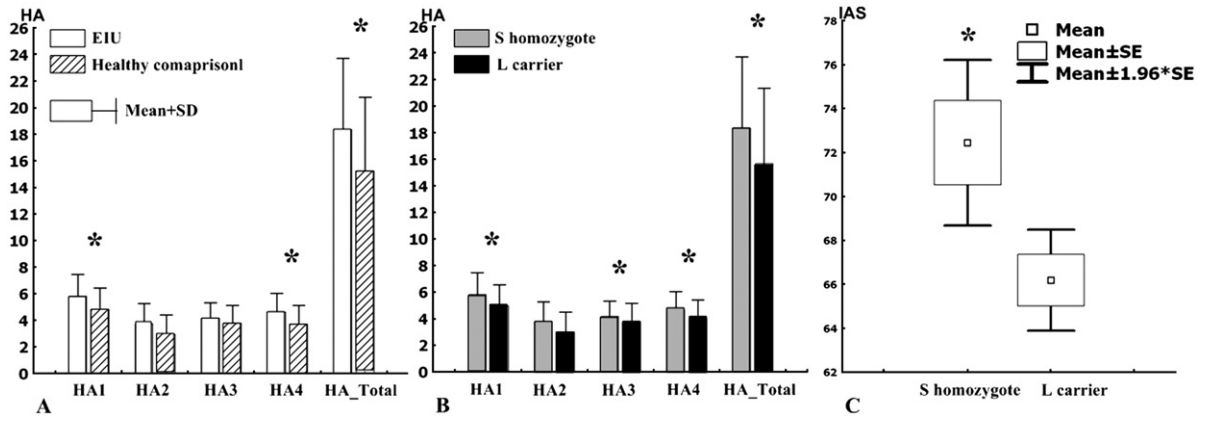


Fig. 1. Comparison of the harm avoidance score and Young's internet addiction scale score. *: statistically significant. A: Harm avoidance scale, Excessive Internet Use (EIU) vs Healthy comparisons. B: Harm avoidance scale, S homozygote vs L carrier (S/L+L/L of 5HTTLPR) in EIU. C: Young internet addiction scale (IAS), S homozygote vs L carrier (S/L+L/L 5HTTLPR) in EIU, HA1: anticipatory worry and pessimism vs optimism, HA2: fear of uncertainty, HA3: shyness with stranger, HA4: fatigability and asthenia.

## 4. Discussion

In current results, short allele 5HTTLPR homozygote and higher harm avoidance were related with excessive internet use. The BDI scores in excessive internet use group were also higher than that in healthy comparisons.

Serotonergic neurotransmission has been a major focus of pharmacological treatment of mood and anxiety disorders (Blier and de Montigny, 1999). Several *in vitro* and postmortem studies have explored the role of 5HTTLPR polymorphism and the reuptake of synaptic serotonin (Little et al., 1998; Greenberg et al., 1999). The presence of the short 5HTTLPR allele has been linked to various forms of drug addiction, such as alcoholism and nicotine dependence, as well as major depressive disorder (Marques et al., 2006; Wrase et al., 2006). Animal studies have supported this finding; one review study on non-human primates found that social stress may be causatively related to reductions in serotonin turnover rate among heterozygous and homozygous carriers of the short allele (Wrase et al., 2006).

The short allele in the promoter region of the serotonin transporter 5-HTTILPR is also considered as a factor in anxiety-related traits, such as neuroticism and harm avoidance (Lesch et al., 1996). Jacob et al. (2004) found that patients with an anxiety spectrum personality type were more likely carriers of the low-activity short allele of the 5-HTTLPR and had higher neuroticism scores than homozygous carriers of the long allele. However, because other studies have failed to show the significant effects of 5HTTLPR (Zalsman et al., 2005; Mann et al., 2000), the present results on serotonin polymorphism should be cautiously interpreted.

Higher HA scores on the TCI has been associated with increased anxiety, pessimism, and shyness (Cloninger, 1987; Cloninger et al., 1993). HA scores may also correspond with depression; Farmer et al. (2003) showed that the harm avoidance trait strongly quantified the degree of vulnerability to future depression, even in individuals who have never previously experienced depression. Furthermore, it is speculated that high HA scores predict poor response to antidepressants (Joyce et al., 2003). Consequently, we believe that depression (Kraut et al., 1998; Shapira et al., 2000; Moody, 2001) and aspects of social fearfulness (Campbell et al., 2006) in EIU adolescents may be related to high harm avoidance.

In the present results, excessive internet users showed depression like characteristics in terms of genetics and temperament. Although the current research was not designed to link depression and EIU, we think that the results suggest vulnerability to EIU among depressed subjects. This finding does not, however, take into account causality. Further research would be needed to determine the distinction between EIU as a self-medicating tool for depression or depression as a comorbidity of EIU. In addition, Shapira et al. (2000) reported that, among 20 problematic internet users, 14 subjects had a life-time history of bipolar disorder. Although there were differences in subject characteristics between Shapira's research and ours in terms of number of subjects, exclusion of psychiatric disease, and age, further research should be considered to follow up on mood symptoms as state markers

There are several limitations to the current study. First, a relatively small number of subjects was enrolled and the reader should cautiously interpret current results in light of multiple comparisons and weak findings ($p<0.05$). In addition, investigators of addiction disorders have largely turned their attention to other neurotransmitters such as dopamine and glutamate, which play a more direct role in reward. Further studies on other neurotransmitters that may be related to internet use are needed to detect the association between specific temperament and genetic predisposing polymorphisms that are involved in excessive internet use. Second, the definition of excessive internet use is somewhat subjective. Third, the current research was focused on mood symptoms; attentional problems were not considered. However, attention deficit hyperactive disorder has been reported to be one of the comorbid disorders in EIU (Ha et al., 2006).

In conclusion, we found that EIU subjects demonstrate characteristics of depression and anxiety in terms of serotonin transporter polymorphism and harm avoidance. Continued study of other forms of genetic polymorphisms and behavioral characteristics as it relates to EIU is needed.

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**Conflict of interest**

All authors are agreed not to have any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three (3) years of beginning the work submitted that could inappropriately influence, or be perceived to influence, our work.

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