INTERNET ADDICTION AMONG UNDERGRADUATE STUDENTS IN SOUTH KOREA: ASSOCIATION WITH COMT (VAL^{158}MET) GENOTYPE AND PSYCHOLOGICAL FACTORS

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A dissertation submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the School of Nursing.

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ABSTRACT

Jeehae Chung: Internet Addiction among Undergraduate Students in South Korea: Association with COMT (Val^{158}Met) Genotype and Psychological Factors
(Under the direction of Cheryl Giscombé)

With the recent diversification and universalization of the Internet, the Internet use rate has increased rapidly. A growing body of research suggests that Internet addiction, defined as pathologically preoccupied Internet use, which results in physical, psychological, social, and/or financial distress, has become a serious health and social problem worldwide. The catechol-o-methyltransferase (COMT) (Val^{158}Met) is one of the candidate genes that have been studied to understand the various illnesses related to dopaminergic neurotransmission, including substance-related and addictive disorders (SRADs). However, little research has been conducted to examine the association between the COMT genotype and Internet addiction.

This dissertation is composed of three papers. The first paper is a systematized review of the literature, which aims to synthesize the findings regarding the psychosocial risk factors of Internet addiction among undergraduate students. The second paper is also a systematized review of the literature, which aims to investigate the relationship between the COMT genotype and SRADs. The third paper is a cross-sectional descriptive study that aims to (a) identify issues related to the feasibility of conducting a study that involves the collection of saliva samples and web-based survey data with participants who are undergraduate students in South Korea and (b)

describe the relationships among Internet addiction, the COMT genotype, and psychological variables (depressive symptoms, social anxiety, self-esteem, self-efficacy, stress, and coping strategy).

The PI recruited 250 Korean undergraduate students from university campuses in Seoul and the Seoul metropolitan area. The study procedure, including the collection of saliva samples and the web-based survey, was found to be feasible. 54.8% of the participants were categorized as having Internet addiction. COMT (Val^{158}Met) was not significantly associated with Internet addiction. However, Internet addiction was significantly associated with all investigated psychological variables.

Studies should not be limited to only one genotype, but should include analysis of the multi-locus genetic profile that may be related to Internet addiction. Research that focuses on gene-gene interactions and gene-environmental interactions in terms of Internet addiction is needed. Future research is needed to continue the development of standardized assessment tools and feasible and effective interventions and treatments for Internet addiction.

To my parents and grandparents,
I could not have done this without your huge support and your prayer.

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LIST OF ABBREVIATIONS

BBL	Bio-Behavioral Laboratory
COMT	Catechol-o-methyltransferase
DNA	Deoxyribonucleic acid
IAT	Internet addiction test
NAc	Nucleus accumbens
PFC	Prefrontal cortex
PI	Principal investigator
PRISMA	Preferred reporting items for systematic reviews and meta-analysis
SNP	Single nucleotide polymorphism
SRAD	Substance-related and addictive disorder
VTA	Ventral tegmental area

CHAPTER 1. INTRODUCTION

This chapter describes the initial proposal generated for this dissertation project and its inherent three studies that are presented as three separate papers in Chapters 2, 3, and 4 as well as the synthesis of findings that is presented in Chapter 5. Thus, Chapter 1 serves as an introduction for the overall dissertation.

Specific Aims

With advancements in information technology, the Internet has become an inevitable component of people's ordinary lives. As portable mobile devices such as smartphones and tablet computers have become increasingly popular based on advanced Internet infrastructure, the use of the Internet likewise has become more commonplace. Although the Internet has provided convenience and entertainment, it also has created adverse effects in terms of its use, which includes Internet addiction (Young, 1998b).

South Korea is a country with one of the highest rates of Internet addiction in the world (Kuss, Griffiths, Karila, & Billieux, 2014), which reflects the negative outcome of having the world's fastest broadband and the most wired environment (Young, 2017). Unlimited data usage plans are common for mobile device users (Ahn, 2012), and 'PC bang', which is an Internet café located in many buildings in communities and cities, provide up-to-date computer facilities that allow people to enjoy online gaming for 24 hours a day (Ahn, 2012; Young, 2017). According to a survey conducted by the Korea Internet & Security Agency (2014), 82.1% of the Korean population aged three or older use the Internet at least once monthly. Furthermore, 99.9% of the Korean population between the ages of 20 and 29 use the Internet at least once a month,

according to the same source. In addition, according to a survey conducted by the National Information Society Agency (2015), the percentage of individuals who are at risk of Internet addiction is much higher among undergraduate students (12.5%) compared to other age groups (6.9%) in South Korea.

Recently, published studies have shed light on the severity of Internet addiction among undergraduate students in South Korea. Noh and Kim (2016), for instance, used the Internet Addiction Test (IAT; Young, 1998a), which is a validated scale that is utilized in numerous countries, to assess Internet addiction among undergraduate students. They found that 25.8% of Korean undergraduate students had moderate to severe Internet addiction. This finding can be compared to a study by Derbyshire et al. (2013) that reported that 5.3% of undergraduate students in the United States had moderate to severe addiction based on IAT scores. Because Internet addiction can severely impact undergraduate students in terms of their time management, finances, academic obligations, and job performance (Kuss, Griffiths, & Binder, 2013), more research regarding prevention and treatment of Internet addiction among Korean undergraduate students is urgently needed.

A growing body of research has demonstrated that Internet addiction is associated with a wide variety of psychosocial factors, including personality traits (Kuss et al., 2013), stress (Yan, Li, & Sui, 2014), low self-efficacy (Yu, Wu, & Pesigan, 2016), mental illness (Ko, Yen, Yen, Chen, & Chen, 2012; Ostovar et al., 2016), lack of social support (Gunuc & Dogan, 2013), and family dysfunction (Yan et al., 2014). More recently, researchers have begun to study ways that Internet addiction may be associated with genetic factors. Such research includes investigations into catechol-o-methyltransferase (COMT) ($Val^{158}Met$) as a candidate gene for substance-related and addictive disorders (SRADs). COMT is an enzyme that catabolizes catechol, which include

catecholamine such as dopamine, epinephrine, and norepinephrine as well as catecholestrogen (Ira, Zanoni, Ruggeri, Dazzan, & Tosato, 2013). COMT plays a key role in the regulation of the level of dopamine in the reward pathway, which addresses the mechanism of addiction (Adinoff, 2004; Di Chiara & Bassareo, 2007). Due to a single nucleotide polymorphism (SNP), which is a common variation of single bases in DNA (deoxyribonucleic acid) sequences (Shen, Abdullah, & Wang, 2009), at the sequence of the COMT gene ($Val^{158}Met$), the enzyme activities of COMT are altered (Baclig et al., 2012; Dauvilliers, Tafti, & Landolt, 2015). Therefore, researchers are interested in the functional SNP of COMT in terms of SRADs.

Although research that investigates the association between the COMT genotype and SRADs is becoming increasingly prevalent, little research has been conducted to examine the association between the COMT genotype and Internet addiction. Given the high rate of Internet addiction among Korean undergraduate students, a deeper understanding of the risk factors of Internet addiction, ways to prevent Internet addiction, and strategies for treating or addressing Internet addiction is needed. Examining the association between Internet addiction and the COMT genotype will result in the identification of potential biological genetic factors that have been suggested as contributors to SRADs. This work will enhance the development of personalized interventions for the prevention and treatment of Internet addiction in future studies. To this end, this dissertation reports the following studies that were conducted as part of this research.

Dissertation Outline

Paper 1. This paper (presented in Chapter 2) is a systematized review of the literature that aims to synthesize the findings the literature that investigated the psychosocial risk factors of Internet addiction among undergraduate students. The Principal investigator (PI) searched four

electronic databases (CINAHL Plus with Full Text, PubMed [MEDLINE], PsycINFO, and Scopus) using search terms that were built according to the variety of terminology associated with Internet addiction. The search results were limited to studies written in English and published in peer-reviewed journals. The PI extracted the following data: author, published year, country, sample size, percentage of male and female participants, the instrument(s) used to assess the Internet addiction of the participants, which included the range of the total scores of each instrument and the cut-off scores to identify Internet addiction, prevalence of Internet addiction, psychosocial risk factors of Internet addiction identified from the analysis, and other risk factors if mentioned in the study.

Paper 2. This paper (presented in Chapter 3) is a systematized review of the literature that aims to investigate the relationship between the COMT genotype ($Val^{158}Met$) and SRADs. The PI searched four electronic databases (CINAHL Plus with Full Text, Embase, PubMed [MEDLINE], and PsycINFO). The search results were limited to studies written in English and published in peer-reviewed journals. The PI extracted the following data: author, published year, country, study participants and their ages for both the case and control groups, sample size, percentage of male and female participants for both the case and control groups, COMT genotype frequency for both the case and control groups, and findings regarding the association between the COMT genotype and each type of SRAD.

Paper 3. This paper (presented in Chapter 4) is a cross-sectional descriptive study that aims to (a) identify issues related to the feasibility of conducting a cross-sectional study that involves the collection of saliva samples and web-based survey data with the participants who were undergraduate students in South Korea, and (b) investigate relationships among Internet addiction, COMT genotype, and psychological variables (depressive symptoms, social anxiety,

self-esteem, self-efficacy, stress, and coping strategies).

The PI anticipated that the specific aims of these three studies/papers would yield the following expected outcomes: (a) identifying issues that would relate to the feasibility of conducting research that involved collecting saliva samples and conducting a web-based survey of a sample of undergraduate students in South Korea, (b) providing preliminary information about the association between the COMT genotype and Internet addiction, and (c) providing information to guide future research for developing successful for individuals with Internet addiction.

Significance and Innovation

Internet addiction is defined as an excessive preoccupation with Internet use that results in physical, psychological, social, and/or financial distress (Weinstein et al., 2015). Because the Internet can be used for various purposes, such as social relationships, cybersex, gaming, online stock trading, gambling, and information surfing, Internet addiction includes various types of addictive behavior (Young, Pistner, O'Mara, & Buchanan, 1999). Individuals with Internet addiction may fail at being able to control themselves when they use the Internet and consequently may suffer from the symptoms that are commonly associated with SRADs, such as dependence, tolerance, and withdrawal symptoms (Kuss et al., 2014; Young et al., 1999).

Researchers have suggested that Internet addiction needs to be regarded as a SRAD, as is the case with gambling disorder (Kuss et al., 2014; Young, 2004). Studies that have explored neuropsychological functioning in individuals with Internet addiction reveal that both structural and functional variations of the brain are similar to those of individuals with SRADs (Hou et al., 2012; Ko et al., 2013; Y. S. Lee, Han, Kim, & Renshaw, 2013). Indeed, Internet gaming disorder has been considered as a condition to be included possibly as a formal disorder in the Diagnostic

and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), as more clinical evidence accumulates (American Psychiatric Association, 2013).

In addition to commonly suggested psychosocial risk factors of Internet addiction, such as stress, impulsivity, and/or impaired social support, Brand, Young, and Laier (2014) asserted that self-regulation could be examined as an important aspect of Internet addiction, because most people with Internet addiction frequently complain of the inability to control their behavior. Brand et al. (2014) proposed a model to illustrate the mechanisms that underlie Internet addiction in terms of cognitive control, or executive functions, which refers to the ability to control one's behaviors or thoughts with flexibility to reach one's internal goal. These executive functions are associated with the prefrontal cortex (PFC) that receives dopamine that extends from the nucleus accumbens (NAc), which takes dopamine from the ventral tegmental area (VTA) (Adinoff, 2004; Brand, Young, et al., 2014; Yuan & Raz, 2014). This tract is one of the dopaminergic pathways, referred to as the mesocorticolimbic pathway (Adinoff, 2004) and/or as the reward pathway, which plays a key role in the mechanism of addiction (Adinoff, 2004; Di Chiara & Bassareo, 2007).

The mesocorticolimbic dopaminergic pathway, which is associated with reward, motivation, pleasure, and further craving, initiates from the VTA, travels to the NAc in the ventral striatum, and then extends to the limbic system and PFC (Malhotra, Basu, Khullar, Ghosh, & Chugh, 2016; Tunbridge et al., 2012). This system is known to be strongly linked to SRADs, and studies have demonstrated similar mechanisms for Internet addiction. For example, Hou et al. (2012) showed that the level of the dopamine transporter, which controls the level of dopamine by re-uptaking dopamine into presynaptic neurons, is lower in the striatum of individuals with Internet addiction than for individuals without Internet addiction. Moreover,

Kim et al. (2011) reported that striatal dopamine D2 receptors, which also regulate dopaminergic neurotransmission, are fewer in individuals with Internet addiction than in individuals without Internet addiction.

In the PFC region of the brain, COMT also plays a key role in the regulation of the level of dopamine (Malhotra et al., 2016; Tunbridge et al., 2012). As aforementioned, COMT is an enzyme that catabolizes catechol, which include catecholamine such as dopamine, epinephrine, and norepinephrine as well as catecholestrogen (Ira et al., 2013). Dopamine is synthesized from the amino acid, tyrosine, in the dopaminergic neurons and is released by synaptic vesicles (Meiser, Weindl, & Hiller, 2013). The level of dopamine is regulated by the receptors or by the dopamine transporter that re-uptakes the dopamine into presynaptic neurons to store it for future use or destroy it via monoamine oxidase or COMT (Meiser et al., 2013). However, because dopamine transporters are relatively rare in the PFC region, the released dopamine is inactivated by the enzyme COMT outside of the neuron (Meiser et al., 2013).

The COMT gene, which codes for the COMT protein, is located on the *q* arm of chromosome 22 (Baclig et al., 2012; Qiu et al., 2015). However, due to SNP, a common variation of single bases in a DNA sequence (Shen et al., 2009), at the sequence of the COMT gene ($Val^{158}Met$), the nucleobase, guanine, is altered to another nucleobase, adenine, so that translation to amino acid also is changed from valine (Val) to methionine (Met), which results in a functional variation of the COMT enzyme (Baclig et al., 2012; Dauvilliers et al., 2015). As a result of a commonly studied functional SNP (rs4680), three genotypes have been identified: Val/Val, Val/Met, and Met/Met, with each conferring difference in COMT activity. For example, the Val/Val genotype shows the highest COMT activity, so it is related to fewer synaptic catecholamine neurotransmitters, such as dopamine especially in the PFC region. In contrast, the

Met/Met genotype shows the lowest COMT activity, so the level of dopamine in the PFC region is higher than for the Val/Val genotype. Chen et al. (2004) showed that the COMT activity of the Met allele is up to 40% lower than that of the Val allele in the PFC region.

Because COMT widely affects the level of the catechol, the functional SNPs of COMT have been widely researched with regard to mental disorders, such as depression (Alvim-Soares et al., 2013; Antypa, Drago, & Serretti, 2013), obsessive-compulsive disorder (Tükel et al., 2013), attention deficit hyperactivity disorder (Halleland, Lundervold, Halmøy, Haavik, & Johansson, 2009; Villemonteix et al., 2015), schizophrenia (Bilder et al., 2002; Mohamed Saini et al., 2015), and substance abuse (Zhang et al., 2013) as well as cancer (Qin et al., 2012), Parkinson's disease (Lechun, Yu, Pengling, & Changqi, 2013), and pain (Schmahl et al., 2012). Moreover, researchers have proposed the possibility of personalized treatments or interventions for these disorders and symptoms analyzing COMT as a candidate gene. For example, H.-Y. Lee and Kim (2010) identified that the COMT genotype is significantly affected in response to mood stabilizers in manic patients, and Corvol et al. (2011) showed a significant effect of the COMT genotype on responses to entacapone in individuals with Parkinson's disease. In addition, Huang et al. (2016) conducted meta-analysis and identified a significant relationship between the COMT genotype and responses to antipsychotic medications in individuals with schizophrenia.

Researchers also have studied associations of the COMT genotype with SRADs and interventions for those conditions. Tunbridge et al. (2012) synthesized studies about relationships between the COMT genotype and substance-related disorders, including alcoholism, illicit drug use, and smoking and smoking cessation. More recently, researchers have investigated associations between the COMT genotype and gambling disorder (Grant, Leppink, Redden, Odlaug, & Chamberlain, 2015; Guillot, Fanning, Liang, & Berman, 2015). With respect to

Internet use, Han et al. (2007) examined the association between the COMT genotype and excessive Internet video game play in adolescents in South Korea. In sum, although studies regarding associations between the COMT genotype and SRADs have been conducted, the specific association between the COMT genotype and Internet addiction rarely has been explored.

Therefore, this dissertation's research is expected to be innovative. The strength of the overall study is that, to the best of the PI's knowledge, it is the first to explore the association between the COMT genotype and Internet addiction among undergraduate students in South Korea. The data from this study should provide ideas for future research to develop successful interventions and to understand differences in responses to the interventions designed for individuals with Internet addiction.

Approach

Rationale of the Study

This study is based on the model suggested by Brand, Laier, and Young (2014). The model addresses that Internet addiction is associated with 1) a person's core characteristics, including psychopathological aspects (depression, social anxiety), personality aspects (low self-esteem, low self-efficacy, stress vulnerability), and social cognition (emotional loneliness, low social support) and 2) a person's specific cognitions, which include dysfunctional coping strategies for everyday stress and Internet use expectancies. The model proposes that an individual's specific cognitions can also mediate the relationship between the core characteristics and Internet addiction.

Brand, Young, and Laier (2014) also asserted that the pathway from the reinforcement of a person's cognitions regarding Internet to Internet addiction is mediated by cognitive control,

which refers to the ability to control one's behaviors or thoughts with flexibility to achieve one's internal goal. This process is in charge of the PFC (Yuan & Raz, 2014) where COMT plays a key role in the regulation of the level of dopamine. In this respect, the functional SNP of the COMT gene can be assumed to be associated with the progress of Internet addiction.

Therefore, this study aimed to identify and examine relationships between the COMT genotype and Internet addiction as well as between individuals' core characteristics and specific cognitions and Internet addiction. Figure 1.1 presents an adapted version of the model (Brand, Laier, & Young, 2014) that provides the basis for this research.

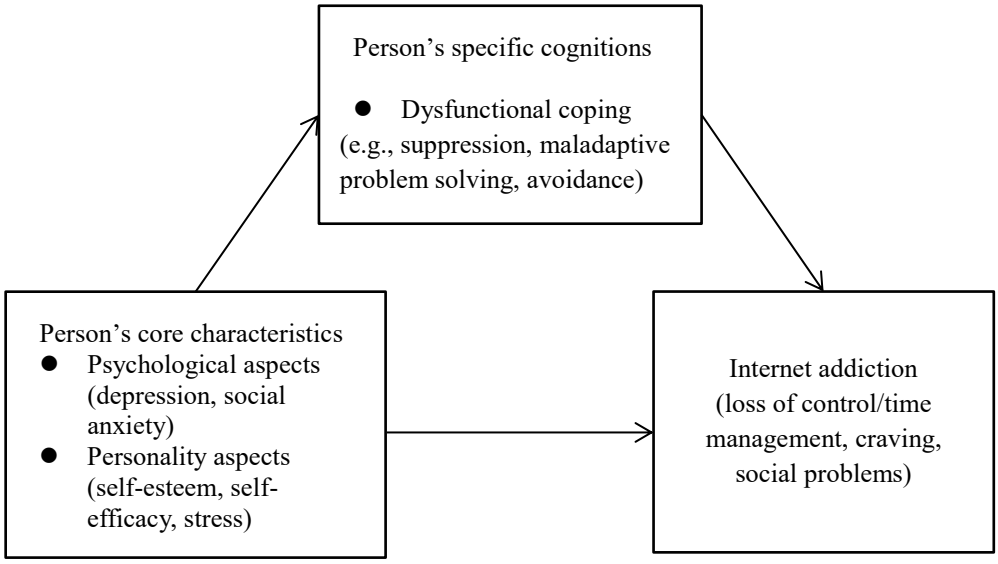

Figure 1.1. Extracted model of Internet addiction. Adapted from "Internet Addiction: Coping Styles, Expectancies, and Treatment Implications" by M. Brand, C. Laier, and K. S. Young, 2014, *Frontiers in Psychology*, *5*(1256), p. 3.

Design

This study was a pilot study examined the feasibility of using a bio-behavioral approach that involved the collection of saliva samples and web-based survey data of the participants who were undergraduate students in South Korea. The study followed a cross-sectional descriptive study design in order to identify associations among Internet addiction, COMT genotype, and

psychological variables (depressive symptoms, social anxiety, self-esteem, self-efficacy, stress, and coping strategies).

Study Sample

Participants. The inclusion and exclusion criteria for the participants of the study were as follows.

Inclusion criteria.

- Individuals who are enrolled as undergraduate students and are 18 years old or older. Because the participants needed to be able to give consent for participation in the research project voluntarily, they needed to be 18 years old or older.
- Individuals who have used the Internet at least once a month recently. The statement that someone has become addicted to the Internet presupposes that he or she has been an Internet user. Thus, each participant for this study needed to be an Internet user, which can be defined as an individual who uses the Internet at least once a month in accordance with the survey conducted by the Korea Internet & Security Agency (2014).
- Individuals who are native Korean and can understand the questions and directions in Korean.

Exclusion criteria.

- Individuals who have taken psychotropic medications, estrogen hormonal drugs, including any type of birth control, and/or dietary supplements that mainly include tea catechin or quercetin in the previous month. Psychotropic medications can alter the activities of the neurotransmitters that in turn could affect the survey results of the psychological variables in this study. Moreover, estrogen, tea catechin, and

quercetin, as well as psychotropic medications, can alter or inhibit COMT enzyme activity (Jiang, Xie, Ramsden, & Ho, 2003; W. J. Lee, Shim, & Zhu, 2005; White et al., 2014).

- Individuals who are pregnant. This is because estrogen, which can impact COMT pathways, is increased during pregnancy (Jiang et al., 2003).

Sampling plan. The PI calculated the total sample size of 241 participants based on power analysis using SAS version 9.4 (SAS Institute, Cary, NC) with 80% power using chi-square tests or t-tests with a 0.05 two-sided significance level. Because this study is the first (to the investigator's knowledge) to examine the association between the COMT genotype and the severity of Internet addiction among Korean undergraduate students, the sample size calculation was based on similar studies that examined the associations between Internet gaming disorder (Han et al., 2007), gambling disorder (Grant et al., 2015; Guillot et al., 2015), or alcohol dependence (Guillot et al., 2015) and the COMT genotype.

The PI estimated the sample size for chi-square testing by comparing the proportion of Internet gaming disorders in the Val/Val group and Met carriers according to Han et al. (2007) and by comparing the proportion of gambling disorders in the Val/Val group and Met carriers according to Grant et al. (2015). In accordance with Guillot et al. (2015), the PI estimated the sample size for the t-tests by comparing the mean scores of the South Oaks Gambling Screen in the Val/Val group and Met carriers and by comparing the mean scores of the Michigan Alcoholism Screening Test in the Val/Val group and Met carriers. As a result, 236 participants were needed, and therefore, 250 participants were recruited for this study, considering the possibility of unexpected missing data or failure of the survey, salivary sample collection, or genotyping processes.

Setting

The PI collected data from a university that has campuses in Seoul and the Seoul metropolitan area of South Korea. The PI collected data during the summer semester in 2016.

Procedures

Recruitment strategy. The PI applied convenience sampling and snowball sampling strategies to recruit participants. The PI placed flyers on notice-boards near the student union and libraries and advertised on student websites to reach a wide variety of students. The advertisement included information about the data collection procedure, including the date and time, process, inclusion and exclusion criteria, information about 5,000 Korean Won [KRW] ($4 ~ $5 based on the current US dollar exchange rate) as incentive for participation, and clarified that the participants must not eat, drink, smoke, or chew gum at least 30 minutes prior to saliva collection.

Survey. The PI used the Qualtrics web-based system to collect the survey data and provided the survey's link address to the potential participants. At the start of the data collection process, the PI explained the proposed study and instructed the participants how to connect to the link to start the survey. The PI prepared laptops and tablet devices for the survey. When the participants clicked on the link, informed consent information first appeared. When they clicked the 'agree' tab to participate in the study, the survey started and the participants were prompted to enter their ID number, which corresponds to the number on the saliva kit. The ID number had been provided to them randomly. After completion of the survey, the PI instructed them about the saliva collection process.

Saliva collection. The saliva samples were collected using an Oragene® DNA OG-500 kit (DNA Genotek, Inc., Ontario, Canada). Cells released from the cheek are in individuals'

saliva, so saliva is easy to collect and the procedure is non-invasive. The PI had asked the participants not to eat, drink, smoke, or chew gum for at least 30 minutes prior to saliva collection in order to extract rich DNA (Chiappin, Antonelli, Gatti, & De Palo, 2007). After the saliva was collected, the PI sealed each of the tubes in accordance with the product protocol and shipped them to the Bio-Behavioral Laboratory (BBL) at The University of North Carolina at Chapel Hill School of Nursing (UNC-CH SON). Because DNA collected using a kit is stable at room temperature for years (Nunes et al., 2012), no special equipment was needed to ship the samples.

DNA extraction. The PI conducted DNA extraction at the BBL at UNC-CH SON. The PI performed DNA extraction to quantification following the prepIT-L2P procedure (DNA Genotek, Inc., Ontario, Canada).

Genotyping. The extracted DNA was shipped to GenoFIND™ services for genotyping using TaqMan SNP Genotyping Assay. TaqMan technology uses a real-time polymerase chain reaction (RT-PCR). In RT-PCR, the differences in sequences are detected by the differences in a certain fluorescent dye detector (VIC® dye versus FAM™ dye) that is separated from the probe. The process uses sequence-specific forward primers and reverses the primers to amplify the sequence and two TaqMan® MGB probes: one VIC®-labeled probe to detect the Allele 1 sequence and a One FAM™-labeled probe to detect the Allele 2 sequence. For the COMT gene, the forward and reverse primers would be TCGAGATCAACCCCGACTGT (forward) /AACGGGTCAGGCATGCA (reverse), and the TaqMan probes for SNP genotyping would be 6FAM-CCTTGTCCTTCACGCCAGCGA/VIC-ACCTTGTCCTTCATGCCAGCGAAAT (Chen et al., 2004).

Contact and consent. Upon approval from the Institutional Review Board of UNC-CH,

the PI placed flyers on notice-boards near the student union and libraries and advertised on student websites. As the participants clicked on the link for the survey, the consent form appeared. The consent form included a description of the study, the risks and benefits of participation in the study, the voluntary nature of participation in that participants could stop the survey at any time, and confidentiality of the data. If the potential participants agreed to participate in the study, they clicked on 'agree' to move forward. Unless the participants agreed to participate in the research, they would not be able to see the survey questions.

Human subject protection. The study proposal was reviewed by the Institutional Review Board of UNC-CH. The participants of the study voluntarily chose to participate in this study. The PI collected the data such that the information was anonymous and kept confidential. The PI informed the participants that they could stop participating at any time. For the participants' time and effort, the PI offered them a 5,000 KRW (about $4 ~ $5 based on the US dollar exchange rate) gift card as compensation.

Data collection. The PI collected the survey data using a web-based survey system, UNC Qualtrics. The saliva collection process utilized an Oragene® DNA OG-500 kit. When the students agreed to participate in the research, they were asked to write their ID on their saliva tubes. The ID was not related to their private information. Once they entered their ID, they could begin responding to the survey questions.

The PI distributed the kit for collecting saliva before the participants began the survey. A barcode on each tube corresponded to each participant's ID. After distributing the kits, the PI explained that the participants needed to spit saliva up to the line on the tube, close the lid tightly, and then shake the tube gently to mix the saliva and reagents. The PI demonstrated the process of saliva collection and helped those students who had difficulty with the process.

Data management. The entered data were stored automatically on the Qualtrics servers. These survey data currently are being stored for at least five years according to UNC's Policies for Storage of Student Research Data. The extracted DNA samples were stored in a freezer and shipped in dry ice to GenoFIND^{TM} services for genotyping. The genotyping data are being stored with the survey data for at least five years.

Measures for data-generating techniques. Table 1.1 provides a summary of the instruments used to measure the outcome variables in this study in terms of variables, features, and reliability.

Internet addiction. The PI applied the Korean language version of the IAT (referred to as the KIAT) to assess the severity of Internet addiction of the participants. The IAT was developed by Young (1998a) and has been translated into various languages, validated, and is widely used. The Korean version was developed by Yun (1999). This instrument is a self-report, 20-item, 5-point Likert questionnaire. Responses range from 1 (never) to 5 (always), so possible total scores range from 20 to 100. The original version was a 6-point Likert questionnaire with the score 0 for the response 'not applicable'; this response was removed from the Korean version. A higher score indicates more severe Internet addiction, and cut-off points of total scores were established to identify each level of Internet addiction: 20-30 (normal level of Internet usage), 31-49 (mild), 50-79 (moderate), and 80-100 (severe). Individuals with a moderate level of Internet addiction are thought to be starting to experience problems with Internet usage. In Yun (1999), Cronbach's alpha for the KIAT was .79.

Table 1.1. *Variables, Instruments, and Reliability*

Variables	Instrument	Feature	Reliability
Feasibility	Final sample size, rate of response, rate of missing data, challenges and facilitators of the study process		N/A
Internet addiction	IAT	Self-report, 20-item, 5-point Likert	α = .79
COMT genotype	SNP genotyping (saliva DNA)	Val/Val, Val/Met, Met/Met	N/A
Demographic characteristics	Age, gender, SES, family members, year, major, religion		N/A
Internet usage	Using the device, the purpose of Internet use, length of Internet use (average per day)		N/A
Health-related behaviors	Drinking (AUDIT-C-K), smoking (CDS-5), exercise, sleep		N/A
Depressive symptoms	CES-D	Self-report, 20-item, 4-point Likert	α = .91
Social anxiety	K-SAD	Self-report, 28-item, 5-point Likert	α = .92
Self esteem	RSES	Self-report, 10-item, 4-point Likert	α = .86-.87
Self-efficacy	Self-Efficacy Scale	Self-report, 10-item, 4-point Likert	α = .88
Stress	PSS	Self-report, 10-item, 5-point Likert	α = .75-.76
Coping	Brief COPE	Self-report, 28-item, 4-point Likert	α = .50-.90

Note. IAT (Internet Addiction Test); COMT (catechol-o-methyltransferase), SNP (single nucleotide polymorphism); SES (socio-economic status); AUDIT-K (Korean version of Alcohol Use Disorders Identification Test-Consumption Questions); CDS-5 (Korean version of the Cigarette Dependence Scale 5-item short version); CES-D (Center for Epidemiologic Studies – Depression scale); K-SAD (Korean version of Social Avoidance and Distress scale); RSES (Rosenberg Self-Esteem Scale); PSS (perceived stress scale)

***Drinking and smoking*.** In order to assess the alcohol use of the participants, the PI applied the Korean version of the Alcohol Use Disorders Identification Test-Consumption Questions (AUDIT-C-K). The original version of the AUDIT was developed by the World Health Organization in 1989. For the purposes of this study, the PI utilized the three-item, AUDIT Alcohol Consumption Questions (AUDIT-C) to assess alcohol consumption. Bush, Kivlahan, McDonell, Fihn, and Bradley (1998) suggested this short version, which has been widely used

with high reliability and validity. B.O. Lee, Lee, Lee, Choi, and Namkoong (2000) developed Korean versions of both AUDIT and AUDIT-C, and Cronbach's alpha values of these Korean versions were .92 and .85, respectively.

To assess the smoking habits of the participants, the PI applied the Korean version of the Cigarette Dependence Scale 5-item short version (CDS-5). The original version of the CDS was developed by Etter, Le Houezec, and Perneger (2003), who also suggested the short version (CDS-5). Kim and Paek (2008) translated the CDS into Korean, and the Cronbach's alpha was .84.

Depressive symptoms. The PI used the integrated Korean version of the Center for Epidemiologic Studies - Depression (CES-D) scale to assess depressive symptoms among the participants. The CES-D was developed originally by Radloff (1977), and Chon, Choi, and Yang (2001) translated it into Korean. This instrument is a self-report, 20-item, 4-point Likert questionnaire, with scores ranging from 0 (rarely) to 3 (most or all of the time), so total scores range from 0 to 60. Higher scores represent severer depressive symptoms, and cut-off points of the total scores are set for each severity of depressive symptoms: 0-15 (normal), 16-20 (mild), 21-25 (moderate), and 26-60 (severe). In Chon et al. (2001), Cronbach's alpha of the Korean version of the CES-D was .91.

Social anxiety. To assess the social anxiety of the participants, the PI applied the Korean language version of the Social Avoidance and Distress (K-SAD) scale. The original version was developed by Watson and Friend (1969), and J. Lee and Choi (1997) later translated it into Korean. The K-SAD instrument is a self-report, 28-item, 5-point Likert questionnaire, with scores ranging from 1 (none) to 5 (completely), so total scores range from 28 to 140. Higher scores indicate a higher level of social anxiety, and cut-off points of the total scores are set for

each social anxiety level: 0-63 (normal), 64-81 (mild), 82-98 (moderate), and over 99 (severe). In J. Lee and Choi (1997), Cronbach's alpha for the K-SAD was .92 among undergraduate students.

Perceived stress. In order to assess the level of perceived stress of the participants, the PI used the Perceived Stress Scale (PSS), developed by Cohen, Kamarck, and Mermelstein (1983) and translated into Korean and validated by J. Park and Seo (2010). This instrument is a self-report, 10-item, 5-point Likert questionnaire, with possible responses ranging from 0 (never) to 4 (very often). Higher scores indicate higher perceived stress. In J. Park and Seo (2010), Cronbach's alpha of this instrument ranged from .75 to .76 for undergraduate students.

Self-esteem. In order to measure the participants' self-esteem, the PI applied the Korean language version of the Rosenberg Self-Esteem Scale (RSES). The RSES was first developed by Rosenberg (1965) and has been translated into 28 languages (J. Lee, Nam, Lee, Lee, & Lee, 2009), including Korean (B. J. Chon, 1974). This instrument is a self-report, 10-item, 4-point Likert questionnaire, with possible responses ranging from 1 (strongly disagree) to 4 (strongly agree). Higher scores indicate higher self-esteem. In B. J. Chon (1974), Cronbach's alpha was .86. J. Lee et al. (2009) reported similar reliability ($\alpha = .87$) with undergraduate students in their study of the item-level validity of the RSES.

Self-efficacy. To measure the general self-efficacy of the participants, the PI applied the Self-Efficacy Scale developed by Jerusalem and Schwarzer (1992). This instrument is a self-report, 10-item, 4-point Likert questionnaire, with possible responses ranging from 1 (not true) to 4 (exactly true). This scale was translated into Korean and validated by Schwarzer et al. (1997). Cronbach's alpha of the Korean version was .88.

Coping strategies. To assess the participants' coping strategies, the PI used the Brief Coping Orientation to Problems Experienced (COPE) scale, developed by Carver (1997) and

translated into Korean by Y. Kim and Seidlitz (2002). This instrument includes 14 coping strategies: self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion, and self-blame. This instrument is a self-report, 28-item (two items for each strategy), 4-point Likert questionnaire, with scores ranging from 1 (I haven't been doing this at all) to 4 (I've been doing this a lot). There is no overall score for this scale, and Cronbach's alpha of each factor ranged from .50 to .90.

Analysis

To identify issues related to the feasibility of conducting a cross-sectional study that involves the collection of saliva samples and web-based survey data with the participants who were undergraduate students in South Korea, the PI examined the response rate to the web-based survey questions and the missing data. The PI specifically assessed patterns of missing data across the survey to identify any commonly missed questions or survey sections among the participants or to determine if data were missing at random. The PI evaluated the rate of the survey responses and compared it to the rate of the saliva sample collection from participants to determine any possible differences. In addition, the PI reported other specific barriers and facilitators to recruitment, data and sample collection, and analysis.

To investigate relationships among Internet addiction, COMT genotype, and psychological variables, using the collected survey data, the PI first assessed the distribution of each variable using descriptive statistics. The PI applied t-tests to examine the association among the variables by comparing the mean total scores. Using chi-square statistics, the PI compared the proportion the Internet addiction according to COMT genotype as well as the proportion the participants with psychological distress according to Internet addiction. For all the statistical

tests, the PI used SAS software version 9.4 (SAS Institute, Cary, NC) with a 0.05 two-sided significance level.

Potential Limitations

Because this investigation was a pilot feasibility study, the PI acknowledges that challenges related to having an adequate sample to meet 80% power could emerge. However, the study, as designed, should be able to provide information about potential challenges and barriers that are related to using web-based surveys to assess psychological risk factors for Internet addiction among Korean undergraduate students as well as the process of procurement and analysis of saliva samples. The PI assessed and addressed issues related to the feasibility of this study to achieve better methodological quality for future study.

Moreover, because the PI applied convenience sampling at university campuses for this study, the participants were not representative of the entire population of undergraduate students in South Korea. In addition, because the participants of this study were solely undergraduate students in South Korea, generalizing the results from this study to a multi-generation population is a limitation. Therefore, further studies will need to be conducted with expanded demographic characteristics of the population.

Synthesis of Dissertation

Upon completion of the research, the PI synthesized the findings from Papers 1, 2, and 3. Chapter 5 presents these findings, which inform implications for future nursing research and nursing practice regarding Internet addiction.

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CHAPTER 2: PSYCHOSOCIAL RISK FACTORS OF INTERNET ADDICTION AMONG UNDERGRADUATE STUDENTS: A SYSTEMATIZED LITERATURE REVIEW

Introduction

Internet Addiction

The Internet has become an irreplaceable part of people's daily lives due to the rapid technological progress made in recent years. The Internet enables users not only to obtain information and complete tasks such as shopping or banking, but also to communicate or play games with others around the world in real time. In addition, the rapid distribution of portable devices allows access to the Internet anytime and anywhere. The percentage of Internet users, although barely reaching 5% in 1995, has jumped to approximately 70% to 98% in major countries (Feng, Ramo, Chan, & Bourgeois, 2017). However, the popularization of the Internet has resulted in numerous adverse effects, such as cybercrime, violation of privacy, and cyber-bullying (Garett, Lord, & Young, 2016; Luppicini, 2014). Furthermore, Internet addiction has become a serious health and social problem worldwide (Feng et al., 2017).

Internet addiction refers to the state of experiencing physical, psychological, social, and economic problems that are caused by excessive preoccupation with the Internet and loss of self-control, accompanied by symptoms related to substance-related and addictive disorders (SRADs), such as dependence, tolerance, and withdrawal symptoms (Kuss, Griffiths, Karila, & Billieux, 2014; Weinstein & Lejoyeux, 2015; Young, Pistner, O'Mara, & Buchanan, 1999). Since Internet addiction was first identified in the mid-1990s, whether or not Internet addiction should be diagnosed and treated like other SRADs has been a controversial issue

(Weinstein, Curtiss Feder, Rosenberg, & Dannon, 2014). As a result, different terminology (i.e. Internet addiction, Internet use disorder, pathological Internet use, problematic Internet use, compulsive Internet use, and Internet abuse) has been used to describe Internet addiction in previous studies depending on the perspective (Koo & Kwon, 2014). Although the term, 'addiction', traditionally has referred to a state that is caused by dependence to some tangible substance, the current trend is to identify addiction as a state that reflects the repetition of specific actions and symptoms of SRADs, even when any intake of substance does not occur (Karim & Chaudhri, 2012). The inclusion of gambling disorder into the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) is a good example of this interpretation (Karim & Chaudhri, 2012). Internet gaming disorder, which is a subcategory of Internet addiction, also was included in Section III of DSM-5 in 2013, providing a description of addictive behavior and emphasizing the need for further research (American Psychiatric Association, 2013).

Since the concept of Internet addiction was first introduced, many researchers have investigated its biological and psychological factors. Research into the biological factors of Internet addiction has focused primarily on neuroimaging and molecular biological analysis. For example, Kuss, Pontes, and Griffiths (2018) reported that individuals with Internet addiction have structural and functional variations of the region near the prefrontal cortex and an altered dopaminergic reward system, which is linked to symptoms such as loss of self-control, dependence, tolerance, withdrawal symptoms, and craving (Adinoff, 2004). These findings highlight that Internet addiction shares some biological aspects with SRADs. Also, Anderson, Steen, and Stavropoulos (2017) reviewed longitudinal studies of Internet addiction among adolescents and young adults and delineated the status of their addiction and risk factors; the

reported risk factors of Internet addiction include stress, low self-esteem, impulsivity, mental disorders, lack of social support, and family dysfunction. Zhang, Lim, Lee, and Ho (2018) conducted meta-analysis of Internet addiction among medical students, and Feng et al. (2017) presented trends in Internet addiction research. However, few studies have specifically targeted undergraduate students regarding the risk factors of Internet addiction.

Internet Addiction among Undergraduate Students

Undergraduate students have received much attention from Internet addiction researchers because the majority of this population are Internet users (Kuss, Griffiths, & Binder, 2013). Because undergraduates need to utilize the Internet for educational or research purposes, they are exposed to an environment that provides easy access to the Internet (Kuss et al., 2013). Undergraduate students are also looking for social networking and entertainment on the Internet, since they are forming new relationships (Kuss et al., 2013). Moreover, undergraduate students are at a developmental stage in which they are consolidating their identities and forming new relationships as well as transitioning from being adolescents under their parents' protection to being independent adults (Skidmore, Kaufman, & Crowell, 2016). Although undergraduates may enjoy freedom from their parents, they may be challenged by the responsibilities related to their newly acquired independence. Therefore, they may be more vulnerable to Internet addiction. In fact, according to the survey conducted by the National Information Society Agency (2015), 12.5% of undergraduate students were reported as being at risk for Internet addiction, which is about twice the average for other age groups (6.9%). Given the traits that undergraduate students show at this developmental stage and their vulnerability to Internet addiction, the risk factors of Internet addiction among undergraduate students need to be investigated. This systematized review aims to achieve this goal by providing a systemized summary of the literature on this

topic, including study characteristics, the prevalence of Internet addiction, and the psychosocial risk factors of Internet addiction.

Method

This study is a review of the literature that attempts to include elements of a systematic review process. However, because only one researcher, i.e., the Principal Investigator (PI) was mainly responsible for the search process, literature screening, and data extraction, this review is considered to be a systematized review, rather than a systematic review (Grant & Booth, 2009).

The PI performed this review following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) (Moher, Liberati, Tetzlaff, & Altman, 2009) guidelines to report studies that address the psychosocial risk factors of Internet addiction among undergraduate students. Figure 2.1 describes the literature search and screening process. The PI searched four electronic databases: CINAHL Plus with Full Text, PubMed (MEDLINE), PsycINFO, and Scopus. When the PI built the search terms, the variety of terminology used to describe Internet addiction was considered as follows: (“internet addiction” OR “addictive internet” OR “pathological internet” OR “problematic internet” OR “excessive internet” OR “internet gaming” OR “compulsive internet” OR “internet overuse” OR “internet use disorder” OR “internet abuse” OR “internet dependency”) AND (undergrad* OR college OR universit*). The search results were limited to studies written in English and published in peer-reviewed journals between January 2014 and December 2018.

The inclusion criteria were: (a) the participants of the reviewed study were undergraduate students only; (b) the original study examined and reported psychosocial risk factors of Internet addiction, and (c) the reviewed study applied a survey using a validated instrument.

The PI assessed the methodological quality of the reviewed studies in accordance with the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies (National Heart, Lung, and Blood Institute, 2014). However, the studies were not excluded based on evaluation of the methodological quality of the study.

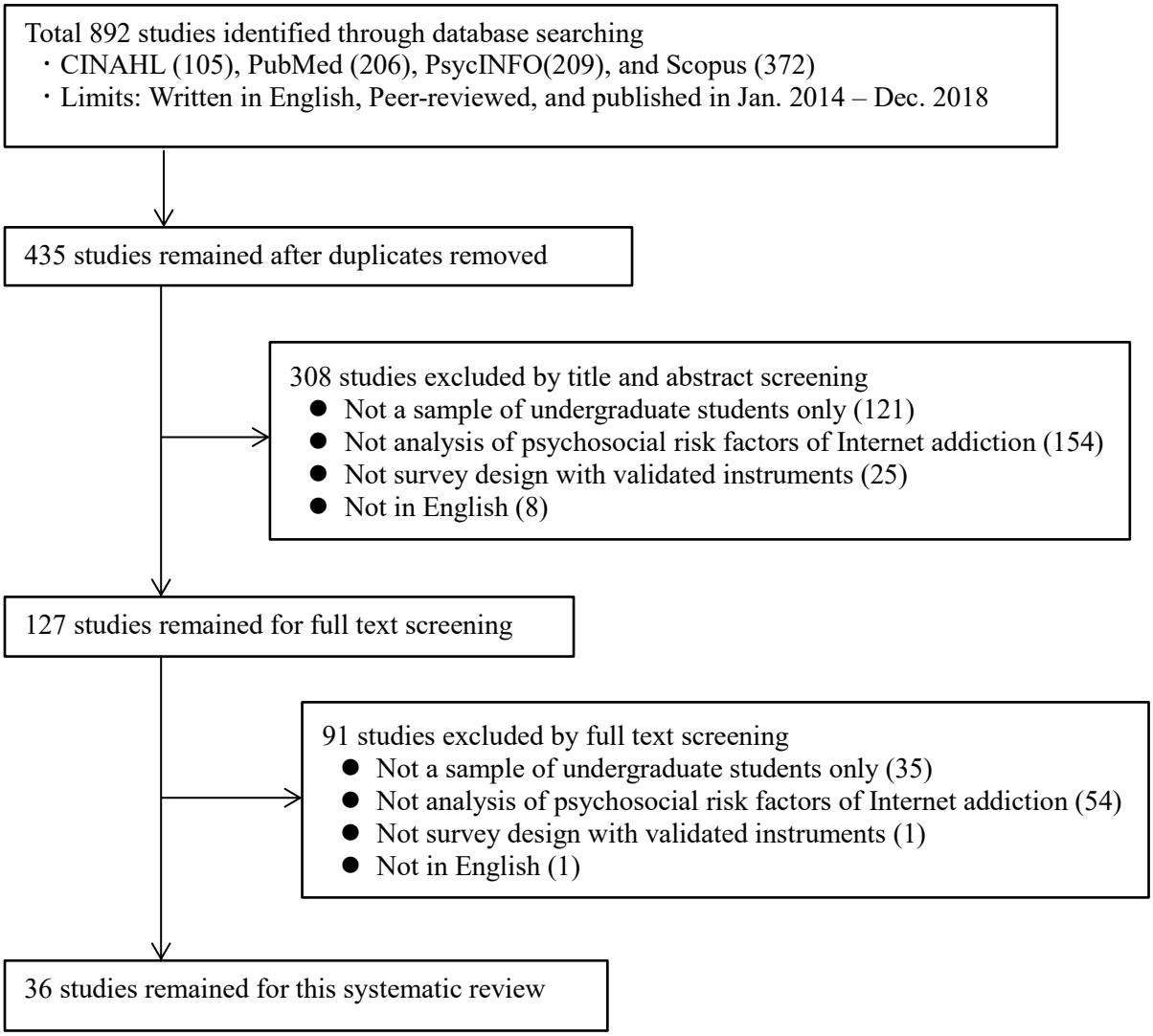

Figure 2.1. The process of literature search and screening

From the four databases, the PI identified 892 studies in total. After removing duplicates, 435 studies remained. Title and abstract screening and full-text screening using the inclusion

criteria yielded 36 studies for this review (Figure 2.1). The PI extracted the following data: author, published year, country, sample size, the percentage of male and female participants, the instrument(s) used to assess the Internet addiction of the participants, including the range of total scores of the instruments and cut-off scores to identify Internet addiction, prevalence of Internet addiction, psychosocial risk factors of Internet addiction identified from the analysis, and other risk factors if mentioned in the study.

Results

Study Characteristics

Table 2.1 presents the characteristics of the reviewed studies in terms of author/year/country, sample size, mean age of participants, cut-off range of the instrument(s) used, prevalence rate, and risk factors. The reviewed studies were conducted in various countries throughout the world, including Italy (n = 8), China (n = 8), Turkey (n = 5), and Taiwan (n = 5). Other studies were conducted in Hong Kong, India, Iran, Poland, South Korea, and the United States. One study was conducted using data from five countries: Indonesia, Malaysia, Myanmar, Thailand, and Vietnam. Among all 36 studies, more than 50% (19 studies, 52.8%) were from Asia, 9 studies (25.0%) were from Europe, and 6 studies (16.7%) were from the Middle-East region. Most of the studies were cross-sectional studies, and five studies applied a longitudinal design (Chou, Yen, & Liu, 2018; Hsieh, Hsiao, Yang, Liu, & Yen, 2018; Tian, Bian, Han, Gao, & Wang, 2017; Wu, Ko, Tung, & Li, 2016; Yao & Zhong, 2014). The sample size of the studies ranged from 159 (Noh & Kim, 2016) to 3,240 (Turnbull et al., 2018). In 29 of the studies (80.6%), more female participants were recruited than male participants. The average age of the participants for all 36 studies was between 18 and 24 years.

Table 2.1. *Summary of Studies: Internet Addiction among Undergraduate Students*

Author (Year) Country	Study Design	Sample Size (M / F %)	Age Mean (SD)	Internet Addiction Instrument (Cut-off) [Score Range]	Internet Addiction Prevalence %/ Mean (SD)	Risk Factors of Internet Addiction Psychosocial	Risk Factors of Internet Addiction Others
Akbari (2017) Iran	CS	413 (51.1/48.9)	20.1	IAT [20-100]	46.4 (3.0)	"Emotional dysregulation" has direct and indirect impact (via metacognition and distress tolerance) on problematic Internet use.	
Anand et al. (2018) India	CS	2776 (39.5/60.5)	18.6 (1.0)	IAT (50-79: moderate 80≤: severe)	Moderate: 16.4% Severe: 0.5%	Depressive symptoms	Male, duration, frequency, and time of Internet use
Casale et al. (2014) Italy	CS	465 (48.3/51.6)	21.9 (2.2)	GPIUS2 [1-8]	2.0 (0.8)	Socially prescribed perfectionism directly (among females) and indirectly affected generalized problematic Internet use through fear of negative evaluations (among males and females) and low perceived social support (among males).	
Casale & Fioravanti (2015) Italy	CS	400 (48.2/51.8)	22.5 (2.1)	GPIUS2 [15-120]	32.1 (15.5)	Social anxiety directly (both males and females) and indirectly affected GPIU through the need for self-presentation (among males).	
Casale et al. (2015) Italy	CS	495 (41.2/58.8)	20.9 (2.0)	GPIUS2 [1-8]	2.3 (0.9)	Low levels of autonomy; less environmental mastery; fewer positive relations with others	
Casale et al. (2016) Italy	CS	293 (48.4/51.6)	21.7 (2.2)	GPIUS2 [1-8]	2.0 (0.9)	"Emotional dysregulation" directly and indirectly predicted problematic Internet use through positive metacognitions	
Choi et al. (2015) South Korea	CS	448 (39.7/60.3)	20.9 (3.1)	SAS [33-198] IAT [20-100]	SAS 68.5 (25.0) IAT 34.1 (11.2)	Smartphone addiction: Internet use, alcohol use, anxiety. Internet addiction: smartphone use, anxiety, and wisdom/knowledge, less courage.	Smartphone: female Internet: male
Chou et al. (2015) Taiwan	CS	500 (47.6/52.4)	22.1 (1.8)	CIAS (68) [26-104]	17%	Less restraint coping; more denial; more mental disengagement Depression mediated between denial and Internet addiction	
Chou et al. (2018)	F/U (1yr)	324 (47.8/52.2)	22.3 (1.9)	CIAS (68)	15.4%	Psychological inflexibility/experiential avoidance; depression; suicidality; less effective coping	

Taiwan				[26-104]			
Craparo et al. (2014) Italy	CS	670 (24.5/75.5)	CD	IAT (40) [20-100]	4.3% 37.2 (11.4)	Shame	
Dalbudak et al. (2014) Turkey	CS	271 (40.6/59.4)	No risk: 22.0 (1.7) Mild risk: 21.7 (1.6) High risk: 21.6 (1.6)	IAS (61-80: mild 81≤: high)	Mild: 38.7% High: 19.9%	Borderline personality features, emotional abuse, depression and anxiety symptoms	
Guo et al. (2018) China	CS	1317 (61.3/ 38.7)	19.9 (1.2)	Revised CIAS [1-4]	2.0 (0.7)	Low quality of social relationships has direct and indirect impact (via loneliness) on Internet addiction	
Gupta et al. (2018) India	CS	380 (62.1/37.9)	19.1 (1.0)	IAT (50) [20-100]	25.3%	Depression, anxiety, stress	Duration of Internet use per week
Hsieh et al. (2018) Taiwan	L F/U (1yr)	T1: 500 (47.6/52.4) T2: 324 (47.8/52.2)	T1: 22.1 (1.8)	CIAS (68) [26-104]	11.2%	Depression; self-harm and suicidal behaviors; uncontrollable sexual encounters	
Jia & Jia (2016) USA	CS	243 (58.0/42.0)	21.5 (1.5)	PIUQ [1-7]	1.7 (0.4)	Attachment anxiety (gender moderates the relationship)	
Kuss et al. (2017) Poland	CS	681 (74.2/25.8)	21.0 (1.5)	AICA-S (13.5) [1-16]	4.0% 4.4 (3.0)	Dysfunctional coping strategies (distraction, denial, self-blame, substance use, venting, media use, and behavioral disengagement)	
Li et al. (2016) China	CS	654 (45.6/54.4)	20.3 (1.4)	CIAS (5) [1-8] OGCAS (32) [16-80]	4.7% OGCAS: 22.9 (9.2)	Avoidant coping strategy and neuroticism mediated between stressful life events and online gaming addiction	
Lu et al. (2017) Taiwan	CS	500 (47.6/52.4)	22.1 (1.8)	CIAS [26-104]	55.6 (13.9)	Borderline personality symptoms have direct and indirect impact (via mental health problems) on Internet addiction	
Ni et al. (2017) China	CS	501 (53.1/46.9)	20.3 (1.8)	IAT [20-100]	NR	Father's refusal or denying; father's overprotectiveness; less mother's emotional warmth; greater psychoticism; avoidant coping; less self-blaming	Older age; grew up in urban area
Noh & Kim (2016)	CS	159 (42.8/57.2)	22.2 (2.1)	IAT (50-79:	Moderate: 25.2%	Dysfunctional attitude fully mediated between depression and Internet addiction, and partially	

South Korea				moderate 80≤: severe)	Severe: 0.6% 41.6 (16.0)	mediated between social anxiety and Internet addiction	
Odaci & Çıkrıkçı (2014) Turkey	CS	380 (40.0/60.0)	19.6 (1.1)	PIUS [33-165]	Mean Male: 64.8 Female: 58.2	Lower subjective well-being; dismissive attachment; preoccupied attachment	Male
Özdemir et al. (2014) Turkey	CS	648 (34.0/66.0)	22.5 (2.5)	IAT [1-6]	1.8 (0.6)	Loneliness; Low self-control mediates depression and loneliness to Internet addiction	
Scimeca et al. (2017) Italy	CS	278 (41.4/58.6)	23.6 (4.4)	IAT [20-100]	36.8 (11.8)	Sexual behavior (low sexual satisfaction; sexual nervousness; sexual shyness; sexual detachment)	
Şenormancı et al. (2014) Turkey	CS	720 (49.7/50.3)	19 [17-35]	IAS (90) [30-150]	7.2%	Depression; perfectionistic attitude	Male; duration of Internet use
Servidio (2014) Italy	CS	190 (38.4/61.6)	21.5 (1.9)	IAT (50-79: moderate 80≤: severe [20-100]	16.3% M: 41.5 (13.2) F: 36.6 (9.8)	Less agreeableness; less extraversion; more openness	Male; frequency Internet use
Servidio et al. (2018) Italy	CS	300 (41.7/58.3)	23.6 (3.2)	IAT (50-79: moderate 80≤: severe) [20-100]	20.7% 41.1 (11.7)	Low self-esteem; avoidance-oriented coping	
Taymur et al. (2016) Turkey	CS	212 (58.5/41.5)	19.4 (1.8)	IAS (81) [31-155]	16.0%	Psychopathological symptoms; dysfunctional attitudes (perfectionist attitude, need for approval, autonomous attitude, and tentative attitude)	
Tian et al. (2017) China	L CL	T1: 500 (44.2/55.8) T3: 361 (38.2/61.8)	T3: 18.6 (0.9)	Chinese IAT [20-120]	T1: 35.0 (10.1) T2: 36.9 (11.9) T3: 37.7 (11.8)	Shyness, loneliness, and interpersonal relationships, maladaptive cognitions Maladaptive cognitions mediated between shyness and generalized pathological Internet use	
Tian et al. (2018)	CS	1621 (32.8/67.2)	21.7 (2.0)	Chinese IAT [19-114]	36.0 (9.1)	Shyness → interpersonal relationships → loneliness → maladaptive cognitions →	

China						generalized pathological Internet use	
Turnbull et al. (2018) Indonesia, Malaysia, Myanmar, Thailand, Vietnam	CS	3240 (37.2/62.8)	20.5 (1.6)	YDQ (5)	35.9%	Childhood physical and sexual abuse; lack of social support; Comorbid symptoms (gambling problem; harmful alcohol use; drug use; depression; sleeping problems; suicide attempting; PTSD)	Heavy Internet use (for recreational purposes); heavy smartphone use
Wong et al. (2015) Hong Kong	CS	229 (31.4/ 68.6)	21.3 (1.5)	IAT [20-100]	Mean: 50.0	Psychological distress (depression, anxiety, stress) mediates need satisfaction to problematic Internet use	
Wu et al. (2016) Taiwan	L (1 yr F/U)	T1: 1826 (38.0/62.0) T2: 623	T2: 19.6 (1.2)	CIAS [26-104]	T2: 53.1 (13.8)	Borderline personality disorder; Internet use expectancy for tension reduction and disinhibition meditated borderline personality to Internet addiction.	
Yan et al. (2014) China	CS	892 (45.6/54.4)	20.5 (1.2)	CIAS (58-63: mild 64≤: severe) [26-104]	Mild: 21.2% Severe: 10.0%	Neuroticism; health & adaptation problems (e.g. severe illness or separation from family)	
Yang et al. (2016) China	CS	450 (38.1/61.9)	19.8	CIAS-R [26-104]	49.9 (12.9)	Parental attachment mediated the relationship between marital conflict and Internet addiction through peer attachment	
Yao et al. (2014) Hong Kong	CL (4 mon)	T1: 636 T2: 361 (51.7/37.6)	21.6 (2.6)	IAT [1-7]	3.4 (1.0)	Online social contacts were not an effective in reducing loneliness; face-to-face contacts could help to reduce symptoms of Internet addiction	
Yu et al. (2016) China	CS	395 (36.7/63.3)	19.1 (1.3)	IAT BFAS (54) [18-90]	Facebook addiction 28.6%	Loneliness; Low optimism was an indirect risk factor of social networking addiction through outcome expectancies and self-efficacy	

Note. M = Male; F = Female; SD = Standard deviation; CS = Cross-sectional; IAT = Internet Addiction Test; GPIUS2 = Generalized Problematic Internet Use Scale 2; SAS = Smartphone Addiction Scale; CIAS = Chen Internet Addiction Scale; F/U = Follow-up; CD = Cannot determine; IAS = Internet Addiction Scale; L = Longitudinal; PIUQ = Problematic Internet Usage Questionnaire; AICA-S = Computer and Internet Addiction – Screener; OGCAS = Online Game Cognitive Addiction Scale; NR = Not reported; CR = Cross-lagged; YDQ = Young's Diagnostic Questionnaire for Internet Addiction; PTSD = Post-traumatic stress disorder; BFAS = Bergen Facebook Addiction Scale.

Assessment of Internet Addiction

The terminology used to describe Internet addiction varied in each reviewed study. The instruments and cut-off scores that were used to assess Internet addiction also varied, as shown in Table 2.1. Table 2.1 presents not only the types of instruments used to measure Internet addiction of the participants, but also the cut-off score applied in each study and the range of possible total scores for each instrument.

There were a number of scales that were used to assess Internet addiction, including the Generalized Problematic Internet Use Scale 2 (Casale, Caplan, & Fioravanti, 2016; Casale, Fioravanti, Flett, & Hewitt, 2014; Casale, Lecchi, & Fioravanti, 2015; Casale & Fioravanti, 2015), the Internet Addiction Scale (Dalbudak, Evren, Aldemir, & Evren, 2014), the Problematic Internet Usage Questionnaire (Jia & Jia, 2016), the Computer and Internet Addiction Screener (Kuss et al., 2017), the Chinese IAT (Tian et al., 2018, 2017), and Young's Diagnostic Questionnaire for Internet Addiction (Turnbull et al., 2018).

However, these scales only rarely appeared in published research studies. The most commonly used scales included the Chen's Internet Addiction Scale (CIAS) and the Internet Addiction Test (IAT). The CIAS is a self-report, 26-item, 4-point Likert questionnaire, with possible total scores ranging from 26 to 104 (Chen, Weng, Su, Wu, & Yang, 2003). A higher score represents more severe Internet addiction. Suggested cut-off points of total scores that were used to identify each level of Internet addiction were: 26-57 (normal), 58-63 (mild), and 64-104 (severe). Three studies (Lu et al., 2017; Wu et al., 2016; Yang, Zhu, Chen, Song, & Wang, 2016) applied the total score as a continuous variable, and four studies (W.-P. Chou et al., 2018; W. P. Chou et al., 2015; Hsieh et al., 2018; Yan et al., 2014) applied the cut-off score to determine the Internet addiction of the study participants. Two studies reported an average point of each item as

a continuous variable (Guo, You, Gu, Wu, & Xu, 2018; Li, Zou, Wang, & Yang, 2016).

The IAT was the most commonly used instrument; it was used in 14 studies. The IAT, developed by Young (1998), has been translated into many languages and validated, and its use is widespread. The IAT is a self-report, 20-item, 5-point Likert questionnaire, with possible total scores ranging from 20 to 100. A higher score indicates more severe Internet addiction. The suggested cut-off points of the total scores that were used to identify each level of Internet addiction were: 20-30 (normal level of Internet usage), 31-49 (mild), 50-79 (moderate), and 80-100 (severe). Five studies (Akbari, 2017; Choi et al., 2015; Craparo et al., 2014; Scimeca et al., 2017; Wong, Yuen, & Li, 2015) applied the total score as a continuous variable, and five studies (Anand et al., 2018; Gupta, Khan, Rajoura, & Srivastava, 2018; Noh & Kim, 2016; Servidio, 2014; Servidio, Gentile, & Boca, 2018) applied the suggested cut-off score to identify Internet addiction of the study participants. However, other studies reported the average point of each item as a continuous variable (Özdemir, Kuzucu, & Ak, 2014; Yao & Zhong, 2014).

Prevalence of Internet Addiction

Among the studies in which the IAT scores were applied as a continuous variable, the mean total scores ranged from 34.1 (Choi et al., 2015) to 50.0 (Wong et al., 2015) out of the total score of 100. According to the studies in which the IAT scores were applied to categorize the level of Internet addiction according to the cut-off scores, 16.3% (Servidio, 2014) to 25.8% (Noh & Kim, 2016) of the participants were experiencing at least moderate Internet addiction. Among the studies in which the CIAS scores were applied as a continuous variable, the mean total scores ranged from 49.9 (Yang, Zhu, Chen, Song, & Wang, 2016) to 55.6 (Lu et al., 2017) out of the total score of 104. According to the studies in which the CIAS scores were utilized to categorize the level of Internet addiction according to the cut-off scores, 10.0% (Yan, Li, & Sui, 2014) to

17.0% (Chou et al., 2015) of the participants were experiencing severe Internet addiction. Overall, across all of the instruments used in the studies, 10% to 25% of undergraduate students were reporting problems with Internet use.

Psychosocial Risk Factors of Internet Addiction

The reviewed studies reported various psychosocial risk factors for Internet addiction, including high psychological distress (depression, anxiety, stress, substance abuse, and suicidality) (Anand et al., 2018; Choi et al., 2015; Chou et al., 2018; Dalbudak et al., 2014; Gupta et al., 2018; Noh & Kim, 2016; Şenormancı et al., 2014; Turnbull et al., 2018; Wong et al., 2015), personality traits (neuroticism, perfectionism, psychoticism, less agreeableness, and less extraversion) (Ni, Qian, & Wang, 2017; Servidio, 2014; Yan et al., 2014), and coping strategies (dysfunctional coping, avoidant coping, denial coping, and mental disengagement) (Chou et al., 2018; Kuss et al., 2017; Li, Zou, Wang, & Yang, 2016; Ni et al., 2017; Servidio et al., 2018). The social risk factors for Internet addiction included loneliness, lack of social support, lack of positive social relationships, problems with parental relationship, and fear of negative evaluations from others (Casale & Fioravanti, 2015; Casale et al., 2014; Guo, You, Gu, Wu, & Xu, 2018; Odaci & Çıkrıkçı, 2014; Turnbull et al., 2018; Yu, Wu, & Pesigan, 2016).

Assessment of Methodological Quality

Table 2.2 presents an assessment of the methodological quality of the reviewed studies. All 36 studies clearly addressed the study's research questions or objectives and clearly specified and defined the study population. Most of the studies did not specify inclusion or exclusion criteria for the participants; only six studies (Anand et al., 2018; Gupta et al., 2018; Hsieh et al., 2018; Scimeca et al., 2017; Taymur et al., 2016; Wu et al., 2016) clearly reported the inclusion and exclusion criteria of the participants.

Table 2.2. *Methodological Quality Assessment*

Author (year)	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Akbari (2017)	Y	Y	NA	NR	Y	N	NA	NR	Y	N	Y	NR	NA	Y
Anand et al. (2018)	Y	Y	NA	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y
Casale et al. (2014)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Casale & Fioravanti (2015)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Casale et al. (2015)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Casale et al. (2016)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Choi et al. (2015)	Y	Y	NA	NR	N	N	NA	Y	Y	N	Y	NR	NA	Y
Chou et al. (2015)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Chou et al. (2018)	Y	Y	NA	NR	N	N	Y	NR	Y	Y	Y	NR	CD	Y
Craparo et al. (2014)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Dalbudak et al. (2014)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Guo et al. (2018)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Gupta et al. (2018)	Y	Y	NA	Y	Y	N	NA	Y	Y	N	Y	NR	NA	Y
Hsieh et al. (2018)	Y	Y	NA	Y	N	N	Y	NR	Y	Y	Y	NR	N	Y
Jia & Jia (2016)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Kuss et al. (2017)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y

Li et al. (2016)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Lu et al. (2017)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Ni et al. (2017)	Y	Y	NA	NR	N	N	NA	Y	Y	N	Y	NR	NA	Y
Noh & Kim (2016)	Y	Y	NA	NR	Y	N	NA	Y	Y	N	Y	NR	NA	Y
Odaci (2014)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Özdemir et al. (2014)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Scimeca et al. (2017)	Y	Y	NA	Y	N	Y	NA	Y	Y	N	Y	Y	NA	Y
Şenormancı et al. (2014)	Y	Y	NA	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y
Servidio (2014)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Servidio et al. (2018)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Taymur et al. (2016)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Tian et al. (2017)	Y	Y	NA	NR	N	N	Y	NR	Y	Y	Y	NR	N	Y
Tian et al. (2018)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Turnbull et al. (2018)	Y	Y	NA	NR	N	N	NA	Y	Y	N	Y	NR	NA	Y
Wong et al. (2015)	Y	Y	NA	NR	Y	N	NA	Y	Y	N	Y	NR	NA	Y
Wu et al. (2016)	Y	Y	NA	Y	N	N	Y	NR	Y	Y	Y	NR	N	Y
Yan et al. (2014)	Y	Y	NA	NR	N	N	NA	Y	Y	N	Y	NR	NA	Y
Yang et al. (2016)	Y	Y	NA	NR	N	N	NA	NR	Y	N	Y	NR	NA	Y
Yao et al.	Y	Y	NA	NR	N	N	Y	NR	Y	Y	Y	NR	N	Y

(2014)														
Yu et al. (2016)	Y	Y	NA	NR	N	N	NA	Y	Y	N	Y	NR	NA	Y

Note. Y = Yes; N = No; NA = Not applicable; NR = Not reported; CD = Cannot determine

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

However, most of the other studies reported only the rationale for excluding study participants after data collection due to missing data. In terms of sample size, only four studies (Akbari, 2017; Gupta et al., 2018; Noh & Kim, 2016; Wong et al., 2015) provided sample size justification or a power description. With regard to measures, all of the studies utilized validated instruments to assess Internet addiction and the psychosocial well-being of the participants. Reliability of the instruments was reported in all 36 studies. For the longitudinal studies, the follow-up rate of the participants ranged from 34.1% (Wu et al., 2016) to 72.2% (Tian et al., 2017).

Discussion

In this systematized review, the PI reviewed 36 studies that investigated the psychosocial risk factors for Internet addiction among undergraduate students. This paper reports where the reviewed studies were conducted, the instruments that the reviewed studies used to assess Internet addiction, and the prevalence of Internet addiction and Internet addiction severity among undergraduate students.

The reviewed studies were conducted in various countries around the world. The findings show that, as the Internet has become increasing popular and an indispensable part of people's daily lives globally, new challenges related to Internet addiction have emerged. Once researchers began to report that Internet addiction can cause physical, psychological, social, and financial distresses, as is the case for other SRADs, researchers' interest in understanding, preventing, and treating Internet addiction has spread around the globe (Vondráčková & Gabrhelík, 2016). Most of the reviewed studies were conducted in Asia, where the prevalence of Internet addiction is reported as being higher than in other regions of the world (even though specific comparisons were difficult for the PI to make due to discrepancies among the different

instruments used in the studies). With regard to Internet addiction in Asia, heavy traffic and pollution, relatively low life satisfaction, stress due to intense competition, and Internet accessibility (e.g., the prevalence of Internet cafés) were reported to be associated risk factors (Cheng & Li, 2014). On the other hand, studies also have reported that the high prevalence of Internet addiction may be related to parents' tendency to pathologize Internet usage that could hinder their child's academic achievement (Griffiths, Kuss, Billieux, & Pontes, 2016). Therefore, consideration of environmental and cultural aspects is needed in future studies of Internet addiction.

In this study, the PI determined that terminology used for Internet addiction was inconsistent in each study due to lack of consensus on the definition of Internet addiction. The instruments and cut-off scores that were used to assess Internet addiction also varied across the reviewed studies. For these reasons, direct comparisons of the prevalence of Internet addiction of undergraduate students reported in each study were impossible to draw. However, roughly 10% to 25% of undergraduate students were reported to have problems with Internet addiction or to have severe symptoms of Internet addiction. Therefore, the development of consented assessment systems regarding Internet addiction is urgently needed in order to establish consistency in study findings.

According to the studies reviewed, psychological distresses, such as depression, anxiety, and stress, dysfunctional coping strategies, problems with interpersonal relationships, and loneliness have been reported as major risk factors for Internet addiction among undergraduate students. These risk factors are similar to risk factors of Internet addiction among children and adolescents reported in previous studies (Gentile et al., 2017; Paulus, Ohmann, von Gontard, & Popow, 2018). The reason for this similarity may be that undergraduate students, who are in a

transition period from adolescence to adulthood in terms of developmental stage, are continuing to develop needed coping skills in the context of various adolescent-related psychosocial problems. Meta-analysis (Ho et al., 2014) of the relationship between Internet addiction and psychological distresses revealed that approximately 20% to 25% of individuals with Internet addiction experience depression and anxiety.

According to a cognitive-behavioral model of Internet addiction (Davis, 2001), certain abnormal behaviors generally result from psychological vulnerability, such as depression, anxiety, stress, or other SRADs. In such a situation in which psychological vulnerability exists, Internet addiction can be developed by maladaptive cognition regarding the Internet. In other words, undergraduate students may be more vulnerable to developing Internet addiction as a result of experiencing a new world and seeking escape from reality and relief through Internet use. This explanation is also relevant to the association between having problems with social relationships and developing Internet addiction. When the Internet is used to obtain positive reactions from others in a non-threatening way while experiencing negative self-appraisal, low self-esteem, or low self-efficiency, vulnerability to Internet addiction may increase (Davis, 2001). Therefore, when planning an intervention for individuals with Internet addiction, their psychosocial vulnerabilities must be considered and the intervention should address maladaptive cognition that results in rewarding use of the Internet.

Limitation of the Study

With the recent and rapid diversification and universalization of the Internet, researchers' interest in Internet addiction also has amplified, resulting in many studies that have been conducted throughout the world. However, in this study, the PI found it nearly impossible to identify and compare the prevalence of Internet addiction among undergraduate students due to

the lack of consensus on the definition of Internet addiction and the measures used to assess it. A growing body of research suggests that people are experiencing physical, psychological, and social distresses due to pathologically preoccupied Internet use. Given that studies that focus on the prevention and intervention of Internet addiction are necessary and must utilize accurate assessment tools, consensus on the definition of Internet addiction and associated measures is imperative.

Many studies reviewed here had methodological limitations. The procedure for sample size justification was not reported in most of the studies and the inclusion and exclusion criteria for participants also were often unclear or nonexistent. Although some studies systematically applied stratified sampling, other studies used participants from only a few of certain college classes. Specifically, the reported prevalence of Internet addiction among undergraduate students showed significant differences, even in the studies that applied the same instrument, were conducted in the same country, and were published within a similar period. These findings limit the generalization of such studies. In future studies, generalization must be considered by dealing with extraneous variables and applying elaborate sampling strategies that can affect the methodological quality of the research.

Lastly, this review was limited to studies written in English. Considering that most of the studies reviewed were conducted in non-English-speaking countries, the reviewed studies might not incorporate all the available evidence due to possible translation issues. Future reviews that incorporate studies written in various languages are needed.

Implications for Nursing Research and Practice

For this research, the PI investigated the psychosocial risk factors of Internet addiction among undergraduate students through a systematized review of the literature. However, given

that Internet addiction is affected by various factors, not only should psychosocial risk factors be investigated, but also biological factors, environmental factors, and cultural factors of Internet addiction, as well as the interactions among these factors.

Healthcare providers should assess in depth whether their patients' psychosocial factors (and other possible risk factors) could influence the development of Internet addiction and then evaluate their maladaptive cognition regarding Internet usage when planning appropriate interventions. As mentioned, undergraduate students are in a transitional stage from adolescence to adulthood and are possibly not fully comfortable with the freedom that they experience upon entering college. As a result, they may become more vulnerable to Internet addiction. Future research that targets the prevention of Internet addiction may benefit from a focus on the development of healthy cognitive-emotional functioning and coping skills as they relate to Internet use.

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CHAPTER 3: RELATIONSHIPS BETWEEN COMT GENOTYPE AND SUBSTANCE-RELATED AND ADDICTIVE DISORDERS: A SYSTEMATIZED LITERATURE REVIEW

Introduction

Substance-related and addictive disorders (SRADs) are chronic conditions that represent physical and psychological dependency on psychoactive substances or behaviors and that accompany symptoms of tolerance, withdrawal, obsession, and compulsion (Zou et al., 2017). SRADs can be related to the use of alcohol, tobacco, and illicit drugs and are considered serious health and social problems worldwide (Peacock et al., 2018). Individuals with SRADs face severe disruptions to their daily lives because of the physical, psychological, social, and financial distresses that result from SRAD symptoms (Lander, Howsare, & Byrne, 2013). Healthcare institutions and services incur considerable direct costs that are required in order to treat individuals with SRADs. Also, substantial indirect costs result from reduced productivity due to the disabilities and premature deaths of individuals with SRADs (Peacock et al., 2018). According to Peacock et al. (2018), in 2015, 18.4% of the total adult population throughout the world, which is approximately one billion people, reported heavy episodic alcohol use and 15.2% reported daily tobacco use. Approximately 5% had experience of illicit drug use and, among them, more than 10% reported that they required treatment for drug use disorder. Across the globe, years of healthy lives are lost due to SRADs; for example, disability-adjusted life years (DALYs) amounted to 28 million years due to illicit drug use and 170 million years due to tobacco use (Peacock et al., 2018).

Neurobiological Mechanism of SRADs: The Dopaminergic Pathway

A neurobiological model that can be used to explain SRADs emphasizes the role of the reward system through the dopaminergic pathway (Koob & Volkow, 2016). Dopamine, which is the key neurotransmitter in this mechanism, is synthesized in the substantia nigra and the ventral tegmental area (VTA) of the midbrain (Adinoff, 2004). The path that takes dopamine from the VTA, travels to the nucleus accumbens (NAc) in the ventral striatum, and then extends to the limbic system and the prefrontal cortex (PFC), is referred to as the mesocorticolimbic pathway (Koob & Volkow, 2016). This pathway is known to influence motivation and reward and is one of the most important biological mechanisms that underlies SRADs. This system is controlled through interactions of the stimulatory and inhibitory neurotransmitters (Koob & Volkow, 2016). Repetitive exposure to addictive substances, including alcohol, nicotine, and various illicit drugs, and behaviors such as gambling and Internet gaming increase dopamine secretion in the NAc of this pathway (Volkow & Morales, 2015). Recurrences of such stimulation result in changes in the synapses in the pathway, and such changes have been implicated as the neurobiological basis for developing SRADs (Volkow & Morales, 2015).

Researchers also have been interested in the molecular, biological, genetic, and epigenetic factors associated with SRADs. One of the most studied epigenetic factors that is related to SRADs is single nucleotide polymorphisms (SNPs), a common variation of single bases in the DNA sequence of the genes related to the neurobiological mechanism of SRADs (Andersen, Dogan, Beach, & Philibert, 2015). The catechol-O-methyltransferase (COMT) gene, which affects the activity of dopamine, is one of the candidate genes that has been researched to understand various illnesses related to dopaminergic neurotransmission, including not only SRADs but also schizophrenia and Parkinson's disease (González-Castro et al., 2016; Jiménez-

Jiménez, Alonso-Navarro, García-Martín, & Agúndez, 2014; Tammimäki & Männistö, 2010).

Dopamine is synthesized from tyrosine, which is a kind of amino acid, and released through synaptic vesicles (Klein et al., 2019). The amount of dopamine that is involved in neurotransmission can be controlled by (a) adjusting the number of neurotransmission receptors, (b) causing a re-uptake of dopamine to the presynaptic neurons via the transporters and restoring dopamine for future use, and (c) destroying the dopamine using enzymes such as COMT or monoamine oxidase within the neuron (Klein et al., 2019). In the prefrontal cortex (PFC) that extends from the dopaminergic mesocorticolimbic pathway, which is related to SRADs, the amount of dopamine is controlled mostly through COMT, because the number of dopamine transporters is relatively low (Diamond, 2007).

COMT Genotype and SRADs

COMT, a postsynaptic enzyme, degrades catecholamines such as dopamine, epinephrine, and norepinephrine. The size of chromosome-encoding COMT is approximately 27 kilobase pairs, and the existence of around 350 polymorphisms has been reported in the chromosome (Klimkiewicz et al., 2017). Among them, one of the single nucleotide polymorphisms is formed in codon 158 by the shift from the nucleobase, guanine, to another nucleobase, adenine. As a result, the translation to amino acid is altered from valine to methionine, which eventually leads to the functional variations of COMT (Dauvilliers, Tafti, & Landolt, 2015).

Three genotypes have been identified through the single nucleotide polymorphism of the COMT gene: Val/Val, Val/Met, and Met/Met. The activation of the COMT enzyme differs according to the genotype (Dauvilliers et al., 2015). Individuals with Val/Val show the highest activity of the COMT enzyme, which leads to a low level of extracellular dopamine, especially in the PFC (Dauvilliers et al., 2015). By contrast, individuals with Met/Met show an approximately

40% decrease in COMT enzyme activity compared to those with Val/Val and, therefore, they have a high level of extracellular dopamine (J. Chen et al., 2004). In this respect, this gene has been the focus of attention in various studies related to neuropsychiatric disorders.

Researchers have conducted numerous studies regarding the relationships between the COMT genotype and SRADs. A literature review (Tunbridge et al., 2012) and meta-analysis (Tammimäki & Männistö, 2010) have been conducted to study relationships between the COMT genotype and SRADs; these studies include alcohol, nicotine, and illicit drug use. Tammimäki and Männistö (2010) performed reviews and meta-analyses of 37 studies published from January 1996 to August 2010. Although most of the reviewed studies reported mixed results, people with the Val allele were thought to have a lower success rate with smoking cessation treatments than those with Met/Met. Tunbridge et al. (2012) reviewed 53 studies published through 2011; their results were similar to those of Tammimäki and Männistö (2010). According to Tunbridge et al. (2012), the Val allele is related to an increased probability of smoking and poor success with smoking cessation, whereas an association with other types of SRADs was weak. Both studies concluded that it is premature to confirm relationships between the COMT genotype and SRADs and that larger studies are needed that target more diverse ethnic groups.

As an extension of these studies, the Principal Investigator (PI) examined possible relationships between the COMT genotype and SRADs by reviewing studies published in 2012 or after. Considering that research into behavioral addictions is sorely needed, the PI included gambling disorder, which is considered a SRAD, and Internet gaming disorder, which was registered in Section III of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) in 2013 (American Psychiatric Association, 2013) in this review.

Method

This paper presents a review of published research that addresses the relationship(s) between the COMT genotype (Val^{158}Met) and SRADs. Because only one researcher, i.e., the PI, was primarily responsible for the search process, literature screening, and data extraction, this review is considered to be a systematized review, rather than a systematic review. (M. J. Grant & Booth, 2009).

The PI followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) guidelines (Moher, Liberati, Tetzlaff, & Altman, 2009) to report studies that examined the relationship(s) between the COMT genotype and SRADs. The PI searched four electronic databases: CINAHL Plus with Full Text, Embase, PubMed, and PsycINFO, using the terms ((((("substance-related disorders"[MeSH Terms]) OR ((drug[Title/Abstract] OR substance)[Title/Abstract] AND (abuse*[Title/Abstract] OR depend*[Title/Abstract] OR addict*)[Title/Abstract])) OR (alcohol*[Title/Abstract] OR smok*[Title/Abstract] OR nicotin*[Title/Abstract] OR gambl*[Title/Abstract] OR internet[Title/Abstract] OR gaming[Title/Abstract]))) AND (("catechol-o-methyltransferase"[Text Word] OR rs4680[Text Word] OR val158met[Text Word])). The search results were limited to studies written in English and published in peer-reviewed journals between January 2012 and December 2018.

The inclusion criteria were that the reviewed studies must (a) include participants who were from the general population or individuals who showed pathological use of alcohol, tobacco, illicit drugs, gambling, or the Internet, as assessed by the DSM or other validated instruments, and (b) be original research that examined the association between the COMT (Val^{158}Met) genotype and the pathological use of alcohol, tobacco, illicit drugs, gambling, or the Internet. Studies were excluded if the participants of the study had comorbidities of diagnosed

cognitive or psychiatric disorders other than SRADs related to the pathological use of alcohol, tobacco, illicit drugs, gambling, or the Internet. The PI assessed the methodological quality of the reviewed studies in accordance with the Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies and Case-Control Studies (National Heart, Lung, and Blood Institute, 2014). However, the studies were not excluded according to the evaluation of the methodological quality of the study.

Figure 3.1 presents the process that the PI used for the literature search and screening. From the four databases, the PI identified 530 studies; after removing duplicates, 284 studies remained. Title and abstract screening and full-text screening using the inclusion and exclusion criteria yielded 20 studies for this review. The PI extracted the following data: author, published year, country, study participants and their ages for both the case and control groups, sample size, the percentage of male and female participants for both the case and control groups, COMT genotype frequency for both the case and control groups, and findings regarding the association between the COMT genotype and each type of SRAD.

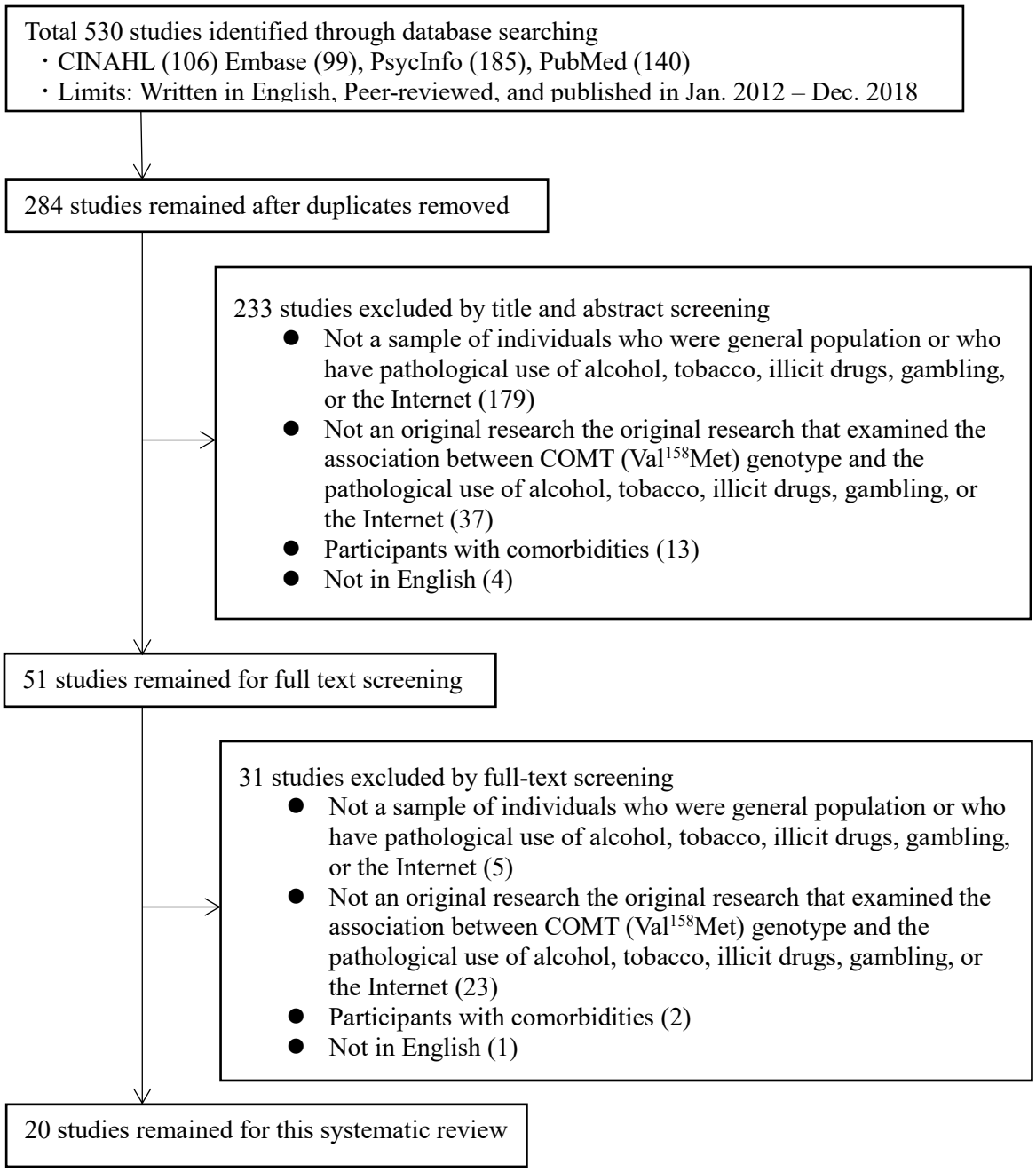

Figure 3.1. The process of literature search and screening

Results

Association between COMT Genotype and Alcohol Dependence

Table 3.1 presents a summary of the reviewed studies with regard to possible

associations between the COMT genotype and alcohol dependence in terms of author(s), year published, country of origin, study design, participants and their ages, sample sizes of the case and control groups, percentages of each genotype for the case and control groups, and any association between the COMT genotype and alcohol dependence.

Study characteristics. Among the 20 studies reviewed, ten studies addressed the association between the COMT genotype and alcohol dependence. Three studies were conducted in the United States (Durazzo, Hutchison, Fryer, Mon, & Meyerhoff, 2012; Guillot, Fanning, Liang, & Berman, 2015; Hendershot, Lindgren, Liang, & Hutchison, 2012), three studies were conducted in the Netherlands (Schellekens et al., 2012, 2013; Van der Knaap et al., 2014), four studies were conducted in Turkey (Altintoprak, Kayahan, Tezcanli, Kosova, & Coşkunol, 2012), Croatia (Erjavec et al., 2014), Poland (Klimkiewicz et al., 2017), and in India (Malhotra, Basu, Khullar, Ghosh, & Chugh, 2016), respectively. All studies were cross-sectional studies and, of those, six studies applied a case-control design. The participants of the studies were mainly individuals with alcohol dependence, but two studies used a sample of the general population: undergraduate students with lifetime alcohol use (Hendershot et al., 2012) and adolescents (Van der Knaap et al., 2014). In the studies with a case-control design, the control group was comprised of healthy individuals without a history of psychiatric disorders. The average age of the participants ranged from 16.1 (Van der Knaap et al., 2014) to 51.0 (Durazzo et al., 2012) years. In terms of sample size, most of the participants were males, and three studies (Malhotra et al., 2016; Schellekens et al., 2012, 2013) recruited only male participants. Among the studies with a case-control design, the Altintoprak et al. (2012) and Guillot et al. (2015) studies showed a relatively big difference in sample size between the case group and the control group.

Table 3.1. *Summary of Studies: Association between COMT (Val[158]Met) and Alcohol Dependence*

Author (Year) Country	Study Design	Participants & Age		Sample Size		COMT (Val[158]Met)		Findings (association between Val[158]Met and alcohol dependence)
		Case Mean (SD)	Control Mean (SD)	Case (M/F %)	Control (M/F %)	Case	Control	
Altintoprak et al. (2012) Turkey	CS CC	Individuals with alcohol dependence with no comorbid psychiatric disorders M: 46 (9.3) F: 36 (7.8)	Physically and mentally healthy subjects	110 (90.9/9.1)	330 (69.4/30.6)	GG = 42.7% GA = 40.9% AA = 16.4%	GG = 41.5% GA = 37.9% AA = 20.6%	No association with alcohol dependence
Durazzo et al. (2012) USA	CS	Individuals seeking treatment for alcohol dependence Age: 51.0 (10.0)		70 (94.3/5.7)		GG = 30.0% GA = 50.0% AA = 20.0%		No association with alcohol dependence. Met homozygotes showed higher executive skills and higher general intelligence and visuospatial skills. Val homozygotes showed better auditory-verbal memory.
Erjavec et al. (2014) Croatia	CS CC	Caucasians of Croatian origin Individuals with alcohol dependence Age: 49.8 (10.2)	Medication-free healthy Caucasian Age: 40.3 (12.3)	690 (81.3/18.7)	580 (90.5/9.5)	GG = 22.3% GA = 48.8% AA = 28.9%	NR	No association with alcohol dependence Increased frequency of Met/Met in suicidal attempt and behavior Increased frequency of Val/Val genotype in early onset of alcohol abuse
Guillot et al. (2015) USA	CS CC	Caucasians non-clinical adults with mildly probable problem drinker Age: 26.0 (7.5)	Caucasians non-clinical adults with probable non-problem drinker,	28	111	Non-AA = 53.6% AA = 46.4%	Non-AA = 75.7% AA = 24.3%	Met/Met were at greater risk of being mildly probable problem drinkers
Hendershot et al. (2012) USA	CS	Undergraduates with lifetime alcohol use. Chinese, Korean, or Japanese ethnicity Age: 20.7 (1.8)		69 (45.5/55.0)		NR		No association with drinking motives. COMT (Met alleles) moderated associations of implicit coping motives with drinking
Klimkiewicz et al.	CS	Individuals with a diagnosis of alcohol dependence		281 (75.4/24.6)		GG = 25.9% GA =46.6%		No association. Co-occurrence of BDNF Val/Val and

(2017) Poland		European Caucasians Age: 43.1 (0.6)				AA = 27.5%		COMT Met/Met was significantly associated to higher alcohol consumption and lower motivation to change drinking patterns.
Malhotra et al. (2016) India	CS CC	North Indian males with alcohol dependence	North Indian males with exposure to alcohol but no alcohol use disorder	210	200	GG = 24.3% GA = 53.3% AA = 22.3%	GG = 32.0% GA = 54.5% AA = 13.5%	Met/Met was associated with risk of alcohol dependence
Schellekens et al. (2012) Netherlands	CS CC	European male patients with alcohol dependence healthy control Age: 41 (11)	People without history (and family history) of psychiatric disorder Age: 39 (9)	109	99	GG = 23.6% GA = 40.9% AA = 35.5%	GG = 22.2% GA = 53.5% AA = 24.2%	No association Met alleles showed higher dopamine receptor sensitivity
Schellekens et al. (2013) Netherlands	CS CC	European male patients with alcohol dependence Age: 41 (11)	People without history (and family history) of psychiatric disorder Age: 39 (9)	110	99	GG = 23.6% GA = 40.9% AA = 35.5%	GG = 22.2% GA = 53.5% AA = 24.2%	No association In people with high scores on childhood adversity, Met allele was associated with a higher risk of alcohol dependence.
Van der Knaap et al. (2014) Netherlands	CS	Dutch adolescents Age: 16.1 (0.6)		463 (49.2/50.8)		GG = 19.7% GA = 49.1% AA = 31.2%		No association with alcohol use.

Note. COMT = catechol-o-methyltransferase; SD = standard deviation; M = male; F = female; CS = cross-sectional; CC = case-control; NR = not reported; BDNF = brain-derived neurotrophic factor

Findings. The allele frequency of the COMT genotype differed according to ethnicity. Among the Turkish population, approximately 40% had Val homozygotes and approximately 20% had Met homozygotes (Altintoprak et al., 2012). However, among the European population, approximately 20% to 25% had Val homozygotes and 25% to 30% had Met homozygotes (Schellekens et al., 2012; Van der Knaap et al., 2014).

In terms of possible associations between the COMT genotype and alcohol dependence, two studies (Guillot et al., 2015; Malhotra et al., 2016) reported that participants with Met/Met had a greater risk of problematic alcohol use or alcohol dependence than those with Val/Val or Val/Met. Schellekens et al. (2013) reported that, among the participants with 'higher childhood adversity', the Met allele also was associated with a higher risk of alcohol dependence. However, most of the studies reported no association between the COMT genotype and alcohol dependence. In addition, Hendershot et al. (2012) reported that Met alleles moderated any association between coping motives and drinking. In contrast, Erjavec et al. (2014) reported that Val homozygotes were associated with early-onset alcohol abuse.

Association between COMT Genotype and Nicotine Dependence

Table 3.2 presents a summary of the reviewed studies with regard to possible associations between COMT and smoking in terms of author(s), year published, country of origin, study design, participants and their ages, sample sizes of the case and control groups, percentages of COMT frequency in the case and control groups, and possible associations between COMT and smoking.

Table 3.2. *Summary of Studies: Association between COMT (Val^{158}Met) and Smoking*

Author (Year) Country	Study Design	Participants & Age		Sample Size		COMT (Val^{158}Met)		Findings (association between Val^{158}Met and smoking)
		Case Mean (SD)	Control Mean (SD)	Case (M/F %)	Control (M/F %)	Case	Control	
Bidwell et al. (2015) USA	CS	African American daily smokers Age: 37.3 (12.6)		268 (57.0/43.0)		GG = 45.1% GA = 41.0% AA = 9.3%		No association
Mutschler et al. (2013) Germany	CS CC	German Caucasian Current smokers Age: 34.7 (12.8)	German Caucasian Non-smokers	551	548	GG = 21.8% GA = 49.9% AA = 28.3%	GG = 21.7% GA = 50.0% AA = 28.3%	No association
Suriyaprom et al. (2013) Thailand	CS CC	Male adult smokers Age: 37.0 [34.0 – 40.0]	Male adult non-smokers Age: 36.0 [33.5 – 38.0]	200	111	GG = 45.5% A carrier = 54.5%	GG = 59.5% A carrier = 40.5%	A carrier was associated with smoking A carrier has significantly higher Thiocyanate
Van der Knaap et al. (2014) Netherlands	CS	Dutch adolescents Age: 16.1 (0.6)		463 (49.2/50.8)		GG = 19.7% GA = 49.1% AA = 31.2%		No association with smoking.
Zhang et al. (2013) USA	CS CC	Drug users (including smoking) Age: 34.3 (9.5)	Healthy individuals Age: 30.3 (8.4)	146 (67.1/32.9)	126 (50.0/50.0)	GG = 27.5% GA = 50.8% AA = 21.7%	GG = 32.5% GA = 52.4% AA = 15.1%	Met/Met showed significantly higher nicotine dependence. Reduced prefrontal white matter integrity in Met/Met drug users.

Note. COMT = catechol-o-methyltransferase; SD = standard deviation; M = male; F = female; CS = cross-sectional; CC = case-control

Study characteristics. Among the 20 studies reviewed, five studies reported an association between the COMT genotype and nicotine dependence or tobacco use. Two studies were conducted in the United States (Bidwell et al., 2015; Zhang et al., 2013), three studies were conducted in Germany (Mutschler et al., 2013), Thailand (Suriyaprom, Tungtrongchitr, & Harnroongroj, 2013), and three studies were conducted in the Netherlands (Van der Knaap et al., 2014). All studies were cross-sectional studies and, of those, three studies applied a case-control design. The participants of the studies were mainly current smokers, except for one study that used a sample of adolescents (Van der Knaap et al., 2014). The average age of the participants ranged from 16.1 (Van der Knaap et al., 2014) to 37.3 (Bidwell et al., 2015) years.

Findings. A difference was evident in the allele frequency of the COMT genotype according to ethnicity. Approximately 20% to 25% of European Caucasians had Val homozygotes and 25% to 30% had Met homozygotes and approximately 45% of African Americans had Val homozygotes and approximately 10% had Met homozygotes (Bidwell et al., 2015).

Regarding possible associations between the COMT genotype and nicotine dependence or tobacco use, the participants with Met/Met or Met alleles showed higher nicotine dependence than the participants with Val alleles (Suriyaprom et al., 2013; Zhang et al., 2013), whereas the remaining studies reported no association between the COMT genotype and nicotine dependence or tobacco use.

Association between COMT Genotype and Illicit Drug Use

Table 3.3 presents a summary of the reviewed studies with regard to possible associations between COMT and illicit drug use in terms of author(s), year published, country of origin, study design, participants and their ages, sample sizes of the case and control groups,

percentages of COMT frequency in the case and control groups, and any association between COMT and illicit drug use.

Study characteristics. Among the 20 studies reviewed, six studies addressed the association between the COMT genotype and illicit drug use. Five studies applied a case-control design. The participants of the studies were mainly illicit drugs users (C. K. Chen, Lin, Chiang, Su, & Wang, 2014; Zhang et al., 2013); the drugs used included inhalants (Intharachuti et al., 2012), cannabis (Verdejo-García et al., 2013), and heroin (Vereczkei et al., 2013). The average age of the participants ranged from 16.1 (Van der Knaap et al., 2014) to 34.3 (Zhang et al., 2013) years. In terms of the sample size, more male participants were recruited than female participants, except for the van der Knaap et al. (2014) study. Most of the studies that used a case-control design showed a large difference in sample size between the case group and the control group; the control group had a larger sample size.

Findings. In the studies that addressed an association between the COMT genotype and illicit drug use, differences in the allele frequency of the COMT genotype according to ethnicity also were confirmed. Specifically, Asians showed the highest percentage of Val homozygotes (50% - 60%) and the lowest percentage of Met homozygotes (5% - 10%) in comparison with other ethnic groups (C. K. Chen et al., 2014; Intharachuti et al., 2012).

In terms of possible associations between the COMT genotype and illicit drug use, the results were mixed. Two studies (C. K. Chen et al., 2014; Van der Knaap et al., 2014) reported that participants with Val/Val showed a greater risk of illicit drug use than Met carriers. Intharachuti et al. (2012) reported that the Met allele was significantly associated with inhalant dependence. Zhang et al. (2013) found no association between the COMT genotype and illicit drug use, but observed reduced prefrontal white matter integrity in Met/Met drug users.

Table 3.3. *Summary of Studies: Association between COMT (Val^{158}Met) and Illicit Drug Use*

Author (Year) Country	Study Design	Participants & Age Case Mean (SD)	Control Mean (SD)	Sample Size Case (M/F %)	Control (M/F %)	COMT (Val^{158}Met) Case	Control	Findings (association between Val^{158}Met and illicit drug use)
Chen et al. (2014) Taiwan	CS CC	Illicit drug users enrolled from a male detention center and psychiatric hospitals Age: 32.4 (9.0)	Healthy individuals with no history of illicit drug use or psychosis Age: 34.3 (10.3)	187 (94.1/5.9)	386 (56.5/43.5)	GG = 53.5% GA = 41.7% AA = 4.8%	GG = 46.4% GA = 44.0% AA = 9.6%	Val allele had higher frequency of illicit drug users
Intharachuti et al. (2012) Thailand	CS CC	Experienced methamphetamine users		456 (54.2/45.8)		GG = 54.6% GA = 37.5% AA = 7.9%		The "Met" allele was significantly associated with inhalant dependence and inhalant ever-use
		Inhalant dependents	Non-dependents	43 (74.4/ 25.6)	413 (52.1/ 47.9)	GG = 34.9% GA = 55.8% AA = 9.3%	GG = 56.7% GA = 35.6% AA = 7.8%	
		Inhalant ever-users	Non-ever-users	136	320	GG = 44.9% GA = 43.4% AA = 11.8%	GG = 58.8% GA = 35.0% AA = 6.2%	
Van der Knaap et al. (2014) Netherlands	CS	Dutch adolescents Age: 16.1 (0.6)		463 (49.2/50.8)		GG = 19.7% GA = 49.1% AA = 31.2%		Val allele was associated with high-frequent cannabis use.
Verdejo-Garcia et al. (2013) Spain	CS CC	European-Caucasian cannabis users Age: 21.5 (2.9)	European-Caucasian non-drug users Age: 23.2 (4.8)	86 (70.9/29.1)	58 (67.2/32.8)	GG = 18.6% GA = 67.4% AA = 14.0%	GG = 32.8% GA = 50.0% AA = 17.2%	Cannabis users carrying the Val allele committed more monitoring/shifting errors
Vereczhei et al. (2013) Hungary	CS CC	Hungarian heroin dependent patients	Hungarian healthy individuals with no psychiatric disorders	303 (69.6/30.4)	555 (69.5/30.5)	GG = 24.8% GA = 50.4% AA = 24.8%	GG = 22.5% GA = 49.6% AA = 27.9%	No association
Zhang et al. (2013) USA	CS CC	Drug users (including smoking) Age: 34.3 (9.5)	Healthy individuals Age: 30.3 (8.4)	146 (67.1/32.9)	126 (50.0/50.0)	GG = 28.2% GA = 51.9% AA = 19.9%	GG = 32.5% GA = 52.4% AA = 15.1%	No association Reduced prefrontal white matter integrity in Met/Met drug users.

Note. COMT = catechol-o-methyltransferase; SD = standard deviation; M = male; F = female; CS = cross-sectional; CC = case-control

Association between COMT Genotype and Gambling Disorder and Internet Addiction

Table 3.4 presents a summary of the reviewed studies with regard to possible associations between COMT and gambling and internet addiction in terms of author(s), year published, country of origin, study design, participants and their ages, sample sizes of the case and control groups, percentages of COMT frequency in the case and control groups, and any association between COMT and gambling and/or internet addiction.

Study characteristics. Among the 20 studies reviewed, two studies addressed an association between the COMT genotype and gambling disorder (J. E. Grant, Leppink, Redden, Odlaug, & Chamberlain, 2015; Guillot et al., 2015) and one study examined an association between the COMT genotype and Internet addiction (C. Sun, Spathis, Sankaranarayanan, Chan, & Lum, 2016). In J. E. Grant et al. (2015), the participants were nontreatment-seeking young adults who had gambled at least five times during the last year. In the Guillot et al. (2015) study, which applied a case-control design, the case group was comprised of adults who were at least at risk of gambling disorder. In Sun et al. (2016), university students and staff were the study participants.

Findings. In terms of possible associations with the COMT genotype, the results were mixed. J. E. Grant et al. (2015) found that Val homozygotes were associated with gambling disorder, but Guillot et al. (2015) reported that participants with Met homozygotes showed a greater risk of being at-risk gamblers. Sun et al. (2016) found no association between the COMT genotype and Internet addiction, although the participants with Val homozygotes engaged in more online activities than the participants with Met alleles.

Table 3.4. *Summary of Studies: Association between COMT (Val^{158}Met) and Gambling Disorder and Internet Addiction*

Author (Year) Country	Study Design	Participants & Age		Sample Size		COMT (Val158Met)		Findings (association between Val^{158}Met and gambling and internet addiction)
		Case Mean (SD)	Control Mean (SD)	Case (M/F %)	Control (M/F %)	Case	Control	
Grant et al. (2015) USA	CS	Non-treatment-seeking young adults who had gambled at least five times during the preceding 12 months		260 (61.2/38.8)		GG = 32.7% GA = 43.8% AA = 23.5%		Val/Val was associated with gambling disorder, frequency of gambling, and worse cognitive performance
Guillot et al. (2015) USA	CS CC	Caucasians non-clinical adults with at-least-at-risk of disordered gambling Age: 26.0 (7.5)	Caucasians non-clinical adults with non-risk of disordered gambling	45	94	Non-AA = 55.6% AA = 44.4%	Non-AA = 78.7% AA = 21.3%	Met/Met were at greater risk of being at-least-at-risk gamblers.
Sun et al. (2016) USA	Pre-post survey	University students and staffs Age: 21.7 (4.1)		73 (44.0/56.0)		GG = 30.0% A carrier = 70.0%		No association with Internet addiction Val/Val participated in more types of online activities

Note. COMT = catechol-o-methyltransferase; SD = standard deviation; M = male; F = female; CS = cross-sectional; CC = case-control

Methodological Quality of the Reviewed Studies

Table 3.5 presents an assessment of the methodological quality of the reviewed studies with the case-control design. All thirteen case-control studies clearly addressed research questions or objectives and clearly defined the study population, case groups, and control groups. Also, all the studies demonstrated reliable inclusion and exclusion criteria for the case and control groups. Only three studies (Erjavec et al., 2014; Guillot et al., 2015; Suriyaprom et al., 2013) reported sample size justification or power analysis. Nine studies reported that the control groups were recruited from a similar population, but three studies reported significant differences between the case and control groups in terms of demographic characteristics. With regard to selection of participants, one study (Mutschler et al., 2013) reported that the participants were randomly selected. All studies applied validated instruments or criteria for the diagnosis of disorders, but only one study (Mutschler et al., 2013) reported that the assessors were blinded from participants in the case and control groups.

Table 3.6 shows an assessment of the methodological quality of the reviewed studies with the cross-sectional design. All seven cross-sectional studies clearly addressed research questions or objectives and clearly defined the study population. All of these studies provided reliable inclusion and exclusion criteria, but none provided sample size justification or power analysis. Most of the cross-sectional studies applied clearly defined and validated instruments and/or criteria for the diagnosis of disorders, but only Bidwell et al. (2015) reported that the investigators were blinded to phenotypic data.

Table 3.5. *Methodological Quality Assessment: Case-Control Studies*

Author (year)	1	2	3	4	5	6	7	8	9	10	11	12
Altintoprak et al. (2012)	Y	Y	N	N	Y	Y	N	NR	NA	Y	NR	Y
Chen et al. (2014)	Y	Y	N	N	Y	Y	N	NR	NA	Y	NR	CD
Erjavec et al. (2014)	Y	Y	Y	Y	Y	Y	N	NR	NA	Y	NR	Y
Guillot et al. (2015)	Y	Y	Y	Y	Y	Y	N	Y	NA	Y	NR	N
Intharachuti et al. (2012)	Y	Y	N	N	Y	Y	N	NR	NA	Y	NR	Y
Malhortra et al. (2016)	Y	Y	N	Y	Y	Y	N	NR	NA	Y	NR	Y
Mutschler et al. (2013)	Y	Y	N	Y	Y	Y	Y	NR	NA	Y	Y	Y
Schellekens et al. (2012)	Y	Y	N	Y	Y	Y	N	NR	NA	Y	NR	Y
Schellekens et al. (2013)	Y	Y	N	Y	Y	Y	N	NR	NA	Y	NR	Y
Suriyaprom et al. (2013)	Y	Y	Y	Y	Y	Y	N	NR	NA	Y	NR	Y
Verdejo-Garcia et al. (2013)	Y	Y	N	Y	Y	Y	N	NR	NA	Y	NR	Y
Vereczkei et al. (2013)	Y	Y	N	NR	Y	Y	N	N	NA	Y	NR	Y
Zhang et al. (2013)	Y	Y	N	Y	Y	Y	N	NR	NA	Y	NR	Y

Note. Y = Yes; N = No; NA = Not applicable; NR = Not reported; CD = Cannot determine

1. Was the research question or objective in this paper clearly stated and appropriate?
2. Was the study population clearly specified and defined?
3. Did the authors include a sample size justification?
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?
6. Were the cases clearly defined and differentiated from controls?
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?
8. Was there use of concurrent controls?
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?
11. Were the assessors of exposure/risk blinded to the case or control status of participants?
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?

Table 3.6. *Methodological Quality Assessment: Cross-Sectional Studies*

Author (year)	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Bidwell et al. (2015)	Y	Y	NA	Y	N	N	NA	Y	Y	N	Y	Y	NA	Y
Durazzo et al. (2012)	Y	Y	NA	Y	N	N	NA	Y	Y	N	Y	NR	NA	Y
Grant et al. (2015)	Y	Y	NA	Y	N	N	NA	Y	Y	N	Y	NR	NA	N
Hendershot et al. (2012)	Y	Y	NA	Y	N	N	NA	NR	Y	N	Y	NR	NA	Y
Klimkiewicz et al. (2017)	Y	Y	NR	Y	N	N	NA	NR	Y	N	Y	NR	NA	Y
Sun et al. (2016)	Y	Y	NA	Y	N	N	CD	Y	Y	Y	Y	NA	NR	NR
Van der Knaap et al. (2014)	Y	Y	NA	Y	N	N	NA	NR	N	N	N	NR	NA	Y

Note. Y = Yes; N = No; NA = Not applicable; NR = Not reported; CD = Cannot determine

1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

Discussion

For this study, the PI reviewed 20 studies that addressed the possible relationships between the COMT genotype and SRADs. Unlike previously published research, the reviewed studies were not limited to the pathological use of alcohol, tobacco, or illicit drugs, but also included gambling disorder and Internet addiction.

In terms of the methodological quality of the studies reviewed, the inclusion criteria and exclusion criteria of the study participants generally were defined well; however, in some of the case-control studies, significant differences were evident between the two groups (case and control) in terms of demographic characteristics. Considering the differences in the allele frequency of the genotype by ethnicity, the demographic characteristics of the case group and control group should be comparable to the extent possible. Moreover, in most of the studies, the rationale for sample size was not adequately reported or justified, nor was statistical power to detect group differences adequately reported.

Overall, the findings of this review regarding possible relationships between the COMT genotype and SRADs were mixed. Although research conducted by Tammimäki and Männistö (2010) and Tunbridge et al. (2012) yielded similar results whereby the Val allele was found to be related to an increased probability of tobacco use or nicotine dependence, the current study found reports that the Met allele leads to a higher probability of tobacco use or nicotine dependence or reports of no significant association. Most types of SRADs were not significantly associated with the COMT genotype. This finding could be due to the fact that SRADs are multifactorial diseases, so a combination of genetic, environmental, and psychosocial factors could also contribute to their occurrence (Kwako, Momenan, Litten, Koob, & Goldman, 2016).

Some studies reported that the Met allele is related to SRADs. This relationship tended

to be shown in the studies that focused on alcohol and nicotine dependence. People with Met homozygotes were reported to have a higher level of dopamine in the PFC than people with Val homozygotes, because the COMT activity that breaks down dopamine is approximately 40% less in people with Met homozygotes than those with Val homozygotes (J. Chen et al., 2004; Dauvilliers et al., 2015). According to the tonic-phasic dopamine hypothesis, individuals with Met homozygotes present high tonic dopaminergic neurotransmission in the cortical region of the brain, but have low phasic dopaminergic neurotransmission in the subcortical region (Klein et al., 2019). In other words, a high level of tonic dopamine and consequently more stimulation of dopamine receptors lead to high levels of impulsiveness of actions, which are related to becoming vulnerable to addictive disorders (Guillot et al., 2015). In addition, consistently high levels of tonic dopamine strengthen the motivation for reward (Guillot et al., 2015). Therefore, the implication is that the Met allele is related to SRADs through high impulsivity and motivation for reward.

However, some studies reported that the Val allele is significantly related to SRADs. These studies focused on working memory to explain the relationship. Specifically, these studies proposed that people with Val homozygotes present less working memory capacity than those with Met homozygotes (H. Sun, Yuan, Shen, Xiong, & Wu, 2014). Researchers have reported that individuals with Val homozygotes have a lower level of dopamine in the PFC than those with Met homozygotes. The PFC, the region of the brain that is responsible for diverse cognitive activities, concerns the functions of executive controls, language, intelligence, and memory (H. Sun et al., 2014). People with a low capacity of working memory are reported to have more problems regarding self-regulation and they tend to show more automatic behaviors, which are behaviors executed subconsciously, than those with a high capacity of working memory (J. E.

Grant et al., 2015). Therefore, based on this perspective, lower self-regulation may occur in the context of Val alleles, which could influence SRADs.

To summarize, the findings of this review regarding the possible relationships between the COMT genotype and SRADs are premature, and more studies are needed in order to reach concrete conclusions.

Limitations of the Study

Given that SRADs can be affected by various biopsychosocial factors, one limitation of this study is that possible relationships between SRADs and only COMT ($Val^{158}Met$) was investigated. Various genes or epigenetic variances could be related to the biological mechanisms of SRADs, and interactions between the genes and psychosocial and environmental factors as well as interactions among the genes may also be important factors. Future studies are required to obtain more information about the potential effects of genetic and epigenetic factors on SRADs.

Secondly, this review was limited to studies written in English. Given that the reviewed studies were conducted in various countries, including non-English-speaking countries, the reviewed studies may not incorporate all the available evidence. The limitation of English-language studies only may also lead to language bias and inaccurate conclusions (Morrison et al., 2012). Future reviews that include studies in various languages are needed.

Implications for Nursing Research and Practice

Epigenetic modifications are important biomarkers that can clarify the susceptibility and/or vulnerability to SRADs (Andersen et al., 2015). SRADs, as multifactorial diseases, can be affected by environmental and other psychosocial factors. According to studies of twins, genetic factors also can affect SRADs, from initiation to addiction (Ducci & Goldman, 2012). Therefore,

in order to gain further insight into the biological mechanisms of SRADs, in-depth studies about genetic factors and epigenetic factors are necessary.

Studies are needed that include a sufficient sample size with enough power that can reflect ethnic differences in allele frequency. Studies should not be limited to only the COMT genotype, but also should include analysis of multiple functional polymorphic dopaminergic markers and research into the multi-locus genetic profile, which are related to SRADs. Research that incorporates polygenic models will help to address gene-environment interactions in terms of SRADs through the cumulative analyses of many genetic variations, each of which affects a small amount of risk of Internet addiction better than analysis of SNPs (Vrshek-Schallhorn, 2015). In this sense, research that focuses on gene-gene interactions and gene-environmental interactions (i.e. gene and psychosocial factors) in terms of SRADs is needed. These studies are expected to contribute to the successful development of individually tailored interventions, from preventive approaches to pharmacological treatments and psychosocial interventions, which will lead to optimal outcomes for individuals with SRADs.

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CHAPTER 4: INTERNET ADDICTION AMONG UNDERGRADUATE STUDENTS IN SOUTH KOREA: ASSOCIATION WITH COMT (VAL^{158}MET) GENOTYPE AND PSYCHOLOGICAL FACTORS

Introduction

Internet Addiction

Internet addiction is a major mental health concern throughout the world (Feng, Ramo, Chan, & Bourgeois, 2017). With advancements in information and communication technology, including the development of smartphones and tablet devices, the Internet has become an important component of many people's ordinary lives. Internet infrastructure has brought about incredible convenience and the ability to network extensively throughout the world, but it has also produced adverse effects, such as Internet addiction (Nakayama, Mihara, & Higuchi, 2017).

Internet addiction is an individual's failure to control Internet use and/or excessive preoccupation with the Internet that results in physical, psychological, social, and/or financial distress (Weinstein & Lejoyeux, 2015; Young, Pistner, O'Mara, & Buchanan, 1999). Individuals with Internet addiction may suffer from symptoms that are commonly associated with substance-related and addictive disorders (SRADs), such as dependence, tolerance, and withdrawal (Kuss, Griffiths, Karila, & Billieux, 2014; Young et al., 1999).

Internet Addiction in South Korea

South Korea is a country with one of the highest rates of Internet addiction in the world (Kuss et al., 2014); this status is a negative outcome of having the fastest broadband and the most-wired environment in the world (Curran, 2018; Young, 2017b). Unlimited data usage plans are common for mobile device users, and 'PC bangs', Internet cafés located in many buildings in

communities and cities, provide up-to-date computer facilities to allow people to enjoy online gaming 24 hours a day (Kang, 2017). According to a survey by the Korea Internet & Security Agency (2014), 82.1% of the South Korean population aged three or older use the Internet at least once per month.

Recently published research emphasizes the severity of Internet addiction among undergraduate students in South Korea. Noh and Kim (2016) reported that 25.8% of South Korean undergraduate students suffer from moderate to severe Internet addiction. Their study was based on the Internet Addiction Test (IAT) (Young, 1998), a scale that has been validated and is utilized in several different countries. The Noh and Kim (2016) findings can be compared to those of Feng et al. (2017) who reported that the prevalence of Internet addiction ranges from 1% to 10% worldwide, although the report synthesized prevalence data from miscellaneous instruments and did not exclusively use a sample of undergraduate students. Because Internet addiction may seriously and negatively affect the time management, finances, academic obligations, and job performance of undergraduate students (Kuss, Griffiths, & Binder, 2013), more research into strategies to prevent or mitigate the prevalence of Internet addiction among Korean undergraduate students is critically needed.

Neurobiological Mechanisms of Internet Addiction

Researchers have explored the neurobiological mechanisms behind Internet addiction and found common structural and functional alterations of the brain among individuals with either Internet addiction or SRADs (Lin, Zhou, Dong, & Du, 2015; B. Park, Han, & Roh, 2017). Researchers have suggested that Internet addiction behavior is related to the structural and functional variations of the region near the prefrontal cortex (PFC) (Kuss, Pontes, & Griffiths, 2018). The PFC is reported to be one of the regions in the brain that is in charge of cognitive

control and receives dopamine from the nucleus accumbens (NAc), which takes dopamine from the ventral tegmental area (VTA) (Adinoff, 2004; Brand, Young, & Laier, 2014). Because this system is associated with reward, motivation, pleasure, and further craving, it is known to be strongly linked to SRADs (Adinoff, 2004). Therefore, researchers have proposed that Internet addiction needs to be regarded as a SRAD. Indeed, Internet gaming disorder, which is a type of Internet addiction, is a condition that could be considered for inclusion as a formal disorder in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as researchers gather more clinical evidence about Internet addiction (American Psychiatric Association, 2013).

Research in Single Nucleotide Polymorphisms of COMT (Val^{158}Met)

Researchers have investigated catechol-O-methyltransferase (COMT) as a candidate gene (Val^{158}Met) for SRADs (Tunbridge et al., 2012). COMT is an enzyme that catabolizes catecholamines, such as dopamine, epinephrine, and norepinephrine (Tunbridge et al., 2012). Dopamine is synthesized from the amino acid, tyrosine, and released by synaptic vesicles (Klein et al., 2019). The level of dopamine is regulated by receptors for dopaminergic neurotransmission or by dopamine transporters that re-uptake the dopamine into presynaptic neurons to store it for future use or destroy it via COMT or monoamine oxidase within the neuron (Klein et al., 2019). However, in the PFC, dopamine transporters are relatively rare, so dopamine is regulated mostly by COMT outside of the neuron (Diamond, 2007).

The activities of COMT can be altered by the gene that codes for COMT (Tunbridge et al., 2012). Due to single nucleotide polymorphism (SNP), which is a common variation of single bases in a DNA (deoxyribonucleic acid) sequence, at the sequence of the gene, Val^{158}Met, the nucleobase, guanine, is altered to become another nucleobase, adenine, such that translation to amino acid also changes from valine (Val) to methionine (Met), which results in the functional

variations of COMT (Dauvilliers, Tafti, & Landolt, 2015).

Based on the commonly studied functional SNP, Val^{158}Met, researchers have identified three genotypes, Val/Val, Val/Met, and Met/Met, with each conferring different COMT activity (Dauvilliers et al., 2015). The Val/Val genotype shows the highest enzyme activity, so it is related to lower levels of dopamine in the PFC region. In contrast, the Met/Met genotype shows the lowest enzyme activity, so the level of dopamine is higher in the PFC region (Dauvilliers et al., 2015). Chen et al. (2004) showed that individuals with Met/Met demonstrate approximately 40% decrease in COMT enzyme activity compared to Val/Val.

Due to these noticeable differences in enzyme activity, the functional SNP (Val^{158}Met) has been widely studied with regard to psychiatric disorders, such as depression (Wang, Ma, Yuan, Su, & Li, 2016), ADHD (Sun, Yuan, Shen, Xiong, & Wu, 2014), schizophrenia (González-Castro et al., 2016), and addictive disorders (alcoholism, smoking, illicit drug use, etc.) (Tunbridge et al., 2012) as well as cancer(s) (Sak, 2017), Parkinson's disease (Jiménez-Jiménez, Alonso-Navarro, García-Martín, & Agúndez, 2014), and pain (Tammimäki & Männistö, 2012). Furthermore, researchers have proposed the possibility of personalized treatments or interventions for these disorders and symptoms using this candidate gene based on studies of differences in responses to certain treatments (Huang et al., 2016). However, little research has been conducted to examine the association between COMT genotypes and Internet addiction.

Aims of the Study

Given the high rate of Internet addiction in Korean undergraduate students, a deeper understanding of the contributions to risk, ways to prevent Internet addiction, and strategies for treating or addressing Internet addiction and its adverse effects is critically needed. Examining possible associations between Internet addiction and the COMT genotype could result in the

identification of potential biological genetic factors that have been suggested as contributors to SRADs.

Thus, the aims of this study are:

1. To identify the feasibility of conducting a study that involves the collection of saliva samples and web-based survey data using participants who are undergraduate students in South Korea.
2. To describe possible relationships among Internet addiction, COMT (Val^{158}Met) genotype, and psychological variables (depressive symptoms, social anxiety, self-esteem, self-efficacy, stress, and coping strategies).

Theoretical Framework

Brand, Laier, and Young (2014) developed a model to illustrate the mechanisms that underlie Internet addiction (Figure 4.1). They asserted that Internet addiction is associated with 1) a person's core characteristics, including psychopathological aspects (depression, social anxiety), personality aspects (low self-esteem, low self-efficacy, stress vulnerability), and social cognition (emotional loneliness, low social support) and 2) a person's specific cognitions, which include dysfunctional coping strategies to address everyday stress and Internet-use expectancies. This model proposes that an individual's specific cognitions can also mediate the relationship between the core characteristics and Internet addiction.

Brand, Young, and Laier (2014) also asserted that the pathway from the reinforcement of a person's cognitions regarding Internet to Internet addiction is mediated by cognitive control, which refers to the ability to control one's behaviors or thoughts with flexibility to achieve one's internal goal. The PFC is responsible for cognitive control (Yuan & Raz, 2014), and COMT plays a key role in the regulation of dopaminergic activity in the PFC (Diamond, 2007). In this

respect, functional SNP of the COMT gene can be assumed to be associated with the progress of Internet addiction.

Therefore, the Principal Investigator (PI) conducted this study to identify possible relationships among the COMT genotype and a person's core characteristics, specific cognitions, and Internet addiction.

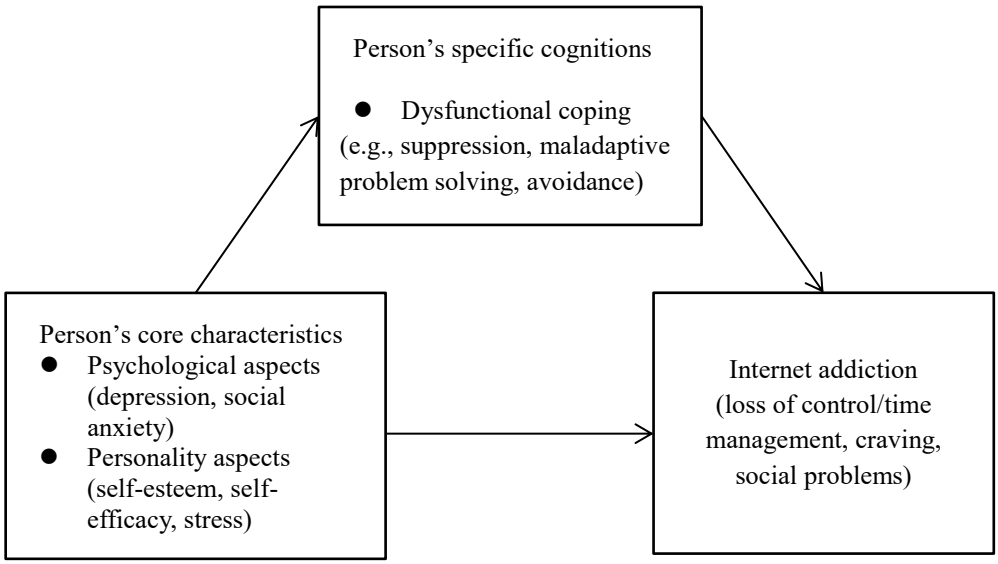

Figure 4.1. Extracted model of Internet addiction. Adapted from "Internet Addiction: Coping Styles, Expectancies, and Treatment Implications" by M. Brand, C. Laier, and K. S. Young, 2014, *Frontiers in Psychology*, *5*(1256), p. 3.

Method

Participants

The eligibility criteria for this study were that each participant was a current undergraduate student registered at a university or college in South Korea, was aged 18 or over, had engaged in Internet use at least once in the previous month, and was native Korean and able to understand the questions and directions in Korean. Individuals were excluded if they had taken psychotropic medications, estrogen hormonal medications (including any type of birth control), or dietary supplements of which a major portion was tea catechin or quercetin in the

previous month, or if they were pregnant (Jiang, Xie, Ramsden, & Ho, 2003; W. J. Lee, Shim, & Zhu, 2005; White et al., 2014).

In terms of sample size and considering all the independent variables, 236 participants would be needed to yield 80% power, based on power analysis using SAS version 9.4 (SAS Institute, Cary, NC). Anticipating some failures related to sample procurement, the PI recruited 250 participants.

Sampling Procedures

The PI conducted this study after obtaining approval from the university institutional review boards in both the United States and South Korea. The PI collected data from July 2016 to September 2016 from students at university campuses in Seoul and the Seoul metropolitan area of South Korea and applied convenience sampling and snowball sampling strategies. To recruit participants, the PI placed flyers on notice-boards near the student union and libraries and advertised on student websites to reach a wide variety of students. The advertisement provided information about the research project, including the date and time, process, inclusion and exclusion criteria, and incentive for participation, which was 5,000 Korean Won [KRW] ($4 ~ $5 based on the current US dollar exchange rate). It also clarified that the participants needed to make sure not to eat, drink, smoke, or chew gum at least 30 minutes prior to saliva collection (Nunes et al., 2012).

Survey

The PI used the Qualtrics web-based system to collect the survey data for this study. When the participants clicked the link to start the survey, informed consent information first appeared on the screen. Once they clicked on the ‘Agree’ tab to participate in the study, the survey automatically started, and participants were prompted to enter their study ID, which the

PI provided randomly in order to collect data anonymously.

Measures

Sociodemographic characteristics. The survey asked for the participants' following sociodemographic characteristics: sex, age, year, major, grade-point average, monthly family income, perceived socioeconomic status, and religion.

Health-related behavior. Regarding the health-related behavior of the participants, the questions were about their alcohol use, tobacco dependence, exercise habits, sleep, and perceived health status. Specifically, to assess the alcohol use of the participants, the PI applied the Korean version of the Alcohol Use Disorders Identification Test – Consumption Questions (AUDIT-C-K). The original version of the AUDIT was developed by the World Health Organization in 1989, and later, Bush, Kivlahan, McDonell, Fihn, and Bradley (1998) suggested a shorter version, AUDIT-C, as a brief screening test with three questions about alcohol consumption taken from the AUDIT. This short version has been widely used with high reliability and validity. Cronbach's alpha values of the Korean version of AUDIT and AUDIT-C were .92 and .85, respectively (B.O. Lee, Lee, Lee, Choi, & Namkoong, 2000). To assess the tobacco dependence of the participants, the PI applied the Korean version of the Cigarette Dependence Scale 5-item short version (CDS-5). The original version of the CDS was developed by Etter, Le Houezec, and Perneger (2003) who also developed the CDS-5. Kim and Paek (2008) translated CDS-5 into Korean and reported Cronbach's alpha to be .72 (Choi et al., 2009). In this study, Cronbach's alpha was .86.

Internet usage. To assess the Internet use of the participants, the PI used questions from the survey conducted by the National Information Society Agency (2015) in South Korea. The PI assessed whether the participants used smartphones, where they usually use the Internet, and

which device they usually employ for Internet use. The PI also asked about the purpose, frequency, and length of their Internet use.

Internet addiction. The PI applied the Korean language version of the IAT, the KIAT, to assess the tendency towards and severity of Internet addiction of the participants. The IAT was developed originally by Young (1998) and has been translated into various languages, validated, and widely used. The KIAT was later developed by Yun (1999). The KIAT is a self-report, 20-item, 5-point Likert questionnaire, and responses range from 1 (never) to 5 (always), so possible total scores range from 20 to 100. The original version was a 6-point Likert questionnaire with the score 0 for the response 'not applicable'; however, this response was removed in the KIAT. A higher score indicates a higher severity level of Internet addiction, and cut-off points of total scores are used to identify each level of Internet addiction: 20-30 (normal level of Internet usage), 31-49 (mild), 50-79 (moderate), and 80-100 (severe). Individuals at the moderate or severe levels are likely to start experiencing problems with Internet usage (Young, 2017a). Therefore, in this study, these individuals are regarded as having Internet addiction compared to Internet users who are at a normal or mild level of Internet use. Cronbach's alpha of KIAT was .79 in the Yun (1999) study and .86 in this study.

Depressive symptoms. The PI applied the integrated Korean version of the Center for Epidemiologic Studies - Depression (CES-D) scale to assess depressive symptoms among the participants. The CES-D was developed originally by Radloff (1977), and Chon, Choi, and Yang (2001) later translated it into Korean. This instrument is a self-report, 20-item, 4-point Likert questionnaire with responses ranging from 0 (rarely) to 3 (most or all of the time). Cut-off points of total scores are set for a normal level and each level of depressive symptoms: 0-15 (normal), 16-20 (mild), 21-25 (moderate), and 26-60 (severe). Cronbach's alpha of the Korean version of

the CES-D was .91 in the Chon et al. (2001) study and .87 in this study.

Social anxiety. To assess social anxiety among the participants, the PI used the Korean language version of the Social Avoidance and Distress (K-SAD) scale. The original version was developed by Watson and Friend (1969), and J. Lee and Choi (1997) later translated this instrument into Korean. The K-SAD is a self-report, 28-item, 5-point Likert questionnaire with responses ranging from 1 (none) to 5 (completely), so the total scores range from 28 to 140. Higher scores indicate a higher level of social anxiety, and cut-off points of the total scores are set for each level of social anxiety: 28-63 (normal), 64-81 (mild), 82-98 (moderate), and over 99 (severe). Cronbach's alpha of the K-SAD was .92 in both the J. Lee and Choi (1997) study and this study.

Perceived stress. To assess the perceived stress among the participants, the PI utilized the Perceived Stress Scale, developed by Cohen, Kamarck, and Mermelstein (1983) and later translated into Korean and validated by J. Park and Seo (2010). This instrument is a self-report, 10-item, 5-point Likert questionnaire with possible responses ranging from 0 (never) to 4 (very often). Higher scores indicate higher levels of perceived stress. Cronbach's alpha of this instrument ranged from .75 to .76 in the J. Park and Seo (2010) study and was .79 in this study.

Self-efficacy. To measure the general self-efficacy of the participants, the PI applied the Self-Efficacy Scale, developed by Jerusalem and Schwarzer (1992). This instrument is a self-report, 10-item, 4-point Likert questionnaire with possible responses ranging from 1 (not true) to 4 (exactly true). This scale was translated into Korean and validated by Schwarzer et al. (1997). Cronbach's alpha of the Korean version was .88 in the Schwarzer et al. (1997) study and .85 in this study.

Self-esteem. To measure the participants' self-esteem, the PI applied the Korean language

version of the Rosenberg Self-Esteem Scale (RSES). The RSES was first developed by Rosenberg (1965) and has been translated into 28 languages (J. Lee, Nam, Lee, Lee, & Lee, 2009), including Korean (B. J. Chon, 1974). This instrument is a self-report, 10-item, 4-point Likert questionnaire with possible responses ranging from 1 (strongly disagree) to 4 (strongly agree). Higher scores indicate higher levels of self-esteem. In the B. J. Chon (1974) study, Cronbach's alpha was .86, and J. Lee et al. (2009) reported a similar result ($\alpha = .87$) in their study with undergraduate students about the item-level validity of the RSES. In this study, Cronbach's alpha was .83

Coping. To assess the participants' coping strategies, the PI used the Brief Coping Orientation to Problems Experienced (COPE). This instrument was developed by Carver (1997) and later translated into Korean by Y. Kim and Seidlitz (2002). The Brief COPE instrument is a self-report, 28-item (two items for each strategy), 4-point Likert questionnaire with responses ranging from 1 (I haven't been doing this at all) to 4 (I've been doing this a lot). Two items form each subscale (which indicates a coping strategy) of the instrument. The 14 subscales are as follows: self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion, and self-blame. In previous studies, Cronbach's alpha of each subscale ranged from .50 to .90 (Y. Kim & Seidlitz, 2002).

In contrast to the other measures used in this study, the Brief COPE instrument has limited psychometric validation data obtained from Korean undergraduate student samples. Therefore, the PI conducted exploratory factor analysis to ensure that the original factor structure of the Brief COPE could be used for the analyses planned for the current study. The PI performed exploratory factor analysis at an item-based level because few studies have explored

the factor structure of this instrument using similar samples.

The PI applied principal components analysis using oblique (direct oblimin) rotation, which considers the correlation of the factors and yields a theoretically accurate solution (Osborne, 2008). First, based on eigenvalues and patterns in a scree plot, the PI performed the analysis using various factors. The initial value of the Kaiser-Meyer-Olkin test was .700. According to the scree plot, the PI determined that five factors would be appropriate for the study samples. Then, the PI checked communalities and item loadings and decided to drop two items: No. 1, 'Turning to work or other activities to take my mind off things', and No. 19, 'Doing something to think about it less, such as going to the movies, watching TV, reading, daydreaming, sleeping, or shopping'. This decision was based on low communality values (less than .3) and low item loading values (less than .40).

The PI then performed subsequent analyses using the 26 items. Table 4.1 presents a factor loading of the 26 Items of Brief COPE. The value of the Kaiser-Meyer-Olkin test was .712, and no items with low communalities were found. However, three items, Nos. 6, 9, and 16, showed item loadings that were less than .40, and three items, Nos. 6, 16, and 25, demonstrated cross-loadings. However, the PI did not drop these items because dropping too many items could affect the integrity of the instrument. Rather, the PI confirmed the factors based on whether the concept of the item fit well with the factor, an approach that yielded a total of 26 remaining items.

Table 4.2 shows five factors yielded from the factor analysis of this study. The first factor, referred to here as 'Positive Reappraisal', loaded eight items that correspond to the following factors from the original study: positive reframing, active coping, acceptance, and planning. The second factor, 'Dysfunctional Coping' also loaded eight items that correspond to self-blame, venting, humor, and behavioral disengagement that were used in the original study. Next, four

items that represented use of instrumental support and use of emotional support in the original study were merged into the third factor, 'Use of Support'. The fourth factor, 'Substance Use', consisted of two items that belonged to the factor, 'Substance Use', in the original study. Lastly, the fifth factor, 'Non-Ruminative Coping', loaded four items that correspond to religion and denial in the original study. Cronbach's alpha of the factors ranged from .61 to .91 in this study.

Table 4.1. *Factor Loading of the 26 Items of Brief COPE*

	Factor Loadings				
Items	F1	F2	F3	F4	F5
12. Trying to see it in a different light to make it seem more positive	**.724**	-.185	.025	.053	.156
7. Taking action to try to make the situation better	**.709**	-.016	.005	-.062	.123
24. Learning to live with it	**.697**	.033	.037	.182	.082
14. Trying to come up with a strategy about what to do	**.694**	.037	.030	-.192	-.086
17. Looking for something good in what is happening	**.693**	-.131	.048	.057	.192
2. Concentrating my efforts on doing something about the situation	**.686**	.022	-.074	-.003	-.011
20. Accepting the reality of the fact that it has happened	**.542**	.328	.017	.034	-.290
25. Thinking hard about what steps to take.	**.414**	.375	.055	-.099	-.061
13. Criticizing myself	-.206	**.654**	-.036	.098	.158
26. Blaming myself for things that happened	-.075	**.641**	.041	.075	.291
21. Expressing my negative feelings	-.038	**.600**	.191	-.208	-.116
28. Making fun of the situation	.149	**.593**	-.050	.085	-.205
18. Making jokes about it	.253	**.409**	-.035	.260	-.087
9. Saying things to let my unpleasant feelings escape.	-.032	.388	.233	-.250	.242
16. Giving up the attempt to cope.	-.074	.372	-.248	.217	.273
6. Giving up trying to deal with it.	-.336	.316	-.127	.050	.362
10. Getting help and advice from other people	.157	.066	**.772**	.084	.085
23. Trying to get advice or help from other people about what to do	.263	.004	**.765**	.100	.061
5. Getting emotional support from others	-.145	.262	**.751**	.134	.063
15. Getting comfort and understanding from someone	-.212	-.271	**.662**	-.018	-.118
11. Using alcohol or other drugs	.002	.000	.162	**.899**	-.031
4. Using alcohol or other drugs to make myself feel better	-.022	.019	.095	**.891**	-.013
27. Praying or meditating	.247	-.051	.036	-.180	**.683**
22. Trying to find comfort in my religion or spiritual beliefs	.131	.035	.078	-.208	**.677**
8. Refusing to believe that it has happened	-.104	.046	.059	.177	**.677**
3. Saying to myself "this isn't real."	.107	-.052	-.060	.255	**.479**

Note. Factor loadings > .40 are in boldface.
F1 = Positive reappraisal; F2 = Dysfunctional; F3 = Use of support; F4 = Substance use; F5 = Non-ruminative

Table 4.2. *Factors of Brief COPE*

Coping strategies	Cronbach's alpha	Items
F1: Positive Reappraisal	.82	12. Trying to see it in a different light to make it seem more positive 7. Taking action to try to make the situation better 24. Learning to live with it 14. Trying to come up with a strategy about what to do 17. Looking for something good in what is happening 2. Concentrating my efforts on doing something about the situation 20. Accepting the reality of the fact that it has happened 25. Thinking hard about what steps to take.
F2: Dysfunctional	.67	13. Criticizing myself 26. Blaming myself for things that happened 21. Expressing my negative feelings 28. Making fun of the situation 18. Making jokes about it 9. Saying things to let my unpleasant feelings escape. 16. Giving up the attempt to cope. 6. Giving up trying to deal with it.
F3: Use of support	.74	10. Getting help and advice from other people 23. Trying to get advice or help from other people about what to do 5. Getting emotional support from others 15. Getting comfort and understanding from someone
F4: Substance use	.91	11. Using alcohol or other drugs 4. Using alcohol or other drugs to make myself feel better
F5: Non-ruminative	.61	27. Praying or meditating 22. Trying to find comfort in my religion or spiritual beliefs 8. Refusing to believe that it has happened 3. Saying to myself "this isn't real."

Saliva Collection

The saliva samples were collected using an Oragene® DNA OG-500 kit. Each collection tube included a barcode that corresponded to each participant's ID. Once the participants received the tubes, they were asked to spit saliva up to the line on the tube (approximately 2.0 mL). The PI then took the tube, closed the lid tightly, and shook the tube gently to mix the saliva and reagents. When the saliva collection process was completed, the PI placed each tube in a

sealed plastic bag, wrapped the bags in bubble wrap, and packed them in cardboard boxes before shipping them to the Biobehavioral Laboratory (BBL) at The University of North Carolina at Chapel Hill School of Nursing (UNC-CH SON). Saliva samples will remain stable at room temperature for up to several years (Nunes et al., 2012); therefore, no additional strategies were needed to prepare the samples for shipping. On average, the BBL received the samples within 14 days after shipment from South Korea.

Analysis

Genotyping COMT (Val^{158}Met). The PI performed DNA extraction in the BBL at the UNC-CH SON following the prepIT-L2P procedure (DNA Genotek, Inc., Ontario, Canada). Then, to determine the average concentrations and purity, the PI quantified the DNA using a spectrophotometer. After quantifying the DNA, the PI shipped the extracted DNA with dry ice to GenoFIND^{TM} services for genotyping using the TaqMan SNP genotyping assay. The GenoFIND^{TM} laboratory then provided a final report that included the genotyping results via an emailed Excel spreadsheet. The PI then imported the data to a SAS (SAS Institute, Cary, NC) dataset to facilitate data analysis.

Statistical Analysis. To examine the feasibility of the study, the PI evaluated the response rate to the web-based survey questions and the rate of missing data in percentiles and compared these rates with those obtained from previous studies. The PI specifically assessed patterns of missing data across the survey to identify any commonly missed questions or survey sections among the participants or if data were missing at random. The PI also investigated the rate of the survey responses and compared this rate to the rate of the saliva sample collection from the participants to determine any differences.

Using the collected survey data, the PI assessed the distribution of each variable using

descriptive statistics. To examine possible associations between the COMT genotype and Internet addiction, the PI compared the proportion of moderate or severe Internet addiction in the Val/Val group and Met carriers using chi-square statistics. Given that the frequency of alleles in the COMT gene differs depending on ethnicity and that approximately 52% of the participants corresponded to Val/Val, 40% corresponded to Val/Met, and 8% corresponded to Met/Met for East Asians (L. O. Lee & Prescott, 2014), the PI decided to combine the Val/Met and Met/Met participants as 'Met carriers'. Also, the PI analyzed possible associations between the psychological variables (depressive symptoms, social anxiety, self-esteem, self-efficacy, stress, and coping strategy) and Internet addiction using t-tests and/or chi-square statistics. For all the statistical tests, the PI used SAS software version 9.4 (SAS Institute, Cary, NC) with a .05 two-sided significance level.

Results

Feasibility of the Study

The PI took approximately eight months to complete the study from the commencement of data collection to completion of the genotyping analysis. The web-based survey was implemented without complications and without significant missing data. The missing data rate was less than 10% for each variable, and the results of the 'missing completely at random' test showed that the missed items were at random.

The saliva samples shipped from South Korea arrived at the UNC-CH SON within two weeks, without any problems related to customs policies in South Korea or in the United States. The samples were not damaged, and none were missing upon arrival. Also, shipping the extracted DNA samples with dry ice from the BBL to the GenoFIND^{TM} services laboratory proceeded without any difficulties. Although several samples showed a low concentration of

DNA, that is, the 260/280 ratio was less than 1.6 (Nunes et al., 2012), adequate genotype data could be obtained from 248 of the 250 samples.

Sociodemographic Characteristics and Internet Addiction

Table 4.3 presents a summary of the participants' sociodemographic characteristics with regard to Internet addiction. Of the 250 Korean undergraduate students who participated in this study, 130 were males (52.0%) and 120 were females (48.0%). The mean age of the participants was 21.64 years. The participants were studying various majors, and approximately 87% of the participants reported a grade-point average of 'B' or higher. Forty-one percent of the participants were in a romantic relationship. Although 52% of the participants were living with their family, 33.2% of the participants were living alone. Approximately 20% of the participants reported that their monthly family income was less than three million Korean Won [KRW] ($2,500 ~ $2,800 based on the current US dollar exchange rate) and perceived their socioeconomic status to be low to lower-middle. Approximately 65% of the participants reported that they did not have any particular religious affiliation. Among all of the sociodemographic variables, only one, being in a current romantic relationship, was significantly associated with a low tendency toward Internet addiction ($X^2 = 5.03$, $p = .025$).

Table 4.3. *Sociodemographic Characteristics and Internet Addiction*

Variables	*n* (%) or M ± SD	IAT		X^2 or *t*	*p*
		Normal Users	Problematic Users		
Sex					
Male	130 (52.0)	61	69	0.32	.569
Female	120 (48.0)	52	68		
Age	21.64 ± 7.30	21.37 ± 2.29	21.87 ± 2.29	1.72	.086
Major					
Arts & humanities	43 (17.2)	14	29	3.96	.266
Engineering	51 (20.4)	22	29		
Medicine & natural sciences	42 (16.8)	21	21		
Social sciences	114 (45.6)	56	58		
GPA					
A	82 (32.8)	39	43	0.63	.729
B	135 (54.0)	61	74		
C and below	33 (13.2)	13	20		
Romantic relationship*					
Yes	103 (41.4)	55	48	5.03	.025
No	146 (58.6)	57	89		
Living					
With family	130 (52.0)	55	75	1.18	.556
With friends (roommates)	35 (14.11)	17	18		
Alone	83 (33.2)	41	42		
Monthly family income (KRW)					
Less than 3 million	51 (20.5)	23	28	0.69	.710
3 million – 7 million	140 (56.3)	61	79		
7 million or over	58 (23.2)	29	29		
Perceived SES					
Low – lower middle	58 (23.3)	24	34	0.69	.707
Middle	117 (47.0)	53	64		
Upper middle - high	74 (29.7)	36	38		
Religion					
No	160 (64.5)	69	91	1.08	.298
Yes	88 (35.5)	44	44		
Buddhism	13 (5.2)				
Catholic	55 (22.2)				
Christian	20 (8.1)				

Note. IAT = Internet addiction test; *n* = number of cases; M = Mean; SD = Standard deviation; X^2= The chi-square distribution; *t* = Student's *t* distribution; GPA = Grade point average; KRW = Korean won; SES = Socioeconomic status; * $p < .05$

Health-related Behavior and Internet Addiction

Table 4.4 presents a summary of the participants' reported health-related behavior with regard to Internet addiction. Among the 250 participants, approximately 90% reported that they drank alcohol, and about 15% reported that they smoked. Slightly more than 50% of the participants exercised regularly, and approximately 64% had regular sleep.

Although drinking alcohol and smoking were not significantly related to a tendency toward Internet addiction, engaging in regular exercise ($X^2 = 5.12$, $p = .024$) and better perceived health status had a significant relationship with a low tendency toward Internet addiction ($X^2 = 9.02$, df = 2, $p = .011$).

Table 4.4. *Health-Related Behavior and Internet Addiction*

Variables	*n* (%) or M ± SD	IAT		X^2 or *t*	*p*
		Normal Users	Problematic Users		
Alcohol use (*n* = 223)	6.20 ± 1.60	6.32 ± 1.50	6.09 ± 1.68	-1.08	.283
Smoke (*n* = 36)	11.36 ± 4.28	11.78 ± 4.08	10.62 ± 4.68	-0.78	.440
Regular exercise*					
Yes	142 (56.8)	73	69	5.12	.024
No	108 (43.2)	40	68		
Regular sleep					
Yes	161 (64.4)	77	84	1.26	.262
No	89 (35.6)	36	53		
Perceived health status*					
Healthy	130 (52.2)	69	61	9.02	.011
Fair	79 (31.7)	32	47		
Poor	40 (16.1)	11	29		

Note. IAT = Internet addiction test; *n* = number of cases; M = Mean; SD = Standard deviation; X^2= The chi-square distribution; *t* = Student's *t* distribution; * $p < .05$

Internet Use Characteristics and Internet Addiction

Table 4.5 presents a summary of the participants' Internet use characteristics with regard to Internet addiction. Almost all (99.6%) participants used smartphones, and 65% reported more frequent smartphone Internet use than personal computer Internet use. However, the level of Internet addiction was not higher among participants who used smartphones compared to those who used computers. Also, Internet use hours were not significantly associated with Internet addiction. More than 50% of the participants reported that they used the Internet to study or work, for fun, to relieve stress, for killing time, or habitually. People who used the Internet to study or work, for fun, to communicate with people, or killing time did not correlate with Internet addiction. However, using the Internet to relieve stress ($X^2 = 9.23$, $p = .002$), to avoid negative emotions ($X^2 = 9.54$, $p = .002$), and habitually ($X^2 = 19.42$, $p < .0001$) showed a significantly high tendency toward Internet addiction.

COMT (Val^{158}Met) and Internet Addiction

Table 4.6 presents a summary of the association between the COMT genotype (Val^{158}Met) and Internet addiction. The COMT genotype was statistically fitted with the Hardy-Weinberg equilibrium ($X^2 = 2.24$, $p = .134$). Of all the participants, 53.2% corresponded to Val/Val, 41.9% to Val/Met, and 4.8% to Met/Met. Having Val/Val homozygotes or Met alleles were not significantly associated with Internet addiction ($X^2 = 0.02$, $p = .876$).

Table 4.5. *Internet Use Characteristics*

Variables	*n* (%) or M ± SD	IAT		X^2 or *t*	*p*
		Normal Users	Problematic Users		
Smartphone use	249 (99.6)		N/A		
Device for Internet use					
Smartphone	163 (65.2)	75	88	0.27	.875
PC	20 (8.0)	8	12		
Both similarly	67 (26.8)	30	37		
Internet use/day					
Less than 2 hours	49 (19.6)	25	24	4.84	.184
2 – 4 hours	139 (55.6)	67	72		
4 – 6 hours	42 (16.8)	13	29		
6 hours or more	20 (8.0)	8	12		
Purpose of the Internet (Select All)					
To study or work	150 (40.0)	68	82	0.00	.959
Yes	100 (60.0)	45	55		
No					
For fun	188 (75.2)	79	109	3.09	.079
Yes	62 (24.8)	34	28		
No					
To relieve stress**	126 (50.4)	45	81	9.23	.002
Yes	124 (49.6)	68	56		
No					
To communicate with people	117 (46.8)	50	67	0.54	.463
Yes	133 (53.2)	63	70		
No					
For killing time	190 (76.0)	84	106	0.31	.576
Yes	60 (24.0)	29	31		
No					
To avoid negative emotions**	31 (12.4)	6	25	9.54	.002
Yes	219 (87.6)	107	112		
No					
Habitually***	188 (75.2)	70	118	19.42	<.0001
Yes	62 (24.8)	43	19		
No					

Note. IAT = Internet addiction test; *n* = number of cases; M = Mean; SD = Standard deviation; X^2= The chi-square distribution; *t* = Student's *t* distribution; N/A = Not applied; PC = Personal computer; ** $p < .01$. *** $p < .001$

figure

Variables	*N* (%) or M ± SD	IAT		X^2 or *t*	*p*
		Normal Users	Problematic Users		
COMT Val^{158}Met					
Val/Val	132 (53.2)	59	73	0.02	.876
Met Carrier	116 (46.8)	53	63		
Val/Met	104 (41.9)				
Met/Met	12 (4.8)				
Depressive symptoms***					
Normal	206 (82.4)	104	102	13.20	.0003
Depressive	44 (17.6)	9	35		
Mild	23 (9.2)				
Moderate	10 (4.0)				
Severe	11 (4.4)				
Social Anxiety**					
Normal – Mild	168 (67.2)	87	81	8.97	.003
Moderate – Severe	82 (32.8)	26	56		
Perceived Stress***	17.39 ± 5.36	15.38 ± 4.75	19.04 ± 5.28	5.71	<.0001
Self-esteem***	30.36 ± 4.57	32.17 ± 3.89	28.86 ± 4.56	-6.10	<.0001
Self-efficacy***	29.34 ± 3.88	30.58 ± 3.31	28.32 ± 4.03	-4.87	<.0001
Coping					
Positive reappraisal*	23.99 ± 4.10	24.72 ± 3.89	23.39 ± 4.19	-2.57	.011
Dysfunctional***	15.83 ± 3.67	14.84 ± 3.48	16.64 ± 3.64	3.97	<.0001
Use of support	11.44 ± 2.60	11.52 ± 2.42	11.38 ± 2.75	-0.43	.667
Substance use	3.65 ± 1.88	3.81 ± 1.99	3.52 ± 1.78	-1.20	.230
Non-ruminative	5.96 ± 2.16	5.84 ± 2.29	6.06 ± 2.05	0.79	.429

Note. COMT = Catechol-o-methyltransferase; IAT = Internet addiction test; *n* = number of cases; M = Mean; SD = Standard deviation; X^2= The chi-square distribution; *t* = Student's *t* distribution; * $p < .05$. ** $p < .01$. *** $p < .001$

Psychological Variables and Internet Addiction

Table 4.6 also summarizes the associations between the psychological variables and internet addiction. Approximately 18% of the participants reported that they had depressive symptoms, and 4.4% of them reported severe depressive symptoms. Among the participants with depressive symptoms, about 80% presented Internet addiction, and about 50% of the participants

with no depressive symptoms presented Internet addiction (i.e., depressive symptoms showed a highly significant relationship with a high tendency toward Internet addiction, $X^2 = 13.20$, $p = .0003$). Approximately 33% of the participants presented moderate to severe social anxiety, and social anxiety also was significantly associated with a high tendency toward Internet addiction ($X^2 = 8.97$, $p = .003$). Because these data were anonymous, it was not possible to follow up the participants to suggest treatment. Perceived stress, self-esteem, and self-efficacy were measured as continuous variables, and the PI compared the total score of each variable for the normal group and the Internet addiction group. As a result, higher perceived stress, lower self-esteem, and lower self-efficacy were significantly associated with a high tendency toward Internet addiction. Lastly, among the five coping strategies, the participants applied positive reappraisal, Internet addiction tendency was significantly lower ($t = -2.57$, $p = .011$). However, use of a dysfunctional coping strategy showed a significantly high tendency toward Internet addiction ($t = -3.97$, $p < .0001$).

Discussion

In this study, the PI investigated the Internet addiction tendencies among a sample of undergraduate students in South Korea. The PI identified issues related to the feasibility of conducting a cross-sectional study to examine possible relationships among Internet addiction, COMT genotype ($Val^{158}Met$), and psychological variables (depressive symptoms, social anxiety, perceived stress, self-esteem, self-efficacy, and coping strategies).

In terms of study feasibility, the PI recruited the participants within the planned time-frame and smoothly carried out saliva sample collection and web-based surveys. The successful recruitment of interested participants was possible not only because of the advertisement flyer that was posted on bulletin boards on the campuses, but also because of the considerable

influence of social media that the students frequently used that served to help publicize the study. Incentives might contribute to the recruitment of the participants. In addition, participants could easily access the web-based survey as a result of stable Wi-Fi connections on their campuses. Almost all the participants completed the study procedures within 30 minutes. This relative quickness may have been due to their familiarity with computer devices and the simplicity and limited invasiveness of the saliva sample collection process. Using randomly assigned ID numbers instead of identifiable information guaranteed the anonymity of the participants and possibly increased their sense of safety and engagement in this study. The saliva samples obtained using Oragene® DNA OG-500 kits could be preserved for several years at room temperature (Nunes et al., 2012), so the transportation and storage of the samples were undertaken with relative ease.

The participants were demographically diverse; they represented a range of academic majors, income levels, relationship status, and religions. The study comprised approximately the same number of men and women. Also, as anticipated, 53% of all participants corresponded to Val/Val and 42% corresponded to Val/Met, with only 5% corresponding to Met/Met. This ratio of each genotype of Val^{158}Met corroborates findings from previous research regarding allele frequency in East Asians (L. O. Lee & Prescott, 2014).

Regarding the prevalence of Internet addiction, 54.8% of all the participants in this study could be categorized as having moderate or severe Internet addiction. Compared to the Noh and Kim (2016) study that also analyzed undergraduate student samples in South Korea using the same instrument, i.e., the IAT, this study found that the prevalence of Internet addiction was higher by more than 200 percent. The IAT is a self-report questionnaire; that is, the results are based on the subjective self-judgments of the respondents' Internet usage, regardless of the

amount of their Internet use. Thus, the higher prevalence of Internet addiction reported in this and other recent studies may suggest that Internet users are increasingly suffering from symptoms related to Internet addiction and having difficulty controlling their Internet usage. These problems could be due to the fact that the Internet is rapidly becoming increasingly popular and its contents are becoming increasingly diverse. Therefore, extensive research into the development of effective interventions to prevent and reduce Internet addiction is a pressing need.

In this study, the PI found that demographic characteristics, including gender and age, were not relevant to tendencies toward Internet addiction, which is in contrast to prior studies that typically have reported that being male and/or young are risk factors for Internet addiction (Alzayyat, A.; Al-Gamal, E.; Ahmad, 2015; Şenormancı et al., 2014). The reason for this finding may be that Internet content is diversified so that people with various backgrounds can enjoy the Internet and fulfill various needs and that the infrastructure required for using the Internet is well constructed and relatively user friendly.

Regarding social relationships and Internet addiction tendencies, the participants who reported being in romantic relationships and participants with less social anxiety showed less tendency toward Internet addiction. Previous studies have demonstrated the importance of social relationships and lack of social anxiety in terms of mitigating Internet addiction. Bozoglan, Demirer, and Sahin (2013) suggested that people who reported greater loneliness had more problems with time management compared to those with less loneliness. Moreover, people with social anxiety have a tendency to choose online interactions instead of face-to-face communication, because online interactions enable them to mask their low confidence with social behavior (Weinstein et al., 2015). Although one of the positive aspects of the Internet is to

enhance social relationships with others as a means of communication, excessive use of the Internet can serve as a substitute for external interaction with individuals and reduce direct, in-person social participation. This phenomenon is referred to as 'Internet paradox' (Kraut et al., 1998) and can threaten not only people's psychological health but also their social relationships, which leads to further isolation from society. Therefore, interventions that develop and maintain healthy social relationships may help to prevent Internet addiction among young adults who are new to broader college social environments. In addition, healthy social relationship interventions may help to reduce the potential adverse effects among undergraduate students who already suffer from Internet addiction.

In this study, the participants with higher perceived stress levels and who applied more dysfunctional coping strategies showed higher rates of Internet addiction than the participants who did not engage in these behaviors. Furthermore, in cases where the purpose of using the Internet was to relieve stress or to avoid negative emotions, the tendency toward Internet addiction turned out to be significantly high. In studies of SRADs, stress is well known to be one of the highly important factors that triggers various risk factors (MacNicol, 2017). In the context of high levels of stress, individuals may initially apply various adaptive methods to relieve stress. However, with persistent and chronic stress, the resources that were used initially to cope may become inadequate. Therefore, the probability of developing addictive disorders increases (MacNicol, 2017). Likewise, Internet addiction is likely to develop if an individual relies on the Internet by falling into the immediate compensation mode and reinforcement in order to escape from stress (McNicol & Thorsteinsson, 2017). Brand (2014) proposed that the expectations of Internet use, that is, the reasons for using the Internet, have a direct impact on Internet addiction tendencies, and that the expectancy of Internet use also mediates the transfer from psychosocial

distresses to Internet addiction. Therefore, the reasons for Internet use and psychosocial distresses must be assessed in planning interventions for individuals with Internet addiction.

In terms of the relationship between the COMT genotype and Internet addiction, the PI could not draw a significant conclusion. To examine the effects of genotype with respect to Internet addiction tendencies, further research with a sufficient sample size and power to detect statistically significant differences among these three genotypes is necessary.

Because Internet addiction is affected by various factors, including psychosocial and environmental ones, the interactions between genes and the psychosocial and environmental factors should be analyzed. Moreover, research is needed into the multi-locus genetic profile that analyzes the multiple functional polymorphic dopamine markers, which are related to the function of dopamine regulatory mechanisms. Research that incorporates polygenic models will help to address gene-environment interactions in terms of Internet addiction through the cumulative analyses of many genetic variations, each of which affects a small amount of risk of Internet addiction better than analysis of SNP (Vrshek-Schallhorn, 2015). In this sense, research that focuses on gene-gene interactions and gene-environmental interactions (i.e. gene and psychosocial factors) in terms of Internet addiction is needed. These studies would contribute to the development of individually tailored interventions, from preventive approaches to pharmacological treatments and psychosocial interventions, which would lead to optimal outcomes for each individual with Internet addiction.

Limitation of the Study

This study has several limitations. First, because the PI applied convenience sampling, participants of this study cannot represent the entirety of undergraduate students in South Korea. In addition, the participants may have had more interest in Internet addiction than average

undergraduate students; thus, a generalization of the results may be inappropriate. Second, this research involved a cross-sectional descriptive study; thus, causal relationships among the variables in this analysis could not be explained. Third, because of limited previous research conducted regarding the association between the COMT genotype and Internet addiction among Korean undergraduate students, the PI performed the power analysis of this study by referring to studies that used samples of adolescents and people with gambling disorder. Therefore, the sample size yielded by power analysis for the current study may have been smaller than is needed to detect significant group differences.

Implications for Nursing Research and Nursing Practice

Recently, with the diversification and universalization of the Internet, the Internet use rate has increased rapidly (Feng et al., 2017). In particular, undergraduate students are exposed to an environment where they can easily access the Internet. Also, in terms of their developmental stage that places them in a transitional period between adolescence and adulthood, such students are not yet experienced in managing themselves with respect to the freedom they are suddenly provided (Skidmore, Kaufman, & Crowell, 2016). Such circumstances can lead students to become more vulnerable to Internet addiction.

Thus, future studies are needed to examine causal relationships among biopsychosocial factors and Internet addiction in undergraduate students. Also, studies with a longitudinal design that can identify long-term effects of biological factors and psychosocial distress on Internet addiction are essential. Analyses of the various genetic factors that are related to Internet addiction are also necessary. In terms of candidate genes that may be related to the biological aspects of Internet addiction, research regarding interactions between genes and between genes and psychosocial factors is required.

Healthcare providers must assess individuals' psychosocial distress before implementing Internet addiction interventions. If these stress factors are related to an individual's Internet addiction, then interventions that target these factors will be important to include. In addition, to prevent the transition from psychosocial distress to Internet addiction, interventions that facilitate the development of healthy coping skills to address psychosocial distress and cognitive, self-regulatory approaches associated with relying on the Internet to gain instant compensation and satisfaction would be vital. Despite the many calls for Internet addiction to be diagnosed as a mental disorder, and because many people are currently suffering physical, psychological, and social distress due to symptoms related to Internet addiction, the development of standardized assessment tools and individualized interventions for Internet addiction is urgently required.

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CHAPTER 5: SYNTHESIS OF DISSERTATION

Synthesis of Findings

Paper 1: Psychosocial Risk Factors of Internet Addiction among Undergraduate Students: Systematized Literature Review

The Internet has become an essential part of people's daily lives due to the rapid technological progress made in recent years. Although Internet infrastructure has brought about incredible convenience and allowed for extensive networking around the world, it also has induced adverse effects, including Internet addiction (Nakayama, Mihara, & Higuchi, 2017). Undergraduate students have received significant attention in Internet addiction research not only because they constitute the majority of Internet users (Kuss, Griffiths, & Binder, 2013), but also because they can be vulnerable to Internet addiction due to their environment that provides easy access to the Internet (Kuss et al., 2013) as well as their developmental transition from being adolescents under parents' oversight to becoming independent adults (Skidmore, Kaufman, & Crowell, 2016). However, synthesized evidence regarding the risk factors of Internet addiction among samples of undergraduate students remains lacking.

For this reason, the first paper of this dissertation (Chapter 2) aims to provide a systemized summary of the literature regarding the psychosocial risk factors of Internet addiction among undergraduate students. The PI reviewed 36 studies that had been conducted in various countries around the world. Although the PI could not confirm the prevalence of Internet addiction of undergraduate students due to lack of consistency in the measurements, approximately 10% to 25% of undergraduate students were reported to have problems with

Internet addiction or to have severe symptoms of Internet addiction. Psychological distresses, such as depression, anxiety, stress, dysfunctional coping strategies, and problems with interpersonal relationships and loneliness have been reported as major risk factors for Internet addiction among undergraduate students.

Paper 2: The Relationship between the COMT Genotype (Val^{158}Met) and Substance-Related and Addictive Disorders: Systematized Literature Review

Substance-related and addictive disorders (SRADs) are considered to be serious health and social problems worldwide (Peacock et al., 2018). The neurobiological explanation for SRADs emphasizes the role of the reward system through the dopaminergic pathway (Koob & Volkow, 2016). The catechol-o-methyltransferase (COMT) gene is one of the candidate genes that has been studied in order to understand the various illnesses and disorders related to dopaminergic neurotransmission, including SRADs, because the functional variations of the COMT gene affect the level of dopamine (Dauvilliers, Tafti, & Landolt, 2015). The association between the COMT genotype and SRADs has been researched, but it has not been confirmed due to mixed results.

Therefore, as an extension of earlier studies, the PI conducted a systematized literature review with the aim to investigate the relationship between the COMT genotype and SRADs. Unlike previously published research, the studies included in this paper's review were not limited only to the pathological use of alcohol, tobacco, or illicit drugs. Studies that focused on gambling disorder and Internet addiction also were included. The PI systematically selected and reviewed 20 studies. However, the findings of this review regarding the relationship between the COMT genotype and SRADs remain mixed.

Paper 3: Internet Addiction among Undergraduate Students in South Korea: Association between the COMT (Val^{158}Met) Genotype and Psychological Factors

South Korea has one of the highest rates of Internet addiction in the world (Kuss, Griffiths, Karila, & Billieux, 2014); this status may be a negative outcome of having the fastest broadband and the most-wired environment (Curran, 2018; Young, 2017). Individuals with Internet addiction may suffer from symptoms that are commonly associated with SRADs, such as dependence, tolerance, and withdrawal symptoms (Kuss et al., 2014; Young, Pistner, O'Mara, & Buchanan, 1999). Researchers have explored the neurobiological mechanisms behind Internet addiction and have revealed common structural and functional alterations of the brain among individuals with either Internet addiction or SRADs (Lin, Zhou, Dong, & Du, 2015; Park, Han, & Roh, 2017). Researchers have suggested that Internet addiction behavior is related to the structural and functional variations of the region near the prefrontal cortex (PFC) (Kuss, Pontes, & Griffiths, 2018), which is responsible for cognitive control (Yuan & Raz, 2014). In the PFC, dopamine transporters are relatively rare, so dopamine is regulated mostly by COMT outside of the neuron (Diamond, 2007). Because the functional variations of the COMT gene affect the activity of COMT, the level of dopamine in the PFC is related to the COMT genotype. However, little research has been conducted to examine the association between the COMT genotype and Internet addiction.

Brand, Laier, and Young (2014) developed a model to illustrate the mechanisms that underlie Internet addiction. They asserted that Internet addiction is associated with (a) a person's core characteristics, including psychopathological aspects (depression and social anxiety), personality aspects (low self-esteem, low self-efficacy, stress vulnerability), and social cognition (emotional loneliness, low social support) and (b) a person's specific cognitions, which include

dysfunctional coping strategies for everyday stress and Internet-use expectancies. Based on this model, the PI conducted this study that aims to (a) identify issues related to the feasibility of conducting a study that involves the collection of saliva samples and web-based survey data with participants who are undergraduate students in South Korea and (b) describe the relationships among Internet addiction, the COMT (Val^{158}Met) genotype, and psychological variables (depressive symptoms, social anxiety, self-esteem, self-efficacy, stress, and coping strategy).

The PI recruited 250 Korean undergraduate students from university campuses in Seoul and the Seoul metropolitan area. The participants provided saliva samples and completed a web-based survey to report their psychological health status. The study procedure, including the collection of saliva samples and the web-based survey, was found to be feasible. The PI categorized 54.8% of the participants as having Internet addiction. COMT (Val^{158}Met) was not significantly associated with Internet addiction. However, Internet addiction was significantly associated with all investigated psychological factors. Specifically, participants with higher levels of social anxiety showed a greater tendency toward Internet addiction. Also, participants with higher perceived stress and participants who applied more dysfunctional coping strategies reported higher rates of Internet addiction. Participants who reported purposefully using the Internet to relieve stress or to avoid negative emotions were more likely to report a higher level of Internet addiction than those who did not report this behavior.

Implications for Nursing Research and Nursing Practice

With the recent diversification and universalization of the Internet, the Internet use rate has increased rapidly. A growing body of research suggests that people are experiencing physical, psychological, and social distresses due to pathologically preoccupied Internet use. Given that studies regarding the prevention and intervention of Internet addiction are necessary

and require accurate assessment, arriving at consensus on the definition and measures of Internet addiction should be imperative. Also, given that Internet addiction is affected by various factors, it is important to investigate not only psychosocial risk factors, but also biological factors, environmental factors, and cultural factors associated with Internet addiction, as well as the interactions among these factors. Future studies that investigate causal relationships among the potential biopsychosocial and environmental factors and Internet addiction also are needed. Studies with a longitudinal design that can identify the long-term effects of biological factors and psychosocial distresses on Internet addiction are essential, as are analyses of the various genetic factors that are related to Internet addiction.

In terms of candidate genes that may be related to the biological aspects of Internet addiction, studies are needed that include a sufficient sample size and are robust enough to capture and reflect the representative proportions of the three genotypes (Val/Val, Val/Met, and Met/Met) used in this study. That is, a larger sample size would allow for a more robust comparative study. Studies should not be limited to only one genotype, but should include analysis of multiple functional polymorphic dopaminergic markers and research into the multi-locus genetic profile that may be related to Internet addiction. Research that incorporates polygenic models will help to address gene-environment interactions in terms of Internet addiction through the cumulative analyses of many genetic variations, each of which affects a small amount of risk of Internet addiction better than analysis of SNPs (Vrshek-Schallhorn, 2015). In this sense, research that focuses on gene-gene interactions and gene-environmental interactions (i.e. gene and psychosocial factors) in terms of Internet addiction is needed. These studies would contribute to the development of individually tailored interventions, from preventive approaches to pharmacological treatments and psychosocial interventions, which

would lead to optimal outcomes for each individual with Internet addiction.

Healthcare providers should comprehensively assess whether psychosocial factors of their patients could influence the development of Internet addiction. Then, it may be helpful to incorporate evaluations of cognitions (e.g., adaptive or maladaptive) regarding Internet use when planning interventions. If psychological distress (e.g., depression or anxiety) is related to an individual's Internet addiction, then interventions and treatments that target such psychological distress clearly would be the most appropriate strategy. Applying Screening, Brief Intervention, and Referral to Treatment (SBIRT), which is an evidence-based approach to implementing early interventions for people with SRADs, should be recommended and implemented (Mumba & Snow, 2017). This approach could contribute to identifying individuals with high risk for Internet addiction and result in the implementation of targeted interventions.

Moreover, to prevent the transition from psychosocial distress to Internet addiction, interventions that facilitate the development of healthy coping strategies may be helpful. Specifically, for undergraduate students, information about healthy lifestyles and healthy relationships can be incorporated. Cognitive self-regulatory approaches, such as cognitive behavioral therapy, could assist undergraduate students to become more aware of their use of the Internet to provide instant psychosocial or emotional compensation and satisfaction. These self-regulatory approaches can assist students to develop new, healthy strategies for psychosocial fulfillment. In short, many people are currently suffering from physical, psychological, and social distresses due to symptoms related to Internet addiction, and the movement towards diagnosing Internet addiction as a mental disorder is underway. Future research is needed to continue the development of standardized assessment tools and feasible and effective interventions and treatments for Internet addiction.

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