Received: 22 April 2021 | Revised: 11 August 2021 | Accepted: 6 September 2021

DOI: 10.1002/kjm2.12454

ORIGINAL ARTICLE

Kaohsiung Journal of Medical Sciences KJMS WILEY

Association of Internet gaming disorder with catechol-O-methyltransferase: Role of impulsivity and fun-seeking

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Funding information
Kaohsiung Medical University, Grant/Award Number: NCTUKMU109-BIO-03; Kaohsiung Municipal Siao-gang Hospital, Grant/Award Numbers: KMHK-104-006, KMHK-108-007; Taiwan Ministry of Science and Technology, Grant/Award Numbers: MOST107-2314-B-037-101-MY2, MOST109-2314-B-037-081-

Abstract

Dopamine functioning is an essential mechanism underlying addictive behaviors. This paper evaluates the association of Internet gaming disorder (IGD) with the catechol-O-methyltransferase (COMT) val158met polymorphism and examines the roles of impulsivity and reinforcement sensitivity in this association. Using diagnostic interviews, this study recruited 69 participants with IGD and 138 participants without. All participants underwent diagnostic interviews for IGD and an evaluation for the COMT val158met polymorphism, impulsivity, and reinforcement sensitivity. Among participants with the Val/Val genotype, the odds ratio (95% confidence interval) for IGD was 2.09 (1.15–3.80). The IGD–Val/Val genotype association was mediated by impulsivity and fun-seeking. The Val/Val genotype is indicative of low frontal functioning and is a predictive factor of IGD, with this effect being confounded by impulsivity and fun-seeking. Interventions targeting impulsivity and fun-seeking might attenuate the risk of IGD, particularly among individuals with the Val/Val genotype. Additional studies are necessary to elucidate the possible role of dopamine functioning.

KEYWORDS
COMT val158met, dopamine, fun-seeking, impulsivity, Internet gaming disorder

1 | INTRODUCTION

Online gaming is one of the most popular leisure activities in modern society, but a portion of gamers lose control of their gaming impulses, resulting in negative life consequences. Internet gaming disorder (IGD) has been listed as an addictive disorder in both the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[1] and *International Classification of Diseases, 11th Revision*[2] because of its considerable adverse effect on mental health. However, to date, the relevant studies have been unable to confirm the underlying neurobiological mechanism of IGD.[3] According to Volkow et al., dopamine plays a critical role in the treatment of addictive disorders,[4] and Le Foll et al. proposed that a genetic study should evaluate this role.[5] Moreover, the catechol-O-methyltransferase (COMT) polymorphism considerably affects the treatment of substance and behavioral addictions.[6,7] Nonetheless, its association with IGD needs further evaluation.

1.1 | COMT Val158met polymorphism in addictive disorder

The COMT genotype on chromosome 22q11.2 is a G-to-A missense single-nucleotide polymorphism encoding either valine (Val) or methionine (Met) at codon 158 and is named the COMT Val158met

polymorphism. It codes for the enzyme COMT, which degrades catechol compounds, such as dopamine, norepinephrine, and catecholestrogens.[7] Compared with the Val allele, the Met allele is more associated with lower COMT enzyme activity, lower dopamine degradation, and higher synaptic dopamine[8]; consequently, the Met allele is associated with more efficient frontal lobe functions.[9] Catechol compounds and the frontal lobes, associated with cognition, have major roles in various psychiatric disorders, including addictive disorders.[6,7]

IGD can weaken frontal lobe functioning when a person is performing executive tasks[10]; in addition, according to Tian et al., IGD causes decreased glucose metabolism in the prefrontal system and low D2 receptor levels in the striatum—these changes have been correlated to years of excessive gaming.[11] Moreover, the effect of the COMT Val158met polymorphism on synaptic dopamine and frontal lobe function is believed to play a role in the development of addictive behaviors.[12] However, its role in IGD has not been evaluated.

1.2 | Impulsivity and reinforcement sensitivity in participants with IGD and the role of COMT polymorphism

Impulsivity and reward sensitivity may be important endophenotypes in the genetic study of addictive disorders.[13] Participants with IGD exhibit more impulsivity,[14] highlighting cognitive control as a key factor underlying IGD,[15] and the COMT Met allele is also associated with more efficient frontal lobe functioning,[9] which indicates cognitive functioning. Therefore, the role of impulsivity in the association of IGD with the COMT Val158met polymorphism should be evaluated to elucidate the possible confounding factors.

Dopamine plays a vital role in reward sensitivity.[16] The COMT Val158met polymorphism is associated with reinforcement sensitivity.[17] The Val/Val genotype is associated with higher novelty-seeking[18] and dependence scores,[19] and individuals with IGD exhibit increased pursuit of desired appetitive goals[20] and fun-seeking.[21] Furthermore, two studies have demonstrated that individuals with IGD exhibited reduced loss aversion in tasks.[22,23] These studies demonstrate an alteration in reinforcement sensitivity among patients with IGD. Therefore, considering reinforcement sensitivity as a factor accounting for the association between IGD and the COMT polymorphism, this study first evaluated the association between IGD and the COMT Val158met polymorphism and then examined the mediating effect of impulsivity and reinforcement sensitivity on this association. To support the mediating effect, the COMT Val158met polymorphism should predict IGD, impulsivity and reinforcement sensitivity should correlate with IGD, the COMT Val158met polymorphism should correlate with impulsivity and reinforcement sensitivity, and the predictive value of the COMT Val158met polymorphism in relation to IGD should attenuate or become insignificant with control of impulsivity or reinforcement sensitivity according to the theory of Baron and Kenny.[24]

2 | METHODS

2.1 | Participants

The present case–control study recruited adults with IGD (IGD group), regular gamers (RG group), and nongamers (NG group) through advertisements placed on university Internet bulletin boards and around the southern Taiwan campus of a university. This research sample was reported in our previous article centered on the validity of the DSM-5 criteria for IGD.[25] The IGD group comprised individuals aged 20–38 years who had >12 years of education, who played online video games for 4 h/day or more on weekdays and for 6 h/day or more on weekends, and who had been maintaining a consistent pattern of gaming for over 2 years. Participants fulfilling the criteria were selected through diagnostic interview according to the DSM-5 IGD criteria.

We matched the participating RGs and NGs with IGD group participants based on sex and age (± 3 years). In the NG group, we included individuals making nonessential use of the Internet for <4 h per day,[26] excluding regular gaming. In the RG group, we recruited individuals who consistently engage in regular gaming for 3 h or more/week without fulfilling the criteria for IGD. The classification of both groups was further confirmed through three-part psychiatric interviews:

1. diagnostic interviews of the IGD group according to the DSM-5 criteria,
2. a Chinese version of the Mini International Neuropsychiatric Interview to exclude those with psychotic disorders, bipolar I disorder, and substance use disorders,[27] and
3. an interview to note their history to exclude those with intellectual disabilities, serious physical disorders, and brain injury.

In total, 69 participants were included in the IGD group and 138 in the control groups (69 RGs and 69 NGs) after they gave their informed consent. The study was approved by the Institutional Review Board of Kaohsiung Medical University Hospital, Taiwan.

2.2 | Measures

2.2.1 | DSM-5 diagnostic criteria for IGD

We conducted a semistructured interview to evaluate the presence of each DSM-5 criterion in all participants. Those fulfilling five or more criteria were recruited to the IGD group.[25]

2.2.2 | Behavioral inhibition system and behavioral approach system scales

The behavioral inhibition system (BIS) and behavioral approach system (BAS) scales, proposed by Gray, are used to evaluate individual

characteristics in the responsiveness of the motivational systems.[28] The BIS scale reveals the degree to which respondents are expected to experience anxiety when confronted with punishment cues, and the BAS scale evaluates the degree to which rewards induce positive emotions and the tendency to actively pursue appetitive goals and impulsively engage in rewarding activities. The Cronbach's alpha of the BIS scale was 0.74, and those of the BAS subscales for reward responsiveness, drive, and fun-seeking were 0.73, 0.76, and 0.66, respectively.[29]

2.2.3 | Dickman's impulsivity inventory

Dickman's impulsivity inventory (DII) comprises a 23-item true/false questionnaire used to evaluate impulsivity, with functional and dysfunctional impulsivity assessed using 11 and 12 questions, respectively. The Cronbach's alpha of the functional and dysfunctional scales was 0.74 and 0.85, respectively.[30] In the present study, we used the dysfunctional impulsivity subscale to assess the participants' impulsivity: the higher the score was, the higher was the dysfunctional impulsivity.

2.2.4 | Chen Internet addiction scale—gaming version

The Chen Internet addiction scale (CIAS) is a 4-point, 26-item self-reported scale used to assess five dimensions of Internet addiction: compulsive use, withdrawal, tolerance, problems with interpersonal relationships, and problems with health and time management.[31] To apply this scale to IGD assessment, its colloquial expressions were modified by Ko et al. (CIAS-G), yielding a Cronbach's alpha of 0.96.[32] The total CIAS scores in their study ranged from 26 to 104, with a higher CIAS score indicating higher IGD severity.

2.3 | Genotyping of the COMT polymorphism

In this study, we obtained the total genomic DNA (gDNA) from peripheral lymphocytes using the QIAamp DNA Blood Mini Kit (Qiagen, Hilden, Germany). Genotyping was performed using a 10-μL mixture containing 1 μL of genomic DNA (30 ng/μL), 5 μL of TaqMan Universal PCR Master Mix (Applied Biosystems, Nieuwerkerk aan den IJssel, The Netherlands), 0.5 μL of 20× SNP assay mix (TaqMan assay ID of COMT rs4680: C__25746809_50; Applied Biosystems), and 3.5 μL of double-distilled H_2O. Amplification was performed using the AB 7900HT fast real-time PCR system for 10 min at 95°C, followed by 45 cycles of 15 s each at 92°C and 60 s each at 60°C. Genotypes were scored using the algorithm and software supplied by Applied Biosystems.

2.4 | Procedure

All participants completed the diagnostic interview, blood test, and assessment questionnaire.

2.5 | Statistical analysis

The differences between the CIAS-G, DII, and BIS/BAS scores of the IGD and those of the control groups were evaluated with the independent *t* test, and the association between IGD and the COMT Val158met polymorphism was analyzed using the chi-square test. The independent *t* test was also used to evaluate differences between the DII and BIS/BAS values of COMT Val/Val and Met genotype carriers. The odds ratio (OR) for the COMT Val158met polymorphism (Val/Val versus Met genotype carriers) in the IGD group relative to the control group was determined using logistic regression analysis after sex and age were controlled for. Next, we regressed IGD on the COMT Val158met polymorphism and its associated factors, such as DII scores or BIS/BAS scores, to test their mediating effect on the association between IGD and the COMT polymorphism.[24] A p of <0.05 was considered significant for all analyses, which were performed using SPSS (version 20.0).

3 | RESULTS

In our study, each group comprised 21.7% female participants (Table 1), and no age difference was evident between the IGD and control groups.

3.1 | Association between IGD, impulsivity, and reinforcement sensitivity

Table 1 indicates that IGD group participants scored higher on the fun-seeking and behavioral inhibition, dysfunctional impulsivity subscales than the control group did, suggesting that they exhibited more dysfunctional impulsivity, behavioral inhibition, and fun-seeking than the control group.

3.2 | Association between COMT Val158met polymorphism, impulsivity, and reinforcement sensitivity

According to the *t* test results, Met genotype carriers had lower scores for dysfunctional impulsivity and fun-seeking than did Val/Val genotype carriers (Table 2), which revealed that participants with the Val/Val genotype experienced higher impulsivity and fun-seeking. Age and IGD severity did not differ between Met carriers and participants with the Val/Val genotype.

3.3 | Association of IGD with COMT Val158met polymorphism

The chi-square test results delineated a significant association between the diagnosis of IGD and the COMT Val158met polymorphism ($\chi^2 = 6.04$, $p = 0.014$; Table 1). The logistic regression analysis

TABLE 1 Severity of Internet gaming disorder (IGD), functional and dysfunctional impulsivity, depression, comorbid attention-deficit/hyperactivity disorder, and COMT val158met polymorphism in the IGD and control groups

	IGD mean (SD)	Control mean (SD)	*t*
Age	25.32(4.20)	25.73(3.78)	−0.71
Severity of IGD	82.87(10.49)	43.36(17.24)	20.40***
Functional impulsivity	5.61(3.03)	5.73(2.66)	−0.31
Dysfunctional impulsivity	6.36(3.42)	2.75(2.34)	7.88***
Behavior inhibition	21.43(2.89)	20.02(2.55)	3.59***
Behavior activation	40.97(4.40)	40.59(5.05)	0.53
Reward drive	12.43(1.60)	12.91(1.82)	−1.82
Reward sensitivity	15.99(1.88)	16.33(2.16)	−1.12
Fun-seeking	12.55(2.10)	11.36(1.94)	4.04***
	IGD n (%)	*Control n (%)*	χ^2
Gender			
Male	54(66.70%)	108(66.70%)	0.00
Female	15(33.30%)	30(33.30%)	
COMT polymorphism			
Val/Val	42(60.90%)	59(42.80%)	6.04*
Met carrier	27(39.10%)	79(57.20%)	

Note: * $p < 0.05$; *** $p < 0.001$. Severity of IGD: Score in Chen Internet addiction scale (CIAS). Functional and dysfunctional impulsivity: Score in Dickman's impulsivity inventory. Behavioral inhibition, behavioral activation, reward drive, reward sensitivity, fun-seeking: Score in subscales of the behavioral inhibition system and behavioral approach system scales (BIS/BAS scales).

TABLE 2 Differences in age, severity of Internet gaming disorder (IGD), impulsivity, and reinforcement sensitivity between COMT val158met Met carrier and participants with the Val/Val genotype

	Val/Val *mean* (SD)	Met carrier *mean* (SD)	*t*
Age	25.37(3.78)	25.80(4.05)	−0.78
Severity of IGD	58.31(25.32)	54.84(22.95)	1.03
Functional impulsivity	5.64(2.68)	5.74(2.89)	−0.26
Dysfunctional impulsivity	4.42(3.34)	3.52(3.07)	2.01*
Behavior inhibition	20.53(2.98)	20.45(2.52)	0.21
Behavior activation	41.34(4.95)	40.13(4.66)	1.80
Reward drive	12.85(1.92)	12.65(1.60)	0.82
Reward sensitivity	16.34(2.20)	16.09(1.94)	0.84
Fun-seeking	12.15(2.66)	11.39(2.01)	2.69**
	n (%)	*n* (%)	χ^2
Gender			
Male	85 (84.2%)	77(72.6%)	4.03*
Female	16(15.8%)	29(27.4%)	

Note: * $p < 0.05$; ** $p < 0.01$. Functional and dysfunctional impulsivity: Score in Dickman's impulsivity inventory. Behavioral inhibition, behavioral activation, reward drive, reward sensitivity, fun-seeking: Score in subscales of the behavioral inhibition system and behavioral approach system scales (BIS/BAS scales).

results revealed that after sex and age were controlled for, compared with the Met genotype carriers, participants with the Val/Val genotype had a higher OR of being diagnosed as having IGD [OR = 2.09, 95% confidence interval (CI) = 1.15–3.80, $p = 0.016$; Table 3, model 1]. Therefore, participants with the Val/Val genotype were more likely to develop IGD.

As shown in Tables 1 and 2, participants with IGD and the Val/Val genotype experienced higher dysfunctional impulsivity and fun-seeking than did the controls. Therefore, dysfunctional impulsivity and fun-seeking were controlled for in the regression model. With dysfunctional impulsivity controlled for, the OR for IGD in participants with the Val/Val genotype decreased and became insignificant (OR = 1.79, 95% CI = 0.89–3.59, $p = 0.10$; Table 3, model 2). In this forward regression model, dysfunctional impulsivity significantly predicted IGD (OR = 1.47, 95% CI = 1.31–1.65, $p < 0.001$), indicating

TABLE 3 Hierarchical logistic regression to evaluate the association between Internet gaming disorder (IGD) and COMT val158met polymorphism with control of impulsivity and fun-seeking

	Wald X^2	Df	Exp(β)	95% CI
IGD versus controls				
Model 1				
Age	0.30	1	0.98	0.91–1.06
Gender	0.07	1	0.90	0.44–1.87
COMT (Val/Val)	5.85*	1	2.09	1.15–3.80
Model 2				
Age	0.17	1	1.02	0.93–1.12
Gender	0.37	1	0.77	0.34–1.77
COMT (Val/Val)	2.65	1	1.79	0.89–3.59
Dysfunctional impulsivity	41.78***	1	1.47	1.31–1.65
Model 3				
Age	0.00	1	1.00	0.92–1.08
Gender	0.04	1	0.93	0.44–1.97
COMT (Val/Val)	3.27	1	1.77	0.95–3.29
Fun-seeking	11.51**	1	1.33	1.13–1.56
Model 4				
Age	0.19	1	1.02	0.93–1.12
Gender	0.37	1	0.78	0.34–1.77
COMT (Val/Val)	2.44	1	1.76	0.87–3.57
Dysfunctional impulsivity	33.20***	1	1.46	1.28–1.66
Fun-seeking	0.06	1	1.03	0.85–1.24

Note: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. COMT (Val/Val): the Val/Val genotype carrier versus Met carrier. Dysfunctional impulsivity: Score in Dickman's impulsivity inventory. Fun-seeking: Score in subscales of the behavioral inhibition system and behavioral approach system scales (BIS/BAS scales).

that impulsivity has a mediating role in the association between IGD and the COMT Val158met polymorphism. With fun-seeking also controlled for, the OR of having IGD among participants with the Val/Val genotype decreased and became insignificant (OR = 1.77, 95% CI = 0.95–3.29, $p = 0.07$; Table 3, model 3). Thus, fun-seeking also significantly predicted IGD (OR = 1.33, 95% CI = 1.13–1.56, $p = 0.001$), suggesting that it plays a mediating role in the association between IGD and the COMT Val158met polymorphism. Finally, with both impulsivity and fun-seeking controlled for, the predictive value of the Val/Val genotype for IGD was insignificant (OR = 1.76, 95% CI = 0.87–3.57, $p = 0.12$; Table 3, model 4). Dysfunctional impulsivity, but not fun-seeking, significantly predicted IGD (OR = 1.46, 95% CI = 1.28–1.66, $p < 0.001$), suggesting impulsivity is the most important mediator in the association between the Val/Val genotype and IGD.

4 | DISCUSSION

According to the study results, the OR of IGD in Val/Val genotype carriers was 2.09 times that of Met genotype carriers. However, because of the relatively small sample size of our genetic analysis, this result should be interpreted with caution. In addition, this study revealed that both IGD and the COMT Val158met polymorphism are positively associated with impulsivity and fun-seeking—two important intermediate phenotypes in the genetic study of addiction.[13] Further analysis demonstrated that impulsivity and fun-seeking mediated the effect of the COMT Val158met polymorphism on IGD. This study highlighted the role of dopamine in the development of IGD.

4.1 | Association of IGD with COMT Val158met polymorphism

According to Lachman et al., carriers of the homozygous Val/Val variant catabolize three to four times more dopamine than do carriers of the homozygous Met/Met variant.[33] The lower catabolism rate of the Met allele causes higher synaptic dopamine levels following neurotransmitter release, ultimately increasing dopaminergic stimulation of the postsynaptic neuron. Hence, given the preferential role of COMT in prefrontal dopamine degradation, individuals with the COMT Met allele exhibit more efficient frontal lobe functioning.[9] In addition, Diamond et al. revealed that those with the Met/Met genotype performed better in a mixed-dots task, indicating functioning of the dorsolateral prefrontal cortex.[34] This suggests that the Met allele is associated with dopamine functioning and contributes to frontal lobe functioning.

In this study, individuals with the Val/Val genotype were more likely to develop IGD than controls. Previous neurocognitive studies have revealed impaired cognitive control in the frontal lobe of individuals with IGD.[23] Tian et al. demonstrated that individuals with IGD experience decreased glucose metabolism in the prefrontal lobe and dysregulation of D2 receptors in the striatum, which are associated with years of excessive gaming.[11] These results indicate that alteration in dopamine functioning involves frontal lobe dysfunction in IGD. Moreover, because COMT Val158met is involved in frontal lobe dopamine functioning,[9] the association between IGD and COMT Val158met might indirectly support dopamine functioning having a possible role in IGD.

4.2 | Role of impulsivity and fun-seeking in the IGD–COMT Val158met polymorphism association

In line with previous studies on IGD,[14,21] the present study revealed that individuals with IGD experienced higher impulsivity and fun-seeking. Both impulsivity and behavioral activation are related to dopamine functioning,[17,35] showing that individuals with IGD present a phenomenon that possibly indicates an alteration in dopamine functioning.

According to the definition of DII, dysfunctional impulsivity results in rapid and inaccurate performance with a rapid and error-prone information-processing pattern rather than deliberative thinking.[30] Thus, because of impulsivity without deliberation, individuals

with IGD neglect the negative consequences of their gaming behavior and exhibit impaired control of such behavior; the results of the present study are consistent with this proposition.

Lower striatal dopamine signaling affects impulsivity and addiction risk[35]; individuals with Val/Val exhibit higher COMT activity,[33] resulting in lower synaptic dopamine levels and inefficient frontal lobe functioning.[9] Thus, the COMT Val/Val genotype is associated with impulsive behaviors, such as gambling and risky decision-making. Consistent with this, our results revealed that individuals with the COMT Val/Val genotype exhibit higher dysfunctional impulsivity.

Given that IGD and COMT Val/Val are associated with impulsivity, impulsivity can thus be considered a confounding factor in the association between the two. The logistic regression analysis demonstrated that impulsivity was the more significant mediator, relative to fun-seeking, in the association between COMT Val/Val and IGD. According to Baron and Kenny,[24] the COMT Val158met polymorphism can increase the risk of IGD through its effect on impulsivity. Because genetic type is a predisposing and unchangeable factor, impulsivity should be handled through intervention, such as by neurofeedback,[36] to attenuate IGD risk, particularly in individuals with the COMT Val/Val genotype.

This study also demonstrated the association between the COMT Val/Val genotype and fun-seeking, a tendency to seek potentially rewarding activity, based on a 2018 report by Su et al.[21] The tendency to seek rewards, such as excitement or novelty, has repeatedly been reported to relate to IGD.[37,38] Online games are typically designed to induce pleasure in the users through rewards, thereby motivating them to play more. Individuals with stronger fun-seeking inclinations might have a stronger tendency to attempt, or continue with, online gaming. Similarly, our study demonstrated that individuals with IGD experience strong fun-seeking inclinations.

Novelty-seeking has been noted more in individuals with the Val allele.[39] Consistent with this finding, our study revealed that individuals with Val/Val experience higher degrees of fun-seeking. This finding might support the notion that the Val/Val genotype, associated with lower dopamine functioning, is associated with fun-seeking. Furthermore, fun-seeking has been found to mediate the association between IGD and the COMT Val/Val polymorphism. Thus, we suggest that alternative healthy recreational activities, such as physical exercise, should be provided to individuals with the COMT Val/Val genotype to prevent excessive engagement in gaming activities.

Further regression analysis demonstrated that impulsivity was a stronger mediator than fun-seeking in the association between the COMT Val/Val genotype and IGD. Thus, more attention should be paid to the impulsivity of individuals with the COMT Val/Val genotype to prevent the risk of IGD. Furthermore, the underlying mechanism of IGD deserves further research (e.g., using PET) to reveal the role of dopamine functioning on IGD.

4.3 | Limitations

The following three limitations to this study deserve mention. First, IGD diagnosis was established by relying solely on participants' responses to a psychiatric interview. Hence, in future studies, additional information should be gathered from other sources, such as parents or partners. Second, because this study was cross-sectional, cause and effect associations between impulsivity, fun-seeking, and IGD were difficult to determine. Third, because our sample size was small, the identified effect of the COMT Val/Met polymorphism should be interpreted with caution.

5 | CONCLUSION

This study demonstrated that individuals with the Val/Val genotype were more likely to develop IGD compared with Met genotype carriers, indicating the possible role of dopamine functioning in the development of IGD. The same individuals were also found to experience higher impulsivity and fun-seeking, which mediate the effect of the Val/Val genotype on IGD. We propose that impulsivity and fun-seeking should be targeted and comprehensively assessed when treating IGD, with impulsivity of particular focus in those with the Val/Val genotype.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

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How to cite this article: Yen J-Y, Lin P-C, Lin H-C, Lin P-Y, Chou W-P, Ko C-H. Association of Internet gaming disorder with catechol-O-methyltransferase: Role of impulsivity and fun-seeking. Kaohsiung J Med Sci. 2022;38:70–6. https://doi.org/10.1002/kjm2.12454