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The effect of negative life events on college students' depression: the mediating role of internet addiction and the moderating role of 5-HTT1A gene rs6449693 polymorphism

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Abstract

Using the differential susceptibility model, the present study examined how (mediator = Internet addiction) and when (moderator = 5-HTR1A gene rs6449693) did negative life events influence college students' depression. A total of 301 Chinese college students (mean age = 19.15 years, SD = 0.93) from southern China completed anonymous questionnaires (the Center for Epidemiological Studies Depression Scale, the Adolescent Self-Rating Life Events Check List, and the Chinese Version of the Internet Addiction Scale). Our findings revealed that negative life events, Internet addiction, and college students' depression were significantly and positively associated with each other. Internet addiction mediated the relationship between negative life events and college students' depression. Further, 5-HTR1A gene rs6449693 polymorphism moderated the relationship between negative life events and college students' depression; specifically, allele G is the susceptibility reason which is manifested, as depression scores of individuals with high level of allele G are significantly lower than those with low level allele A. These findings underscore the importance of the differential susceptibility model in understanding how and when negative life events impact college students' depression.

Keywords Negative life events · Internet addiction · College students' depression · 5-HTR1A gene rs6449693

Introduction

Nowadays, depression has become a prominent psychological adjustment and health problem. It not only has a high incidence rate, but also can seriously harm the social function and quality of life of individuals (Kvam et al., 2016). College students who are at a critical period for the transition to maturity have a higher risk of depression (Ibrahim et al., 2013). Some studies have shown that the detection rate of college students' depression in China is about 11.7% to 24.8%, and rises each year in China (Chen et al., 2013; Song et al., 2008). Because of the high incidence of suicide rates due to depression (Natsuaki et al., 2009), it is imperative to explore the influencing factors and mechanisms of college students' depression.

Negative life events are the various problems that individuals face in life, which cause psychological stress and have negative effects on individuals (i.e., depression and anxiety) (Liu et al., 1997). As a psychosocial stressor, negative life events can be upsetting and lead to depression and other negative emotional experiences, thus seriously affecting an individual's physical and mental health and development (Assari & Lankarani, 2016; Kendler & Gardner, 2016). Beck and Weishaar (2000) cognitive theory of depression suggests that individuals with high cognitive susceptibility are prone to depression when impacted by negative life events. At the same time, a large number of studies have found that negative life events are important risk factors for depression and have a significant positive correlation for an individual developing

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depression. A higher amount of negative life events directly causes individual depression, and can effectively predict the occurrence of depression in college students (Sun et al., 2017). This current study proposes hypothesis H1: Negative life events are risk factors for college students' depression. To date, studies into the relationship between negative life events and college students' depression have reached a relatively consistent conclusion that negative life events are a risk factor for college students' depression (Herbison et al., 2017; Stikkelbroek et al., 2016). Yet, there are few previous studies on whether negative life events influence college students' depression through other mediating or moderating factors, and the internal mechanism between the two still needs further investigation.

Internet Addiction as a Mediator

Internet addiction, a subtype of problematic Internet use, refers to the uncontrollable, excessive, and compulsive use of Internet that causes physiological, social and/or emotional problems for an individual (Yu et al., 2015). Young's Internet addiction ACE model (Young, 1998) argues that individuals can simply hide their real identity (i.e., Anonymity), just moving their fingers to do or say anything they want to do (i.e., Convenience) in the network. At the same time, these individuals can always find help on the Internet when faced with hardship, so this sense of freedom and infinity entice individuals to turn to the Internet instead of to reality (i.e., Escape). Therefore, when individuals are faced with negative life events, they are more likely to turn to the Internet to escape their sense of frustration with life's pressures, and thus become addicted to the Internet (Li et al., 2010). Previous studies have found a significant positive correlation between negative life events and Internet addiction, with a higher level of negative life events significantly predicting Internet addiction (Torres-Rodríguez et al., 2018). A study of the relationship between negative life events and Internet addiction using 892 college students (Yan et al., 2014) found that when compared with non-addicted subjects, subjects with severe Internet addiction had more negative life events and more health and adaptation problems. Furthermore, in a study that examine the association between Internet addiction and stressful life events and psychological symptoms among Chinese adolescent internet users, Tang et al. (2014) found a significant correlation between negative life events and Internet addiction.

At the same time, a large number of studies have found that Internet addiction often coexists with other psychological problems, such as depression, anxiety, insomnia, and low self-esteem due to long-term addiction to the virtual world and a lack of face-to-face communication with others and real social support (Bhandari et al., 2017; Younes et al., 2016). Some studies have found that Internet addiction can lead to depression, and the prevalence of depression increases with the severity of Internet addiction (Seki et al., 2019). Moreover, in a 12-month cohort study exploring the relationship between Internet addiction and depression among Chinese adolescents, Lau et al. (2018) found that baseline Internet addiction could significantly predict depression in non-depressed people after adjusting for sociodemographic factors. Kim et al. (2006) has suggested that the Internet is used to replace social activities and online relationships to replaces social relationships, but these online activities and relationships are relatively weak in impact and connection compared to those offline. Therefore, college students with Internet addiction often encounter difficulties in study, life, and interpersonal communication, and they are more prone to cause experiencing depression. Based on this, this current study proposes hypothesis H2: Internet addiction acts as a mediator between negative life events and depression in college students.

5-HTR1A Gene rs6449693 Polymorphism as a Moderator

With the discovery of molecular genetics, research on the genetic mechanism of depression has reached the molecular level, and studies have shown that the heritability of depression is about 24% ~ 55% (Rice et al., 2002). Using molecular genetics technology and psychological research methods to explore the interaction mode between genetics and environmental factors related to depression (G × E) has since become a prime research topic in this field (Banny et al., 2013; Zhang et al., 2016). The diathesis-stress theory is the mainstream theory for research on the interaction between genetics and the environment on depression. It was originally used in psychopathology to explain why not all individuals show psychological disorders when experiencing the same stressful environment (Rosenthal, 1963). Developmental psychologists also used it to explain the "vulnerability" of individuals in negative environments. The diathesis-stress theory suggests that some individuals are more sensitive to stressful events in the environment due to their own "vulnerability" (Belsky & Pluess, 2009). Gene-environment interactions manifest in some individuals because their genes are more susceptible to negative environmental influences than those of individuals with non-susceptibility genes; could gene-environment interactions also manifest in individuals with susceptibility genes as those genes are more susceptible to positive environmental influences than those of individuals with non-susceptibility genes? A newly emerging theoretical model, the differential susceptibility model, strongly suggests that the same genes can affect an individual become both positively or negatively (Babineau et al., 2015; Belsky & Pluess, 2009). Therefore, with lower level of negative life events or Internet addiction, could individuals with susceptibility genes perform lower levels of depression than those with non-susceptibility genes?

5-HTR1A (Serotonin 1a receptor), no intron, located in human chromosome 5q11.2–13, is an important candidate gene for depression (Kishi et al., 2009). Existing pathological physiology and genetics studies suggest serotonin system dysfunction is the risk factor of major depressive disorder (Jans et al., 2007). 5-HTR1A is one of the important influencing factors of depression that could reduce the discharge of raphe nucleus neurons and inhibit the synthesis and release of 5-HT, and thus the lower serotonin level is associated with depression (Kraus et al., 2017). Therefore, 5-HT and damaged 5-HTR1A are often applied to the etiology of psychiatric disorders. The 5-HTR1A gene has multiple polymorphisms such as rs749098, rs1799921, rs6295 and rs6449693 (Drago et al., 2008). More research focuses on the rs6295 locus, but empirical results often differ or can even be contradicting. Dhingra et al. (2007) has argued that individuals who carry allele C may have an increase incidence of depression, but there are also studies which have shown that allele G carriers' anxiety and depression level are higher than those of allele C carriers, and the reason may be that the expression of locus in the human is not good (Wang et al., 2015). In a study about the function of the 5HTR1A gene locus polymorphism, Yoshikawa et al. (2019) found that rs6449693 polymorphism was associated with effectiveness of schizophrenia treatment and was significantly correlated with the total score and all dimensions of the Positive and Negative Syndrome Scale. Thus, could rs6449693 polymorphism regulate the production of 5-HTR1A, and thus interact with the environment to influence depression? The current study also proposed hypothesis H3: 5-HTR1A gene rs6449693 polymorphism plays a moderation role in the direct/indirect relationship between negative events and depression.

The Current Study

This study proposed a moderated mediation model based on previous studies (as shown in fig. 1), and investigated three questions: (1) whether negative life events are risk factors for depression in college students; (2) whether Internet addiction plays a mediation role between negative life events and college students' depression; (3) whether 5-HTR1A gene rs6449693 polymorphism could moderate the mediation model. fig. 2

Method

Participants

A total of 301 college students (74 males = 24.6%, 227 females = 75.4%; 133 only children = 44.2%, 168 non-only children = 55.8%), aged 17–20 years of age ($M = 19.15$, $SD = 0.63$), participated in the study.

Procedures

After explaining the study purpose and procedures, trained research assistants distributed questionnaires to the college student participants in their classrooms after school hours. Participants provided information regarding their personal and family demographics, and completed the Center for Epidemiological Studies Depression Scale, the Adolescent Self-Rating Life Events Check List, and the Chinese Version of the Internet Addiction Scale. Professional nurses extracted 2.5-ml venous blood in an EDTA anticoagulant tube (blood: EDTA = 5: 1) from every participant in the study, then placed it in the refrigerator (−70 °C). Three months later the DNA was extracted and typed.

College Students' Depression

The college students' depression was measured using the Center for Epidemiological Studies Depression Scale (CES-D). CES-D has a total of 20 items, and uses a five point scale ranging from 0 ("never") to 3 ("always") to assess four dimensions: depressed affect (e.g., "I feel depressed"), positive affect (e.g., "I feel as good as anyone"), somatic and retarded activity (e.g., "It's hard for me to concentrate"), and interpersonal (e.g., "People are not friendly to me"). The total score is between 0 and 60. The CES-D has a good validity coefficient

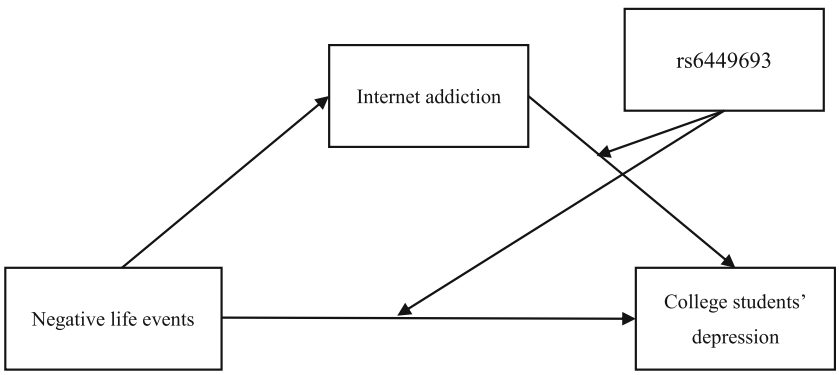

Fig. 1 Theoretical hypothesis model

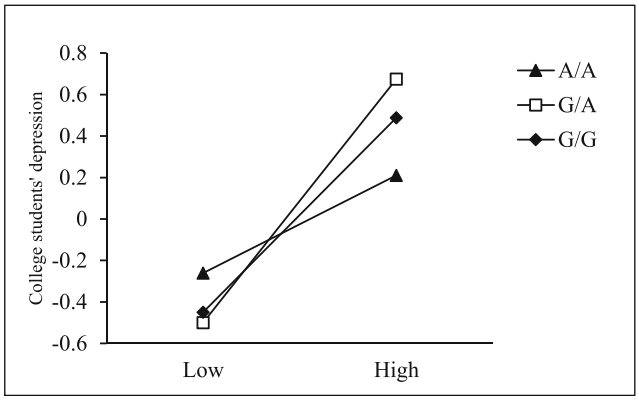

Fig. 2 Simple slope diagram. *Notes.* 'Low' means the low level of negative life events (-1SD) and 'High' means the high level of negative life events (+1SD)

and reliability. Sijtsma (2009) has proven that Guttman's lambda coefficient has a better lower limit of reliability estimation than Cronbach's lambda. In this research, the Guttman's lambda coefficient of the CES-D is good reliability (0.824 > 0.7; Bland & Altman, 1997).

Negative Life Events

The Adolescent Self-Rating Life Events Checklist (ASLEC) was compiled by Liu in Liu et al., 1997. The ASLEC has a total of 27 items, and uses a six point scale ranging from 1 ("never") to 6 ("great influence") to assess six dimensions: interpersonal relationships (e.g., "To be misunderstood or wronged"), academic pressure (e.g., "Failing in an exam"), punishment (e.g., "To be criticized or punished"), loss (e.g., "The death of a family member or friend"), adaptation (e.g., "Great changes have taken place in life habits"), and other symptoms (e.g., "People are not friendly to me"). The higher the factor score, the greater the negative psychological response the individual has to the life events contained in the scale. The ASLEC has good reliability and validity coefficients, and has been proven to be an effective tool for evaluating the psychological stress of adolescents in China. The Guttman's lambda coefficient of the ASLEC in this research was 0.925.

Internet Addiction

The Chinese Version of the Internet Addiction Scale (IAD) was compiled by Chen et al. (2003) to measure Internet addiction. The IAD has a total of 26 items, and uses a four point scale that ranges from 1 ("extremely inconsistent") to 4 ("very consistent") to assessed five dimensions including: force (e.g., "I can't control my impulse to surf the Internet"), addiction (e.g., "No matter how tired I am, I always feel energetic when surfing the Internet"), tolerance (e.g., "I find myself spending more and more time online"), interpersonal and health issues (e.g., "I have had back pain or other physical problems since surfing the Internet"), and time management issues (e.g., "I've been told more than once that I spend too much time online"). The higher the score, the more serious one' the degree of addiction. The IAD has been proven to be applicable in Chinese college students. In this research, the Guttman's lambda coefficient of the Chinese IAD was 0.932.

Genotyping

DNA was genotyped from 301 samples using the TIANGENBIOTECH™ DNA kit. After the DNA samples had been obtained, the imLDRTM Multi-SNP typing kit of made by Shanghai Tianhao Biotechnology Co., Ltd. was used to classify each of the 301 samples. PCR (Polymerase Chain Re - aAction, Poly Synthase Chain Reaction) primers for F: CGGCGGCTGTGTGT ACAGTTTA; R: CTTCCCCCAACCCTAGGGAATC were used. PCR reaction strips were: Step1: 95 °C for 2 min; Step2: 11 cycles were performed at 94 °C for 20s, 65 °C for 40s, and 72 °C for 1.5 min; Step3: there are 24 cycles at 94 °C for 20s, 59 °C for 30s, 72 °C for 1.5 min; Step4: 72 °C for 2 min, 4 °C forever. The acquired raw data files are then analyzed with Gene Mapper4.1 (Appliedbiosystems, USA).

Statistical Analyses

SPSS 24.0 and PROCESS 3.4 were used for data processing and analysis. SHEsis software was used to test the anastomosis of Hardy-Weinberg equilibrium, and the main statistical analysis methods were chi-square test, correlation analysis and regression analysis.

The data of this study are all from the self-report of the subjects. Inevitably, there will be the problem of common method deviation. Exploratory factor analysis (EFA) was carried out for all subjects by Harman single factor method. The analysis results of unrotated principal component factors showed that there were 15 factors with characteristic root greater than 1, and the variance interpretation rate of the first factor was 21.88% (lower than 40%). The results showed that there was no serious common method deviation problem.

Results

Three sets of results are presented in this section, first the Hardy - Weinberg equilibrium test, then the preliminary and descriptive results, and finally the results from the moderated mediation model test.

Distribution of 5-HTR1A rs6449693 Genotypes

The genotype groups found were 63% A/A, 32% A/G, and 5% G/G; using the Hardy - Weinberg equilibrium, $\chi 2$ (1, N = 301) = 0.123, $p > .05$. The two gender groups did not differ significantly in genotype frequency, $\chi 2$ (2, N = 301) = 0.717, $p = .70$) in Table 1.

Descriptive and Correlational Analyses

Table 2 shows the mean, standard deviation and correlational matrix of each research variable. Only G/A polymorphism is significantly correlated with negative life events, thus excluding the possibility of a gene-environment correlation. Genes and environmental indicators are independent with each other, in line with the G × E research paradigm standard as proposed by Dunn et al. (2011). College students' depression, negative events, and Internet addiction are positively correlated with each other.

Testing the Moderated Mediation Model

To test the moderated mediation model, a moderated mediation analyses was conducted using three regression models, as outlined by Muller et al. (2005). In the first model, the moderating effect of 5-HTT1A gene rs6449693 polymorphism on the way in which negative life events impact on college students' depression was estimated. In the second model, the influence of negative events on Internet addiction was estimated. In the third model, the moderating effect of 5-HTT1A gene rs6449693 polymorphism on both the partial effect of negative life events on college students' depression and the residual effect of Internet addiction on college students' depression were estimated. As previous studies have shown that gender and only-child status have a greater impact on college students' depression, these were used as control variables in the test to eliminate their effects (Gilman et al., 2017).

All variables were standardized to reduce multicollinearity. In Model 1 (Table 3), an overall effect of negative life events on college students' depression was found ($\beta = 0.30$, $p < .001$). This effect was moderated by rs6449693 polymorphism, ($\beta = 0.39$, $p = .008$). In Model 2, the mediator, Internet addiction, was the criterion. There were two main effects: negative life events, ($\beta = 0.30$, $p < .001$) and gender ($\beta = 0.34$, $p = .009$). Finally, the third model showed that the effect of negative life events on college students' depression was significant ($\beta = 0.23$, $p < .001$), and that this effect was moderated by rs6449693 polymorphism, with significant affective associations in the rs6449693 polymorphism interaction ($\beta = 0.35$, $p = .022$). In addition, the effect of Internet addiction on college students' depression was significant ($\beta = 0.22$, $p = .002$). These results suggest that negative life events, Internet addiction, depression in college students, and rs6449693 polymorphism together constitute a moderated mediation effect model. Internet addiction plays a partial mediating role between negative life events and college students' depression, and rs6449693 polymorphism moderates the direct effect in the model. The mediating effect values of different genotypes of rs6449693 are listed in Table 4, and the mediating effect of Internet addiction was significant for individuals with A/A genotypes.

Table 1 Hardy-Weinberg Equilibrium Test

Gender	A/A	G/A	G/G
Male	50	21	3
Female	141	75	11
$\chi 2$		0.123*	

Notes. *$p < .05$, **$p < .01$, ***$p < .001$

Discussion

College is a unique period in life, during which one experiences rapid changes in physical, psychological, and social characteristics; it is also a period of a high incidence of depression (Dunn et al., 2011; Thapar et al., 2012). Negative life events are an important key risk factor for depression (Liu et al., 1997). The results of the current study showed that negative life events could negatively predict college students' depression, consistent with previous research (Sun et al., 2017). To further explore the mechanism of negative life events' influence on college students' depression in, based on the differential susceptibility model theory of depression, the current study included Internet addiction and 5-HTR1A gene rs6449693 polymorphism to construct a moderated mediation model.

There are many studies on negative life events and depression, and most of them found that negative life events are a risk factor for depression (Stikkelbroek et al., 2016; Sun et al., 2017), but the specific mechanism between them still needs to be further explored. The current study found that negative life events could not only directly lead to depression in college students, but also that they could predict the likelihood of depression of college students through the mediating effect of Internet addiction. Individuals who have experienced more negative life events feel less supported socially (Liu et al., 2020; Tham et al., 2020). Howerve, aspects of the online world (virtuality) can offer college students some support and relieve their pain to a certain extent, virtual network communication tends to replace face-to-face communication, which reduces one's sense of security and belonging, thus leadings to deeper depression (Yates et al., 2012). Moreover, Meng et al. (2011) found in a study on the relationship

Table 2 Means and standard deviations of major variables and correlations

Variables	1	2	3	4
1 rs6449693	A/A; G/A; G/G			
2 Negative events	0.070; −0.115*; 0.096	1		
3 Internet addiction	−0.023; −0.014; 0.080	0.300**	1	
4 depression	−0.022; −0.027; 0.111	0.366**	0.320**	1
M±*SD*	–	53.68±20.62	50.15±13.50	13.10±7.74

Notes. rs6449693 was virtualized into dummy variables for correlation; *$p < .05$, **$p < .01$, ***$p < .001$

between negative life events, coping styles and depression in 13,512 college students that coping styles played a mediating role between negative life events and depression in college students, and negative coping styles was more able to explain the mediating effect of this relationship than positive coping styles. This finding shows that negative life events lead directly to college students' depression, as well as indirectly predicting depression through Internet addiction (negative coping styles). The results are consistent with previous findings. In a study that explored depression symptoms and predictors in 5634 adolescents, the results showed that males who used negative coping (e.g., Internet and phone) had a higher risk of depressive symptoms after experiencing a negative life event (Sawyer et al., 2009).

The nature-nurture controversy, namely, the role of heredity and the environment in the occurrence and development of depression, has received increasing attention within the realm of psychology (Normann & Buttenschøn, 2019). Caspi et al. (2003) shifted the discussion in combining the two to explore their combined influence on depression, introducing G × E paradigm as a new method to explore the occurrence and development of depression. Our results offer support for differential susceptibility model, showing that Internet addiction plays a partial mediating role in negative life events, and that 5-HTR1A gene rs6449693 polymorphism moderates the direct pathway. Specifically, allele G is the susceptibility gene, which is manifested in that depression scores of individuals with allele G are significantly lower than those of individuals with allele A when both report a low level of negative life events. In addition, depression scores of individuals with allele G are significantly are higher than those of individuals with allele A when both report a high level of negative life events. Although the slope of G/G genotype isn't significant (0.48), this could be due to the fact that the homozygous sample of G/G was a relatively small sample size (only 14). The results of the current study also give indirect evidence that allele G is the susceptibility gene, given that this research used a random sampling method. Although G/G homozygotes are not significant, the simple slope analysis shows that the slopes of both allele G (G/A and G/G) are significantly higher than that of A/A homozygotes. Overall, the results of the current study offer support for the differential susceptibility model.

Table 3 Moderated mediation effects of negative life events on college students' depression

Predictors	Model 1 (dependent variable: Y)				Model 2 (dependent variable: M)				Model 3 (dependent variable: Y)			
	β	SE	t	95%CI	β	SE	t	95%CI	β	SE	t	95%C
Gender	.05	.13	−.38	[−.26,.18]	.34	.13	2.62**	[.08,.60]	−.03	.13	−.24	[−.28,.22]
Only child	−.04	.11	−.38	[−.26,.18]	−.10	.11	−.86	[−.32,.13]	−.03	.11	−.24	[−.24,.19]
X	.30	.06	4.95***	[.18,.42]	.30	.05	5.49***	[.19,.41]	.23	.06	3.75***	[.11,.36]
W1	.13	.12	1.07	[−.11,.36]					.11	.12	.98	[−.11,.34]
W2	.22	.28	.77	[−.34,.78]					.04	.41	.10	[−.78,.86]
X*W1	.39	.15	2.66**	[.10,.68]					.35	.15	2.31*	[.05,.65]
X*W2	.09	.28	.31	[−.46,.64]					.24	.32	.76	[−.38,.86]
M									.22	.07	3.11**	[.08,.36]
M*W1									.01	.12	.01	[−.23,.23]
M*W2									.05	.48	.11	[−.90,.99]
R^2	0.16			0.11				0.20				
F	7.89***			12.39***				7.34***				

Notes. Virtual coding of rs6449693 polymorphism is performed. X is the independent variable for negative life event; M is the mediating variable for Internet addiction; Y is the dependent variable for college students' depression. *$p < .05$, **$p < .01$, ***$p < .001$

Table 4 Mediating effects of internet addiction on rs6449693 polymorphism

Mediation	rs6449693	Intermediate effect value	Bootstrap SE	CI Low	CI High
Internet addiction	A/A	0.068	0.023	0.025	0.117
	G/A	0.068	0.036	−0.003	0.140
	G/G	0.084	0.239	−0.427	0.438

To facilitate the interpretation of this interaction, Fig. 2 shows a plot of how negative life events are related to college students' depression in different rs6449693 genotypes. Simple slope testing revealed that for A/A, G/A, and G/G genotypes, negative life events was significantly associated with college students' depression (β_{simple} = 0.24, $p < .001$; $\beta_{simple} = 0.59$, $p < .001$; $\beta_{simple} = 0.48$, $p = .12$, respectively). When individuals carried the G/A heterozygous genotype, the influence of negative life events on college students' depression was significantly enhanced.

The current study adopted G × E paradigm, and included susceptibility factors (5-HTR1A gene rs6449693 polymorphism) and psychosocial factors (negative life events and Internet addiction) which have already been noted as being important key risk factors for depression (Assari & Lankarani, 2016; Lam, 2015). The constructed moderated mediation model enriches the current theories of the occurrence and development of depression. However, it should be noted that although the results of this study support the differential susceptibility model, only 301 samples were included in this study. Therefore, we plan to systematically explore the influence of genes and environment on depression using a larger sample size in future studies. Also, the current study found only an interaction between the 5-HTR1A gene and negative life events, not with Internet addition. The reason for this could be that Internet addiction is relatively difficult to measure. Since most of the subjects in this study are female (75.4%), they are less addicted to the Internet, and related studies have found that the proportion of college students addicted to mobile phones is higher than that of Internet addiction (Gao et al., 2018; Sahu et al., 2019). Future studies may consider other factors, or use larger sample sizes to verify the interaction of genes and environment. Finally, in the current research, the main effect of the 5-HTR1A gene was not significant, while previous studies have found that multi-genes have significant interactions with individual depression (Comasco et al., 2011). Therefore, future research could adopt a multi-genes and multi-environments design to explore the pathogenesis of depression.

Conclusion

The current study explored how negative life events and 5-HTR1A gene rs6449693 polymorphism relate to college students' depression. Internet addiction mediated the risk effect of negative life events on college students' depression. Moreover, the risk effect of negative life events with college students' depression was moderated by the 5-HTR1A gene rs6449693 polymorphism. These findings add to the wider understanding of the mediating and moderating factors at play between negative life events and college students' depression. The results also provide further direct empirical evidence for the validity of the differential susceptibility model, providing a new approach to further exploring and understanding the mechanisms of college students' depression.

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Data Availability All data, models, or code generated or used during the study are available in a repository or online in accordance with funder data retention policies. https://osf.io/yquzw/

Declarations

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and / or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Conflict of Interest The authors declare that they have no conflict of interest.

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