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Neuroticism affects nightmare distress through rumination

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Abstract

Background/Aims The role of neuroticism in predicting nightmare distress have been highlighted, and negative coping style may contribute to this relationship, but how these variables interact is limited. The present study aimed to explore how neuroticism and ruminative response contribute to producing nightmare distress, and to explore whether sex influences this relationship.

Methods We recruited 758 university students, aged an average of 19.07. A moderated mediation model was built to examine the relationships among neuroticism, rumination, and nightmare distress (measured by dream anxiety scale), and explore whether sex could affect this relationship, using the SPSS PROCESS 3.5 macro.

Results The moderated mediation analyses results showed that ruminative response-depression related can significantly partially mediate the relationship between neuroticism and dream anxiety (β =0.32), dream anxiety-sleep-related disturbances (β =0.11) and dream anxiety-daytime dysfunctions (β =0.21). However, the moderating effects of sex were not significant in all path from neuroticism to dream anxiety.

Conclusion The study provides a novel architecture on the underlying psychological mechanisms of neuroticism and night-mare distress. This interplay is assumed to be facilitated by ruminations, suggesting that interventions for individuals who suffer from nightmares may focus on their repetitive negative response strategies, especially in people with high neuroticism, irrespective of sex differences.

Keywords Nightmares distress · Neuroticism · Rumination · Mediation effect

Introduction

Nightmare is defined as vivid, intensely unpleasant, or frightening dreams characterized by intense negative emotions such as anxiety, fear, and a sense of threat, and can lead to sudden awakening with a startle response [1]. Epidemiological studies have shown that 35–45% of adults reported

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at least one nightmare per month and 2-6% reported frequent nightmares [2-4] in general population. Meanwhile, a sex difference has been found with regard to the prevalence of nightmare. Females report nightmares more frequently than males do at any age, according to several large-scale studies [5, 6]. Nightmares can result in many poor health outcomes such as abnormal secretion of hormones [7], sleep disturbances at night, daytime emotional problems [8, 9], and dysfunction [10]. It is repeatedly documented that frequent nightmares were significantly associated with psychopathological conditions [11], including anxiety [8], depression [9], schizophrenia [12], posttraumatic disorder [1, 13, 14], and even suicide behavior [9]. It is worth noting that the consequences of nightmares are not only related to the frequency of nightmares, but also closely related to the nightmare distress [14, 15]. Certain evidence indicated that the link between nightmares and psychopathology might primarily stem from a dispositional dimension tied to emotional distress, as opposed to nightmare frequency. This is particularly notable for psychological disorders



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characterized by elevated levels of negative affect (e.g., anxiety and depression) [16]. Dream anxiety is the waking anxiety and dysfunction caused by frightening dreams, and is a direct reflection of the negative effects of nightmares, which is more predictive of psychological perturbations [17]. However, not everyone who experiences nightmares elicits negative daytime emotional and functional consequences, suggesting that other factors are involved in the relationship between nightmares and negative consequences, which should be further explored.

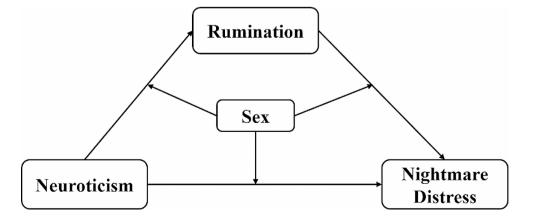
Most nightmare etiological hypotheses are based on diathesis-stress models, which emphasize the interaction between disposition and present stressors [18-20]. Personality traits, especially neuroticism, are considered to be closely related to nightmares. Neuroticism has been shown to be a predisposing factor for many mental health symptoms and can significantly predict some mental disorders such as depression and anxiety. There is an association between neuroticism and people's painful emotions, and individuals with higher neuroticism are more inclined to experience adverse life events [21]. The relationship between neuroticism and nightmares has been reported in several studies, and showed that individuals with frequent nightmares [8, 15] and higher nightmare distress [22], are usually at a higher level of neuroticism. Although this association has been established, it is still unclear how neuroticism contributes to nightmares.

The "emotional cascade model" highlighted the role of cognitive factors in developing distress and affect [23], which suggested that the negative "rumination" plays an important role in the occurrence of nightmares and their distress. Rumination, a typical maladaptive emotion regulation technique, is defined by a propensity to continuously dwell on upsetting events and the origins and effects of those events [24]. People with higher levels of rumination experience higher levels of cognitive arousal and thus experience greater nightmares [23]. Negative emotions experienced by individuals who experience nightmares are augmented by higher levels of rumination, thus producing a series of

negative effects, even affecting daytime function. Rumination is also closely related to neuroticism [25]. Roelofs et al. [26] found that individuals with higher scores on neuroticism were associated with higher scores on rumination. Some studies in China have also drawn similar conclusions [27, 28]. Thus, the rumination response style may play an important role in the relationship between neuroticism and nightmares distress. Studies have shown that the impact of neuroticism on depression and anxiety can be through the mediation of self-esteem, rumination, worry, and cognitive response [29, 30], suggesting some cognitive factors (e.g., rumination) may also exist in the relationship between neuroticism and nightmare distress given the nature of negative emotional experiences and dysfunction of nightmare distress. Individuals with high neuroticism may be more likely to ruminate about the negative emotions experienced in nightmares, and thus are more likely to have greater emotional distress, which may even affect daytime function. Therefore, the cognitive mechanisms of how neuroticism contributes to negative consequences caused by nightmares need to be considered, which could help us deliver effective prevention and interventions for individuals suffering from frequent nightmares.

As a result, the first hypothesis of this research is: rumination mediates the relationship between neuroticism and nightmare distress. Due to the sex differences in neuroticism [31] and rumination [32], the path by which neuroticism affects nightmare distress directly, or indirectly through rumination, may be influenced by sex. Thus, the second hypothesis is: sex may function as a moderator between neuroticism and nightmare distress either separately, or in both the direct effects (neuroticism → nightmare distress) and indirect path (neuroticism → rumination → nightmare distress). Our primary objective is to investigate the conceptual model depicted in Fig. 1 in current study. This involves two key aspects: firstly, evaluating whether rumination mediates the link between neuroticism and nightmare distress; secondly, exploring how the direct and indirect associations between neuroticism and nightmare distress are moderated

Fig. 1 The proposed model





by sex. This research can help clarify the psychological mechanism of neuroticism in nightmare distress, providing theoretical guidance for clinical intervention, and promote the mental health of university students.

Methods

Participants and survey

Participants in the present study were recruited from two universities in Hunan province, China, by convenience sampling. A total of 800 university students were enrolled in this survey. We distributed the survey questionnaires to participants during a class break, providing them with detailed information about the study. Before completing the measures, all participants received written informed consent to ensure their understanding and agreement. Ultimately, 758 students (448 female, 310 male, Mean Age = 19.07, SD Age = 1.11, ranged from 17 to 22 years old) agreed to participate and provided fully completed questionnaires, giving a response rate of 94.75%. The study received approval from the local ethics committee and was conducted in accordance with the Declaration of Helsinki.

Measures

Nightmare distress

Nightmare distress was measured using the Chinese version of Van Dream Anxiety Scale (CVDAS). The original VDAS is an assessment instrument that can evaluate nightmare frequency and nightmare distress (dream anxiety) caused by frightening dreams and was developed by Agargün in 1999 [33]. The VDAS encompasses 17 items designed to assess a range of content, including nightmare frequency, sleep disturbances arising from nightmares, dream recall frequency, morning anxiety triggered by nightmares, psychological challenges, functional impairment, and autonomic symptoms. This comprehensive approach ensures that the VDAS covers the majority of the health-related impacts associated with nightmares. The Chinese version of VDAS was developed by Wang et al. [16] and its factor structure was explored for the first time, showing a two-factor structure: sleep-related disturbances caused by nightmares (SDs) and daytime dysfunction caused by nightmares (Dys). The Chinese version of VDAS showed good reliability and validity in Chinese university students. Cronbach's α (s) for SDs, Dys, and total scale in the current sample were 0.850, 0.918, and 0.924, respectively.

Neuroticism

The Neuroticism was assessed using the neuroticism subscale of Eysenck Personality Questionnaire-revised: short Form (EPQ-R) [34]. As a widely recognized personality assessment tool, EPQ initially comprised 100 items. Subsequently, Eysenck et al. introduced a revised version, condensed to 48 items. Similar to its precursor, the Chinese version of EPQ-R also comprises 4 subscales. The respondents indicate agreement with each item using a binary "Yes" or "No", resulting in scores of 1 or 0, respectively. Cronbach's alpha coefficient for the neuroticism subscale in the current sample was 0.834.

Rumination

The rumination thought was measured using the Chinese version of the Ruminative Response Scales (RRS-C) [35]. The RRS-C contains 21 self-reported items, with 1–4 Likert scale. Higher scores indicate that the individual was more prone to a ruminative response style. Three-factor structure of RRS-C was confirmed (depression-related, brooding, and reflection). The Cronbach's alpha coefficient of the total scale, and its subscales in the current sample were 0.956, 0.920, 0.852, and 0.850, respectively.

Statistical analyses

Descriptive analyses were conducted by SPSS 24.0. Research variables (neuroticism, rumination, and dream anxiety) were analyzed by Pearson correlation analyses. The moderated mediation analysis was conducted using the SPSS PROCESS 3.5 macro [36], for the purpose of testing the hypothesized model (Fig. 1). Firstly, we tested whether the association between neuroticism and nightmare distress was mediated by rumination thoughts using Model 4. Subsequently, Model 59 was employed to investigate the presence of moderated mediation effects. To ensure robustness, we adopted the non-parametric percentile bootstrap technique for bias correction. We executed bootstrapping with 5000 samples and established a 95% confidence interval. An effect was deemed significant if the confidence interval did not encompass 0. In addition, all models were controlled for age.

Results

A total of 758 university students from university students participated in our study. Means, standardized deviations, and correlation matrix for several crucial research variables are presented in Tables 1 and 2.



Table 1 Descriptive statistics

| | Total sample $(n=758)$ | Males $(n=310)$ | Females $(n=448)$ | t | p |
|-----------|------------------------|-------------------|-------------------|--------|-------|
| DA | 5.18 ± 6.60 | 4.44 ± 6.45 | 5.69 ± 6.66 | -2.576 | 0.010 |
| DA_SDs | 2.65 ± 3.10 | 2.22 ± 2.88 | 2.95 ± 3.22 | -3.269 | 0.001 |
| DA_Dys | 2.53 ± 4.11 | 2.22 ± 4.06 | 2.74 ± 4.13 | -1.722 | 0.085 |
| RR | 42.33 ± 11.33 | 42.28 ± 12.26 | 42.36 ± 10.65 | -0.092 | 0.925 |
| RR_D | 21.82 ± 5.99 | 21.75 ± 6.41 | 21.88 ± 5.69 | -0.297 | 0.767 |
| RR_B | 10.66 ± 3.00 | 10.65 ± 3.32 | 10.66 ± 3.77 | -0.040 | 0.968 |
| RR_R | 9.85 ± 2.96 | 9.88 ± 3.15 | 9.82 ± 2.82 | 0.290 | 0.772 |
| EPQ-R-N | 48.42 ± 11.77 | 47.55 ± 10.98 | 49.02 ± 12.27 | -1.724 | 0.085 |

Abbreviations: DA, dream anxiety; DA_SDs, dream anxiety-sleep-related disturbances; DA_Dys, dream anxiety-daytime dysfunction; RR, ruminative response; RR_D, ruminative response-depression related; RR_B, ruminative response-brooding; RRS_R, ruminative response-reflection; EPQ-R-N, Eysenck Personality Questionnaire-revised: short Form-Neuroticism subscale-T score. *t*, *p*, values for differences between males and females.

Table 2 Correlation analyses among major variables

| | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|-------------|---------|---------|---------|---------|---------|---------|---------|---|
| 1.CVDAS | 1 | | | | | | | |
| 2.CVDAS_SDs | 0.888** | 1 | | | | | | |
| 3.CVDAS_Dys | 0.937** | 0.672 | 1 | | | | | |
| 4.RRS | 0.390** | 0.310** | 0.392** | 1 | | | | |
| 5.RRS_D | 0.402** | 0.318** | 0.406** | 0.977** | 1 | | | |
| 6.RRS_B | 0.338** | 0.284** | 0.329** | 0.909** | 0.834** | 1 | | |
| 7.RRS_R | 0.335** | 0.255** | 0.345** | 0.928** | 0.870** | 0.779 | 1 | |
| 8.EPQ-R-N | 0.436** | 0.359** | 0.430** | 0.448** | 0.454** | 0.392** | 0.397** | 1 |

Abbreviations: DA, dream anxiety; DA_SDs, dream anxiety-sleep-related disturbances; DA_Dys, dream anxiety-daytime dysfunction; RR, ruminative response; RR_D, ruminative response-depression related; RR_B, ruminative response-brooding; RRS_R, ruminative response-reflection; EPQ-R-N, Eysenck Personality Questionnaire-revised: short Form-Neuroticism subscale-T score.

Table 3 Mediation effect of rumination (by parallel mediation analysis)

| Outcomes | RR_D | RR_B | RR_R | DA | DA_SDs | DA_Dys |
|-------------|------------------------|------------------------|------------------------|------------------------|------------------------|------------------------|
| | β [LCI, UCI] | | ' | | | |
| Neuroticism | 0.45** [0.20, 0.26] | 0.39** [0.08, 0.12] | 0.40** [0.08, 0.12] | 0.32** [0.14, 0.22] | 0.27** [0.05, 0.09] | 0.31** [0.08, 0.13] |
| RR_D | | | | 0.31** [0.17, 0.49] | 0.22** [0.03, 0.20] | 0.31** [0.11, 0.32] |
| RR_B | | | | 0.008 [-0.22, 0.28] | 0.07 [-0.05, 0.20] | -0.03 [-0.20, 0.11] |
| RR_R | | | | -0.07 [-0.44, 0.14] | -0.10 [-0.25, 0.03] | -0.03 [-0.22, 0.14] |

Notes: significance was set as p < 0.05; ** p < 0.01, * p < 0.05

Abbreviations: β, standardized regression coefficient; LCI, lower bound of 95% confidence interval; UCI, upper bound of 95% confidence interval; DA, dream anxiety; DA_SDs, dream anxiety-sleep-related disturbances; DA_Dys, dream anxiety-daytime dysfunction; RR, ruminative response; RR D, ruminative response-depression related; RR B, ruminative response-brooding; RRS R, ruminative response-reflection.

We first examined simple mediation models to explore the relationships among neuroticism, rumination, and dream anxiety. As shown in Table 3, the results indicated that the mediating effects of "ruminative response-depression related" on the relationships between neuroticism and dream anxiety (as well as subdimensions of dream anxiety) were significant. However, "ruminative response-brooding" and "ruminative response-reflection" have no mediation effects on the relationship between neuroticism and dream anxiety.

Then, moderated mediation analyses were performed. As shown in Table 4; Fig. 2, "ruminative response-depression related" can mediate the relationship between neuroticism and dream anxiety (β =0.32; 95% CI: 0.16 to 0.49), dream anxiety-sleep-related disturbances (β =0.11; 95% CI: 0.03 to 0.19) and dream anxiety-daytime dysfunctions (β =0.21; 95% CI: 0.11 to 0.31). However, the moderating effects of sex were not significant in the path from neuroticism to dream anxiety and its subdimensions. The final moderation result was shown in Fig. 2.



Table 4 Moderated mediation analysis results

| Outcome | RR_D | RR_B | RR_R | DA (Y1) | DA_SDs (Y2) | DA_Dys (Y3) |
|----------------|---------------|---------------|---------------|---------------|---------------|---------------|
| | β [LCI, UCI] | | | | | |
| Neuroticism | 0.23** | 0.10** | 0.10** | 0.19** | 0.07** | 0.12** |
| (X) | [0.19, 0.27] | [0.07, 0.12] | [0.08, 0.12] | [0.14, 0.24] | [0.05, 0.10] | [0.09, 0.15] |
| RR_D (M1) | | | | 0.32** | 0.11** | 0.21** |
| | | | | [0.16, 0.49] | [0.03, 0.19] | [0.11, 0.31] |
| RR_B (M2) | | | | 0.03 | 0.08 | -0.04 |
| | | | | [-0.22, 0.29] | [-0.05, 0.20] | [-0.20, 0.11] |
| RR_R (M3) | | | | -0.13 | -0.10 | -0.03 |
| | | | | [-0.42, 0.16] | [-0.24, 0.04] | [-0.21, 0.15] |
| Sex (W) | | | | 0.43 | -0.36 | 0.79 |
| | | | | [-3.59, 4.45] | [-2.34, 1.62] | [-1.71, 3.30] |
| X*W | 0.01 | 0.01 | 0.01 | -0.04 | -0.01 | -0.03 |
| | [-0.06, 0.08] | [-0.02, 0.05] | [-0.02, 0.04] | [-0.13, 0.04] | [-0.05, 0.03] | [-0.08, 0.02] |
| M1*W | | | | 0.13 | 0.03 | 0.09 |
| | | | | [-0.21, 0.46] | [-0.13, 0.20] | [-0.12, 0.30] |
| M2*W | | | | 0.002 | 0.08 | -0.08 |
| | | | | [-0.50, 0.51] | [-0.17, 0.33] | [-0.39, 0.24] |
| M3*W | | | | -0.20 | -0.13 | -0.07 |
| | | | | [-0.79, 0.39] | [-0.43, 0.16] | [-0.44, 0.30] |
| \mathbb{R}^2 | 0.2064** | 0.1545** | 0.1592** | 0.2500** | 0.1734** | 0.2450** |
| F | 65.3490 | 45.9100 | 47.5972 | 27.7045 | 17.4325 | 26.9664 |

Notes: significance was set as p < 0.05; ** p < 0.01. Abbreviations: β , unstandardized regression coefficients; LCI, lower bound of 95% confidence interval; UCI, upper bound of 95% confidence interval; DA, dream anxiety; DA_SDs, dream anxiety-sleep-related disturbances; DA_Dys, dream anxiety-daytime dysfunction; RR, ruminative response; RR_D, ruminative response-depression related; RR_B, ruminative response-brooding; RRS_R, ruminative response-reflection.

Discussion

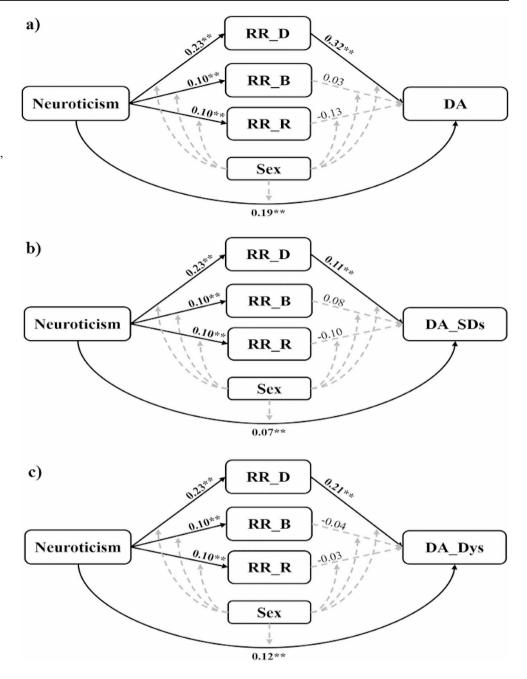
In the current study, we tested the hypothesis with moderated mediation models in which neuroticism was associated with dream anxiety as mediated by rumination (depression related, brooding, and reflection) and moderated by sex (see Fig. 1). We found that the ruminative response-depression related, rather than brooding and reflection, could partially mediate the relationship between neuroticism and dream anxiety (including sleep related disturbances and daytime dysfunctions). However, the moderation effects of sex were not significant. Our findings provided insight into the associations between neuroticism, rumination, and nightmare distress in university students, understanding of the potential psychological mechanism of rumination on the relationship between neuroticism and the development of negative influences caused by nightmares.

Consistent with our hypothesis 1, the results of mediation analyses showed that the ruminative response-depression related partially mediated the relationship between neuroticism and dream anxiety. That is, neuroticism not only directly influences dream anxiety, but also impacts dream anxiety through the mediation effect of rumination.

Neuroticism was significantly positively correlated with dream anxiety (including sleep related disturbances and daytime dysfunctions). Previous research found that individuals with frequent nightmares generally have higher levels of neuroticism compared to controls [8, 15, 22]. A recent longitudinal study revealed that changes of nightmare frequency were related to changes in neuroticism [18]. In addition to nightmare frequency, nightmare distress was also associated with neuroticism. Schredl et al. demonstrated that nightmare distress was correlated with a variety of factors including neuroticism [22, 37]. In our study, we also found that neuroticism was more correlated with "daytime dysfunctions" than "sleep related disturbances". This may be due to the fact that people with higher levels of neuroticism have greater responses to negative stimuli and poorer emotional regulation. Therefore, after experiencing nightmares, they are more likely to have negative emotions such as anxiety and depression, which affect their daytime mental state and function. In addition to the direct effect of neuroticism on dream anxiety, our mediation analysis results showed that "ruminative response-depression related" significantly mediated the relationship between neuroticism and dream anxiety, which confirmed that neuroticism could affect dream anxiety through the use of ruminative response. According to reactive style theory, rumination is the coping style used when dealing with negative emotions. The positive correlation of neuroticism with rumination has been found in several previous research results [26–28]. As noted above, individuals with higher levels of neuroticism are more inclined to experience negative emotions and tend to ignore the positive side of things, that is, they have a negative processing bias. Meanwhile, we also found that



Fig. 2 The final moderated mediation model. Notes: significance was set as p < 0.05. ** p < 0.01. For all coefficients (unstandardized) of each path, please see Table 4. The grey dotted line indicates the path is no significant. Abbreviation: RR D, ruminative responsedepression related; RR B, ruminative response-brooding; RR R, ruminative response-reflection: DA, dream anxiety; DA SDs, dream anxiety-sleep related disturbances; DA Dys, dream anxiety-daytime dysfunctions



there is a significant positive correlation between rumination and dream anxiety. Although there is a lack of understanding of the relationship between rumination and dream anxiety, this correlation may be due to the cognitive processes that rumination is associated with negative emotions. Previous studies have shown that rumination could significantly mediated the relationships between neuroticism and negative emotions, such as depression and anxiety [29, 30]. As a series of negative consequences caused by nightmares that involve emotions and functions, dream anxiety can also be influenced by rumination. Our results supported this hypothesis. Individuals with high neuroticism tend to use

ruminative response when facing nightmare experiences and are more prone to focus on negative emotions caused by nightmares (such as anxiety, worries), thereby exacerbating the negative emotional experiences brought about by nightmares and resulting in more severe emotional and functional consequences. Given that rumination engages cognitive processes, it is unsurprising that the correlation between rumination and "daytime dysfunctions" (r=0.392, p<0.01) were pronounced compared to its correlation with "sleep disturbances" (r=0.310, p<0.01) in our study. This observation can be attributed to the fact that "daytime dysfunctions" encompass a range of emotional and functional



disruptions during the day, stemming from the negative emotions triggered by nightmare experiences.

It is noted that only "ruminative response-depression related" could significantly mediated the relationship between neuroticism and dream anxiety. This may be due to the fact that they represent different aspects of the ruminative response. "Ruminative response-depression related" represents symptom-based rumination, reflecting repeatedly experience with negative feelings (symptoms) [38]. "Ruminative response-brooding" represents rumination on cause [38] and is usually correlated with affective disorders. Brooding makes individuals pay excessive attention to and process self-related negative events and think why it has happened (self-blame), leading to a decrease in individual self-evaluation, thereby activating and strengthening of negative self-schemas. While "ruminative responsereflection" is beneficial, and it is a behavior that exists in all individuals [39]. Therefore, it is obvious that dream anxiety is primarily produced through symptom-based rumination rather than excessive focus on causes, as well as reflection. For people with high levels of neuroticism, they are more inclined towards rumination to repeatedly experience bad feelings of nightmares, and therefore exacerbate these negative emotional states, and extreme emotions further affect daytime work, social interaction, and other functions.

The second hypothesis of the current study was not hold, indicating that the relationships among neuroticism, rumination, and dream anxiety do not vary across sex, although sex differences were observed in nightmare distress (total score and SDs). In fact, a previous study also found that the typical sex difference in nightmare frequency was no longer significant when neuroticism was introduced in the regression analysis [22], supporting neuroticism is a factor that at least partially explains the sex differences in the nightmare frequency [40]. The results of the current study may also indicate that neuroticism could partially contribute to the sex differences in nightmare distress (especially in sleeprelated disturbances). To sum up, the results of moderated mediation analyses showed that sex did not alter the mediating role of rumination in the relationship between neuroticism and dream anxiety.

There are inevitably some limitations in this study. Firstly, the current study is a cross-sectional design, which limits the determination of causality. Future studies would especially benefit from longitudinal design to test the dynamic changes of neuroticism, rumination, and dream anxiety, to determine causal relationships. Secondly, the current study only enrolled university students, which limits the generalizability of the conclusions. Future studies should validate the current results in other population groups, such as clinical patients. Nonetheless, the current study has illuminated how neuroticism influences dream anxiety (nightmare

distress) through the cognitive style among university students. It enhances our understanding of the psychological mechanisms underlying the impact of neuroticism on the emergence of negative effects resulting from nightmares, helping implement interventions and strategies aimed at the reducing negative consequences caused by nightmares. The efficiency of such interventions targeted cognitive styles (rumination), especially in people with high neuroticism, should be further examined in future studies.

Conclusions

In conclusion, the current study provides a novel architecture on the underlying psychological mechanisms of neuroticism and nightmare distress. Neuroticism can impact nightmare distress through the ruminative response, and this relationship is stable across sex. Accordingly, interventions for individuals who suffered from chronic nightmares may focus on their repetitive negative thoughts and maladaptive beliefs, especially in people with high neuroticism, irrespective of sex differences. This paves the way for healthcare providers to adopt tailor-made clinical interventions and psychotherapies for emotional well-being.

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Data availability The data that support the findings of the study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Declarations

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the subject matter or materials discussed in this manuscript.

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 (IRB of the Third Xiangya Hospital of Central South University) 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.

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