

Comorbidity Network Analysis of Depression, Anxiety and Stress During the COVID-19 Pandemic

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Abstract

Background: Stress caused by the COVID-19 pandemic is highly correlated with depression and anxiety disorders, and there is currently a lack of understanding of the comorbidity network of these disorders. The purpose of this study is to explore the comorbidity network of depression, anxiety and stress during the COVID-19 pandemic through network analysis.

Method: 887 participants are conducted a DASS 21 mental state survey across the country from February 18 to 22 in the outbreak of the COVID-19 pandemic in China. The network analysis method was used to explore the network relationship between these disorders, including the use of indicators of expected influence and bridge expected influence to explain the centrality of the network.

Results: The strongest six edges were the connections between the symptoms within each group, including three depressive symptom edges initiative-anhedonia, hopeless-meaningless and worthless-meaningless, one anxiety symptom edge dyspneic-heart sick and two stress symptom edges over reactive-touchy and agitated-relax. Centrality indicators show that symptoms blue, relax, and intolerable have the strongest expected influence centrality. The results show that symptoms intolerable, sad mood and blue have the strongest bridge expected influence centrality.

Conclusion: We found that symptoms blue, intolerable and relax are the core ones in the network, while dry and heartsick are less important ones. In addition, symptoms intolerable, sad mood and blue were also found to have the strongest bridge symptoms. Interventions against the core symptoms in this study will be more precise.

Background

A new coronavirus (COVID-19) broke out in Wuhan, China, in December 2019. The virus causes pneumonia and is extremely harmful to humans. Subsequently, COVID-19 broke out worldwide and spread as quickly as thought. As of June 30, 2020, more than 10 million people were diagnosed (World Health Organization, WHO), which caused great damage to human society. In response to the spread of the pandemic, governments have adopted a series of interventions, including virus detection and social isolation. Worries about the virus and the quarantined environment tend to cause more mental health problems [1, 2]. Studies have shown that COVID-19 pandemic can cause psychological problems such as anxiety, depression (16–28%) and stress (8%) [3]. Due to the limited resources of mental health services in many countries and the limited awareness of psychological problems in public health emergencies, mental health interventions face a huge challenge [4, 5], a lack of professional psychological intervention for a great number of people.

Public health emergencies often trigger a series of psychological problems, leading to chronic stress and mental health burden, and constitute risk factors for anxiety and depression [6]. Psychological stress is the reaction of choosing to fight or avoid during the adaptation process. It can cause a variety of physiological reactions, which can be harmful in some cases [7]. Stress is one of the main causes leading

to the development of depression and anxiety [8]. During the COVID-19 pandemic, a vicious circle of reduced coping strategies and immune system capacity due to psychological stress was formed [6]. Studies have shown that college students with depression also feel stress [9]. In addition, stress is positively related to anxiety. Studies have shown that people with higher anxiety show greater stress [10].

These external environmental stressors are thought to be related to depression episodes [11, 12], and studies have also shown that early life stress may lead to depression [13]. The main life stressors, especially those that involve interpersonal stress and social exclusion, are the strongest risk factors for depression [14]. The social isolation measures taken during the COVID-19 pandemic were undoubtedly effective to stop the spread of the virus, but they also led to greater health anxiety, financial worries, loneliness, and stress [15, 16]. According to the hypothesis of social signal transduction theory, social threats and adversity experiences increase the immune system components associated with inflammation, such as proinflammatory cytokines, which in turn can cause a series of behavioral changes, including depression, anxiety and physical diseases. Increased levels of actual or perceived threats caused by these factors increase anxiety and activate social signal transduction pathways that upregulate inflammatory activity[14]. These evidences indicate that social stress increases the risk of depression and anxiety. Moreover the co-occurrence of anxiety and depression is more common. Studies have shown that up to 25% of all general patients have depression and anxiety. About 85% of depression patients suffer from severe anxiety. Meanwhile, 90% of anxious patients suffer from depression [17]. Depression and anxiety are two-way risk factors for each other [18]. These results indicate that stress, anxiety and depression are highly co-occurring.

Network analysis has been widely used in recent years to explore the connection between symptoms of mental illness, especially in the comorbidity network that explores depression and anxiety [19–21]. There is little research on the comorbidity network of the three factors of stress, depression and anxiety symptoms. Recent studies have shown that strength centrality is more reliable than intermediary centrality and near centrality in network analysis indicators [22]. When there are negative correlation edges in the network, the representative edge absolute value and strength centrality may distort the actual impact of these nodes in the network. Therefore, in this study, the expected influence is used to replace the strength centrality as the index of centrality[23]. In addition, there are three clusters in this study. Bridge symptoms can explain the spread of mental disorders, while blocking the combination of bridge symptoms prevents one disease from activating another disease [24]. Therefore, in this study, two main indicators of expected influence centrality and bridge expected influence centrality are employed.

In summary, stress, depression and anxiety are often closely related to each other. During the COVID-19 pandemic, the psychological problems generated by the public included psychological stress, depression, and anxiety, and these symptoms often coexisted. The current network comorbidity mainly focuses on the study of depression and anxiety, ignoring stress is closely related to them, which may miss some important information in the comorbidity network. The current study will explore the co-occurrence of depression, anxiety and stress during the COVID-19 pandemic. Through the network analysis method, we expect to find out the most important symptoms in depression, anxiety and stress comorbidity network

via the central indicator of expected influence and bridge expected influence, which will help to understand the comorbidity of depression and anxiety more comprehensively, and also provide some guidances for psychological problem intervention in public health emergencies.

Method

Participants

A total of 888 participants from 31 provinces and cities in China completed the survey on depression, anxiety and stress (DASS-21), and were excluded due to the lack of data from one participant. Finally, 887 data were included in the analysis. Among the participants, 368 were male (41.44%) and 520 were female (58.56%). The education level of all participants is junior college and above, and the age is between 18–65 years old.

Measuring Tools

The depression, anxiety and stress scale (DASS-21)[25] composing of 21 items was applied to this survey. The scale uses Likert's 4-point scoring method, ranging from 0 (not inline) to 3 (very inline). Previous studies have shown that the scale has good credibility [26]. In this study, Cronbach's α is 0.95, and values of Cronbach's α for depression, anxiety and stress are respectively 0.87, 0.83 and 0.89.

Research Steps

This study was reviewed by the Ethics Committee of the Department of Medical Psychology of the Chinese Army Medical University as part of the "Mental Health During Outbreak" project. The study used an online questionnaire survey conducted between February 18–22, 2020. The survey is snowball sampling. All samples are collected by researchers to release survey information on WeChat. The survey questionnaire briefly introduces the basic purpose and answer form of the survey in the guidance section and informs that the survey is anonymous and only used for scientific research. After completing the survey, participants can view the results and get suggestions.

Statistical analysis

The construction and visualization of the network are completed through the R package *qgraph* [22], and the Gaussian graphical model (GGM) is used to fit the data [27]. The estimation of GGM is based on the non-parametric Spearman rho correlation matrix. We use the graphical LASSO (Least Absolute Shrinkage and Selection Operator) algorithm to regularize GGM. This step shrinks all edges and makes small edges zero to obtain a more stable and interpretable network [28]. The GGM tuning parameter is set to the recommended value of 0.5 to well judge and weigh the sensitivity and specificity of finding true edges [29]. In the visual network, red edges represent negative partial correlations, and blue edges represent

positive partial correlations between nodes. The thicker edges indicate a stronger correlation between nodes.

The importance of each node in the current network is evaluated by the expected influence centrality in the R software *networktools* [24]. The expected influence centrality of a given node is similar to the strength centrality, but the absolute value of its edges is not taken before summing [23]. A higher expected influence center value indicates that it is more important in the network. Then, we use the bridge tool of the R package *networktools* to estimate the centrality of the bridge expected influence [24]. Bridge expected influence is calculated by summing all edges that appear between a given node and nodes in the other clusters [24]. A higher value of the bridge expected influence means that the diffusion of activation from one cluster to the others is promoted to a greater extent. In the present network, nodes are a priori divided into three clusters: a series of depression symptoms (for example, sad mood-meaningless), a series of anxiety symptoms (for example, dry-scared), and a series of stress symptoms (for example, uneasy-touchy).

The robustness of the network was checked through the R package *bootnet* [22]. First, the accuracy of edge weights is evaluated by constructing a 95% confidence interval (CI) using a non-parametric bootstrap program (2000 bootstrap samples). Second, the stability of expected influence and bridge expected influence of the node are evaluated by calculating the correlation stability (CS) coefficient using case-dropping subset, bootstrapped with 2000 samples. The value of the CS coefficient should not be lower than 0.25, preferably higher than 0.5 [22]. Third, we conducted bootstrapped difference tests (2000 bootstrap samples, $\alpha = 0.05$) for edge weight, node expected influence and node bridge expected influence to confirm whether there are significant differences among two edge weight, two node expected influence or two node bridge expected influence. The results of the robustness analysis for the current network are provided in the supplementary materials (Figures S1-S6 in Supplemental Material).

Results

The comorbidity network is depicted in Fig. 1. First, among 210 possible edges of the comorbidity network, 128 edges are not 0 (60.95%) and mostly positive (except two edges are negative: one edge is between uneasy and meaningless, and the other one is between nervous and worthless). Then, network shows that the six edges with the strongest edge connections are located between symptoms within one cluster. The strongest edges of depression are between symptoms motor and anhedonia (weight 0.38), hopeless and meaningless (weight 0.33), and worthless and meaningless (weight 0.26). The strongest edge of anxiety is within symptom dyspneic-heart-sick (weight 0.28) and the remaining strongest edge of stress is between symptoms over reactive-touchy (weight 0.25) and agitated-relax (weight 0.25). These edge weights are significantly different from others.

The value (z-scored) of expected influence and bridge expected influence for each node is depicted in Fig. 2. The depression symptom blue has the strongest expected influence, indicating it is the most connected node in the network and followed by stress symptoms relax and intolerable. Three symptoms

with the lowest expected influence are trembling, dry and heart-sick. Moreover, the symptoms with strongest bridge expected influence are stress symptoms intolerable and depression symptoms sad mood and blue. And the symptoms with lowest bridge expected influence are anxiety symptoms heart-sick and trembling, and depression symptom meaningless. Bootstrapped 95% confidence interval indicating the accuracy of edge weights is accurate (Please refer to Figure S1 and Figure S5 in the supplementary material). In addition, the values of the CS coefficient of node expected influence and bridge expected influence are both 0.75 which indicate an adequate stability for node centrality indices (Please refer to Figure S3 and Figure S5 in the supplementary material). The bootstrap difference test for edge weights shows that in the current network, a medium proportion of the difference between edge weights is significant (Please refer to Figure S2 in the supplementary material). Figures S4 and S6 describe the bootstrap difference tests (in the supplementary material) for the node expected influence and bridge expected influence. These results indicate that in the current network, a large part of the differences between the node expected influence and bridge expected influence are significant.

Discussion

This study used network analysis to explore the comorbidity network of depression, anxiety and stress among 887 Chinese citizens during the COVID-19 pandemic. In the network, we determined the network structure and the expected influence and bridge expected influence of each node. The network structure shows that many symptoms (128/210) in the network are directly connected, which is consistent with the results of previous studies [30, 31]. Moreover, the network structure shows that there are many correlations between stress and depression and anxiety symptoms. We found that the edges of symptoms motor -anhedonia and hopeless-meaningless have the strongest edge weight, followed by edge weight of symptoms dyspneic-heart sick, worthless-meaningless and over reactive-touchy. These results indicate that the connection of edges within factors in the network has a greater connection than the connection of edges between factors, consisting with previous research results [19, 32]. This study also found that the strongest edge of the relationship between disorders is the stress symptom uneasy and depression symptom sad mood. People under long-term stress may weaken body's immune response-ability, especially acute stress causes sympathetic-adrenaline-mediated increase, and induces chemotaxis and adhesion molecule expression, thereby promoting immune cell migration to infection or inflammation, while chronic stress impairs this mechanism [33]. Inflammation plays a key role in the pathogenesis of depression. Larger, more frequent or longer-term inflammatory reactions may have a negative impact on mental and physical health [34], meanwhile chronic Low-level inflammation can also trigger mental and health problems. These evidences indicate that both acute stress and continuous chronic stress during the COVID-19 pandemic may trigger an inflammatory response, reduce a body's immunity and increase risks of depression and infecting COVID-19. Our results support that stress is closely associated with depression, not just anxiety closely associated with it [35, 36].

The results of this study show that depression symptoms blue and stress symptoms relax and intolerable have the strongest expected influence, which indicates that in COVID-19 pandemic due to the influence of social isolation, depression-related symptom blue and stress-related symptoms relax and intolerable

become the most important symptoms in the present symptoms network[2]. The intervention of these symptoms could have a good effect to reduce the severity of overall symptoms in the network. However, in previous studies depression symptom sad mood [19, 37] and depression symptom fatigue [32] have the strongest centrality. Similar to the network results of depression, anxiety, and traumatic stress disorder, symptom feeling blue has the greatest strength in this network [38]. In this study, most notably stress symptoms relax and intolerable have the strongest centrality. The possible reason is that this study was conducted when there were the largest number of diagnosed patients with COVID-19 pandemic in China (the information from the official website of the National Health and Health Commission). The increasing number of infections and deaths has increased people's pessimistic experiences and stress feelings. The physical symptoms of anxiety disorder, dry and trembling, are the least important symptoms in this network, although some studies have shown that some physical symptoms coexist with anxiety and depression [39]. Network analysis studies also show that physical symptoms such as finger tingling and muscle pain are the least important symptoms [40]. This may indicate that physical symptoms are not important nodes in similar depression and anxiety networks.

Three symptoms with the highest bridge expected influence are stress symptom intolerable and depressive symptoms sad mood and blue which is different from the previous research results — the dysphoria/avoidance-related symptom [38] and the anhedonia, sad mood and fatigue symptoms [32] showing high bridge centrality values. This means that stress symptom intolerable during the COVID-19 pandemic is a key node for activating depression and anxiety. Previous network studies did not involve stress variable, but in the context of COVID-19 pandemic, the stress symptom intolerable has the strongest bridge expected influence, indicating that stress symptom intolerable is a significant node during the COVID-19 pandemic. That means stress is a crucial research variable in public health emergencies. Therefore, future research should further explore the co-occurrence of stress, depression and anxiety symptoms.

The prevention of bridge symptoms can block the spread of comorbidities, and it is more effective to eliminate the bridge symptom nodes than do on traditional central nodes [24]. The outbreak of COVID-19 pandemic severely impaired mental health, leading to psychological problems such as stress, anxiety and depression [41, 42]. The bridge symptom results of this study indicate that symptoms intolerable, sad mood and blue are the optimal intervention targets in order to better prevent these mental health problems. Symptom intolerable is connected to many nodes in the network, especially having the strongest connection with symptom blue, meanwhile blue and sad mood have the strongest connection, indicating that these three symptoms play the most important connection role in the comorbid network. These results support studies of mechanisms related to depression and stress. Symptom sad mood is closely related to abnormal brain connectivity in depression patients. It induces increased activation of the ventrolateral thalamus nucleus [43], while the abnormality of the ventral thalamus nucleus is the important abnormal brain regions of GRI model mice [44]. Besides depressive symptoms, stress symptom intolerable is the most important factor. Research shows that intolerable (intolerance of Uncertainty) is not only significantly related to stress [45], but also exacerbates people's anxiety [46]. The results of this study provide some support for targeted interventions. During the COVID-19 pandemic, for symptoms sad

mood and blue, people should do some exercise activities especially before bedtime, listen to music, have a bath or read a book to relax or do other things making themselves happy [47]; For symptom intolerable, it may be alleviated by obtaining pandemic information, such as current situation or treatment, or taking special preventive measures, such as paying attention to hygiene and wearing masks [2].

It is the first time to explore Chinese people's depression, anxiety and stress during the COVID-19 pandemic with an approach of network analysis. Our data involve 887 citizens from 31 cities in China. The network results have high stability (CS = 0.75) and are very representative. Some limitations must be considered in this study. First, the data in this study is cross-sectional, so the results of the analysis cannot determine whether these symptoms will change dynamically with time. Future research should consider whether the degree or types of the psychological problem caused by COVID-19 pandemic at different stages is different, which can help us provide more targeted interventions at different stages of the pandemic. The second is that the data only include people with college or above education background, and the result cannot be extended to a larger group. In addition, network analysis methods also have certain limitations. Network analysis is mainly a network constructed by correlation coefficients rather than causal relations between symptoms. Finally, a network constructed by network analysis is limited by collected symptoms and behaviors. For example, if other physical symptoms are added to the network, there may be different networks.

Conclusion

We used network analysis to explore the comorbidity network of depression, anxiety and stress. Overall, we found that blue, intolerable and relax are the core symptoms in the network. In addition, intolerable, sad mood and blue were also found to have the strongest bridge symptoms. Recent studies[5] have shown that the public has more mental health problems during the COVID-19 pandemic. In order to reduce the impairments from depression and anxiety, more effective intervention should focus on the core symptoms of this study: stress item intolerable, and depressive items blue and sad mood. Of course, due to the limitations of cross-sectional studies and participants, these results still need to be carefully understood.

Abbreviations

CI

confidence interval; CS:correlation stability; GGM:Gaussian graphical model; LASSO:Least Absolute Shrinkage and Selection Operator; DASS:depression, anxiety and stress scale

Declarations

Ethics approval and consent to participate

Due to the quarantine during the epidemic, participants knew an introduction of the investigation online, and consent obtained from participants was verbal. An IRB approved this method of obtaining consent. The current study was reviewed and approved by the Medical Ethics Committee of the Department of Medical Psychology, Army Military Medical University(CWS20J007). We guarantee that all participants are informed before participating in the survey, and Their taking part in this study is completely voluntary. We will try to protect participants' privacy. The data is restricted to this study.

Consent for publication

Not applicable.

Availability of data and materials

data on participants with COVID-19 have not been reported in any other submission by us or anyone else. The datasets analyzed during the current study are available in the supplementary material.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Among the authors, LX, and LKL conducted the conception and writing of the article, and RL conducted the data analysis and method part. FZZ provides support for the article's overall idea. All authors read and approved the manuscript submitted.

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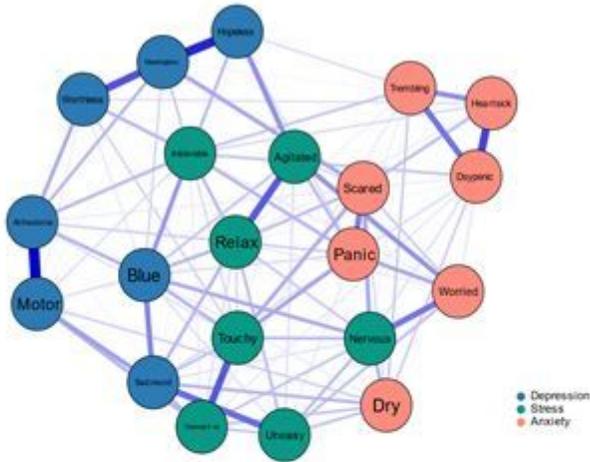
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Figures



- Uneasy : I found it hard to wind down.
- Dry : I was aware of dryness of my mouth.
- Sad-mood : I couldn't experience any positive feeling.
- Dyspnic : I experienced breathing difficulty.
- Motor : I found it difficult to work up the initiative to do things.
- Overreactive I tended to over-react to situations.
- Trembling : I experienced trembling (e.g., in the hands).
- Nervous : I felt that I was using a lot of nervous energy.
- Worried : I was worried about situations in which I might panic and make a fool of myself.
- Hopeless : I felt that I had nothing to look forward to.
- Agitated : I found myself getting agitated.
- Relax : I found it difficult to relax.
- Blue : I felt downhearted and blue.
- Intolerable : I was intolerant of anything that kept me from getting on with what I was doing.
- Panic : I felt I was close to panic.
- Anhedonia : I was unable to become enthusiastic about anything.
- Worthless : I felt that I wasn't worth much as a person.
- Touchy : I felt I was rather touchy.
- Heartick : I was aware of the action of my heart in the absence of physical exertion.
- Scared : I felt scared without any good reason.
- Meaningless I felt that life was meaningless.

Figure 1

Network analysis of stress, depression, anxiety symptoms in epidemic isolation. Blue lines represent positive connection, and red lines represent negative connection. Colors representing the 3 clusters solutions resulting.

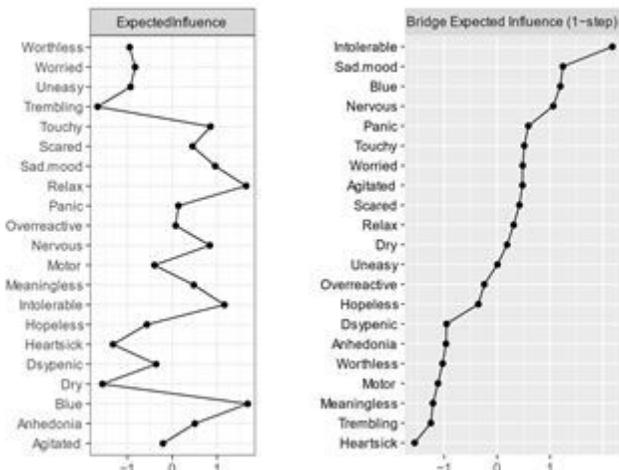


Figure 2

Node expected influence centrality and bridge expected influence centrality in network analysis of stress, depression, anxiety symptoms.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [DASStotal.csv](#)
- [SupplementaryFigurelegends.docx](#)