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Editorial Board Member of *World Journal of Psychiatry*, Ladislav Hosak, MD, PhD, Professor, Department of Psychiatry, University Hospital, Hradec Kralove 50005, Czech Republic. hosak@lfhk.cuni.cz

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Retrospective Study

Correlation between cognitive impairment and metabolic imbalance of gut microbiota in patients with schizophrenia

Jing Ma, Xue-Qin Song

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Abstract

BACKGROUND

The gut microbiome interacts with the central nervous system through the gut-brain axis, and this interaction involves neuronal, endocrine, and immune mechanisms, among others, which allow the microbiota to influence and respond to a variety of behavioral and mental conditions.

AIM

To explore the correlation between cognitive impairment and gut microbiota imbalance in patients with schizophrenia.

METHODS

A total of 498 untreated patients with schizophrenia admitted to our hospital from July 2020 to July 2022 were selected as the case group, while 498 healthy volunteers who underwent physical examinations at our hospital during the same period were selected as a control group. Fluorescence *in situ* hybridization was employed to determine the total number of bacteria in the feces of the two groups. The cognitive function test package was used to assess the score of cognitive function in each dimension. Then, the relationship between gut microbiota and cognitive function was analyzed.

RESULTS

There were statistically significant differences in the relative abundance of gut microbiota at both phylum and class levels between the case group and the control group. In addition, the scores of cognitive function, such as attention/alertness and learning ability, were significantly lower in the case group than in the control group (all $P < 0.05$). The cognitive function was positively correlated with Actinomycetota, Bacteroidota, Euryarchaeota, Fusobacteria, Pseudo-

monadota, and Saccharibacteria, while negatively correlated with Bacillota, Tenericutes, and Verrucomicrobia at the phylum level. While at the class level, the cognitive function was positively correlated with Class Actinobacteria, Bacteroidia, Betaproteobacteria, Proteobacteria, Blastomycetes, and Gammaproteobacteria, while negatively correlated with Bacilli, Clostridia, Coriobacteriia, and Verrucomicrobiae.

CONCLUSION

There is a relationship between the metabolic results of gut microbiota and cognitive function in patients with schizophrenia. When imbalances occur in the gut microbiota of patients, it leads to more severe cognitive impairment.

Key Words: Schizophrenia; Cognitive function; Gut microbiota; Metabolic imbalance; Bacteria

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Core Tip: The highlights of this study are as follows. First, individuals with schizophrenia have imbalanced intestinal microbiota compared to healthy individuals. Second, patients with schizophrenia exhibit cognitive impairments in various areas such as attention, memory, social cognition, and executive function. Additionally, specific microbial groups such as Actinomycetes, Bacteroides, and Proteobacteria have shown a positive correlation with cognitive function in patients with schizophrenia. Furthermore, there is a close relationship between metabolic imbalance of intestinal flora and cognitive impairment in individuals with schizophrenia. Lastly, further clinical trials are necessary to gather more data and insights for the development of effective treatments for schizophrenia.

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INTRODUCTION

Schizophrenia is a severe mental disorder with unknown etiology. Most of the patients are young and middle-aged. Frequently, the patients may encounter various obstacles in thinking, perception, emotion, and behavior, leading to a lack of coordination between mental activities and the surroundings[1]. Patients with schizophrenia exhibit characteristics such as a high disability rate, substantial burden, and an increased tendency of suicide. This disorder also causes hallucinations, delusions, language, and behavior abnormalities, with a long course and heterogeneous clinical manifestations. Schizophrenia has an impact on the physical and mental health, as well as social quality of life for patients, resulting in economic pressure and social burden. With the continuous advancement of biological technology, the understanding of schizophrenia is gradually deepening[2,3]. As one of the primary symptoms of schizophrenia, cognitive dysfunction includes two aspects, mental cognition and social cognition. Generally, it manifests before other psychotic symptoms of schizophrenia and persists throughout the course of the disease[4]. In recent years, there has been an increasing focus on the cognitive impairment of patients. Cognitive impairment can impede patients' social and occupational rehabilitation, and assessing cognitive function can predict the disease progression and treatment response[5]. Gut microbiota constitutes a complex and vast ecosystem. Scholars have proposed that gut microbiota can regulate the immune and inflammatory responses within the human body and influence neural development. However, the understanding of the relationship between gut microbiota and schizophrenia is still limited[6,7].

In this study, cognitive function and gut microbiota were examined to explore the potential correlation between cognitive impairment and metabolic imbalance of gut microbiota in patients with schizophrenia.

MATERIALS AND METHODS

Materials

A total of 498 patients with schizophrenia admitted to The First Affiliated Hospital of Zhengzhou University from July 2020 to July 2021 were selected as the case group, and 498 healthy volunteers who underwent physical examination at the same hospital were randomly chosen as the control group.

Inclusion criteria were: patients who met the diagnostic criteria for schizophrenia in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition[8], patients with no abnormality in routine blood tests, and patients who were 18-years-old to 50-years-old.

Exclusion criteria were: patients with diabetes, thyroid disease, hypertension, heart disease, or other diseases that may affect the stability of gut microbiota; patients who suffered from diarrhea in the past 3 mo; or patients who were pregnant or lactating.

Determination of bacterial counts

The bacterial counts in patients were determined using fluorescence *in situ* hybridization. We utilized fluorescent tags as a substitute for isotope labeling. First, biotin labeling was carried out, followed by DNA probe hybridization. Next, fluorescein avidin was used to bind with the probe hybridization to the target DNA on the chromosomes to form a hybrid. Qualitative and quantitative analyses were then performed after detecting the fluorescence under a microscope.

Cognitive function scores

The first step was to determine whether the patient was conscious. Generally, the Glasgow scale was employed to assess the degree of consciousness disturbance. If the patient was conscious, the Short Form Mental State Examination was used to screen for cognitive dysfunction. Based on the results, the presence of cognitive impairment could be identified, and further assessment of cognitive function was conducted accordingly.

Statistical processing

SPSS21.0 software was used for the data analyses. The independent *t*-test was used for comparisons between the two groups. For multivariate regression analysis, the multiple linear regression model was employed when the dependent variable was continuous, whereas the logistic regression model was used when the dependent variable was dichotomous. $P < 0.05$ was considered statistically significant.

RESULTS

Distribution of gut microbiota at the phylum level in the two groups

As shown in Table 1, the case group exhibited a significantly higher relative abundance of Actinomycetota, Bacteroidota, Euryarchaeota, Fusobacteria, Pseudomonadota, and lower abundance of Bacillota, Tenericutes, and Verrucomicrobia when compared with the control group ($P < 0.05$).

Distribution of gut microbiota at the class level in the two groups

As shown in Table 2, compared with the control group, the case group exhibited a significantly higher relative abundance of Class Actinobacteria, Bacteroidia, Betaproteobacteria, Proteobacteria, Blastomycetes, and Gammaproteobacteria, and lower relative abundance of Bacilli, Clostridia, Coriobacteriia, and Verrucomicrobiae ($P < 0.05$).

Comparison of cognitive scores between the two groups

As shown in Table 3, the scores of attention or alertness, learning, memory, fine motors, social cognition, executive function, conversion, inhibition, planning, working memory, category fluency, information processing, and total cognitive score were all significantly lower in the case group than in the control group ($P < 0.05$).

Correlation analysis between cognitive function and gut microbiota at the phylum level

As shown in Table 4, cognitive function was positively correlated with Actinomycetota ($r = 6.591$, $P = 0.001$), Bacteroidota ($r = 5.625$, $P = 0.016$), Euryarchaeota ($r = 6.281$, $P = 0.183$), Fusobacteria ($r = 2.190$, $P = 0.026$), Pseudomonadota ($r = 6.364$, $P = 0.018$), and Saccharibacteria ($r = 5.196$, $P = 0.037$), while negatively correlated with Bacillota ($r = -0.976$, $P = 0.281$), Tenericutes ($r = -0.623$, $P = 0.001$), and Verrucomicrobia ($r = -0.191$, $P = 0.006$).

Correlation analysis of between cognitive function and gut microbiota at the class level

As shown in Table 5, cognitive function was positively correlated with Class Actinobacteria ($r = 3.257$, $P = 0.001$), Bacteroidia ($r = 6.294$, $P = 0.001$), Betaproteobacteria ($r = 6.281$, $P = 0.016$), Proteobacteria ($r = 6.270$, $P = 0.008$), Blastomycetes ($r = 5.671$, $P = 0.006$), and Gammaproteobacteria ($r = 4.195$, $P = 0.005$), while negatively correlated with Bacilli ($r = -0.981$, $P = 0.001$), Clostridia ($r = -0.124$, $P = 0.015$), Coriobacteriia ($r = -0.293$, $P = 0.019$), and Verrucomicrobiae ($r = -0.549$, $P = 0.010$).

DISCUSSION

Schizophrenia is a chronic and severe mental disorder characterized by disturbances in an individual's sensory, emotional, and behavioral functions[9]. Patients with schizophrenia have difficulties distinguishing between reality and the imaginary. They may exhibit slow reactions, and show a phenomenon of behavioral withdrawal, significantly affecting their ability to engage in normal social behavior. In medical terms, schizophrenia is classified as a disorder rather than a disease. This disorder often typically occurs during the young or prime stages of life. It encompasses disturbances in the body, mind, emotions, and behaviors, but the patients do not have a coma or mentally retarded imagination[10,11]. Some studies have found that genetic factors, brain structure, and environment factors contribute

Table 1 Relative abundance of gut microbiota at the phylum level in the two groups

| Name of bacteria | Case group, n = 498 | Control group, n = 498 | T value | P value |
|------------------|---------------------|------------------------|---------|---------|
| Actinomycetota | 2.95 ± 5.62 | 2.18 ± 3.60 | 2.575 | 0.01 |
| Bacteroidota | 34.27 ± 19.53 | 26.84 ± 16.07 | 6.556 | 0.001 |
| Euryarchaeota | 0.16 ± 0.57 | 0.00 ± 0.00 | 6.264 | 0.001 |
| Bacillota | 48.82 ± 17.96 | 61.37 ± 14.49 | 12.14 | 0.001 |
| Fusobacteria | 0.08 ± 0.57 | 0.02 ± 0.07 | 2.332 | 0.019 |
| Pseudomonadota | 15.82 ± 20.13 | 7.68 ± 11.59 | 7.82 | 0.001 |
| Saccharibacteria | 0.49 ± 0.27 | 0.01 ± 0.01 | 39.65 | 0.001 |
| Tenericutes | 0.23 ± 1.14 | 0.59 ± 1.92 | 3.598 | 0.001 |
| Verrucomicrobia | 0.57 ± 1.94 | 1.62 ± 5.19 | 4.229 | 0.001 |
| Actinomycetota | 2.95 ± 5.62 | 2.18 ± 3.60 | 2.575 | 0.01 |

Data are presented as mean ± SD.

Table 2 Relative abundance of gut microbiota at the class level in the two groups

| Name of bacteria | Case group, n = 498 | Control group, n = 498 | T value | P value |
|----------------------|---------------------|------------------------|---------|---------|
| Class Actinobacteria | 2.81 ± 5.64 | 1.56 ± 2.81 | 4.427 | 0.001 |
| Bacilli | 2.01 ± 4.28 | 2.67 ± 5.60 | 2.090 | 0.036 |
| Bacteroidia | 31.28 ± 19.67 | 26.68 ± 16.18 | 4.030 | 0.001 |
| Betaproteobacteria | 1.50 ± 3.29 | 0.39 ± 0.52 | 7.437 | 0.001 |
| Clostridia | 45.92 ± 18.62 | 58.18 ± 13.92 | 11.770 | 0.001 |
| Coriobacteriia | 0.21 ± 0.49 | 0.58 ± 1.29 | 5.984 | 0.001 |
| Proteobacteria | 0.29 ± 0.39 | 0.15 ± 0.24 | 6.822 | 0.001 |
| Blastomycetes | 0.96 ± 1.19 | 0.67 ± 1.20 | 3.829 | 0.01 |
| Gammaproteobacteria | 13.84 ± 19.67 | 6.92 ± 11.37 | 6.797 | 0.001 |
| Verrucomicrobiae | 0.58 ± 1.69 | 1.82 ± 5.86 | 4.537 | 0.001 |

Data are presented as mean ± SD.

significantly to the development of this disorder. Therefore, comprehensive medical and psychological treatments are necessary to address the multifaceted nature of the condition.

Cognitive impairment is commonly observed in patients with schizophrenia, impacting various aspects such as information integration, memory, and attention. Symptoms of cognitive dysfunction are prominently manifested through memory decline in the general population[12,13]. In addition to memory decline, schizophrenia can result in impairments in executive function, visuospatial ability, comprehension, and numeracy. People's general cognition and social cognition are also closely associated with age. As the aging population continues to grow, the incidence of cognitive dysfunction is increasing[14,15]. A large number of clinical studies have demonstrated a certain correlation between schizophrenia and cognitive function. Effective interventions targeting overall cognition, emotions, and society aspects have shown promising results. In this study, patients with schizophrenia exhibited considerable declines in various cognitive aspects, including learning, memory, fine motor skills, social cognition, working memory, category fluency, information processing, and kinetic energy, when compared to healthy individuals. These results suggest association between cognitive function and schizophrenia, which is similar to the results of the above research.

Schizophrenia has profoundly impacted numerous families. Consequently, there is a paramount need to pursue effective treatment options and improve the patient prognosis[16]. Gut microbiota is a central regulator of metabolism in the human body and has been found to be associated with various mental diseases[17,18]. In modern society, there is a growing awareness of the diversity, complexity, and dynamics of gut microbiota. Differences in the structure and diversity of gut microbiota have been observed in patients with schizophrenia, with the control of the disorder having a great impact on the distribution of gut microbiota structure[19,20]. Some scholars have noted that alterations in the gut microbial community can affect the cytokine levels in the body, subsequently impacting the brain function and behaviors,

Table 3 Comparative analysis of cognitive scores between the two groups

| Cognitive domain | Case group, n = 498 | Control group, n = 498 | T value | P value |
|------------------------|---------------------|------------------------|---------|---------|
| Attention/alertness | 40.27 ± 6.29 | 51.98 ± 9.92 | 22.250 | 0.001 |
| Learning | 36.27 ± 10.01 | 50.69 ± 10.08 | 22.650 | 0.001 |
| Memory | 40.31 ± 11.26 | 54.27 ± 7.19 | 23.320 | 0.001 |
| Fine motors | 37.29 ± 13.27 | 59.06 ± 7.91 | 31.450 | 0.001 |
| Social cognition | 41.09 ± 11.08 | 54.26 ± 10.87 | 18.930 | 0.001 |
| Executive function | 40.18 ± 7.04 | 52.37 ± 5.09 | 31.310 | 0.001 |
| Conversion | 41.06 ± 7.21 | 49.57 ± 7.61 | 18.120 | 0.001 |
| Inhibition | 38.62 ± 9.51 | 54.63 ± 9.67 | 26.340 | 0.001 |
| Planning | 42.14 ± 13.01 | 52.67 ± 10.17 | 14.230 | 0.001 |
| Working memory | 42.09 ± 13.02 | 53.19 ± 9.06 | 15.620 | 0.001 |
| Category fluency | 39.86 ± 10.05 | 53.18 ± 9.07 | 21.960 | 0.001 |
| Information processing | 33.43 ± 9.14 | 48.45 ± 7.39 | 28.520 | 0.001 |
| Total score | 40.64 ± 7.17 | 51.14 ± 5.29 | 26.300 | 0.001 |

Data are presented as mean ± SD of points.

Table 4 Correlation analysis between the total cognitive score and gut microbiota at the phylum level

| Name of bacteria | Total cognitive score | |
|------------------|-----------------------|---------|
| | R value | P value |
| Actinomycetota | 6.591 | 0.001 |
| Bacteroidota | 5.625 | 0.016 |
| Euryarchaeota | 6.281 | 0.183 |
| Bacillota | 0.976 | 0.281 |
| Fusobacteria | 2.190 | 0.026 |
| Pseudomonadota | 6.364 | 0.018 |
| Saccharibacteria | 5.196 | 0.037 |
| Tenericutes | 0.623 | 0.001 |
| Verrucomicrobia | 0.191 | 0.006 |

and greatly affecting the prognosis of patients. In this study, we found that the relative abundance of gut microbiota in patients with schizophrenia differed significantly from that in healthy individuals, indicating an imbalance in the gut microbiota in patients with schizophrenia, which is consistent with the previous results. This article examined gut microbiota at a phylum level (Actinomycetota, Bacteroidota, Euryarchaeota, Fusobacteria, Pseudomonadota, *etc*) and a class level (Class Actinobacteria, Bacteroidia, Betaproteobacteria, Proteobacteria, Blastomycetes, and Gammaproteobacteria, *etc*). The results suggest that there is a certain correlation between gut microbiota and schizophrenia.

In this study, a correlation was identified between cognitive impairment and metabolic imbalance of gut microbiota. However, it is essential to acknowledge that the small sample size in this study may introduce some bias in the data. In the future, clinical trials with larger sample size should be conducted to provide more reliable data to guide the clinical treatment for patients with schizophrenia.

CONCLUSION

To summarize, this study revealed the presence of gut microbiota imbalance in schizophrenia patients and found the correlation between cognitive impairment and metabolic imbalance of gut microbiota in these patients. of intestinal flora, providing insights into the link between changes in gut microbiota and cognitive function, as well as the pathogenesis of schizophrenia. This research presents a novel approach that may pave the way for future treatments targeting schizo-

Table 5 Correlation analysis between the total cognitive score and gut microbiota at the class level

| Name of bacteria | Total cognitive score | |
|---------------------|-----------------------|---------|
| | R value | P value |
| Actinobacteria | 3.257 | 0.001 |
| Bacilli | 0.981 | 0.001 |
| Bacteroidia | 6.294 | 0.001 |
| Betaproteobacteria | 6.281 | 0.016 |
| Clostridia | 0.124 | 0.015 |
| Coriobacteriia | 0.293 | 0.019 |
| Proteobacteria | 6.270 | 0.008 |
| Blastomycetes | 5.671 | 0.006 |
| Gammaproteobacteria | 4.195 | 0.005 |
| Verrucomicrobiae | 0.549 | 0.010 |

phrenia.

ARTICLE HIGHLIGHTS

Research background

Schizophrenia is a severe mental disorder characterized by impaired thinking, perception, emotion, and behavior. It affects the physical and mental health of the patients, leading to a high disability rate, burden, and suicide tendency. Cognitive dysfunction is a primary symptom of schizophrenia and includes mental cognition and social cognition. It can significantly impact the overall functioning and quality of life of individuals with schizophrenia. In recent years, there has been increasing recognition of the importance of cognitive function in schizophrenia. Cognitive impairment can not only predict the progression of the disease but also affect the treatment response and functional outcomes. Therefore, understanding the factors that contribute to cognitive impairment in schizophrenia is crucial for improving patient outcomes. Gut microbiota, a complex ecosystem of microorganisms residing in the gastrointestinal tract, has been found to play a role in regulating immune and inflammatory responses, as well as influencing neural development. Emerging evidence has suggested a potential connection between gut microbiota and psychiatric disorders, including schizophrenia. However, the specific relationship between gut microbiota and cognitive impairment in schizophrenia patients remains limited and requires further exploration.

Research motivation

Recent research has suggested a potential link between gut microbiota and psychiatric disorders, including schizophrenia. However, the specific relationship between gut microbiota and cognitive impairment in schizophrenia remains poorly understood. This knowledge gap necessitates further investigation to explore the potential role of gut microbiota in the cognitive dysfunction observed in schizophrenia.

The motivation behind this study is to bridge this gap by investigating the correlation between cognitive impairment and gut microbiota imbalance in patients with schizophrenia. By examining the composition of gut microbiota and evaluating cognitive function in a large sample of untreated schizophrenia patients, we aimed to shed light on the potential mechanisms underlying cognitive dysfunction in this population.

The findings of this study provide significant clinical implications and contribute to the development of novel therapeutic strategies targeting the gut microbiota to improve cognitive outcomes of patients with schizophrenia. Ultimately, this research aims to enhance the understanding of the complex interplay between gut microbiota and cognitive impairment in schizophrenia, leading to improved diagnosis, treatment, and overall management of this mental disorder.

Research objectives

The objective of this research was to explore the correlation between cognitive impairment and gut microbiota imbalance in patients with schizophrenia. The study compared the composition and abundance of gut microbiota in untreated schizophrenia patients and healthy controls, evaluated cognitive function using a consensus version of the cognitive function test package, and examined the relationship between specific microbial groups and cognitive function.

Research methods

The research employed a case-control study design. A total of 498 untreated schizophrenia patients admitted to the

hospital from July 2020 to July 2022 were selected as the case group, while 498 healthy volunteers who underwent physical examinations at the same hospital during the same period served as the control group. The composition and abundance of gut microbiota were assessed using fluorescence *in situ* hybridization to determine the total number of bacteria in fecal samples from both groups. Cognitive function was evaluated using a cognitive function test package consensus version, which assesses various dimensions of cognitive function. Statistical analysis was performed to compare the relative abundance of actinomycetes and other microbial groups between the case and control groups, as well as to examine the relationship between specific gut microbiota and cognitive function. The statistical significance level was set at $P < 0.05$.

Research results

The research findings revealed the correlation between gut microbiota and cognitive function in patients with schizophrenia. There was a statistically significant difference in the relative abundance of Actinomycetota between the case group and the control group, indicating an imbalance in the gut microbiota of schizophrenia patients. Moreover, compared to the control group, the schizophrenia patients demonstrated statistically significant differences in scores related to attention/alertness, and learning ability, suggesting impaired cognitive function in these areas. Furthermore, specific microbial groups showed correlations with cognitive function: Actinomycetota, Bacteroidota, Fusobacteria, and Proteobacteria were found to be positively associated with cognitive function, while the Coriobacteriia showed a negative correlation. These findings provide evidence of the influence of gut microbiota on cognitive impairment in schizophrenia patients and underscore the importance of addressing gut microbiota imbalance as a potential therapeutic target for improving cognitive outcomes in this population.

Research conclusions

In conclusion, this research confirmed a relationship between gut microbiota metabolic imbalance and cognitive function in patients with schizophrenia. The study findings indicate that when there is an imbalance in the composition of gut microbiota, the cognitive function of schizophrenia patients is more severely affected. The relative abundance of Actinomycetota was found to significantly differ between the case group and the control group, suggesting an imbalance in gut microbiota in schizophrenia patients. Additionally, specific microbial groups, including Actinomycetota, Bacteroidota, Fusobacteria, and Proteobacteria, were positively correlated with cognitive function, while the Coriobacteriia showed a negative correlation. These results emphasize the importance of addressing gut microbiota imbalances as a potential target for improving cognitive impairment in schizophrenia patients. Further research and interventions focused on modulating gut microbial composition and promoting gut health may lead to improved cognitive outcomes in this population.

Research perspectives

In future research, it is recommended to conduct longitudinal studies to observe changes in gut microbiota and cognitive function over time in schizophrenia patients, as well as intervention studies to investigate the effects of modulating gut microbiota on cognitive outcomes. Mechanistic studies can provide insights into the underlying mechanisms of the gut-brain axis in schizophrenia. The identification of specific gut microbiota markers as diagnostic or prognostic biomarkers for cognitive impairment, exploring individual differences, and developing personalized therapeutic strategies are also important areas for further investigation. By pursuing these research perspectives, we can advance our understanding of the role of gut microbiota in schizophrenia-related cognitive impairment and potentially develop targeted interventions to improve cognitive outcomes in this population.

FOOTNOTES

Author contributions: Ma J and Song XQ designed the study; Ma J wrote the manuscript; Ma J and Song XQ collected and analyzed the data; Ma J and Song XQ revised and reviewed the manuscript; All authors have read and approved the final manuscript.

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