ISSN 2220-3206 (online)

World Journal of *Psychiatry*

World J Psychiatry 2023 May 19; 13(5): 131-261

Published by Baishideng Publishing Group Inc

World Journal of Psychiatry

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Monthly Volume 13 Number 5 May 19, 2023

SYSTEMATIC REVIEWS

World Journal of Psychiatry

Monthly Volume 13 Number 5 May 19, 2023

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RESPONSIBLE EDITORS FOR THIS ISSUE

NAME OF JOURNAL

World Journal of Psychiatry

ISSN

ISSN 2220-3206 (online)

LAUNCH DATE

December 31, 2011

FREQUENCY

Monthly

EDITORS-IN-CHIEF

Rajesh R Tampi, Ting-Shao Zhu, Panteleimon Giannakopoulos

EDITORIAL BOARD MEMBERS

https://www.wjgnet.com/2220-3206/editorialboard.htm

PUBLICATION DATE

May 19, 2023

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https://www.wjgnet.com/bpg/gerinfo/242

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World Journal of Psychiatry

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World J Psychiatry 2023 May 19; 13(5): 131-137

DOI: 10.5498/wjp.v13.i5.131

ISSN 2220-3206 (online)

EDITORIAL

Catatonia: "Fluctuat nec mergitur"

Gabor S Ungvari, Stanley N Caroff, Levente Csihi, Gábor Gazdag

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Jaimes-Albornoz W, Spain; Kar SK, India; Sahoo S, India

Received: January 21, 2023
Peer-review started: January 21, 2023
First decision: January 31, 2023
Revised: February 2, 2023
Accepted: April 17, 2023
Article in press: April 17, 2023
Published online: May 19, 2023

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Abstract

In the beginning of the 1900s, the prevalence of catatonia in inpatient samples was reported to be between 19.5% and 50%. From the mid-1900s, most clinicians thought that catatonia was disappearing. Advances in medical sciences, particularly in the field of neurology, may have reduced the incidence of neurological diseases that present with catatonic features or mitigated their severity. More active pharmacological and psychosocial treatment methods may have either eliminated or moderated catatonic phenomena. Moreover, the relatively narrow descriptive features in modern classifications compared with classical texts and ascribing catatonic signs and symptoms to antipsychotic-induced motor symptoms may have contributed to an apparent decline in the incidence of catatonia. The application of catatonia rating scales introduced in the 1990s revealed significantly more symptoms than routine clinical interviews, and within a few years, the notion of the disappearance of catatonia gave way to its unexpected resurgence. Several systematic investigations have found that, on average, 10% of acute psychotic patients present with catatonic features. In this editorial, the changes in the incidence of catatonia and the possible underlying causes are reviewed.

Key Words: Catatonia; Historical overview; Frequency of catatonia; Diagnostic and Statistical Manual of Mental Disorders-5; Wernicke–Kleist-Leonhard school; Bush-Francis Catatonia Rating Scale

Core Tip: Although the prevalence of catatonia was reported to be between 19.5% and 50% in the early 1900s, most clinicians thought that catatonia was disappearing by mid-century, However, more recent systematic investigations have found that catatonia continues to be a common clinical disorder with an average prevalence of 10%. The apparent historical changes in the prevalence of catatonia reflects shifts in the socio-cultural context of psychiatry, the type of service, diagnostic criteria, research methods, and advances in treatment and clinical practice. We propose the establishment of an international society and journal dedicated to the study of catatonia to facilitate understanding and research.

Citation: Ungvari GS, Caroff SN, Csihi L, Gazdag G. Catatonia: "Fluctuat nec mergitur". *World J Psychiatry* 2023; 13(5): 131-137
URL: https://www.wjgnet.com/2220-3206/full/v13/i5/131.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i5.131

INTRODUCTION

During most of the last century, in line with the prevailing Kraepelinian tradition, catatonia essentially was used to refer to catatonic schizophrenia, although a careful reading of Kraepelin's textbook shows a more sophisticated view of catatonia[1-4]. In the two authoritative classical textbooks, the prevalence of catatonia in inpatient samples is reported to be between 19.5%[1] and 50%[5], whereas it was 35.4% according to the Wernicke–Kleist–Leonhard school[6]. However, from the mid-1900s, there was a growing consensus among clinicians that catatonia was becoming nearly extinct, as Mahendra[7] famously asked, "Where have all the catatonics gone?". Such clinical impressions were supported by a few, although not all[8,9], epidemiological studies that attempted the nearly impossible task of determining the changes in the real prevalence of catatonia across several years or decades against the background of shifts in the socio-cultural context of psychiatry, the type of service (inpatient, outpatient, and community), diagnostic criteria, research methods, and advances in treatment and clinical practice in general.

DISCUSSION

Relatively comparable, albeit not necessarily reliable, rough estimates of the changes in the frequency of catatonia can be made by focusing on single sites when comparing two time periods. For example, between 1850 and 1950, the rate of first admissions for catatonia decreased from 6% to 0.5% in the Bethlem royal hospital, a leading hospital and academic center in London, United Kingdom[10]. Another example from Finland showed a decline in the frequency of admissions for catatonic schizophrenia from 40.1% to 11% over just 20 years from 1933–1935 to 1953-1955[11]. In two Polish hospitals, where catatonia was diagnosed very conservatively, the frequency of catatonic schizophrenia diagnoses decreased 190-fold from 1924–1929 to 1994–1999 and 36-fold from 1958–1963 to 1994–1999[12]. From 1964 to 1984, catatonic schizophrenia nearly disappeared entirely in a university hospital in Santiago, Chile[13]. In a Belgian academic center, based on a chart review of 19309 admissions, the diagnosis of catatonic schizophrenia decreased from 7.8% to 1.3% in the two consecutive decades of 1980–1989 and 1990–2000[14].

Several plausible reasons have been proposed for the decline in the rate of catatonia observed in the second part of the last century. Advances in medical sciences, particularly in the field of neurology, may have reduced the incidence of neurological diseases that present with catatonic features or mitigated their severity[7]. More active pharmacological and psychosocial treatment methods may have either eliminated or moderated catatonic phenomena. Moreover, the relatively narrow descriptive features in modern classifications compared with classical texts and ascribing catatonic signs and symptoms to antipsychotic-induced motor symptoms may have contributed to the reduced incidence of catatonia[15, 16]. The application of catatonia rating scales introduced in the 1990s[17] revealed significantly more symptoms than routine clinical interview, suggesting that insufficient diagnostic practices were responsible for the under-recognition of catatonia[14].

From the 1990s, the situation changed, and within a few years, the notion of the disappearance of catatonia gave way to its unexpected resurgence[18,19] (Figure 1). Several systematic investigations have found that, on average, 10% of acute psychotic patients present with catatonic features[20], with a wide range of frequencies from 1% in Nigeria[21], 3.7% in Mexico[22] to 38% in Greece[23], 50% in Belgium[24] and 68% in the United States[25]. The corresponding figures reached 20% for depression [26], 31% for mania[27], and almost 100% for the chronically hospitalized psychotic population[28]. Awareness has also broadened to encompass catatonia occurring in the context of general medical conditions[16,18]. Since the 1990s, interest in the epidemiological[16], clinical[29,30] and neurobiological [31,32] aspects of catatonia has continued unabated, stimulated by its semi-independent place in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition[33,34] and in addition to secondary catatonia occurring in the context a wide range of psychiatric and medical conditions also appeared as an independent diagnostic category in the International Classification of Diseases, 11th revision[35].

The apparent disappearance of catatonia from psychiatric practice and research for decades and its recent re-discovery raises serious questions. The intriguing fact is that a well-known and easily observable motor phenomena, which has been reported in such a high proportion in acute psychiatric admissions over the past two decades, was declared to be essentially extinct for approximately four decades in the second part of the last century. The logical argument is that, if catatonia had temporarily become extinct, there must have been a very significant environmental and/or neurobiological change responsible for this, which went unnoticed for a while and then stopped. However, there has been no suggestion that such panoramic environmental or biological changes affecting motor symptoms in psychiatric patients have occurred. However, if catatonia did not actually disappear, which is the likely scenario, the question remains how mainstream psychiatry missed an important aspect of mental disorders for decades. A possible answer to this puzzling question may provide important information about the nature of catatonia and psychiatric diagnostic practice. However, this is a complex issue and reaching a firm conclusion is unlikely as the available studies on catatonia are fraught with major methodological flaws that make it difficult to make comparisons between studies across time[16].

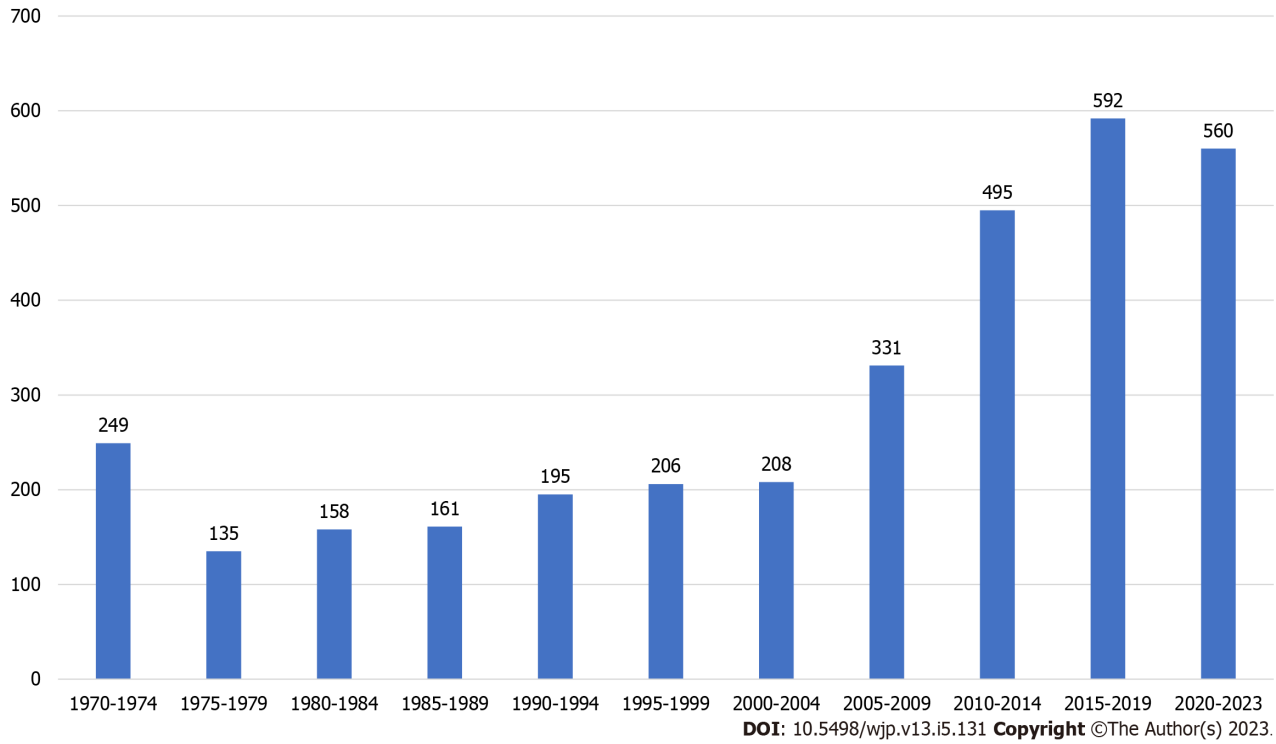
We posit that catatonia may have been modified in its manifestations and may have lessened in intensity and frequency due to advances in treatment of schizophrenia and mood disorders, but never disappeared entirely[15]. Rather, it was not given adequate attention by clinicians, particularly in the internationally dominant Anglo-American psychiatry with pockets of exceptions in Europe, such as at the Wernicke–Kleist-Leonhard school of psychiatry[6,36]. There are also indications that catatonia never disappeared in developing countries[37], but has occurred at a similar or even higher frequency and severity to those in Western settings[38] albeit possibly with a different symptom profile[39]. Over the past three decades, several Indian studies examined the phenomenology[40,41] and the frequency of catatonia in acute inpatient admissions that ranged from 4.8%[40] to 10.3%[41], 16.3%[42] and 37.2%[43].

In the following section, we outline some of the factors that support our view that the disappearance of catatonia was apparent, but not real. From a broader perspective, the temporary disappearance of catatonia in psychiatric research and practice during the middle decades of the 20th century is the logical consequence of the development of psychiatry in the last century.

In the second part of the 20th century, the whole fabric of psychiatric practice moved away from traditional stand-alone institutions that existed at the fringes of society to a more community and office-based model focused on outpatient therapy. From the 1920s, psychodynamic psychiatry, based on psychoanalysis and its versions, had an increasingly large impact on mainstream psychiatry, mainly in the United States and to a lesser degree in other Western countries, although isolated examples of biologically-oriented descriptive psychiatry, such as the Wernicke–Kleist–Leonhard school or French neuropsychiatry[44] never ceased to exist in continental Europe. As psychodynamic psychiatry focuses on the inner psychic life of the patients and not the observation of patients' manifest behavior or motor symptoms, catatonia lost its significance in English-language psychiatry, and its signs and symptoms were glossed over in diagnostic practice.

Diagnostic practices have also undergone profound changes from the 1960s with the introduction of objective rating scales[45] and then operationalized diagnostic criteria in the 1970s[46]. The original psychopathological descriptions, including those for catatonia, were made by psychiatrists who had the opportunity to observe their patients every day in different situations over several weeks, months, or years. Many of these psychiatrists actually lived in the institutions and had fewer commitments outside of their clinical work than their modern counterparts. The democratization and decentralization of psychiatric practice, coupled with the widespread introduction of simplified cross-sectional diagnosis, as in the Diagnostic and Statistical Manual of Mental Disorders third edition[47], greatly altered the relationship between patients and psychiatrists and the diagnostic process.

In the developed world, this situation emerged starting in the 1960s with the arrival of de-institutionalization; the establishment of short-term acute psychiatric wards in general hospitals; community outpatient psychiatry evolving to brief 15-min "med checks"; and the collaborative role of allied mental health professionals providing psychiatric services, just to mention a few important factors. As a result, psychiatrists began spending less and less time in direct contact with their patients in the modern era, which may have reduced the likelihood of detecting catatonic symptoms. For instance, restructuring a regional psychiatric service in the United Kingdom resulted in psychiatrists having access to "less than 20% of the total case-load"[48].



DOI: 10.5498/wjp.v13.i5.131

Figure 1 Published articles on catatonia based on PubMed broken down by 5 years.

Another aspect of contemporary psychiatric practice that may have hindered the easy detection of catatonia is exemplified by a landmark study conducted at the Institute of Psychiatry in London, one of the leading academic psychiatric centers in the world that have provided the scientific foundation to sanction diagnostic practices in the modern era[49]. In a series of diagnostic exercises, 28 psychiatrists with at least 4 years of clinical experience were asked to diagnose patients during the same 5-min diagnostic interviews based on either a video of the patients during the interview, a soundtrack recording of the interview, or only written transcripts. Surprisingly, the diagnostic accuracy measured against the final hospital discharge diagnoses was essentially identical in these three different diagnostic situations. Kendell came to the important conclusion that observing the patients' behavior did not improve diagnostic accuracy, indicating that behavioral or motor symptoms had no, or negligible, currency in the diagnostic process although this academic center stressed the importance of behavioral symptoms and careful observations. Kendell also found that diagnostic accuracy did not increase after 4 years spent in psychiatric practice, thereby questioning the value of accumulated experience and the power of observation developed during this experience in making a diagnosis. Furthermore, based on the diagnostic accuracy of 70% reached after 5 min in each rating situation, the author suggested significantly shortening the standard 1-hour diagnostic interview. The implications of these findings on the under-recognition of catatonia are obvious.

It is well known from classical textbooks that the frequency and intensity of catatonic episodes fluctuate over time[1,5,6] and that they may not manifest at the time of cross-sectional assessment, which is how modern catatonia rating scales are conducted, resulting in a potential failure to detect the whole scope of catatonic symptomatology, particularly in chronically ill patients. For example, the Bush–Francis Catatonia Rating Scale (BFCRS)[17], the most widely used rating instrument, requires only 5–10 min to complete, although raters are encouraged to consult their medical notes covering the previous 24-h period, albeit only for the items of "withdrawal" and "autonomic abnormality." The BFCRS has been shown to be adequate for assessing acute catatonic episodes[17], but it may not be entirely sufficient for persistent or periodic catatonia in patients with chronic illness[50], as previously suggested[51]. A study comparing the number and severity of catatonic signs and symptoms covered by the BFCRS, rated by skilled clinicians, with the "gold standard" of extended, unobtrusive observations by an experienced clinician found that the latter method yielded significantly higher ratings[52]. Signs and symptoms that were most frequently missed by cross-sectional assessment, but captured by longitudinal clinical observations were mannerisms, stereotypy, grimacing, perseveration, and apparently purposeless impulsivity[52].

Following the widespread introduction of antipsychotic drugs in psychiatric practice in the mid-1950s, it took about a decade to recognize the full spectrum and significance of drug-induced motor symptoms and syndromes referred to as extrapyramidal side effects (EPS). The importance of EPS in psychiatry may have overshadowed catatonic and other illness-related motor symptoms in clinical practice. Catatonic signs and symptoms may have been obscured by and ascribed to drug-induced EPS

[15]. EPS-like motor symptoms have been consistently reported in drug-naïve patients since the 1990s, raising the possibility that, in many instances, catatonia may have been indeed misdiagnosed as EPS [53]. Even if this were not the case, the recognition of motor symptoms in drug-naïve patients helped refocus attention to catatonia.

CONCLUSION

We believe that the growing number of publications on catatonia and the number of clinicians and researchers displaying a keen interest in this subject have reached the level that warrants the establishment of an international society and a journal dedicated to the study of catatonia, to bring together interested parties, promote and coordinate research, and disseminate relevant knowledge to the broader mental health community. This may be one the avenues to further facilitate a greater understanding of catatonia, thereby improving the lives of patients with catatonia.

FOOTNOTES

Author contributions: Gazdag G and Ungvari GS outlined the content of the editorial; Ungvari GS prepared the first draft of the manuscript, Caroff SN, Csihi L and Gazdag G critically reviewed and corrected the manuscript; All authors approved the final version of the text.

Conflict-of-interest statement: Dr. Caroff received research grants for unrelated projects from Neurocrine Biosciences and Eagle Pharmaceuticals and served as consultant for Neurocrine Biosciences and Adamas Pharmaceuticals. The other authors have no declarations of interest to report.

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S-Editor: Li L
L-Editor: A
P-Editor: Zhao S

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World Journal of Psychiatry

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World J Psychiatry 2023 May 19; 13(5): 138-143

DOI: 10.5498/wjp.v13.i5.138

ISSN 2220-3206 (online)

OPINION REVIEW

Differences between DSM-5-TR and ICD-11 revisions of attention deficit/hyperactivity disorder: A commentary on implications and opportunities

Rapson Gomez, Wai Chen, Stephen Houghton

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Hosak L, Czech Republic; Jiménez DR, Spain; Wang DJ, China

Received: December 16, 2022
Peer-review started: December 16, 2022
First decision: February 20, 2023
Revised: March 2, 2023
Accepted: April 18, 2023
Article in press: April 18, 2023
Published online: May 19, 2023

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Abstract

Current ICD-11 descriptions for attention deficit hyperactivity disorder (ADHD) were recently published online, in the same year as the DSM-5-TR (text revised edition) was released. In this commentary, we compare and contrast the DSM-5/DSM-5-TR and ICD-11 diagnostic criteria, summarize important differences, and underscore their clinical and research implications. Overall, three major differences emerge: (1) The number of diagnostic criteria for inattention (IA), hyperactivity (HY) and impulsivity (IM) symptoms (*i.e.*, DSM-5-TR has nine IA and nine HY/IM symptoms, whereas ICD-11 has eleven IA and eleven HY/IM symptoms); (2) the clarity and standardization of diagnostic thresholds (*i.e.*, the diagnostic thresholds for symptom count in IA and HY/IM domains are explicitly specified in DSM-5-TR, whereas in ICD-11 they are not); and (3) the partitioning of HY and IM symptoms into sub-dimensions (*i.e.*, difference in partitioning HY and IM symptom domains relates to the differences between the current and previous editions of DSM and ICD, and this has important research implications). Currently, no ICD-11 based ADHD rating scales exist and while this absence represents an obstacle for respective research and clinical practice, it also presents opportunities for research development. This article highlights these challenges, possible remedies and novel research opportunities.

Key Words: Attention deficit hyperactivity disorder; ICD-11; DSM-5-TR; Clinical implication; Diagnostic threshold; Taxonomy; Research

Core Tip: Three major differences between DSM-5-TR and ICD-11 are: (1) The number of diagnostic criteria for inattention, hyperactivity (HY) and impulsivity (IM) symptoms; (2) the clarity and standardization of diagnostic thresholds; and (3) the partitioning of HY and IM symptoms into sub-dimensions between previous and current editions of DSM and ICD. Currently, no ICD-11 based attention deficit hyperactivity disorder (ADHD) rating scales exist. The absence of research evidence to inform and reconcile these differences represents opportunities for research. Emerging research findings suggest that 'impulsivity' is likely the key latent factor underlying different expressions of ADHD symptoms; and the current criteria merging HY/IM could limit such explorations.

Citation: Gomez R, Chen W, Houghton S. Differences between DSM-5-TR and ICD-11 revisions of attention deficit/hyperactivity disorder: A commentary on implications and opportunities. *World J Psychiatry* 2023; 13(5): 138-143
URL: https://www.wjgnet.com/2220-3206/full/v13/i5/138.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i5.138

INTRODUCTION

ICD-11 descriptions for attention deficit hyperactivity disorder (ADHD) were recently published online [1]. In addition, the DSM-5-TR[2] was published in print along with a more extended digital e-edition version. While there is greater alignment between ICD-11 and DSM-5-TR, there are nevertheless differences (albeit subtle in parts), which entail important implications for research and clinical application. This commentary paper critically distils and articulates these differences (particularly diagnostic symptoms and symptom threshold for diagnosis). As no revisions were made to the diagnostic criteria of ADHD in DSM-5-TR, the remainder of this commentary refers to DSM-5-TR instead of 'DSM-5' or 'DSM-5 and DSM-5-TR', unless otherwise specified. A more severe variant of ADHD is called hyperkinetic disorder (HKD) in ICD-10[3]. The symptom compositions for HKD in ICD-10 are comparable with the 'combined presentation' of ADHD in DSM-5-TR, but not the 'predominantly inattentive' or 'predominantly hyperactive-impulsive' presentations. The ICD-11 revision of ADHD is now more aligned with DSM-5-TR, by including less severe presentations/types other than HKD.

With reference to DSM and ICD comparisons, we first summarize the major differences between DSM-5/DSM-5-TR and ICD-11 diagnostic criteria. The implications of these differences for clinical practice and research are then discussed. To place our discussion in context, we present first a summary of DSM-5-TR and ICD-11 and compare them. By undertaking this commentary we seek to facilitate a deeper understanding and appreciation of these different, but related, classification systems, and how they contribute to better research and clinical practice.

Summary of DSM-5-TR and ICD-11

Table 1 provides a summary of DSM-5-TR and ICD-11 diagnostic criteria for ADHD in relation to their descriptions, onset, presentation patterns, and symptom criteria, with regards to settings, duration and impairment. As can be seen in Table 1, while there is much alignment between ICD-11 and DSM-5-TR, important differences exist, especially in terms of symptom composition and criteria. We will focus on these in the next section.

MAJOR DIFFERENCES BETWEEN DSM-5-TR AND ICD-11

There are at least four major differences between DSM-5-TR and ICD-11 and their previous editions that are noteworthy of consideration.

Difference in splitting one inattentive symptom criterion

First, in contrast to DSM-5-TR which lists nine inattention (IA) symptoms, ICD-11 has 11 IA symptoms. The specific DSM-5-TR IA symptom for "Often fails to give close attention to details or makes careless mistakes in schoolwork, at work, or with other activities" is split into two separate IA symptoms in ICD-11: "Lacking attention to detail", and "Making careless mistakes in school or work assignments". This gives rise to the first extra symptom.

Additional IA and hyperactivity/IMP symptoms in ICD-11

In addition, the specific DSM-5-TR IA symptom "Is often forgetful in daily activities" is also partitioned into two separate similar IA symptoms in ICD-11: "Is forgetful in daily activities" and "Has difficulty remembering to complete upcoming daily tasks or activities". This gives rise to the second extra

Table 1 Comparison of DSM-5-TR and ICD-11 diagnostic criteria for attention-deficit/hyperactivity disorder

	DSM-5-TR	ICD-11
Name	ADHD	ADHD
Onset	Some symptoms present before 12 yr	Some symptoms present before 12 yr
Symptoms	9 IA symptoms	11 or 9 IA symptoms
	9 HY/IM symptoms	11 or 10 HY/IM symptoms
Presentation types/symptom criteria for children	(1) ADHD combined: At least 6 IA and 6 HY/IM symptoms; (2) ADHD predominantly inattentive: At least 6 IA symptoms; and (3) ADHD predominantly hyperactive/impulsive: At least 6 HY/IM symptoms	(1) ADHD combined: IA and HY/IM symptoms present with neither predominating; (2) ADHD predominantly inattentive: IA symptoms predominating; and (3) ADHD predominantly hyperactive/impulsive: HY/IM symptoms predominating
Presentation types/symptom criteria for persons aged ≥ 17	(1) ADHD combined: At least 5 IA and 5 HY/IM symptoms; (2) ADHD predominantly inattentive: at least 5 IA symptoms; and (3) ADHD predominantly hyperactive/impulsive: At least 5 HY/IM symptoms	
Settings	Present in at least 2 settings	Multiple settings–but symptoms may vary according to the structure and demands of the setting
Duration	≥ 6 mo	≥ 6 mo
Impairment	Social, academic, or occupational functioning	Social, academic, or occupational functioning–IA symptoms less evident in stimulating and rewarding activities and HY/IM during free-play

ADHD: Attention deficit hyperactivity disorder; IA: Inattention; HY: Hyperactivity; IM: Impulsivity.

symptom. A new IA symptom for ICD-11, not present in DSM-5-TR, is "Frequently appears to be daydreaming or to have mind elsewhere". This is the third extra symptom. However, this symptom could be regarded as being more in line with the "sluggish cognitive tempo (SCT)" symptom when considered in light of the SCT literature[4]. In addition, the specific DSM-5-TR IA symptom "Often has trouble holding attention on tasks or play activities" is not present in ICD-11.

With reference to hyperactivity (HY)/impulsivity (IM) symptoms, ICD-11 lists 10. Two of these relate to overactive behavior: "Has difficulty sitting still without fidgeting" and "Feelings of physical restlessness, a sense of discomfort with being quiet or sitting still". ICD-11 specifies that the former be applied to younger children, and the latter be applied to adolescents and adults (*i.e.*, age 17 years or older). These can be regarded as developmental variants of the same symptom. For this reason, there are in reality 10 HY/IM symptoms in ICD-11. The symptom of "is often 'on the go', acting as if 'driven by a motor….' experienced by others as being restless…" in DSM-5-TR is absent in ICD-11; however, this could potentially be comparable to 'feelings of physical restlessness' in ICD-11. A new HY/IM symptom in ICD-11, which is absent in DSM-5-TR, is "A tendency to act in response to immediate stimuli without deliberation or consideration of risks and consequences (*e.g.*, engaging in behaviors with potential for physical injury; impulsive decisions; reckless driving)". This symptom captures the classical description of dispositional trait IM. In contrast, in DSM-5-TR, IM is solely represented by three directly observable behavioral symptoms (*i.e.*, 'blurt out', 'can't wait' and 'interrupt'), as an absence of deliberation or risk consideration that cannot be directly observed, but often only inferred or disclosed by the actor upon retrospective reflection.

In summary, DSM-5-TR has nine IA and nine HY/IM symptoms, whereas ICD-11 has 11 IA and 11 HY/IM symptoms (but 10 if 'fidgeting' in children and 'mental restlessness' in adults are combined as one).

Differences in partitioning of HY and IM symptom sub-dimensions

The third difference relates to previous and current editions of DSM and ICD. Specifically, whether HY and IM symptoms should be considered as separate dimensions by contrasting DSM-IV-TR[5] with DSM-5-TR, and by contrasting ICD-10 with ICD-11. Currently, in DSM-5-TR, HY and IM symptoms are considered to represent a single dimension regarding threshold for diagnosis. This means an adult will meet diagnostic threshold of the HY/IM domain regardless of whether they have HY or IM symptoms. The HY/IM threshold can be met by two different adults: One with five HY symptoms and another with mixed two HY symptoms and 3 IM symptoms. Although ICD-11 also groups HY and IM as a single dimension, diagnostic thresholds are not specified for either children or adults.

In the previous DSM-IV-TR edition, symptoms were listed separately under HY and IM subheadings. Likewise, ICD-10 contemporaneous with DSM-IV-TR also considered them separately, but with 'talkativeness' listed within the IM grouping. By applying the ICD-10 framework, it can be postulated that out of the 10 ICD-11 HY/IM symptoms, five symptoms are HY ('motor activity', 'leaving seat', 'running

about', 'difficulty setting still'/'physical restlessness', and 'difficulty in not engaging in activity quietly'), while the other five symptoms ('talkativeness', 'blurt out', 'can't wait', 'interrupt', and 'immediate response without considering consequences') are IM symptoms. Recent empirical findings from factor analytic studies provide support that HY and IM symptoms should be grouped separately, and that 'talkativeness' should be grouped with IM rather than HY in line with ICD-10 configuration[6,7].

Differences in clarity and standardization of diagnostic thresholds

Fourth, the diagnostic thresholds for symptom count in IA and HY/IM domains are explicitly specified in DSM-5-TR (*i.e.*, six for each domain for children and five for each domain for adolescents/adults aged 17 or above), whereas in ICD-11 they are not.

Noting that ADHD symptoms may vary with developmental age and ADHD severity, ICD-11 states that "several symptoms" from the IA and HY/IM clusters need to be present. This approach is however consistent with the general approach used by ICD-11[8], in order to avoid arbitrary cutoffs related to symptom counts and duration; and as such, terms such as "several days", "several weeks", and "several symptoms" are used in ICD-11.

The approach used by ICD-11 is considered to be more in line with how clinicians actually make diagnoses, allowing more flexibility in exercising clinical judgment and avoiding algorithmic requirements (regarded by some as 'pseudo-precision'), such as a prescribed threshold of symptom counts. This flexibility is an innovative feature in ICD-11, and is more consistent with the dimensional classification[8]. However guidelines on how to establish thresholds are not provided in ICD-11. Therefore, when using ICD-11, the onus is placed on individual clinicians to apply their own judgement in determining clinical thresholds. The potential problems with this approach include diagnostic difficulty (especially for less experienced clinicians) and the increased heterogeneity of ADHD above and beyond that yielded by the DSM-5-TR defined ADHD diagnostic criteria.

IMPLICATIONS OF THE DIFFERENCES BETWEEN DSM-5/DSM-5-TR AND ICD-11 FOR RESEARCH AND CLINICAL PRACTICE

With reference to ADHD diagnostic criteria, the differences related to the number of criteria, the thresholds for ADHD diagnosis, and whether the HY and IM symptom groups are merged or grouped separately have a number of implications for clinical practice and research.

First, in relation to clinical practice, as mentioned previously, the thresholds for the different symptom domains are unspecified in ICD-11, thereby increasing the likelihood of greater diagnostic heterogeneity. Greater standardization generally improves diagnostic reliability, but this prescribed algorithmic approach is not adopted by ICD-11 per se; in contrast, ICD-11 prefers the dimensional approach. In this respect, we suggest that until clearer guidance from ICD-11 and its future revision is forthcoming, researchers using ICD-11 should be cognizant of providing very detailed descriptions of the samples (including symptom count) examined in their studies. Moreover, it is anticipated that ICD-11 will in due course release its Clinical Descriptions and Diagnostic Guidelines (CDDG). These will likely provide more operationalized diagnostic guidance for clinicians and researchers, and with more than a decade of work invested in their development[8], be 'designed to assist mental health clinicians in making a confident diagnosis'. We therefore highly recommend readers to access and study in detail the ICD-11 CDDG for more information, when it becomes available.

Secondly, for DSM-5/DSM-5-TR, questions have been raised about whether the proposed/implied two-factors (*i.e.*, IA and HY/IM dimensions) is the optimum structural model. This is because many studies that have compared different latent structural models of ADHD have reported less support for the two-factor model than for three-factor models (especially IA, HY and IM factors aligned to ICD-10 [3]. Relatedly, recent studies[7,9] have provided empirical support for the S-1 bifactor model to account for the latent factor structure of ADHD. That is, ADHD is likely a disorder predominantly driven by latent IM substrates[7] in line with the 'trait impulsivity hypothesis'[10]. In this S-1 bifactor model, 'impulsivity' is best represented by four ICD-10 IM items ('talkativeness', 'blurt out', 'can't wait' and 'interrupts') in line with the ICD-10 configuration, rather than the DSM-5-TR three IM items ('blurt out', 'can't wait' and 'interrupts'). A consistent finding in these studies is that the HY factor is poorly defined (insignificant and/or negative loadings) and lacks reliability (omega coefficient levels below 0.50). Therefore HY is observable in individuals with ADHD, the relevance of HY for ADHD at the latent trait levels is questionable.

These considerations have important research implications that can potentially be compromised by the current ICD-11 and DSM-5-TR definitions. At present we lack knowledge about the psychometric properties of ICD-11 ADHD symptoms, and therefore need to use caution when using ICD-11 for clinical practice relating to ADHD. Indeed, for this reason, some in clinical practice may question the present clinical utility of ICD-11, until greater clarity emerges.

Thirdly, the differences indicate that existing measures, such as DSM-5 based ADHD ratings scales, may not be appropriate for ICD-11 defined ADHD assessment, and that there is a need to develop new ADHD rating scales based on ICD-11. The absence of ICD-11 based rating scales for ADHD can be

considered an important obstacle for research and clinical practice using ICD-11. However, as a temporary solution, researchers could utilize the listed criteria as defined by ICD-11. Notwithstanding this, the absence of a validated ICD-11 defined rating scale, or a measurement instrument or semi-structured diagnostic tool to capture the full range of ICD-11 symptom criteria, provides opportunities for researchers to construct appropriate measures with empirically derived reliability and validity. This is important as the identification of the underlying structure will be determined not only by the clinical elements, but also by the scope of the tools that are used in its recognition. The absence of thresholds for the IA and HY/IM symptom groups in ICD-11 means that for clinicians who still wish to use ICD-11 for clinical diagnosis of ADHD, the onus is placed upon them to use their own cut-off scores to establish clinical caseness. This approach is likely to reduce inter-rater and test-retest reliability, thereby increasing the heterogeneity of ADHD beyond what we currently observe when DSM-5 ADHD diagnostic criteria are applied. Additionally, such a scenario would limit the comparability of findings across studies in which the diagnostic caseness is based on ICD-11. It is also conceivable that the failures of DSM-5-TR and ICD-11 in classifying and partitioning HY/IM symptoms into respective HY and IM subdimensions will dissuade researchers from further exploring the three-factor structure of ADHD (*i.e.* IA, HY and IM three subdimensions), or the S-1 bifactor modelling in which different patterns of partitioning HY and IM symptoms are evaluated[7].

Another issue relevant to research and clinical practice here is biomarkers. The World Federation of Societies of Biological Psychiatry and the World Federation of ADHD previously concluded that there is still no reliable biomarker for ADHD[11]. Nevertheless potential promising candidates should be further explored[12,13]. When the roles of different biological markers become established, they may play a role in improving diagnostic precision and reducing heterogeneity, and may contribute towards differentiating the validity and utility of DSM-5-TR and ICD-11 with respect to their differences as identified in this review.

CONCLUSION

In this commentary, we have articulated the differences in diagnostic criteria of ADHD between DSM-5-TR and ICD-11 and the implications of these differences for clinical practice and research. The major differences were noted in symptom composition and diagnostic thresholds for the IA and HY/IM domains. The clinical and research implications of these include: (1) The current lack of rating scales and measurement tools to capture the full spectrum of ICD-11 symptom items; and (2) the lack of standardized diagnostic threshold for the IA and HY/IM symptom domains in ICD-11, with ensuing problems for validity, reliability and increased heterogeneity. Moreover, the lack of distinction between HY and IM symptoms run contrary to recent empirical findings and limit future opportunities to explore the three-factor or S-1 bifactor modelling of IA, IM and HY as key components in the latent structure of ADHD. In closing, this commentary seeks to provide clinicians and researchers with a succinct summary of the issues, as well as important insights, regarding the clinical and research implications of the recent changes in DSM-5-TR and/or ICD-11.

FOOTNOTES

Author contributions: Gomez R reviewed the literature and drafted the manuscript; Chen W conceived the idea for the manuscript, reviewed the literature and revised the manuscript; Houghton S reviewed the literature and revised the manuscript.

Conflict-of-interest statement: Nil. Wai Chen served as a reviewer for the DSM-5 Clinical and Public Health Committee during the DSM-5 revision; but this role did not and has not led to any conflict of interest.

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S-Editor: Fan JR
L-Editor: A
P-Editor: Chen YX

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 May 19; 13(5): 144-159

DOI: 10.5498/wjp.v13.i5.144

ISSN 2220-3206 (online)

REVIEW

Resilience by design: How nature, nurture, environment, and microbiome mitigate stress and allostatic load

Souhad Chbeir, Victor Carrión

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Liu XQ, China; Muneoka K, Japan

Received: December 16, 2022
Peer-review started: December 16, 2022
First decision: January 12, 2023
Revised: February 11, 2023
Accepted: April 17, 2023
Article in press: April 17, 2023
Published online: May 19, 2023

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Abstract

Resilience to psychological stress is defined as adaption to challenging life experiences and not the absence of adverse life events. Determinants of resilience include personality traits, genetic/epigenetic modifications of genes involved in the stress response, cognitive and behavioral flexibility, secure attachment with a caregiver, social and community support systems, nutrition and exercise, and alignment of circadian rhythm to the natural light/dark cycle. Therefore, resilience is a dynamic and flexible process that continually evolves by the intersection of different domains in human's life; biological, social, and psychological. The objective of this minireview is to summarize the existing knowledge about the multitude factors and molecular alterations that result from resilience to stress response. Given the multiple contributing factors in building resilience, we set out a goal to identify which factors were most supportive of a causal role by the current literature. We focused on resilience-related molecular alterations resulting from mind-body homeostasis in connection with psychosocial and environmental factors. We conclude that there is no one causal factor that differentiates a resilient person from a vulnerable one. Instead, building resilience requires an intricate network of positive experiences and a healthy lifestyle that contribute to a balanced mind-body connection. Therefore, a holistic approach must be adopted in future research on stress response to address the multiple elements that promote resilience and prevent illnesses and psychopathology related to stress allostatic load.

Key Words: Resilience; Stress; Allostatic load; Epigenetics; Circadian rhythm; Attachment; Oxytocin; Diet; Microbiome; Exercise

Core Tip: There are multiple reviews in the literature that address different factors contributing to resilience, an adaptation to stress. To our knowledge, none of these reviews takes into consideration the complexity of the system that leads to allostasis or allostatic load, an indicator of physiologic "wear and tear" resulting from repeated exposure to stress and inability to cope. The purpose of this review is to shed light on the complexity of the system and discuss the molecular mechanisms that may contribute to resilience. Lastly, we conclude by emphasizing the need for a comprehensive approach to reduce stress allostatic load.

Citation: Chbeir S, Carrión V. Resilience by design: How nature, nurture, environment, and microbiome mitigate stress and allostatic load. *World J Psychiatry* 2023; 13(5): 144-159
URL: https://www.wjgnet.com/2220-3206/full/v13/i5/144.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i5.144

INTRODUCTION

According to the American Psychological Association (APA), "resilience is the process and outcome of successfully adapting to difficult or challenging life experiences, especially through mental, emotional, and behavioral flexibility and adjustment to external and internal demands". Adaptation to adversities depends on several factors: Individual's engagement and view of the world, the availability of social and communal resources, and the use of specific coping strategies (APA, 2022, https://www.apa.org/topics/resilience). It is worth noting that resilience and coping are inter-related but have different constructs with respect to their impact on behavioral changes[1]. While coping manages stressful events by using cognitive and behavioral strategies[2], resilience refers to the adaptive capacity to recover from traumatic or stressful situations[3].

Research in humans over the last two decades has demonstrated that resilience and use of adaptive coping skills in the face of adversity in both children and adults are the main factors that protect from developing mental and physical illnesses. While personal characteristics such as personality traits of persistence and determination, and cognitive flexibility are key elements, perceived parental care, adolescent peer relationships, adult romantic relationships, community support systems, dietary lifestyle, exercise, and circadian rhythm are all implicated in building resilience[4-11]. Resilience is an active adaptive process that helps mitigate negative social, psychological, and biological consequences of extreme stress[12]. The adaptive behavioral manifestations of resilient people are described as enhanced internal locus of control, self-efficacy, happiness, life satisfaction, the ability to derive a sense of life meaning, ability to foster social and communal interactions, and problem-solving skills[13,14].

Fostering resilience early in life may be an effective preventative measure prior to the development of trauma[15]. It is estimated that 60% of men and 50% of women would experience at least one potentially traumatic event in their lifetime, however only 8% of women and 4% in men develop post-traumatic stress disorder (PTSD) (National Center of PTSD, 2022, https://www.ptsd.va.gov/). The development of resilience is an ongoing dynamic process throughout the lifespan in both children and adults, even in those who have suffered from adverse early life experiences, to successfully adapt to or overcome traumatic stress-related illnesses[16,17]. Indeed, resilience can aid in developing positive changes in the aftermath of traumatic events, such as gaining the capacity to relate to others, personal strength, spirituality, and life appreciation[18]. Resilience is implicated in changes in brain regions involved with the social networks that promote empathy, social connectedness, and modulation of central responses to stress[19].

The objective of this review is to summarize the existing knowledge about the multitude factors and molecular alterations that result from resilience to stress response. Our aim is to create awareness for future research studies on allostatic load and stress response about the intricate network contributing to resilience. The methodology we used is Literature Review performed through PubMed, PsycINFO and Scopus databases for peer-reviewed English-language articles published prior to December 2022 using the following keywords: Chronic stress, allostatic load, trauma, biomarkers, circadian rhythm, resilience, neurobiology, genetic, epigenetic, attachment, oxytocin, gut microbiome, diet, mindfulness, exercise, and psychotherapy. We will first describe the existing knowledge about the biologic aspects of the stress response and implications of chronic stress. Then we will present the different factors that contribute to resilience and associated molecular changes.

STRESS RESPONSE AND HYPOTHALAMIC-PITUITARY-ADRENAL ACTIVATION

The neurohormonal mechanism of stress response

The stress response involves a neurohormonal mechanism activated by the cross talk of the hypothalamic-pituitary-adrenal (HPA)-axis and the sympathetic-adrenal-medullary (SAM)-axis that results in widespread hormonal, neurochemical, and physiological alterations. The SAM axis activates the peripheral sympathetic nervous system to release epinephrine and norepinephrine[20,21]. HPA axis activation leads to a cascade of events whereby corticotropin releasing hormone released from the hypothalamus stimulates the release of adrenocorticotropic (ACTH) from the pituitary gland, which in turn results in production of glucocorticoids (GCs) from the adrenal cortex. GCs, also known as cortisol in mammals and corticosterone in rodents, regulate cellular function by interacting with steroid receptors that modulate the neural circuitry and neuroendocrine systems involved in behavioral responses to stress[21]. These receptors, glucocorticoid receptors (GR) and mineralocorticoid receptors (MR), are expressed throughout the brain, mostly in the prefrontal cortex (PFC), hippocampus, amygdala, and other limbic and midbrain structures[17,22]. Under conditions of threat, HPA activation leads to increased release of GCs to promote acute survival by mobilizing stored energy, hence contributing to a state of increased arousal and vigilance. The stress response is then terminated by a negative feedback loop that attenuates the HPA-axis at the level of GR, causing GCs levels to return to normal (Figure 1)[23]. In contrast to GR, MR modulates basal and stress-induced HPA-axis activity to appraise stress and fear-related memories. Enhanced expression and function of MR may improve resilience to traumatic stress and reduces the risk for psychiatric disorders[21]. Studies have shown that MR dampen glucocorticoid receptor sensitivity to stress *via* regulation of FK506-binding protein 5 (FKBP5), a potent negative regulator of glucocorticoid signaling that plays an important role in fine-tuning the MR:GR balance in the hippocampus[24].

When the HPA axis is activated, dehydroepiandrosterone (DHEA) is also released by the adrenal glands along with GCs. DHEA is an important mediator of the HPA axis since it facilitates the N-methyl-D-aspartate receptor function, antagonizes g-Aminobutyric Acid A receptors, and facilitates metabolism of cortisol to the inactive metabolite cortisone. DHEA-Sulfate (DHEA-S), a more potent form than DHEA, plays a neuroprotective role by inhibiting GC effects at the level of the GR as well as supporting neurogenesis[25-28]. Cortisol/DHEA-S ratio represents a balance between the catabolic effects of cortisol and the anabolic, regenerative function of DHEA-S[27,29]. In fact, a higher DHEA-S to cortisol ratio predicted stress resilience in male military personnel, lowering symptoms of PTSD and showing greater improvement over time[30]. On the other hand, a lower resting DHEA/cortisol ratio has been associated with childhood trauma[26].

Circadian control of the HPA axis

Multiple studies have demonstrated the close connection between the circadian rhythm and stress systems to maintain allostasis. The homeostasis of the HPA axis, which produces the primary mediators in adaptation to stress, is closely regulated by the circadian rhythm output[31]. The nearly 24-h periodic peripheral rhythms are controlled by the master circadian pacemaker located in the hypothalamic suprachiasmatic nucleus (SCN). The SCN generates a daily rhythm of transcription and translation feedback loop that align with the 24-h external light-dark environment[32]. The central clock in the SCN orchestrates peripheral clocks at the cellular level to synchronize physiological and behavioral rhythms and regulates the activity of various humoral and neuronal allostatic mediators, among which GCs that show a robust time-of-day dependence[33-35]. These robust circadian dynamics of the allostatic mediators enable the host to flexibly respond and adapt to various physiological stressors[36,37]. In this current modern society and lifestyle that humans live in, where light at night is widespread due to adoption of electrical light, we developed a deranged temporal adaptation that our physiological systems have not evolved to cope with. The chronic disruption of circadian rhythms predisposes to physiologic and behavioral changes that can lead to maladaptive allostatic mechanisms and compromising resilience[32,36].

Animal studies have shown that disruption of the circadian rhythm by misalignment to the natural light/dark cycle in mice results in neurobehavioral changes resulting in decreased complexity of neurons in the prefrontal cortex, the brain center involved in executive and emotional control, and reduction in cognitive flexibility[38]. Even short-term circadian misalignment has been shown to disrupt memory consolidation in response to fear-conditioning that could compromise resilience[39]. The bidirectional communication between the central clock and HPA axis is also evident by circadian disruption in response to early life stress that contributes to metabolic derangement occurring later in life[40]. Hence, re-alignment of circadian rhythms by following the natural light/dark cycle can enhance allostatic adaptive resilience and can be especially beneficial for individuals with psychiatric disorders who struggle with sleep disturbances[41-43]. Interestingly, timing of Trauma Exposure therapy to specific trauma-associated cues can have a different outcome in the process of healing. One study found that exposure to trauma cues is more efficacious when administered during the morning time compared to the evening[44,45].

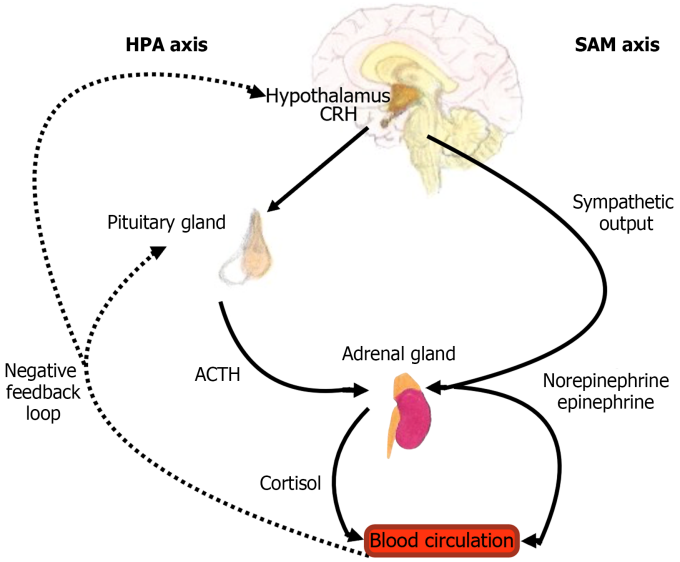

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Figure 1 Hypothalamic-pituitary-adrenal and sympathetic-adrenal-medullary axes, neurohormonal output, and feedback loop. CRH: Corticotropin releasing hormone; HPA: Hypothalamic-pituitary-adrenal; SAM: Sympathetic-adrenal-medullary; ACTH: Adrenocorticotropic; ACTH: Adrenocorticotropic hormone.

Chronic stress and allostatic load

As presented above, exposure to stress triggers several biological mechanisms in the body that release stress hormones as primary mediators in order to adapt to short term or acute stress. Maintaining stability through change is a phenomenon known as allostasis[46,47]. Allostasis is considered a beneficial adaptive mechanism that promotes host survival through the appropriate activation of energetic resources[48]. However, repeated exposure to stress, also known as chronic stress, can result in prolonged activation of the HPA and SAM axes, which may lead to activation of secondary inflammatory and metabolic mediators, and ultimately lead to deleterious effect on metabolic, immune, and cardiovascular functions as well as brain and behavior (Figure 2)[49-52]. The cumulative effects of chronic stress reduce the ability of the host to flexibly cope with subsequent stressful situations, which lead the system to shift from allostasis to allostatic load or physiological "wear and tear"[53-56].

Impact of chronic stress on brain and gene expression

While it is beyond the scope of this minireview to discuss all the structural, biological and genetic modifications in response to chronic or developmental stress, we will briefly discuss few structural changes and gene variants involved in the stress response, which may result in either negative or positive associations to resilience. Animal studies have shown structural changes in different brain regions whereby chronic stress increases dendritic spine number or branching in the amygdala and nucleus accumbens, reduces dendritic arborization and glutamatergic dendritic spine density of pyramidal neurons in PFC and hippocampus, and decreases hippocampus neurogenesis[57].

The impact of the environment and specifically early life stress profoundly alters key genes involved in stress response *via* epigenetic modification. Many of these genes can be modified through epigenetic alterations and variation in microRNAs (miRNA), short non-coding RNAs detected in body fluids, in response to environmental influences[58,59]. Little is known about the role of miRNA in psychiatric disorders and resilience. One animal study showed that the systemic knockdown of miRNA-144-3p reduced the depression-like phenotype in stress-susceptible mice[60]. Another study demonstrated that knockdown of miRNA-144 and miRNA-33 in the hippocampus increased the proportion of resilient female animals[61]. Studies also showed that low maternal care is associated with epigenetic modification by increased methylation of the gene encoding GR (*NR3C1*), leading to decreased GR expression in the hippocampus[62,63]. Another important player in regulating the stress response is the *FKBP5* gene. This gene modulates intracellular glucocorticoid signaling and homeostatic regulation of the stress response[64]. Studies have shown that epigenetic modifications induced by early life stress or single nucleotide polymorphisms (SNPs) in human *FKBP5* gene result in differential induction of the FKBP5 protein upon glucocorticoid stimulation, thereby adding to the variability of stress perception and response, and increasing the risk of developing stress-related psychiatric disorders[65,66].

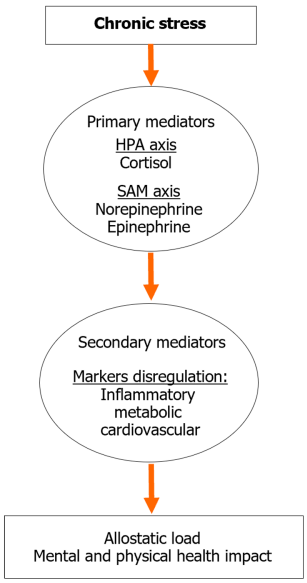

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Figure 2 Impact of chronic stress on allostatic load mediated by primary and secondary biomarkers. HPA: Hypothalamic-pituitary-adrenal; SAM: Sympathetic-adrenal-medullary.

FACTORS CONTRIBUTING TO BUILDING RESILIENCE

Role of psychosocial interventions: Brain and epigenetic alterations

While early-life stress can induce permanent changes in behavioral and physiological responses to stress through epigenetic modification, DNA methylation is potentially reversible through intervention. Using blood samples from human, methylation levels of specific regions within *FKBP5* and brain derived neurotrophic factor (*BDNF*) were changed in response to psychotherapy and were associated with recovery and improvement[67,68]. For example, Exposure-based Cognitive Behavioral Therapy results in a decrease in *FKBP5* methylation and leads to a positive treatment response[69]. Furthermore, maternal stroking and tactile stimulation can normalize DNA methylation in the leukocytes of infants who had been exposed to high levels of pre- and postnatal maternal depression[70]. Mindfulness practice is well known to improve cognitive and social functioning, and reduce symptoms of depression and anxiety[71,72]. The mechanisms whereby mindfulness regulates the stress response is through activation of brain regions involved in interoception, self-awareness, emotion regulation, and threat detection[73-75]. Mindfulness practice has been shown to alter different immune and endocrine pathways, as well as epigenetic methylation of the *FKBP5* gene in adults with PTSD[76-78].

These findings are in line with animal studies demonstrating that intervention by enrichment can reverse the epigenetic, plasticity, and behavioral deficits in rats exposed to early life stress[79]. Indeed, our group has recently published a new treatment approach, Cue Centered Therapy (CCT) for complex developmental trauma in children and adolescents. CCT emphasizes resiliency and positive adaptation factors by using the life timeline as a core component for both positive and negative events in youth's life. CCT has shown effectiveness in improving functioning and reducing child and parent post-traumatic stress. Treatment outcome research of CCT have demonstrated PTSD symptom improvement as measured by cortical activation patterns using functional near-infrared spectroscopy, a non-invasive neuroimaging technique[80,81].

Role of oxytocin and attachment

Another important molecular determinant of resilience is oxytocin (OXT), which is closely tied to attachment. Humans are considered social mammals that develop various forms of social attachments and bonds from infancy throughout life[82,83]. The influence of secure attachment to a caregiver modulates physiology and behavior and is essential for a healthy psychological development and well-being. Attachment is a psychological/behavioral construct for infant's self-regulation that is promoted and facilitated by caregiver's ongoing emotional availability. Infants internalize their interactions with their caregiver and build internal working models that represent their attachment figures in relation to themselves[82]. Attachment styles during early life predict moderate stability of attachment over the years but can be susceptible to change by significant relationship experiences[84]. The different attachment styles are believed to have a profound shaping of an individual's emotional and psychosocial functioning as well as resilience or predisposition to psychopathology[85-87].

It is established that sudden separation of children from their parents, interpreted as abandonment, threatens the attachment bond and results in profound sense of shame and complex emotions especially in the absence of adequate support[88,89]. In addition to the impact of separation on secure attachment, transgenerational maternal experiences with unresolved attachment to their own caregivers can influence the quality of bonding of those mothers to their children. Children of mothers who exhibit higher distress and disruptive behavior exhibited a significantly higher cortisol compared to ones with no disruptive behavior[90]. These differences in cortisol levels and behavior may be related to gene polymorphism of the OXT and OXT receptor (OXT-R) in children from mothers with negative maternal experiences. These genes moderate the stress response of children, and polymorphisms can be associated with the disorganized behavior independent of maternal experiences[91].

The OXT system activated through social interaction is thought to have an important implication in building resilience by playing an important role in the regulation of affective and social behaviors as well as modulating stress response[92-94]. OXT is a neuropeptide produced by hypothalamic paraventricular, supraoptic, and accessory nuclei, and is released to the posterior pituitary gland and ultimately to the peripheral blood circulation[95,96]. In addition to OXT's role in parturition and lactation[97], the neuropeptide plays a key role in promotion of postnatal sensitive maternal caregiving to optimize infant's social and emotional development[98-100]. Higher levels of OXT have been linked with increased attention to social cues[101] while lower levels have been seen in maltreated children [102]. A positive association between OXT level and interpersonal bonding and affiliation, as well as stress modulation in interpersonal situations is well established. In animal models, OXT facilitates mating-induced pair bonds *via* mesolimbic dopamine system, however, variation in striatal OXT-R density predicts resilience and susceptibility to neonatal social neglect[103,104]. Growing evidence from animal and human studies showed that OXT signaling early in life by parental nurturing can buffer against physical and emotional stressors and help establish the neural networks needed during adult life to form social bonds[105-110].

Maternal care during early life, which overlaps with behaviors involving OXT in mother and infant through embedded hidden regulators, maintains the stress hyporesponsive period and direct HPA maturation during heightened plasticity[62]. It has been established that early life stress in human and non-human primates is associated with changes in cerebrospinal fluid OXT level and social behavior, as well as the ability of parental presence to attenuate stress response to a novel environment[111-113]. Animal studies have shown that OXT controls the secretion of ACTH under stress condition and enhance the long-term HPA axis response to stress in adult rats, which may act as a feedback regulator to enhance recovery from stress-related symptoms[114-116].

OXT seems to play an important role in fear modulation where it strengthens fear memory to predictable or cued fear while attenuating fear memory to unpredictable, diffuse threats (contextual fear and non-cued fear)[117-122]. Thus, OXT fosters adaptive defensive behaviors and accurate fear discrimination of relevant and imminent threats, yet reducing sustained fear responses to distant threats[123]. Animal studies have shown that administration of OXT by intracerebroventricular injection or intranasally facilitated cued fear extinction and reduced chronic stress-induced deficits in fear extinction in male rats, respectively. In contrast, administration of OXT-R antagonist impaired fear extinction in male rats[124,125]. These studies emphasized the role of OXT in reducing sustained fear responses and anxiety-like behaviors while strengthening fear responses to relevant and predictable threats. Nuclei of the central amygdala are the main output that connect to the brainstem to eventually mediate the fear response, including freezing behavior. OXT-R transmission in the amygdala switches from passive freezing to active escape behaviors in confrontation with an imminent, but escapable threat[126-128]. OXT also mediates affiliate and prosocial behaviors. OXT-R signaling facilitates social transmission of fear between familiar conspecifics, which might serve as warning system of impeding threat[129,130].

SNPs of the OXT-R gene, rs53576, has been shown to be associated with individual differences in social and emotional abilities, predisposition to psychopathology, and environmental adversity in the prediction of anxiety and depression[131-138]. Human brain-imaging studies in repeated childhood trauma and emotional neglect have demonstrated structural and functional variations in the amygdala, hypothalamus and cingulate gyrus in response to OXT-R gene polymorphism leading to variations in social and behavioral outcomes[139]. Furthermore, epigenetic alterations to specific OXT-R gene polymorphisms can attenuate resting parasympathetic tone and increasing central amygdala grey volume, thereby altering traumatic stress reactivity[140].

Role of diet, gut microbiome, and exercise

There is an extensive connection between the mind and body in which the wellbeing of one influences the other. A major element of this mind-body connection is the brain-gut axis. Indeed, there is an association between early life adversities and changes in the brain-gut axis that may occur *via* pathways related to glutamatergic excitotoxicity and oxidative stress, predisposing to negative mood and stress [141].

Maternal diet and resilience: The quality of dietary interventions during a critical period of neural development predicts the function of the brain-gut axis and plays a key role in building resilience to stress. Earlier studies showed that maternal nutrition during pregnancy plays a fundamental role in

intrauterine developmental programming and predicts child's resilience to stress and vulnerability to psychiatric disorders, such as anxiety and depression. Maternal malnutrition during fetal development has a detrimental long-term impact on the physical, cognitive, and emotional development[142,143]. A deficit in maternal dietary protein during pregnancy alters the brain neurochemistry and behavior by reducing 5-hydroxytryptamine 1A receptor and the responsiveness to stress during adult life[144]. It has been shown that branched-chain amino acids such as leucine, isoleucine or valine are essential nutrients that promote resilience *via* activation of hippocampal BDNF signaling[145]. An unbalanced diet during pregnancy is linked to heightened HPA axis responses to stress and higher cortisol levels as well as epigenetic changes in genes controlling glucocorticoid action in adult offspring[146-148].

Microbiome and gut-brain axis: The gut microbiota plays a major role in shaping how the body responds to stress. Animal studies have shown that Germ-free mice with absent microbiota have significant variations in their stress response caused by abnormal development of the HPA axis that was reversed by inoculation of Bifidobacteria infantis[149]. Exposure to early life adversity is correlated with changes in microbial diversity of the gut where taxonomic abundances predicted PFC activity[150].

The microbiome-derived short-chain fatty acids (SCFA) are the most studied metabolites because they ameliorate the gut-brain axis and stress-induced cortisol release in humans and rodents[151]. The composition of diet is essential because it can impact gut-brain pathways involved in stress response. A healthy diet rich in fibers, phytochemicals, or live bacteria can increase microbial diversity and enhances production of SCFA and other bioactive compounds[152,153]. Western diet, lacking in dietary fibers, is associated with suboptimal gut microbiota composition and a low-grade systemic inflammation that can predispose to mental illness, gastrointestinal and metabolic disorders, and obesity[154,155]. In addition to diet, exercise has been shown to increase SCFA availability, thereby influencing microbiome composition[156]. Gut microbes also play a major role in synthesizing key neuroactive molecules such as serotonin, gamma-aminobutyric acid, and catecholamines like norepinephrine and dopamine. For example, *Lactobacillus* can stimulate the conversion of dietary tryptophan into 5-hydroxytryptamine by enterochromaffin cells, which then interacts with the autonomic nervous system and conveys the signal to other brain structures, such as the hypothalamus, nucleus accumbens, and ventral tegmental area [157-159].

Microbiome-targeted therapies known as "psychobiotics" that include administration of live organisms, fecal microbial transplants, and dietary interventions to reshape the microbiome composition and function have beneficial effects on brain and behavior[152,160,161]. Administration of the probiotic organisms *Bifidobacterium* and *Lactobacillus* is known to confer resilience in social defeat model and has been tested in clinical depression[161,162]. Additionally, probiotics supplementation results in higher DHEA-to-corticosterone fecal metabolite ratios and reduces microglia immunoreactivity in the basolateral amygdala in rodent models, thereby mitigating the pervasive effects of early life stress on anxiety and depressive behavior as well as HPA axis activity[163].

Modulating the microbiota–gut–brain-axis through diet is also a promising approach to prevent and treat mental health disorders. Consumption of a Mediterranean diet resulted in a significant improvement in depressive symptoms after 12 weeks of dietary intervention compared to control group among patients with major depressive disorder[164,165]. Studies have also shown that adherence to Mediterranean diet, consumption of fruits and vegetable-based dietary pattern and dietary polyphenols were positively associated with psychological resilience[166]. Polyphenols are stress-modifying phytochemicals composed of hydroxylated phenyl moieties and are abundant in fruits, vegetables, tea, caffeine, curcumin, herbs, citrus peel, and grape seeds. They have anti-inflammatory actions, which may be involved in fighting psychosocial stress. Therefore, polyphenols are considered adaptogens (stress response modifiers that have beneficial effects to protect from chronic diseases) because of their ability to adapt to and survive external stressors[167-171]. Polyphenols are also considered 'prebiotics' because of their ability to enhance the growth of specific beneficial bacteria that produce bioactive phenolic acids, which promotes cognitive resilience to depression and anxiety[172-175].

Exercise and resilience: Exercise is well known for its benefit in enhancing resilience and longevity. Physical activity through exercise activates endocrine, paracrine, and autocrine pathways through the release of exerkines (signaling particles that have a potential role in improving health in response to exercise), cytokines, nucleic acids, lipids, and metabolites from multiple organs[176]. Exercise is well known to improve brain function, most notably the effect on learning and memory. Indeed, aerobic exercise increases hippocampal volume and improves memory, increases plasma levels of BDNF, and delays the onset of neuro-degenerative conditions in older adults human studies[177-179]. These findings are in line with animal studies on rodents where chronic exercise resulted in upregulation of BDNF in the hippocampus, leading to hippocampal neurogenesis, neural plasticity, and improved cognition and mood[180]. A possible mechanism of the upregulation of BDNF in hippocampus is through the release of irisin from myokines, which plays an important role in hippocampal neurogenesis, increased neurotrophin levels, and enhanced mood and cognition[181]. Another benefit of exercise is the release of adiponectin from adipocyte that seems to have neuroprotective effects by crossing the blood–brain barrier and resulting in increased neurogenesis and reduced depression-like behaviors[182]. Kynurenic acid, another molecule of interest produced in muscles in response to chronic

aerobic exercise, has been shown to protect the brain from stress-induced depression[183]. Vigorous exercise is also associated with lower emotional distress, depression, and anxiety[184,185].

Studies have linked the adaptative changes in opioid systems to regular exercise, which reduces noradrenergic-induced stress responses. Regular exercise activates the endogenous opioid in the peripheral and central nervous system and is implicated in mood improvement[186,187]. The stress-reducing effect of exercise in response to both physical and psychological challenge is reversed by administration of naloxone, an opioid antagonist[188,189].

DISCUSSION

We have addressed in this minireview the biological basis of resilience as an outcome of structural and molecular alterations resulting from various determinants. Understanding the molecular aspect of resilience can provide insight for therapeutic discoveries and interventions to promote resilience in face of adverse life events. Here we showed that building resilience requires an intricate network of positive experiences and healthy lifestyle that contribute to a balanced mind-body connection (Figure 3). Indeed, positive childhood experiences such as interpersonal social and emotional support can mitigate the impact of adverse childhood experiences, thereby reducing the risk for adult onset depression and poor mental health[190].

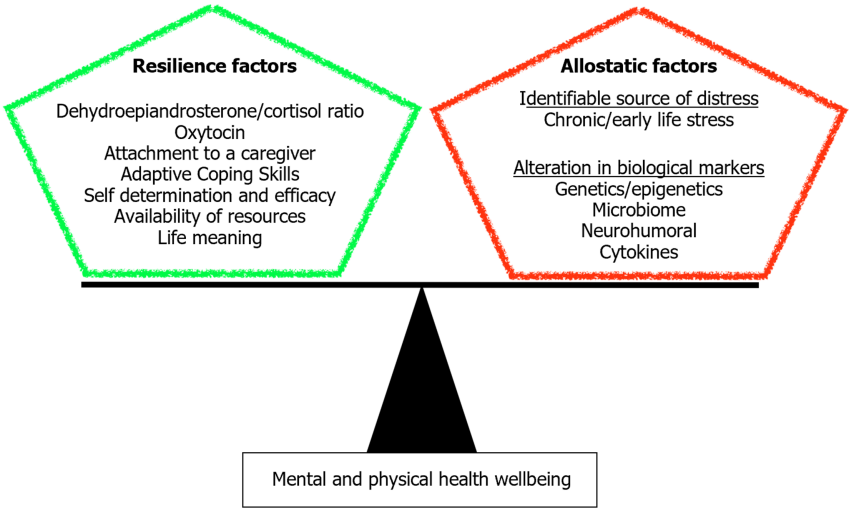
Clinical and preclinical investigations showed that resilience is implicated in molecular alterations and changes in brain regions involved with the social networks that promote empathy, social connectedness, and modulation of central responses to stress. DNA methylation in response to early life stress is potentially reversible through intervention. Resilience promoted by psychotherapy and mindfulness practices reverses the epigenetic modification of *FKBP5* and *BDNF* genes caused by stress response and alters cortical activation to improve PTSD symptoms[76-78,80,81]. Investigations also showed that DHEA-S, OXT and enhanced expression of MR can be used as important predictors of resilience[21,24,30]. OXT, a neuropeptide tied to attachment, plays a key role in promotion of postnatal sensitive maternal caregiving to optimize infant's social and emotional development and establish the neural networks needed during adult life to form social bonds[105-110]. OXT is also a feedback regulator of the HPA axis that enhance recovery from stress-related symptoms[114].

Recent studies also showed the association between early life adversities and circadian rhythm disruption as well as changes in brain-gut axis that may occur *via* pathways related to glutamatergic excitotoxicity and oxidative stress, predisposing to metabolic derangement, negative mood and stress [37,141]. Re-alignment of circadian rhythms to the natural light/dark cycle is an important health behavior that enhances resilience and adaptation to various stressors[41-43]. Additionally, a healthy brain-gut axis plays an important role in building resilience where gut microbial diversity, healthy diet and exercise can ameliorate the gut-brain axis and stress-induced cortisol release in humans and rodents. Administration of probiotics confer resilience in social defeat model and results in higher DHEA-to-corticosterone fecal metabolite[161,162], thereby mitigating the pervasive effects of early life stress on anxiety and depressive behavior as well as HPA axis activity[163].

Despite the advances in studying resilience and the multitude of contributing factors, there are still gaps in literature about genetic determinants that differentiate resilient individuals from vulnerable ones. Here we reviewed that epigenetic modification of *FKBP5* and *BDNF* genes in response to stress can be reversed by interventions to reduce stress[67,68]. Our group is currently conducting a large-scale study to determine what other genes are implicated in resilience in response to CCT psychotherapy. The advances in miRNA research can also be a powerful tool that can serve as a therapeutic target to improve resilience.

CONCLUSION

This minireview emphasized the dynamic process of resilience and showed that it continually evolves by the intersection of different domains in human's life; nature, nurture, environment, and microbiome. Despite the large number of research studies on resilience to stress, none have established one causal factor that differentiates a resilient person from a vulnerable one. This minireview demonstrated that a holistic approach, both clinically and for research purposes, must be adopted to address the multiple elements that promote resilience and prevent physical illnesses and psychopathology. Our future direction is to further understand the role of epigenetic gene silencing in chronic stress in order to identify potential resilience genes that can be reactivated by psychotherapy and the other resilience-promoting interventions mentioned above.



DOI: 10.5498/wjp.v13.i5.144

Figure 3 Wellbeing as a measure of resilience and allostatic factors balanced output.

FOOTNOTES

Author contributions: Chbeir S and Carrión V conceived the manuscript idea; Chbeir S did writing and literature research; Carrión V did reviewing and editing.

Conflict-of-interest statement: No conflict of interest for both authors.

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S-Editor: Chen YL
L-Editor: A
P-Editor: Cai YX

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World Journal of Psychiatry

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World J Psychiatry 2023 May 19; 13(5): 160-173

DOI: 10.5498/wjp.v13.i5.160

ISSN 2220-3206 (online)

MINIREVIEWS

Neurobiological risk factors for problematic social media use as a specific form of Internet addiction: A narrative review

Sergey Yu Tereshchenko

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B, B
Grade C (Good): C
Grade D (Fair): D
Grade E (Poor): 0

P-Reviewer: Oliveira AP, Portugal; Ye B China

Received: December 27, 2022
Peer-review started: December 27, 2022
First decision: February 2, 2023
Revised: February 13, 2023
Accepted: April 7, 2023
Article in press: April 7, 2023
Published online: May 19, 2023

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Abstract

Problematic social media use (PSMU) is a behavioral addiction, a specific form of problematic Internet use associated with the uncontrolled use of social networks. It is typical mostly for modern adolescents and young adults, which are the first generations fully grown up in the era of total digitalization of society. The modern biopsychosocial model of the formation of behavioral addictions, postulating the impact of a large number of biological, psychological, and social factors on addictive behavior formation, may be quite applicable to PSMU. In this narrative review, we discussed neurobiological risk factors for Internet addiction with a focus on current evidence on the association between PSMU and structural/functional characteristics of the brain and autonomic nervous system, neurochemical correlations, and genetic features. A review of the literature shows that the vast majority of the mentioned neurobiological studies were focused on computer games addiction and generalized Internet addiction (without taking into account the consumed content). Even though a certain number of neuroimaging studies have been conducted for PSMU, there is practically no research on neuropeptide and genetic associations for PSMU to date. This fact points to the extremely high relevance of such studies.

Key Words: Internet addiction; Problematic social media use; Addictive behavior physiopathology; Neurobiology; Genetics

Core Tip: The analysis of sources showed that the vast majority of neurobiological research was focused on the study of computer games addiction and generalized Internet addiction (without taking into account the content consumed). There is practically no research on neuropeptide and genetic associations for problematic social media use to date. This fact points to the extremely high relevance of such studies.

Citation: Tereshchenko SY. Neurobiological risk factors for problematic social media use as a specific form of Internet addiction: A narrative review. *World J Psychiatry* 2023; 13(5): 160-173
URL: https://www.wjgnet.com/2220-3206/full/v13/i5/160.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i5.160

INTRODUCTION

The last few decades have been characterised by the complete digitalization of society and the ubiquitous penetration of Internet technologies into our daily lives[1,2]. The advantages associated with the widespread introduction of Internet technologies into people's daily lives are undeniable (for example, quick access to a large amount of information and various services, rapid dissemination of news on a global scale, the introduction of Internet technologies related to health, *etc*.). However, a certain number of Internet users, mainly adolescents and young adults, experience the phenomenon of Internet addiction or "problematic/compulsive use of the Internet" which is associated with several psychosocial problems[2,3]. The global concern about the impact of problematic Internet use (PIU) from the public and social health points of view became especially acute during the coronavirus disease (COVID) pandemic when each person had to use the Internet more often, and initially, predisposed individuals were losing control, showed more and more signs of pathological addictive behavior when diving into the network[4]. In particular, this trend has affected the most technologically advanced segments of society – the first generations who grew up surrounded by the Internet and gadgets – adolescents and young adults[5]. The situation can be significantly aggravated by the neurophysiological consequences of the pandemic, predisposing to the development of depression and anxiety, which are important risk factors of problematic social media use (PSMU)[6].

The modern "component bio-psychosocial model" of behavioral addiction formation postulates an individual combination of genetic/biological, psychological, social, and cultural factors leading, in the case of PSMU, to overuse of social media and negative consequences (Figure 1).

In this narrative review, we shall discuss neurobiological risk factors for Internet addiction with a focus on current evidence on the association between PSMU and structural/functional characteristics of the brain and autonomic nervous system, neurochemical correlations, and genetic features.

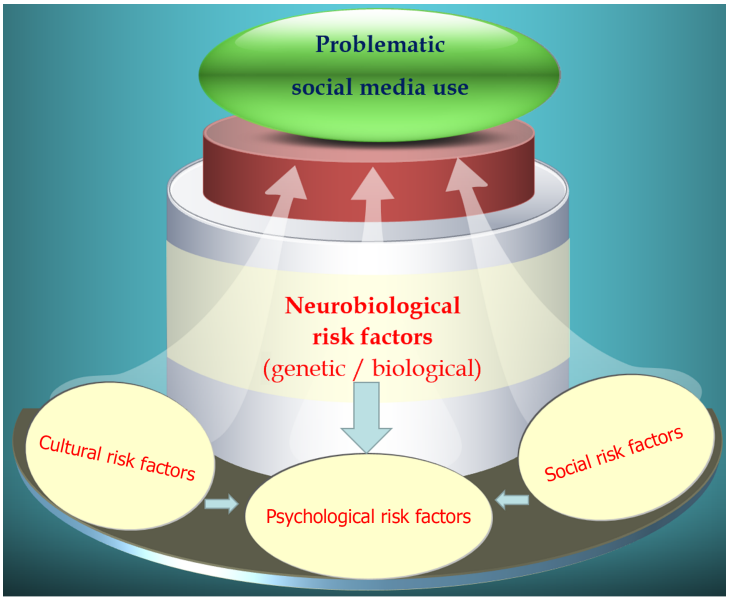
To find relevant publications, a search was conducted in PubMed, Scopus, Web of Science, and Reference Citation Analysis (https://www.referencecitationanalysis.com) for English-language sources using the following keywords and MeSH terms: "Internet addiction", "problematic social media use", "pathological social network use", "social media", "social networking", "specific Internet addiction", "video game addiction", "gaming disorder", "neurobiology", "behavior, addictive/physiopathology", "brain/physiopathology", "sympathetic nervous system", "parasympathetic nervous system", "neural pathways/physiopathology", "neurotransmitters", "biochemical correlates", "twin study", "genetics", "gene frequency", "genetic predisposition to disease", "polymorphism, single nucleotide".

TERMINOLOGY

The phenomenon of Internet addiction[7,8] was first described in the mid-1990s. There is currently no accepted formal definition of addictive online behaviour. Specialized literature offers such interchangeable terms as "problematic interactive media use"[9], "problematic Internet use", "pathological Internet use", "compulsive Internet use", and, finally, "Internet addiction". The European Network for Problematic Usage of the Internet (European research group) recommended in a recent review (2022) to use the term "problematic Internet use", as the most appropriate at this moment[4].

All of the above are umbrella terms, *i.e.*, reflect generalized (without reference to specific content and technology) PIU. Among the specific types of Internet activity, the following can be considered potentially addictive: Problematic video game use, PSMU, problematic Internet pornography use, Internet gambling, and web surfing addiction[10,11].

Only one of these five addictive behavior types, namely the problematic use of video games, is currently officially considered a mental disorder (Internet gaming disorder, diagnostic and statistical manual of mental disorders, fifth edition, American Psychiatric Association, 2013; gaming disorder, international classification of diseases-11, 2019). Recently, other specific forms of PIU have also been singled out: Online gambling disorder (it also includes intensive betting on online exchanges), online



DOI: 10.5498/wjp.v13.i5.160

Figure 1 Component bio-psychosocial model of problematic social media use.

buying-shopping disorder, Internet streaming disorder, cyberchondria, cyberbullying, and digital hoarding[4].

PSMU is a behavioral addiction, a specific form of PIU associated with the uncontrolled use of social networks. It is typical mostly for modern adolescents and young adults, which are the first generations fully grown up in the era of total digitalization of society. There are currently no universally recognized and official criteria for the diagnosis of PSMU. The European Network for Problematic Usage of the Internet (European research group) suggests the following definition[4]: PSMU is a persistent state of control loss when using social networks, manifested by: Violation of control over interaction with social websites (for example, in terms of time, frequency, and duration of use); predominance of time spent on social networks over other life interests and activities; negative consequences, *i.e.*, the use of social networks leads to significant distress or deterioration in personal, family, social, educational, professional activities, or other important areas of functioning; continued or increased use of social networks, despite the negative consequences (for example, poor school performance, negative impact on health, social isolation, interpersonal conflicts, neglect of duties); duration, *i.e.*, the use of social networks can be continuous or episodic and repetitive but manifests itself over a long period (at least 12 mo).

Although the criteria for the diagnosis of PSMU are not formally established, the existing validation methods using questionnaires are based on the interpolation of classical symptoms for chemical and non-chemical types of addictive behavior[12]. Currently, there is a consensus on diagnostic criteria that clearly distinguish the pathological component of addiction from the normal daily use of the Internet by adolescents: The clinical diagnosis of PSMU, as well as generalized Internet addiction, should include six obvious signs[11,13,14]: Salience and mood modification, such as behavioral, cognitive, and emotional preoccupation: The growing importance of a social network for an adolescent in his or her system of interests and values; the use of a social network leads to a positive change in the emotional state; Compulsivity and loss of control: An obsessive desire to use the social network, impulsivity, loss of time control, excessive use of the social network (especially while reducing the allocated time for other activities); Tolerance: The need to spend more and more time communicating on a social network, including to alleviate episodes of dysphoria; Withdrawal/abstinence symptoms: Mood changes in the absence of access to a social network (depression, anxiety, aggressiveness); Conflict, impaired role performance: Loss of previous interests and entertainment, loss of educational, cultural, sports, and other opportunities as a result of excessive use of social networks; disputes and lies regarding the use of the social network; continued use of social networks, despite the negative consequences. Relapse: Rapid return to the use of the network after abstinence, unsuccessful independent attempts to control the use of the social network.

However, PSMU must be distinguished from intensive adaptive use of social networks. Adaptive intensive use of social networks itself does not have obvious negative consequences, has little effect on the parameters of well-being, and in many individual cases can play a positive role in the development of an adolescent by increasing a "social capital"[15-17].

PREVALENCE

The latest summarized data show that the average prevalence of PSMU among adolescents in 29 European countries is 7.4%[18]. The recent systematic review by Cheng *et al*[19] showed a high ethnic and geographic heterogeneity of PSMU prevalence within 5%–26%. The highest levels of PSMU prevalence are registered in collectivist societies in Asia and Africa[19]. Recent cross-national analysis of the psychometric characteristics from the social media disorder scale (SMDS) questionnaire among adolescents from 44 countries has shown high levels of validity and reliability (comparative fit index and Tucker–Lewis index = 0.963 and 0.951, root mean square error of approximation = 0.057)[20]. SMDS is recommended by the research group European Network for Problematic Usage of the Internet as preferred, since it evaluates primarily the psychopathological aspects of addiction, while the recently criticized Bergen social media addiction scale questionnaire does not clearly distinguish between simple excessive or prolonged use of social networks from pathological one, with signs of addiction[4]. The prevalence figures obtained by the authors of the SMDS were 7.3%-11.6% for the Dutch adolescent cohort[21]. Other studies using the SMDS have found similar results: 9.9%-10.0% in a Dutch sample in a longitudinal study[22], 9.4% in a representative sample of 3408 Finnish adolescents[23], and 8.0% in a large sample of Russian adolescents (n = 4514)[24].

PSYCHIATRIC AND SOMATIC COMORBIDITY

A large number of foreign studies have convincingly shown the pronounced comorbidity of Internet addiction with a wide range of psychopathological conditions. Depressive disorder and attention deficit hyperactivity disorder have the strongest association with Internet addiction, while anxiety disorder, obsessive-compulsive disorder; social phobia, and suicidal behavior also have a smaller but significant association[25-28]. A recent meta-analysis by Shannon *et al*[12] has shown that PSMU, as a specific form of Internet addiction, also reveals a moderate, but statistically significant, association with depression, anxiety, and stress[12]. Another recent meta-analysis demonstrated a significant but weak negative association of PSMU with life satisfaction and self-esteem (as parameters of well-being) and a moderate positive association with depression and loneliness (as indicators of distress)[29].

At present, not much is known about the association of Internet addiction with psychosomatic diseases, although such a connection is highly likely, given the presence of common pathogenesis factors (anxiety-depressive and obsessive-compulsive disorders). The study by Wei *et al*[30] based on an Internet survey demonstrated the association of Internet addiction with chronic pain syndromes, which the authors link with psychosomatic diseases and muscle overstrain. The study conducted by Cerutti *et al*[31] did not reveal a statistically significant association between Internet addiction and tension headache/migraine, although, in general, somatic symptoms were more often reported in the Internet addiction group[31]. In addition, it was discovered that PIU among adolescents was associated with chronic conditions, back pain, overweight, musculoskeletal pain, and also with sleep disorders[32,33]. According to a recent systematic review, a wide range of somatic health problems are associated with smartphone addiction among adults[34]. A general decrease in immune functions was observed in Internet-addictive individuals, which the authors link with a common risk factor, *i.e.*, stress, which can affect the activity of the sympathoadrenal axis and increase cortisol production[35]. It is characteristic that the high activity in the sympathetic part of the autonomic nervous system was detected when analyzing the heart rate of adolescents with Internet addiction[36,37]. A decrease in the quality of life, including the parameters of somatic health, was demonstrated in a systematic review by Masaeli and Billieux[38]. A pronounced connection between Internet addiction with the general level of somatization was revealed among young adults[39].

PATHOGENESIS OF INTERNET ADDICTION FROM A NEUROBIOLOGY POINT OF VIEW

To date, several etiopathogenetic models of the formation of Internet-dependent behavior among adolescents and young adults have been proposed[40]. Some researchers suggest the presence of mainly neurobiological risk factors linked with the lack of maturity in certain parts of the adolescent brain, which is manifested by insufficient effectiveness of volitional control, high impulsivity, and an overly activated brain reward circuitry[41,42]. However, the most recognized by researchers at present is the "component biopsychosocial model", which assumes a combination of psychosocial problems and neurobiological risk factors[40,43-45].

Middle and late stages of adolescence in brain development are characterized by different time frames of the formation of the limbic system and prefrontal cortex lobes[46]. The prolonged development of the prefrontal cortex in comparison with the limbic system during adolescence leads to weakened inhibition from cortex lobes concerning underlying subcortical structures and increased impulsivity, which contributes to a high risk of addictive behavior[47].

To date, a large number of studies have been devoted to the pathogenesis of Internet addiction using various neuroimaging techniques, including magnetic resonance imaging, positron and single photon emission computed emission tomography. These techniques have revealed a number of structural brain changes associated with Internet addiction[48-50]: Dcreased grey matter density in several areas, including prefrontal and orbitofrontal cortical layers and an additional motor area[51]; abnormal functional activity of brain regions associated with reward dependence[41]; activation of sensorimotor synchrony with a concomitant decrease in audiovisual synchrony[52]; activation of brain regions associated with compulsive craving and impulsivity; increased glucose metabolism in brain regions associated with impulsivity, reward dependence and the urge to repeat sensations[53]; increased dopamine secretion with a concomitant decrease in dopamine receptor availability in the striatum[54]. Meta-analysis of 40 neurophysiological studies of PIU has shown that, regardless of the content, Internet-dependent behavior is characterized by a significant violation of inhibitory control, stop-signal task, decision-making, and working memory[55]. The meta-analysis by Zhang *et al*[56] has revealed the presence of a common pattern in a brain structural change related to chemical and behavioral addictions: Changes in prefrontal and insula areas associated with increased impulsivity[56]. Several meta-analyses and reviews have been published recently: Structural and functional brain alterations for a specific form of PIU – computer games addiction[57-59]. The features of electroencephalography in Internet addiction were analyzed in a recent review by Sharifat and Suppiah[60]. Distinctive characteristics of functional electroencephalography were revealed among patients with computer game addiction[61].

It should be noted that most of the above-mentioned studies have been conducted for cases of computer games addiction or generalized (undifferentiated by the content consumed) Internet addiction. The recently proposed for various types of behavioral addictions updated interaction of person-affect-cognition-execution (I-PACE) model theoretically substantiates the neurobiological mechanism of addictive behavior, which consists in an imbalance between structures of frontostriatal circuits (limbic/reward-oriented brain circuits and prefrontal control)[62]. The model has been intensively studied for gambling and gaming disorders, but not for PSMU. Despite this, a line of structural and functional neuroimaging findings concerning the I-PACE model for PSMU was published to date[63-68]. Neuroimaging studies for PSMU were analyzed by Wegmann *et al*[69]; a conclusion was made about the significant association of PSMU with reward processing and reinforcement learning. A recent study by Sadeghi *et al*[70] has revealed that email addiction positively correlates with depression and gray matter volume of the left rostrolateral prefrontal cortex closely involved in cognitive processes[70].

There is some evidence of autonomic nervous system dysfunction involvement in the pathogenesis of Internet addiction, in particular, by the imbalance of the sympathetic and parasympathetic divisions[71, 72]. A general decrease in immune functions was revealed among Internet-addictive individuals. The authors link this fact with a common risk factor, *i.e.* stress, which can affect the activity of the sympathoadrenal axis and increase cortisol production[35]. The role of chronic stress in the formation of PSMU has been shown by several studies[12,73,74]. It is characteristic that the high activity of the autonomic nervous system's sympathetic part was observed when analyzing the heart rate of adolescents with Internet addiction[36,37]. Data on the level of cortisol for Internet addiction are contradictory[75-77]; additional research is required, in particular, concerning the long-term cortisol content, which can be a good marker of chronic stress and mental problems[78].

Several neurotransmitters and neurotrophic factors may be involved in the neurobiological mechanisms of Internet addiction formation[79-81]. Neurochemical pathways include metabolic disorders of dopamine, serotonin, opioids, and some other neurotransmitters that affect reward processing, executive functioning, salience attribution, and habit formation, as well as in the case of substance-use disorders[82]. The participation of these neurotransmitters is partially confirmed by the effectiveness of some pharmacological agents controlling the corresponding neurochemical pathways [83,84]. Exercise-based interventions also may be efficient for Internet addiction (including PSMU)[85], by regulating the autonomic nervous system, the morphology of some parts in the central nervous system, and the exchange of neurotrophic factors and neurotransmitters, in particular dopamine[72].

Oxytocin, which is called the hormone of trust, social connection, and emotional attachment, is promising for the PSMU study. It plays an extremely important role in establishing emotional social contacts, including those using social networks[80,86]. Bonassi *et al*[87] showed that a low level of parental care was associated with low activity on Instagram for carriers of the A-allele in the polymorphic region rs2254298 for the oxytocin receptor gene[87]. The same group of researchers identified a greater number of followers among carriers of the A/A genotype in the region rs53576 for the oxytocin receptor gene in comparison with carriers of the G-allele[88].

A significant number of studies show a pathophysiological relationship between the functioning of the oxytocinergic system and the formation of various forms of addictive behavior[89]. The effectiveness of exogenous oxytocin in the treatment of various addiction types has been shown both in experimental animal studies[90] and in a whole series of clinical studies[89]. It is assumed that the relief of physical symptoms and an increase in emotional tone during withdrawal, reduction of anxiety, increased susceptibility to verbal interventions, facilitating the restoration of social contacts, and, finally, the physiological reduction of established tolerance are the main mechanisms of oxytocin therapeutic

impact for chemical addictions. The hypothesis of oxytocin's antistress effect as a possible protective factor seems convincing since psychological stress is an important etiological cause of the development of pathological addictions[91].

The following are promising neurotransmitters and neurotrophic factors in addition to oxytocin, whose role in the pathogenesis of addictive Internet behavior in adolescents is also highly probable, but still insufficiently studied:

Melanocortin (α-Melanocyte-stimulating hormone). An important role of melanocortin in the development of pathological addiction is suggested by recent studies by Orellana *et al*[92]. There was a tendency to increase melatonin levels in the presence of computer games addiction[93];

Neurotensin. It is actively involved in the modulation of dopamine signalling and the formation of pathological addictions, attempts have been made to treat some addictions with synthetic neurotensin [94];

Orexin. It is supposed to be involved in the formation of sleep disorders and addictive behavior[95]. Choi *et al*[93] demonstrated an increase of orexin in the plasma of adolescents with Internet gaming disorder a while ago[93];

Substance P (neurokinin A). Impairment in the production of substance P is thought to be associated with the development of various pathological addictions; active attempts are currently being made to treat addiction by modulating the activity of neurokinin receptors[96,97];

Brain-derived neurotrophic factor (BDNF). This is a neurotrophic factor that plays a role in the development of addiction[98,99]. Data on the association of BDNF expression with Internet-addictive behavior are contradictory. Some authors found elevated plasma levels among addicts, the others did not confirm such an association[72,81]. A recent study by Choi *et al*[93], which has been mentioned above, found no direct link between addiction and BDNF levels, although it revealed a negative correlation with the time spent playing a computer game[93].

Glial cell line-derived neurotrophic factor (GDNF). It is a neurotrophic factor that plays an important role in supporting the function of dopaminergic neurons. A decrease in the level of GDNF in plasma was detected among Internet gaming addicts; besides, the expression of BDNF was negatively correlated with the severity of computer games addiction[100].

It is important to note that the vast majority of studies on neuropeptides and neurotrophic factors have been conducted for computer game addiction, as in the case of neuroimaging and neurophysiological research methods.

GENETICS OF INTERNET ADDICTION

Unlike other types of addictive behavior (for example, substance abuse or gambling), a very small number of studies have been devoted to the search for genetic predictors of Internet addiction. In the first twin study (2014) the authors managed to prove the presence of an innate component based on the results of a survey of 825 adolescents from the Chinese population. The component was estimated at 58%–66%[101]. Similar results were obtained a little later in the study of Turkish (19%–86%, 2014[102]) Dutch (48%, 2016[103]), Australian (41%, 2016[104]), and German (21%–44%, 2017[105]) twin cohorts. Positive genetic correlations (20%–40%, 2012) were also discovered in the study of various mobile phone use patterns by twins[106]. Although these data are limited by the volume of samples and various ethnic and geographic conditions, there is likely a tendency for a greater contribution of genetic factors in males.

Thus, the presence of a genetic component in Internet addiction formation has been convincingly shown by twin studies by the example of different populations, but no specific genes involved in the mechanisms of such heritability have been identified. Small pilot studies, however, verified polymorphic regions of nine candidate genes, the following are among those:

r1800497 [dopamine D2 receptor gene (*DRD2*), Taq1 A1 allele] and rs4680 [methionine variant of dopamine degradation enzyme catecholamine-o-methyltransferase gene (*COMT*)] – the first of such studies (2006–2007) conducted among adolescents in South Korea and showed an association between minor alleles connected with low dopamine production (rs4680) and a low number of dopamine receptors in the prefrontal cortex (rs1800497) with the presence of pathological Internet gaming disorder [107]. At the same time, *DRD2* A2 allele (high-activity) homozygotes and A1 allele (low-activity) carriers demonstrated no significant differences concerning Internet addiction; neither differences were revealed when comparing *COMT* high-activity (H) variant homozygotes and low-activity (L) variant carriers [108]. Later, the association of the C allele carrier rs1800497 (*DRD2* gene) with computer games addiction was confirmed for young adults[109]. Another study did not prove such a fact[110]. It is known that the *DRD2* gene is in linkage disequilibrium with the *ANKK1* gene, which plays a significant role in the formation of chemical addictions[111]. Therefore, by now, it is not possible to accurately establish the association of Internet addiction with the reception of dopamine at the DRD2 level[45]. The association of the homozygous variant Val/Val (GG) rs4680 (Val158Met, *COMT* gene) with addiction to computer games was further confirmed by the study by Yen *et al*[112] in 2022; In addition, a recent study by Kim *et al*[113] showed that the presence of interpersonal stress for *DRD2* rs6277 T allele and

rs1800497 Taq1 A1 allele showed higher scale values of computer games addiction[113].

rs6277 (promoter of the *DRD2* gene, *141C Ins/Del* polymorphism) – although a direct association between rs6277 polymorphism and Internet addiction has not been established, the *-141C* polymorphism may play a role in the pathogenesis of addiction as a mediator of temperament characteristics[110]; the dopamine D4 receptor gene (*DRD4* gene, VNTR polymorphism in exon 3) – as it was shown, the carriers of *DRD4* 4R/4R variants are more predisposed to the formation of generalized Internet addiction[108]. More recent studies have not shown an association with Internet-addictive behavior[114,115];

rs25531 (serotonin transporter gene (*SS-5HTTLPR*), short allelic variants) – the research by Lee *et al*[116] demonstrated that short allelic variants of the serotonin transporter gene might be associated with Internet addiction. Similar data were later obtained by Sun *et al*[108] but for men only[108]. As a large number of studies have shown, these genetic variants are also linked to a predisposition to depression, which is the most frequently detected comorbid condition among Internet-addictive individuals. Recent studies revealed that a link between depression and autistic personality traits with generalized Internet addiction could be modulated by such polymorphism (*5-HTTLPR*/rs25531), as well as ethnic and geographic factors[115,117].

rs1044396 [nicotinic acetylcholine receptor subunit alpha 4 gene (*CHRNA4*)] – study by Montag *et al*[118] revealed an association between Internet addiction and the rs1044396 CC genotype, which can also be associated with nicotine addiction and attention disorders. Later, Jeong *et al*[119] conducted a pilot study of the target exome, involving 30 adults with addiction to computer games and 30 healthy individuals, which included a study of 72 candidate genes. This study showed a statistically convincing association with one site only – rs1044396. No such association was found in another study[114];

rs2229910 [neurotrophic tyrosine kinase receptor type 3 gene (*NTRK3*)]– Kim *et al*[120] have conducted in turn a pilot study of the target exome involving 30 adults with addiction to computer games and 30 healthy individuals, which included a study of 83 polymorphic sites. Their study also revealed a statistically convincing association with one site only – rs2229910, presumably also associated with anxiety-panic, depressive disorders, obsessive-compulsive disorder, and psychologically determined eating disorders;

rs28364027 [Corticotropin Releasing Hormone Receptor 1 gene (*CRHR1*)] – a study involving Korean adolescent boys revealed that carriers of the AA genotype and the A allele were more predisposed to online computer games addiction[114]. It was previously determined that corticotropin-releasing hormone was involved in the mechanisms of negative effects realization when weaning from the addiction factor[121] and was associated with the risk of alcohol dependence for adolescents, especially when combined with stressful effects[122-124];

rs1137070 [monoamine oxidase-A gene (*MAOA*), EcoRV polymorphism] – the association of this polymorphism with an addiction to computer games with a mediator effect of hostility was evaluated for young adults. Participants with the TT rs1137070 genotype had a higher odds ratio of 2.52 (1.37-4.64) for gambling addiction compared with carriers of the C allele[125];

rs2268498 [oxytocin receptor gene (*OXTR*)] – it has been shown that male carriers of the TT genotype (but not female) have lower levels of generalized Internet addiction compared to C allele carriers[126];

rs6265 (*BDNF* gene) – Russian researchers discovered in 2019–2020 that genetic polymorphism of *BDNF* rs6265 (Val66Met), as well as the abovementioned *DRD4* exon 3 VNTR and *NTRK3* rs2229910, are were with the risk of generalized Internet addiction for young adults[127].

The latest (2022) review by Werling and Grünblatt[128] and the data presented in this article demonstrate that all currently known studies of genetic associations have been conducted for computer games addiction or (less often) for generalized Internet addiction. As far as is known, not a single study of genetic associations concerning PSMU has been published.

DISCUSSION

Neurobiology and genetics research on Internet-addictive behavior conducted over the last 10–15 years has allowed accumulating the necessary amount of knowledge to make certain intermediate conclusions, summarized recently in a significant number of meta-analyses and reviews. A large number of neuroimaging and neurophysiological studies have shown that Internet addiction is characterized by certain structural and functional features of the brain, accompanied by a significant violation of inhibitory control (increased impulsivity as a common factor in various forms of addictive behavior), stop-signal task, decision-making, and working memory. It has been discovered that, like other types of chemical and behavioral addictions, Internet addiction is characterized by an impairment of the metabolism of dopamine, serotonin, opioids, and some other neurotransmitters, which affects reward processing, executive functioning, salience attribution, and habit formation. A small number of pilot projects partially confirm the genetic basis of Internet addiction pathogenesis, previously demonstrated by twin studies.

An important aspect and trend in modern research on Internet-addictive behavior is an attempt to avoid the study of generalized, undifferentiated Internet addiction in favor of analyzing its specific

forms, such as computer games addiction and PSMU[24,129,130]. At the same time, the vast majority of the mentioned neurobiological studies were focused on computer games addiction (*e.g.* 85% of patients for functional magnetic resonance imaging[131]) and generalized Internet addiction (without taking into account the consumed content). Even though a certain number of neuroimaging studies have been conducted for PSMU[66,67,69], there is practically no research on neuropeptide and genetic associations for PSMU to date. Attempts to use neuroimaging to look for common neurobiological mechanisms between PSMU and other addictions have so far produced conflicting results, at least in relation to the prefrontal cortex[66,67,132-134].

Although studies of generalized Internet addiction – especially for women – can be partially extrapolated to PSMU (taking into account common gender and psychosocial characteristics for some populations[24]), it is extremely important to study the directly verified PSMU, which differs significantly from computer games addiction. Further research is needed to better identify commonalities and differences in the neurobiology of different types of addictive online behavior in the context of the content consumed, the devices and technologies used, and the stability of symptoms across age. The study of neuropeptides directly involved in social bonding: Oxytocin and vasopressin, as well as orexin, melatonin, and neurotrophic factors (BDNF and GDNF), looks promising for PSMU neuromolecular associations.

Genetic studies conducted on small samples, conflicting and still quite scarce, should also be expanded to specific forms of Internet addiction, such as PSMU and smartphone addiction. Replication studies with a large number of participants are urgently needed, as well as genome-wide association and polygenic risk score estimate projects.

CONCLUSION

In this narrative review, we discussed neurobiological risk factors for Internet addiction with a focus on current evidence on the association between PSMU and structural/functional characteristics of the brain and autonomic nervous system, neurochemical correlations, and genetic features. A review of the literature shows that the vast majority of the mentioned neurobiological studies were focused on computer games addiction and generalized Internet addiction (without taking into account the consumed content). Even though a certain number of neuroimaging studies have been conducted for PSMU, there is practically no research on neuropeptide and genetic associations for PSMU to date. This fact points to the extremely high relevance of such studies.

FOOTNOTES

Author contributions: Tereshchenko SY analyzed the data and wrote the manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Li L
L-Editor: A
P-Editor: Cai YX

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 May 19; 13(5): 174-181

DOI: 10.5498/wjp.v13.i5.174

ISSN 2220-3206 (online)

MINIREVIEWS

Deep brain stimulation for autism spectrum disorder

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Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Kaur M, United States; Moshref RH, Saudi Arabia

Received: December 23, 2022
Peer-review started: December 23, 2022
First decision: March 1, 2023
Revised: March 9, 2023
Accepted: March 29, 2023
Article in press: March 29, 2023
Published online: May 19, 2023

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Abstract

Deep brain stimulation (DBS) is a medical treatment that aims to obtain therapeutic effects by applying chronic electrical impulses in specific brain structures and neurological circuits. Over the years, DBS has been studied for the treatment of many psychiatric disorders. Scientific research on the use of DBS in people with autism has focused this interest mainly on treatment-resistant obsessive-compulsive disorder, drug-resistant epilepsy, self-injurious behaviors (SIB), and aggressive behaviors toward the self. Autism spectrum disorder (ASD) includes a group of developmental disabilities characterized by patterns of delay and deviance in the development of social, communicative, and cognitive skills and the presence of repetitive and stereotyped behaviors as well as restricted interests. People with autism often have numerous medical and psychiatric comorbidities that worsen the quality of life of patients and their caregivers. Obsessive-compulsive symptoms can be found in up to 81.3% of people with autism. They are often severe, refractory to treatment, and particularly difficult to treat. SIB has a high prevalence in severely retarded individuals and is often associated with autism. Drug treatment of both autism and SIB presents a therapeutic challenge. To describe the current state of the art regarding the efficacy of DBS in people with ASD, a literature search was conducted for relevant studies using the PubMed database. Thirteen studies have been considered in this paper. Up to date, DBS has been used for the stimulation of the nucleus accumbens, globus pallidus internus, anterior limb of the internal capsule, ventral anterior limb of the internal capsule, basolateral amygdala, ventral capsule and ventral striatum, medial forebrain bundle, and posterior hypothalamus. In the total sample of 16 patients, 4 were adolescents, and 12 were adults. All patients had symptoms resistant to multiple drug therapy. Many patients taken into consideration by the studies showed clinical improvements as evidenced by the scores of the psychopathological scales used. In some cases, clinical improvements have varied over time, which may require further investigation. Among the new therapeutic perspectives, DBS could be a valid option. However, further, and more in-depth research is needed in this field.

Key Words: Deep brain stimulation; Autism spectrum disorder; Comorbidities; Drug

resistant; New therapeutic perspectives

Core Tip: Deep brain stimulation (DBS) is a medical treatment that aims at obtaining therapeutic effects by applying chronic electrical impulses in specific brain structures and neurological circuits. Autism spectrum disorder comprises a group of developmental disabilities that are often associated with numerous medical and psychiatric comorbidities that worsen the quality of life of patients and their caregivers. Comorbidities often require multiple drug treatments with an increasing rate of treatment resistance. Thirteen studies have been considered in this paper. Up to date, DBS has been used for the stimulation of the nucleus accumbens, globus pallidus internus, anterior limb of the internal capsule, ventral anterior limb of the internal capsule, basolateral amygdala, ventral capsule and ventral striatum, medial forebrain bundle, and posterior hypothalamus. In the total sample of 16 patients, 4 were adolescents (all males), and 12 were adults (5 males and 7 females). All patients had symptoms resistant to multiple drug therapy. Only one patient was considered not a responder to DBS. Among the new therapeutic perspectives, as evidenced by the studies presented in this article, DBS could be a valid option. However, further, and more in-depth research is needed in this field.

Citation: Marini S, D'Agostino L, Ciamarra C, Gentile A. Deep brain stimulation for autism spectrum disorder. *World J Psychiatry* 2023; 13(5): 174-181
URL: https://www.wjgnet.com/2220-3206/full/v13/i5/174.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i5.174

INTRODUCTION

Deep brain stimulation (DBS) is a medical treatment that aims at obtaining therapeutic effects of certain neurological and psychiatric disorders by applying chronic electrical impulses in specific brain structures and neurological circuits[1]. The modern beginning of DBS can be traced back to the work of Benabid, Pollak, and colleagues at the Joseph Fourier University in Grenoble in the 1980s[2], based on several decades of clinical work and biophysical discoveries[3]. The clinical success of DBS has opened the door to other neurostimulation therapies such as transcranial magnetic stimulation and has motivated an intense analysis of the neural circuits affected by neurological disorders such as Parkinson's disease[4]. The first use of DBS for a psychiatric indication was published by Nuttin *et al*[5] in 1999. Over the years, DBS has been studied for the treatment of obsessive-compulsive disorder (OCD)[6], tardive dyskinesia (TD)[7], treatment-resistant depression[8-10], Tourette's syndrome[11], treatment-refractory anorexia nervosa[12].

Autism spectrum disorder (ASD) includes a group of developmental disabilities characterized by patterns of delay and deviance in the development of social, communicative, cognitive skills and the presence of repetitive and stereotyped behaviors as well as restricted interests[13]. In addition to core symptoms, people with ASD often have numerous medical and psychiatric comorbidities that worsen the quality of life of patients and their caregivers[14]. Obsessive-compulsive symptoms can be found in up to 81.3% of people with ASD. They are often severe, refractory to treatment, may be clinically confused with core symptoms of ASD, and are particularly difficult to treat[15,16].

Self-injurious behavior (SIB) has been defined as "behavior which produces physical injury to the individual's own body"[17]. SIB has a high prevalence in severely retarded individuals and is often associated with autism. Indeed, up to 42% of people with autism may exhibit repetitive SIBs[18]. Additionally, over 75% of children with SIB will have these behaviors persist into adulthood sometimes resulting in serious harm and even death[19-21].

In approximately two-thirds of cases, SIB is maintained by social variables[22], while in approximately one-quarter of cases, SIB occurs independently of social consequences [automatic reinforcement subtype, automatically maintained SIB (ASIB)][23]. ASIB is considered the most challenging subtype to treat, because the events that cause and maintain it are not known. Currently, ASIB is classified into three subtypes[24,25]. Subtype 1 ASIB is characterized by higher rates of SIB in conditions with minimal external stimulation. Subtype 2 ASIB is characterized by high or variable rates of SIB across high and low stimulation conditions. Subtype 3 ASIB is characterized by the presence of self-restraint[26].

Drug treatment of both autism and SIB presents a therapeutic challenge. Some drugs such as risperidone, aripiprazole, and fluoxetine have shown positive efficacy evidence for treating irritability in people with ASD but not for specifically reducing self-harm[27-30]. Currently, the most successful therapeutic strategies for SIBs are based on applied behavioral analysis techniques[31,32] combined

with pharmacological treatments with neuroleptics, mood stabilizers, sedatives, but some patients remain refractory[33].

The present work aims to describe the current state of the art regarding the efficacy of DBS in people with ASD.

A literature search was conducted for relevant studies using PubMed database. In drafting this paper, the authors decided to consider the published articles, classifying them according to the brain regions stimulated by DBS and not according to the pathologies treated.

There are clinical studies on animal models in the literature, but in this article, we will only consider human clinical studies, as we are more interested in the usefulness and efficacy of DBS in clinical practice.

Scientific research on the use of DBS in people with autism has focused this interest mainly on treatment-resistant OCD, drug-resistant epilepsy (DRE), SIBs, and aggressive behaviors toward self. Four studies in the literature have used DBS to treat OCD and other comorbidities in people with ASD [34-37] (see Table 1). Five studies investigated the efficacy of DBS in the treatment of SIB in people with autism[38-42]. A protocol for the application of DBS in children and young adults has recently been published, but the results are not yet available[43]. Furthermore, Heiden *et al*[44] published a retrospective study of the use of DBS in ten patients, including two patients with autism, but the results were not extrapolated for the different pathologies. This makes it impossible to consider the efficacy of DBS in the autistic patients included in the study. Torres *et al*[45] also published a study on the use of DBS for aggression in 7 patients, 5 of whom had autism. The results were not divided for a single patient not allowing to identify of the efficacy of DBS for autistic patients. Recently Benedetti-Isaac *et al* [46] published a follow-up study on the use of DBS in 5 pediatric autistic patients with aggressive behaviors resistant to drug therapy, but the results were not divided by single patient.

In the total sample of 16 patients, 4 were adolescents (all males), and 12 were adults (5 males and 7 females). All patients had symptoms resistant to multiple drug therapy. Generally, treatment resistance consists of three core components: Correct psychiatric diagnosis, adequate treatment, and symptoms not responding adequately despite treatment[47].

USE OF DBS IN PEOPLE WITH AUTISM

In patients with autism, the literature published so far has used DBS for the stimulation of the nucleus accumbens (NAc), Globus Pallidus internus (GPi), anterior limb of internal capsule (ALIC), ventral ALIC (vALIC), basolateral amygdala, ventral capsule and ventral striatum, medial forebrain bundle (MFB), posterior hypothalamus (PHyp).

Three studies[33,34,39] have applied DBS to the NAc of people with autism and numerous comorbidities. Past literature has shown that the NAc may be a key structure for the control of OCD symptoms[48,49], in modulating aggression[50], and in improving the response to social stimuli in ASD [51].

Segar *et al*[34] showed the efficacy of DBS in a 24-year-old female patient with Kleefstra Syndrome with comorbidities of ASD, OCD, and Tourette-like symptoms. The clinical improvements mainly concerned the patient's compulsive behaviors, coprolalia, language, and social interaction, with marked improvement in the global assessment of functioning scores.

In 2019, Doshi *et al*[35] reported a 42-year-old woman with autism who underwent bilateral NAc DBS for control of severe OCD and aggression (violent outbursts against others and hitting and injuring others and herself) refractory to pharmacological treatments. In the days following the surgery, the patient had shown a marked difference in her behavior and eye contact, and appropriate laughter. Clinical improvements were consistent with improvements in administered psychopathology scale scores [Yale-Brown obsessive-compulsive scale (Y-BOCS), Hamilton depression scale, Hamilton anxiety scale, and social communication questionnaire].

Park *et al*[40] observed remarkable clinical improvements in a 14-year-old boy with ASD and SIB treated with bilateral NAc DBS. The clinical improvements (assessed with the Y-BOCS, clinical global impression scale, attention deficit hyperactive disorder rating scale, and social responsiveness scale), were accompanied by functional and structural changes in the brain after DBS, demonstrated using fluorodeoxyglucose positron emission tomography/computed tomography imaging. Furthermore, at the 2-year post-operative evaluation, the boy showed improved language comprehension and expression skills, and improved eye contact.

Two studies[38,41] have applied GPi DBS to people with autism to improve movement impairments. Stocco *et al*[39] applied GPi DBS to two people with ASD, severe stereotypies, and SIB (one patient simultaneously received DBS in GPi and the Anterior limb of the internal capsule). Only the patient who received GPi DBS had maintained clinical improvements over time, even reducing drug therapy. As suggested by the authors, GPi DBS may provide relief for severe pharmacologically unresponsive stereotypies in some patients. Indeed, the characteristics of the ideal patient to be subjected to DBS should be better explored.

Table 1 Summary of deep brain stimulation studies for autism spectrum disorder

Ref.	Patients' age/sex	Diagnosis and comorbidities	Indications for DBS	DBS targets	Pre-BDS scores	Post-BDS scores	Main outcomes
Segar *et al*[34]	24, F	KS, OCD, ASD, epilepsy	Biting hands, picking skin	NAc	GAF 20	GAF 50-60	Clinical improvements mainly for compulsive behaviors, coprolalia, language and social interaction
Doshi *et al*[35]	42, F	OCD, ASD, epilepsy	OCD, aggression	NAc	Y-BOCS 19, HAMD 20, HAS 30, SCQ 26	Y-BOCS 5, HAMD 15, HAS 18, SCQ 16	Marked improvements in OCD symptoms, aggressive behavior, eye contact and appropriate laughter
Park *et al*[40]	13, M	ASD, Develop-mental Delay	Self-mutilation, face-hitting	NAc	CGI-S 6; ABC 106; CY-BOCS 22; K-ARS 54; SRS 101	CGI-S 4; ABC 40; CY- BOCS 7; K-ARS 36; SRS 98	Decreased in SIB and improvement in verbal communication
Stocco *et al* [39]	19, F	ASD, ID, monosomy 2q and trisomy 20p	Self-picking, Severe stereotypes	GPi	JHMRS 46	JHMRS 4	Marked improvement in the SIB and dystonia
	17, M	ASD, ID, anxiety	Punching of arms and legs, biting, Severe stereotypes	GPi and ALIC	JHMRS 67	JHMRS 19	Substantial initial improvement in SIB, but the benefit disappeared after 6 mo and was not regained
Kakko *et al* [42]	19, M	ASD, ID, epilepsy, TD	Aggression, self-mutilation, lacerations	GPi	NR	NR	TD symptoms were markedly improved. The anxiety, behavioral symptoms had ceased
Sturm *et al*[38]	13, M	Kanner's Autism, ID, infantile cerebral palsy	Self-aggression	Basolateral amygdala	Parental score of 6	Parental score of 2	Decreased in SIB and core symptoms of the autism spectrum in the emotional, social, and cognitive domains
Davis *et al*[36]	44, M	OCD, ASD, MDD, tics, epilepsy	OCD, aggression	Ventral capsule/ventral striatum	Y-BOCS, MADRS, YGTSS	Y-BOCS, MADRS and YGTSS scores decreased by 68%, 66%, and 75% respectively	The clinical improvements were maintained, albeit with fluctuations, after 3 yr. No effect on core symptoms of ASD
Graat *et al*[37]	39, F	OCD, ASD, Depressive episodes	OCD	vALIC	Y-BOCS 33, HAMD 27	Y-BOCS 12, HAMD 7	50% reduction of OCD symptoms following DBS, especially obsessions
	54, F	OCD, ASD	OCD	vALIC, then MFB	Y-BOCS 38, HAMD 30	Y-BOCS 18, HAMD 4	Initially did not benefit from DBS. Thereafter OCD symptoms improved and decreased by more than 50%
	32, M	OCD, ASD, ADHD	OCD, aggressive intrusions	vALIC	Y-BOCS 31, HAMD 18	Y-BOCS 23, HAMD 12	Partial responder probably due to several transient side effects of DBS
	31, F	OCD, ASD, DD, OCPD, AN	OCD	vALIC	Y-BOCS 34, HAMD 30	Y-BOCS 32, HAMD 27	Only some subjective improvements
	51, M	OCD, ASD	OCD	MFB	Y-BOCS 34, HAMD 5	Y-BOCS 0, HAMD 2	Obsessive-compulsive symptoms disappeared entirely. Improved confidence and less social

							shyness
	30, F	OCD, ASD, PDD, GAD, UPD	OCD,	MFB	Y-BOCS 34, HAMD 23	Y-BOCS 22, HAMD 22	35% reduction of OCD symptoms following DBS
Benedetti-Isaac *et al*[41]	27, M	ASD, TBI, epilepsy	Aggressive behavior towards self	PHyp	OAS 9	OAS 1	Improvements in seizures, in aggressive behavior, in quality of life, in daily living skills
	16, M	ASD, epilepsy, Developmental Delay	Self-aggression	PHyp	OAS 8	OAS 1	Aggressive behavior controlled for a month. After 2 mo it reappeared as before surgery

ABC: Antecedent, behavior, consequence; ADHD: Attention deficit hyperactive disorder; ALIC: Anterior limb of internal capsule; AN: Anorexia nervosa; ASD: Autism spectrum disorder; CGI-S: Clinical global impressions-severity; CY-BOCS: Children's Yale-Brown obsessive-compulsive scale; DBS: Deep brain stimulation; DD: Depressive disorder; F: Female; GAD: Generalized anxiety disorder; GAF: Global assessment of functioning; GPi: Globus Pallidus internus; HAMD: Hamilton depression scale; HAS: Hamilton anxiety scale; ID: Intellectual disability; JHMRS: Johns Hopkins motor stereotypy rating scale; K-ARS: Korea attention deficit hyperactive disorder rating scale; KS: Kleefstra syndrome; M: Male; MADRS: Montgomery-Asberg depression rating scale; MDD: Major depressive disorder; MFB: Medial forebrain bundle; NAc: Nucleus accumbens; NR: Not reported; OAS: Overt aggression scale; OCD: Obsessive-compulsive disorder; OCPD: Obsessive-compulsive personality disorder; PDD: Persistent depressive disorder; PHyp: Posterior hypothalamus; SCQ: Social communication questionnaire; SRS: Social responsiveness scale; TBI: Traumatic brain injury; TD: Tardive dyskinesia; UPD: Unspecified personality disorder; vALIC: Ventral anterior limb of the internal capsule; Y-BOCS: Yale-Brown obsessive-compulsive scale; YGTSS: Yale global tic severity scale.

Tardive dyskinesia (TD) is probably the most severe form of extrapyramidal symptoms (EPS) secondary to antipsychotic drugs, manifesting usually after months or years of therapy with involuntary choreiform movements and dystonia, frequently affecting the face and tongue[52]. While there are drug treatments for TD, it is often chronic and irreversible. Furthermore, patients with intellectual disabilities (ID) are more susceptible to EPS[53]. Past literature has shown encouraging evidence of DBS in the treatment of dystonic cerebral palsy in children[54]. GPi DBS in a young adult diagnosed with ASD and ID markedly improved TD symptoms[42]. The anxiety, restlessness, behavioral symptoms, and self-destructive behavior have ceased. Furthermore, the patient's skills, especially communication skills, have returned to the level before the presentation of aggressive seizures.

In 2013 Sturm *et al*[38] treated a 13-year-old boy with ASD and SIB with DBS in the amygdaloid complex and supra-amygdaloid projection system. The implantation of the electrodes in the two areas had been made necessary to testify that possible mechanical irritations, micro-lesions or inflammations in the projections of the amygdala were not effective in controlling the symptoms. Only stimulation of the basolateral nucleus of the amygdala proved effective in improving self-harm and core symptoms of ASD in the emotional, social, communicative, and cognitive domains in a 24-mo follow-up.

Davis *et al*[36] subjected a 44-year-old man with treatment-resistant OCD, major depressive disorder, ASD, and tics to DBS. DBS targets were represented by the ventral capsule and ventral striatum. After 3 years, the clinical improvements obtained within 6 mo of the surgery were maintained, albeit with fluctuations. Indeed, the scores on the Y-BOCS and the Montgomery-Asberg depression rating scale indicated that his symptoms were in the mild range, while the scores on the Yale global tic severity scale were much improved. On the other hand, as expected by the authors, full resolution of symptoms was never achieved and the patient continued to experience the clinical features of ASD.

In 2022, Graat *et al*[37] published the results of six patients with refractory OCD comorbid with ASD who underwent DBS of the vALIC or MFB. The efficacy of DBS on obsessive-compulsive and depressive symptoms was tested with the Y-BOCS and the Hamilton depression rating scale, respectively. Considering Y-BOCS scores, four patients were responders (> 35% decrease Y-BOCS), one patient was a partial responder (25%–35% decrease Y-BOCS) probably due to transient side effects of DBS, and one patient was a non-responder (< 25% decrease Y- BOCS), even though she had subjective symptom improvements.

After considering previously published studies[55,56] on the evidence of surgical treatment of the PHyp in aggressive drug-resistant behaviors, Benedetti-Isaac *et al*[41] published the results of PHyp DBS in 5 patients with DRE associated with intractable aggressive behavior. Only two patients among those recruited were also affected by ASD. A 27-year-old man with ID associated with severe autism, reported improvement in quality of life, better access to special education, and improvements in daily living activities. On the other hand, the aggressive behavior of a 16-year-old boy with ID and severe autism, was partially controlled for a month, but after 2 mo it reappeared as before surgery despite stimulation.

Only one study[37] reported adverse effects of DBS. One patient showed severe transient side effects: an infection of the DBS system that required removal of the system and, at a later stage, a suicide attempt (overdosed of quetiapine). Suicidality resolved without changing stimulation settings. Other

transient adverse effects were represented by restlessness, hypomania, tics, impulsivity, agitation, forgetfulness, cramp/joint pain, headache, memory complaints, agitation, hallucinations, and delusions.

CONCLUSION

The multiple comorbidities associated with ASD and the drug resistance in some patients lead to a decrease in the quality of life of patients and their family members or caregivers. To date, DBS has been used in people with autism solely to treat comorbid conditions. Despite encouraging results for the treatment of drug-resistant diseases, positive effects on core symptoms of ASD have only occasionally been reported. Finding new and innovative treatments is a fundamental aspect for those who take care of people with autism and comorbid conditions resistant to conventional treatments. Among the new therapeutic perspectives, as highlighted by the studies presented in this article, DBS could be a valid option to improve the management of disabling pathologies comorbid with autism and consequently the quality of life. However, further, and more in-depth research is needed in this field.

FOOTNOTES

Author contributions: Marini S and D'Agostino L wrote the article; Ciamarra C performed the research; Gentile A designed the research study. All authors have read and approved the final manuscript.

Conflict-of-interest statement: This paper was entirely funded by the authors, and no pharmaceutical companies were informed of or were involved in the paper. The authors have no potential conflicts of interest that are directly relevant to the contents of the paper.

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S-Editor: Zhang H
L-Editor: Filipodia
P-Editor: Zhang H

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World Journal of Psychiatry

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World J Psychiatry 2023 May 19; 13(5): 182-190

DOI: 10.5498/wjp.v13.i5.182

ISSN 2220-3206 (online)

MINIREVIEWS

Therapeutic role of psilocybin and 3,4-methylenedioxymethamphetamine in trauma: A literature review

Lakshan N Fonseka, Benjamin KP Woo

Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: He L, China; Pantelis AG, Greece

Received: January 19, 2023
Peer-review started: January 19, 2023
First decision: February 20, 2023
Revised: February 28, 2023
Accepted: April 13, 2023
Article in press: April 13, 2023
Published online: May 19, 2023

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Abstract

With the Food and Drug Administration designation in 2017 of 3,4-methylenedioxymethamphetamine (MDMA) as a breakthrough therapy in post-traumatic stress disorder and psilocybin in treatment-resistant depression, psychedelic drugs have continued to garner the attention of researchers and clinicians for their promise of unmatched, rapid improvement in a multitude of psychiatric conditions. Classic psychedelic drugs including psilocybin, lysergic acid diethylamide, and ayahuasca, as well as non-classic drugs such as MDMA and ketamine, are currently being investigated for a potential therapeutic role in trauma, depressive disorders, and other psychopathologies. However, psilocybin and MDMA each have a functional profile well-suited for integration with psychotherapy. The present review focuses on psilocybin and MDMA in psychedelic-assisted therapy (PAT), as these studies compose most of the literature pool. In this review, we discuss the current and future uses of psychedelic drugs, with an emphasis on the role of MDMA and psilocybin in PAT in the setting of trauma and related comorbidities on the efficacy of psychedelic drugs across multiple psychiatric disorders. The article concludes with thoughts for future research, such as incorporating wearables and standardization of symptom scales, therapy styles, and assessment of adverse drug reactions.

Key Words: Psychedelics; Trauma; Depression; Methylenedioxymethamphetamine; Ecstasy; Psilocybin

Core Tip: Psychedelic-assisted therapy with psilocybin or 3,4-methylenedioxymethamphetamine (MDMA) is strongly supportive across psychiatric conditions, especially trauma and related comorbidities, as demonstrated through a pattern of rapid and sustained symptom relief. Both treatments seem to have benefits beyond the Food and Drug Administration breakthrough designations of treatment-resistant depression for psilocybin and post-traumatic stress disorder for MDMA.

Citation: Fonseka LN, Woo BK. Therapeutic role of psilocybin and 3,4-methylenedioxymethamphetamine in trauma: A literature review. *World J Psychiatry* 2023; 13(5): 182-190
URL: https://www.wjgnet.com/2220-3206/full/v13/i5/182.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i5.182

INTRODUCTION

The psychedelic renaissance of modern psychiatry can trace its resurgence to 2017-2018, when the Food and Drug Administration (FDA) designated breakthrough therapy status to psilocybin in treatment-resistant depression and 3,4-methylenedioxymethamphetamine (MDMA) in post-traumatic stress disorder (PTSD). Psychedelics can be broadly categorized as classic psychedelics that act as agonists at the 5-HT_{2A} receptor [*i.e.*, psilocybin, lysergic acid diethylamide (LSD), ayahuasca/dimethyltryptamine], empathogens that increase serotonin levels (*i.e.*, MDMA), antagonists at N-methyl-D-aspartate receptors (*i.e.*, ketamine), and atypical hallucinogens with effects across neurotransmitter systems[1,2]. Psychedelic-assisted psychotherapy (PAT) involving MDMA or psilocybin composes most of the literature pool, though studies involving other psychopathologies and compounds have also been investigated to a lesser extent. The predominance of both psilocybin and MDMA in the literature may be attributed to the properties that make each an ideal adjunct to psychotherapy.

Psilocybin and its active metabolite psilocin are derived from psychoactive mushroom species originally used in ceremonial settings to facilitate spiritual experiences in Central and South America, later introduced to Western culture in the 1950s[1,3]. As a classic psychedelic, psilocybin is a 5-HT_{2A} receptor agonist that was found to produce rapid yet enduring improvement in treatment-resistant depression and major depressive disorder (MDD)[4-6]. More recently, psilocybin was compared to escitalopram in a double-blind trial. Both treatments were found to have similar efficacy in depression, which will be discussed in more detail in the present article[7].

Psilocybin further enhances its synergism with psychotherapy by evoking a sense of unity, ego-dissolution, and awe through "mystical" experiences[8-10]. As described by Vaid *et al*[11] (2022), PAT may enable the processing of emotional experiences that were previously inaccessible due to trauma blocks. This promotes reconnection with the self and "foundational identity deficit repair," a re-stabilization of the core ideas that together represent the conscious identity, self-esteem, and other aspects of the self[11]. As will be described later in this article, patients in recent studies report significant reductions in symptom rating scales, with benefits partly attributed to this mystical component-experiences of oneness or ego-dissolution, connection to self-essence, and a broadened perspective beyond self-imposed limits on thought processes and rigid mental frameworks that may once have been adaptive responses to life events[12,13].

MDMA was initially developed by Merck & Co. for hemostasis in 1912, and its psychoactive effects were not published until 1978. After becoming popularized as recreational drug "ecstasy" in the 1980s [1,14,15], the Drug Enforcement Agency cited concerns of abuse potential and neurotoxicity and assigned schedule I status to MDMA in 1985. MDMA is part of a class of psychedelics, termed empathogens or enactogens, that increase empathy and social connection. Its effects are primarily mediated by serotonergic activity, including serotonin/norepinephrine transporter reuptake inhibition and partial agonism of serotonin receptors (5-HT_{2A}, 5-HT_{1A}, 5-HT_{2C})[1]. By far, MDMA studies formed most of the research elicited by the PubMed search terms. The reasons for the clear bias in the literature and its consequences are varied and discussed in the future directions section. Nevertheless, the research has yielded promising results across psychopathologies, though most research aligns with its FDA designation for PTSD. A recent double-blind, phase 3 clinical trial found that 67% of participants receiving MDMA-assisted psychotherapy no longer met PTSD criteria after 2 mo[16]. These improvements are attributed to several downstream changes in cognition that further complement psychotherapy.

MDMA has been previously shown to decrease amygdala response when patients are presented with angry faces, as well as increase ventral striatum response when viewing happy faces, further supporting that MDMA reduces threat response, enhances reward, and facilitates positive social interactions[1,17,18]. MDMA has the reputation of generating feelings of closeness, connection, and emotional empathy, although similar features also exist in classic psychedelics[19,20]. However, MDMA uniquely offers augmentation of the therapeutic alliance, easefully lowering barriers and enabling the patient to process traumatic memories without feeling overwhelmed[1,21].

MDMA, psilocybin, and other psychedelics appear to induce a temporary period of increased neuroplasticity with associated changes in psychological flexibility[21,22]. Psilocybin studies have demonstrated increased neurogenesis, spinogenesis, and synaptogenesis that facilitate the reconditioning of fear memory and the reversal of stress-induced changes to the prefrontal cortex[23-25]. The plasticity counters the deficits in fear memory extinction seen in PTSD, alleviating distress from the cycle of avoidance and flashbacks associated with persistent traumatic memories[26-28]. Kéri *et al*[29] suggest that psychedelic-induced serotonin-glutamate interactions affect memory pathways responsible for memory destabilization and reconsolidation[29]. The neuroplastic and fear memory changes enrich the benefits drawn from combination with psychotherapy.

The present focus is on psychedelics involved in PAT, namely MDMA and psilocybin as these studies compose much of the literature pool. A literature review was conducted through PubMed database search of ((psilocybin) OR (MDMA)) AND (trauma). The search was also performed on Reference Citation Analysis (https://www.referencecitationanalysis.com/). The aim is to summarize the literature on psychedelic drugs, with an emphasis on the role of MDMA and psilocybin in PAT in the setting of trauma and related depressive disorders, from 2020 to 2022, bridging the gap from Reiff *et al*'s review encompassing articles from 2007 to 2019 on the efficacy of psychedelic drugs across multiple psychiatric disorders[1]. The article concludes with thoughts for future research, such as incorporating wearables and standardization of symptom scales, therapy styles, and assessment of adverse drug reactions.

PSILOCYBIN

With its FDA designation for treatment-resistant depression, it follows to begin the discussion of psilocybin with updates in depression, a common comorbidity in trauma-related conditions. Carhart-Harris *et al*[7] published a clinical trial comparing psilocybin *vs* escitalopram in 59 patients with MDD [7]. The psylocibin group (n = 30) received 25 mg of psilocybin at the start and a second dose at 3 wk, all while receiving 6 wk of daily placebo. The escitalopram group (n = 29) received 1 mg of psilocybin at the start and a second dose of 1 mg at 3 wk, with daily oral escitalopram 10 mg throughout the 6-wk study. The primary outcome measure was changes from baselines scores (range 0 to 27) on the quick inventory of depressive symptomatology (QIDS-SR-16), with a response defined as reduction in score of at least 50% and remission defined as a score of 5 or less.

A response occurred in 70% of the psilocybin group and 48% of the escitalopram group, while remission occurred in 57% of the psilocybin group and 28% of the escitalopram group. Although these differences do not reach significance, it is notable that both psilocybin and escitalopram appear, at a minimum, to have equivalent impacts. The lack of control group prevents the comparison of each treatment to a baseline population, but it is promising that the efficacy is similar between psilocybin and escitalopram. The authors report that while the initial trial design included a placebo group, this became too practically complex and expensive. Other limitations of the study include the duration, as escitalopram may require more time to display its full efficacy. Additionally, the patients in the trial were not from varying socioeconomic or ethnic backgrounds, limiting external validity. The study also included many secondary outcomes, including scores on other symptom scales, but these were not considered useful as the data were unadjusted for multiple comparisons.

Further analysis of the study was conducted by Murphy *et al*[30] regarding the influence of therapeutic alliance. It was found that increased strength of therapeutic alliance led to greater emotional breakthrough and mystical experiences across two PAT sessions[30]. Interestingly, the average symptom severity scores at baseline were in the range for moderate depression[7], highlighting an additional application for psilocybin beyond treatment-resistant depression.

In a patient population with moderate to severe MDD, Davis *et al*[31] performed an 8-wk intervention consisting of two psilocybin dosing sessions less than two weeks apart with supportive psychotherapy. Exclusion criteria illustrate the reduced the severity of depression within the sample population: Selected patients were screened to avoid current antidepressant use, past diagnosis with a psychotic disorder, serious suicide attempts, or prior psychiatric hospitalization. However, enrolled patients required a score of at least 17 on the GRID-Hamilton depression rating scale (GRID-HAMD), the scale used to evaluate outcomes in this study at weeks 1 and 4 post-treatment with psilocybin. A total of 27 patients were selected and randomized into an immediate-treatment group (weeks 1-4, n = 14) and delayed-treatment group (weeks 5-8, n = 12), which served as a waiting list control condition that later received PAT as well. At baseline, the mean GRID-HAMD score was 22.8 with SD 3.9. Patients receiving immediate treatment showed significant reductions at weeks 1 and 4, with mean scores returning at 8.0

(SD 7.1) during week 1 and 8.5 (SD 5.7) at week 4. Overall, 17 patients demonstrated reductions in GRID-HAMD scores of at least 50%, 14 patients went into remission, and 3 patients dropped out before completing the intervention. Although preliminary, the effect sizes seen with psilocybin in this trial are several times larger than that seen in psychotherapy or antidepressant monotherapy[31-33].

The efficacy of psilocybin seen in depression studies likely offers benefits in a trauma-centered approach, due to the widespread comorbidity of trauma with depressive disorders. The role of psilocybin continues to expand outside its FDA designation for treatment-resistant depression. Khan *et al*[34] reported on an open-label study that provided psilocybin-assisted therapy in traumatized AIDS survivors. The authors noted reductions in PTSD symptoms, attachment anxiety, and demoralization. The intent underlying psychedelic use appears to be important. One survey demonstrated that therapeutic intent behind past psychedelic use in patients with history of child maltreatment showed significant reductions in complex trauma symptoms and internalized shame[35]. This further suggests that psilocybin's benefits extend beyond depression and into trauma-related pathologies. Though outside the scope of the present article, psilocybin is being explored across several domains including substance use disorders, neurodegenerative diseases such as Alzheimer's disease[36].

Adverse reactions

In the psilocybin and escitalopram study, the escitalopram group had a higher prevalence of anxiety, dry mouth, sexual dysfunction, and reduced emotional responsiveness. Due to these side effects, four patients self-discontinued the medication and one patient modified regimen to half a daily dose. No patients in the psilocybin group requested dose adjustment or discontinuation[7]. In the trial by Davis *et al*[31], participants reported mild-to-moderate headache, as well as difficult emotions during in-session time only. No serious adverse events were reported or observed[31].

MDMA

In 2021, Mitchell *et al*[16] reported data from a double-blind, phase 3 clinical trial found that 67% of participants receiving MDMA-assisted psychotherapy ceased to meet PTSD criteria after 2 mo[16]. The MDMA-treated group (n = 46) showed significant decreases on clinician-administered PTSD Scale for DSM-5 (CAPS-V) compared to inactive placebo with therapy (n = 44). Participants attended three experimental sessions, spaced four weeks apart. The first session started with 80 mg MDMA and the option for a supplemental half-dose of 40 mg, 1.5-2.5 h later. For the next two sessions, the initial dose was increased to 120 mg with supplemental half-dose of 60 mg. No tolerability issues led to participants being withheld the supplemental doses.

MDMA-assisted therapy led to increases in posttraumatic growth, encompassing increased positivity towards self-perception, relationships, or philosophy of life[37]. Scores from 60 participants, pooled from three phase 2 clinical studies meeting PTSD criteria, were assigned to treatment with 75-125 mg MDMA (n = 45) or active control (0-40 mg MDMA, n = 15). The MDMA group had significantly improved scores on the posttraumatic growth inventory and greater reduction in PTSD symptom severity at 12 mo, and 67% of participants no longer met criteria for PTSD. MDMA may promote adaptive stress responses in PTSD that lead to the downstream benefits seen in recent research, such as reduced ratings of PTSD symptom severity by clinicians[38,39].

MDMA has also been studied in the setting of couples therapy, in which one partner has a current diagnosis of PTSD. One study included 6 romantic dyads, in which both partners received MDMA followed by couples' cognitive behavioral therapy. This led to improved happiness and significant reductions across PTSD symptoms, as unanimously rated by patient, partner, and clinician[40]. Further analysis of this study found enduring improvements in post-traumatic growth, social intimacy, and relational support at 6-mo follow up[41].

These benefits extend to common comorbidities seen in PTSD such as depression[42], substance use [43] and sleep disorders[44], with improvements in Pittsburgh sleep quality index scores that remained significant at one-year follow up. MDMA also shows promise in various other psychopathologies including eating disorders[45] and end of life anxiety associated with life-threatening illness[46], in which patients reported increased ability to cope as they faced illness and existential fears, as well as overall improved quality of life. See Table 1 for a summary of relevant articles discussed in the above psilocybin and MDMA sections.

Adverse reactions

Mitchell *et al*[16] concluded that MDMA was safe and well-tolerated and note that the treatment did not induce abuse potential, suicidality, or QT prolongation[16]. Other studies show that risk factors for developing hyperthermia may include adolescent age and increased alcohol consumption[47-49]. Hyperthermia and rhabdomyolysis are likely context-dependent, occurring at lower frequency when used with therapeutic intent rather than recreational use in the setting of other risk factors[47,50]. Likewise, the "come downs" previously associated following MDMA use may be due to research confounds related to environment and drug sourcing, as clinically administered MDMA has noticeably

Table 1 Relevant articles to the discussion with the corresponding treatment investigated

Ref.	Publication year	Treatment	Psychiatric diagnosis
Carhart-Harris *et al*[7]	2021	Psilocybin	Depression
Murphy *et al*[30]	2021	Psilocybin	Depression
Davis *et al*[31]	2021	Psilocybin	Depression
Khan *et al*[34]	2022	Psilocybin	Trauma-related disorders in AIDS patients
Healy *et al*[35]	2021	Psilocybin	Complex Trauma
Kozlowska *et al*[36]	2022	Psilocybin	Neurodegenerative disorders
Mitchell *et al*[16]	2021	MDMA	PTSD
Gorman *et al*[37]	2020	MDMA	PTSD
Hoskins *et al*[38]	2021	MDMA	PTSD
Arluk *et al*[39]	2022	MDMA	PTSD
Monson *et al*[40]	2020	MDMA	PTSD
Wagner *et al*[41]	2021	MDMA	PTSD
Bird *et al*[42]	2021	MDMA	Depression
Nicholas *et al*[43]	2022	MDMA	Substance use disorders
Ponte *et al*[44]	2021	MDMA	Sleep disorders
Brewerton *et al*[45]	2021	MDMA	Eating disorders
Barone *et al*[46]	2022	MDMA	End-of-life anxiety associated with life-threatening illness

AIDS: Acquired immunodeficiency syndrome; MDMA: 3,4-methylenedioxymethamphetamine; PTSD: Post-traumatic stress disorder.

lacked this side effect[51]. Other reports in the literature include hepatotoxicity that improved with vitamin E[52], and a case of spinal cord injury suspected to be due to the serotonin surge induced by MDMA, as the vasoconstrictive properties of serotonin may have induced ischemia[53].

FUTURE DIRECTIONS

Dual therapy

As the evidence for each treatment builds independently, the future may include the integration of both treatments in sequence. In this scenario, MDMA would likely be used first as it has a larger influence on building therapeutic alliance. The augmented therapeutic alliance would allow for a potentially improved psilocybin experience upon switching at next session, aligning with previously discussed research that strong therapeutic alliances are associated with greater mystical experiences and emotional breakthroughs. Treatment with MDMA has been associated with persistent depressive symptoms, and the antidepressant effects of psilocybin may alleviate this following administration[42]. In a model described by Oehen and Gasser[54], MDMA tended to be used in the first phase to build the therapeutic alliance and increase the patient's openness to change, leading to enhanced resilience and lowered stress levels. Once further changes were noticed, such as improved self-regulation, less negative self-perception, and increased tolerance to trauma exposure, LSD was introduced to assist psychotherapy. The deepening of the therapeutic process led to improvement per clinical judgment, without adverse events.

Standardization

Although variation in research methodology is needed to enrich the literature pool, standardization in several aspects may allow for more informed comparisons between treatment modalities. Symptom rating scales for depression (*i.e*, QIDS-SR, GRID-HAMD) and PTSD (*i.e*, CAPS-IV, CAPS-V) varied, with some studies using subjective reports of PTSD diagnostic criteria. Similarly, the therapy modalities that accompanied psychedelic administration were diverse, including uniquely developed forms of therapy as in the accept-connect-embody manualized therapy developed in a psilocybin trial[7,30], supportive therapy[31], and couples' cognitive behavioral therapy[40]. The future may look more like the manualized MDMA-assisted therapy provided through public benefit corporation Multidisciplinary Association for Psychedelic Studies (MAPS). MAPS also has an ethics code, a vital addition to future

protocols as patients are placed in a state of increased suggestibility and affective instability during and after the treatment[55]. This critical period requires a trauma-informed approach to care, with support for transgender and gender diverse patients[56]. Lastly, the method of eliciting adverse drug reactions may benefit from standardization. Studies varied in terms of asking open-ended questions, prompting for specific symptoms, and documenting clinical observations. It is comforting that current studies have not shown any serious adverse events, and future studies may benefit by drawing upon a standardized set of common symptoms.

Wearables

Wearable technology has previously demonstrated efficacy as a bridge between patients and providers in mental health, such as in MDD, dementia, schizophrenia[57-59]. Wearables are likewise being used in non-psychiatric contexts, including medical monitoring in oncology and gastroenterology[60,61]. It follows that wearables may have clinical utility in monitoring patient symptoms during and after PAT. Daily functioning, including wearable-derived sleep and activity data, is incorporated in a protocol examining the effects of microdosed psychedelics and may be a useful metric to track long term changes following psychedelic treatment[62].

CONCLUSION

The literature on PAT using psilocybin or MDMA is strongly supportive across psychiatric conditions, especially trauma and related comorbidities. Both treatments seem to have benefits beyond the FDA breakthrough designations of treatment-resistant depression for psilocybin and PTSD for MDMA. As adjuncts to psychotherapy, psilocybin and MDMA show a pattern of rapid and sustained symptom relief. Future studies may consider the advantages of a standardized approach to symptom rating scales, therapy styles, and assessment of adverse drug reactions. Wearables may also offer additional metrics to examine the long-term trends in activity and sleep. As clinical trials continue to show positive results, providers and patients become closer to seeing the effects translate to the clinic and the community.

FOOTNOTES

Author contributions: Fonseka LN and Woo BKP both performed the collection of data and contributed to the manuscript drafting; All authors have read and approve the final manuscript.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Li L
L-Editor: A
P-Editor: Chen YX

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World Journal of Psychiatry

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World J Psychiatry 2023 May 19; 13(5): 191-202

DOI: 10.5498/wjp.v13.i5.191

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Case Control Study

Effect of exercise prescription teaching on exercise quality and mental health status of college students

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Specialty type: Psychology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Blanc R, France; Griffiths MD, United Kingdom

Received: March 6, 2023
Peer-review started: March 6, 2023
First decision: March 15, 2023
Revised: March 21, 2023
Accepted: April 19, 2023
Article in press: April 19, 2023
Published online: May 19, 2023

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Abstract

BACKGROUND

The teaching mode of fitness exercise prescriptions for college students in physical education conforms to the scientific principles and rules of fitness, which can adapt to the characteristics of students' individual physiological functions and stimulate their interest in learning.

AIM

To analyze the effect of prescribed exercise teaching on the sports quality and mental health of college students.

METHODS

The participants of the study were 240 students in our class of 2021, of which 142 were men and 98 were women. The 240 students were randomly divided into an experimental group using the exercise prescription teaching model and a control group using the conventional teaching model. The experimental and control groups were divided into four classes of 30 students each. The teaching activities of the two teaching mode groups were strictly controlled, and the same tests were used before and after the experiment to test the subjects' exercise quality (including standing long jump, 50 m race, 800 m race, sit-ups, sit-and-reach), physical form (including height, weight, Ketorolai index), cardiopulmonary function (including heart rate, blood pressure, spirometry, 12-min running distance, maximum oxygen intake) and mental health (SCL-90, including somatization, obsessive-compulsive, interpersonal, depression, anxiety, hostility, phobia, paranoia, psychotic symptoms) to understand the effects of the exercise prescription teaching mode on students' physical and mental health status.

RESULTS

There were differences in the exercise scores of standing long jump, 50 m, 800 m/1000 m running, sit-ups, and sit-and-reach in the experimental group after the experiment compared with those before the experiment, and the above indices of

the experimental group were different from those of the control group after the experiment ($P < 0.05$). There were differences in body weight and Ketorolai index in the experimental group after the experiment compared to those before the experiment, and the indices of the experimental group were also different from those of the control group after the experiment ($P < 0.05$). After the experiment, there were differences in spirometry, 12-min running distance, and maximum oxygen intake in the experimental group compared to those before the experiment, and the indices of the experimental group were also different from those of the control group after the experiment ($P < 0.05$). After the experiment, the indicators of somatization, interpersonal sensitivity, depression, anxiety, and hostility in the experimental group were different from those in the pre-experimental group, and the indexes of the experimental group were also different from those of the control group after the experiment ($P < 0.05$).

CONCLUSION

Exercise prescription teaching can mobilize college students' consciousness, enthusiasm, and initiative; expand personalities; enhance physical fitness and improve their mental health more than the conventional fitness exercise prescription teaching method.

Key Words: Exercise prescription teaching; College students; Exercise quality; Mental health status

Core Tip: In order to better create a positive and optimistic outlook on life for college students and increase their interest in physical exercise, it is necessary to apply the physical health prescription course in the process of school physical education teaching. By using sports prescription teaching, teachers develop targeted teaching contents and methods in the teaching class according to the physical quality and health status of students, combine the teaching materials with students' self-learning, self-exercise, self-control, self-regulation and self-evaluation, give full play to students' main role, mobilize students' subjective initiative, realize the transformation from exam-oriented education to quality education, and promote students' all-round development. In view of the continuous decline in the physical and mental health of college students, based on the perspective of special teaching of physical education in colleges and universities, this study starts with the diagnosis of students' physique, provides students with personalized sports prescription teaching experiments with the main purpose of promoting physique, and provides scientific basis for improving students' current physical and mental health, guiding students to conduct scientific and reasonable physical exercise, and improving the effectiveness of school physical education.

Citation: Zhong XL, Sheng DL, Cheng TZ, Zhang ZW. Effect of exercise prescription teaching on exercise quality and mental health status of college students. *World J Psychiatry* 2023; 13(5): 191-202
URL: https://www.wjgnet.com/2220-3206/full/v13/i5/191.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i5.191

INTRODUCTION

Higher general education institutions are the cradles of training qualified personnel of comprehensive quality[1]. College students, as practitioners of China's social, economic development and socialist core values, play the role of the backbone in the future development of society. Ensuring the mental health of college students is increasingly becoming a real problem in the development of China[2,3]. In recent years, problems concerning the physical and mental health of college students have also become the focus of attention, and the results of a large number of surveys and studies[4-6] have shown that the physical conditions, psychological and mental health problems of contemporary college students are more prominent than previously. Therefore, there is an urgent need to find practical and effective measures to strengthen the mental health education and physical exercise of college students, and to strive to improve the physical and mental health of college students.

To create a more positive and optimistic outlook on the lives of college students, as well as to increase their interest in physical exercise, it is necessary to apply physical health prescription courses in the process of physical education in schools[7]. In the traditional process of teaching physical education in institutions, the lack of attention given to exercise health by teachers and students has left many college students facing health problems. Exercise prescription teaching is a highly targeted teaching content and method developed by teachers according to students' physical fitness and health status. It combines teaching according to the material with students' self-learning, self-practice, self-control, self-regulation,

and self-assessment, which can realize the transition from examination-based education to quality education and promote students' overall development by providing full attention to the main role of students and mobilizing their subjective initiative[8-10]. Currently, colleges and universities are making unremitting efforts to continuously "enhance students' physical fitness" and implement "lifelong sports." The physical education mode of self-management and self-development for college students by developing different exercise and fitness prescriptions is beneficial to the physical and mental development of college students.

In response to the trend of continuous decline in the physical and mental health of college students, based on the perspective of college physical education special teaching, this study conducted physical fitness tests on students before the experiment, analyzed the students' various test results, corresponding indices, and provided students with personalized exercise prescription teaching experiments with the main purpose of promoting physical fitness for students' deficiencies in endurance, speed, and strength. It is expected to provide a scientific basis for improving students' current physical and mental health, guide students toward scientific and reasonable fitness, and improve the effectiveness of school physical education.

MATERIALS AND METHODS

Study population

In this study, 240 students from our school class of 2021 were randomly selected (142 men and 98 women), and all participants had no contraindications to sports after taking their medical history and physical examination. The 240 students were randomly divided into an experimental group using the exercise prescription teaching model and a control group using the conventional teaching model. In the experimental group, there were four classes of 30 students each with a total of 120 students, including 69 men and 51 women, aged 18-21 years, with a mean of (19.21 ± 0.61) years. In the control group, there were four classes of 30 students each with a total of 120 students, including 73 men and 47 women, aged 18-20 with a mean of (19.16 ± 0.39) years. The differences in baseline information such as sex, age, height, and weight between the two groups of students were not statistically significant ($P > 0.05$) and were comparable. The study was approved by our ethics committee and all participants signed an informed consent form.

Literature method

We reviewed many articles and textbooks related to exercise prescription teaching as well as teaching curriculum reform and collected the results of domestic and international research on exercise prescription in recent years through Internet searches and other methods for an in-depth understanding of the current state of research and cutting-edge development. Simultaneously, relevant literature was organized and analyzed to provide more informative theoretical data and case support for the study.

Questionnaire method

Questionnaire content: A questionnaire was developed for the implementation of exercise prescription teaching, and the students were divided into experimental and control groups; the results were analyzed and compared in depth. The survey effectively reflected students' opinions on physical education classes, which laid the foundation for the future development of exercise prescription teaching. The survey reflected students' exercise attitudes, learning habits, interests, and other aspects. This way, a scientific exercise prescription curriculum could be effectively developed.

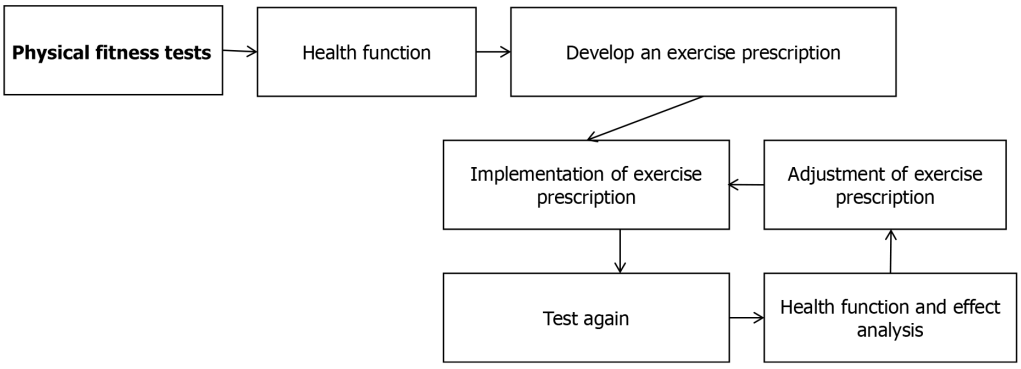
Distribution and recovery of questionnaires: Students in the experimental and control groups participated in a questionnaire survey (Table 1).

Experimental content

Exercise prescription teaching is a highly targeted teaching method developed by the teacher according to the physical fitness and health status of students in the teaching class. It was a method in which the teacher combined the teaching of students according to their abilities with self-learning, self-practice, self-control, self-regulation, and self-assessment. By providing full attention to the main role of students and mobilizing their initiative to achieve the transition from examination-based to quality education, we promoted the overall development of students. The experimental group and the control group were both taught by the same physical education teacher. The experimental group used "exercise prescription" as the basic teaching procedure, the implementation process was cyclic and repetitive (Figure 1). A physical fitness test was conducted to evaluate the exercise ability of students and will be used as the basic basis for exercise prescription control. Teachers analyzed the students' physical fitness according to comprehensive scoring levels in the National Student Physical Fitness Standards and assessed their health functions. Corresponding to the weaknesses of the students in the experimental group, relevant exercise prescriptions (development of speed quality exercise prescription, development of muscle strength exercise prescription, development of endurance exercise prescription, improvement

Table 1 Statistics on the distribution and return of questionnaires

Number of actual issue	Number of recoveries	Recovery rate (%)	Effective number	Effective rate (%)
240	240	100%	240	100%



DOI: 10.5498/wjp.v13.i5.191

Figure 1 Diagram of the implementation process of exercise prescription in the experimental group.

of physical function exercise prescription, *etc.*) were designed to develop appropriate exercise content, exercise load, intensity, frequency, and duration; each exercise prescription determines the upper and lower limits of effective physical exercise for the students[11,12]. The experimental group participated in one physical education class (two class periods) and two extracurricular physical activities every week and exercised according to the formulated exercise prescription. Teachers conducted physical fitness tests every four weeks and adjusted the exercise program according to the actual situation of students to ensure the scientific nature of students' physical exercise. The control group was taught according to the normal physical education syllabus (including formation and assembly, teachers and students greeting each other, teacher briefly introducing the teaching content and requirements, yoga to warm up, and starting exercise), with one physical education class (two class periods) per week and two extracurricular physical activities conducted by the students themselves.

Teaching plan

The exercise prescription intervention lasted for 16 wk, as shown in Table 2.

Observation index

Motor quality: The test items included the standing long jump, 50-meter run, 800-meter run, sit-up, and sit-and-reach. The tests were conducted and scored on a standard athletic field using standard sports equipment. The test content and test methods were tested in accordance with the requirements of the "Student Physical Fitness Standards (pilot program)" published by the People's Education Publishing House. Measurements were taken before and after the experiment, and specific values were recorded.

Body shape: Included height, weight, and Ketorai index. The equipment used for height and weight measurement was the XTC series of student body mass measurement instruments sold by Dandong Tiankang Sporting Goods Co. Measurements were taken before and after the experiment, and specific values were recorded.

Cardiopulmonary function: Heart rate was measured directly by an electronic meter using the manual pulse measurement method; blood pressure was measured using a mercury sphygmomanometer; spirometry was measured using a Tiankang XTC series student physical measurement spirometer, and a total of three measurements were taken at 15 s interval each time, and the maximum value was taken as spirometry. Maximal oxygen uptake: Extrapolation was done by 12 min running distance performance, and a 12 min running distance was measured on the track of a 400 m standard athletic field. After measuring the 12-min running distance, the maximum oxygen uptake per kilogram of body weight was determined using an extrapolation table developed by the Japan Sports Science Center. Measurements were taken before and after the experiment, and specific values were recorded.

Mental health: A name-based questionnaire was used to assess the mental health status of students using the SCL-90, a self-assessment scale for mental health and psychiatric conditions in China. The scale has 90 items, and the severity level is classified according to the weight of each item (Table 3). This scale consists of 10 main factors: somatization, obsessive-compulsiveness, interpersonal sensitivity, depression, anxiety, hostility, fear, paranoia, psychoticism, and others. The high-weighting factor also

Table 2 Specific contents of the exercise prescription teaching program in the experimental group

Teaching content	Number of exercise sets	Exercise intensity	Exercise time	Heart rate (beats/min)	
				Average	Highest
In-class exercise					
1 Preparatory activities: Jogging and marching unarmed exercise.		30-40	15	100	130
2 Normal teaching content.		50-75	40	140	160
3 Exercise content: Focus on the development of strength, agility, speed and endurance qualities.		60-80	30	150	180
(1) Fast moving exercises.	2-3				
(2) Chest, back, abdominal, arm muscles and other parts of the comprehensive apparatus strength exercises.	6-8				
(3) Single and double leg jumping steps.	3-4				
(4) Standing jump, multi-level jump.	3-4				
(5) Various development of aerobic endurance quality exercise.	4-5				
4 Relaxation and finishing exercises.	2-3	20-40	5	100	120
Extracurricular sports					
1 Preparatory activities: Jogging and marching unarmed exercise.		30-40	10	100	120
2 Exercise content: Focus on the development of strength, agility, speed and endurance qualities.		60-80	15	150	180
(1) Fast moving exercises.	3-4				
(2) Holding light equipment strength exercises.	8-10				
(3) Single and double leg jumping steps.	3-4				
(4) Standing jump, multi-level jump.	3-4				
(5) Various development of aerobic endurance quality exercise.	4-5				
3 Relaxation and finishing exercises.	2-3	30-40	5	100	120

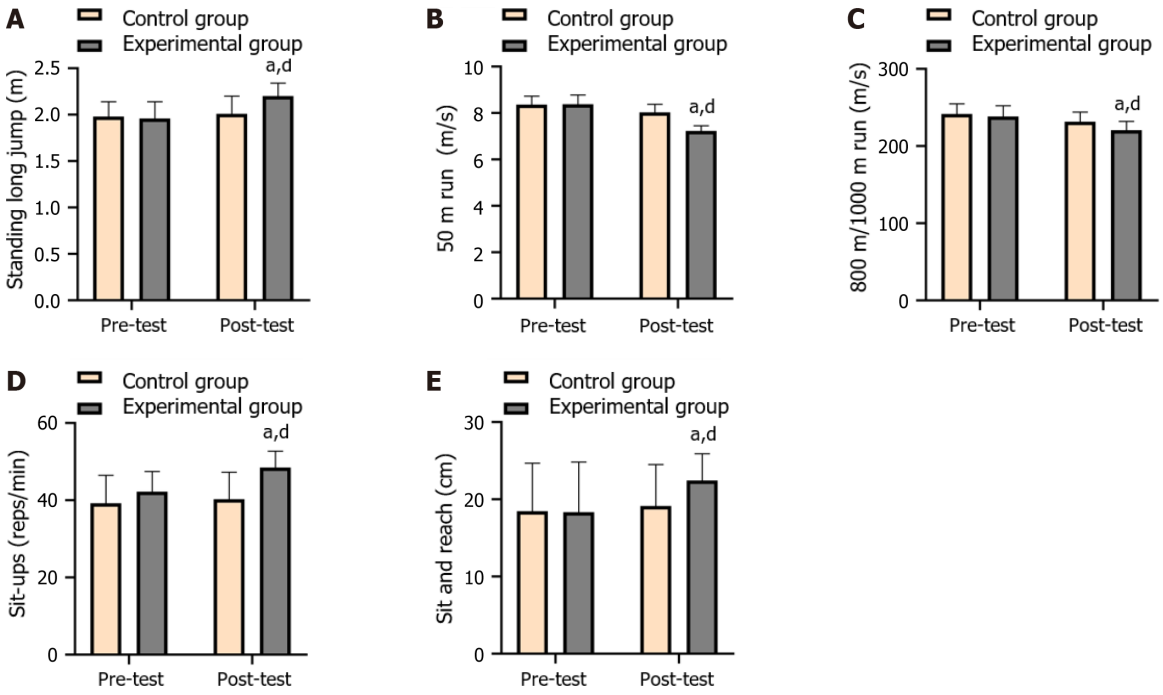
Table 3 Classification of SCL-90 severity levels

Serial number	Grade	Symptom
1	No	Self-perceived absence of symptoms
2	Mild	Conscious presence of the symptom, but no real effect on the subject
3	Moderate	Conscious presence of the symptom, with some effect on the subject
4	Fairly severe	The symptom is often perceived and has a significant impact on the subject
5	Severe	The frequency and intensity of symptoms are very severe

laterally reflects the presence of mental health problems. Measurements were taken before and after the experiment, and specific values were recorded.

Statistical analysis

The relevant data obtained from the survey and test before and after the experiment were analyzed using SPSS 20.0, and a *t*-test was conducted to verify whether there were differences between the experimental and control groups. Therefore, the experimental results were quantified and the objectivity and feasibility of the study were ensured.



DOI: 10.5498/wjp.v13.i5.191

Figure 2 Comparison of exercise quality between the two groups before and after the experiment. A: Standing long jump test (m); B: 50 m run test (m/s); C: 800 m/1000 m run test (m/s); D: Sit-up test (reps/min); E: Sit and reach test (cm). $^{a}P < 0.05$ *vs* the same group before test. $^{d}P < 0.05$ *vs* the control group after test.

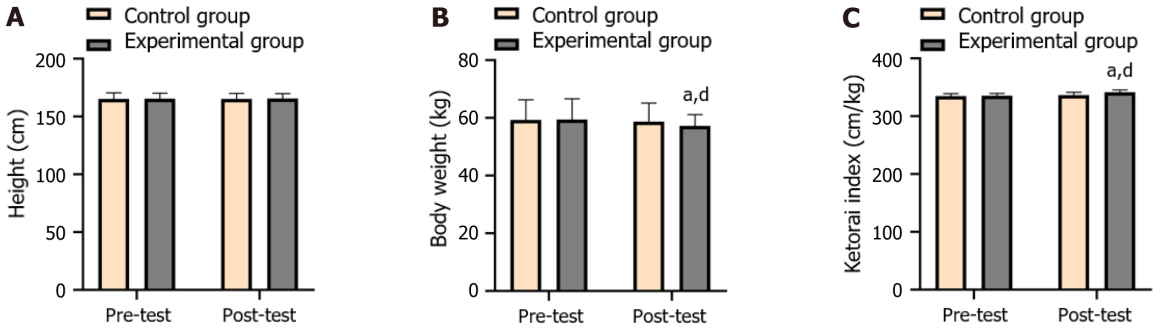


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Figure 3 Comparison of body morphology between the two groups before and after the experiment. A: Height (cm); B: Weight (kg); C: Ketorai index (cm/kg). $^{a}P < 0.05$ *vs* the same group before teaching. $^{d}P < 0.05$ *vs* the control group after teaching.

RESULTS

Comparison of exercise quality between the two groups before and after the experiment

The differences between the two groups in the pre-experimental exercise test scores for standing long jump, 50 m, 800 m/1000 m running, sit-ups, and sit-and-reach were not significant ($P > 0.05$). After the experiment, there were differences in the exercise scores of standing long jump, 50 m, 800 m/1000 m running, sit-ups, and sit-and-reach in the experimental group compared with those before the experiment, and the indices of the experimental group were also different from those of the control group after the experiment ($P < 0.05$) (Figure 2).

Comparison of body morphology between the two groups before and after the experiment

The differences in height, weight, and Ketolai index before the experiment were not significant between the two groups ($P > 0.05$). There were differences in body weight and Ketolai index in the experimental group after the experiment compared with the pre-experimental group. The above indices of the experimental group were also different from those of the control group after the experiment ($P < 0.05$), and there were no significant differences in height between the two groups before and after the experiment ($P > 0.05$) (Figure 3).

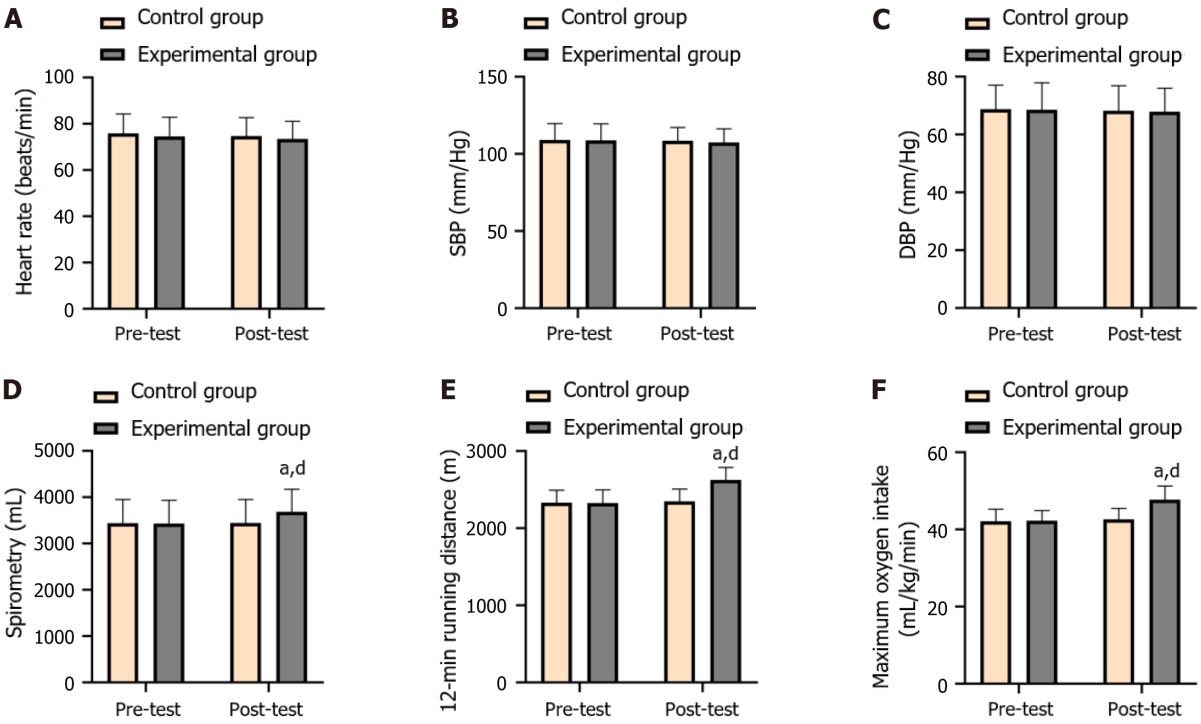

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Figure 4 Comparison of cardiopulmonary function between the two groups before and after the experiment. A: Heart rate (beats/min); B: Systolic blood pressure (mm/Hg); C: Diastolic blood pressure (mm/Hg); D: Spirometry (mL); E: 12-min running distance (m); F: Maximum oxygen intake (mL/kg/min). [a]*P* < 0.05 *vs* the same group before teaching. [d]*P* < 0.05 *vs* the control group after teaching. SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

Comparison of cardiopulmonary function between the two groups before and after the experiment

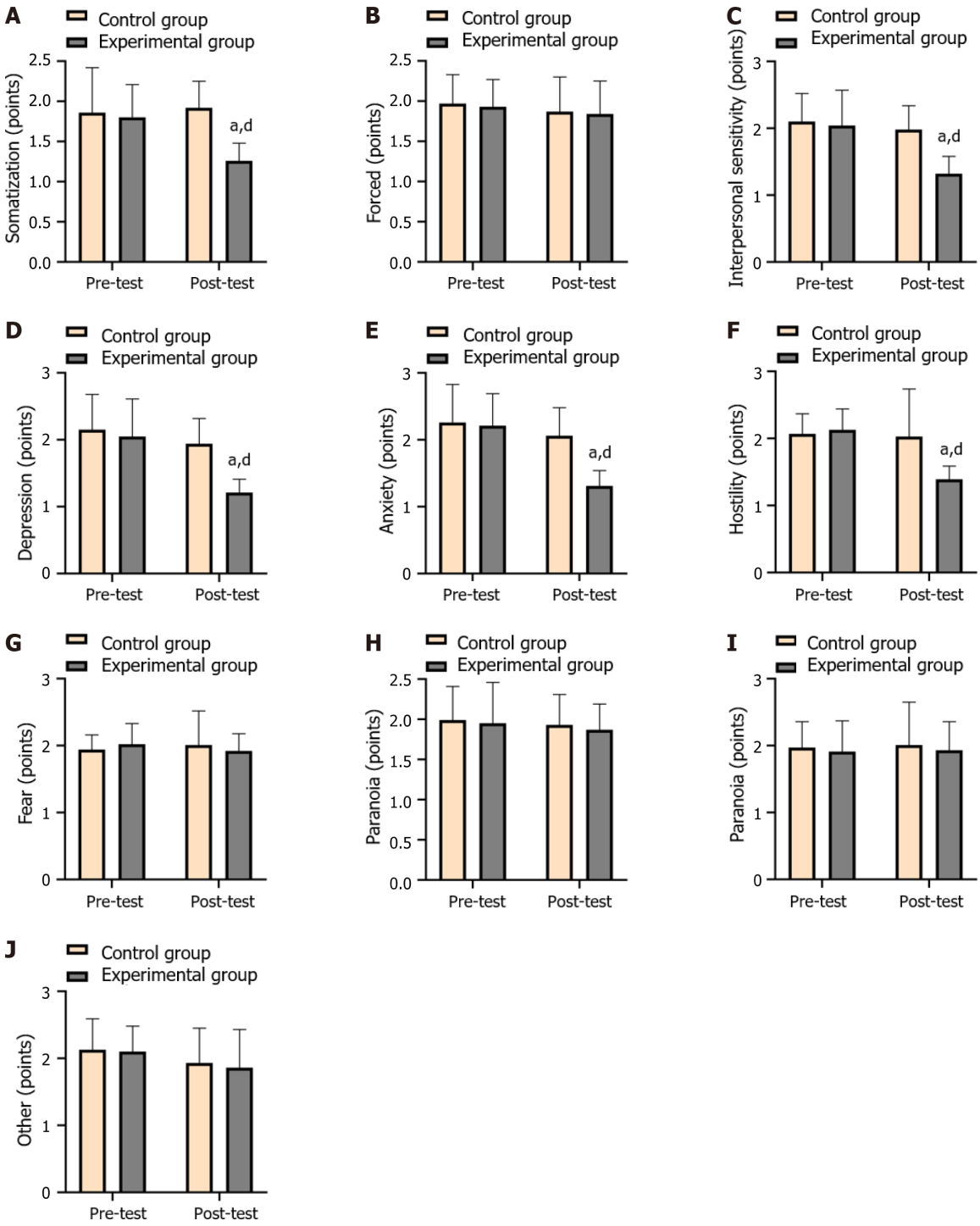
The differences between the two groups in heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), spirometry, 12-min running distance, and maximum oxygen intake before the experiment were not significant ($P > 0.05$). There were differences in the post-experimental spirometry, 12-min running distance, and maximum oxygen uptake in the experimental group compared with those before the experiment; the above indices of the experimental group were also different from those of the control group after the experiment ($P < 0.05$), and there were no significant changes in heart rate, SBP, and DBP levels before and after the experiment in both groups ($P > 0.05$) (Figure 4).

Comparison of the mental health status of the two groups before and after the experiment

Differences in the indicators of somatization, obsessive-compulsive symptoms, interpersonal sensitivity, depression, anxiety, hostility, and paranoia were not significant between the two groups before the experiment ($P > 0.05$). Post-experimental somatization, interpersonal sensitivity, depression, anxiety, hostility, and other indicators in the experimental group differed from the pre-experimental comparison. These indices of the experimental group were also different from those of the control group after the experiment ($P < 0.05$). The post-experimental compulsion, fear, paranoia, psychoticism, and other index scores of the experimental group did not differ significantly from the pre-experimental scores, nor did they differ significantly from those of the control group ($P > 0.05$). No significant changes were seen in the index scores of the control group before and after the experiment ($P > 0.05$) (Figure 5).

DISCUSSION

In recent years, problems regarding the physical and mental health of college students have become a focus of attention, and the results of a large number of surveys and studies have shown that the physical conditions, psychological and mental problems of contemporary college students are very prominent [13,14]. The exercise prescription teaching mode interrupted the teaching material system of teaching competitive sports technology and established a fitness-centered fitness teaching system that realized the consistency of teaching purpose, content, and form and made the enhancement of physical fitness come into practice[15-17]. This study explored interventions for college students' mental health through sports and the use of exercise prescriptions to find new ways to improve college students' mental health.



DOI: 10.5498/wjp.v13.i5.191

Figure 5 Comparison of the mental health status of the two groups before and after the experiment. A: Scores of somatization (points); B: Scores of forced (points); C: Scores of interpersonal sensitivity (points); D: Scores of depression (points); E: Scores of anxiety (points); F: Scores of hostility (points); G: Scores of fear (points); H: Scores of paranoia (points); I: Scores of psychotic (points); J: Scores of other (points). $^{a}P < 0.05$ *vs* the same group before teaching. $^{d}P < 0.05$ *vs* the control group after teaching.

Effect of exercise prescription teaching on students' motor quality

As can be seen from Figure 2, the results of motor quality tests after the experiment for students in the experimental group showed significant changes in motor ability such as a 50 m run, 800 m/1000 m run, standing long jump, sit up, and sit-and-reach show significant changes, indicating that the students' speed, endurance, spring, and upper body strength have been greatly improved. The reason for this may be that the exercise prescription instruction is well arranged and has a good effect on improving all aspects of students' abilities The above suggests that college students should pay attention to strength training, especially the strength training of lower limbs and shoulder belt muscles[18,19].

Effect of exercise prescription teaching on students' body morphology

After the exercise prescription teaching mode exercise, body morphological indices such as height, weight, and Ketorai index before and after the experiment in the control group were not significantly different, whereas there was little change in height before and after the experiment in the experimental group, which was related to the basic stability of bone development in college students. The weight and Ketorolai index of the experimental group differed significantly after the experiment compared with those before the experiment, which may be related to an increase in physical exercise and energy consumption. Slight weight loss is a good adaptation to exercise, and a more significant weight loss may be related to the physical condition of the subject and the content of the exercise received; however, these are all normal conditions[20].

Effect of exercise prescription teaching on students' cardiorespiratory function

From the changes of cardiopulmonary function assessment indexes before and after the experiment. There was no significant difference between the cardiopulmonary function indexes of the experimental group and the control group before the experiment. After the experiment, the vital capacity, 12-min running distance, maximum oxygen intake, step index, and other indices of the experimental group were different from those before the experiment and from those of the control group. The changes in the indexes of students' cardiorespiratory fitness indicate the enhancement of physical fitness and the improvement of exercise capacity, and that the physical exercise of the exercise prescription teaching model has greatly improved students' physical quality and mastery of athletic skills[21,22].

Effect of exercise prescription teaching on students' mental health status

The average score of the SCL-90 scale in the experimental group showed that after 16 wk of exercise prescription teaching, the scores of all factors in the experimental group were decreased, and the scores of interpersonal relationship, anxiety, and depression factors were significantly decreased, and there were very significant differences when compared with those before the experiment. This shows that the implementation of a fitness exercise prescription affected the psychological health of the experimenter. The university stage is a period of gradual maturation of students' psychological processes and complex psychological changes. In a good classroom atmosphere, students experience the pleasure of living with teachers and other students through the medium of cognition and emotion. The elimination of negative emotions caused by the social environment through exercise can have good short- and long-term benefits on the psychological quality of students[23,24].

CONCLUSION

Students can master practical methods to strengthen their bodies and be better prepared for "lifelong sports" activities. Through this study, we found that the application of an exercise prescription teaching model in tertiary institutions has some limitations, such as venues, instruments, equipment, resulting in the limited tests and exercises that can be completed. Therefore, it is impossible to develop comprehensive, effective, and targeted exercise prescriptions. In a follow-up study, we may consider combining social professional outreach training with college sports to provide the necessary conditions for a comprehensive design of exercise prescription training.

ARTICLE HIGHLIGHTS

Research background

The teaching mode of fitness exercise prescriptions for college students in physical education conforms to the scientific principles and rules of fitness, which can adapt to the characteristics of students' individual physiological functions and stimulate their interest in learning.

Research motivation

The physical, psychological, and mental health problems of contemporary college students are more prominent than ever. Therefore, there is an urgent need to find practical and effective measures to strengthen mental health education and physical exercise for college students, and strive to improve their physical and mental health. In order to have a more positive and optimistic view of the lives of college students and increase their interest in physical exercise, it is necessary to apply physical fitness prescription courses in school physical education teaching. In the traditional physical education teaching process in colleges and universities, teachers and students pay insufficient attention to sports health, resulting in many college students facing health problems.

Research objectives

Currently, the main research is to assess the physical fitness and mental health of college students, and this field will continue in the future.

Research methods

Total 240 students were randomly divided into an experimental group and a control group. The experimental group used exercise prescription teaching mode, while the control group used traditional teaching mode. The experimental group and the control group were divided into four classes with 30 students in each class. Strictly control the teaching activities of the two teaching mode groups, and use the same tests before and after the experiment to test the exercise quality, body shape of the subjects, Cardiopulmonary function and mental health to understand the impact of sports management teaching models on students' physical and mental health.

Research results

In response to the trend of continuous decline in the physical and mental health of college students, based on the perspective of college physical education special teaching, this study conducted physical fitness tests on students before the experiment, analyzed the students' various test results, corresponding indices, and provided students with personalized exercise prescription teaching experiments with the main purpose of promoting physical fitness for students' deficiencies in endurance, speed, and strength. It is expected to provide a scientific basis for improving students' current physical and mental health, guide students toward scientific and reasonable fitness, and improve the effectiveness of school physical education.

Research conclusions

Sports prescription teaching can mobilize college students' consciousness, enthusiasm, and initiative, and improve their mental health level.

Research perspectives

Through this study, we found that the application of an exercise prescription teaching model in tertiary institutions has some limitations, such as venues, instruments, equipment, resulting in the limited tests and exercises that can be completed. Therefore, it is impossible to develop comprehensive, effective, and targeted exercise prescriptions. In a follow-up study, we may consider combining social professional outreach training with college sports to provide the necessary conditions for a comprehensive design of exercise prescription training.

FOOTNOTES

Author contributions: Zhong XL conceptualized and designed the study, and collected and compiled the data; Sheng DL provided administrative support; Chen TZ provided the research materials and patients; Zhang ZW and Chen TZ analyzed and interpreted the data; and all authors wrote and approved the final version of the manuscript.

Institutional review board statement: The study was approved by the Institutional Review Committee of Zhejiang Police Academy.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors disclosed no relevant relationships.

Data sharing statement: Relevant raw data for this test are available upon reasonable request.

STROBE statement: The authors have read the STROBE Statement, and the manuscript was prepared and revised according to the STROBE Statement.

Country/Territory of origin: China

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S-Editor: Wang JL

L-Editor: A
P-Editor: Chen YX

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 May 19; 13(5): 203-214

DOI: 10.5498/wjp.v13.i5.203

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Retrospective Study

Functional near-infrared spectroscopy in elderly patients with four types of dementia

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Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C, C, C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Masaru T, Hungary; Ni YC, Taiwan

Received: December 7, 2022
Peer-review started: December 7, 2022
First decision: February 20, 2023
Revised: March 2, 2023
Accepted: April 4, 2023
Article in press: April 4, 2023
Published online: May 19, 2023

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Abstract

BACKGROUND

Functional near-infrared spectroscopy (fNIRS) is commonly used to study human brain function by measuring the hemodynamic signals originating from cortical activation and provides a new noninvasive detection method for identifying dementia.

AIM

To investigate the fNIRS imaging technique and its clinical application in differential diagnosis of subtype dementias including frontotemporal lobe dementia, Lewy body dementia, Parkinson's disease dementia (PDD) and Alzheimer's disease (AD).

METHODS

Four patients with different types of dementia were examined with fNIRS during two tasks and a resting state. We adopted the verbal fluency task, working memory task and resting state task. Each patient was compared on the same task. We conducted and analyzed the fNIRS data using a general linear model and Pearson's correlation analysis.

RESULTS

Compared with other types of dementias, fNIRS showed the left frontotemporal and prefrontal lobes to be poorly activated during the verbal fluency task in frontotemporal dementia. In Lewy body dementia, severe asymmetry of prefrontal lobes appeared during both verbal fluency and working memory tasks, and the patient had low functional connectivity during a resting state. In PDD, the patient's prefrontal cortex showed lower excitability than the temporal lobe during the verbal fluency task, while the prefrontal cortex showed higher

excitability during the working memory task. The patient with AD showed poor prefrontal and temporal activation during the working memory task, and more activation of frontopolar instead of the dorsolateral prefrontal cortex.

CONCLUSION
Different hemodynamic characteristics of four types of dementia (as seen by fNIRS imaging) provides evidence that fNIRS can serve as a potential tool for the diagnosis between dementia subtypes.

Key Words: Functional near-infrared spectroscopy; Frontotemporal lobe dementia; Lewy body dementia; Parkinson's disease dementia; Alzheimer's disease

Core Tip: Four types of dementia showed different patterns of activation when examined by functional near-infrared spectroscopy (fNIRS) during two tasks and a resting state. The patient with frontotemporal dementia showed the lowest activation during the verbal fluency task and the patient with Alzheimer's disease showed the lowest activation during the working memory task. During the resting state, functional connectivity was poor in the patients with Lewy bodies dementia and Parkinson's disease dementia. fNIRS imaging in dementia patients may be able to differentiate between types of dementia, and may be useful in diagnosis for these patients.

Citation: Mei X, Zou CJ, Hu J, Liu XL, Zheng CY, Zhou DS. Functional near-infrared spectroscopy in elderly patients with four types of dementia. *World J Psychiatry* 2023; 13(5): 203-214
URL: https://www.wjgnet.com/2220-3206/full/v13/i5/203.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i5.203

INTRODUCTION

Dementia is a disease commonly studied in psychiatry and neurology. Clinical diagnosis is based on symptoms and is supplemented by neuropsychological scales and laboratory examinations. Brain imaging technology is an important tool for exploring brain diseases, and has undergone a period of rapid development in the past 20 years. To improve the accuracy of diagnosis between types of dementia, different technologies have been developed, including computed tomography (CT), positron emission tomography (PET) and magnetic resonance imaging (MRI) to examine brain structure, electroencephalography (EEG) to examine electrical physiology[1]. In addition to functional MRI (fMRI), EEG, and event-related potentials, functional near-infrared spectroscopy (fNIRS) to examine functional connectivity between regions has become an important supplement to existing functional imaging technologies[2,3].

fNIRS imaging evaluates human brain activity by measuring the oxygen level in the prefrontal and temporal cortices[4]. While participants perform different tasks, the fNIRS system provides continuous and real-time oxygen change display of oxy-hemoglobin (oxy-Hb) and deoxygenated hemoglobin values[5]. In aspects of specificity and temporal resolution, fNIRS assessment of cognitive function eliminates many shortcomings of fMRI[6]. While PET and MRI studies have generated insights into the pathological changes in brain oxygenation and activity associated with mild cognitive impairment (MCI) and dementia, these methods have some limitations involving the injection of radioactive compounds and motion artifacts[7].

fNIRS imaging systems possess high temporal and spatial resolutions, which are critical to withstand interference (both electromagnetic and from head motion). The temporal resolutions of fNIRS (11 Hz in this study) and EEG are in the order of seconds and milliseconds, respectively. The spatial resolution of fNIRS (3 cm in this study) was higher than that of EEG[8,9]. Because EEG recording is a surface potential change of skull, the accuracy of spatial localization is not high. fNIRS probe acquires the cortical activity directly and has a centimeter level of resolution[10]. fNIRS is used to monitor hemodynamic changes evoked by neural activity by taking advantage of the fact that biological tissues are relatively transparent to near-infrared light 700-1000 nm[11]. Recent studies on fNIRS detection of dementia focused on MCI and Alzheimer's disease (AD)[12,13]. It was shown that resting-state fNIRS recordings from prefrontal regions can provide a potential methodology for detecting MCI and its progression[14]. The sensitivity and specificity increase as the cognitive impairment worsens[15].

Amnestic MCI is more predictive of AD than nonamnestic MCI, and nonamnestic MCI is more predictive of other types of dementia including Lewy bodies dementia (LBD) and frontotemporal dementia (FTD)[16,17]. To measure cortical activation in patients with behavioral variant of the FTD (bvFTD), fNIRS was used while performing the verbal fluency task[18]. The flexible of fNIRS makes the possibility of measurement of the neurology of gait in cognitive dysfunction or dementia during dual-task gait assessment[19]. Similar studies focused on old people with risk of dementia, such as those with subjective memory complaints, were reported to be examined by fNIRS indual-task gait[20].

The use of optical techniques, specifically fNIRS, to study brain hemodynamics and to assess prefrontal cortex's activity of older adults for detection of certain types of seizures and cortical spreading deactivation in cognitive tasks is also important. fNIRS can be useful to investigate the altered prefrontal mechanisms of neurological and neuropsychiatric diseases and discover neuroimaging biomarkers for different neurodegenerative disorders[21-24]. The reliability of fNIRS in estimating global cerebral function was supported by previous studies[25]. fNIRS measurements are reproducible and can be reliable used in single subjects for neuroscientific research and clinical applications[26]. It could be a critical tool to investigate frontal lobe oxygenation in patients with different types of dementia and age-related decline of neurovascular coupling responses[27,29].

In this study, using fNIRS, we examined brain functional patterns in patients with four types of dementia: FTD, LBD, Parkinson's disease dementia (PDD), and AD. Because of neurovascular coupling, different types of dementia may cause different hemodynamic alterations. Here, we report four subjects in which fNIRS was used to examine the brain function of patients with dementia (during two tasks and a resting state).

MATERIALS AND METHODS

fNIRS data acquisition

Patients with FTD, LBD, PDD, and AD signed an informed consent form and underwent routine fNIRS examinations at a brain function testing center in the hospital. A multi-channel continuous-wave fNIRS imaging system (Nirscan, Danyang Huichuang Medical Equipment Co. Ltd, China) was employed to measure signals from the frontal and bilateral temporal cortices as described in our previous study[8]. This light-emitting diode-based fNIRS system contained 24 light sources and 24 detectors. The distance between detectors was 3 cm, as shown in Figure 1. The center detector of the middle probe set row was placed at FPz, according to the 10/20 international system. The sampling rate was 11 Hz and the wavelengths used were 780, 808, and 850 nm.

Verbal fluency task

The verbal fluency task consisted of three steps: (1) Participants repeatedly counted from 1 to 5 for 30 s to obtain the baseline value of cognitive performance; (2) during the task period, participants were instructed to generate as many words as possible, they continuously named different words beginning with a specific letters for 20 s (trials for three letters totaled 60 s); and (3) participants repeated step 1 for 70 s to return to baseline. The task took less than three minutes total. Other matters needing attention were described in previous studies on verbal fluency task of fNIRS[30-33].

Memory task

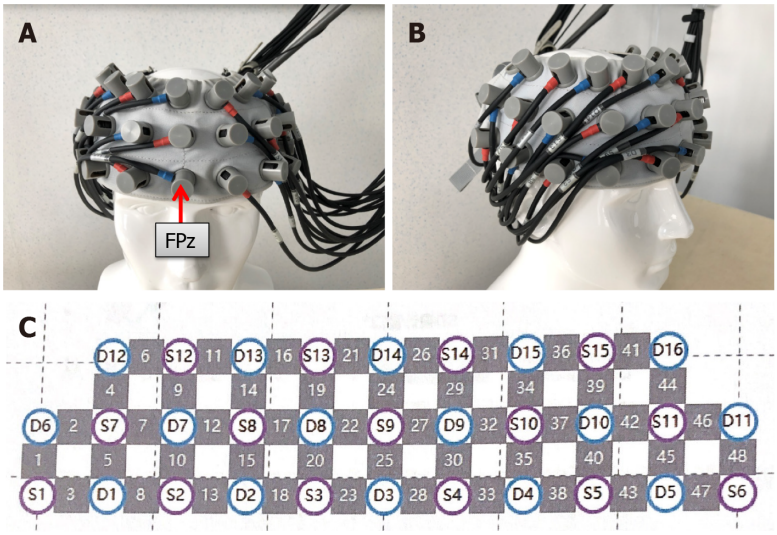
The memory task contained two components on a tablet computer: A working memory search task and a non-working memory search task. In the working memory search task, three graphic icons appeared. Participants were instructed to remember the colors, shapes, and order in which they appeared; subsequently, they were asked to identify the icons in the summary diagram. In the non-working memory search task, participants only needed to select the icons when prompted. The two sets of tasks were alternated and repeated four times. Working memory performance was used to reflect the cognitive function in many studies[34-36].

Resting state

The resting-state signal was recorded continuously for at least 10 min, during which participants were required to sit still and close their eyes without falling asleep. Functional connectivity was calculated on a scale from 0 to 1, where 0.3 represents an average level of functional connection strength (Supplementary Figure 1).

fNIRS experiment

The participants were guided to the experimental room, and seated on a wooden stool with a wooden table. During the experimental preparation phase, the participants were asked to wear an electrode cap. The experimenter repeatedly adjusted the electrode cap to maximize the signal channel gain. When the experiments begin, participants performed the task by listening to the instruction (verbal fluency task) or using an ipad (working memory task), as our previous work[8].



DOI: 10.5498/wjp.v13.i5.203

Figure 1 Diagrammatic sketch of localization of the functional near-infrared spectroscopy probe set over left and right frontotemporal cortex. A: Anterior view; B: Lateral view; C: Probe arrangement. Blue circle: Detectors; Purple circle: Light source.

Data analysis

The NirSpark software package (Danyang Huichuang Medical Equipment Co. Ltd, China) was used to analyze the fNIRS data, as previously described[37-39]. Physiological noises (including respiration, cardiac activity, and low-frequency signal drift) were corrected by a band-pass filter with cutoff frequencies of 0.01-0.20 Hz. The cubic spline interpolation method was adopted to eliminate motion artifacts. The modified Beer-Labert law was used to convert the optical density into changes in oxy-Hb and deoxy-Hb concentrations. A general linear model was used to calculate brain activation strength. Functional connectivity was calculated by conducting Pearson's correlation analysis between the time series of every pair of measurement channels.

RESULTS

Subject 1 FTD

Clinical manifestation: A 57-year-old man was diagnosed with FTD. Two years prior, the patient began to show impaired judgment without warning and was defrauded of 700000 yuan. He reported insomnia, anxiety, and depression. His mental state continued to deteriorate, and he was initially diagnosed with "recurrent depressive disorder". He also exhibited memory problems such as being unable to recall whether he had eaten or not, and he was often unable to complete tasks assigned to him by his family. For the past 2 years, the patient had been treated with systematic antidepressants (such as sertraline, doxetine, mirtazapine) and modified electroconvulsive therapy. His depression partially eased, but his memory problems persisted. One month previously, the patient again showed nervousness and fidgeting. The patient also experienced hallucinations, slow walking, and involuntary limb shaking. He had been admitted to the neurology department, who had ruled out Parkinson's disease before he was admitted to our department for further treatment.

Examinations: The patient's psychiatric examination at admission showed clear consciousness, accurate orientation, lack of cooperation, less autonomous language, decreased language expression ability, poor vocabulary, stereotypes and imitation speech, stable mood, no obvious manifestations of emotional depression, and partial decline in memory intelligence. Physical examination revealed that the patient's right lower limb twitches could be relieved after massage. A brain MRI showed cystic foci in the left medial temporal lobe and senile brain changes. His Mini-Mental State Examination (MMSE) score was 22/30. Considering to his education level of high school, the severity of dementia was moderate. The patient was diagnosed as FTD accompanied by mild depression.

fNIRS results: In Figure 2A, fNIRS showed global lower activation in frontotemporal lobe when the patient performed the verbal fluency task. This was consisted with his clinical manifestation of poor verbal function. During the working memory task, the patient's prefrontal lobe activation was lower than that of the temporal lobe, and the frontal lobe activation was also low. Frontalpolar and temporopolar area showed most activation than other regions. The overall pattern was different from other three subtypes of dementia. During a resting state, the average strength functional connection of

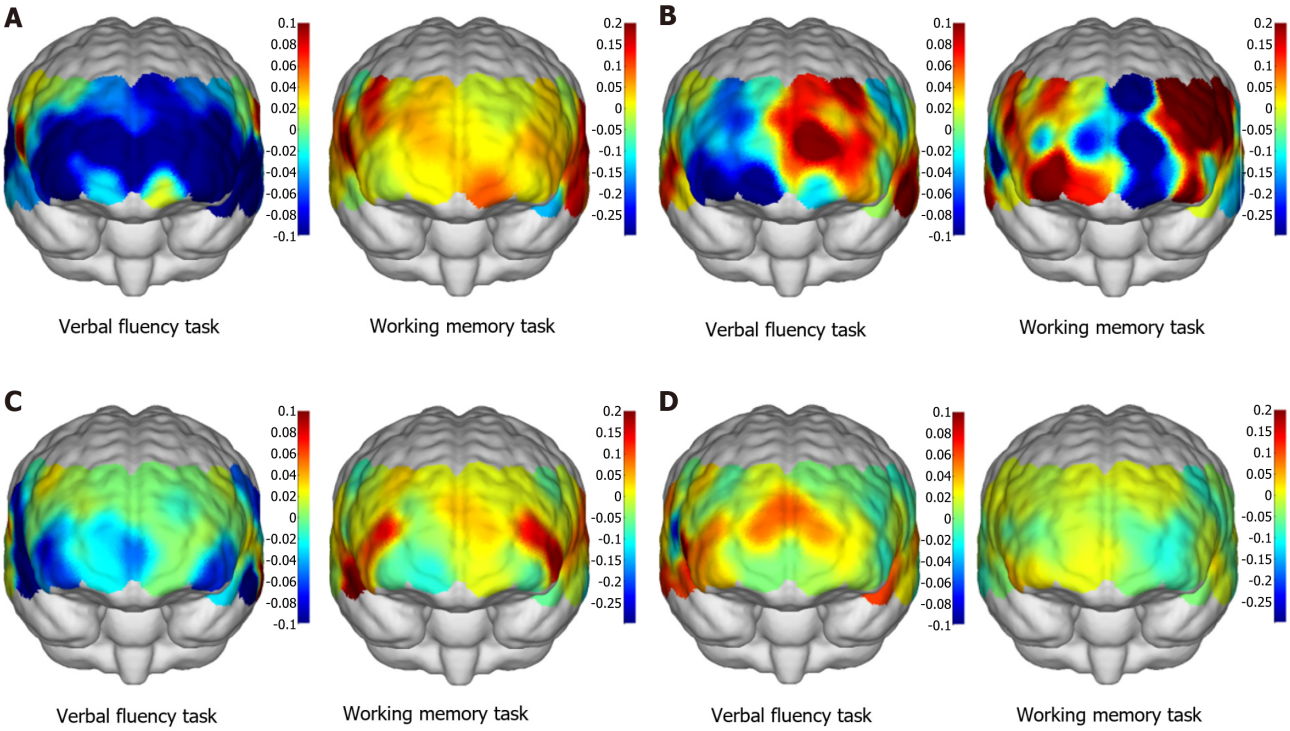


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Figure 2 Comparison of functional near-infrared spectroscopy patterns and task performances during the verbal fluency task (left) and the working memory task (right) between four types of dementia patients. A: Frontotemporal lobe dementia; B: Lewy body dementia; C: Parkinson's disease dementia; D; Alzheimer's disease. Red indicates higher activation, while blue indicates lower activation.

all channels was considered high at 0.559 as shown in Figure 3A.

Subject 2 LBD

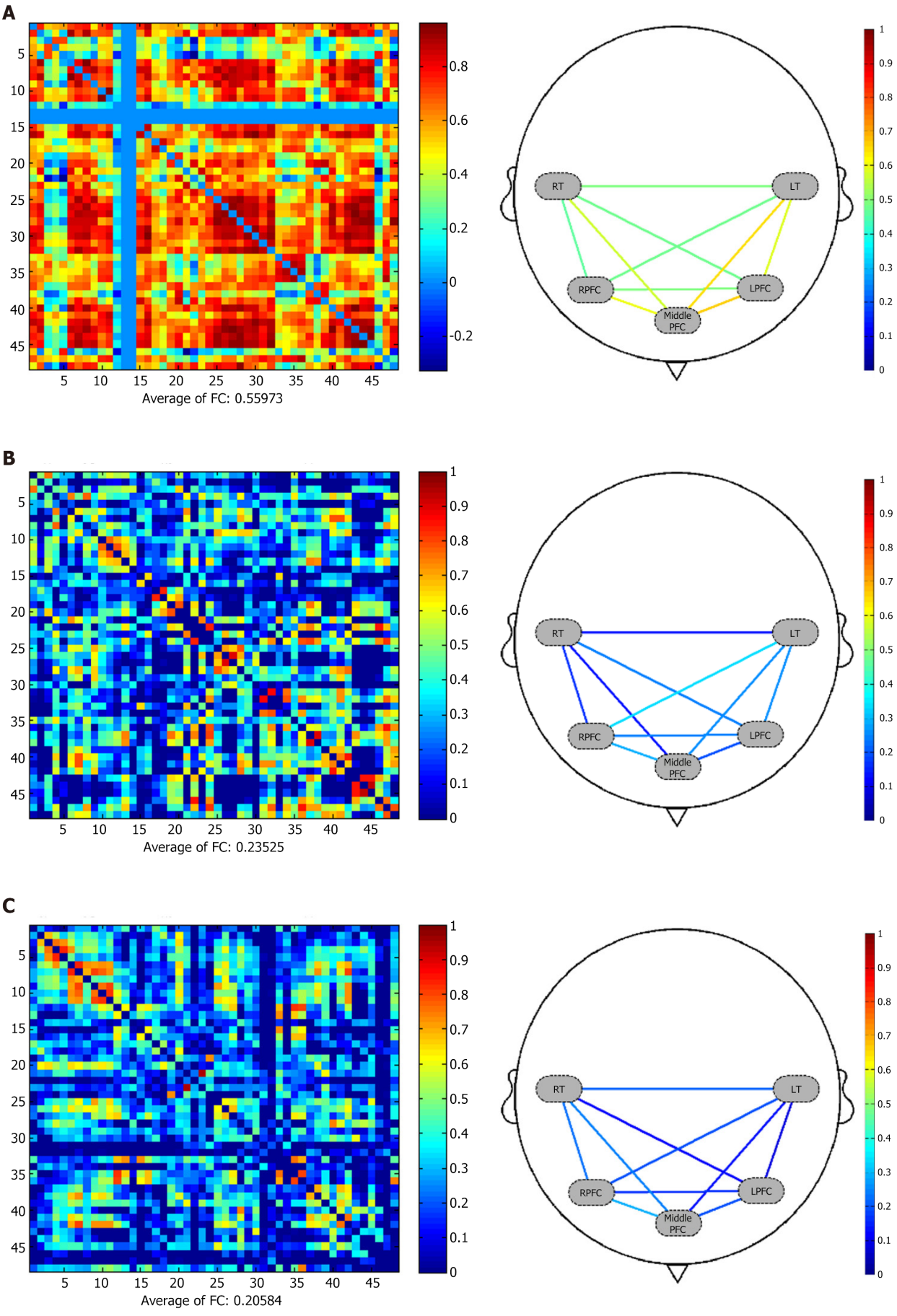
Clinical manifestation: A 74-year-old man was diagnosed with LBD. He had been experiencing progressive memory loss for three years, as well as symptoms such as hand shaking and bradykinesia; the neurology department considered him to have Parkinson's disease. Over three years, the patient's memory waxed and waned, while symptoms such as slow walking persisted. The patient occasionally experienced hallucinations such as seeing vivid images of dead people. In the last six months, his memory problem had significantly worsened; sometimes, he could not recall a family member's name. His speech was not very fluent, and he had difficulty communicating with others. His sleep was poor. His ability to perform daily living had significantly declined and he needed someone to take care of him.

Examinations: The patient was admitted to our hospital for further treatment, and his psychiatric examination at admission showed clear consciousness, loss of sense of smell, unsteady gait, varying degrees of limb tremor, and increased muscle tone. He had slow thinking, aphasia, impaired memory, impaired common sense, reduced calculation ability, and visual hallucinations. A brain MRI showed localized atrophy in the temporal, frontal and parietal lobes. His MMSE score was 6/30. The degree of dementia was severe. The patient was diagnosed as primary neurodegenerative disease LBD.

fNIRS results: The fNIRS showed severe asymmetry in both hemispheres during both the verbal fluency and working memory tasks, particularly that the left frontal lobe showed more activation than the right lobe as shown in Figure 2B. In Figure 3B, the patient had low functional connection strength of 0.235 during a resting state.

Subject 3 PDD

Clinical manifestation: A 79-year-old man was diagnosed with PDD. Two years prior, the patient began to develop symptoms such as hand tremor and slow gait, and was subsequently diagnosed with "Parkinson's disease" by the neurology department. He was given symptomatic treatment of dopamine (0.0625 g tid) and pramipexole (0.25 mg bid) in oral form since then, and symptoms such as hand tremors and slow gait improved. About six months ago, his family reported development of memory problems. The patient forgot things immediately after being told, and forgot where he put things. His ability to perform daily tasks slowly declined, sometimes requiring family members to help him dress.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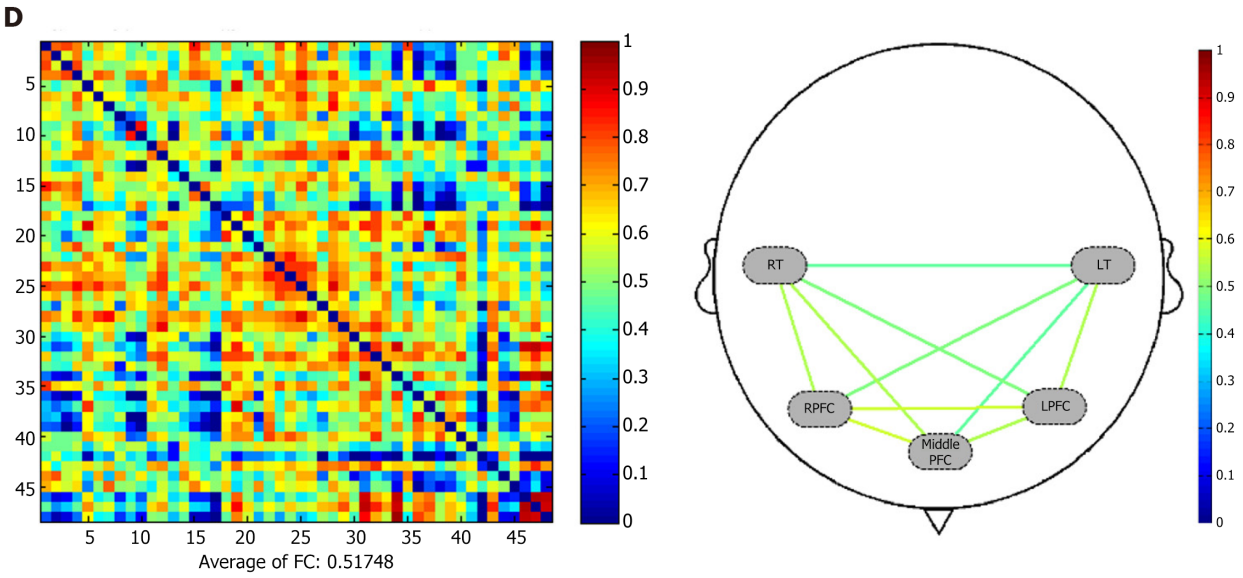

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Figure 3 Resting state functional connections were calculated by conducting Pearson's correlation analysis between the time series of every pair of measurement channels. A: Frontotemporal lobe dementia; B: Lewy body dementia; C: Parkinson's disease dementia; D: Alzheimer's disease. Red indicates higher activation, while blue indicates lower activation.

Two months prior, the patient's mental state worsened due to sleep disorders and frequent nightmares. On occasion, he wakes in the middle of the night and begin to choke his wife. The patient was admitted for further treatment, and reported a family history of AD (in his sister).

Examinations: Upon mental examination, the patient's consciousness was clear. His recent memory decline was evidenced by his report of no memory of events after he went to bed. He gave simple answers to questions and demonstrated limited vocabulary and emotional instability, particularly irritability. His risk-taking behavior had increased, particularly in dangerous movements that may lead to falls or rejecting advice from others. CT showed multiple ischemic foci in both the frontal and parietal lobes and periventricular white matter. His MMSE score was 13/30. The degree of dementia was severe. The patient was diagnosed as typical PDD accompanied by sleep disorders.

fNIRS results: fNIRS showed that the patient's prefrontal cortex had lower excitability than the temporal lobe during the verbal fluency task, while the patient's prefrontal cortex had higher excitability during the working memory task. As shown in Figure 2C, the dorsolateral prefrontal cortex (DLPFC) was activated strongly (symmetrical pattern; in red color region) during the working memory task. During a resting state in Figure 3C, the average strength functional connection of all channels was 0.206, lower than the normal level.

Subject 4 AD

Clinical manifestation: A 73-year-old woman was diagnosed with dementia secondary to AD. About one year prior, the patient began to experience short-term memory loss, such as forgetting what she had said and done and failing to find the objects she had just placed. The ability to perform daily tasks declined slowly, requiring partial assistance from family members. The patient had a history of recurrent depressive disorder for approximately 10 years and long-term antidepressant treatment was moderately effective.

Examinations: The mental examination on admission found memory decline, computing power decline, orientation impairment, comprehension and expression ability decline, language vocabulary reduction, and emotional stability. A brain MRI showed reduced hippocampal volume and internal olfactory cortex volume bilaterally (MTA-score > 2). Her MMSE score was 14/30. The degree of dementia was moderate to severe due to her education level of 1 year. The patient was diagnosed as typical AD accompanied with mild depression.

fNIRS results: fNIRS revealed poor prefrontal and temporal activation during the working memory task (Figure 2D). The patient had high functional connection strength of 0.518 during a resting state (Figure 3D). The contrast of the two demented subjects (PDD *vs* AD) was characterized by a nearly symmetrical pattern in both task contrasts: prefrontal lobe was more activated in verbal fluency task in the AD than in PDD, while the frontotemporal lobe was more activated in working memory task in the PDD than in AD (Figure 2C and D). Regarding to the working memory task, the activation of brain in

AD was the weakest of four dementias.

DISCUSSION

The results of this study indicate that cortical activation measured with fNIRS while performing a verbal fluency and working memory task differs in patients suffering from four types of neurodegenerative dementia including FTD, LBD, PDD, and AD. Furthermore, this activation differs between the four types of neurodegenerative dementia, a result shown for the first time using fNIRS in antidiastole of dementia subtypes.

Patients with FTD show low function or atrophy of the frontotemporal lobe that may be accompanied by low levels of oxy-Hb low function of the frontotemporal lobe[40]. Although patients with FTD and those with psychiatric disorders behave similarly, differences can exist in hypoperfusion and hypometabolism of the frontotemporal lobe regions[41]. A reduction in cortical activation during verbal fluency task performance in FTD patient compared to other three dementias has been shown in this study. FTD disorders include behavioral variant FTD (bvFTD), nonfluent/agrammatic variant primary progressive aphasia (nfvPPA), and semantic variant PPA (svPPA)[42]. PPA patients showed differential linguistic features of verbal fluency from bvFTD[43]. In this FTD case, the patient showed the poor verbal function. The fNIRS pattern showed low activation during the verbal fluency task. He had been treated with antidepressants. Currently, antidepressants are routinely used in the treatment of dementia to supplement serotonin availability[44]. There was no effect on vasculature at the relevant therapeutic dose for this patient, so it is unlikely that this affected blood flow in this patient. Furthermore, depressive pseudo dementia can also manifest as cognitive decline, but the brain functions, as well as neurovascular coupling, are not as poor in these patients compared to patients with dementia[45]. Thus, fNIRS can distinguish between depressive pseudo-dementia and dementia.

The AD pattern is weaker and more similar to the healthy pattern, whereas the bvFTD pattern is qualitatively different, namely more frontopolar and without frontoparietal compensation activation [18]. Our results showed the AD patient have lower and slower activation in the bilateral PFC and left parietal cortex during working memory maintenance. This was consisted with previous study on moderate to severe AD[2]. aMCI patients, as early stage AD, were reported a larger reduction in frontal deoxy-Hb during the memory task[46].

Regarding to the functional connection reflected by fNIRS, connections between different brain regions, as well as synergies between them, work together to provide comprehensive cognitive functions. As shown in Figure 3, the total scores of MMSE of patient with PDD and AD were similar in our study, but the functional connection strength is much different. The MMSE scale included six cognitive domains of orientation, immediately recall, attention, delayed recall, language and executive, and visual function[47]. Although the total MMSE scores of PDD and AD patients are close, they have different sub-scores in different cognitive domains, which reflect different brain area functions. In this aspect, the functional connectivity reflected by fNIRS can distinguish these differences, and enhanced the diagnostic accuracy as an auxiliary method.

The blood supply to the brain can reflect local changes in functional activity. In dementia patients, brain activity demonstrates a gradual increase in oxygenated hemoglobin and decrease in deoxygenated hemoglobin[48]. The working mode is believed to require networks across the entire brain; that is, no complex function is performed by a single brain area[6]. Imaging of the resting-state networks can also reveal information, such as the correlations between neural activities and the efficiency of transmission [49]. This is especially significant for patients with a low degree of cooperation[50]. Regarding to prefrontal cortex, primarily DLPFC, activation has a positive correlation with working memory load and performance until the working memory load exceeds the capacity[51].

fNIRS technology is widely used in the detection of neuropsychiatric disorders and brain functions individuals abusing different types of drugs[52-54]. Changes to oxy-Hb concentration of the bilateral prefrontal cortex in a schizophrenia group were reported to be significantly lower than those in a healthy group[55]. fNIRS has also been used to accurately distinguish patients with major depression from those with bipolar disorder or schizophrenia who have depressive symptoms[56]. When fNIRS technology was utilized to explore functional connectivity and network changes in patients with attention-deficit/hyperactivity disorder (ADHD), the development pattern of brain networks in children with ADHD was different from that of healthy children[57]. fNIRS also has applications in the field of sleep research to study brain activation during dreaming[49,57].

Limitations and future directions: one limitation is that a single patient for each group may introduce individual differences, including sex, age, and education. A larger sample size would help to eliminate the impact of such individual differences. Our results show that further study is needed to examine the diagnostic utility of fNIRS in dementia. Although our fNIRS recording technique was a multichannel flexible tool to detect the brain function in patients with different type of dementia, it focused on the frontal and temporal lobe of the brain, not the global brain region. This can be improved by using whole brain detection of fNIRS in the future.

CONCLUSION

Although subtypes of dementia may have similar clinical symptoms, they have different objective indicators; some that are observable during a resting state and some that are observable during the task state. Since fNIRS can detect changes in both states, it may be a useful tool for differential diagnosis. This study visualized four different types of dementia (FTD, LBD, PDD, and AD) using fNIRS, and found differences of brain activation during the task condition and functional connectivity during the resting state for all four types. The patient with FTD showed the lowest activation during the verbal fluency task and the patient with AD showed the lowest activation during the working memory task. During the resting state, functional connectivity was poor in the patients with LBD and PDD. These differences could be used as biomarkers to distinguish the different subtypes of dementia. In the future, as a non-invasive tool, multichannel fNIRS technology can provide high spatial and temporal resolution signals to continuously assess regional cerebral oxygenation. The sensitivity of fNIRS increased its use as a wide-spread clinical tool for the robust assessment of brain function.

ARTICLE HIGHLIGHTS

Research background

In addition to functional magnetic resonance imaging, electroencephalography, and event-related potentials, functional near-infrared spectroscopy (fNIRS) to examine functional connectivity between regions has become an important supplement to existing functional imaging technologies.

Research motivation

fNIRS technology will be widely used in the detection of neuropsychiatric disorders.

Research objectives

fNIRS could be a potential tool for the diagnosis between dementia subtypes.

Research methods

We tested four types of dementia by using fNIRS in the verbal fluency task, working memory task and resting state task.

Research results

fNIRS examinations were adopted to test the fNIRS paramters. The results shown that different types of dementia have different fNIRS patterns.

Research conclusions

fNIRS can be used as a potential method to diagnose dementia and cognitive decline.

Research perspectives

We want to study whether the fNIRS can be a potential tool for the diagnosis between dementia subtypes.

FOOTNOTES

Author contributions: Mei X and Zou CJ performed fNIRS protocols, data collection, and wrote the manuscript; Mei X, Zou CJ, Liu XL, and Hu J performed data analysis; Zheng CY and Zhou DS proofread the manuscript; all authors read and approved the final manuscript.

Supported by the Ningbo Medical and Health Leading Academic Discipline Project, No. 2022-F28; Zhejiang Medical and Health Science and Technology Project, No. 2021KY1066; and Ningbo City Public Welfare Science and Technology Plan Project, No. 2022S025.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Ningbo Kangning Hospital.

Informed consent statement: All subjects enrolled in the study signed the written consent and agreed to publish the details of their medical case and any accompanying images.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: All data are included in the manuscript. However, the raw data used and/or analyzed in the

present study are available from the corresponding author on reasonable request.

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S-Editor: Chen YL
L-Editor: A
P-Editor: Chen YX

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 May 19; 13(5): 215-225

DOI: 10.5498/wjp.v13.i5.215

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Estimated prevalence and sociodemographic correlates of mental disorders in medical students of Hebei Province, China: A cross-sectional study

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Specialty type: Psychiatry

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Dimopoulos N, Greece; Kar SK, India

Received: February 21, 2023
Peer-review started: February 21, 2023
First decision: March 24, 2023
Revised: April 5, 2023
Accepted: April 17, 2023
Article in press: April 17, 2023
Published online: May 19, 2023

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Abstract

BACKGROUND

In China, the identification rate and treatment rate of mental disorders are low, and there are few surveys on the prevalence of mental disorders among college students using diagnostic tools such as Mini-International Neuropsychiatric Interview (MINI), so the prevalence and treatment of mental disorders among college students are unclear.

AIM

To estimate prevalence of mental disorders among medical students in Hebei

Province, and provide guidance for improving their mental health.

METHODS

This was a cross-sectional study based on an Internet-based survey. Three levels of medical students in Hebei Province were randomly selected (by cluster sampling) for screening. Using the information network assessment system, the subjects scanned the 2D code with their mobile phones, clicked to sign the informed consent, and answered a scale. A self-designed general status questionnaire was used to collect information about age, gender, ethnicity, grade, and origin of students. The MINI 5.0. was used to investigate mental disorders. Data analysis was performed with SPSS software. Statistically significant findings were determined using a two-tailed *P* value of 0.05.

RESULTS

A total of 7117 subjects completed the survey between October 11 and November 7, 2021. The estimated prevalence of any mental disorders within 12 mo was 7.4%. Mood disorders were the most common category (4.3%), followed by anxiety disorders (3.9%); 15.0% had been to psychological counseling, while only 5.7% had been to a psychiatric consultation, and only 10% had received drug therapy in the past 12 mo.

CONCLUSION

Although the estimated prevalence of mental disorders in medical students is lower than in the general population, the rate of adequate treatment is low. We determined that improving the mental health of medical students is an urgent matter.

Key Words: Medical students; Estimated prevalence survey; Mental disorders; Mood disorders; Treatment rate

Core Tip: College students' mental health is important to national mental health. In most previous studies of medical students, there have been few investigations using Mini-International Neuropsychiatric Interview (MINI) as a diagnostic tool to assess the prevalence of mental disorders. In this study, MINI 5.0 was used to investigate the prevalence of mental disorders among medical students in Hebei province, representing the largest series of mental disorders among medical students in China ever reported. Based on these data, the prevalence and treatment of mental disorders among medical students in Hebei were introduced.

Citation: Lu WT, Hu PH, Li N, Wang L, Wang R, Wang Z, Song M, Zhao TY, Guo SJ, Huang FF, Liu BF, Ren RJ, Yang L, Lin Q, Xu YH, Jin N, Chen H, Gao YY, Wu ZF, Shi GY, Liu DP, Pan ZQ, Du CC, An CX, Wang XY. Estimated prevalence and sociodemographic correlates of mental disorders in medical students of Hebei Province, China: A cross-sectional study. *World J Psychiatry* 2023; 13(5): 215-225
URL: https://www.wjgnet.com/2220-3206/full/v13/i5/215.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i5.215

INTRODUCTION

From a sociological perspective, college students have a variety of social roles: they continue to seek knowledge, while developing social and interpersonal skills, and face more complex roles in society, personal relationships, and employment. With a growing number of college students in China, there is an increasing pressure in terms of learning, interpersonal relationships, and career decisions. Psychological health of college students has gradually become a focus of attention. In 2021, the General Office of the Ministry of Education issued a "Notice to Strengthen the Management of Students' Mental Health," which required the construction of a psychological counseling service platform. That year, the report "Exploring the Characteristic Service Plan for Prevention and Treatment of Depression" was issued by the General Office of the National Health Commission of China. This requires that depression screening should be included in students' physical examination.

Compared to the general population, college students have the ability to assess their own mental health, and most will turn to the psychological counseling center at their school when they suspect that they have psychological problems[1]. The prevalence of depression and anxiety among college students

has increased compared with before the coronavirus disease 2019 (COVID-19) pandemic. According to a survey by Hong Kong researchers, the fraction of students with moderate to higher levels of depression was significant (40.0%), including general anxiety (50.7%)[2]. Kavvadas *et al*[3] found that depression and anxiety in college students increased in the past 2 years. Hossain *et al*[4] conducted a 15-mo longitudinal study of 1140 college students. They found that, with time, there was a 22.5% and 27.1% increase in depression and anxiety, respectively. Mental disorders have increased each year, suggesting the importance of regular assessment of mental health issues.

Despite many studies on students' mental health, most had shortcomings, such as small sample size or lack of complete and structured diagnostic interviews. Huang *et al*[5] conducted a nationwide survey on the prevalence of mental disorders, without inclusion of college students. There has been no large sample study on the mental health of medical students in Hebei Province. This study screened the prevalence of mental disorders among medical students and analyzed the psychosocial risk factors. This will provide some direction for college student mental health services in the future.

MATERIALS AND METHODS

Study design and sampling

This was a cross-sectional study based on the Internet. We screened medical undergraduates at a university in Hebei Province from October to November 2021, which was a relatively stable period for the COVID-19 pandemic in Shijiazhuang, and randomly selected three levels of students by cluster sampling. Freshmen (grade 1), sophomores (grade 2), and juniors (grade 3) were concentrated at school, and we selected two of the above three grades for random evaluation. Most students in the senior and fifth grades had completed internships and were scattered among several hospitals, and their grades were randomly selected for evaluation.

Assessment tools

The screening tool for this study was an information network evaluation system developed by Saitron Information Co. Ltd. (Cangzhou, Hebei, China). Subjects scanned the QR code and clicked to sign the informed consent. For screening information so stay confidential, subjects logged into the system with a virtual student number and their initials. A one-to-one correspondence between the virtual student number and the actual student number was kept by the instructor. Subjects could check screening results on their mobile phones, and physicians interpreted screening results on site. This allowed subjects to know their mental health status at any time.

A self-designed status questionnaire was used to collect the subjects' basic information: age, gender, nationality, grade, and region were included. The Mini-International Neuropsychiatric Interview (MINI) was translated into Chinese by Sheehan *et al*[6]. MINI is a structured interview that assesses 16 categories of mental disorders. Research shows that it has good reliability, validity, and high consistency among different studies. The version used in this study was MINI 5.0.

Quality control

The screening staff comprised physicians and medical students from the Mental Health Center of Hebei Medical University. Before participating in the survey, screening personnel were trained with standardized guidelines, developed to ensure consistency of survey results. Some students were randomly selected for pretesting before formal screening. We summarized and revised ambiguities, using PowerPoint to explain subjects' biases, and to reduce biased screening.

Statistical analysis

Quantitative data were expressed as mean ± SD, and qualitative data were described by numbers and percentages. Comparison between groups with theoretical frequency $T \geq 5$ was tested by Pearson's χ^2 test; comparison between groups with theoretical frequency < 5 but ≥ 1 was tested by continuity correction χ^2 test; and comparison between groups with theoretical frequency < 1 was tested by Fisher's exact test. All data were analyzed using SPSS version 26.0 (SPSS, Chicago, IL, United States). The statistical significance of our findings was assessed with a two-tailed P value of 0.05.

Ethical approval

This study was approved by the Ethics Committee of the First Hospital of Hebei Medical University (approval No: 20210354).

RESULTS

A total of 7555 undergraduates from three grades were selected for MINI assessment; 218 refused to participate in the screening and 7337 were screened. A total of 163 students with incomplete data and 57

with inaccurate data caused by careless attitudes in answering questions were excluded. Finally, 7117 students were included in the statistical analysis. The average age was 19.9 ± 2.06 years, with 36.7% males and 63.3% females. There were 3471 sophomores, 2974 juniors and 672 seniors (Table 1).

Among medical students in Hebei Province, 7.4% suffered from at least one mental disorder in the past 12 mo, 15.0% had psychological counseling, 5.7% went to a psychiatric hospital, and only 10% received drug treatment. Mood disorders were the most common category, followed by anxiety disorders. Lifetime estimated prevalence of each subcategory of mood disorders ranged from 0.5% to 4.9%, with the 12-mo estimated prevalence ranging from 0.2% to 3.5%. Major depressive disorder (MDD) was the most prevalent mood disorder (lifetime estimated prevalence 4.9% with 12-mo estimated prevalence of 3.5%), followed by bipolar disorder (0.5% and 0.4%) and dysthymia (12-mo estimated prevalence of 0.2%). Obsessive–compulsive disorder (OCD) was the most common anxiety disorder (12-mo estimated prevalence of 2.1%), followed by generalized anxiety disorder (1.7%) and social phobia (1.4%). The estimated prevalence of other anxiety disorders was < 1%, with the lowest estimated prevalence being agoraphobia without panic disorder (0.1%). The 12-mo estimated prevalence of substance disorders ranged from < 0.1% to 0.4%, with alcohol abuse the most prevalent (0.4%) and substance abuse the lowest (< 0.1%). The estimated prevalence of any alcohol disorder was higher than that of any drug disorders (0.6% *vs* < 0.1%). Lifetime estimated prevalence of any type of schizophrenia was 0.2% and 30-d estimated prevalence was 0.1%. The 12-mo estimated prevalence of any eating disorder or antisocial personality disorder was < 0.1 (Table 2).

Among mood disorders, the estimated prevalence of MDD was 4.3% in males, and was higher than 3.1% in females. The estimated prevalence of bipolar disorder was 0.6% in males and 0.2% in females, with a significant difference. Among anxiety disorders, the estimated prevalence of OCD was 2.8% in males and 1.6% in females. For individual substance disorders, the estimated prevalence of alcohol abuse and dependence was higher in males than in females (0.5% *vs* 0.1% for alcohol dependence, 0.7% *vs* 0.2% for alcohol abuse). There was no significant gender difference for other diseases, except MDD (Table 3).

The estimated prevalence of MDD was 3.8% in sophomores, 2.9% in juniors, and 4.9% in seniors. There were significant differences between junior and senior college students. There was no significant difference in the estimated prevalence of some diseases among medical students from different areas of origin. Regarding the experiences of left-behind children, results showed that the estimated prevalence of individual substance disorders had different etiologies. The estimated prevalence of alcohol dependence in left-behind children was higher than in children without being left-behind (1.0% *vs* 0.2%). There were also significant differences in drug dependence and eating disorders, but the estimated prevalence of these diseases was < 0.1%.

For treatment, the rate of medical students who were in psychological counseling varied between 14.4% and 36.4%, whereas 36.4% of students with dysthymia had counseling, and 35.3% of medical students with psychotic symptoms had counseling. Moreover, 25% of patients with agoraphobia without history of panic disorder, 20% with panic disorder, 18.4% with compulsive disorders, and 16.4% with MDD had counseling. The proportion of students who visited a psychiatric hospital varied between 3.9% and 33.3%; of which 23.5% were for psychotic disorders, 20.0% for post-traumatic stress disorder (PTSD), 18.2% for MDD, 13.2% for bipolar disorder, and 8.8% for OCD. The rate of treatment in 12 mo varied between 9.1% and 33.3%, with 26.7% for PTSD, 33.3% for substance dependence, 15.8% for bipolar disorder, and 9.6% for MDD (Table 4).

DISCUSSION

The rapid development of the Chinese economy, along with a change in the learning and employment environment, may have caused an increase in pressure on college students. Medical students are a special group – as compared to college students, as they have more academic pressure, take a longer time to obtain a degree, and have less diversity, which can lead to pressure and increased mental disease. As such, it is critical to investigate such disorders among medical students.

It was also found that 7.4% of medical students in Hebei had suffered from one mental disorder over the past 12 mo, but only a few sought help with a healthcare professional, and fewer received adequate medication within 12 mo – contrary to previous results. The World Health Organization-World Mental Health International Undergraduate Program conducted an Internet-based self-assessment questionnaire among freshmen at 19 universities in eight countries. It included screening for the 12-mo prevalence of six common Diagnostic and Statistical Manual of Mental Disorders-IV psychiatric disorders (MDD, mania/hypomania, generalized anxiety disorder, panic disorder, alcohol use disorder, and substance use disorder). It was shown that 31% of students had at least one of these disorders within 12 mo, with 16.4% receiving psychiatric treatment[7]. Compared to this study, Winkler *et al*[8] found that the 12-mo prevalence was higher, possibly related to the survey population, the survey time, or the assessment tools. Previous studies found that depression and other diseases were more common in freshmen than for those in other grades. This study did not include freshmen, so prevalence could more easily be reduced[9].

Table 1 Participant demographics, *n* (%)

	Frequency (*n* = 7117)
Gender	
Male	2610 (36.7)
Female	4507 (63.3)
Grade	
Sophomore year	3471 (48.8)
Junior year	2974 (41.8)
Senior year	672 (9.4)
Nationality	
Han	6746 (94.8)
Ethnic minorities	371 (5.2)
Region	
Urban	4049 (56.9)
Rural	3068 (43.1)
Left-behind children	
Yes	306 (4.3)
No	6811 (95.7)

Unlike the findings of many western scholars, the estimated prevalence of drug abuse and eating disorders in this study was low[10,11]. This may have something to do with the differences between Chinese and western cultures. In terms of drug abuse, China has strict supervision on addictive drugs, so students have less exposure to addictive drugs. Moreover, medical students have some understanding of pharmacology and are more aware of the harm of drug abuse[12-14]. In terms of eating disorders, most medical students focus on finishing school and pay less attention to habitus index, so fewer of them lose weight through excessive dieting, which may explain the lower incidence of anorexia[15]. Medical students understand nutritional metabolism and the importance of regular diet, which may also explain the low prevalence of eating disorders[16].

The proportion of students seeking treatment was lower in this study compared to others. It mirrors national conditions in China: patients tend to have an insufficient appreciation of diseases associated with stigma, resulting in lower diagnosis and treatment rates[17,18]. In the future, it will be necessary to increase publicity about mental diseases and increase their understanding, so that individuals can objectively evaluate diagnosis and treatment rate. In previous studies, the 12-mo rate in the Chinese population was 9.3%, which was higher than in this study. This may be because the population was aged 18-24 years and did not include any other age groups. In addition, Yueqin *et al*[5] found that those aged 50-64 years had the highest prevalence of mental health problems. However, medical subjects with psychiatric symptoms, substance abuse, and other diseases that affect social function was consistently lower than for social personnel, with an overall prevalence slightly lower as well.

It is well-known that increasing targeted treatment for mental disorders (*e.g.*, anxiety disorders, affective disorders, and alcohol and drug abuse) is a recognized issue in academic circles. In this study, 58 (16.4%) of the 354 patients with depression had psychological counseling, 17 (4.8%) visited psychiatric hospitals, and 34 (9.6%) received adequate medication. Lu *et al*[19] examined the prevalence and treatment of depression in China in 2021 and found that of 1007 participants with a 12-mo history of depression, only 84 (weighted 9.5%) had received treatment at any facility: 38 (3.6%) were in specialized mental health groups, 20 (1.5%) in general medicine, two (0.3%) in public services, and 21 (2.7%) in complementary/alternative medicine. Only 12 (0.5%) of 1007 patients with depression received adequate treatment. In the medical student population, treatment was higher than in the general population. This may be attributed to how the school attends to students' mental health, with sufficient awareness of the disease. Premedical students better understand depression and take the initiative for both diagnosis and treatment. Yet, compared to other physical diseases, these measures are still low.

The 12-mo estimated rate of depression, OCD, and other mental diseases was higher in males than females, similar to the research of Li *et al*[20]. This could be a function of adolescent males being more likely to show symptoms of the MINI diagnosis, such that prevalence would gradually decrease with age. While comparing different grades, we found the detection rate of depression in seniors to be higher than in juniors, confirming results of previous research. It may be that the pressure of graduation, plus postgraduate entrance examinations, in tandem with COVID-19, may have led to increased depression

Table 2 Lifetime and 12-mo prevalence of mental disorders in medical students (*n* = 7117)

	Lifetime prevalence		12-mo prevalence	
	Frequency	Prevalence, % (95%CI)	Frequency	Prevalence, % (95%CI)
Mood disorders				
Any mood disorders	95	1.3 (1.08-1.63)	307	4.3 (3.86-4.81)
Depressive disorders	354	4.9 (4.48-5.51)	260	3.7 (3.23-4.12)
Major depressive disorder	354	4.9 (4.48-5.51)	249	3.5 (3.09-3.96)
Dysthymic disorder			11	0.2 (0.08-0.28)
Bipolar disorder	38	0.5 (0.38-0.74)	26	0.4 (0.24-0.55)
Anxiety disorders				
Any anxiety disorders	17	0.2 (0.14-0.39)	278	3.9 (3.48-4.39)
Panic attack	35	0.5 (0.35-0.69)	18	0.3 (0.15-0.40)
Agoraphobia without history of panic disorder			8	0.1 (0.05-0.23)
Social phobia			97	1.4 (1.11-1.66)
Obsessive–compulsive disorder			147	2.1 (1.76-2.44)
Post-traumatic stress disorder			15	0.2 (0.12-0.36)
Generalized anxiety disorder			118	1.7 (1.38-1.99)
Substance-use disorders				
Any substance-use disorders			46	0.7 (0.48-0.87)
Alcohol use disorders			42	0.6 (0.43-0.80)
Alcohol dependence			16	0.2 (0.13-0.37)
Alcohol abuse			26	0.4 (0.25-0.55)
Drug use disorders			4	< 0.1 (0.02-0.16)
Drug dependence			3	< 0.1 (0.01-0.13)
Drug abuse			1	< 0.1 (0.00-0.08)
Psychotic disorder				
Any psychotic disorder	17	0.2 (0.14-0.39)	5	0.1 (0.03-0.17)
Eating disorders				
Any eating disorders			4	< 0.1 (0.01-0.13)
Anorexia			3	< 0.1 (0.01-0.13)
Bulimia			1	< 0.1 (0.00-0.08)
Personality disorder				
Antisocial personality disorder	2	< 0.1 (0.01-0.12)		

in the population and in undergraduate students as well[21].

We found that the estimated prevalence of alcohol dependence and abuse was higher in males than in females. This is consistent with previous research. It may be that males make friends more quickly when drinking at parties, and drinking with a greater preference for alcohol[22-24]. We also found that the estimated prevalence of alcohol dependence among those who were left-behind was higher than among people who did not have that experience. Left-behind children deal with emotional neglect and are more likely to engage in behaviors such as smoking and drinking, and then develop alcohol dependence [25].

The 12-mo estimated prevalence of mental disorders, according to MINI (7.4%), is low, considering that the recognition and acceptance of mental disorders among medical students is higher than among other undergraduates. College students are the future of any nation, with a responsibility to promote social development, so that more attention is given to mental health; this also coincides with implementing effective intervention measures.

Table 3 12-mo prevalence of mental disorders by gender in medical students (*n* = 7117)

	Male		Female		*P* value
	Frequency	Prevalence, % (95%CI)	Frequency	Prevalence, % (95%CI)	
Mood disorders					
Depressive disorders	114	4.4 (3.63-5.24)	146	3.2 (2.75-3.81)	0.014[a]
Major depressive disorder	111	4.3 (3.52-5.11)	138	3.1 (2.59-3.62)	0.008[b]
Dysthymic disorder	3	0.1 (0.03-0.36)	8	0.2 (0.08-0.37)	0.517
Bipolar disorder	15	0.6 (0.33-0.96)	11	0.2 (0.13-0.45)	0.026[a]
Anxiety disorders					
Panic attack	7	0.3 (0.12-0.58)	11	0.2 (0.13-0.45)	0.845
Agoraphobia without history of panic disorder	4	0.2 (0.05-0.42)	4	0.1 (0.03-0.25)	0.434
Social phobia	42	1.6 (1.18-2.19)	55	1.2 (0.93-1.60)	0.173
Obsessive compulsive disorder	73	2.8 (2.22-3.53)	74	1.6 (1.30-2.07)	0.001[b]
Post-traumatic stress disorder	7	0.3 (0.12-0.58)	8	0.2 (0.08-0.37)	0.421
Generalized anxiety disorder	46	1.8 (1.31-2.36)	72	1.6 (1.26-2.02)	0.599
Substance-use disorders					
Alcohol use disorders	30	1.2 (0.79-1.66)	12	0.3 (0.15-0.48)	< 0.001[b]
Alcohol dependence	13	0.5 (0.28-0.88)	3	0.1 (0.02-0.22)	< 0.001[b]
Alcohol abuse	17	0.7 (0.39-1.06)	9	0.2 (0.10-0.39)	0.002[b]
Drug use disorders	2	< 0.1 (0.01-0.31)	2	< 0.1 (0.01-0.17)	0.580
Drug dependence	2	< 0.1 (0.01-0.31)	1	< 0.1 (0.01-0.13)	0.281
Drug abuse	0		1	< 0.1 (0.00-0.14)	0.447
Psychotic disorder					
Any psychotic disorder	3	0.1 (0.03-0.36)	2	< 0.1 (0.01-0.17)	0.279
Eating disorders					
Anorexia	1	< 0.1 (0.00-0.25)	2	< 0.1 (0.01-0.17)	0.904
Bulimia	0		1	< 0.1 (0.00-0.14)	0.447

[a]$P < 0.05$ (male *vs* female).
[b]$P < 0.01$ (male *vs* female).

Our study had some limitations. First, subjects were medical students, excluding other college students, and there was also some selection bias in overall estimation of college students. Second, this study was cross-sectional, so that there may have been recall bias that affected the lifetime prevalence of mental disorders.

CONCLUSION

Our study provided supplemental data on mental health disorders in the medical students, not investigated by Huang *et al*[5]. College students' mental health is important to national mental health. The purpose of this study was to establish mental health records for students, and psychiatrists were involved in the whole screening process. Our mental health department has opened a convenient channel for students diagnosed with mental diseases by MINI 5.0. Students can voluntarily go to the hospital for treatment, and psychiatrists will give more comprehensive examination and evaluation at any time. We will thus expand our research in exploring the prevalence of mental disorders in other college students, followed by more information on mental health care for Chinese students in general.

Table 4 Health care treatment in the past 12 mo of medical students with mental disorders (*n* = 7117)

	Psychological consultative center		Psychiatric specialty hospital		Treatment	
	Frequency	Prevalence, % (95%CI)	Frequency	Prevalence, % (95%CI)	Frequency	Prevalence, % (95%CI)
Mood disorders						
Major depressive disorder	58	16.4 (12.76-20.75)	17	4.8 (2.91-7.72)	34	9.6 (6.83-13.28)
Dysthymic disorder	4	36.4 (12.36-68.38)	2	18.2 (3.21-52.24)	1	9.1 (0.48-42.88)
Bipolar disorder	6	15.8 (6.59-31.93)	5	13.2 (4.95-28.89)	6	15.8 (6.59-31.93)
Anxiety disorders						
Panic attack	7	20.0 (9.06-37.46)	6	17.1 (7.17-34.29)	8	22.9 (11.05-40.56)
Agoraphobia without history of panic disorder	2	25.0 (4.45-64.42)	2	25.0 (4.45-64.42)	2	25.0 (4.45-64.42)
Social phobia	14	14.4 (8.40-23.37)	7	7.2 (3.20-14.80)	8	8.3 (3.89-16.07)
Obsessive compulsive disorder	27	18.4 (12.66-25.78)	13	8.8 (4.98-14.94)	20	13.6 (8.71-20.47)
Post-traumatic stress disorder	5	33.3 (12.99-61.31)	3	20.0 (5.31-48.63)	4	26.7 (8.92-55.17)
Generalized anxiety disorder	19	16.1 (10.21-24.26)	13	11.0 (6.23-18.44)	13	11.0 (6.23-18.44)
Substance-use disorders						
Alcohol dependence	3	18.8 (4.97-46.31)	1	6.3 (0.33-32.29)	1	6.3 (0.33-32.29)
Alcohol abuse	4	15.4 (5.04-35.72)	1	3.9 (0.20-21.59)	3	11.5 (3.03-31.28)
Drug dependence	1	33.3 (1.76-87.47)	1	33.3 (1.76-87.47)	1	33.3 (1.76-87.47)
Drug abuse	0		0		0	
Psychotic disorder						
Any psychotic disorder	6	35.3 (15.26-61.38)	4	23.5 (7.82-50.24)	2	11.8 (2.06-37.74)
Eating disorders						
Anorexia	1	33.3 (1.76-87.47)	1	33.3 (1.76-87.47)	1	33.3 (1.76-87.47)
Bulimia	0		0		0	
Personality disorder						
Antisocial personality disorder	0		0		0	

ARTICLE HIGHLIGHTS

Research background

In China, the identification rate and treatment rate of mental disorders are low, and there are few surveys on the prevalence of mental disorders among college students using diagnostic tools such as Mini-International Neuropsychiatric Interview (MINI), so the prevalence and treatment of mental disorders among college students are unclear.

Research motivation

To clarify the prevalence and treatment of mental disorders in college students, and to provide protection for their mental health.

Research objectives

This study firstly conducted diagnostic assessment for medical students to understand the estimated prevalence and treatment of medical students, so as to provide protection for the mental health of medical students.

Research methods

MINI 5.0 was used in this study to evaluate medical students in Hebei and collect their treatment information, which can provide a more accurate understanding of the prevalence and treatment rate of

mental disorders.

Research results

Among medical students in Hebei Province, 7.4% suffered from at least one mental disorder in the past 12 mo, 15.0% had psychological counseling, 5.7% went to a psychiatric hospital, and only 10% received drug treatment.

Research conclusions

The results of screening for prevalence using MINI have high confidence. The estimated prevalence rate of mental disorders among medical students in Hebei is lower than that of the general population, but the treatment rate is also lower. In the future, it is necessary to increase the awareness of medical students to mental diseases and improve the treatment rate, so as to ensure their mental health.

Research perspectives

In the future, the scope of screening should be gradually expanded to more than one university, so as to comprehensively understand the prevalence of mental disorders among college students, and contribute to the development of mental health field.

FOOTNOTES

Author contributions: Wang XY was the guarantor and designed the study; Lu WT and Hu PH participated in the acquisition, analysis, and interpretation of the data, and drafted the initial manuscript; An CX, Li N, Wang L, Wang R, Song M revised the article critically for important intellectual content; Zhao TY, Guo SJ, Huang FF, Liu BF, Ren RJ, Yang L, Lin Q, Xu YH, Jin N, Chen H and Gao YY participated in the acquisition of the data; Wang Z, Wu ZF and Shi GY involved in organizing the students to conduct the test and participated in the acquisition of the data; Liu DP, Pan ZQ and Du CC were responsible for software technical support and participated in the acquisition of the data.

Supported by S&T Program of Hebei, No. SG2021189; Project of Clinical Medical Research Center for Psychiatric and Psychological Disorders of Hebei Province, No. 199776245D; Medical Science Research Project, No. 20230167; Provincial Science and Technology Program of Hebei Province, No. 21377711D; Hebei Medical University Clinical Research Innovation Team, No. 2022LCTD-A1 and Introduce Foreign Intellectual Projects of Finance Department in Hebei Province, No. YZ202204.

Institutional review board statement: This study was approved by the Ethics Committee of the First Hospital of Hebei Medical University (approval No: 20210354).

Informed consent statement: All study participants provided informed electronic consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Country/Territory of origin: China

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S-Editor: Zhang H
L-Editor: A
P-Editor: Zhao S

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 May 19; 13(5): 226-233

DOI: 10.5498/wjp.v13.i5.226

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Effect of hyperbaric oxygen on post-stroke depression

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Specialty type: Psychology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Opuni FF, Ghana; Prati G, Italy

Received: March 8, 2023
Peer-review started: March 8, 2023
First decision: March 28, 2023
Revised: April 8, 2023
Accepted: April 12, 2023
Article in press: April 12, 2023
Published online: May 19, 2023

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Abstract

BACKGROUND

In patients with post-stroke depression (PSD) in diabetes, the situation may be more complex, requiring simultaneous treatment of blood glucose, depressive symptoms, and neurological dysfunction. Hyperbaric oxygen (HBO) therapy can improve tissue oxygen content and improve the situation of ischemia and hypoxia, thus playing a role in protecting brain cells and restoring the function of brain cells. However, there are few studies on HBO therapy for patients with PSD. This study explores the clinical efficacy of such therapy for stroke complicated with depression and diabetes mellitus, and to provide reference and basis for clinical treatment and development through the application of relevant rating scales and laboratory test indicators.

AIM

To evaluate the clinical effects of HBO therapy on patients with diabetes with PSD.

METHODS

A total of 190 diabetic patients with PSD were randomly divided into observation and control groups (95 patients per group). The control group received escitalopram oxalate 10mg once a day for eight weeks. In addition, the observation group was also given HBO therapy, once a day, five times a week, for eight weeks. The Montgomery Depression Rating Scale (MADRS), National Institutes of Health Stroke Scale (NIHSS), hypersensitive C-reactive protein, tumor necrosis factor (TNF)-α, and fasting glucose levels were compared.

RESULTS

There were no significant differences in age, sex, or depression course between the groups (P > 0.05). After HBO treatment, MADRS scores in both groups decreased significantly (14.3 ± 5.2), and were significantly lower in the control group (18.1 ± 3.5). After HBO treatment, NIHSS scores in both groups decreased significantly, and scores in the observation group (12.2 ± 4.0) decreased more than in the control group (16.1 ± 3.4), the difference was statistically significant (P < 0.001). The levels of hypersensitive C-reactive protein and TNF-α in both groups were significantly decreased, and the observation group was significantly lower than the control group (P < 0.001). Fasting blood glucose levels in both groups decreased significantly, and those in the observation group decreased more (8.02 ± 1.10) than in the control group (9.26 ± 1.04), with statistical significance (t = -7.994, P < 0.001).

CONCLUSION

HBO therapy can significantly improve depressive symptoms and neurological dysfunction in patients with PSD, and reduce the levels of hypersensitive C-reactive protein, TNF-α and fasting blood glucose.

Key Words: Hyperbaric oxygen therapy; Post-stroke depression; Diabetes; Hypersensitive C-reactive protein; Tumor necrosis factor-α; Fasting plasma glucose

Core Tip: Post stroke depression is one of the common complications of stroke patients. It affects stroke patients in the acute phase and also occurs in the rehabilitation phase, with an incidence rate of about 33%. However, many patients with post-stroke depression may still not be diagnosed and treated. It is currently believed that biological and psychological factors are involved in the occurrence and development of post-stroke depression. Risk factors of post-stroke depression include gender, psychiatric history, size and location of stroke, poor social support and degree of physical injury. Post-stroke depression may not only affect the emotional state and quality of life of patients, but also hinder the recovery of neurological function, and even increase the mortality of patients. Studies have shown that changes in ischemic hypoxia and brain cell damage are common mechanisms of stroke and post-stroke depression, so improving ischemic hypoxia may be an effective treatment. Diabetes is a chronic disease characterized by elevated blood sugar and other metabolic disorders. diabetes is associated with an increased risk of stroke and post-stroke depression.

Citation: Guo H, Ge YR, Dong YB, Zhao XC, Su GL, Wang JC. Effect of hyperbaric oxygen on post-stroke depression. *World J Psychiatry* 2023; 13(5): 226-233
URL: https://www.wjgnet.com/2220-3206/full/v13/i5/226.htm
DOI: https://dx.doi.org/10.5498/wjp.v13.i5.226

INTRODUCTION

Post-stroke depression (PSD) is a common complication in stroke patients, which can affect those in the acute stage and also occur in the convalescence stage, with an incidence of approximately 33%. However, many patients with PSD may remain undiagnosed and untreated[1]. Biological and psychological factors are currently believed to be involved in the occurrence and development of PSD[2]. Risk factors include gender, history of mental illness, size and location of stroke, poor social support, degree of physical impairment, and so on[3]. PSD may not only affect patients' emotional state and quality of life, but also hinder the recovery of neurological function and even increase patient mortality[4]. Studies have suggested that changes in ischemic hypoxia and brain cell damage are the common mechanisms of stroke and PSD, so improving ischemic hypoxia may be an effective treatment[5]. Diabetes is a chronic disease characterized by elevated blood glucose and other metabolic disorders, and is associated with increased risk of stroke and PSD[6]. Therefore, in patients with PSD in diabetes, the situation may be more complex, requiring simultaneous treatment of blood glucose, depressive symptoms, and neurological dysfunction. Hyperbaric oxygen (HBO) therapy can improve tissue oxygen content and improve the situation of ischemia and hypoxia, thus playing a role in protecting brain cells and restoring the function of brain cells[7]. However, there are few studies on HBO therapy for patients with PSD. This study explores the clinical efficacy of such therapy for stroke complicated with depression and diabetes mellitus, and to provide reference and basis for clinical treatment and development through the application of relevant rating scales and laboratory test indicators.

MATERIALS AND METHODS

Patients

From June 2018 to June 2021, a total of 190 diabetic patients with PSD diagnosed and treated in the General Hospital of Chinese PLA were recruited, all of whom met the diagnostic criteria of PSD. Inclusion criteria: (1) Patients aged ≥ 18 years in line with PSD[8]; (2) The vital signs were stable, and the clinical laboratory indicators related to stroke were basically normal; (3) No serious complications or comorbidities, normal consciousness, and cognition; and (4) Diabetes was diagnosed before stroke and in line with the diagnostic criteria of the American Diabetes Association in 2018[9]. Exclusion criteria: (1) Complicated with serious dysfunction of heart, liver, kidney, and other organs; (2) Complicated with malignant tumor and coagulation diseases; and (3) Failure to cooperate with treatment or adherence. The study protocol was approved by the Ethics Committee of the General Hospital of Chinese PLA, and all patients or their families were informed and signed the consent. Among the 190 patients, there were 52 males and 43 females in the control group, with an average age of 63.7 ± 9.3 years, 49.2 ± 14.5 d of depression and 5.9 ± 3.4 years of diabetes. There were 55 males and 40 females in the observation group, with an average age of 62.9 ± 6.1 years, 50.1 ± 12.6 d of depression and 5.6 ± 3.6 years of diabetes. Data on the patients' age, sex, smoking history, past disease history, and disease course were collected. The patients' height and weight were measured, and their body mass index (BMI) was calculated. Their blood pressure was measured in the resting state.

Patient grouping and treatment methods

The patients were divided into observation and control groups using the random number table method, with 95 patients in each group. Patients in both groups were given nutritional cerebrovascular application (including mecobalamin 0.5 mg), once a day, three times a week, intramuscular or intravenous injection, which can be increased or decreased according to age and symptoms, anti-platelet (thromboxane A2 inhibitor aspirin, 75-100 mg/time, Once a day), hypoglycemic [exenatide's initial dose is 5 μg twice a day, and can be increased to 10 μg twice a day after 1 mo of treatment according to the patient's clinical response; injections should be given within 60 min before breakfast and dinner (or before 2 main meals per day; Approximately 6 h or longer)] and other conventional treatments. The control group received oral escitalopram oxalate, 10 mg, once a day (Sichuan Kelun Pharmaceutical Co., Ltd.) for eight weeks., In addition to the oral drug regimen of the control group, the observation group received HBO therapy, once a day, five times a week, for eight weeks.

The HBO treatment was as follows: An HBO chamber (OxyHealth Europe, Vitaeris 320™) was pressurized for 20 min to reach 0.25 mpa. The patient then put on a mask and breathed pure oxygen for 40 min, breathing cabin air at 10-min intervals. Finally, patients decompressed for 30 min to normal pressure, and then left the cabin. Treatment was once a day, 10 times for a course of treatment, each course of intermittent 7-10 d, for a total of two months of observation.

Observation indicators

The following observation indexes were used to evaluate the efficacy before and after treatment: (1) Depression evaluation: The Montgomery Depression Rating Scale (MADRS) scale was used to evaluate patients' depression. The scale is divided into 10 items, with each item being rated from 1 to 6. On a scale of 0 to 60, the higher the score, the more severe the depression; (2) Neurological function evaluation: The National Institutes of Health Stroke Scale (NIHSS) scale was used to evaluate patients' neurological function. The scale includes 14 items, scored from 0 to 42. The higher the score, the more severe the neurological impairment; and (3) Measurement of hypersensitive C-reactive protein and tumor necrosis factor (TNF)-α: 10 mL of fasting venous blood was taken before and after treatment, and the upper serum was centrifuged after standing. Levels of the aforementioned were determined by enzyme-linked immunosorbent assay as per the manufacturer's instructions.

Statistical analysis

Enumeration data were expressed as frequencies (percentage) and the χ^2 test was used to assess differences between the two groups. mean ± SD was used to represent measurement data, and the difference between the two groups was assessed *via* *t*-test. The differences of MADRS score, NIHSS score, hypersensitive C-reactive protein, TNF-α and fasting blood glucose levels between the two groups before and after treatment were determined by *t*-test. $P < 0.05$ was considered statistically significant (bilateral), and IBM SPSS 21.0 was used for statistical analysis of the data.

RESULTS

General patient information

This study included 190 patients with diabetes and PSD. Patients in the observation group were aged 64.4 ± 9.4 years, and male patients accounted for 57.9% (55/95). The course of depression was 50.8 ± 15.3

d, and the course of diabetes was 6.2 ± 3.6 years. The proportion of patients with hypertension, coronary heart disease and hyperlipidemia was 54.7% (52/95), 38.9% (37/95) and 66.3% (63/95), respectively. BMI of patients in the observation group was 25.8 ± 3.8 kg/m^2, and systolic blood pressure was 139.2 ± 13.3 mmHg. In the observation group, 57 patients (60%) had ischemic stroke and 38 (40%) had hemorrhagic stroke. In the control group, the patients were aged 63.0 ± 9.2 years, 51.6% (49/95) male, the course of depression was 47.5 ± 13.4 d, and the course of diabetes was 5.7 ± 3.2 years. In the control group, 48.4% (46/95) had a history of hypertension, 33.7% (32/95) had a history of coronary heart disease, 54.7% (52/95) had a history of hyperlipidemia. The BMI of the control group was 26.2 ± 4.1 kg/m^2, and the systolic blood pressure was 137.6 ± 12.3 mmHg. In the observation group, 48 patients (50.5%) had an ischemic stroke and 47 (49.5%) had a hemorrhagic stroke. There were no significant differences in these characteristics between the two groups ($P > 0.05$, Table 1).

Depressive state and neurological function scores

Before treatment, the MADRS score of observation group (33.7 ± 5.0) was not statistically significant compared with the control group (33.0 ± 4.0, $P > 0.05$). After HBO treatment, the MADRS scores in both groups decreased significantly; that of the observation group (14.3 ± 5.2) was significantly lower than that of the control group (18.1 ± 3.5), and the difference was statistically significant ($P < 0.001$). Before treatment, the NIHSS score of the observation group (21.9 ± 4.1) was compared with the control group (21.0 ± 3.9), and there was no statistical significance ($P > 0.05$). After HBO treatment, NIHSS scores in both groups decreased significantly; scores in the observation group (12.2 ± 4.0) decreased more than those in the control group (16.1 ± 3.4), the difference being statistically significant ($P < 0.001$) (Table 2).

Levels of hypersensitive C-reactive protein and TNF-α

Before treatment, there was no statistical significance in the level of hypersensitive C-reactive protein in the observation group (7.71 ± 1.73) compared with the control group (7.43 ± 1.53, $P > 0.05$). After HBO treatment, the level in both groups decreased significantly, and the level in the observation group (2.87 ± 1.49) was significantly lower than that in the control group (4.52 ± 1.42); the difference was statistically significant ($P < 0.001$). Before treatment, there was no significant difference in TNF-α between the observation group (57.2 ± 13.6) and control group (58.6 ± 11.9, $P > 0.05$). After HBO treatment, TNF-α in both groups decreased significantly, and decreased more in the observation group (26.7 ± 12.5) than in the control group (33.9 ± 11.1), with statistical significance ($P < 0.001$) (Table 3).

Fasting blood glucose level

Before treatment, there was no significant difference in fasting blood glucose level between the observation group (10.96 ± 0.91) and control group (11.16 ± 0.93). After HBO treatment, the level decreased significantly in both groups, and that in the observation group decreased more than that in the control group (9.26 ± 1.04); the difference was statistically significant ($t = -7.994$, $P < 0.001$, Table 4).

DISCUSSION

We found that HBO therapy improved depressive symptoms and neurological dysfunction in patients with PSD, and reduced levels of hypersensitive C-reactive protein and TNF -α compared with the control group. It is worth noting that patients with diabetes and PSD who underwent HBO therapy had lower fasting glucose levels.

Stroke is an acute cerebrovascular disease with high disability and mortality rates, and PSD is a common complication that may affect nearly one-third of patients[10-12]. Importantly, PSD not only affects the patient's psychosis but may also affect the treatment effect and recovery of neurological dysfunction in patients with stroke, and even increase the incidence of recurrent stroke and all-cause mortality[13,14]. Diabetes, a chronic disease mainly characterized by elevated blood glucose, may increase the risk of stroke and PSD[15,16]. Additionally, PSD combined with diabetes may increase the risk of recurrent stroke, aggravate depressive symptoms, and even increase patient mortality[17]. Therefore, diabetes is a major cause of stroke. With the development of diabetes, patients are prone to metabolic abnormalities, cholesterol will be further increased, and thrombosis will be formed, finally leading to ischemic stroke[18]. Timely control of blood glucose is an important prevention of stroke.

Currently, escitalopram is the main first-line drug for the treatment of PSD, and the use of this drug can improve patients' emotional symptoms, but studies have demonstrated that some patients with PSD still have depressive symptoms after using escitalopram, with poor efficacy[19]. Treatment includes changing the antidepressant, adding another antidepressant, or augmenting the treatment by adding another drug, such as an atypical antipsychotic or lithium. Non-pharmacological forms of augmentation of depression treatment have also been proven to be effective, including cognitive-behavioral psychotherapy, psychoeducation, aerobic exercise, neuromodulatory treatment through vagus nerve stimulation, electroconvulsive therapy (ECT), transcranial direct current stimulation (TDCS), repetitive transcranial magnetic stimulation (rTMS) or deep brain stimulation and light therapy; however, non-pharmacological forms of biological treatment used in the treatment of treatment-resistant depression

Table 1 Clinical characteristics of patients in two groups, *n* (%)

Clinical characteristics	Observation group	Control group	t/χ^2	*P* value
Patients	95	95	-	-
Age (yr)	64.4 ± 9.4	63.0 ± 9.2	1.052	0.294
Male	55 (57.9)	49 (51.6)	0.765	0.382
Depressive course (d)	50.8 ± 15.3	47.5 ± 13.4	1.579	0.116
Smoking history	38 (40.0)	31 (32.6)	1.115	0.291
Diabetes course (yr)	6.2 ± 3.6	5.7 ± 3.2	0.941	0.348
History of hypertension	52 (54.7)	46 (48.4)	0.759	0.384
History of coronary heart disease	37 (38.9)	32 (33.7)	0.569	0.451
History of hyperlipidemia	63 (66.3)	52 (54.7)	2.666	0.103
Body mass index (kg/m^2)	25.8 ± 3.8	26.2 ± 4.1	-0.676	0.500
Systolic blood pressure (mmHg)	139.2 ± 13.3	137.6 ± 12.3	0.873	0.384
Stroke type			1.724	0.189
Ischemic stroke	57 (60.0)	48 (50.5)		
Hemorrhagic stroke	38 (40.0)	47 (49.5)		

Table 2 Depressive state and neurological function scores of the two groups

Group	Patients	MADRS scores		NIHSS scores	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	95	33.7 ± 5.0	14.3 ± 5.2[a,d]	21.9 ± 4.1	12.2 ± 4.0[a,d]
Control group	95	33.0 ± 4.0	18.1 ± 3.5[a]	21.0 ± 3.9	16.1 ± 3.4[a]

[a]*P* < 0.001 *vs* before treatment in this group.
[d]*P* < 0.001 *vs* control group after treatment.
MADRS: Montgomery Depression Rating Scale; NIHSS: National Institutes of Health Stroke Scale.

Table 3 The levels of hypersensitive C-reactive protein and tumor necrosis factor-α in the two groups

Group	Patients	Hypersensitive C-reactive protein (mg/L)		Tumor necrosis factor-α (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	95	7.71 ± 1.73	2.87 ± 1.49[a,d]	57.2 ± 13.6	26.7 ± 12.5[a,d]
Control group	95	7.43 ± 1.53	4.52 ± 1.42[a]	58.6 ± 11.9	33.9 ± 11.1[a]

[a]*P* < 0.001 *vs* before treatment in this group.
[d]*P* < 0.001 *vs* control group after treatment.

also do not show substantial efficacy. Despite the improvement achieved during electroshocks, ECT has no lasting effect, and despite continued pharmacotherapy, relapses are observed in a large (37%) proportion of patients[20]. TDCS has been used with a moderate effect on depression, similar to rTMS, which also has moderate and short-term efficacy in improving mood and cognitive function in people with depression[21]. Light therapy has proven to be ineffective in enhancing the effects of antidepressants in both seasonal and recurrent depression[22]. Currently, HBO therapy is known to be an effective and safe method for treating PSD, which has been the subject of numerous studies. This study found that HBO therapy can improve depressive symptoms and neurological dysfunction in patients with PSD, specifically improving the blood supply to the lesion and facilitate the blood supply to the focal point of the stroke. Under the action of HBO, the phenomenon of counter-stealing blood will appear in the tissue, which is conducive to the blood supply to the ischemic lesion. Increase vertebrobasilar artery blood flow: Under HBO, the vertebrobasilar artery system is the only blood vessel that

Table 4 Fasting blood glucose levels of the two groups

Group	Patients	Before treatment	After treatment	*t* value	*P* value
Observation group	95	10.96 ± 0.91	8.02 ± 1.10	20.177	< 0.001
Control group	95	11.16 ± 0.93	9.26 ± 1.04	13.256	< 0.001
t value	-	-1.475	-7.994	-	-
P value	-	0.142	< 0.001	-	-

does not contract but dilates, thus increasing the blood supply and oxygen supply to the brain stem and reticular structure, which is conducive to the improvement of the patient's wakefulness and mood. HBO therapy was found to improve depressive symptoms and neurological dysfunction in patients with PSD. Similar to this study, a meta-analysis established that HBO treatment reduced NIHSS scores (mean difference = 2.77 points, 95%CI from 3.57 to 1.98 points, $P < 0.001$) and improved Hamilton Depression Scale scores (mean difference = 4.33 points, 95%CI from 4.82 to 3.84 points, $P < 0.001$)[7].

Ischemic anoxic injury may be a common initiating factor of stroke and PSD, and inflammatory processes may also be involved in the occurrence and development of depression. It has been suggested that patients with PSD had higher levels of TNF-α compared with non-depressed patients (25.65 ± 9.24 *vs* 17.29 ± 4.27, $P < 0.001$)[23]. In this study, diabetic PSD patients in the observation group had lower levels of hypersensitive C-reactive protein and TNF-α compared with the control group. This suggests that inflammatory factors can be used as biomarkers of PSD in patients with diabetes and may be effective early treatment targets[24]. Interestingly, the present study found that patients with PSD and diabetes who underwent HBO therapy had lower fasting glucose levels. Previous studies have suggested that HBO therapy can promote insulin secretion in patients with diabetes and enhance glucose uptake by brain cells[25].

This study has some limitations. Owing to the small sample size, fewer variables were collected, and the observation time was short. Large randomized controlled clinical trials are required to validate the role of HBO therapy in patients with diabetes and PSD.

CONCLUSION

In conclusion, HBO therapy can significantly improve depressive symptoms and neurological dysfunction in patients with PSD, and reduce the levels of hypersensitive C-reactive protein, TNF-α and fasting blood glucose, which is worthy of clinical promotion.

ARTICLE HIGHLIGHTS

Research background

This study explores the clinical efficacy of such therapy for stroke complicated with depression and diabetes mellitus, and to provide reference and basis for clinical treatment and development through the application of relevant rating scales and laboratory test indicators.

Research motivation

Changes in ischemic hypoxia and brain cell damage are common mechanisms of stroke and post-stroke depression, so improving ischemic hypoxia may be an effective treatment. Diabetes is a chronic disease characterized by elevated blood sugar and other metabolic disorders. diabetes is associated with an increased risk of stroke and post-stroke depression.

Research objectives

This study explores the clinical efficacy of such therapy for stroke complicated with depression and diabetes mellitus, and to provide reference and basis for clinical treatment and development through the application of relevant rating scales and laboratory test indicators.

Research methods

Patients in both groups were given nutritional cerebrovascular application, once a day, three times a week, intramuscular or intravenous injection, which can be increased or decreased according to age and symptoms, anti-platelet, hypoglycemic and other conventional treatments. The control group received oral escitalopram oxalate, 10 mg, once a day for eight weeks., In addition to the oral drug regimen of the control group, the observation group received hyperbaric oxygen (HBO) therapy, once a day, five times

a week, for eight weeks. The HBO treatment was as follows: an HBO chamber was pressurized for 20 min to reach 0.25 mpa. The patient then put on a mask and breathed pure oxygen for 40 min, breathing cabin air at 10-min intervals. Finally, patients decompressed for 30 min to normal pressure, and then left the cabin. Treatment was once a day, 10 times for a course of treatment, each course of intermittent 7-10 d, for a total of two months of observation.

Research results

There were no significant differences in age, sex, or depression course between the groups. After HBO treatment, Montgomery Depression Rating Scale scores in both groups decreased significantly, and were significantly lower in the control group. After HBO treatment, National Institutes of Health Stroke Scale scores in both groups decreased significantly, and scores in the observation group decreased more than in the control group, the difference was statistically significant. The levels of hypersensitive C-reactive protein and tumor necrosis factor (TNF)-α in both groups were significantly decreased, and the observation group was significantly lower than the control group. Fasting blood glucose levels in both groups decreased significantly, and those in the observation group decreased more than in the control group, with statistical significance.

Research conclusions

HBO therapy can significantly improve depressive symptoms and neurological dysfunction in patients with post-stroke depression, and reduce the levels of hypersensitive C-reactive protein, TNF-α and fasting blood glucose.

Research perspectives

The future research direction is mainly to study the influence of depression in diabetes patients.

FOOTNOTES

Author contributions: Guo H and Ge YR concepted the study; Guo H, Dong YB and Zhao XC collected the data; Guo H, Zhao XC, Wang JC and Ge YR contributed to the formal analysis; Guo H and Zhao XC contributed to the investigation; Guo H, Zhao XC and Su GL contributed to the methodology; Guo H, Zhao XC, Su GL and Dong YB supervised the study; Zhao XC validated the study; Guo H and Ge YR contributed to the visualization of the study; Guo H and Wang JC originally drafted the manuscript; Guo H, Ge YR, Wang JC and Dong YB reviewed and edited the manuscript.

Institutional review board statement: The study was reviewed and approved by The First Medical Center, Chinese PLA General Hospital Institutional Review Board (Approval No. 20180068).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: We declare that there are no conflicts of interest.

Data sharing statement: No additional data are available.

STROBE statement: The authors have read the STROBE Statement, and the manuscript was prepared and revised according to the STROBE Statement.

Country/Territory of origin: China

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S-Editor: Wang JL
L-Editor: A
P-Editor: Chen YX

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World Journal of Psychiatry

Submit a Manuscript: https://www.f6publishing.com

World J Psychiatry 2023 May 19; 13(5): 234-246

DOI: 10.5498/wjp.v13.i5.234

ISSN 2220-3206 (online)

ORIGINAL ARTICLE

Observational Study

Associations between Borg's rating of perceived exertion and changes in urinary organic acid metabolites after outdoor weight-bearing hiking

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Specialty type: Psychology

Provenance and peer review: Unsolicited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): B
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Gokce MI, Turkey; Narain R, Canada

Received: March 9, 2023
Peer-review started: March 9, 2023
First decision: March 23, 2023
Revised: March 31, 2023
Accepted: April 7, 2023
Article in press: April 7, 2023
Published online: May 19, 2023

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Abstract

BACKGROUND

Developing methods to monitor exercise load and evaluate body fatigue and muscle injury over time in hiking training remains a key problem to be solved. A widely used psycho-physical tool to assess the subjective perception of effort during exercise is Borg's rating of perceived exertion (BRPE) scale. Data on the relationships and validity of the BRPE compared to objectively assessed metabolic criteria are still lacking, especially urinary organic acid concentrations.

AIM

To verify whether the BRPE scale could be used in the prescription of outdoor hiking with weight-bearing and reveal the relationship between the BRPE scale and urinary physiological measures.

METHODS

Eighty-nine healthy men (average age: 22 years) were enrolled in a 40 km (6 h) hiking training exercise with a 20 kg load. After training, the BRPE scale (6-20) was completed. All participants were divided into three groups according to the rating of the BRPE scale. Urine samples were collected before and after training. Urinary myoglobin levels were measured immediately using the fluorescent immunoassay method. The remaining urine was subpacked and frozen for the subsequent detection of urinary organic acids using gas chromatography and mass spectrometry.

RESULTS

The contents of organic acids and myoglobin in urine were significantly increased after participants hiked 40 km (6 h) with a 20 kg load. Only orthogonal partial

least-squares discrimination analysis performed well in separating the group with a BRPE score of 6-12 from the group with a BRPE score of 13-20. Significant differences in the urine levels of several organic acids were observed between the two groups, and the heatmap also presented different metabolic profiles based on BRPE. According to the standard of a variable importance in the projection > 1, fold change > 1.5 and $P < 0.05$, 19 different metabolites of urinary organic acids were screened and enriched in pathways mainly including the citrate cycle (tricarboxylic acid cycle) and alanine, aspartate and glucose metabolism.

CONCLUSION

The BRPE scale identified significantly different urinary organic acid profiles between the higher and lower BRPE value groups, and, thus, could be used to monitor body fatigue in individuals participating in long-distance outdoor hiking with weight bearing.

Key Words: Borg's rating of perceived exertion; Urine; Organic acid metabolism; Exercise intensity; Myoglobin; Hiking

Core Tip: Developing methods to monitor exercise load and evaluate body fatigue over time in endurance training is a key problem to be solved. Borg's rating of perceived exertion (BRPE) scale has been widely used as a psycho-physical tool to assess the subjective perception of effort during exercise. In this study, we aimed to verify whether the BRPE scale could be used in the prescription of outdoor hiking with weight-bearing and reveal the relationship between the BRPE scale and urinary physiological measures, particularly urinary organic acid concentrations. Underlying mechanisms related to body fatigue and metabolic disorders were also analyzed in this study.

Citation: Sang PP, Li J, Tan XD, Peng W, Zhou HH, Tian YP, Zhang ML. Associations between Borg's rating of perceived exertion and changes in urinary organic acid metabolites after outdoor weight-bearing hiking. *World J Psychiatry* 2023; 13(5): 234-246

URL: https://www.wjgnet.com/2220-3206/full/v13/i5/234.htm

DOI: https://dx.doi.org/10.5498/wjp.v13.i5.234

INTRODUCTION

Long-distance weight-bearing hiking in the field is an important part of physical training, that helps improve cardiopulmonary endurance and muscle endurance. Many countries use this type of exercise as an essential component of endurance training for soldiers[1,2]. In this process, an excessive exercise load may lead to fatigue accumulation, which imposes risks of physical and mental stress[3]. It represents an inconspicuous and gradual process. If overtraining continues, more severe injury in soft tissue or skeletal muscle will occur[4,5]. Therefore, developing methods to monitor exercise load and evaluate muscle injury and body fatigue over time remains a key problem to be solved.

Exercise tests have been conducted for more than 60 years[6]. Many indices, such as lactate, creatine kinase, and myoglobin, which are based on blood biochemical tests, have been applied during exercise monitoring[7,8]. However, these invasive tests with complex methodologies and high costs are difficult to implement in the field. Noninvasive tools and indices are needed to assess the intensity of physical activity during outdoor hiking exercise interventions.

A widely used psycho-physical tool to assess the subjective perception of effort during exercise is Borg's rating of perceived exertion (BRPE) scale[9-11]. It assesses the mental load of exercise with the subjective level of physical exertion. First, the subjective level of physical exertion is divided into scores ranging from 6-20[9]. Later, other rating methods, such as methods with 10 levels and 100 levels, also appeared[12,13]. A BRPE value of 10 times was used to estimate the heart rate of the trainer. The American College of Sports Medicine has suggested that the BRPE value may be considered to add precision to heart rate when monitoring exercise intensity and even replace it once the relationship between the heart rate and BRPE value is known for an individual[14]. With the advantages of simplicity, economy and strong operability, the BRPE scale facilitates the collection of training load data efficiently and conveniently. Many studies have revealed that the BRPE value is useful both in the prescription of alternated-intensity training exercises and continuous tests in a laboratory[15-17], underlining the strong relationships between the BRPE value and the indices of physiological strains. Nevertheless, only a few studies have been performed within a more ecologically valid environment.

Previous studies examining hiking have reported that the BRPE scale is significantly higher as load mass increases[18]. However, data revealing the relationships and validity of the BRPE value compared to objectively assessed metabolic criteria, especially urine organic acid concentrations, are still lacking.

In the present study, we examined the relationship between the BRPE scale and physiological measures (urinary organic acid metabolite and myoglobin levels) of exercise intensity after 40 km outdoor hiking with weight-bearing of approximately 20 kg. The aim of this study was to verify whether the BRPE score collected after hiking could be used to prescribe these training exercises.

MATERIALS AND METHODS

Participants

This study included 89 healthy young men (average age: 22 years, range from 18 to 24 years). Individuals with basic diseases, such as heart and lung disease, anemia, bone injury, and hypertension, and those who were taking drugs were excluded. Individuals with fever or musculoskeletal or soft tissue injury in the 7 d before hiking were also excluded. All participants signed the informed consent form. This study was reviewed and approved by the Ethics Committee of Chinese PLA General Hospital (S2021-019-01).

Hiking walking settings

All participants experienced a hiking training exercise of 40 km with 20 kg carriages in plain areas. The whole training exercise lasted from 8:00 to 14:00. Two short 10-min breaks were allotted to supply water and a longer 30-min break was provided at 11:00 am for the prescribed lunch.

At the end of training, everyone truthfully completed the BRPE scale (Table 1), and urine samples were collected before and after training. The level of myoglobin in urine was measured immediately, and the remaining urine was separated and frozen at -80 °C for organic acid measurements.

Detection of the urine myoglobin concentration

According to the instructions of the myoglobin assay kit (fluorescence immunochromatography) (Beijing Danda Biotechnology Co., Ltd. Beijing, China), the level of myoglobin in urine was determined using a fluorescence immunoassay analyzer (Beijing Danda Biotechnology Co., Ltd. Beijing, China). First, information from the calibration card was input into the analyzer, and the standard curve of the urine sample type was selected. Then, the test card was removed, and 80 μL of the urine sample was added into the sampling hole of the test card. After 15 min, the test strip was placed into the dry fluorescent immunoassay analyzer to read the data. The chemical signal was measured and analyzed to quantitatively obtain the myoglobin concentration in the tested sample.

Detection of urine organic acids

Sample prehandling: One hundred microliters of urine was mixed with 30 μL of urease and incubated at 37 °C for 30 min. Next, 100 μL of the internal standard (margaric acid, 100 ppm) and 1 mL of absolute ethanol were added and the mixture was centrifuged at 13000 rpm for 5 min at 4 °C. The supernatant was extracted, and after adding 2% hydroxylamine hydrochloride, it was added to the supernatant, it was incubated at 60 °C for 10 min. After cooling at room temperature, the supernatant was transferred to a glass bottle and dried with nitrogen. Finally, 100 μL of BSTFA + TMCS (99:1) were added and incubated at 80 °C for 30 min, and gas chromatography and mass spectrometry (GC/MS, TSQ 8000 EVO, Thermo Scientific, United States) was used for the organic acid analysis.

GC/MS parameters: The chromatography column was a DB-5 column (30 m × 0.25 mm × 0.25 μm) purchased from Agilent Technologies Inc. The injection temperature and transfer line temperature were set to 250 °C and 290 °C, respectively. The injection volume was 1 μL, the split mode was selected with a ratio of 1:20, and the flow rate of high purity helium was 1 mL/min. The initial oven temperature was set to 100 °C and maintained for 4 min; then it was heated at a rate of 4 °C/min to 280 °C and maintained for 7 min.

GC/MS acquisition: Standard solutions (Zhejiang Biosan Biochemical Technologies Co., Ltd., China) of organic acids were prepared using the procedures described above and analyzed with a scan range of 50-550 m/z using Xcalibur software (ver. 2.1, Thermo Scientific, United States). The characteristic retention time and fragment ions of each organic acid were determined, and an organic acid database was established. Next, the instrument acquisition method was established by performing timed acquisition with the scan type of single iron monitoring (SIM). Timed acquired SIM data were analyzed using Trance Founder software (ver. 3.0, Thermo Scientific, United States). The GC/MS data of urine samples were qualitatively compared with the spectrometry database, and the final results were reported as the ratio of the peak area of the detected compound to the peak area of the internal standard.

Table 1 The Borg's rating of perceived exertion scale (6-20)

Score	Perceived exertion
6	No exertion at all
7	Extremely light
8	
9	Very light
10	
11	Light
12	
13	Somewhat hard
14	
15	Hard
16	
17	Very hard
18	
19	Extremely hard
20	Maximal exertion

Statistical analysis

Data are presented as the means ± SD for normally distributed data or medians + interquartile ranges for nonnormally distributed data. For statistical comparisons, independent sample *t* tests or Mann-Whitney *U* tests (nonnormally distributed data) were performed using SPSS 25.0 and GraphPad Prism 8.0 software. SIMCA14.1.0 software was used for principal component analysis (PCA) and orthogonal partial least-squares discrimination analysis (OPLS-DA). Heatmaps and radar charts were processed on the Xiantao website (http://www.xiantao.love). The pathway analysis was performed using MetaboAnalyst 5.0 (https: //www.metaboanalyst.ca/).

RESULTS

Changes in organic acid and myoglobin levels before and after exercise

The volcano map of the results for organic acid metabolism before and after exercise is shown in Figure 1. Log2 (fold change) was set as the abscissa and -Log10 (*P* value) was set as the ordinate. The results showed that the levels of oxalic acid, pyruvic acid, 3-OH-butyric acid, 2-OH-isovaleric acid, 2-methyl-3-OH-butyric acid, benzoic acid, maleic acid, glyceric acid, fumaric acid, 3-methylglutaric acid, 3-methylglutaconic acid, glutaconic acid, decanoic acid, malic acid, adipic acid, creatinine, 2-OH-glutaric acid, pimelic acid, 2-ketoglutaric acid, phenylpyruvic acid, aconitic acid, vanillic acid, homovanillic acid, azelaic acid, citric acid, sebacic acid and palmitic acid were significantly increased after exercise. The myoglobin level was also increased after exercise ($P = 0.0133$).

Differentiation in the BRPE scale groups based on urinary organic acids

Figure 2 shows the PCA and OPLS-DA scores of the BRPE scale and urine organic acid levels. An unsupervised PCA was performed as the statistical analysis to evaluate the difference in organic acid metabolites among the groups with scores of 6-12, 13-16 and 17-20. PCA results showed no significant separation among the three groups. The supervised OPLS-DA model was subsequently used for analysis, and the results showed a clear separation between the groups with scores of 6-12 and 13-16 (Figure 3A) and between the groups with scores of 6-12 and 17-20 (Figure 3B). The model parameters of Q_2Y and R_2Y for those two group separations were 0.315 and 0.452 and 0.299 and 0.527, respectively. Although the groups with scores of 12-15 and 16-20 could not be separated (Figure 3C), the model parameters of Q_2Y and R_2Y were 0.0777 and 0.312, respectively.

Since the distinction between the groups with scores of 13-16 and 17-20 was not obvious, groups with scores of 13-16 and 17-20 were combined into one group (score of 13-20) for analysis. The OPLS-DA results showed that the two groups were separated (Figure 3D), and the model parameters of Q_2Y and R_2Y were 0.236 and 0.368, respectively. The statistical results also showed significant differences in the levels of most of the organic acid indicators between the two groups (Table 2).

Table 2 Change of Borg's rating of perceived exertion scale and organic acids

Compound	6-12 scale (*n* = 10), mean ± SD (range)	13-20 scale (*n* = 79), mean ± SD (range)	*t*	*P* value	Freedom	Effect size
Lactic acid	0.016 (0.013, 0.018), 0.008-0.038	0.028 ± 0.024 (0.010-0.150)	-2.933	0.006	32.954	-0.295
2-OH-isobutyric acid	0.003 ± 0.002 (0.001-0.006)	0.005 ± 0.003 (0.002-0.026)	-2.371	0.028	19.844	-0.279
Glycolic acid	0.246 ± 0.095 (0.098-0.393)	0.347 ± 0.115 (0.111-0.617)	-3.086	0.009	87	-0.431
2-OH-butyric acid	0.001 ± 0.000 (0.000-0.002)	0.002 ± 0.001 (0.001-0.008)	-5.425	0.000	26.692	-0.517
Glyoxylic acid	0.005 (0.004, 0.007), 0.004-0.010	0.009 (0.007, 0.011), 0.004-0.023	-4.554	0.000	14.629	-0.540
Oxalic acid	0.006 ± 0.003 (0.003-0.011)	0.008 ± 0.005 (0.000-0.031)	-1.382	0.182	20.192	-0.166
Pyruvic acid	0.026 ± 0.007 (0.013-0.036)	0.044 ± 0.021 (0.017-0.149)	-5.621	0.000	35.797	-0.503
3-OH-butyric acid	0.092 ± 0.035 (0.053-0.173)	0.219 ± 0.148 (0.054-1.025)	-2.689	0.009	87	-0.508
2-OH-isovaleric acid	0.007 ± 0.003 (0.004-0.013)	0.014 ± 0.009 (0.003-0.073)	-5.280	0.000	41.164	-0.468
2-methyl-3-OH-butyric acid	0.002 (0.002, 0.003), 0.001-0.015	0.004 (0.003, 0.006), 0.001-0.012	-3.159	0.002	87	-0.548
2-keto-isovaleric acid	0.001 ± 0.000 (0.000-0.001)	0.001 ± 0.001 (0.000-0.004)	-3.589	0.001	87	-0.614
Benzoic acid	0.001 (0.001, 0.001), 0.001-0.015	0.003 ± 0.002 (0.001-0.013)	-2.77	0.787	9.575	-0.056
2-keto-3-methylvaleric acid	0.001 ± 0.000 (0.000-0.001)	0.001 ± 0.001 (0.000-0.006)	-2.869	0.005	87	-0.535
Maleic acid	0.001 ± 0.000 (0.000-0.001)	0.001 ± 0.001 (0.000-0.003)	-4.047	0.001	16.432	-0.474
Succinic acid	0.007 ± 0.005 (0.002-0.019)	0.018 (0.013, 0.022), 0.005-0.032	-4.814	0.000	87	-0.673
Glyceric acid	0.003 ± 0.002 (0.001-0.006)	0.004 (0.003, 0.007), 0.002-0.014	-3.959	0.001	16.204	-0.468
Fumaric acid	0.019 ± 0.010 (0.004-0.042)	0.050 ± 0.030 (0.012-0.183)	-3.261	0.002	87	-0.573
Glutaric acid	0.002 ± 0.001 (0.000-0.004)	0.006 (0.004, 0.010), 0.002-0.018	-4.359	0.000	87	-0.684
3-methylglutaric acid	0.003 ± 0.003 (0.001-0.010)	0.006 (0.004, 0.009), 0.001-0.020	-3.262	0.006	13.322	-0.438
3-methylglutaconic acid	0.006 ± 0.004 (0.002-0.013)	0.016 ± 0.008 (0.004-0.043)	-6.149	0.000	19.746	-0.603
Glutaconic acid	0.006 ± 0.004 (0.001-0.014)	0.016 ± 0.011 (0.001-0.052)	-2.857	0.005	87	-0.516
Decanoic acid	0.000 (0.000, 0.001), 0.000-0.001	0.001 (0.001, 0.001), 0.000-0.004	-2.754	0.007	87	-0.486
Malic acid	0.002 (0.002, 0.004), 0.001-0.010	0.009 ± 0.008 (0.001-0.057)	-4.364	0.000	29.065	-0.429
Adipic acid	0.006 ± 0.007 (0.001-0.024)	0.019 ± 0.021 (0.003-0.123)	-3.932	0.000	35.442	-0.378
Creatinine	2.717 ± 3.056 (0.279-10.426)	5.955 ± 3.663 (0.012-13.452)	-3.157	0.008	12.488	-0.433
Mandelic acid	0.002 ± 0.002 (0.001-0.003)	0.003 ± 0.001 (0.001-0.007)	-5.460	0.000	15.516	-0.598
2-OH-glutaric acid	0.006 ± 0.003 (0.002-0.013)	0.017 ± 0.009 (0.000-0.044)	-3.867	0.000	87	-0.634
Pimelic acid	0.002 ± 0.001 (0.000-0.004)	0.005 ± 0.003 (0.000-0.014)	-3.978	0.000	87	-0.645
2-keto-glutaric acid	0.002 ± 0.003 (0.000-0.009)	0.020 ± 0.013 (0.000-0.087)	-4.268	0.000	87	-0.684
Phenylpyruvic acid	0.013 ± 0.008 (0.005-0.032)	0.034 (0.023, 0.043), 0.005-0.136	-7.031	0.000	31.925	-0.599
Aconitic acid	0.002 (0.001, 0.012), 0.000-0.028	0.053 ± 0.041 (0.001-0.174)	-8.287	0.000	64.322	-0.605
Vanillic acid	0.023 ± 0.025 (0.001-0.075)	0.035 (0.016, 0.080), 0.000-0.357	-3.146	0.004	27.007	-0.330
Homovanillic acid	0.011 (0.007, 0.017), 0.004-0.060	0.044 ± 0.022 (0.009-0.129)	-4.900	0.000	13.464	-0.588
Azelaic acid	0.008 ± 0.007 (0.000-0.022)	0.017 ± 0.012 (0.002-0.084)	-3.418	0.003	16.749	-0.410
Citric acid	0.001 ± 0.001 (0.000-0.003)	0.005 ± 0.005 (0.000-0.030)	-2.517	0.014	87	-0.487
Sebacic acid	0.078 (0.042, 0.168), 0.023-0.481	0.252 ± 0.183 (0.034-1.039)	-2.135	0.053	12.500	-0.316
Palmitic acid	0.025 ± 0.007 (0.014-0.033)	0.040 ± 0.012 (0.024-0.095)	-6.076	0.000	16.511	-0.627

Comparison of metabolic profiles in urinary metabolites between the low and high BRPE score groups

The heatmap cluster analysis (Figure 4) revealed the metabolic profiles of organic acids between the groups with scores of 6-12 (low BRPE score group) and 13-20 (high BRPE score group). The redder color represents a higher content. The urine contents of organic acids in the group with a score of 6-12 were generally low.

According to a fold change > 1.5, variable importance in the projection > 1 and $P < 0.05$ for organic acids, the differentially abundant compounds between the groups with scores of 6-12 and 13-20 were screened, and 19 differentially abundant compounds were identified (Table 3). A radar chart of these metabolites was then constructed based on the abundance of organic acids (Figure 5). Compared with the group with a score of 6-12, the organic acid levels in the group with a score of 13-20 were significantly increased. Because of the high order of magnitude for creatinine, which was significantly different from the other organic acids, the creatinine index was removed, and a radar chart without creatinine was constructed, as shown in Figure 5B. Figure 6 shows the metabolic pathways of the differentially abundant metabolites, and the results revealed significant differences in the metabolic pathways of the citrate cycle [tricarboxylic acid (TCA) cycle] and alanine, aspartate and glucose metabolism.

Correlation analysis between the BRPE score and myoglobin level

The statistical results for the myoglobin levels among the groups with BRPE scores of 6-12 and 13-20 are shown in Figure 7A. No significant differences were observed between the groups with scores of 6-12 and 13-20. The results of Spearman's analysis of the Borg scale showed no significant correlation between the Borg scale and myoglobin level (Figure 7B).

DISCUSSION

In this study, 89 healthy young men were enrolled in a 40 km (6 h) outdoor hiking training exercise. We compared urine organic acid and myoglobin levels before and after hiking and analyzed the underlying correlation between the BRPE score and urine organic acid levels.

The results showed that the levels of most of the organic acid metabolites increased after hiking. Organic acids are a class of carboxylic acids produced from amino acids, fats and carbohydrates in the metabolic process of the body, which directly participate in many biochemical reactions involved in life activities. They are also related to the metabolic activities and mutual transformation of sugar, fat and protein. Previous studies have shown an increased level of glycolysis products, such as TCA cycle intermediates, nucleotide products and branched-chain amino acids, which are usually related to energy metabolism, during endurance training[19-21].

Urine myoglobin levels were also detected before and after exercise. Myoglobin exists in cardiac muscle and skeletal muscle cells and has a close relationship with exercise-related fatigue and sports injury[22,23]. When exercise causes skeletal muscle injury, the content of myoglobin in blood or urine may consequently increase. Our results showed that urinary myoglobin levels increased after exercise but were within the normal range, indicating that exercise-related fatigue may have occurred after exercise, but we could not clearly determine what extent of fatigue occurred.

The BRPE scale is a simple method to quantify the degree of self-perceived exertion of the human body, particularly in fatigue evaluations[24,25]. We collected the BRPE scores of the trainees after exercise and divided them into groups with scores of 6-12, 13-16 and 17-20 according to self-perceived exertion measured using the BRPE scale. Only the supervised OPLS-DA model performed well in separating trends between groups. We observed that the 6-12 score group was significantly separated from the 13-16 and 17-20 score groups. However, the latter two groups were not separated because no obvious differences in metabolism were detected between the two groups. Therefore, we combined those two groups into a 13-20 score group. This result indicates that organic acid metabolism changed when "somewhat hard" was reported as a psychological perception of exercise. The heatmap of the BRPE score and organic acid metabolites directly showed that the contents of organic acids increased in the higher BRPE score group (13-20). These findings support the results of our study that individuals with higher BRPE values experienced more metabolic changes related to body fatigue. There is a need to individualize the recovery or training strategies in the same excises. Our study is the first to compare metabolomic responses controlled by the BRPE in hiking training. Our data indicate that for individuals undergoing the same training, the BRPE score may discriminate those with different stress ranges at a biochemistry level. This result is also consistent with previous research that the BRPE could show the relevance of individual recovery treatments and the sensitivity and predictability of metabolomics to prevent biochemical and physiological disturbances[26].

Then, we screened differentially abundant metabolites according to the multivariate and univariate statistical significance criteria. Nineteen differentially abundant metabolites identified between the groups with scores of 6-12 and 13-20 are shown in Table 3 and Figure 5. A subsequent pathway enrichment analysis showed that the TCA cycle and alanine, aspartate and glutamate metabolism were the main distinctive metabolomic characteristics in the 13-20 score group. The TCA cycle is the process

Table 3 Differential organic acid metabolites between Borg's rating of perceived exertion 6-12 scale and 13-20 scale

Compound	KEGG ID	VIP	Fold change	*P* value
Succinic acid	C00042	1.38	2.45	0.000
Homovanillic acid	C05582	1.29	2.76	0.000
Glutaric acid	C00489	1.27	3.52	0.000
Palmitic acid	C00249	1.25	1.64	0.000
3-methylglutaconic acid	-	1.21	2.64	0.000
Pimelic acid	C02656	1.19	3.54	0.000
2-keto-glutaric acid	C00026	1.19	8.52	0.000
2-OH-glutaric acid	-	1.18	3.00	0.000
Mandelic acid	C01984	1.16	1.91	0.000
Glyoxylic acid	C00048	1.15	1.63	0.000
3-methylglutaric acid	-	1.11	2.08	0.006
2-keto-isovaleric acid	-	1.09	2.01	0.001
Aconitic acid	C00417	1.08	7.11	0.000
Phenylpyruvic acid	C00166	1.08	2.92	0.000
Glutaconic acid	C02214	1.05	2.64	0.005
2-methyl-3-OH-butyric acid	-	1.04	2.00	0.002
2-OH-butyric acid	C05984	1.04	1.89	0.000
Fumaric acid	C00122	1.01	2.66	0.002
Creatinine	C00791	1.00	2.22	0.008

KEGG: Kyoto encyclopedia of genes and genomes; VIP: Variable importance in the projection.

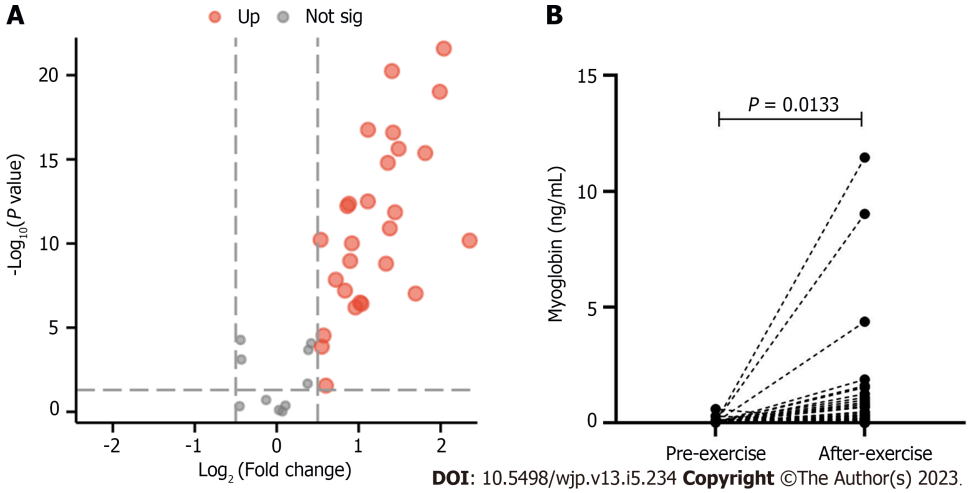

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Figure 1 Changes in organic acids and myoglobin levels before and after exercise. A: Volcano maps before and after training; B: Statistical analysis of myoglobin levels before and after training.

supplying energy through aerobic metabolism in the body[27]. Aerobic metabolism has a long oxygen supply capacity and is an important pathway of energy metabolism[28]. Exercise-related fatigue after long and intense exercise is related to metabolic changes in TCA cycle[29]. High intensity training significantly increased the content of intermediates in the TCA cycle, Tsai *et al*[30] reported that succinic acid and fumaric acid were significantly elevated after exhaustion. In this study, we also observed higher levels of intermediate products of the TCA cycle in the higher BRPE scale group, which is consistent with previous studies mentioned above, suggesting fatigue occurrence in higher BRPE scale individuals. Interactions between the amino acid pool and the TCA cycle are suggested to play a central

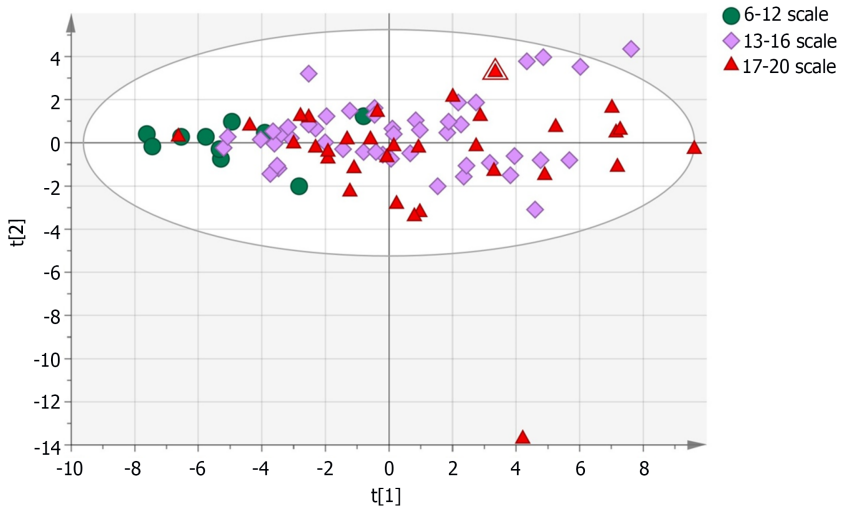

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Figure 2 Principal component analysis scores of organic acid metabolites among the 6-12, 13-16 and 17-20 score groups.

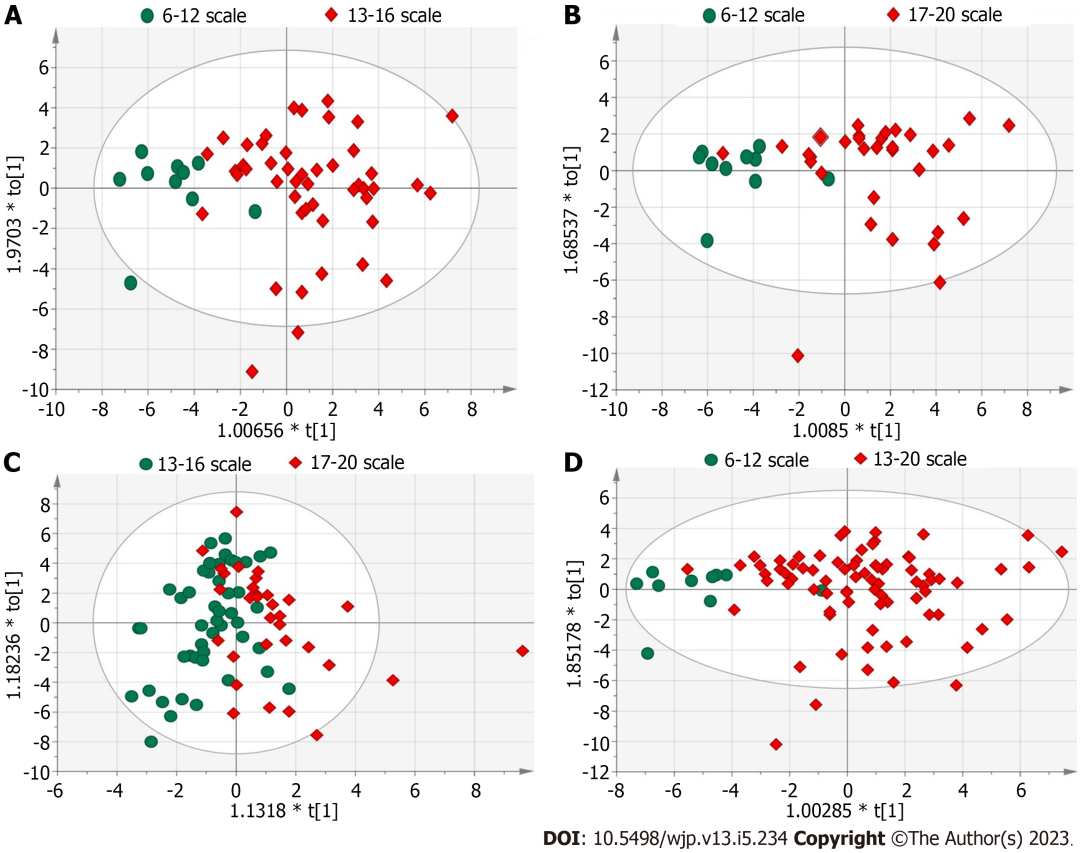

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Figure 3 Orthogonal partial least-squares discrimination analysis of Borg's Rating of Perceived Exertion Scale and organic acid metabolism. A: Orthogonal partial least-squares discrimination analysis (OPLS-DA) between the groups with scores of 6-12 and 13-16; B: OPLS-DA between the groups with scores of 6-12 and 17-20; C: OPLS-DA between the groups with scores of 13-16 and 17-20; D: OPLS-DA between the groups with scores of 6-12 and 13-20.

role in the energy metabolism of the exercising muscle[31]. These results were consistent with the current "wear out doctrine" and "blockage doctrine" for the mechanism of training-induced fatigue; namely, the consumption of a large amount of energy substances and accumulation of metabolites during physical exercise/training leads to a decrease in the functional capacity of tissues, muscles, and organs, ultimately resulting in fatigue[1].

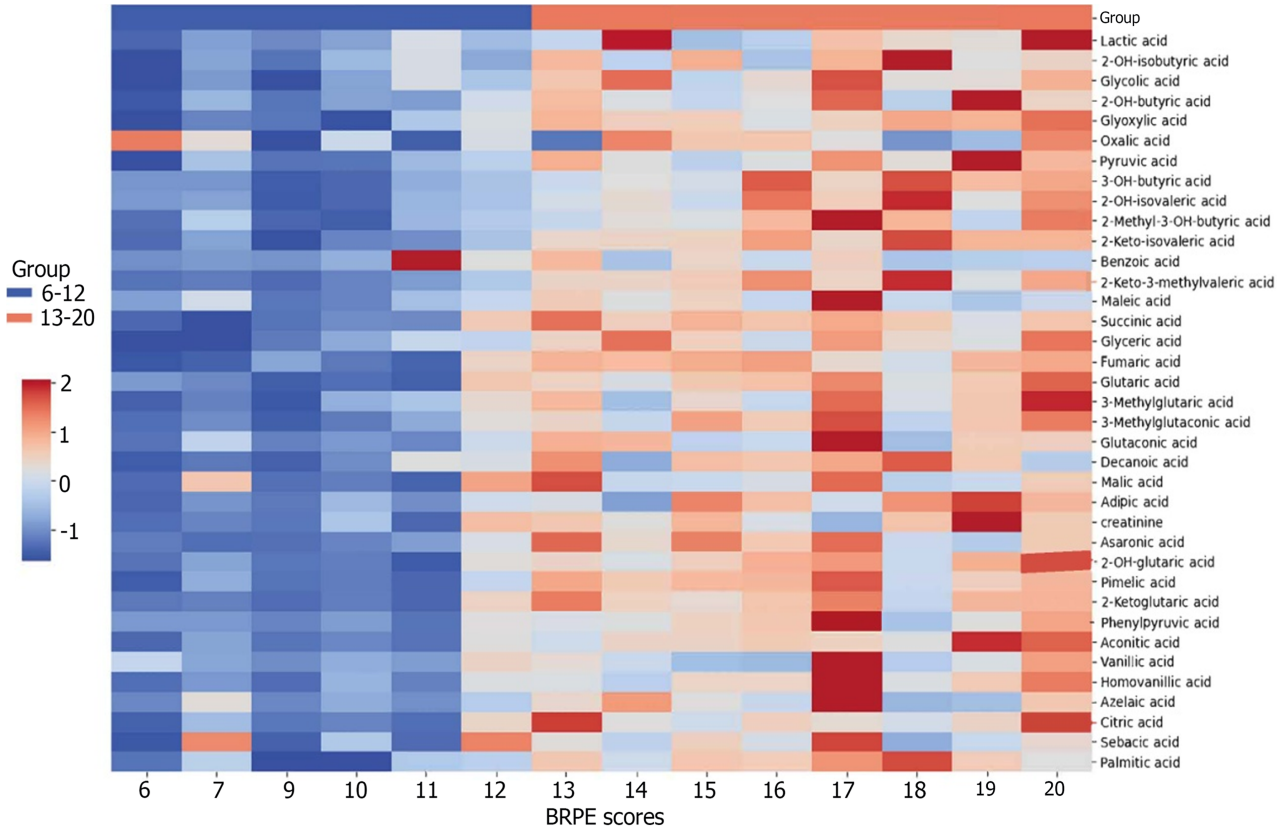

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Figure 4 Heatmap of Borg's rating of perceived exertion Scale and organic acid metabolites. BRPE: Borg's rating of perceived exertion.

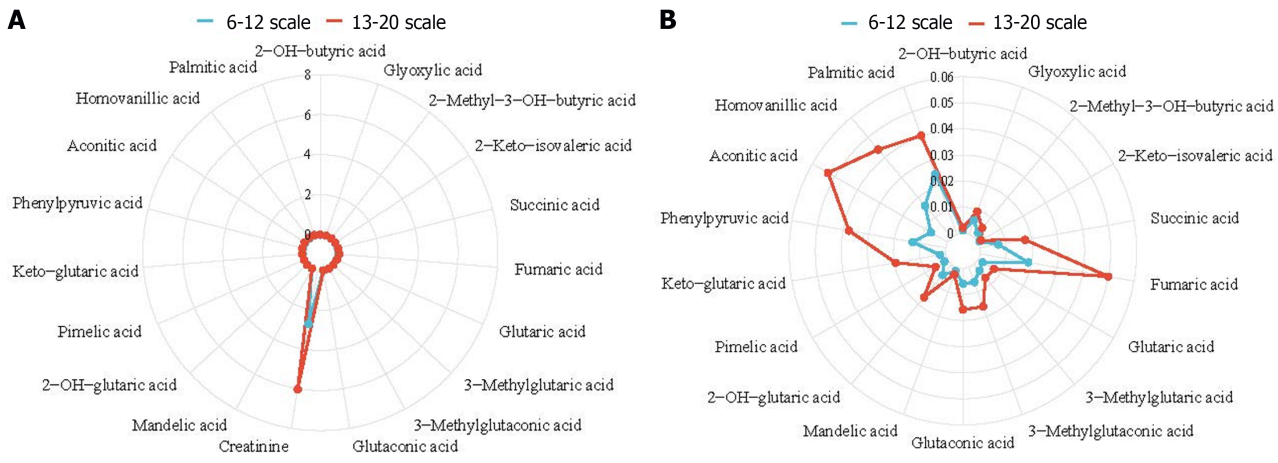

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Figure 5 Radar chart of the metabolism of different organic acids. A: Radar chart including creatinine; B: Radar chart excluding creatinine.

In addition, there was no significant difference between groups with scores of 6-12 and 13-20, and no correlation between myoglobin levels and BPRE scores. This result explains why serious muscle injury does not occur in the body even if a participant feels very tired psychologically during the 40 km exercise. However, at this time, organic acid metabolism has changed significantly and precedes the occurrence of muscle injury.

There are still some limitations in this research. First, the number of people in the group with a score of 6-12 was slightly small, which may have affected the data to a certain degree. Second, the population in this study only included men, and the difference between men and women was not assessed. Third, there was an absence of more direct assessment indicators, such as heart rate, blood biomarkers and others, which might be correlated with metabolic data. Combining all of these data might further help to confirm the ability of higher and lower BRPE values to differentiate metabolic profiles.

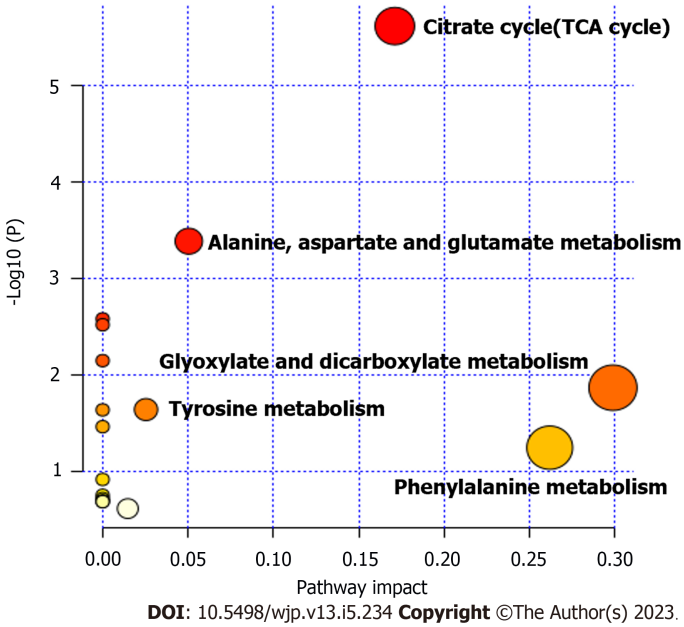

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Figure 6 Pathway analyses of different organic acid metabolites between the groups with Borg's rating of perceived exertion scores of 6-12 and 13-20. TCA: Tricarboxylic acid.

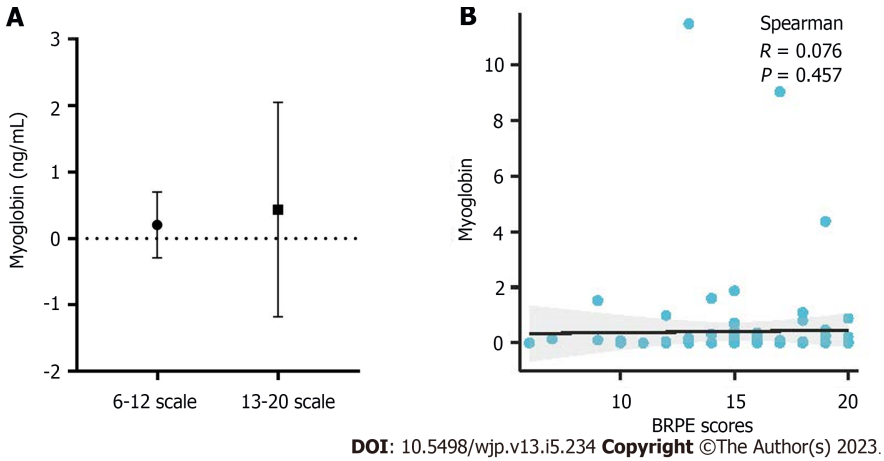

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Figure 7 Correlation analysis between Borg's rating of perceived exertion scale and myoglobin levels. A: Statistical analysis between the groups with scores of 6-12 and 13-20; B: Spearman's correlation analysis between the Borg's rating of perceived exertion scale and myoglobin levels. BRPE: Borg's rating of perceived exertion.

CONCLUSION

In conclusion, our results showed that after long-distance hiking with weight bearing, individuals with high BRPE values have a significant higher disturbance in organic acid metabolism. The differentially abundant metabolites are concentrated in the energy metabolism pathway. The BRPE value is not correlated with urine myoglobin levels but was shown to be able to discriminate individuals with exercise-related fatigue as a convenient predictor.

ARTICLE HIGHLIGHTS

Research background

The Borg's rating of perceived exertion (BRPE) scale was widely used to access subjective perception of effort during exercise, but the relationship between BRPE scale and urinary organic acids metabolism has not been studied.

Research motivation
Our article mainly explored the relationship of urinary organic acids metabolism and the BRPE scale during exercise and reflected the psychological perception degree of effort from an objective physiological perspective.

Research objectives
In this work, we aimed to evaluate whether the BRPE scale could be used in the prescription of outdoor hiking with weight-bearing based on urinary organic acids metabolism, which provides an objective physiological data support for the application of BRPE scale in outdoor hiking training.

Research methods
Eighty-nine healthy men participated in this project and underwent 40 km (6 h) training with 20 kg carriages. After the training, they truthfully filled in the BRPE scale and urinary organic acids were detected. We used multidimensional statistical analysis including principal component (PCA) analysis and orthogonal partial least-squares discrimination (OPLS-DA) analysis and heat map analysis to explore the differences in metabolic profiles of organic acids with different BRPE scale. At last, differential metabolites were screened and pathway analysis was performed.

Research results
There were significant statistical differences in urinary organic acids before and after exercise. According to the BRPE scale, individuals were divided into groups of 6-12 scale (easy), 13-16 scale (somewhat hard) and 17-20 scale (very hard). PCA results showed no separation trend among the three groups. Further analysis with OPLS-DA showed that, group of 6-12 scale and 13-16 scale, 6-12 scale and 17-20 scale could be separated obviously, and group of 13-16 scale and 17-20 scale could not be separated, so group of 13-16 scale and 17-20 scale were combined into group 13-20 scale. OPLS-DA results showed that group 6-12 scale and 13-20 scale could be separated. Heat map results also showed significant metabolic differences between group of 6-12 scale and 13-20 scale. According to the standard of a variable importance in the projection > 1, fold change > 1.5 and $P < 0.05$, 19 different metabolites were screened, which mainly in citrate cycle (tricarboxylic acid cycle) and alanine, aspartate and glucose metabolism.

Research conclusions
Our results showed that the BRPE scale could be used to monitor body fatigue in long-distance outdoor hiking with weight bearing.

Research perspectives
We provide an objective method to evaluate body fatigue in outdoor-hiking exercise.

FOOTNOTES

Author contributions: Sang PP and Zhang ML designed the study; Sang PP, Li J, Tan XD and Peng W performed the research; Sang PP and Zhou HH analyzed the data; Sang PP wrote the paper; and Tian YP and Zhang ML revised the manuscript for final submission.

Supported by the National Key Research and Development Program of China, No. 2020YFC2004604 and 2020YFC2002700.

Institutional review board statement: The study was reviewed and approved by the Chinese PLA General Hospital Review Board (Approval No. S2021-019-01).

Informed consent statement: All participants signed the informed consent form.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: No data were shared.

STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

Country/Territory of origin: China

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S-Editor: Wang JJ
L-Editor: A
P-Editor: Cai YX

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World Journal of Psychiatry

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World J Psychiatry 2023 May 19; 13(5): 247-261

DOI: 10.5498/wjp.v13.i5.247

ISSN 2220-3206 (online)

SYSTEMATIC REVIEWS

Knowledge, attitudes and experiences of genetic testing for autism spectrum disorders among caregivers, patients, and health providers: A systematic review

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Specialty type: Psychiatry

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): A
Grade B (Very good): B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

P-Reviewer: Nwabo Kamdje AH, Cameroon; Seetharaman RV, India

Received: December 30, 2022
Peer-review started: December 30, 2022
First decision: March 1, 2023
Revised: March 10, 2023
Accepted: April 17, 2023
Article in press: April 17, 2023
Published online: May 19, 2023

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Abstract

BACKGROUND

Several genetic testing techniques have been recommended as a first-tier diagnostic tool in clinical practice for diagnosing autism spectrum disorder (ASD). However, the actual usage rate varies dramatically. This is due to various reasons, including knowledge and attitudes of caregivers, patients, and health providers toward genetic testing. Several studies have therefore been conducted worldwide to investigate the knowledge, experiences, and attitudes toward genetic testing among caregivers of children with ASD, adolescent and adult ASD patients, and health providers who provide medical services for them. However, no systematic review has been done.

AIM

To systematically review research on knowledge, experiences, and attitudes towards genetic testing among caregivers of children with ASD, adolescent and adult ASD patients, and health providers.

METHODS

We followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines and searched the literature in three English language databases (PubMed, Web of Science, and PsychInfo) and two Chinese databases

(CNKI and Wanfang). Searched literature was screened independently by two reviewers and discussed when inconsistency existed. Information on characteristics of the study, characteristics of participants, and main findings regarding knowledge, experience, and attitudes of caregivers of children with ASD, adolescent and adult ASD patients, and health providers concerning ASD genetic testing were extracted from included papers into a charting form for analysis.

RESULTS

We included 30 studies published between 2012 and 2022 and conducted in 9 countries. Most of the studies (n = 29) investigated caregivers of children with ASD, one study also included adolescent and adult patients, and two covered health providers. Most (51.0%-100%) of the caregivers/patients knew there was a genetic cause for ASD and 17.0% to 78.1% were aware of ASD genetic testing. However, they lacked full understanding of genetic testing. They acquired relevant and necessary information from physicians, the internet, ASD organizations, and other caregivers. Between 9.1% to 72.7% of caregivers in different studies were referred for genetic testing, and between 17.4% to 61.7% actually obtained genetic testing. Most caregivers agreed there are potential benefits following genetic testing, including benefits for children, families, and others. However, two studies compared perceived pre-test and post-test benefits with conflicting findings. Caregivers concerns included high costs, unhelpful results, negative influences (*e.g.*, causing family conflicts, causing stress/risk/pain to children *etc.*) prevented some caregivers from using genetic testing. Nevertheless, 46.7% to 95.0% caregivers without previous genetic testing experience intended to obtain it in the future, and 50.5% to 59.6% of parents previously obtaining genetic testing would recommend it to other parents. In a single study of child and adolescent psychiatrists, 54.9% of respondents had ordered ASD genetic testing for their patients in the prior 12 mo, which was associated with greater knowledge of genetic testing.

CONCLUSION

Most caregivers are willing to learn about and use genetic testing. However, the review showed their current knowledge is limited and usage rates varied widely in different studies.

Key Words: Autism spectrum disorder; Genetic testing; caregivers; Child and adolescent psychiatrists; Knowledge; Experience; Attitudes

Core Tip: More action should be taken to improve the knowledge level about genetic testing among caregivers of patients with autism spectrum disorder (ASD). Health education from health providers such as physicians and psychiatrists appear the most effective method. Improving the knowledge level of ASD genetic testing among health providers is necessary for better utilization of genetic testing in ASD practice. Caregivers of patients with ASD and patients themselves generally hold a positive attitude toward genetic testing. More comprehensive knowledge is needed to avoid potential misunderstandings.

Citation: Zhou M, Zhang YM, Li T. Knowledge, attitudes and experiences of genetic testing for autism spectrum disorders among caregivers, patients, and health providers: A systematic review. *World J Psychiatry* 2023; 13(5): 247-261

URL: https://www.wjgnet.com/2220-3206/full/v13/i5/247.htm

DOI: https://dx.doi.org/10.5498/wjp.v13.i5.247

INTRODUCTION

Autism spectrum disorder (ASD) is a group of severe neurodevelopmental disorders currently with limited treatment effectiveness[1]. The prevalence of ASD is around 1% but has been steadily increasing over the past two decades[2]. Diagnosis of ASD lacks objective biomarkers and primarily relies on subjective parameters such as clinical observation and evaluation of individuals' behavioral and developmental characteristics[3]. However, most patients are too young to express their feelings, clinical symptoms are complex and heterogeneous, not easily detected by parents and many patients do not receive timely diagnosis and treatment. This can lead to severe social dysfunction and heavy economic burden to families and society[4-6]. Although the specific etiology of ASD is unknown, it is widely accepted that both genetic and environmental factors contribute to the pathogenesis of ASD. The estimated heritability of ASD ranges from 64% to 91%[7], and there are a large number of studies to

elucidate the genetic mechanism of this disorder. Thousands of ASD risk genes carrying different kinds of mutations have been reported, such as rare *de novo* mutations, single nucleotide polymorphisms (SNPs), and copy number variations (CNVs)[8-10]. There are several comprehensive databases that aim to summarize all ASD risk genes and SFARI Gene (gene.sfari.org)[11] is one of the most well-recognized. SFARI Gene features a ranking system that gives users an estimate of the strength of the evidence in favor of each gene. For example, there are 232 genes with high confidence, which means these genes have been clearly implicated in ASD. As a result, several genetic testing techniques have been applied as an auxiliary examination tool when diagnosing ASD.

In clinical practice, genetic testing, such as Karyotype analysis, fluorescence in-situ genomic hybridization (FISH), fragile X testing, chromosome microarray analysis (CMA), and next-generation sequencing have all been utilized for ASD patients. Karyotype analysis was first used in the 1970s to identify extremely large CNVs[12] and FISH has been performed to identify submicroscopic CNVs since the 1990s[13]. In 2005, the American College of Medical Genetics and Genomics (ACMG) recommended karyotype analysis and FISH as standard testing for children with developmental delay or mental retardation, which included ASD[13-15]. For ASD with specific genetic causation, genetic testing could be utilized as the first-tier diagnostic tool. For example, 30%-50% fragile X syndrome caused by > 200 repeats of the CGG motif in FMR1 was shown to manifest as ASD[16]. In 2007, the American Academy of Pediatrics recommended Fragile X testing to be performed when ASD was diagnosed[17-19]. Given that ASD is polygenic, screening mutations genome-wide is necessary. CMA that could detect CNVs and SNPs across the genome has been increasingly used in the clinical practice of ASD[20]. The latest next-generation sequencing with higher resolution, including Whole Exome Sequencing (WES) and Whole Genome Sequencing could be used to detect single nucleotide variants, indels and other variants in patients[21]. CMA and WES have been recommended as the first-tier clinical diagnostic test for individuals with developmental disabilities, including ASD by the ACMG in 2010 and 2013, respectively [12,22]. So far, the clinical diagnostic yield of CMA and WES for ASD was 9.3 to 24.1%[23], and 8.4% to 15.4%[24,25] respectively.

There are many potential benefits of genetic testing for patients with ASD and their families, including promoting early diagnosis and intervention, identifying etiology, reducing medication compliance, providing scientific suggestions for parents' fertility planning, and reducing parents' guilt and anxiety[26,27]. However, the usage rate of genetic testing varies dramatically across countries and regions. As far as we know, the highest rate of receiving any type of genetic testing was reported in France in 2014 (61.7%)[28]. Much lower rates were reported in America in 2020 (17.4%) and Malaysia in 2022 (19.8%)[29,30]. Even within the same country in the same year (for example, America in 2018), rates ranged from 28.0% to 57.1%[31,32]. This could be due to several factors. First, genetic testing does not always identify pathogenic variants because the complex genetic architecture of ASD is still not fully understood[33,34]. Second, a positive finding from genetic testing is not always helpful in clinical management. Third, the test is costly for some families[31]. Furthermore, the usage rate of genetic testing is affected by awareness and attitudes of both caregivers and health providers who are involved in the diagnosis and care of children with ASD, especially child and adolescent psychiatrists (CAP)[31, 35]. In a previous study, 67.5% of parents reported that the main reason why they did not get genetic testing was they did not receive suggestions from physician[36].

To maximize the benefit of genetic testing in ASD clinical practice, it is very important to understand caregivers' and health providers' opinions towards genetic testing for ASD. To date, several studies have investigated knowledge, experiences, and attitudes toward genetic testing for ASD. In the present article, we systematically reviewed the literature published up to October 2022 to outline the current state of knowledge level, experiences, and attitudes toward ASD genetic testing among caregivers of children with ASD, adolescent and adult ASD patients, and health providers. In addition, to summarize factors related to the underutilization of genetic testing and provide a direction for future improvement.

MATERIALS AND METHODS

Literature search

We searched the literature in 3 English databases (PubMed, Web of Science, and PsychInfo) and 2 Chinese databases (CNKI and Wanfang). The search items were (caregivers* OR caretakers* OR parents * OR psychiatrist* OR specialists*) AND (autism spectrum disorder OR ASD* OR autism* OR autistic) AND (genetic testing OR genetic assessment OR genetic risk assessment) AND (knowledge* OR awareness* OR perception* OR attitudes* OR experiences* OR utilization* OR utility* OR interest*). The final search was done on October 7, 2022, and searched literature was exported to Endnote X9.

Inclusion and exclusion criteria

Peer-reviewed articles that met all the following criteria were included in our research: (1) The targeted disease was ASD; (2) participants were either caregivers of children with ASD, adolescent and/or adult ASD patients, or health providers who provided medical services for them; and (3) the article focused on evaluating the knowledge, experiences, or attitudes about ASD clinical genetic testing. Articles were

excluded if: (1) Participants other than the target population described above were included; (2) none of the three topics of interest was covered; (3) the study focused on prenatal genetic testing; (4) the article was not written in English or Chinese; (5) the study was a review; or (6) full-text was unavailable.

Selection of sources of evidence

We first screened the searched papers by reading titles and abstracts. Then, full texts of the remaining studies were read and those that met the eligibility criteria were included for further study. These two steps were carried out by two independent reviewers. When there was non-conformity, a discussion was organized, and a senior reviewer was invited if necessary. The whole process of selection was displayed in the PRISMA flowchart (Figure 1)[37].

Data charting process

Relevant information of included papers was extracted into a charting form, including: (1) Characteristics of the study (author affiliation, country, year of publication, time period(s) of the study, study setting, sample size, sampling method, survey methods, and tools); (2) characteristics of participants (age of child at diagnosis and at survey time, financial insurance of child, relationship with ASD patients, age, gender, marital status, educational level, annual income, current employment status, number of children, number of children with ASD, and family history of ASD); and (3) main findings of the study (knowledge, experience, and attitudes concerning ASD genetic testing). The details were displayed in supplementary materials. After reading all 30 included articles and discussing them, a coding instruction was summarized by two reviewers. The data were then extracted by one reviewer and checked by another reviewer.

RESULTS

Search results

The original search yielded 483 records. After removing duplications and screening abstracts, 78 remained for full-text screening, after which, 30 records were included. Reasons for exclusion were a. inclusion of subjects other than the target population, for example, caregivers of patients with developmental disorders other than ASD, such as intellectual disability, developmental disorder (n = 16), general population (n = 16); b. not covering any of the three topics of our interest (n = 5). The process of article selection is displayed in Figure 1.

Characteristics of studies

Among the final included 30 studies, 20 (66.7%) investigated knowledge, 17 (56.7%) investigated experience, and 22 (73.3%) investigated attitudes toward ASD genetic testing. They were published between 2012 and 2022, and conducted in 9 countries, with 19 (63.3%) in United States. More than half (n = 17, 56.7%) utilized convenience sampling. Other sampling methods included purposive sampling (n = 6, 20.0%), random sampling (n = 3, 10.0%), and snowballing sampling (n = 3, 10.0%). Investigating methods included online surveys (n = 16, 53.3%), face-to-face interviews (n = 9, 30.0%), and telephone calls (n = 7, 23.3%). The most frequently used instrument was a questionnaire with open-ended questions (n = 14, 46.7%). Some instruments included both close-ended and open-ended questions (n = 7, 23.3%), or only close-ended questionnaires (n = 7, 23.3%). More details can be found in Table 1. A standard questionnaire which was defined as a questionnaire with focused themes and standard evaluating methods and could be utilized by other researchers with a similar research purpose was used in two studies—Perceptions of ASD Genetic Testing Survey developed by Zhao *et al*[38] and The Centers for Autism and Related Disabilities developed by Cuccaro *et al*[39].

Characteristics of participants

The majority of the studies (n = 29, 96.7%) investigated parents of children with ASD, including 23 (75.9%) that only covered parents, 4 (13.8%) that also covered other caregivers[27-29,31], one also included health providers[32], and 1 (3.4%) that included adolescent and adult patients[40]. Only one study investigated CAP alone[41]. The sample size of the 30 included studies ranging from 20 to 1444. Of 19 studies that provided gender information, 60%[35] to 95%[42] of the participants were female. Of 13 studies that reported the mean age of parents, these ranged from 37.4[36] to 46.7[43]. Of 8 studies that reported the marital status of parents, 81.3%[44] to 92.3%[45] were married or living as married. Of 8 studies that investigated current employment status, 51%-71.1% of caregivers were employed. Of 16 studies that provided information about the educational level of caregivers, 21.0%-69.4% had a college or higher degree. The lowest educational level of parents was reported in 2 studies that only involved parents of children with ASD who had taken CMA testing[46,47].

Age information of children with ASD was provided in some studies, including 7 (24.1%) that reported mean current age ranging from 5.2 to 16.5 years old[26,43] and 5 (16.7%) that reported mean age at diagnosis ranging from 3.0[29] to 4.7[48] years old. Among 7 studies that reported the number of

Table 1 Characteristics of included studies

	Percentage	Raw count
Year of publication		
2012-2015	26.7%	8
2016-2019	43.3%	13
2020-2022	30.0%	9
Research country		
America	63.3%	19
Taiwan	13.3%	4
Europe	13.3%	4
Other (Canada, Jordan, Malaysia)	10.0%	3
Sampling method		
Convenience sampling	56.7%	17
Purposive sampling	20.0%	6
Random sampling	10.0%	3
Snowball sampling	10.0%	3
Missing	3.3%	1
Study setting		
Online	53.3%	16
Face to Face	30.0%	9
Telephone	23.3%	7
Missing	10.0%	3
Assessment tools		
Open-ended questionnaire	46.7%	14
Close and open-ended questionnaire	23.3%	7
Close-ended questionnaire	23.3%	7
Standard questionnaire	6.7%	2

children with ASD, most families (17.8%-93.7%) had only one child with ASD, while 5.9%-17.9% of families had two or more children diagnosed with ASD. Of 7 studies that addressed family history, 10.5%-34.6% of participants had a positive family history of ASD.

Knowledge, experiences, and attitudes

Specific questions related to the three topics of interest were (1) Knowledge: perceived cause(s) of ASD, knowledge about genetics and genetic testing, pathways to acquire such knowledge, and information needs prior to genetic testing; (2) Experience: experience of being referred to genetic testing and using genetic testing; and (3) Attitudes: why participants supported genetic testing and their concerns about genetic testing; for participants who have not done genetic testing, their intention to pursue genetic testing in the future; for participants who had done genetic testing, their satisfaction with ASD genetic testing and willingness to recommend genetic testing to others (Table 2).

Knowledge of genetics and ASD clinical genetic testing among parents and other caregivers: In total, there were 7 studies that surveyed the perceived cause(s) of ASD of the parents and other caregivers. These studies found that 51.0%-100% of the them thought ASD was partly or fully explained by genetic factors, and 11.9%-12.0% thought ASD was entirely explained by genetic factors. Parents who believed that their child's ASD was permanent tended to attribute ASD to genetic factors[16]. One study reported parents' understanding of genetics: parents stated that they were familiar with and knew the meaning of DNA (94%), genes (92%), chromosomes (86%), genetic testing (87%), and CMA (21%)[39].

In addition, there were 14 studies that investigated caregivers' knowledge of genetic testing for ASD. Of seven studies that asked them whether they were aware of ASD genetic testing before the study, 17.0% to 78.1% answered yes[29,49-54]. However, one study reported that 95% of the participants said

Table 2 The topics covered by 30 included studies

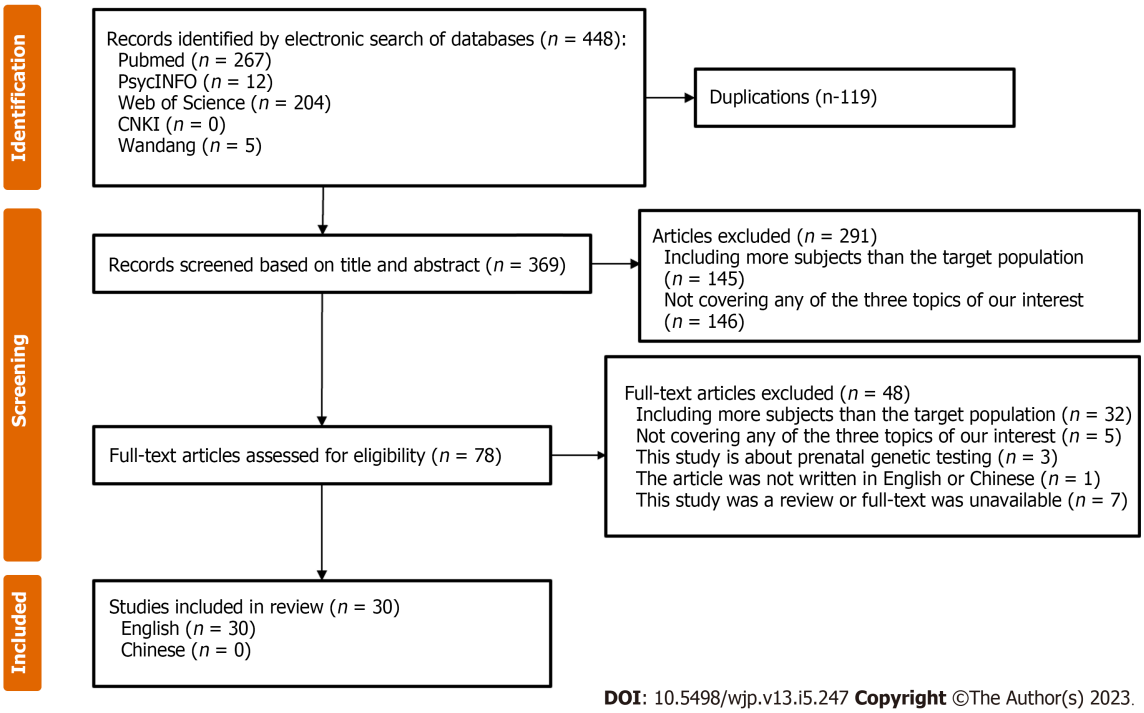
ID	Year	Country/Region	Main findings										Ref.
			Knowledge				Experience		Attitude				
			Cause (s) of ASD	Genetics and genetic testing	Pathway to acquire knowledge	Information needed	Being referred	Using	Perceived benefits	Perceived concerns	Intention to pursue	Intention to recommend	
1	2012	America						a		a			[55]
2	2013	America	a					a	a		a		[45]
3	2013	America		a	a				a	a	a		[51]
4	2014	America	a	a			a	a	a				[36]
5	2014	America, France	a					a					[25]
6	2014	Taiwan	a										[42]
7	2015	America							a				[43]
8	2015	America								a			[41]
9	2016	America		a					a	a			[32]
10	2016	America		a		a		a					[50]
11	2016	America, Canada	a										[39]
12	2017	Norway							a	a			[40]
13	2017	Spain					a	a	a	a	a		[53]
14	2017	America	a										[44]
15	2018	America	a	a					a	a			[23]
16	2018	America					a	a	a	a	a		[28]
17	2018	America					a	a					[29]
18	2019	America		a	a			a	a	a		a	[46]
19	2019	Taiwan		a	a								[47]
20	2019	America		a	a	a							[52]
21	2020	America		a			a	a	a	a	a		[26]
22	2021	America		a							a		[54]
23	2021	America						a	a				[38]

24	2021	America						a	a				[35]
25	2021	Taiwan	a					a	a	a			[48]
26	2022	Sweden	a			a		a	a		a		[37]
27	2022	Taiwan	a							a			[49]
28	2022	America					a	a					[24]
29	2022	Jordan					a		a				[33]
30	2022	Malaysia	a				a		a				[27]

they did not know what genetic tests can test[26]. Furthermore, in one study of participants without genetic testing experience conducted in Sweden in 2020, only 16.2% of parents and 19.6% of autistic adolescents and adults believed that genetic testing for ASD was available[40]. There were three studies from the same team using the same seven-item questionnaire about knowledge of ASD genetic testing. In this questionnaire, wrong and correct answers were scored 0 and 1, with a total score ranging from 0 to 7. The three studies were all performed among parents with children with ASD from United States in 2019. The mean score for those studies were 2.4 ± 1.2 (n = 411), 2.5 ± 1.2 (n = 552), and 2.5 ± 1.2 (n = 443), respectively[18,24,26]. Caregivers' knowledge of ASD genetic testing was positively associated with their educational level, the number of children with ASD, and socioeconomic status, and negatively related to the severity of the child's ASD diagnosis[52,54,55]. Furthermore, caregivers who had visited a genetic service and who had received information from physicians rather than other sources also had a higher level of knowledge[55,56].

In 4 studies that reported the pathways through which the parents had acquired knowledge about ASD genetic testing, 18.3%-57.7% of the participants received related information from physicians[49,50,54,55]. Other main resources include the internet or mass media (23.9%-45.7%)[50,54,55], ASD organization or support groups (12.0%-42.9%)[50,54,55], and other parents of children with ASD (17.0%-36.4%)[50,54,55]. Two studies reported what information parents wanted to know to improve their knowledge about genetic testing. This information included: accuracy of genetic testing (38% and 88.4%), cost (60.0% and 85.9%), benefits of genetic testing (48.0% and 83.8%), testing procedure (29.0% and 77.8%), eligibility to undergo genetic testing (62.4%), potential harms caused by genetic testing (29.0% and 56.1%), previous use and experience among individuals affected by ASD (50.8%), and confidentiality issues (12.0% and 48.0%)[53,55].

Experiences of ASD clinical genetic testing: Parents and other caregivers: Three (10.0%) of the 30 studies only included parents of children with ASD who had undergone CMA testing, and one only included parents who had been offered any genetic testing for their child with ASD. Among the remaining studies, 6 reported that 9.1% to 72.7% of caregivers and 2.8% of autistic adolescents/adults [40] had been referred to genetic testing, and 13 (43.3%) studies reported rates of using any type of genetic testing ranging from 17.4% in United States[29] to 61.7% in France[28]. Regarding specific types of genetic testing, fragile X testing was most widely used by parents, with utilization rates ranging from 4.4% to 39.2%[36,39,49,56]. The utilization rates of CMA and karyotype tests were 7.4%-13.1%[49,56],



DOI: 10.5498/wjp.v13.i5.247

Figure 1 PRISMA flowchart.

and 0.7%-37.6%[36,49,56], respectively. Only one study in Jordan reported that the usage rate of WES was 3.3%[36]. The associated factors of caregivers' usage of genetic testing were reported in 4 studies. Those who had a higher awareness level of genetic testing[49], who received related information from healthcare providers rather than other sources[31,49], who had visited geneticists[31,56], and those with higher household income[36] were more likely to conduct genetic testing for their child.

Health providers: Only one study was of CAP and was performed in United States in 2021. It showed that 54.9% of respondents had ordered ASD genetic testing for their patients in the prior 12 mo. Psychiatrists who accepted a higher percentage of ASD cases, who had more knowledge about genetic testing and higher perceived utility of ASD genetic testing, and who were at a University medical center were more likely to request genetic testing for their patients with ASD; participants with more years of working experience tended not to order genetic testing for their patients with ASD[41].

Attitudes towards ASD clinical genetic testing: Parents and other caregivers: There were 15 surveys among caregivers which reported participants' reasons for supporting genetic testing. Reasons could be categorized into three groups: (1) Benefits for the child, including getting better intervention (n = 13), finding out the cause(s) of ASD (n = 11), getting a definitive diagnosis (n = 8), getting a better understanding of their condition (n = 6), and additional resources (n = 5); (2) Benefits for family and parents, including helping with family planning (n = 8), and future reproductive decisions (n = 5), identifying risk of associated children (n = 2), and reducing stigma (n = 1); and (3) Benefits for other people, including promoting scientific research (n = 6), and providing an indication for other children with ASD (n = 1) (Figure 2A).

Of caregivers who had taken their child for genetic testing, more than half held positive attitudes toward their experience of genetic testing, reporting that genetic testing had been helpful for their child and their family[29,46,49]. Getting additional resources (81.8%), getting a definitive diagnosis (81.8%), contributing to scientific knowledge (61.8%), identifying associated medical risks (25.0%), playing a role in future reproductive decisions (19.1%), helping with treatment planning (12.5%, 16.2%, 90.9%), gaining a better understanding of the child (10.3%), finding a cause of ASD (10.3%, 12.5%), and helping with family planning were reasons why they thought genetic testing was useful[29,31,46,49]. Two studies compared perceived benefits between caregivers, one who had taken their children for genetic testing and the other who never had. The first showed that the post-test group had more positive attitudes toward ASD genetic testing[31], the second reported less positive attitudes[27].

There were 15 studies that reported caregivers' concerns about genetic testing. They can be divided into four areas: (1) High cost (n = 6); (2) useless results: Would not provide any useful information (n = 9), would not help with treatments (n = 5), and would not make changes to daily life (n = 4); (3) negative influences: Would cause family conflicts (n = 4), would cause stress/risk/pain to children (n = 3), cause parental concern (n = 2), would do more harm than good (n = 2), and contradict their religious or cultural beliefs (n = 1); would cause discrimination when buying financial insurance (n = 3) and public

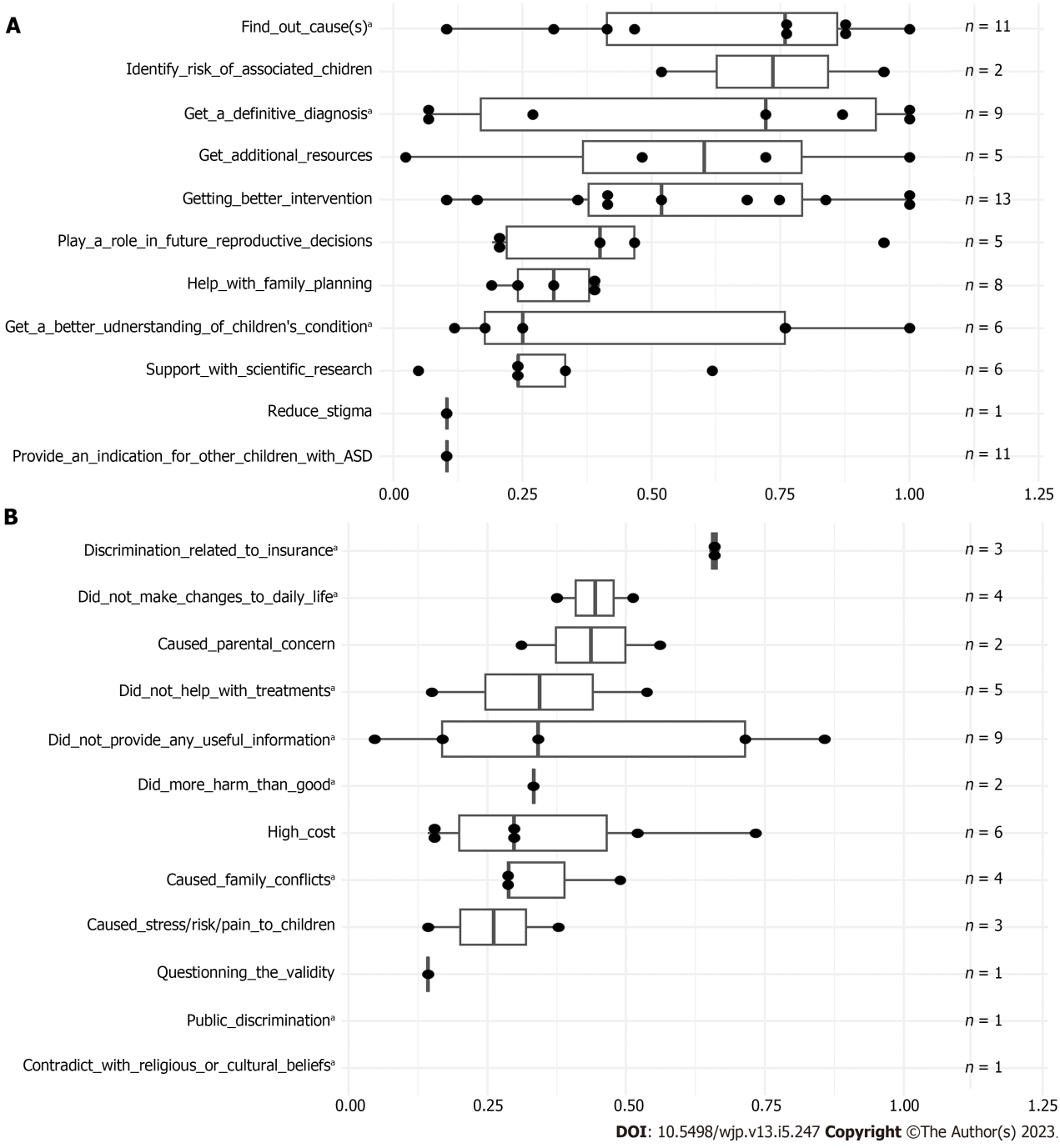


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Figure 2 The support rates of potential benefits and concerns of autism spectrum disorder genetic testing. A. Potential benefits of autism spectrum disorder (ASD) genetic testing; B. Potential concerns about ASD genetic testing. Each dot represents a study and the total number of studies that report the corresponding benefit/concern is displayed on the right side of the figure. Benefits/concerns were sorted by the median of the reported support rate of the participants. [a]indicates that there are studies that only report a qualitative description.

discrimination (n = 1); and (4) other: The test had poor validity (n = 1) (Figure 2B). Four studies reported concerns of participants who had taken their child to genetic testing: lack of detailed information and did not help with further treatment and financial costs were the main reasons for dissatisfaction[26,40,44,49]. Parents' attitudes towards genetic testing were positively related to their perceived severity of ASD[57] and negatively related to their perceived barriers in conducting genetic testing[57], and parents' age and educational level[52].

There were 8 (26.7%) studies which reported that 46.7%[54] to 95%[56] of caregivers without previous genetic testing experience intended to pursue genetic testing in the future, and 2 studies showed that 50.5% and 59.6% parents who have purchased genetic testing services for their children would recommend genetic testing to other parents. It is reported that parents' willingness to pursue genetic testing for their children with ASD was positively associated with their attitudes towards genetic testing, their perception of other people's opinions, and their self-efficacy in pursuing genetic testing

[57].

Health provides: Only one survey among CAP reported why they order genetic testing for their patients. The main reason is to diagnose ASD and reported by 59.9% of those who had ordered a genetic testing in the prior 12 mo[41].

DISCUSSION

To the best of our knowledge, this is the first study that systematically reviewed caregivers', patients', and health providers' knowledge, experiences, and attitudes toward genetic testing for ASD. We searched the related literature without area and time limitations, extracted, and analyzed information from 30 studies. We found that most caregivers agreed that genetic mutations are causes of ASD and knew a little about ASD genetic testing but lacked a deeper understanding of the tests. Caregivers can obtain information about ASD genetic testing from several sources, including physicians, the internet, ASD organizations, and other caregivers of ASD patients. Most obtained information from non-professionals, although obtaining information from professionals contributes to better knowledge and more willingness to use ASD genetic testing. The usage rate of ASD genetic testing is generally low and varied dramatically among studies, even within the same country in the same year, as did the rate of being referred for ASD genetic testing by health providers. In addition, caregivers generally held positive attitudes toward genetic testing. More than half of the parents who had used genetic testing would recommend it to other parents and 46.7% to 95% of caregivers without previous genetic testing experience intended to pursue genetic testing in the future.

Although it is repeatedly reported that awareness level of genetic testing was closely associated with its usage rate and users' attitudes[41,49,56,58]. the awareness level of ASD genetic testing among both caregivers and health providers was not ideal. Most caregivers had heard a little about genetic testing, but few of them had a deep understanding. For example, less than 5% knew the diagnosis rate/yield of ASD genetic testing and the legitimate rights of children with ASD[57]. In contrast, over half of participants showed an interest in gaining more knowledge about genetic testing[55]. This indicates that caregivers generally have limited access to such knowledge. Given that a variety of methods to obtain relevant knowledge have been reported, the problem of the low knowledge levels among caregivers can easily be resolved if appropriate actions are taken.

Health providers, such as physicians and psychiatrists are key to improving the knowledge level of caregivers about ASD genetic testing because parents who acquire genetic information from them were more likely to agree to genetic testing[27,46]. However, most parents did not receive such knowledge from their health providers. For example, one study reported that only 35.3% of parents who were aware of genetic testing received information from their physicians[55]. In addition, another study, not included in our review, reported that more than half of caregivers had not received any additional information about ASD from their physicians following diagnosis, let alone knowledge about genetic testing[59]. This may be linked to lack of knowledge about screening and diagnosis of children with ASD among physicians[60]. A previous study reported that about half of pediatricians who had cared for children with ASD did not know the clinical guideline regarding genetic testing for children with ASD[61]. It is possible and of concern that physicians who know related guidelines may not comply with them. This could result in even lower usage rate of genetic testing[62]. Not receiving doctors' recommendations was also an important reason why ASD genetic testing usage rate was low[46]. Only 18% of physicians would recommend genetic testing to all children with ASD[61]. Physicians should be encouraged to learn more about genetic testing. They can also recommend genetic counseling to patients, which could help to increase parents' awareness level about genetic testing[30].

Although genetic testing is more widely approved and prices are decreasing, the usage rate has not recently increased. For example, in United States, the usage rate was 17.4% in a survey conducted in 2018, whilst four years earlier the rate was 57.1%[29,32]. The usage rate of 57.1% was reported in a survey in Washington[32]. As the capital of the United States, Washington is economically more developed than other regions in America, which contributes to a higher usage rate. The usage rate differed dramatically among different areas. The usage rate of any type of genetic testing was 19.8% in Malaysia in 2022, which was much lower than that in Spain in 2017 (51.0%) and in France in 2012 (61.7%)[28,30,56]. This might be caused by different level of economic development. Also, a study reported large difference in usage rate of genetic testing between America and France, with 27.8% in America and 61.7% in France[28]. The free access to care in France may be associated with higher compliance with genetic testing recommendations[28].

Although most caregivers agreed with the benefits of ASD genetic testing and expressed positive attitudes towards future testing, many concerns still exist which prevent them from seeking genetic testing. The most frequently reported concern was that they thought genetic testing would not provide any useful information for them and could not help with further treatment. This was also an important explanation for why they were unsatisfied with genetic testing[44]. Parents may hold high expectations, hoping test results bring a definitive diagnosis and etiology of ASD[44,49]. However, only 35% of ASD cases had genetic abnormalities, and about 80% of cases received negative results from CMA testing[25,

46]. Visiting genetic counselors should also be encouraged before and after testing to help caregivers make an informed decision, understand, and use testing results more wisely[63]. Besides, the high cost of genetic testing and lack of insurance were also important reasons why genetic testing was underutilized. A study in Jordan indicated that 72% of families reported overall costs of CMA and fragile X testing constituted over 30% of their annual income, and lack of testing resources and insurance coverage further increased the financial burden[36]. However, in the long term, genetic testing may promote an earlier diagnosis and improve the prognosis of children with ASD, consequently, saving future costs[25]. Governments are therefore encouraged to offer affordable genetic testing. For example, government-funded CMA tests are freely available for children diagnosed with ASD in Israel[25]. However, genetic testing results can cause negative emotions for parents and children. For example, some parents believed that they would be blamed or discriminated against if the ASD was verified as inherited from one of them[51], the testing procedure, especially blood draws, would make their child uncomfortable, and the stigma attached to mental illness would increase their level of stress[43,52]. Genetic counseling before and after testing is therefore necessary to minimize misunderstanding about genetic causes and psychological or marriage counseling may need to be considered to alleviate negative emotions.

There were some limitations in this systematic review. Firstly, published research was limited and mainly concentrated in United States and other developed countries. Understanding implementation of ASD genetic testing in low and middle-income countries could not be achieved from this review. Secondly, only two studies targeted health providers. Because it is one of the most effective ways to impart knowledge about genetic testing to caregivers, it is very important to understand both health providers' understanding and attitudes toward genetic testing. Furthermore, there was little uniformity in instruments used in studies lack uniformity making it difficult to synthesize and compare results.

Clinical implications

Firstly, more actions should be taken to improve the knowledge level of genetic testing among caregivers of patients with ASD. Health education through health providers, like physicians and psychiatrists, is the most effective way. Secondly, improving the knowledge of genetic testing among health providers is necessary for better utilization of genetic testing in ASD practice. Thirdly, caregivers of patients with ASD and patients themselves generally hold a positive attitude toward genetic testing. More comprehensive knowledge is needed to avoid potential misunderstandings.

CONCLUSION

The usage rate varied widely in different studies. It is mainly affected by the knowledge level of related parties. However, the review showed that although most caregivers are willing to learn about and use genetic testing, their current knowledge is limited.

ARTICLE HIGHLIGHTS

Research background

The popularity of genetic testing for patients with autism spectrum disorder (ASD) varies dramatically across countries. It is highly dependent on the knowledge, experiences, and attitudes toward genetic testing among caregivers of children with ASD, adolescent and adult ASD patients, and health providers. As a result, many related studies have been conducted worldwide but no systematic review has been done.

Research motivation

Getting a better knowledge of factors that are associated with the usage rate of genetic testing for patients with ASD has the potential to maximize the benefits of the test for patients.

Research objectives

To systematically review research on knowledge, experiences, and attitudes towards genetic testing among caregivers of children with ASD, adolescent and adult ASD patients, and health providers.

Research methods

We conducted a systematic review by searching the related literature without area and time limitations in both English language and Chinese language databases.

Research results

In 30 studies conducted in 9 countries,17.0% to 78.1% of caregivers/patients were aware of ASD genetic

testing. However, they lacked a full understanding of it. Between 9.1% and 72.7% of caregivers in different studies were referred for genetic testing, and between 17.4% and 61.7% actually obtained genetic testing. Among caregivers, 46.7% to 95.0% without previous genetic testing experience intended to obtain it in the future, and 50.5% to 59.6% of parents who previously obtained genetic testing would recommend it to other parents. In a single study of child and adolescent psychiatrists, 54.9% of respondents had ordered ASD genetic testing for their patients in the prior 12 mo.

Research conclusions

The usage rate varied widely in different studies. It is mainly affected by the knowledge level of related parties. However, the review showed that although most caregivers are willing to learn about and use genetic testing, their current knowledge is limited.

Research perspectives

Firstly, more actions should be taken to improve the knowledge level of genetic testing among caregivers of patients with ASD. Health education through health providers, like physicians and psychiatrists, is the most effective way. Secondly, improving the knowledge of genetic testing among health providers is necessary for better utilization of genetic testing in ASD practice. Thirdly, caregivers of patients with ASD and patients themselves generally hold a positive attitude toward genetic testing. More comprehensive knowledge is needed to avoid potential misunderstandings.

FOOTNOTES

Author contributions: Zhou M and Zhang YM contributes equally to this paper. Zhang YM and Zhou M provide the conceptualization; Zhang YM and Zhou M contributed to the methodology, literature searching, data extraction; Li T contributed to the administration resources, and supervision; Zhou M contributed to writing the original draft; Zhang YM and Li T contributed to reviewing the draft; all authors have read and approved the final manuscript.

Supported by the National Natural Science Foundation of China, No. 81920108018 (Li T and Sham P), No. 82001409 (Zhang YM), the Key R & D Program of Zhejiang, No. 2022C03096 (Li T); Project for Hangzhou Medical Disciplines of Excellence.

Conflict-of-interest statement: There is no conflicts of interest for this article.

PRISMA 2009 Checklist statement: The authors have read the PRISMA 2009 Checklist, and the manuscript was prepared and revised according to the PRISMA 2009 Checklist.

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S-Editor: Chang KL
L-Editor: A
P-Editor: Cai YX

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