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Review Article

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The Effects of Different Treatment Modes with Attention-Deficit/Hyperactivity Disorder: A Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: ADHD is associated with high rates of many adverse functional outcomes, including comorbid psychiatric disorders, academic impairments, accidents and injuries, driving accidents, and so on. It can be employed to alleviate symptoms and functions of ADHD with drug and non-drug treatment methods. **Methods:** A systematic review of studies published in PUBMED, EMBASE, Web of Science, and the Cochrane Library databases from Jan 01, 2010 until Jan 2021. **Results:** A total of 12 studies were included in the analysis of ADHD. The combined effect of drug treatment and placebo comparison was SMD= -6.84,95% CI(-10.48,- 3.21). According to subgroup analyses of methylphenidate and methylphenidate combined with other therapies in ADHD treatment, it is found that in hyperactivity/impulsivity subtype methylphenidate combined with other therapies in ADHD treatment is superior to drugs alone (SMD = -2.02, 95% CI, -3.61 to 0.43; I2 = 37%).It reveals no significant difference between drug therapy and physical therapy groups ((SMD =-7.41, 95% CI, -16.31 to 1.48; I2 = 95%). **Discussion:** Children with ADHD require a multi-mode treatment mode, simultaneously with drug treatment, mental health education should be provided, and other non-drug interventions should be combined according to specific functional and behavioral goals to facilitate the comprehensive recovery of children's social function.

Keyword: ADHD; Pharmacotherapy; Non-pharmacotherapy

Introduction

ADHD is a common neurodevelopmental disorder characterized by symptoms of hyperactivity/impulsivity, inattention, or both [1], with prevalence rates of 3-5% in childhood [2,3]. As a result, adolescents and adults with underdeveloped attention, inhibitory control, and executive functions are at heightened risk for compromised driving safety. It is associated with high rates of many adverse functional outcomes, including comorbid psychiatric disorders, academic impairments, accidents and injuries, driving accidents, and so on [4]. In recent years, the deficiency of central neurotransmitter monoamines and related cytokines have been proved to be widely implicated in clinical treatment of ADHD patients, but obtaining satisfactory curative effect is difficult. In recent years, based on the characteristics of brain plasticity, scholars at home and abroad have paid increasing attention to drug combined executive function rehabilitation training for ADHD children to realize the targeted intervention of nerve defects. In terms of treatment, drug and non-drug treatment methods can be employed to alleviate symptoms and functions. Stimulants and non-doping drug treatments can quickly improve ADHD symptoms, but social function and academic level cannot be enhanced even for long-term use of drugs. Therefore, non-drug

treatment for ADHD has garnered considerable attention, such as physical therapy, behavioral intervention, social skills training, and cognitive behavioral therapy [5,6]. At present, there is still controversy about ADHD treatment methods at home and abroad.

Methods

Literature Search

For nearly ten years, we searched PUBMED, EMBASE, Web of Science, and the Cochrane Library databases from Jan 01, 2010 until now. We also reviewed the reference lists of selected full-text articles. The search terms used were as follows: attention deficit disorders with hyperactivity, ADHD, atomoxetine hydrochloride, methylphenidate, non-drug treatment including group treatment, parental treatment, neurological treatment, placebo treatment, Randomized (and randomised) Controlled Trial (RCT), trial, child, and adolescent.

Study selection and inclusion criteria

The studies were included if they met the following criteria: (1) patients: participants met DSM-IV or DSM–5 ADHD criteria as determined by an interview with study staff or using a standardized, normed rating scale incorporating DSM criteria; (2) study type: RCT and double-blind trials with parallel group or placebo control group; (3) intervention type: study tested differences in MPA treatment, MPA in combination other medicines and non-drug therapies. Non-drug treatment methods include various treatments such as parent group treatment, psychotherapy, etc. (4) intervention duration: at least four weeks; (5) treatment goal was to reduce ADHD symptoms or related impairment; and (6) the main outcome index was the decrease in SNAP score, and the secondary index was symptom or syndrome score.

The exclusion criteria were as follows: case reports, conference abstracts, reviews, duplicates, and non-English studies. We included only randomized case-control studies published in peer-reviewed journals since the inception of databases. We limited our search to published studies to ensure a level of methodological adequacy and rigor among included studies and avoid inevitable problems with securing access to a full set of unpublished studies and bias that would introduce [7].

In the second step, all potentially eligible studies were re-evaluated in full text. Data collection were extracted independently by two authors (F.L and Y.Y) using a predesigned extraction form that included the following data: title, year of publication, design of study (parallel vs. cross-over), blinding strategy, medication name, dropouts and adverse effects, the method used to evaluate results (questionnaires and scales to assess symptoms). In Jan 2021, we completed systematic searches of PubMed, EMBASE, Web of Science, and the Cochrane Library. We searched the full text of database entries using multiple combinations of search terms.

Literature quality evaluation

Jadad 3-item 5-point quality evaluation scale was used to evaluate randomization, double-blinding, withdrawal, or loss of follow-up. More than 3 points corresponded to high-quality literature, while 0 ~ 2 points corresponded to low-quality literature.

Statistical Methods

We used Comprehensive Meta-Analysis Version 3 to conduct all statistical analyses and generate data plots. For each study and measure listed previously, we calculated Hedges g and 95% Confidence Intervals (CIs) using means (Ms), SD, and sample sizes (N) in each group. For controlled studies, we calculated effects based on the difference between treatment and control groups at study outcome. For pre-to-post treatment change, we calculated Hedges g for pre-treatment versus post treatment scores using M, SD, and N at each time point for the treatment group. The studies were subjected to a heterogeneity test. When $I^2 < 50\%$, $P > 0.1$, homogeneity was good, and the fixed effect model was used to combine the effect quantity. On the contrary, the random effect model was used when the test results were heterogeneous and $P < 0.01$ was statistically significant.

Bias Assessment

Clinical trials suffered from significant publication bias, including detection and selection bias.

Results

Study Selection

Using electronic search engines and strategies, we identified 1497 articles. Of these, 1381 were excluded due to duplication and during the review of abstract and titles as they did not meet the inclusion criteria (Figure 1 for a flow chart of search). Following that, all titles fulfilling our inclusion criteria (116 studies) were reviewed in terms of abstract. When disagreements arose, reviewers consulted with each other until a consensus was reached. Ultimately, 46 full-text articles were retrieved for further screening, and 34 of these were excluded. Two independent reviewers collected and extracted data on ADHD status and diagnostic procedures, emotion regulation/dysregulation as defined above, gender composition (male, female), age, and comorbidity.

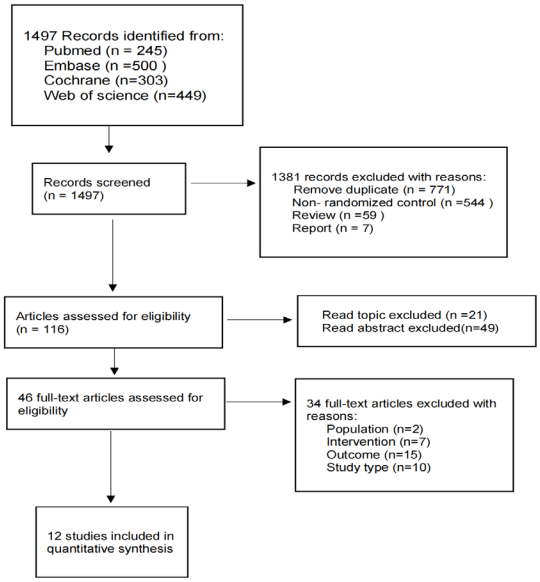


Figure 1: Flowchart for the selection of studies.

Participants

The meta-analysis included 1202 children and adolescents diagnosed with ADHD (males/females: 859/343). The subjects were diagnosed with ADHD by a psychiatrist or psychologist through clinical interview or using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) (American Psychiatric Association 2002). There were more boys than girls (71.46%).

Study Characteristics and Medications

This meta-analysis included 12 articles [8-19], including Pharmacotherapy of Methylphenidate (MPA), Atomoxetine (ATX), Guanfacine Extended-Release (Grx), Lisdexamfetamine Dimesylate (LDX), and tipepidine, as well as non-drug therapies such as psychotherapy, parent training, cognitive therapy, and placebo treatment.

Outcomes Measures

All studies analyzed absolute ADHD-RS-IV total symptom scores (Dupaul et al. 1998) and subtypes (inattention and hyperactivity/impulsivity). ADHD-RS-IV was selected for its internal consistency and concurrent validity with attention problems assessed using Achenbach scale.

Meta-Analysis Results

Meta-Analysis Results of Drug Treatment and Placebo Comparison

Revman 5.3 was used to test heterogeneity of included literatures, and the results revealed significant heterogeneity between studies (x^2=31.38, P < 0.00001, I2 = 87%), necessitating the employment of a fixed-effect model. The results of forest plot indicated that rhombus was located on the left side of midline and did not intersect with the midline. The combined effect SMD = -6.84, 95% CI (-10.48, -3.21) indicates that clinical symptoms of ADHD drug treatment group were significantly alleviated compared with the placebo group, and the difference was statistically significant, as depicted in Figure 2.

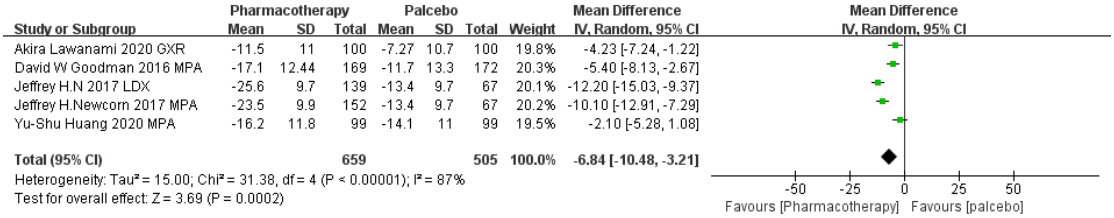


Figure 2: Forest plot total score.

Subgroup analysis: according to ADHD-RS-IV scale score, there are hyperactivity/impulsivity and inattention subtypes, as illustrated in Figure 3. The results revealed statistically significant differences between the two subgroups ($x^2 = 30.57$, $P < 0.00001$, $I^2 = 90\%$; $X^2 = 32.86$, $P < 0.00001$, $I^2 = 91\%$), implying that the efficacy of drug therapy in children with ADHD is much better than that in placebo group.

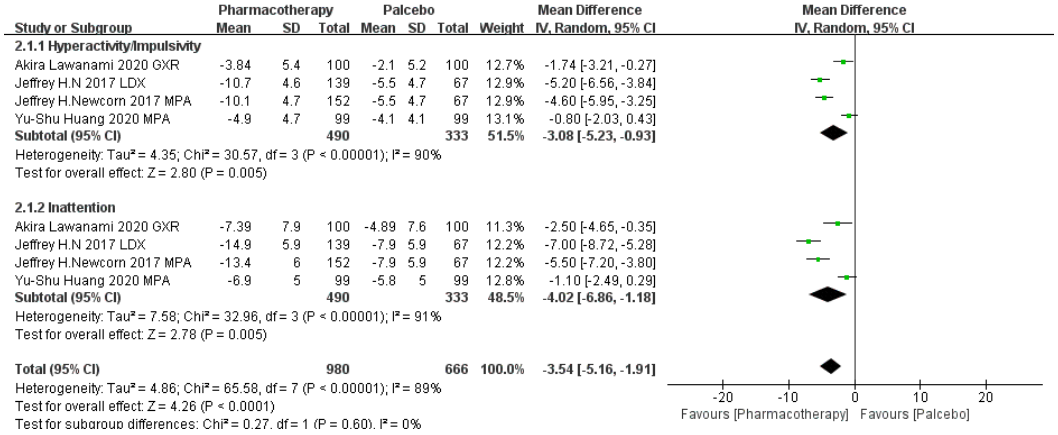


Figure 3: Forest plot sub score.

According to subgroup analyses of methylphenidate and methylphenidate combined with other therapies in ADHD treatment (Figure 4), four studies found that the effect of drugs combined with other treatments was superior to that of drugs alone, but there was no significant difference in the ADHD total score (SMD = -2.95, 95% CI, -4.85 to -1.05; I2 = 0%). However, in hyperactivity/impulsivity subtype, methylphenidate combined with other therapies in ADHD treatment is superior to drugs alone (SMD = -2.02, 95% CI, -3.61 to 0.43; I2 = 37%) (Figure 5).

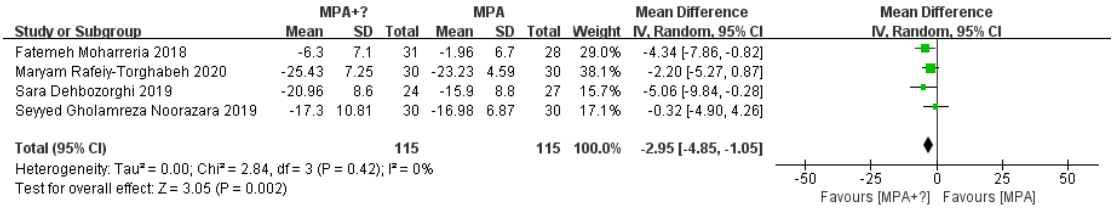


Figure 4: Forest plot total score.

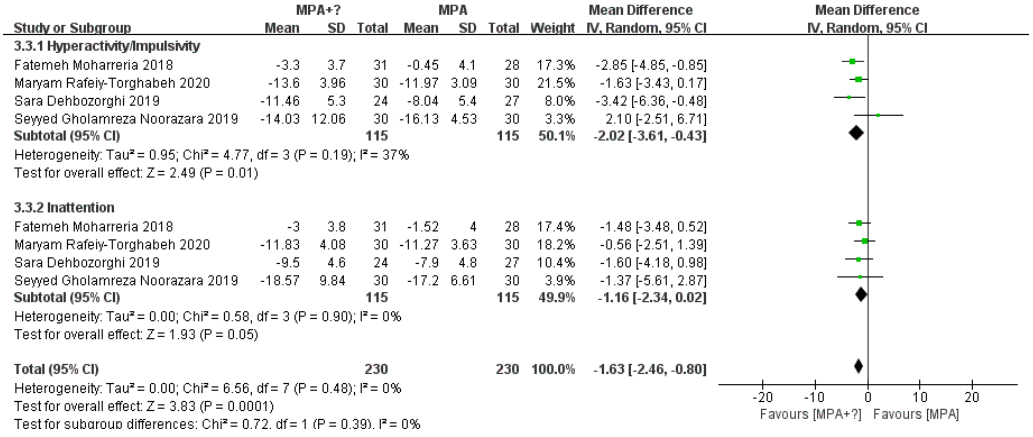


Figure 5: Forest plot sub score.

Subgroup analyses were conducted to determine whether drug and physical therapies were different. Research revealed no significant difference between drug therapy and physical therapy groups ((SMD =-7.41, 95% CI, -16.31 to 1.48; I2 = 95%). Further analysis indicated that drug therapy had medium effect to physical therapy in inattention subtype (SMD =-0.78, 95% CI, -1.93 to 0.37; I2 = 89%), but no significant difference existed in hyperactivity/impulsivity subtype (SMD =-1.11, 95% CI, -2.21 to -0.01; I2 =93%) (Figure 6).

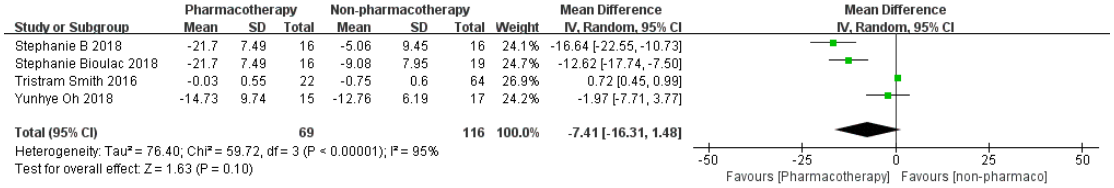


Figure 6: Forest plot total score.

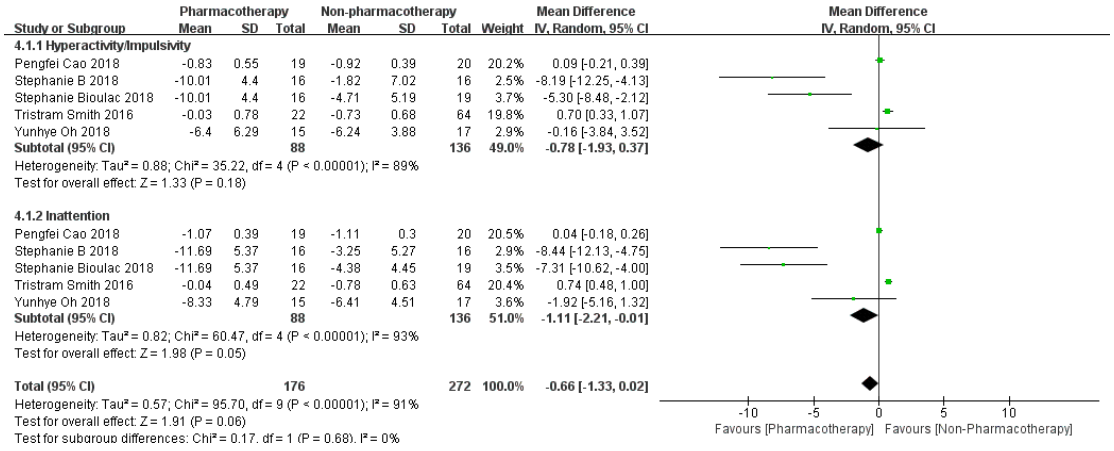
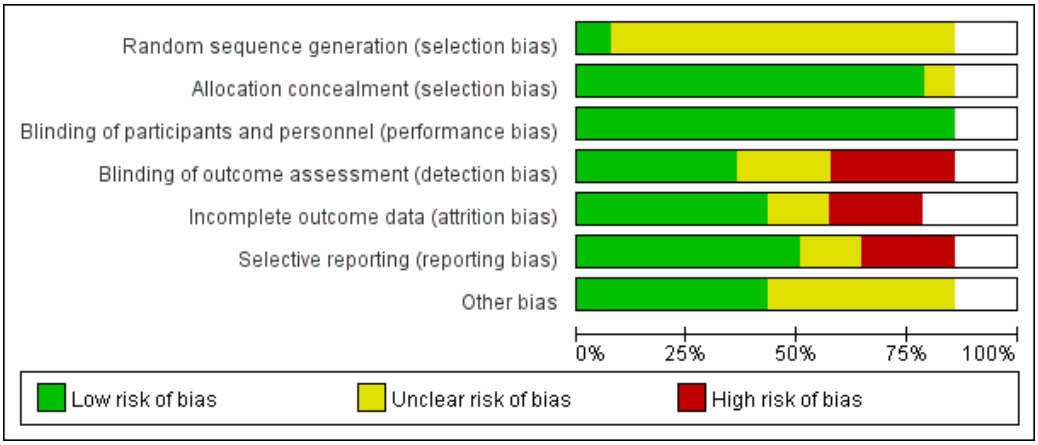
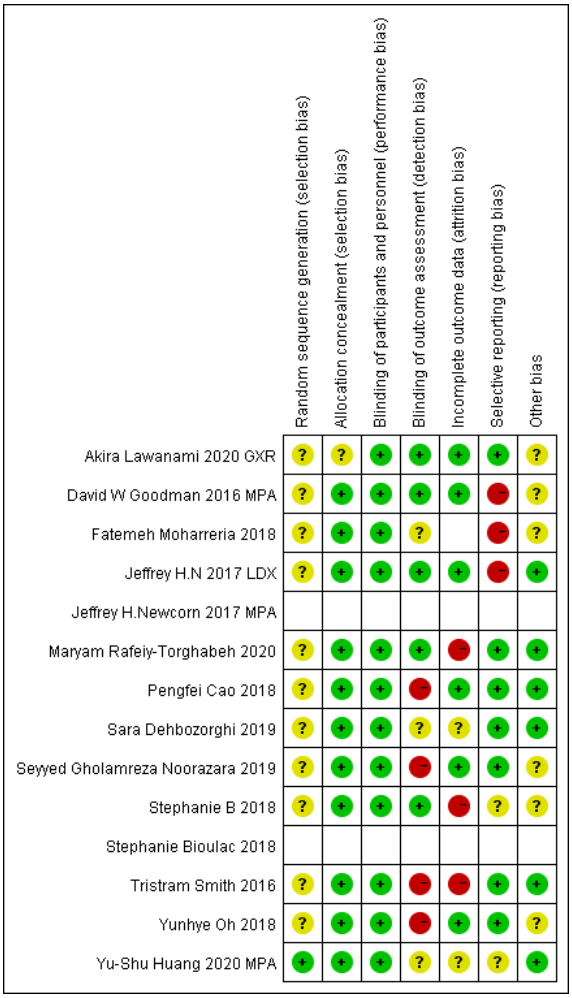


Figure 7: Forest plot subscore.





Grade Assessment of the Main Analyses

Pooled data for ADHD-RS-IV total score and inattention and hyperactivity/impulsivity subtypes were classified as moderately high evidence for symptom changes of ADHD.

Publication Bias and Sensitivity Analysis

In future research, the inclusion and exclusion criteria of literature should be strict as far as possible, and the unified criteria should be clear. Furthermore, in the sensitivity analysis, with each study deleted once from the model, the results remained statistically significant across all deletions.

Discussion

ADHD could cause a serious impact on children's learning, emotion, development, and life. Thus, it is critical to identify therapeutic interventions for children with ADHD. The common treatment modalities include drug therapy, cognitive behavioral therapy, sensory integration training, etc. The drug therapy of ADHD mainly includes central stimulants, antidepressants, antihypertensive drugs, etc.

This study systematically searched and evaluated case-control studies of different treatment modalities in children with ADHD in the last five years and finally included 11 English-based reports for meta-analysis. To the best of our knowledge, this is the first meta-analysis that focuses specifically on examining evidence regarding the impact of various treatments on ADHD symptoms using the same outcome measure (ADHD-RS-IV).

In this study, the treatment approaches for ADHD were divided into three categories, single-drug treatment as a group, multiple drugs or method treatment as a group, non-drug treatment such as physical therapy, equestrian therapy, and other treatment methods as a group. We conducted a meta-analysis of 11 included publications, and we tried to compare various treatment modalities for ADHD to evaluate their safety and effectiveness.

This meta-analysis revealed that the symptom score of ADHD children in drug treatment group was significantly lower than that in placebo control group [95% CI (-10.48, -3.21)], indicating that drug treatment was significantly more effective than placebo treatment for ADHD children. This finding is consistent with previous studies [15, 20-23]. Further research revealed that MPA combined with other drugs was more effective than MPA alone in ADHD patients [95% CI (-4.85, -1.05)]. However, no significant difference existed between the two groups, including pharmacotherapy and non-pharmacotherapy [95% CI (-16.31, 1.48)] [24]. The findings indicate that ADHD pharmacotherapy is effective, and when combined with various treatment schemes, the clinical effect is enhanced. However, no significant difference existed between pharmacotherapy alone and physical therapy alone, implying that ADHD individuals require psychological treatment [25]. Physical therapy and other treatment methods will be beneficial for ADHD children.

Multi-dimensional treatment has recently become a new trend in ADHD treatment. Multi-dimensional therapy refers to combining drug therapy with a series of behavioral interventions. Research shows that multi-dimensional combined therapy exhibits a certain effect in ADHD treatment and intervention in children. It is consistent with Coelho LF research. They has found that there was no significant difference in the cognitive and behavioral patterns between the single mode (drug therapy alone) and the multimode (drug and CBT combination therapy), but the application of the social skills in the multimode treatment group increased significantly [26], which could obviously improve patient adherence and ADHD peripheral symptoms. The same results are obtained that mindfulness-based cognitive therapy (MBCT) can improve symptom [27]. Neuroscientific studies showed that cognitive meditation may be associated with structural and functional changes in brain areas responsible for the regulation of attention and emotion [28]. Adamou M. also has studied of adult patients with ADHD and found that patients with hyperactivity symptoms lasting to adulthood can also receive occupational psychotherapy [29], which has a great impact and help on the occupational performance and social function recovery of ADHD patients. Conversely, Hodgson et al. evaluated seven types of intervention for children and adolescents with ADHD (behavioral modification, neuro feedback, multimodal psychosocial treatment, school-based programs, memory improvement techniques, self-monitoring, and parental guidance) [30]. In terms of statistical significance, a different pattern emerged in which behavioral modification and neuro feedback led to statistically significant improvement.

The above research suggests that both pharmacotherapy and non-pharmacotherapy can improve the social function of ADHD patients. Meta-analyses of fMRI studies have shown brain function abnormalities in several frontal, striatal, parietal, and cerebellar regions in ADHD. Recent independent meta-analyses of fMRI studies showed that the most consistent abnormality in ADHD is the reduced activation of Inferior Frontal Cortex (IFC), followed by anterior cingulate, both areas that are crucial for cognitive control, during tasks of cognitive control, including motor and interference inhibition and switching tasks [31]. Compared with placebo, drug treatment can enhance the activation of lower frontal lobe, anterior motor lobe, inferior parietal lobe, cingulate cortex, cerebellum and precuneus in patients with ADHD, and cognitive training can also improve the functional status of relevant brain regions [32]. Rubia K. also confirms that adolescents of ADHD accepted real-time functional magnetic resonance neuro feedback of the Right Inferior Frontal Cortex (rIFC) progressively increased activation in 2 regions of the rIFC which was associated with clinical symptom improvement [33]. The findings show that fMRI-Neuro feedback of a typically dysfunctional frontal region in ADHD adolescents leads to strengthening within fronto-cingulo-striatal networks and to weakening of functional connectivity with posterior DMN regions and that this may be underlying clinical improvement.

Therefore, the treatment of ADHD should not be limited to drug treatment, but the combination of drug treatment and non-drug treatment to comprehensively improve the core symptoms and corresponding social functions of ADHD patients, so as to enable ADHD patients to maintain a stable and good social function.

Limitations and Directions for Future Research

1. There are numerous treatment options for ADHD, and there are many drug types, which may affect the research results; 2. Our inclusion criteria specified that only studies evaluating ADHD using ADHD-RS-IV scale were included. Reduce the heterogeneity of the study by using the most commonly accepted scale, which is conducive to the accuracy and effectiveness of the study; However, due to the single scale, the evaluation of clinical symptoms is limited; This limitation should be considered in future research. Studies did not specify which version of ADHD-RS-IV scale was employed (parent's vs school) or if it was through an interview by the researcher; therefore, the reliability of data collection procedures is unexpected. Children with ADHD require a multi-mode treatment mode as part of a personalized and comprehensive parenting plan. Simultaneously with drug treatment, mental health education should be provided, and other non-drug interventions should be combined according to specific functional and behavioral goals to facilitate the comprehensive recovery of children's social function.

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Competing Interests

The remaining authors declare that they have no competing interests.

Availability of Data, Materials Code, and Other

The datasets used or analysed during the current study are available from the corresponding author on reasonable request.

Contributors

Xudong Yao and Fang Liu designed the study. Fang liu and Yang Yang acquired the data which Yang Yang, Liu Fang, Lan Zheng, Yalan Hu and Jianyan Peng analyzed. Xudong Yao wrote the article, which Lan Zheng, Yalan Hu and Jianyan Peng reviewed. All authors approved the final version to be published.

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