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Advanced progress in Pharmacotherapy Research for ADHD

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Abstract. Currently, the most popular method of curing ADHD is pharmacotherapy. The mechanism of ADHD is the key to decide how to cure it. The actual mechanism of ADHD has been widely discussing and hasn't reached the end. Pharmacotherapy is the therapy with the most significant efficacy in a short period of time. Moreover, it's easier for the patients to access the drugs. However, there are some existing problems. There are side effects of ADHD such as poor appetite. Additionally, some of the patients may be resistant to central agonists. CBT aims to cure ADHD patients by treating their behaviors decently and is the most likely therapy that can fully cure ADHD. The problem of CBT is that it needs a systematic schedule designed by professionals and takes a lot of time. Recent researches show that BCI is an effective way to relieve the symptoms of ADHD as well as a promising future. On the contrary, BCI cost highly that the normal families can hardly afford it. What's more, the efficacy of BCI is still investigating. This paper aims to review the mechanism of ADHD and the current therapies for curing ADHD, involving the most widely used one, pharmacotherapy, behavioral therapy (mainly discussing cognitive behavioral therapy (CBT)) as well as brain-computer interface (BCI) by analyzing their main mechanism, advantages and disadvantages towards curing ADHD.

Keywords: therapy of ADHD, pharmacotherapy, cognitive behavioral therapy, brain computer interface, mechanism of ADHD.

1. Introduction

In 1902, neuroscientists begin to study some abnormal behavior among children. They fail to sit still in the classroom for the whole class or cannot shut up at the proper time. Although this set of disorders had changed its name for several times, the researches towards it stops at behavioral problem performed by boys until 1980. In this year, the disorder was first named as attention deficit disorders (ADD). Furthermore, neuroscientists explored that ADD was not simply some behavioral problems, they are actually illness of brain management. Moreover, neuroscientists find out that some of the ADD patients may have no or slight symptoms during their whole life. Later, the disease changed its name to attention deficit hyperactivity disorders (ADHD, familiar to more people).

According to a study in 2020, the USA's national ADHD rate was estimated at 12.9%, with a 95% Confidence Interval of 11.5% to 14.4% [1]. There were significant geographic variations in the prevalence rates. Counties in certain regions such as the West South Central, East South Central, New England, and South Atlantic had a higher estimated prevalence of ADHD compared to other regions like the Mountain, Mid Atlantic, West North Central, Pacific, and East North Central [1]. As the samples of ADHD patients enhances over time, this illness catches more attention in recent society. The symptoms of ADHD varies, but can be classified into inattention, hyperactivity and impulsive.

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Inattention includes students fail to listen carefully to their teachers and the loss of ability to do a long term work. Hyperactivity refers to climbing and running at an improper time or behaved over active. The mechanism is then widely discussed. Although the mechanism of ADHD is still underestimated, there are some theories that seems reliable. They are problems with the frontal lobe and brain intersection with the perspective of neuroanatomical abnormality and the neurotransmitter disorder in the sight of neurophysiological abnormality. Some targeted therapies are then carried out. Pharmacotherapy is first design targeting on adjusting the level of neurotransmitters such as dopamine. CBT is then carried out in order to cure frontal lobe development abnormality and brain intersectional connection disorders. BCI is currently researched aimed on neuroanatomical abnormality as well. There is no certain claim or key evidence to show to fundamental mechanism of ADHD. Since then, current therapies of ADHD cannot be the most effective ones. Nevertheless, through more researches done on finding out the real mechanism as well as better-designed BCI system, ADHD will be cured more efficiently.

2. Mechanism of ADHD

Scientists first find mechanism of ADHD in order to give specific plan towards the illness. The mechanism of ADHD can be complex as it is the illness is in the most complicated part in human body—brain. Inherited, brain developmental, environment, mental and biological problems all can be factors leading to ADHD. As the study going more deeply, more biologically, the factors are divided into three main parts, neuroanatomical abnormality, neurophysiological abnormality and neurobiochemical abnormality. Impulsive means patients often disrupt others, cannot control their emotions well and make some impulsive decisions.

2.1. Neuroanatomical abnormality

Neuroanatomical abnormality refers to abnormalities in structure of brain or nervous system. The abnormality can be related to various mental diseases. When it comes to ADHD, the main problems are frontal lobe development abnormality and brain intersectional connection disorders.

2.1.1. Frontal lobe development abnormality. Frontal lobe is the most advanced part of the cerebral cortex. It plays an essential role in cognitive functions and behavioral control. Frontal lobe is considered as one of the most important parts towards ADHD as some region of frontal lobe have direct relationship with the central symptoms . The related function of frontal lobe are behavioral control, attention adjustment, memory, emotions, decision making, restrain power and social behaviors.

2.1.2. Brain intersectional connection disorders: Besides frontal lobe itself, connection problems involved frontal lobe can also lead to ADHD. The loop of frontal lobe-corpus striatum-cerebellum disorders which lead to ADHD catches more attention nowadays [2].

2.2. Neurophysiological abnormality

Neurophysiology is the study of functions of nervous system and how these functions support cognition, motion, behavior and perception. The neurophysiology abnormality lead to generally two reasons: neurotransmitter disorders and electroencephalogram abnormality

2.2.1. Neurotransmitter disorders: Neurotransmitters are a kind of chemical substance between the neurons. Its main function is to connect neurons and adjust brain. dopamine which related to reward and motion control, norepinephrine which take the responsibility of attention and emotion, serotonin which is responsible for emotion and pain are three main neurotransmitters that related to ADHD. Actions at D1 and D5 is the way dopamine modulates the prefrontal cortex [3]. If you plot a graph of the amount of stimulation of D1/D5 receptors on the working memory against attention regulation processes of the prefrontal cortex, it will produce an inverted 'U'-shaped dose–response [3]. Norepinephrine controls post-synaptic, α2A receptors in order to improves prefrontal cortex function. However, prefrontal cortex can also be damaged by high level of norepinephrine release from α1 receptors.

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3. Therapy for ADHD

After finding out the sources of ADHD, neuroscientists start to discover methods to cure ADHD. A bunch of methods such as making a typical schedule for young children, the way of using medicines, behavioral therapy, and the latest one, the application in the field of brain computer interface.

3.1. Pharmacotherapy for ADHD

Pharmacotherapy is the most commonly used way of curing ADHD as it has the best efficacy. The medicines can be classified into stimulants and nonstimulants

3.1.1. Central agonists: The mechanism of central agonists is to stimulate the neurotransmitters to make people more excited and energetic. The application of central agonists in curing ADHD is also to modulate the level of neurotransmitters to a normal level. The most mainly used central agonist is Methylphenidate HCL (MPH). Dopamine and norepinephrine play a critical role in the regulation of attention, motivation, impulse control, and motor activity. However, in individuals with ADHD, there is a reduction in the availability of these neurotransmitters, and MPH helps to enhance these functions by increasing their levels. The mechanism of action for MPH involves the blocking of dopamine and norepinephrine transporters in the brain. This blockade leads to an increase in the concentration of these neurotransmitters in the synaptic cleft, thereby enhancing neural signal transmission. The metabolism and excretion of MPH in the body are also part of its mechanism of action. Immediate-release MPH has an average time to maximum plasma concentration (Tmax) of 1.9 hours in children, with a half-life of about 2.5 hours, determining its short-term effects on symptoms. Studies have shown that MPH maintains its efficacy during long-term treatment. Most patients continued to use MPH 13 months after reaching an optimal dose. Study have also shown that MPH may also enhance health-related quality of life and ameliorate social behaviors in patients. A patient's response to MPH may be related to dosage, with some requiring higher doses to achieve normalization of symptoms. Different subtypes of ADHD (such as ADHD-C vs. ADHD-I) may necessitate different dosages [4]. A typical example of MPH that is mainly used is called Ritalin. The way MPH adjust the pathway of dopamine resembles to cocaine's way [5]. As we know the jeopardize of cocaine, the application of methylphenidate should be controlled to prevent the change the effect of Ritalin from medicine to drug. Another research have shown that about 30%-50% of the adult ADHD patient are resist to central agonists. Moreover, the side effects of MPH should also be considered. Insomnia, anorexia, stomach pains, and weight loss are the four most commonly reported side effects of Ritalin [6]. MPH also have side effects that may influence ADHD patients' gene. Genetic factors may play a role in an individual's reaction to MPH and its potential side effects. For example, variations in the dopamine transporter gene (SLC6A3/DAT1) have been researched for their influence on stimulant response.

3.1.2. Inhibitors: There are seventy percent to ninety percent of the ADHD patients who can be healed by stimulants [7]. Nevertheless, there are a few patients who have little response to stimulants or have vigorous side effects. Hence, nonstimulants are investigated. The main part the inhibitors affect is norepinephrine transporter. These inhibitors work by blocking the reuptake of norepinephrine, leading to increased levels of the neurotransmitter in the synaptic cleft and enhancing noradrenergic signaling. This can help alleviate symptoms of depression and improve focus and attention in individuals with ADHD. In addition to reboxetine and atomoxetine, other NET inhibitors have also been developed and are being studied for their potential therapeutic effects. These inhibitors may have varying degrees of potency, selectivity, and side effect profiles, making them suitable for different patient populations and conditions. Overall, targeting the norepinephrine transporter with inhibitors has proven to be a valuable strategy for managing mental health disorders and improving quality of life for individuals affected by these conditions. Further research and development in this area may lead to the discovery of even more effective and safe NET inhibitors for a range of neuropsychiatric disorders. At present the selective norepinephrine reuptake inhibitors and the alpha-2 agonists are the two classes of regulatory-approved non-stimulant agents. Atomoxetine, a kind of norepinephrine reuptake inhibitors. Atomoxetine increases

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the synaptic norepinephrine by combining to norepinephrine transporter. Besides, it can also regulate the reuptake of prefrontal dopamine in the prefrontal cortex. As its usage involved decreasing the activity of dopamine, the probability of abuse was decreased. However, the efficacy of norepinephrine reuptake inhibitors is relatively lower compared to the stimulants as the lower level of activity of striatum. There are also some side effects such as bad appetite, insomnia, irritability and decrease in weight and height, which are generally less vigorously than side effects stimulants produced[8]. Guanfacine and clonidine are two types of alpha-2 agonists. The nonstimulant can enhance the neurotransmission of norepinephrine.

3.1.3. Drugs in clinic: There are a bunch of drugs in clinic researching nowadays. Some of them will be introduced. Viloxazine (SPN-812), a new Norepinephrine Reuptake Inhibitor (NRI)[9]. By testing on children with a randomized double-blind trial comparing with placebo, its tolerability is worse than placebo but shows advantage after the fourth week. Duloxetine is a Selective Serotonin-Norepinephrine Reuptake Inhibitor (SNRI). Studies in adolescents and adults with this drug suggests a reduction in ADHD symptoms but it have a relatively low tolerability. Bupropion is a Norepinephrine-Dopamine Reuptake Inhibitor (NDRI). A research in children and adults shows that it can be used as methylphenidate which is more tolerable. Amantadine, an NMDA receptor non-competitive antagonist, is tested in children and it turns out that it has a similar efficacy to methylphenidate. Melatonin and Agomelatine presents as the melatonin receptor agonists. It is studied in children and shows that it can act as adjunctive therapy to methylphenidate, as well as showing potential to improve sleep issues [9]. Although these drugs in clinic is not stable enough for widely sell currently, they have a potential to cure more and more patients in the future.

3.2. Behavioral therapy

Behavioral therapy is the way of healing ADHD more mildly than medical therapy. The most popular one is called cognitive behavioral therapy. Cognitive Behavioral Therapy is a thoroughly employed approach for managing ADHD, incorporating cognitive and behavioral intervention components. Cognitive behavioral therapy operates on the premise that thoughts, feelings, and behaviors are interconnected, and modifying one aspect of this triad will impact the others. Most CBT interventions adhere to the "mediational position," positing that cognitive activity mediates an individual's response to the environment [10]. A group of 46 adolescents aged 14 to 18, who are undergoing stable medication treatment for clinically significant ADHD symptoms, were studied using BCI. They were randomly assigned to receive either CBT or placed on a wait-list control in a crossover design. Of the participants, 24 were assigned to the CBT group, 22 to the wait-list, and 15 crossed over from the wait-list to CBT. The assessment involved a blinded independent evaluator (IE) rating symptom severity on the ADHD Current Symptom Scale based on adolescent and parent reports. Additionally, each subject was rated using the Clinical Global Impression Severity Scale (CGI) at baseline, 4 months (post-CBT or post-wait-list), and 8 months (post-treatment for those originally assigned to the wait-list condition and at a 4-month follow-up for those initially assigned to CBT). The results showed that participants who received CBT had significantly lower mean scores: specifically, they scored an average of 10.93 points lower on IE-rated parent assessments of symptom severity, as well as scoring an average of 5.24 points lower on IE-rated adolescent assessments and an average of1 .17 points lower on IE-rated CGI assessments. These findings remained consistent across all100 multiple imputations conducted during analysis [11]. The research shows that CBT is an effective way of curing ADHD and can permanently cure ADHD. Nevertheless, CBT requires a large period of time to make effect and a group of professional doctors

3.3. Computer brain interface

Brain-computer interface is the science and technology of devices and systems which directly respond to neural and cognitive processes [12]. A company designed a training game to based on computer brain interface and using electroencephalogram [10]. The game allow the ADHD patients to directly use their

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attention to play the game by measuring and recording the level of electroencephalogram. There are three channels, two from frontal(Fp1,Fp2) and one from parietal (Pz) [11]. The first move for these electroencephalogram signals was to pass though a filter [10]. The filter broke them into different frequencies within the range of 4Hz to 36Hz, which covered theta, alpha, beta 1, and beta 2 waves. After that, the signals were sent to the homologous band in order to improve the detection of information [11]. The signals are then employed to clarify whether the player pays attention or not. In this way, attention can be successfully quantified [12]. An investigation is conducted. They find ten ADHD patients from seven years old to twelve years old whose parents refuse to use medical therapy and exclude children who receive methylphenidate or atomoxetine treatment, have comorbid severe psychiatric condition or known sensori-neural deficit such as complete blindness or deafness, have epilepsy previously or IQ is lower than 70 as the participants of this experiment [12]. The participants received two individual brain computer interface intervention sessions per week for ten weeks [12]. Children play a series of games of enhancing difficulties and have a test when the difficulty of the game is alternating and the attention level is detected by the BCI system [12]. As controls, the experiment invite children with the same experience but do not take the courses [12]. Although the result of the test is the intervention group had a significant change in scores, there are limitations that the sample size in the experiment is not enough. There are another BCI game shows a better effect. Subjects wear head-mounted electrodes, facing a display screen. Brain signals are collected through a g. USBamp amplifier and sent to a computer running the application and Matlab. According to the 10-20 system, three gold-plated electrodes are placed on the subject's scalp at the Oz (signal), Fpz (ground), and Fz or A1 (reference) positions. The application is designed as a game where subjects will represent a superhero academy to train their attention to battle supervillains. Members in the 3D classroom distract the subjects, affecting their score in the 2D game on the blackboard. The game includes 2D games and a 3D environment with distractions running in the 3D setting. EEG signals are pre-processed using an 8th order bandpass (5-30Hz) Butterworth filter to reduce both internal and external noise, with a sampling rate set to 512Hz. The classifier for detecting SSVEPs is based on the amplitude spectrum and threshold logic, using the most recent one-second EEG data (SData) and the concatenated recent 3 sets of SData (CData) for iterative examination. Subjects undergo nine different tests, each involving three levels of game settings with different 2D game scenarios; some with only positive elements falling, and others with both positive and negative elements. Three random routes with 30 steps each are prepared for the nine tests. Each step is a predefined directional red arrow in the middle of the flickering squares, indicating which square the subject must attend to. Selection times, selection accuracy, and total selections are recorded. Eleven healthy subjects (8 males and 3 females, aged 27.5 ± 4.5 years) participated in the experiment. The results showed that as the difficulty of the game increased, so did the difficulty of maintaining attention. But even in the more complex 3D environment, the subjects achieved an average accuracy of 92.26%, with an average selection time of 3.07 seconds. The BCI system demonstrates its potential use for attention training in ADHD, with fast selection times and high accuracy[13]. In all, BCI shows its spectacular potential in curing ADHD as the patients' attention level improves permanently with no side effects. However, BCI is too expensive for normal families to afford

4. Conclusion

The three therapy of ADHD shows both advantages and challenges. The pharmacotherapy is most commonly applied way nowadays as the effect of pharmacotherapy is the most vigorous for it is directly related to the release of neurotransmitters. Moreover, it can be used on most of the people and generations and a personal plan can be easily designed. Nonetheless, the abuse and addiction of medicines should also be considered. In addition, dependence of the medicine will be built if you take it for a long term. If patients choose behavioral therapy, they do not need to worry about the risk of abuse and addiction. Moreover, the patients that are cured by behavioral therapy tend to fit the society better but the therapy time and the environment requirement is very strict. The use of brain computer interface is a really potential therapy as it will not bring any side effects and the therapy can be personal. However, the technology is exploiting now and the cost for this kind of therapy would be high. In all,

shortage of each therapy still exists. Hence, scientists are expected to improve the therapies by first investigating the fundamental mechanism of ADHD and then covering the weakness individually. The side effects of pharmacotherapy can be reduced by better composition of chemical substances. CBT can be enhanced by designing a more decent schedule. Most importantly, more creative thoughts of using BCI for curing is the key to eliminate the effect of ADHD to minimum.

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