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Final dissertation

Non-pharmacological interventions in ADHD: a compelling insight on the application of Neurofeedback

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Chapter 1

Attention Deficit Hyperactivity Disorder

1.1.   ADHD: Definition, Diagnostic Criteria and Types

Attention Deficit Hyperactivity Disorder (ADHD) is one of the most common neurodevelopmental disorders among children. It is usually first diagnosed during childhood and may also last into adulthood (Centers for Disease Control and Prevention [CDC], 2023).

ADHD is a condition that affects child's behavior and is marked by an ongoing pattern of inattention (i.e. difficulty paying attention) and/or hyperactivity-impulsivity (i.e. being overly active and having trouble controlling impulsive behaviors; National Institute of Mental Health [NIMH], 2023).

Depending on the type of symptoms presented by the child, there are three types of ways in which ADHD can manifest itself:

- **Predominantly Inattentive Presentation**: the individual can be easily distracted and can forget details of daily routines. It becomes consequently hard for the person to maintain focus, pay attention to details, organize, or finish a task, or to follow instructions or conversations. The individual may be distracted by external or unimportant stimuli and might avoid or disincline to engage in activities requiring concentration.

- **Predominantly Hyperactive-Impulsive Presentation**: in this case the individual experiences restlessness, might move or fidget and talk a lot even in situations when it is not appropriate, and it may be hard to sit still for a long amount of time. Additionally, the individual may struggle with impulsivity and may engage in impulsive behaviors such as taking decisions without considering long-term consequences, interrupting others when they are talking, not being able to wait for their turn, speaking at inappropriate times, and grabbing objects from others. Impulsivity can also involve the desire for immediate rewards and the inability to delay gratification.

- **Combined Presentation**: symptoms include both those of the Inattentive type and those of the Hyperactive-Impulsive type (CDC, 2023; NIMH, 2023).

To diagnose ADHD, symptoms must be present before 12 years of age, not be better explained by another psychiatric disorder (such as mood disorder or anxiety disorder) and should not occur exclusively during a psychotic episode (for example, in the case of schizophrenia).

Furthermore, symptoms and/or behaviors must be present and persist for at least 6 months and in more than 2 settings (such as school, home, work, with friends or relatives, or in other activities), negatively impacting academic, social and/or occupational functioning.

Six or more symptoms must be present in children up to 16 years of age to meet the diagnostic criteria; meanwhile, for people aged 17 or older, five or more symptoms are necessary for the diagnosis (American Psychiatric Association, DSM-5; 2013).

1.2. Epidemiology

As mentioned above, ADHD is one of the most common mental disorders.

In 2023, ADHD was estimated to affect 8% of children and adolescents worldwide, with males (10%) twice as likely as females (5%) to develop the disorder. Furthermore, the inattentive type of ADHD was found to be the most common among the three subtypes, followed by the hyperactive type and finally by the combined type (Ayano et al., 2023).

In the U.S. only the reported prevalence of ADHD among children between the ages of 3 and 17 was 9.3% (CDC, 2023).

Furthermore, older children aged between 12 and 17 years are more affected by the disorder (13.5%) as compared to younger children (between 4 and 11 years) with a prevalence rate of 7.7% (Xu et al., 2018).

Data from studies conducted in the U.S. also shows that ADHD is more commonly diagnosed among Black non-Hispanic children and White non-Hispanic children, with a prevalence rate of 12% and 10% respectively.

As shown in Figure 1.1, the number of children in the U.S. with a diagnosis of ADHD has changed over the years. However, it must be noted that this evolution of the data does not demonstrate whether it can be regarded as a growth in the number of children who actually have ADHD, or rather an increase in the number of diagnoses (CDC, 2023).
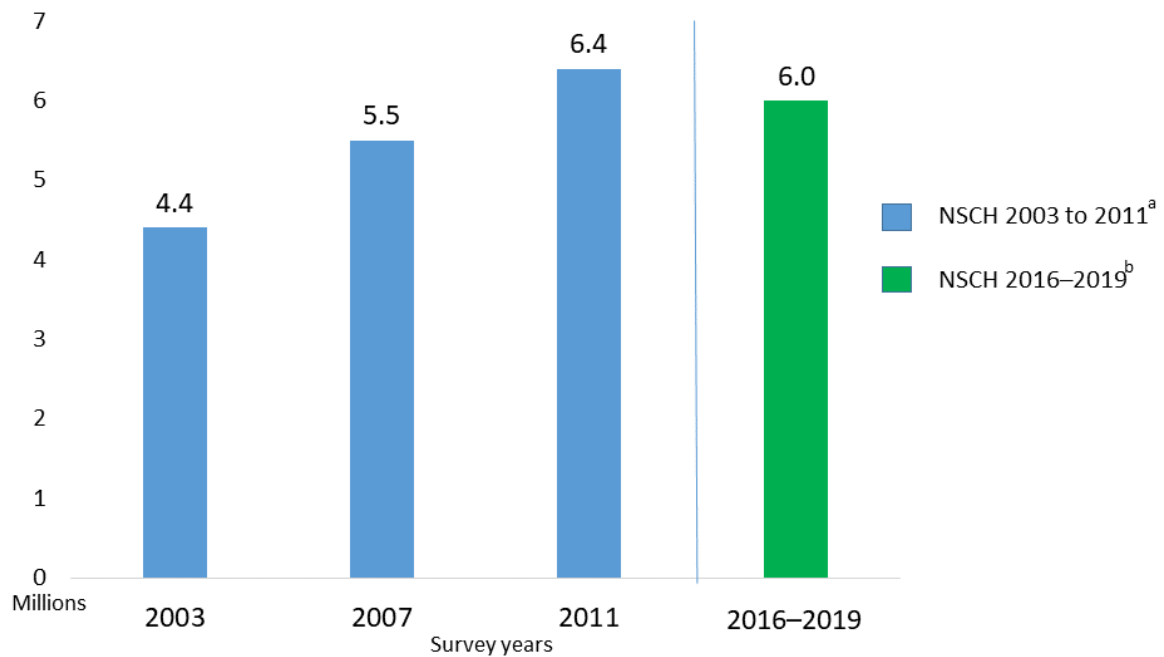
Figure 1.1 Estimate of the number of children aged 17 years diagnosed with ADHD in the U.S. (National Survey of Children's Health [NSCH], 2019).

Interestingly, as reported in Figure 1.2, more than half (64%) of patients with a diagnosis of ADHD also meet the criteria for the diagnosis of at least one other psychiatric disorder.

More specifically, 52% of children diagnosed with ADHD also develop a behavioral or conduct problem, 33% of them have an anxiety disorder, and 17% suffer from depression. Patients can also be less commonly affected by conditions such as autism spectrum disorder and Tourette Syndrome (CDC, 2023).
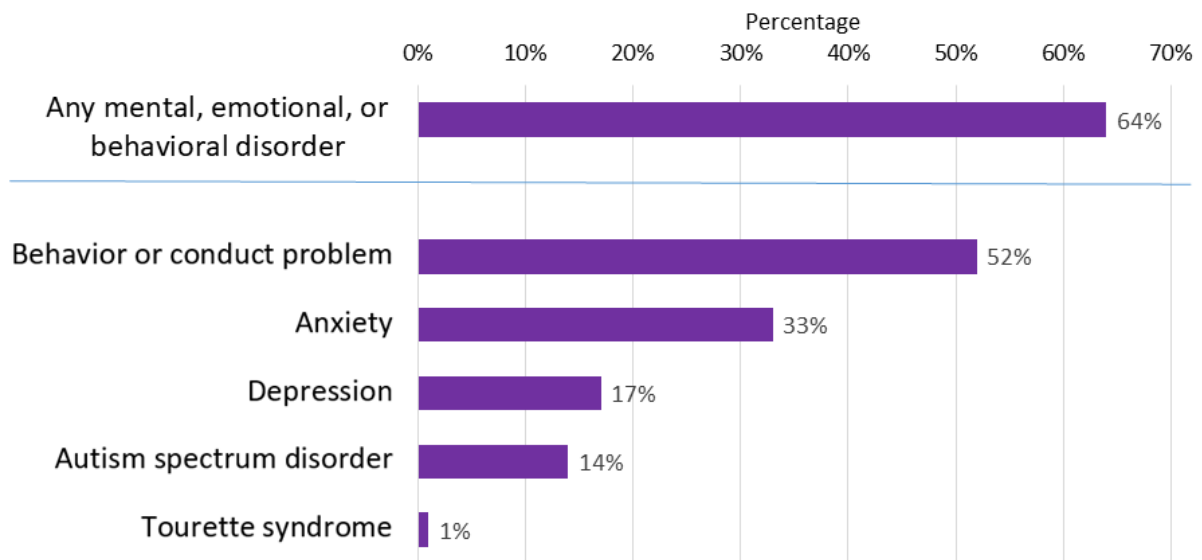
Figure 1.2 The graph shows the percentage of children with ADHD who also develop at least another disorder (CDC, 2023).

Generally, the treatment planned for individuals diagnosed with ADHD includes the prescription of medication (the most common ones are methylphenidate, e.g. Ritalin, or antidepressants in the case in which stimulants cause serious side effects or are ineffective; WHO, 2019), which helps reduce the symptoms, and the introduction of psychotherapy, to better cope with the problems that might arise from the disorder, and skills training, to learn, for example, some social skills that might be helpful to a child with the diagnosis (National Center on Birth Defects and Developmental Disabilities, 2021).

In a 2016 survey, it was reported that 77% of children with ADHD were receiving treatment, 30% of whom received medication alone, 15% of them received behavioral treatment alone, and overall, 32% of children with ADHD were treated with medication and psychotherapy. On the other hand, the remaining 23% were treated with neither behavioral treatment nor medication (CDC, 2023).

1.3. Etiopathogenic Mechanisms

It is difficult to specifically determine what are the causes for the development of ADHD because genetic, environmental, and biological factors can all interact and participate in the etiology of the condition.

Genetics seems to play an important role in the development of ADHD, because the disorder can occur in families. As a matter of fact, it is very likely that parents and siblings of patients with ADHD also have the disorder (World Health Organization [WHO], 2019).

Many are the other possible risk factors for ADHD.

One of them may be brain injuries and lesional factors, where prenatal and perinatal events seem to be especially relevant. In fact, brain damage can occur in the womb or after a severe head injury later in life (Hagiescu, 2021).

Exposure to traumatic events or environmental risks and toxins (for example, exposure to lead) of the mother during pregnancy or at a young age can alter the normal development of the child.

Risky behaviors, such as the consumption of alcohol or tobacco, carried out by the mother or the experience of high levels of stress during pregnancy, can also harm the infant (CDC, 2023; NHS, 2021; WHO, 2019).

Furthermore, additional elements that may increase the child's probability of maturing the disorder is being birthed prematurely (i.e. before 37th week of pregnancy) and/or low weight at birth (CDC, 2023; NHS, 2021; WHO, 2019).

1.4. Brain alterations in ADHD

There is significant evidence on the neuroanatomical correlates of ADHD.

One of the facts that emerged from Magnetic Resonance Imaging (MRI) studies conducted on children with ADHD is that their brain is often considerably smaller compared to healthy children throughout childhood and adolescence (Castellanos et al., 2002; Durston et al., 2001, 2004). To be more precise, brains of individuals with ADHD were found to be 3.2% smaller compared to those of healthy controls and this reduction was established to affect all four lobes without distinction. This discovery was supported by a study that investigated the differences between 30 boys with ADHD, their healthy siblings and controls. Participants with ADHD showed a reduction of 4% of the intracranial volume, similarly, although in a less marked percentage, to their unaffected siblings (Durston et al., 2004).

It has been suggested that a distributed circuit, consisting of frontal regions, basal ganglia, cerebellar hemispheres, and a sub-region of the cerebellar vermis, could be considered the origin of ADHD symptoms (Durston, 2003).

Furthermore, altered functioning of the frontal lobes are hypothesized to be of major influence in the manifestation of symptoms of ADHD. These conjectures were confirmed in a study where 48% of the reduction of total brain volume was demonstrated to be accounted for by the decreased frontal lobe and, more specifically, by the prefrontal cortex (Castellanos et al., 1996; Durston et al., 2004; Filipek et al., 1997; Kates et al., 2002; Mostofsky et al., 2002).

Another brain region of interest in the studies on the brain of ADHD patients is the cingulate gyrus, which was also affected by right focal thinning as shown in Figure 1.3 (Qiu et al., 2010).
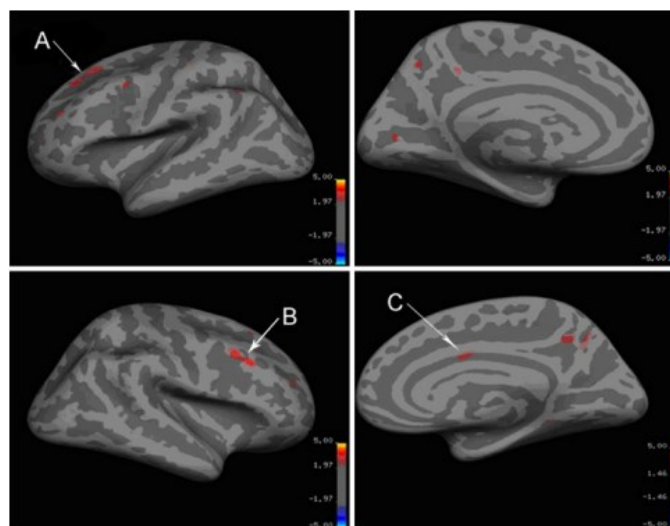
Figure 1.3 Focal thinning in bilateral frontal regions (*A*, *B*) and right cingulate cortex (*C*) in patients with ADHD (Qiu et al., 2010).

Furthermore, a bilateral reduction of approximately 4mm was found in the lateral anterior temporal cortices and in the inferior portion of dorsolateral prefrontal cortices. For what concerns the right parietal cortex of patients with ADHD, the cortical surface was found to be reduced and consequently closer to the center of the brain, probably because of diminished local growth (Hesslinger et al., 2002).

Moreover, research has demonstrated reductions in volume and asymmetry differences in the caudate nucleus in ADHD patients (Aylward et al., 1996; Castellanos et al., 2002; Hill et al., 2003).

It has been noted that ADHD is the most common among the psychiatric disorders to develop after a brain injury (Max et al., 1997) and/or stroke (Max et al., 2002) during childhood. Lesions to the posterior ventral putamen are more likely to trigger the

development of ADHD in those affected (Herskovits et al., 1999; Max et al., 2002). The putamen is a region associated with primary and supplementary motor functions and its dysfunction might therefore cause the motoric symptoms of ADHD.

Another brain region that has been studied in relation to ADHD is the cerebellum. The cerebellum is associated with functions such as motor movements and coordination and its connection to the frontal areas are responsible for other tasks such as attentional shifting and timing (Allen et al., 1997; de Zubicaray et al., 2000; Desmond, Gabrieli, & Glover, 1998; Desmond et al. 1997; Rao et al., 1997; Thomas et al., 1999; Tracy et al., 2000). ADHD patients have been found to have smaller than normal cerebellar hemispheric volumes (Berquin et al., 1998; Durston et al., 2004; Hill et al., 2003).

Many different studies also confirmed white matter reduction in the left prefrontal cortex and gray matter reduction in both hemispheres in patients with ADHD (Filipek et al., 1997; Overmeyer et al., 2001; Kates et al., 2002; Mostofsky et al. 2002).

Decreased gray matter was found primarily in the right posterior cingulate gyrus, putamen, and superior frontal gyrus, and bilaterally in the globus pallidus (Overmeyer et al., 2001). In contrast, research has found gray matter density to be increased in the posterior temporal lobes and inferior parietal lobes bilaterally by 15-30% in individuals with ADHD (Sowell et al., 2003).

The corpus callosum was discovered to be significantly smaller in patients with hyperkinetic disorders (Hill et al., 2003; Hynd et al., 1991; Semrud-Clikeman et al., 1994).

In general, findings of several studies report that smaller regional brain volumes are associated with more severe ADHD symptoms.

To be more specific, cerebellar, caudate, frontal and temporal gray volumes are reported to be negatively correlated with both medical and parent ratings of attention problems in ADHD (Castellanos et al., 2002).

Density of gray matter in the left occipital lobe was also found to negatively impact attention in patients with ADHD (Sowell et al., 2003).

In general, smaller or reduced brain volumes have been found to be correlated with greater severity of ADHD symptoms.

For what concerns the hyperactivity and impulsivity symptoms, they were shown to be affected by the size of the rostral body of the corpus callosum (Giedd et al., 1994).

Several other studies have focused on the influence of regional brain volumes on the performance of children with ADHD on neuropsychological functioning tasks.

More specifically, performance on tasks of sensory selection (e.g. forced-choice discrimination task in which subjects were asked to discriminate which one among the three objects presented on the computer screen was unique according to its shape and color) were found to be correlated with right prefrontal and caudate volumes, whereas performance on tasks of selection (e.g. tasks in which the subject was presented with four numbers and was then asked to respond to stimuli based on compatible mappings, i.e. press the button corresponding to the number presented on the screen, or incompatible mappings, i.e. press the buttons in a reversed order) and response execution (e.g. tasks in which subjects were asked to respond to a stimulus consisting of a single tone and refrain from responding when they heard a double tone) were mainly correlated with caudate symmetry and left globus pallidus size. By contrast, performance on inhibitory conditions (e.g. asking subjects to inhibit attention and refrain from responding to salient but irrelevant stimuli, compared to control conditions that were simple detection tasks) was shown to be influenced by the volume of prefrontal regions, while both control and inhibitory conditions seem to be associated with basal ganglia volumes (Casey et al., 1997).

Furthermore, a proton magnetic resonance spectroscopy study conducted on a group of ADHD children demonstrated that larger volumes in the right dorsolateral regions were correlated with poorer performance on the Conner's CPT composite (i.e. a test of attention), reaction time standard error scores and variability, therefore, since this result was not found in healthy controls, the more tissue in this region seems to be highly implicated in greater disruption in attention (Qiu et al., 2010).

Finally, tasks requiring higher levels of attention were also found to be influenced by smaller volumes of white matter of the anterior-superior region of the brain of patients with ADHD (Semrud-Clikeman et al., 2000).

Chapter 2
Neurofeedback

2.1. Neurofeedback: Definition and Main Protocols

Biofeedback of brain activity is called neurofeedback. In particular, among different neurofeedback applications, EEG (electroencephalogram) neurofeedback, is the most common. In general, neurofeedback is a technique which consists in teaching the individual how to regulate and control brain activity by providing individuals immediate feedback on their brainwave's activity (Marzbani, Marateb, & Mansourian; 2016).

The first study on this practice was conducted in the 1950s by Joe Kamiya who researched the relationship between alpha waves and relaxation (Kamiya, 1979).

Later, Barry Sterman discovered bursts of spindle-shaped, synchronous EEG activity across the sensorimotor areas of the cortex while doing animal studies in the 1960s. This discovery then took the name of sensorimotor rhythm (or SMR; Wyrwicka and Sterman, 1968).

Neurofeedback is usually applied through computer-based programs, in which the computer allows monitoring of EEG activity and brain waves, and also provides audio and/or visual feedback which enables the individual to become more aware of his/her brain activity in order to modulate brain activity to reach desirable brain activity to help understand brain processes and consciously adjust them accordingly to their biofeedback scope.

This type of immediate feedback stimulates the individual to pursue more positive feedback in order to be able to modify his/her activity and improve it.

Neurofeedback is considered a safe and non-invasive procedure which can be used as a complementary treatment to improve cognitive performance, and also, alleviate symptoms of neurological and mental disorders.

Generally, neurofeedback protocols last 30 up to 100 sessions and each session can last for about 30 to 60 minutes. The duration of the therapy depends on the patient since some people may need more or less sessions than others. The number of sessions needed varies according to individual factors, such as the severity of the symptoms, age, premorbid history and the motivation to commit to the therapy (Kadosh & Staunton, 2019).

2.2. Neurofeedback protocols

Neurofeedback training protocols include different EEg frequency bands such as alpha, beta, delta, theta and gamma brainwaves, which can also be used in combination such as in the case of the alpha/theta ratio treatment, beta/theta ratio treatment.

Specifically, brain waves are the result of the electrical signals generated by neurons to transfer information to one another.

They can be measured by applying EEG electrodes on the patient's scalp to detect the superficial cortex layers electrical activity.

In particular, the synchronous activity of pyramidal neurons is what is recorded by the electrodes located on specific parts of the skin. The different patterns of the electrical activity produced by pyramidal neurons correspond to what is identified as brain waves.

Brain waves can differ in frequency and amplitude (Figure 2.1). Frequency is measured in Hertz (Hz), which represents the number of waves per second, and it basically indicates how fast the waves oscillate. Amplitude, on the other hand, refers to the power of the waves and it is measured in microvolts (Marzbani, Marateb & Mansourian, 2016).
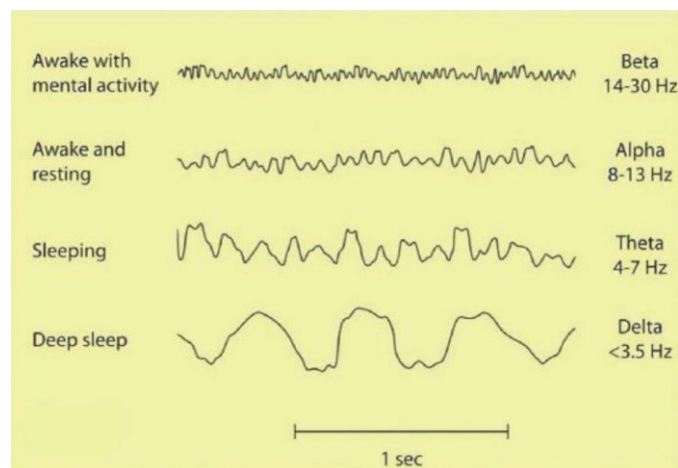
Figure 2.1 Example of brain waves of a normal adult (Demos, 2005).

Among brainwaves, alpha were the first waves to be discovered. Alpha activity (8-13 Hz) is visible all over the scalp. They're produced when one's awake but in a resting state, therefore calm and peaceful. Elevated alpha activity in different parts of the brain could result in conditions like depression and ADHD (Demos, 2005). Specifically, it

has been demonstrated that patients diagnosed with Major Depressive Disorder (MDD) are characterized by higher alpha activity over the left frontal lobe and, considered the contrasting relationship between alpha rhythms and cortical excitability, that would explain the symptoms of individuals with MDD such as hopelessness and helplessness. An increase in alpha activity is also displayed by individuals with ADHD during high-demanding cognitive tasks and when anticipating the presentation of relevant stimuli during tasks (Ippolito et al., 2022).

Sensorimotor rhythms (SMRs) are oscillations recorded in the mu (8-12 Hz), beta (14-30 Hz) and gamma (above 30 Hz) frequency bands over the sensorimotor cortex (Lopes Da Silva, 1991; Neuper and Pfurtscheller, 2001) These rhythms are not only employed during simple voluntary movements but also during cognitive tasks entailing cued motor responses, specifically those that involve selective responding and inhibitory control (Cheyne, 2013).

Beta (14-30 Hz) is associated with concentration, cautiousness and mental effort. Elevated beta activity is found in disorders such as ADHD, depression, anxiety, obsessive compulsive disorder, learning disorders and sleep disorders (Demos, 2005).

Delta (0-3.5 Hz) has been related to the slowest frequency and is usually elevated and clearly visible during sleep. In infants at birth 40% of the amplitude is in the Delta frequency band and only 10% in the Alpha frequency band (Thatcher et al., 1999). High delta amplitudes could reflect sleep deprivation, meanwhile low delta amplitudes could be a sign of anxiety, sleep disturbances, ADHD and traumatic brain injury (Demos, 2005).

Theta waves are considered to be related to creativity and spontaneity since, in an optimal state, they lead to improvements in intuition and make us feel more natural. Theta activity in the frontal regions has been associated with the enhancement of creative insight and assimilation of new information associated with satisfaction (Wang et al., 2024). When we engage in forms of creative thinking, such as daydreaming, alpha or theta waves are typically more elevated. However, excessive theta activity may indicate depression, anxiety or other emotional disorders. For example, theta activity may be inhibited with neurofeedback in children with ADHD (Figures 2.2 and 2.3; Demos, 2005).
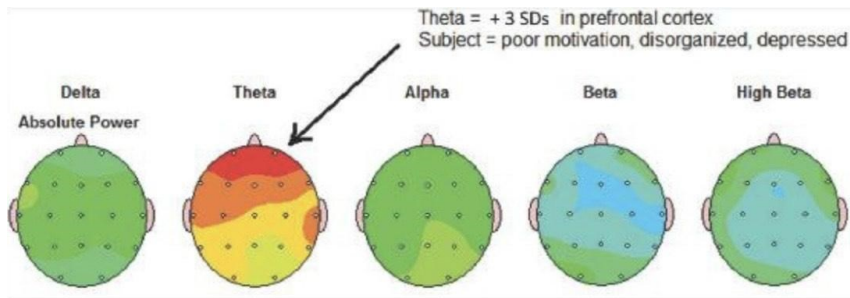
Figure 2.2 Poor executive functioning causing unmotivation in patients with ADHD (Demos, 2005).
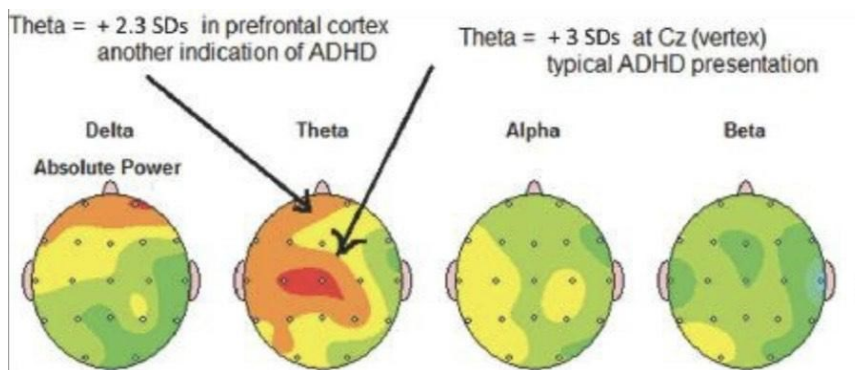
Figure 2.3 Elevated dorsal and frontal lobe theta activity in ADHD (Demos, 2005).

Finally, Gamma waves have the highest frequency (above 30 Hz) and are produced when in deep thought and concentration, and, as a matter of fact, gamma training enhances learning and memory (Larsen, 2012). It is thought to promote learning and organization in the brain. Significant reduction in gamma activity (30-50 Hz) may indicate the presence of a learning disorder or mental deficits (Demos, 2005).

2.3. Main Protocols

In neurofeedback training we can either focus on high frequency or on low frequencies, depending on the aim of the treatment. High frequencies are used to strengthen relaxation and focus, meanwhile low frequencies are applied to obtain activation, organization and inhibition of distractibility.

There are various Neurofeedback treatment protocols.

One of them is the alpha protocol. As previously mentioned, alpha waves are associated with calmness and alert relaxation and are therefore used for the treatment of conditions like anxiety and brain injury, to reduce stress and pain, and also to improve mental performance and memory (Demos, 2005).

The 7-10 Hz frequency range is the most common one for treatment aimed at enhancing alpha activity and the increase of the power of EEG in this frequency range is associated with sleep, meditation and the reduction of stress and anxiety. Also, muscle relaxation, pain relief, regulation of breathing rate, and decreased heart rate can be the result of 10 Hz frequency (Dempster, 2012; Vernon, 2005).

SMR training is aimed at improving and increasing SMR activity and it is usually recorded at Cz. Directing training towards the enhancement of SMR power activity is useful to treat conditions like anxiety and panic disorders, hyperactivity, seizures, and sleep disorders (Liu et al., 2022). Training focused on increasing 11-14 Hz seems to be more beneficial for younger children (Demos, 2005).

Excessive levels in beta activity are associated with disorders like anxiety, high levels of arousal and inability to relax, whereas excessively low beta power can lead to ADHD, daydreaming, poor cognition and depression (Priyanka et al., 2016). Specifically, low beta waves (12-15 Hz) are associated with focus, concentration and quiet, mid-range beta waves (15-20 Hz) are associated with increased energy, and high beta waves (18-40 Hz) lead to stress and anxiety (Priyanka et al., 2016). As a result, training aimed at decreasing beta activity is applied to enhance focus, attention, precision, reading ability and, as a result, school performance. In addition to that, it can also lead to the improvement of abilities like computational performance, cognitive processing, and the reduction of rumination, obsessive compulsive disorder (OCD), insomnia and alcohol abuse (Marzbani, Marateb & Mansourian, 2016).

The alpha/theta protocol is one of the most used treatments for stress reduction (Gruzelier, 2009; Raymond et al., 2005). It is also employed to help with deep levels of depression, anxiety and addiction but it is also expected to simultaneously increase creativity, relaxation, musical performance and resolve trauma (Egner & Gruzelier, 2003; Gruzelier, 2009).

This treatment is usually conducted under eyes-closed conditions to increase the ratio of theta to alpha waves and the frequency range used with the alpha/theta protocol is 7-8.5 Hz (Egner & Gruzelier, 2003; Thompson & Thompson, 2003).

NF to increase gamma activity can be applied to enhance mental activity, cognition and problem solving, as well as calculation, the speed of information processing, and short-term memory (Hughes & Vernon, 2005).

2.4.   Clinical Applications of Neurofeedback Training

The advantages and benefits of NF training have been studied in a number of different disorders and conditions.

A field of research where NF was found to have positive results is that of the Autism Spectrum Disorder (ASD). Subjects affected by this disorder often display absence of functions like social interaction, communication, but also problems with emotion regulation and mental retardation. These abnormalities are thought to be caused by high beta activity, which would cause anxiety, followed by high activity of the theta/beta components, causing hyperactivity and impulsivity, as well as seizure activity. Therefore, in this case NF training would aim at lowering the theta-alpha ratio while enhancing beta activity (Coben, Linden, & Myers, 2010; Kouijzer, van Schie, de Moor, Gerrits, & Buitelaar, 2010).

NF is also known to improve sleep and can therefore be helpful to people who suffer from insomnia to be able to fall asleep faster without taking as much to prepare their mind and body to go to sleep (Hammer et al., 2011).

Moreover, EEG biofeedback shows promising results also in the case of epilepsy. In fact, in most of the cases, medication proves to be ineffective in epileptic patients. However, NF turned out to be a good alternative able to guarantee desired outcomes, that is the reduction of the rate of seizures, in severe epilepsy (Hughes et al., 2009; Walker, 2010).

Furthermore, NF training can help deal with temptation and craving of drugs like cocaine (Horrell et al., 2010) in patients suffering from addiction and alcoholism (Moradi et al., 2011).

Taking into account the promising results displayed by the employment of NF in many and different occasions, the field of research is expanding.

In fact, other disorders found to benefit from the EEG biofeedback technique are learning disabilities (Wang & Sourina, 2013), obsessive compulsive disorder (Sürmeli & Ertem, 2011), Parkinson's disease (Rossi-Izquierdo et al., 2013), eating disorders (Bartholdy, Musiat, Campbell, & Schmidt, 2013), migraines (Walker, 2011) and other mental illnesses (Heinrich, Gevensleben, & Strehl, 2007). Interestingly, NF is also employed by artists and surgeons to improve their performance in the fields of music and microsurgical operation, respectively.

Furthermore, NF can be used in adjunction with other forms of therapy in order to be able to improve the quality of the results.

2.5. Most Common Treatment Protocols in ADHD

There are many studies aimed at investigating the effectiveness of NF training on the symptoms of ADHD.

Joel Lubar, after studying the effectiveness of NF on patients affected by epilepsy, was the first one to publish a study on the successfulness of the training on a child with ADHD (Shouse & Lubar, 1976). He advocated and promoted the use of SMR and other EEG states to train patients with ADHD how to attain behavioral stillness and ameliorate their attention.

Nowadays, most of the research on the fruitfulness of the practice of neurofeedback on the symptoms of ADHD focuses on the application of theta/beta Sensorimotor rhythm and Slow Cortical Potential protocols.

2.5.1. Theta/Beta Ratio

The theta/beta ratio (TBR) protocol is one of the most established forms of NF.

This technique was developed on the basis that theta activity in the brain is negatively associated with attention and could therefore cause symptoms like inattention in ADHD patients, meanwhile beta activity is related to mental focus and concentration. Consequently, the theta/beta ratio protocol consists in teaching the patient to decrease the theta activity while simultaneously increasing the activity in the beta frequency band in the frontal and central locations. This protocol targets electrophysiological features, namely high theta/beta ratios, high theta activity and low beta power which are often found in patients with ADHD (Bresnahan & Barry; 2002).

Moreover, TBR is associated with attentional control (Angelidis et al., 2016; Putman et al., 2010, 2014; van Son et al. 2018) and higher tolerance to stress related to task-performance (Putman et al. 2014).

According to recent research on ADHD patients, in order to observe improvements in what concerns the inattention and hyperactivity symptoms, 30 to 40 sessions at C_z were adequate to obtain remarkable results (Duric et al.; 2012).

2.5.2. Sensorimotor Rhythm

One of the first NF protocols to be developed and tested was the Sensorimotor-rhythm. In 1970, Sterman et al. published a study in which cats were trained to increase activation at 12-15 Hz in the sensory motor cortex which is the brain wave associated with motor stillness and mental vigilance. These findings were then applied to humans,

establishing the ability of increased SMR activity to decrease the frequency, duration and severity of seizures (Wyrwicka & Sterman, 1968).

Later, Lubar and Lubar in 1984 were able to demonstrate that applying this same protocol to children with ADHD led to alleviation of the excessive motor activity and inattention which are typical symptoms of the disorder (Lubar & Lubar, 1984).

SMR activity that is composed of spindle-like bursts of activity originating in the thalamus, reflect to the areas of the cortex located across the sensorimotor strip which is considered to be a bottom-up mechanism. The increase in SMR promotes the inhibition of the interference of somatosensory information, preventing the motor activity to potentially hinder the integration of information processing in the cortex and consequently impair cognitive performance (Egner & Gruzelier, 2004).

Furthermore, SMR-NF training is able to decrease the hyperactivity and impulsivity symptoms in patients with ADHD to the same degree as TBR training and with approximately the same number of sessions. However, SMR NF was revealed to have positive effects on patients' quality of sleep as well, and this improvement is thought to be responsible for the enhanced attention post-treatment (Arns et al., 2014).

On top of that, Lubar demonstrated that the combination of SMR/theta NF can manage to train patients to maintain the reduction of the hyperactivity symptoms even after the withdrawal of psychostimulants (Shouse & Lubar, 1979).

2.5.3. Slow Cortical Potential

Another well-established NF protocol is based on the regulation of slow cortical potentials (SCPs).

SCPs are event related potentials which can be either negatively or positively electrically charged and can last from about 300 milliseconds to several seconds in length.

SCPs are considered to be of significant importance in mechanisms of attention regulation and short-term memory as well as for preparing the organism for physical and cognitive activities (Birbaumer et al., 1990), therefore their modulation is hypothesized to be advantageous for the treatment of disorders caused by the impairment of the balance between excitation and inhibition, which is necessary for the correct neural signal formation, synchrony and transmission to maintain information processing (Larsen, 2012). In fact, higher excitation/inhibition ratio is

thought to be responsible for core symptoms of disorders such as ASD and schizophrenia (Foss-Fieg et al., 2017).

More specifically, negative shifts lead to lower thresholds for neural excitability and therefore to increased firing probabilities, whereas positive shifts decrease them leading to inhibition (Birbaumer et al., 1990).

SCPs NF aims at training patients to intentionally induce positive and negative shifts. Training is usually done at C_z (as for theta/beta protocol), and it consists of several trials of 6-10s each. SCP training requires a greater number of sessions (25 to 35) compared to both TBR and SMR, but the sessions are shorter in duration since every trial lasts for about 6 up to 10 seconds and every session is composed of five runs with 30 to 40 trials each, as recommended by the "European protocols" (Strehl, 2009). Moreover, a segment of about 2s which acts as a baseline of the NF phase is presented before each trial. The active NF phase is usually preceded by an acoustic stimulus and a prompting cue and it is during this period that the desired shift is expected to be generated, either by increasing or decreasing the cortical activity compared to the baseline value. As feedback, the patient's performance is also displayed on the screen in real time (Hasslinger, Meregalli & Bölte, 2022).

In addition, in order to enable the patients to transfer this type of self-regulation ability into their daily life, they are presented with trials of delayed feedback in which they are exclusively prompted by the acoustic signal and the cue, but they do not receive real time feedback on screen; if the trial is successful then the reward is displayed (Hasslinger, Meregalli & Bölte, 2022).

Usually, TBR and SMR protocols are considered to be unidirectional in the sense that they both focus on either increasing or decreasing the frequency or the amplitudes of the EEG. On the contrary, self-regulation of SCPs is bidirectional, meaning that it aims at generating both cortical inhibition and activation (Hasslinger, Meregalli & Bölte, 2022).

Chapter 3
Application of Neurofeedback in ADHD

3.1.   Effectiveness of Neurofeedback Compared to Stimulant Medication or in Combination

At present, the standard line of treatment to alleviate ADHD symptoms and improve patients' functioning comprises psychostimulant medication (i.e. methylphenidate, such as Ritalin, or antidepressants), often accompanied by psychotherapy (WHO, 2019).

Nevertheless, not all patients respond well to psychostimulants: they may not succeed in reducing symptoms of ADHD and they could also cause side effects such as nausea, fatigue and loss of appetite. Furthermore, one problem associated with stimulant medication is the short duration of the treatment effects (American Psychiatric Association, 2013; Clavenna & Bonati, 2014).

NF has been taken into consideration as an alternative to psychostimulants for the treatment of ADHD and several studies have been dedicated to the evaluation of its effectiveness on symptoms of impulsivity, inattention and hyperactivity (Duric et al., 2012; Meisel et al., 2014; Duric et al., 2014; Duric et al., 2017).

A number of studies employing different NF protocols (but mainly theta/beta protocol) found that 20 to 40 sessions with a duration ranging from 25 to 50 minutes of NF was as effective as stimulant medication in the treatment of ADHD (Duric et al., 2012; Meisel et al., 2014; Duric et al., 2014; Duric et al., 2017). These studies demonstrated through parents/teacher assessments and self-reports that NF training was able to achieve results in the reduction of symptoms of both inattention and hyperactivity comparable to those obtained with psychostimulants, with effects persistent also at 6 months follow-up (Meisel et al., 2014; Duric et al., 2017).

Nonetheless, research demonstrated that the application of NF in combination with medication actually produced better and more long-lasting results. As a matter of fact, studies examining objective outcome measures, such as neurocognitive tests, EEG parameters and Event Related Potentials (ERPs), found that the application of neurofeedback and stimulant medication in combination produced significant reduction in theta power and in alpha waves, which was maintained even at 6 months follow-up (Janssen et al., 2016; Lee and Jung, 2017; Li et al., 2013).

Furthermore, the application of NF treatment allowed to reduce the dosage of psychostimulants at 6 months follow-up (Li et al., 2013).

However, these results are not consistent since some studies actually found medication to be more superior than NF in the reduction of symptoms of ADHD (Ogrim & Hestad, 2013; Geladé et al., 2016) and it seems that NF could be more useful to patients who are more resistant to medication or are more sensitive to side effects (Bink et al., 2014; Duric et al., 2012; Li et al., 2013).

Furthermore, research that did not exclude children based on psychiatry comorbidity (i.e. diagnosed with both ADHD and other disorders such as mood disorders, anxiety disorders and ASD) suggests that patients with ADHD may be more responsive to neurofeedback techniques compared to children diagnosed with both ADHD and comorbid disorders who may be more in need of stimulant medication due to their psychiatrically more complex diagnosis (Ogrim & Hestad, 2013; Bink et al., 2014; Geladé et al., 2016). Another explanation for these results is that clinicians should take into consideration the specific presentation type of ADHD and eventual comorbid disorders when arranging the electrophysiological treatment targets (Razoki, 2018).

It should be noted that, as in other active interventions, motivation is an essential element to ensure the best possible outcome out of NF training and it could be of influence on the effectiveness of the treatment, therefore patients' pretreatment motivation could be a useful predictor of NF response (Razoki, 2018).

Identity markers, such as neuropsychological parameters (such as neurocognitive tests, EEG parameters and ERPs), environmental influences (e.g. parents and teacher influence) and psychological factors (such as motivation, controllability, learnability and perceptibility), are hypothesized to be potential markers able to discriminate between responders and non-responders to NF techniques and developing tailored NF training following these potential markers could be useful to support the implementation of NF as a clinically established treatment for ADHD (Razoki, 2018).

3.2. How to Enhance the Effectiveness of Neurofeedback to Reduce Symptoms of ADHD

Research has been conducted to investigate which conditions might improve the effectiveness of NF as a technique to alleviate symptoms of ADHD.

As mentioned above, not all patients may benefit from NF training and responders and non-responders could differ for a number of characteristics.

3.2.1. Pre-Treatment Cognitive Testing and Computational Modeling

Researchers have theorized the influence of cognitive components on treatment outcomes (Karbach et al., 2017; Lövdén et al., 2012). Specifically, the *magnification account* and the *compensation account* have been developed as hypotheses for the moderating role of individuals' cognitive abilities in response to treatment.

The *magnification account* suggests that high cognitive abilities imply the potential to employ cognitive resources and can therefore better improve through the implementation of non-NF psychosocial interventions to acquire new skills and strategies, whereas the latter claims that psychosocial interventions might be more suitable for individuals with lower cognitive abilities to enhance their potential. These theories could serve as baselines for the studies on the development of tailored NF techniques.

However, general cognitive task performance entails many concepts and might not be considered sufficiently sensitive to detect salient cognitive abilities responsible for individual differences. Computational modeling differentiates and discriminates between the different cognitive components and might therefore be more suitable for the purpose of investigating the role of individual variability on treatment effectiveness (Ging-Jehli et al., 2021; 2022; Ratcliff et al., 2010).

In particular, the diffusion decision model (Ratcliff, 1978) was able to explain the performance on a number of tasks in the context of various disorders, such as anxiety, depression, autism and ADHD (Ging-Jehli et al., 2021; 2022; Pe et al., 2013; Pirrone et al., 2020; White et al., 2010). Specifically, this model includes different very specific components that constitute the process of decision making (i.e. drift rate, drift bias, boundary separation, non-decision time and starting point[1]).

There is evidence from several studies that two of these components (drift rate and drift bias) are particularly relevant in ADHD. Specifically, ADHD patients manifest lower ability to gather information from stimuli that are presented to us and larger variation in context sensitivity of cognitive processes (especially those employed in

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[1] Drift rate (v) refers to the ability to gather information from stimuli that are presented to us. Drift bias (c_v) concerns context sensitivity of the abilities employed during information processing. Boundary separation (a) indicates speed accuracy of the response. Non-decision time (T_{er}) represents the latency of the processes involved in stimulus identification and in the response implementation. Starting point (z) refers to the initial bias for a response.

information integration) compared to healthy individuals during a number of cognitive tasks (Ging-Jehli et al., 2021; Huang-Pollock et al., 2017, 2020; Mowinckel et al., 2015; Shapiro & Huang-Pollock, 2019; Weigard & Huang-Pollock, 2014; Weigard & Sripada, 2021).

This information can be particularly useful to differentiate between patients who might benefit more from NF training and those who might benefit more from standard treatment. In fact, research has demonstrated that children with more similar scores on these components (reflecting standard cognitive abilities) obtain better results with control treatment, whereas patients with substantial impairments in these components (i.e. with poorer cognitive abilities) and those with higher cognitive abilities show greater improvements with NF training (Ging-Jehli et al., 2023). These results showed that NF technique benefits more children with altered patterns of cognitive abilities than those with average abilities, confirming both the *magnification* and the *compensation* accounts (Ging-Jehli et al., 2023).

3.2.2. Neurofeedback Treatment Personalization and Combination with other Interventions

Further research in line with a precision psychology approach demonstrated that treatment personalization might enhance the effectiveness of NF training. These findings are supported by evidence on differences among individuals in the generation and management of patterns of neural activity (Enriquez-Geppert et al., 2013; Alkoby et al., 2018). In studies where the authors decided which standard NF protocol (namely TBR, SCP or SMR) to assign participants on the basis of their individual baseline QEEG (quantitative EEG) signal characteristics, instead of randomly assigning them to one of the protocols, the effectiveness of the treatment appeared to be improved (Monastra et al., 2002; Arnold et al., 2013; Krepel et al., 2020).

Furthermore, adjusting NF training to the specific characteristics of ADHD may additionally enhance the effectiveness of the treatment. One of such characteristics is the tendency of ADHD patients to be particularly sensitive to reward as it was demonstrated in studies where children preferred smaller but more frequent rewards compared to larger but delayed ones, where the presentation of rewards actually improved their motivation and feedback monitoring, and where their instrumental learning was strengthen when the reward was presented shortly after the response (Luman et al., 2007).

A second ADHD feature that might influence the effectiveness of NF is motor activity and attention. Specifically, by presenting feedback, instructions, directions and rewards, NF helps children to learn how to appropriately regulate their behavior and to focus.

Research has also demonstrated that the effectiveness of treatment is improved when NF training is associated with additional treatment modalities and interventions.

Parental involvement was demonstrated to influence the outcome of the treatment, as the unfailing use of reinforcement and response cost by parents was shown to benefit children with hyperactivity and inattention symptoms (Monastra et al., 2002). Yet, these results were not replicated in teacher ratings, revealing that these effects might be context-specific or influenced by parental expectations (Pimenta et al., 2021).

Evidence also supports the benefits of adequate sleep and nutrition on the outcome of NF training. As a matter of fact, research demonstrated that having a balanced and counseled diet can by itself slightly benefit ADHD symptoms (Sonuga-Barke et al., 2013).

With respect to sleep regulation, there is a high co-occurrence between ADHD and sleep disorders (Bijlenga et al., 2019). Therefore, targeting sleep modulation by improving quality and quantity of sleep, by using NF training to specifically improve sleep related brain waves could help reduce ADHD symptoms (Arns & Kenemans, 2014).

In conclusion, the personalization and combination of NF training with other types of interventions (i.e. parental, sleep, nutrition, as well as behavioral motor training and rewards presentation) has demonstrated to be more long-lasting and clinically effective than medication monotreatment.

What makes NF such an appealing technique is the fact that it can be considered a non-pharmacological alternative to other interventions, and it has been shown to be able to obtain positive effects which are demonstrated to be sustained even after its completion. NF has therefore proved to be a valid and well-established option for the reduction of symptoms associated with ADHD for its specificity and long-term effectiveness.

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