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Neurofeedback: A new therapeutical perspective for Psychiatric Disorders as an alternative to excessive psychotropics consumption

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Dedication

To the three most important women in my life, my mother, my sister and my grandmother

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Resumo Alargado

Os transtornos psiquiátricos são conhecidos como um contributo major de comorbidade a nível mundial. Stress e distúrbios de ansiedade e sono desempenham um importante papel no processo de instabilidade da integridade da saúde mental. Apesar dos contínuos esforços para o controlo da crescente prevalência de tais transtornos, continuam a surgir questões na hora da decisão diagnóstica, na escolha da melhor opção terapêutica e no que diz respeito aos efeitos secundários e sintomas resistentes a tratamento.

Os transtornos depressivos e de ansiedade, assim como o transtorno de deficit de atenção/hiperatividade (TDAH) são vistos como transtornos mentais cujos fatores que influenciam o processo de saúde-doença são similares. A medicina alopática trata estes transtornos com o recurso a psicotrópicos e psicoterapia e enfrenta o crescente dilema da dependência de substâncias. Isto deve-se ao uso prolongado de medicação psicotrópica, ao abuso e a ineficiente monitorização. Atualmente o consumo de psicotrópicos está a aumentar em grande escala e é também considerado como um importante contributo de comorbidade.

Para o tratamento do TDAH, as guidelines recomendam o uso de metilfenidato e psicoterapia. O metilfenidato, um estimulante, pertence ao grupo dos psicotrópicos e o seu mecanismo de ação ainda não é completamente compreendido. Muitas crianças mostram-se resistentes ao tratamento, bem como sofrem de efeitos adversos à medicação. Para além disso, os efeitos secundários da aplicação de psicotrópicos no comportamento e humor das crianças, são uma preocupante questão nesta área.

Para contribuir para uma melhor abordagem face ao mau uso de psicotrópicos, esta monografia pretende incentivar o recurso a técnicas alternativas para ambos diagnóstico e tratamento de crianças com TDAH. Sintomas como impulsividade, hiperatividade e desatenção influenciam diretamente a vida da criança em casa, na escola ou nas habilidades sociais. Apesar da elevada prevalência deste transtorno e anos de investigação, persiste a marcada incerteza diagnóstica e terapêutica.

Através da pesquisa documental, pesquisa online através de databases como Pubmed, Medscape e Science Direct, da análise e tratamento de dados, é possível constatar que o neurofeedback se trata de uma técnica promissora. Os critérios de inclusão bibliográfica basearam-se em artigos de língua inglesa, no Manual de diagnóstico e estatístico de transtornos mentais (DSM) e nas guidelines da American Academy of Child and Adolescent Psychiatry. Foram preferidos artigos mais recentes com as seguintes palavras-chave: biofeedback, neurofeedback, psychiatric disorders, attention deficit hyperactivity disorder e cognition.

O treino por neurofeedback é um método não invasivo que pode ser ajustado a cada utente, de acordo com uma base de dados quantitativa de eletroencefalogramas (qEEG). Esta técnica funciona através de condicionamento operante, cujo feedback imediato, visual ou auditivo, é fornecido cada vez que o cérebro emite um nível correto de ondas cerebrais. Permite ao doente a alteração subconsciente da atividade cerebral, levando a alterações comportamentais no sentido da normalização. Posto isto, padrões eletrofisiológicos apropriados irão ser permanentemente restaurados.

A revisão analítica indicou que o padrão qEEG de crianças com TDAH, apresenta um nível de ratio theta: beta significativamente mais alto no córtex frontal, relativamente a crianças saudáveis. Com o recurso a esta informação, os clínicos são capazes de diagnosticar com maior precisão e simultaneamente fornecer um protocolo de treino de neurofeedback indicado. Isto vai permitir o reequilíbrio do padrão de produção de ondas cerebrais em áreas afetadas do cérebro. Este método permitiu melhorias na desatenção e comportamentos impulsivos de crianças com TDAH. Em alguns casos pode permitir a redução ou até a descontinuação da farmacoterapia.

Abstract

Psychiatric Disorders are known as a major contributor for comorbidity worldwide. The roles of stress, anxiety and sleep disturbances are considerable factors in the process of instability of mental health integrity. Despite the efforts continuously made to control the growing prevalence of such disorders, there are still emerging issues at the time of giving a proper diagnosis, choosing the best therapeutic option and dealing with adverse effects and resistant symptoms.

Depressive and anxiety disorders as well as attention deficit hyperactivity disorder (ADHD) are regarded here as mental disorders with similar factors influencing the health disease process. Allopathic medicine with the resource of psychotropics and psychotherapy to deal with mental disorders are facing the growth of substance dependence dilemma. This is due to the prolonged use of psychotropic medicine, improper use, abuse and inefficient monitoring. Psychotropic consumption is increasing on a larger scale at the present time and known as a major contributor for comorbidity.

The guidelines recommend the use of methylphenidate as well as psychotherapy to treat ADHD. Methylphenidate is a stimulant medicine, belonging to the psychotropic group of medication, which the mechanism is not completely understood. Many children have shown to be resistant to these treatments or to suffer from side effects related to the use of the medication. Moreover, the side effects of psychotropics use on children's mood and behavior are a major topic of concern in this field.

To contribute to a better approach towards psychotropic misuse, this dissertation aims to stimulate the use of alternative techniques for both diagnose and treatment of children with ADHD. Symptoms like impulsivity, hyperactivity, and lack of attention and focus, can directly influence the child's life in school, home and social skills. Despite of the high prevalence of this disorder and of years of research there is still a marked uncertainty regarding both its diagnose and treatment.

Through online research on database websites like PubMed, Medscape and Science Direct, documental research, analyzing and gathering data it is recognized that Neurofeedback is a very promising tool. The criteria for filtering information is based on the English language articles, the Diagnostic and Statistical Manual of Mental Disorder (DSM), as well as the American Academy of Child and Adolescent Psychiatry practice guidelines. The search phrases used were biofeedback, neurofeedback, psychiatric disorders, attention deficit hyperactivity disorder and cognition.

Neurofeedback training is a safe and noninvasive method that can be tailored for each patient according to a baseline quantitative electro encephalogram (qEEG) analysis of the brain. This technique functions through operant conditioning training, which is through an immediate visual and auditory feedback each time the brain emits the correct level of brainwaves. This enables the patientto subconsciously change his/her brain activity, leading to behavioral changes towards the norm. A certain amount of neurofeedback sessions will eventually induce plasticity in appropriate areas of the brain. Therefore, the most appropriate electrophysiological patterns will be permanently restored.

Our analytic review indicated that the qEEG pattern of children with ADHD has a significantly higher ratio level of theta: beta in the frontal cortex, compared to normal children. Using this information, clinicians are able to accurately diagnose children with ADHD, and at the same time to expose them to a proper neurofeedback training protocol. This would rebalance their brain waves in the affected areas of the brain. This method have led to remarkable improvements in inattention and impulsive behaviors of children with ADHD. In some cases, reduction or even in the termination of taking the medication.

Keywords

Neurofeedback; Psychotropics; Brain wave; EEG; Psychiatric Disorders; Self-Medication

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List of Acronyms

UBI	Universidade da Beira Interior
WHO	World Health Organization
DSM-V	Diagnostic and Statistical Manual of Mental Disorders
ADHD	Attention Déficit Hyperactivity Disorder
YLDs	Years Lived with Disability
PMDD	Premenstrual Dysphoric Disorder
SM	Selective Mutism
GAD	Generalized Anxiety Disorder
EEG	Electroencephalography
MRI	Magnetic Ressonance Imaging
APA	American Psychiatric Association
AACAP	American Academy of Child an Adolescent Psychiatry
CNS	Central Nervous System
SSRI	Selective Serotonin Reuptake Inhibitors
MAOIs	MAO Inhibitors
GABA	Gamma-aminobutyric Acid
RH	Right Hemisphere
LH	Left Hemisphere
qEEG	Quantitative EEG
NFB	Neurofeedback

Chapter 1

Introduction

Psychiatric disorders are acknowledged worldwide as an important cause of morbidity in one of the latest (World Health Organization) WHO reports, In which it is asserted that, only a small minority of the people affected by these disorders are able to receive high quality treatment (1).

In this dissertation we mention the Diagnostic and Statistical Manual of Mental Disorder (DSM-V) due to the fact of being a wide system used by the medical community to evaluate and categorize several clusters of psychiatric symptoms. There were a few modifications on the latest edition of the DSM-V, mainly on the Mood Disorders chapters – depression and anxiety, and Neurodevelopmental Disorders – Attention Deficit/Hyperactivity Disorder (ADHD) (2). Our main focus in this research will be on diseases namely, depression, anxiety and ADHD. They are chosen for our study because of being caused due to the new stressful lifestyle in nowadays societies of developed countries, for presenting medical treatment with the use of psychotropic substances, for being part of the differential diagnosis of each one, and for showing promising results with implementation of Neurofeedback therapy(3, 4).

It´s observed that ADHD is presented as a disorder which the diagnosis can be amplified until adulthood, with the persistence of the symptoms of the alteration in attention, hyperactivity and impulsiveness. A reliable treatment in childhood and its maintenance supported by behavior monitoring and proper therapeutics, becomes beneficial(5).

Being the most common treatment, psychotropic substances are the most recent problem with a rising concern about the growing amount of their intake, and developing resilience(6). Based on this assessment, it´s possible to identify the necessity of new treatment options as a support for standard pharmacological therapy and to contribute to the enhancement of the mental health status of society.

The present study aims to present the neurotherapy as a safe, noninvasive and painless therapeutic option for the symptomatic relief of many disorders. Neurofeedback is a therapy focusing on the neuroplasticity that is induced through operant conditioning practice, and enabling the patients to release the debilitating symptoms, and offer him/her a healthier way to live(7).

Chapter 2

Mental Disorders

In Europe mental disorders have a major role in Years Lived with Disability (YLDs), presenting a 36.1% of the assignable to all the causes(8). The percentage of money granted to psychotropic medication, and the pharmacological therapy for the most of these disorders, is growing exponentially compared to pharmacotherapy in general(9).

Quoting the DSM-V, mental disorder can be defined as "… a syndrome featured by a clinically meaningful disorder on cognition, emotional adjustment or on a Pearson behavior that shows a disorder on the psychological process, biological or of underlying development of mental functions."

Only the unipolar depressive disorder contributes to 11% of all the YLDs, and is the major chronic condition in Europe. On the other hand, anxiety disorders rank the sixth position with 4% of the YLDs. In addition, according to WHO, it is expected that in 2020 the depressive disorders will take the second rank considering the disease overall load, closely behind the ischemic heart disease(8).

This anticipation is a disturbing public health warning, with the additional disadvantage that 40% of the countries do not have mental health policies and nearly 30% don't have mental health programs. This leads to the failure of the heath Care and presents inconsistences on the high quality diagnosis and therapeutic systematization(1).

2.1 – Depressive and Anxiety Disorders

According to the classification on DSM-V, the depressive and anxiety disorders are presented in separate chapter, even though its complete separation and differential diagnosis is often very complex. Despite all the efforts made to control these diseases, their prevalence seems to increase year after year. It still is a rather disabling reality that affects social, professional and other important daily activities(2).

The depression disorders are essentially distinguished by the persistent presence of sad or irritable feeling, and decrease of interest or pleasure. There are a set of criteria that must be present for two weeks or more to be considered as symptoms of depression. Some of these are significant weight gain or loss, insomnia or hypersomnia, psychomotor agitation or retardation, loss of energy, feelings of worthlessness or excessive or inappropriate guilt, concentration decrease and even thoughts of death or suicide. The classical clinical

presentation is the depressive disorder major that must be specified as a unique or recurrent episode and classified regarding its mild, moderate or severe intensity.

The specific etiology of this disorders is still to be determined and the it is proved that the causes are countless and multi-factor. There are some reports discussing the possibilities of a genetic and/or neurobiological causality to depression; however, in most studies are still inconclusive. In certain cases, structural or neurochemical are shown to be the cause of the development of depressive disorder. On the other hand, in many others the causes are related with subjective factors such as personality disorders, environment or socio-economics (10). In addition, there are also depressive disorders induced by Substance/Drug, due to a Medical Condition, and are still regarded as specified or non-specified.

On DSM-V new diagnosis are added in this chapter to improve the clinical and therapeutic assertiveness of each individual. It's the case of the Disruptive Mood Dysregulation Disorder, the children who until the age of 12 develop persistent irritability and extreme uncontrolled behavior for at least one year, normally develop depressive and anxiety episodes later in life. According to the Premenstrual Dysphoric Disorder (PMDD), there is another type of depression called Persistent Depressive Disorder (previously known as dysthymia); which is defined as a significant depressed mood for most of the day, for at least 1 year in children and 2 years in adults. The key for a well accurate diagnosis and an adjusted therapy for the patient is an interview focusing on biopsychosocial model, in which it must be thoroughly perceived all the specifiers that can alter the prognosis and the course of the disease.

The new diagnosis methods for Depressive Disorders incorporate anxiety symptoms that could go from nervousness or tension to loss of control or fear of something terrible happens. Mixed specifiers are characterized by the presence of maniac/hippomaniac symptoms with changes of behavior, which are insufficient to diagnose a bipolar I and II disorder. The melancholic characteristics surface on the most serious episodes of the current depressive disorder and are qualified as a distinct feature of mood, in which there is psychomotor changes and an absence of pleasure in all or almost all the activities. Atypical features show mood reactivity which might become euthymic for some periods and psychotic features (delusions and hallucinations), that when presents, may or may not be coherent with the mood. The catatonia presence is more usual in hospitalized patients and points to a serious psychomotor disturbance. The depressive episode can also start at peripartum with a greater risk of developing depressive disorder in the postnatal period. Finally, the seasonal pattern is applied to recurrent episodes with the beginning of the symptoms related with certain seasons and completely free of any episodes in others. Regarding its severity are classified from mild to severe.

It's well described the relation between the high prominence of the anxiety symptoms with the worth prognosis of the depressive disorders, the resistance to treatment, the higher risk of suicide. The relation of the previous symptoms will have important implications on the therapeutic decision.

Essentially, the criteria for depressive diagnosis inclusion don´t have significant changes, with the exception of the removing of the mourning as an exclusion of the diagnosis. It's an important psychosocial stressor that can trigger episodes of major depressive disorders in vulnerable individuals with prior personal or familiar history on depressive disorder. It can be prolonged for more than two months and presenting similar symptoms to a depressive disorder that can naturally remit. In situations that a depressive major episode happens in a mourning state, the occurrence risk of somatic symptoms, (the suffering, and the suicidal ideation increases), as is similar to depressive episodes with anxiety features. These new specifiers helped to improve the diagnostic guide with the purpose of assisting physicians in the critical assessment of the symptoms of mourning, anxiety and bipolar, and its severity(11).

Excessive fear and anxiety are the common symptoms of anxiety disorders. Fear is defined as an emotional response to threat and the anxiety an anticipation of it. These two symptoms are related to behavior manifestations that can be of caution or elusive, and they can originate panic attacks if they become sever. They are differences between the normal fear and anxiety, according to its severity and duration. These explanations also appear in children, but in minor extents.

This chapter also has some variations regarding the DSM-IV, and the distinction between several classes of anxiety disorders that, can be comorbid among themselves, guided by a kind of precipitant capable of engender symptoms persistently as well by a cognitive response related with it. Females are more affected by this disorders, and once started in childhood without effective treatment are likely to persist throughout the adulthood.

Specific Phobia induces inflated apprehension, anxiety and elusive behaviors facing a specific situation or object. Phobia is distinguished from other anxiety disorders by the absence of specific cognitive ideation.

The Separation anxiety disorder in most of the cases is developed during childhood with apprehension or anxiety concerning the separation of attachment figures on an unbalanced level, which mostly is followed by nightmares and physical distress symptoms that are inadequate to their stage of development. Moreover, these children might develop selective mutism (SM), leading to persistent failure to public speaking and implying serious scholastic which cause professional and social consequences.

On the other hand, Social anxiety disorder is represented by the persistence of anxiety due to the fear in social situation related with humiliation, judgement and negative feelings by observing the others(12, 13).

Regarding Panic disorders, there are recurrent and unexpected panic attacks of variable frequency, with a sudden appearance of fear and severe discomfort that cause unsuitable concerns with a new panic attack occurrence. Common physical symptoms can be named as palpitations, shivering, sweating, asphyxia sensation, paresthesia, or even depersonalization or fear of dying. When the panic attacks are expected they become similar to other mental disorder symptom just like the other anxiety, depressive, and psychotic disorders. In this case they should be used as panic attacks specifiers on the main diagnosis, and contribute as a prognosis factor to the severity and the course of the disease going beyond the anxiety disorders.

The Agoraphobia is diagnosed when fear, anxiety and elusive are triggered by a real or expected exposition of certain situations, mainly social, such as the use of public transportation, going out of the house alone or remain in open areas which eventually make the patient avoid going out. This feature should be persistent for more than six months to be diagnosed as Agoraphobia. The symptoms can be in the form of an expected panic attack or even total isolation, depressive symptoms and frequently using alcohol and sedatives as a coping strategy.

The Generalized anxiety disorder (GAD) holds an apprehensive expectation related with several activities, mainly unequal to the real impact of the anticipated episode. At least three (one regarding children) of the following physical symptoms are present: irritability, muscle tension, restlessness, difficulty in concentrating and sleep disorder. Symptoms of autonomous excitability are not as prominent as in the other anxiety disorders, such as, Panic disorder. The psychosocial symptoms of this disease also needs to be observed for more than six months before being diagnosed.

The anxiety disorder can also be induced by Substance/Drug, whether by poisoning or by abstinence, in which severe anxiety or panic attacks prevail in the clinical aspect. Furthermore, there is Another Medical condition also capable of having a direct physiological effect in anxiety or panics attack and are severe enough to affect the patient in everyday life. It must be distinguished from the GAD in this case, there is a concern with the body, pain or the disease itself and there may be no underlying medical disease.

Specific types of anxiety disorders have different implications concerning the therapeutic results, both pharmacological and psychotherapeutically. Of notice, despite the frequent comorbidity with other mental disorders, the combination of anxiety disorder with

depressive, would cause much of difficulties, especially negatively affecting the treatments results in the long term(2, 14).

2.2 – Attention Deficit/ Hyperactivity Disorder (ADHD)

The ADHD is part of an altered chapter in the DSM-V, the Neurodevelopment disorder that is characterized by the beginning of the development period. ADHD Is more common on the male gender and although the beginning of the symptoms may occur previously, they are usually identified at school age. It is characterized by the persistent inattention and disorganization and therefore incapacity to remain focused in an activity, and/or hyperactivity – impulsivity, implying excessive activity, restlessness and unable to wait and seat still. These problems persist for at least six months, which cause damages, and excessive levels for the patient age and developmental stage, that can be extended through adulthood followed by professional and social incapacity. There are three different clinical forms of ADHD with features of inattention or hyperactivity, combined or singly.

Inattention is typically qualified as a behavior manifestation not meaning lack of comprehension but a digression in tasks, problems on focusing, lack of persistence and disorganization. Hyperactivity is mentioned as an excessive motor activity in improper situations for children and restlessness for adults. Finally, impulsivity addresses hasty and thoughtless action that can mean harm to himself.

These symptoms must be well distinguished from the defiance, oppose, and hostility behaviors, and the difficulty to comprehend instruction. Concerning inattention type, six of the following symptoms must be present in children: lack of attention to details, difficulty to sustain attention on recreation activities, even without distractions appears not to be listening when spoken to, difficulty to follow instructions until the end, problems on planning and organizing tasks, frequent refusal to do tasks that need prolonged mental effort, loss of important and necessary material, unrelated thoughts and forgets the everyday life activities. Regarding hyperactivity- impulsivity the symptoms are: unable to seat still, squirming in the seat, wiggling the feet and touching everything frequently, recurrent movements unsuitable for the situation which for teenagers and adults can be interpreted as a fidget feeling, incapacity to play quiet and orderly, talks to much and often rambles around, difficulty to wait for his/her turn, and disrupts the other activities. This symptomatic appear in different locations and environments, such as school, home, and in other activities until the age of twelve, affecting the social, professional and scholar performance.

Children with ADHD have a typical increasing of slow waves on the encephalogram (EEG) and a total decrease of the encephalic volume on the magnetic resonance imaging (MRI) although this finding is not diagnostic(2, 15).

2.3 Diagnosis Difficulties

Despite the wide use of the DSM-V in the clinical practice, we often see incorrect diagnosis, both in psychiatric consults and in general clinic(16). The clinical handling of the mental disorders goes through several important assessments before taking a therapeutic decision that must integrate all the treatment stages: the establishment and maintenance of a therapeutic alliance, a full psychiatric evaluation, and the patient safety. At this stage, specifiers are identified as mental disorders, characterizing factors for the assessment for the suicidal risk. Note that, the most challenging patients are the ones who present depressive symptoms and most of the time show low self-esteem and lack of motivation(17). Nevertheless, there are cases that different symptoms collide or they are insufficient to complete the diagnosis, which still does not mean that these individuals don't need treatment. In these cases that the diagnosis isn´t fulfill, or "non-specified", criteria such as "specified" are then applied. This nomination, other specified disorder or non-specified, is excessive due to the large heterogeneity of the clinical presentations, which require a high diagnosis flexibility depending on the physician.

To make it even more difficult, the diagnosis classification inside and among the constant chapters in the DSM-V, there is a meaningful number of comorbidities. This is due to the large range of genetic and/or environmental interactions that damage the emotional, behavioral and cognitive function throughout the human development(2).

The intercultural differences also contribute to a wide variety of individual experiences of signs, symptoms, and behaviors that makes the adjustments difficult and influence their comparison with the sociocultural standards in which the individual is part of. The normal and pathological boundaries of the symptoms and behaviors differ according to the culture, the social background and the patient's family. Phenomenology is the psychopathology movement, which includes observation and the categorization of abnormal psychiatric events, patient's internal experiences and subsequent behavior. It allows the "refinement" of the diagnosis evaluation, in which the empathy process is crucial, that requires an understanding of the patient and his personal experiences.

Consequently, is necessary to take into consideration certain foundations that equally influence the diagnosis. These foundations are neurobiological, neuropsychological, behavior and also related with pharmacotherapy. However, often it is not possible to completely distinguish the normal symptoms from the pathological criteria added to the diagnosis, mainly on the absence of obvious biological markers. It's helpful for the assessment of the treatment needs to contain additional information of relatives and people close to the patient. Many times mental disorder diagnosis aren't synonymous in the need for treatment. The last challenge found refers to the implementation of all the criteria to a great diversity of the

patients. Furthermore, there is also a gap to recognize the first symptomatic manifestation of the mental disorder(18).

Concerning the ADHD, in this classification is also difficult to distinguish between primary symptoms of and those secondary to other primary symptom. Distraction also can be present in other disorders, considering the differential diagnosis of other neurodevelopment disorders, intermittent explosive, specific learning, reactive attachment, bipolars, obsessive-compulsive, depressive, anxiety and also of personality disorder. Many times this disorders are closely related, sharing symptoms and factors of environmental risk, genetic and even the neural substrates(5). These factors can be disguised by compensation mechanisms when under supervision or when receive rewards. Although the cognitive assessment tests, like memory and executive function, aren't sensitive or specific enough to provide a diagnosis, often this function is undermined in individuals with ADHD.

On the topic of neurobiological factors, scientific evidence state that in ADHD there are brain activity alterations in the frontostriatal circuits. This abnormal activity pattern is a result of a dysfunction on the pre-frontal circuits, implied in the human behavior. In agreement, image results from imaging techniques show the existence of hypermetabolism in this regions with deregulation in the dopaminergic and noradrenergic systems(19).Dopamine is presumed to be one of the neurotransmitters that control the impulsivity observed by the phenomenology. Despite these neurochemical differences, children with different etiology are placed in the same ADHD category, and often diminishing neuropsychological measures or therapeutic effects. On the other hand, factors linked to pharmacotherapy show that ADHD is mainly responsive to dopamine agonist and that stimulating drugs present symptomatic relief.

Finally, scientific studies that use adults with ADHD, as a representative sample, are still very rare, and the ones that use children many times are constrained to clinical non-random samples, producing bias in the results.

2.4 Treatment Difficulties

In spite of the scientific breakthroughs regarding drug therapy, it is expected that 50% of the adults with medical treatment will not have a suitable response to the chosen therapy(20). The need of treatment shouldn't be restricted when the criteria are insufficient to accomplish the DSM-V classification. On the other hand, It should involve a complex clinical decision that takes many factors into consideration, namely the severity and the importance of the symptoms, the suffering and the disabilities caused by it, risks and benefits of the available treatments, the patients' capability to take care of themselves and collaborate with the therapeutic guide and etc. Hospitalization is contemplated for certain psychiatric and medical comorbidities, for unsuitable responses to outpatient care, or even situations that undermine the safety and truthfulness of the patient and the ones close to him/her(2).

Another challenge is to improve the patient's therapeutic compliance, and to do so is important to identify potential boundaries like negative therapeutic effects, and economic and/or cultural factors. Usually the depressive disorders are more difficult to reach due to the low motivation and frequent memory losses. Such features become unsuited with the required time to the acute symptomatic relief that many times lasts for four weeks.

Reduction in the symptoms is different for each disorder, but generically can be partial or total. For instance, the guidelines of the American Academy of Child and Adolescent Psychiatry (AACAP) has shown that the ADHD remission show signs such as unnecessary adjustments of the therapeutic doses, which is related with growth and non-deterioration, and the power of concentration during drug abstinence. Additionally, the therapeutic discontinuation is recommended in situations that show low levels of stress, like vacation. Still, the medication must be retaken if the performance is affected and reduced(21). The risk of recurrence is inversely proportional to the reduction time, and is bigger in younger individuals with multiple disorders, and the ones that have shown severe episode in the past or persistence in the symptoms(2).

The wide and improper use of drugs display a potential risk of dependence and toxicity with adverse effects. The WHO defines the substance misuse as a purpose, inconsistent with the medical or legal guidelines. The term "bad use" is preferable than abuse due to the lower judgment. Under the DSM-V observation, the dependence syndrome as a Substance use disorder is seen as: "… a presence of a group of cognitive, behavior and physiological symptoms that show a continuous use by the individual despite the significant problems related with the substance"(2). Self-medication boundaries that distinguish the bad use of the dependence are vague, but the diagnosis of the first is proposed only if the second is excluded. Psychotropic drugs are highly susceptible to a bad use and individuals with a low self-control are particularly prone to have a substance use disorder(22).

Psychotropic drugs are still enhancers of many physical illness, one of the main causes of death in patients with a severe mental disorder, and compromise the psychological stability. Furthermore, it seems that the greater the severity of the mental disorder is, the greater is the number of comorbidities(23). Other concerns are the access to medical help that still seems to be very restricted, and possible use of high doses of powerful psychotropic drugs in a combination scheme, with significant adverse effects(22, 24, 25).

The resource to drugs that work directly in the Central Nervous System (CNS) and in the behavior, should be grounded in two issues, the alteration of abnormal pathophysiological events in the CNS, and the mimicking of healthy neurobiological mechanisms. Here the impediment is owed to the great variety of neural circuits, anatomical areas, and neurotransmitters involved in the mental disorder that hinder the option of a therapeutic

agent. Furthermore, the psychotropic drugs act in numerous places, producing many times unexpected adverse or even opposite effects(22). The scientific knowledge of these exact physiological mechanisms, are not totally clear, complicating the reduction range of the phenotypic manifestations(26). Regarding the depressive disorder, the APA guidelines state the use of antidepressant, namely: Selective Serotonin Reuptake Inhibitors (SSRI), Norepinephrine–Dopamine Reuptake Inhibitor, Serotonin–Norepinephrine Reuptake Inhibitors, Serotonin Modulators, Serotonin–Norepinephrine Modulators, Tricyclic and Tetracyclic, and finally MAO Inhibitors (MAOIs). The APA guidelines also refer that the effectiveness of the majority of these drugs is similar and that its precise mechanism of action isn´t totally understood. An adverse effect of the antidepressant which might be potentially fatal, is a development of serotonergic disorder. Besides, they resemble drugs prone to be used improperly by the discontinuation disorder that they cause, mainly those with short half-lifetime(17, 27).

Despite the fact of being poorly understood, the depression resistant to treatment is considered when at least two failures of previous treatment are presented. The first line of the therapeutic choice is very important since antidepressants lose effectiveness after two treatment remissions, mostly making the pharmacological options exhausted. That's why, most of the times, physician handle the treatment resistance with alternative to pharmacotherapy or more powerful drugs, and consequentially with more damaging adverse effects.

The preferential psychotherapy is the cognitive behavior therapy and the interpersonal psychotherapy. It is especially suitable to detect and stop pharmacological adverse effects and for situations that compromise family or conjugal relations. Pharmacotherapy and psychotherapy combination is beneficial, mainly for chronic, critical and complex diseases(28). Even with the lack of scientific proofs of clinical effectiveness and efficacy, that many non-pharmacological therapies miss, comparative studies between pharmacological and non-pharmacological therapies in the depression treatment are very scarce, like neurofeedback therapy, but all present equal satisfactory results(29).

There are still no evidences to know when and how terminate the pharmacological therapy. The major concern still is recurrent, in which its risk is bigger in the first two months and the psychotherapy is more effective and sustainable during this phase. Discontinuation should be progressive (a few weeks to months), and avoided before events known to be stressful for the patient(22).

In ineffective response of antidepressant, the dose should be increased, and the therapy extended. Then, if these strategies still are not effective, the "augmentation strategy" is prolonged; which is adding another antidepressant from another class or other

pharmacological group, namely mood stabilizers (e.g. lithium), thyroid hormone and second generation antipsychotics. In the presence of anxiety symptoms or disabling insomnia, anxiolytics and sedative-hypnotic medication (buspirone, benzodiazepines, gabaergic [Zolpidem]) should be used. Nevertheless, In the case of failure of the psychotherapy, the intensity and frequency of the sessions must be increased or the therapy should be adapted, and also the quality of the therapeutic alliance should be evaluated. The antidepressant dose must be continuous during a period of four to nine months, as well as the psychotherapy continuation in question, in order to achieve total remission of the symptoms.

For Anxiety Disorders the same guidelines show the following therapeutic objectives: reducing the intensity and frequency of the panic attacks, the anticipatory anxiety, agoraphobic avoidance, having an excellent and total remission on the symptoms, and returning to the level of pre-morbid functioning(30). The first pharmacotherapy approach to the anxiety disorders is antidepressant, such as SSRI, serotonin–norepinephrine reuptake inhibitors, tricyclic. Of importance that the first two groups more safe and with less side effects. In the absence of depressive disorder or the resistance to antidepressant treatment, monotherapy with Benzodiazepines can be recommended. Even though this psychotropic class was used before as the first choice for many disorders, nowadays is mainly considered as a second or third choice.

Despite having a small effect on the psychiatric factors (e.g. concern, apprehension…), benzodiazepines are suggested as an adjunctive therapy to the antidepressants, since they are extremely helpful in the relief of the somatic anxiety symptoms. It also presents effects in GABA receptors, sedatives and anticonvulsant, which might make them appealing to the patients who are in desperate need of the symptomatic relief(26). With the high risk of relapse, it is recommended to extend pharmacotherapy for at least one year, followed by gradually reduction and then termination. This issue is more likely to occur with the benzodiazepines that provoke withdrawal symptoms. In this case, psychotherapy is seen as adjunct of the pharmacological termination(30, 31).

The AACAP guidelines for ADHD recommend the use of brain stimulators. However, the great challenge is to decide between pharmacotherapy or behavior therapy or even the combination of both, which should be grounded on empiric evidences(21). Behavior therapy is suitable as an initial treatment when the ADHD shows mild symptoms, or parents reject drug treatment, or when there are inconsistencies between parents and teachers repertoire regarding the clinical presentation. It’s important to assess the family dysfunction due to the influence that has on the evolution and on the effectiveness of the treatment.

There are two kinds of treatments recommended for the pharmacological treatment in the ADHD, the methylphenidate (MPH) (D- and DL- methylphenidate) and amphetamines

(dextroamphetamines and mixed salts amphetamines). Although the second one is more beneficial due to the minor frequency of the dose, they both have similar efficacy and have the form of immediate or prolonged release. The SSRI are an adjunct option in the cases that show concomitant drugs abuse or severity in the stimulators side effects, such as emotional lability, tics, weight loss or insomnia. The initial dose should be adapted to the patient and gradually increased until the regulatory functioning is achieved. In case of failure in the response to the adjusted pharmacotherapy, the diagnosis must be reconsidered. Nevertheless, the AACAP guidelines have recommend behavior therapy before any kind of medication, such as beta blockers, bupropion or tricyclic antidepressants.

In the presence of a bad response to the pharmacological treatment, meaningful comorbidities or stressor factors in family household, it has shown that adding psychosocial therapy to the treatment is highly beneficial. These patients are prone to worsen the clinical picture, despite the accurate prescription, and need a bigger number of medical appointments comparing with the uncomplicated cases that only needs two to four sessions per year(21).

Chapter 3

Neurofeedback

Neurofeedback is a procedure that induces therapeutic effects in a wide variety of mental disorders and also improves the performance of the healthy patients. The advantage of this treatment is the absence of pharmacotherapy and their side effects. It is a revolutionary neurotherapy method with a totally different way to approach medical conditions, such as ADHD, depressive and anxiety disorders, insomnia, and brain injuries, and etc(32). Its mechanism is defined by the neuroplasticity, causing new intracerebral connections. aiming to overcome symptoms linked to several neurological conditions.

The history of this procedure has come from more than 40 years of clinical research. The first work was reported in 1969 by Joe Kamiya, who explored neurofeedback as an effective adjuvant in the anxiety decrease(32, 33). Neurofeedback is based on operant conditioning, in which the individual receives "rewards" (feedback) for certain behaviors. Through this conditioning we can associate the behavior to its result, affecting the probability to reoccur. When the feedback is a positive reinforcement, increases the probability of associated behavior happening again. In the case of NFB, the patient receives feedback for producing the correct type of brain waves. The reward can be in forms of auditory, visual, or both, depending on the patient, type of the training protocol, and equipment used.

In a neurofeedback training session, electrodes are placed on the patient scalp, in a non-invasive and painless way, to detect and measure brain waves. There isn't any kind of input, since the electroencephalogram (EEG) is used only to instantly give information of the brain activity(34). The placement of the electrodes is defined by the International 10-20 EEG placement System, in which letters and numbers are given to specific places of the scalp dividing it into 10 and 20% portions. Odd numbers are circumscribed to the left side of the head and even numbers to the right side. The letters relate with different lobes of the brain: F – frontal lobe; T- temporal lobe; P – parietal lobe; O – occipital lobe. The letters C regard the central vertex composed by sensorimotor cortex. The letters Z show the brain midline corresponding to the medial longitudinal fissure that separates the right hemisphere (RH) from the left hemisphere (LH). In addition, both ears are used as reference points, named as A1 (For the LH locations) and A2 (For the RH locations)(32).

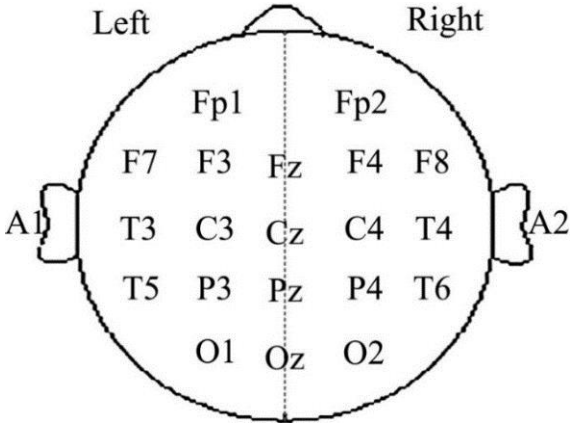

Fig. 1 Locations of EEG scalp electrodes according to the international 10–20 system (35)

A brain wave pattern is then displayed on a screen of the software system connected to it. This system is responsible for reading the brainwaves, analyzing it in real time, and immediately sending a feedback that signals the brain when the correct brain activity pattern is being produced. In this process, the patient, while sitting in a comfortable condition, should try to play a computer game only by thinking. Each time the brain emits the correct brainwave the patient gains a score in the game. This is a reinforcement that trigger the reward system of the brain and causes excitement and motivation in both the brain and the patient to try harder to be able to get more scores in the game. After a certain amount of sessions, experiencing and practicing, the brain learns what is the correct and desired brainwave. This learning pattern induces the production of permanent new neural connections and synapses. All these change toward the correct brainwave production guide the brain to the optimal condition and increased functionality. Subsequently, the patient learns how to emit the correct brain wave sub-consciously(36).

The neurological deregulation refers to the abnormal production of brain waves. The purpose of the neurofeedback is to correct this irregularity of the brain waves that can be caused by bad nutrition, physical or emotional trauma, stress, drugs or toxins. The abnormal pattern of brain waves can result in pathological manifestations and each manifestation is connected to a specific pattern and to an anatomical brain region. The imaging techniques state that disorders like anxiety and depression present metabolic and electrical differences in both hemispheres.

3.1 Anatomical and Functional Notes

It is known that the frontal lobe is responsible for the immediate and sustained attention, executive functions, empathy, social skills, emotions and memory. It has strong links with the amygdala, an integral part of the limbic system that controls emotions and behavior. Excessive fear owing anxiety disorder is related with the amygdala hyperactivation, with

strong influence on the prefrontal cortex. Neurofeedback training on this lobe (locations such as Fz) have an impact over the social behavior of the person.

The parietal lobes have been identified as the association cortex, in which the peripheral feelings from skin, such as cold/warmth, pain, and touch are interpreted. The RH parietal lobe is mostly involved in spatial recognition, and left and right distinctions.

The left temporal lobe is linked to verbal memories, word recognition, reading and writing. It is also connected to music, object and facial recognition and social parameters. Due to the proximity of the limbic system, these two lobes also influence the emotion (amygdala) and the memory (hippocampus).

On its turn, the occipital lobe is related to the visual function and also has numerous connections, which spread until the amygdala.

Is also important to mention the sensorimotor cortex, divided by the central sulcus into the primary motor cortex located anteriorly and the somatosensory cortex located posteriorly. This cortex is not restricted to motor and sensory functions; it also integrates cognitive processes. Adjacent to it lies the cingulate cortex, cortical portion of the amygdala. The deregulation of these two areas implies a bad function in ADHD patients and the application of the neurofeedback training on Cz influences these two regions.

Regarding the neuronal activity of the brain, we can mention the five main types of brain waves: Delta, Alpha, Beta, Theta and sensorimotor rhythm (SMR) waves.

Delta waves are the most slow (1-4 Hz) and are produced during the deep sleep stage, being involved in the healing process in adults and growth in children, for their influence on the production of growth hormones.

Theta waves (4-7 Hz) are characteristics of the mental state precisely before the deep sleep and are connected with creativity. Patients with ADHD produce too many theta waves that, regarding the behavior, show an incapacity to pay and keep attention for long period.

Alpha waves (8-12 Hz) are produced in states of meditation and their increase is associated with physiological benefits, particularly lowering of the blood pressure, minoring the severity and frequency of migraines and increasing energy levels. There is a Normal Alpha Asymmetry that occurs in healthy individuals who produce more alpha waves in the right hemisphere than in the left.

Beta waves (12-30 Hz) are related with mental states connected with problem solving, attention and warning. When the deregulation of the brain waves patterns is showed through

a decrease of beta waves, inattention symptoms can be experienced, just as in ADHD cases. In the opposite sense, excess of beta waves causes symptoms like hyperactivity, anxiety and impulsivity. In these waves can also be found Normal Asymmetry in healthy individuals that produce more beta waves in left hemisphere than in the right(4, 15).

Finally, SMR waves are produced in large quantities in states of maximum alert. They produce a calming effect throughout the body.

3.2 – Applications of Neurofeedback

Although it is ambiguous in the spatial resolution, the initial 19 channel quantitative EEG (gEEG) assessment, identifies neurophysiological abnormalities, with a good temporal resolution. Neurofeedback focus on frequency and amplitude more than the wave morphology, and also its application is based on changing of amplitude (intensity) of a certain frequency band. The EEG signals being emitted from the brain are amplified and filtered in small frequency bands that display the different types of brain waves(32).

Then, the recorded 19 channel qEEG data will be statistically analyzed by a specific software, and will be organized in topographic brain maps. In this way electrophysiological disorders are correlated, the locations of abnormal production are identified, and targets are marked to apply neurotherapy with the purpose of normalizing such variants(37). This assessment is performed by the comparison of the qEEG of each individual with a great database that includes a large number of healthy assigned individuals without the influence of ethnic or cultural factors.

This is a powerful tool that the qEEG offers to identify the entitled regions of interest and the application targets. Establishing a relation between specific anatomic locations and symptoms, is able to add valuable information to the diagnosis, that sometimes is not accurate due to the symptoms overlapping. All these parameters influence the decision to determine the protocol adjusted to the patient(34, 38).

3.3 Protocols

There are 2 different types of training with neurofeedback technique:

One is the classical method, called amplitude training and the other one is according to a normative data base training, called Z score training.

Amplitude training can be done by one, two, or four channels. For any of these choices we need an electrode that makes a ground connection, which can be located in any location on the scalp, and 1 or 2 reference electrodes, which can be located on the earlobes. In 1 channel training we will have only one active electrode for training which can be in any of

brain hemispheres. And in 2 or 4 channel training, we will have 2 or 4 active electrodes for training, which can be designed to train both hemispheres at the same time. In this way the concept of coherence becomes important concerning the communication between different neurological regions. Synchrony occurs when two anatomical regions are in the same phase of brain activity, being by the increase or decrease of waves production. Asymmetry, as mentioned before, is a quantitative difference of the brain waves production between hemispheres and it can be physiological or pathological, Asymmetry disturbances are identified in depressive and anxiety disorders(32).

To gain a reasonable result and a stabilized brain condition, numerous neurofeedback training sessions are needed, even if after a session there is a transitory relief. The progress of the clinical picture is seen by the desired change in the bandwidth amplitude, that only becomes permanent after a certain number of neurofeedback sessions. During the neurofeedback sessions the threshold of the task challenge must be kept constant and assessed permanently. The most reliable manner of doing it is through the percentage of success of the patient, in a way that doesn't make the training to much easy or difficult, with a high probability of demotivation by the patient.

3.4 – Therapeutic Effects of NFB

Depressive disorders are related with an alpha deregulation, in which there is a productive excess of alpha waves and the brain is considered as being inhibited. On the other hand, anxiety disorders are more connected with excessive beta production, in which there is fast processing speed and the brain is considered like over-excited(32).

Specifically for ADHD, neurofeedback was considered as effective (39). In this disorder there is an increase of the cortical activity of slow waves (theta) and/or a decrease of the beta activity resulting on an increase of the theta/beta ratio. The brain is considered less excited with a slow processing speed. The anterior cingulate cortex is also involved in this disorder(15, 40, 41).

Establishing a good protocol is sometimes difficult, and sometimes a different types and locations of training is needed to be effective to decrease similar symptoms and sometimes on the same patient. It also depends on the therapist extensive experience and of the equipment.

Usually, protocols like amplitude training, theta down training in the central regions (cz) is beneficial. In this case, the success of the training is achieved when the theta waves production is lower than a specific threshold, determined according to the individual information of the qEEG. Thereby, the feedback is only given to the patient when the

amplitude of the theta waves is below a certain value. For individuals with hyperactivity symptom SMR up training protocol is necessary to reduce the excessive motor activity(34).

In the Z-score training, the base of the treatment is formed by instantaneous comparison of the pattern produced by the patient with the one produced by the standard data base, through statistics multivariable of Z-score. These are computed in real-time while the EEG recording is happening, and determine the continuous deviations of the Gaussian curve regarding the standard(42).

The results of these two types of protocols are comparable concerning the decrease of the ADHD symptoms(15, 42).

Chapter 4

Helpful Perspective

It still is not possible to establish a precise comparative relation between effectiveness of the gold standard therapy for ADHD (stimulant medicines) and the Neurofeedback application. As noted previously, the main guidelines recommend the use pharmacotherapy and/or psychotherapy. On the other hand, there is significantly rising number of studies that show the efficiency of neurofeedback therapy on certain patients(43). For example, the obtained results on a controlled and randomized clinical trial of 102 children have showed effectiveness in the symptomatic relief in these children only through neurotherapy. More interestingly, other studies have reported the persistence of these beneficial effects for a period of years. Another randomized and controlled study with 6 months of follow-up, in a sample of 23 children with ADHD, gave a group only neurofeedback training and to another group only methylphenidate therapy. Nevertheless, it showed that there were no significant differences between groups regarding sex, age, IQ and ADHD subtype, in the way they experienced the relief(40, 43, 44).

The methylphenidate is a stimulant that acts on the dopamine and norepinephrine reuptake inhibition, and has been widely used in the clinical practice for the symptomatic control of ADHD. The mechanism of action of this drug is still not fully understood. Due to the consequent increase of catecholamines, the methylphenidate has stimulating effects over CNS increasing the patients' alert state(26). In short-term, this drug could often cause the following side effects: insomnia, loss of appetite, irritability and migraines. In a long-term, undesirable effects are also shown after months or even years of stimulant drugs use – repercussions regarding the growth, loss of appetite, psychotic and maniac symptoms, increased risk of suicide attempt, cardiovascular effects and even changes in the brain structure(38).

Of notice, the neurofeedback protocols related with symptomatic control of ADHD need a full understanding concerning the exact beneficial mechanisms. However, it has been reported that in a non-invasive way neurofeedback induces neuroplasticity, with development of neural interconnections and increase of the patient's alert state. Furthermore, neurofeedbackimplies symptomatic relief of attention and hyperactivity symptoms based on reports of family members of children with this disorder(29, 41).

Chapter 5

Conclusion

All together we can conclude that neurotherapy should be regarded as a new practice worthy of interest. This work led to an understanding of an alternative approach to mental disorders, which are influenced by a great variety of sociocultural, genetic and metabolic factors.

The clinical reports of the psychiatric disorders are highly diversified and could lead to uncertain judgments from the physician. Sometimes, diagnostic assessment of mental disorders can be exhaustive, complex and vulnerable to doubts due to symptoms overlapping. To overcome this uncertainty new techniques that could clear some doubts regarding the human errors are necessary, which could be complementary on the current DSM-V.

On the other hand, factors such as symptoms resistant to pharmacological or psychotherapeutic treatment, relapses after discontinuation, improper use, or dependence syndrome illustrate the necessity of new techniques that could overcome the barriers of the current clinical practice. In situations of these kind of uncertainty, the choice of a therapeutic alternative can be problematic. For decades, the treatment for many mental disorders is psychotropic medication very susceptible to improper use, dependency and side effects. Allied to psychotropic discontinuation, the withdrawal syndrome is an additional aggravating factor that can compromise the clinical practice.

ADHD was chosen to do the therapeutic comparison due to the large number of studies assigned to this disorder. It's one of the world's main pediatric neuropsychiatric disorder and seriously affects children's emotional, social, and educational component. Additionally, induce a high social stigma, often difficult to overcome, that complicates the therapeutic response.

Neurofeedback has been investigated by the clinical practices since 1960. This neurotherapy rises from the merging technology, electronics, behaviorism, physiology and neurology with the purpose of consciously recognize physiological processes. Through a detailed analysis of the brain functions, a useful tool could be provided for situations whose clinical phenomenology involves a certain ambiguity. With the qEEG technique is possible to identify and relate a certain brain region to a symptomatic expression of the mental disorders. With this information, the DSM diagnostic classification could be complemented with specific imaging data.

The different neurofeedback training protocols gives the change that only the identified anatomic region to be the training target and not the other locations which are healthy and functional. Regarding the brain activity, this approach to the standard allows a symptomatic decrease through the capacity to control the brain activity. Because the brain cells go through neuroplasticity, the structural changes that happen after the recommended training are persistent. In children with ADHD, the neurofeedback applications were effective in order to maintain attention, impulsivity control, and to decrease restlessness. This effects are noticeable in different environments such as school or at home, allowing the patient's symptomatic relief, a lesser predisposition to social stigma, a better understanding with the peers and a greater capacity to tolerate the mental disorder. Thus, this neurotherapy can be seen as a beneficial alternative, comparatively to psychotropic medication, in the ADHD symptomatic relief. In situations whose safety profile in the diagnostic assessment and therapeutic option might be doubtful, neurofeedback could be useful to control important symptoms without the risk of developing side effects.

Finally, it's possible to conclude that neurofeedback can be considered as a supporting therapy to pharmacotherapy for the mental disorders. Still has a long way to go in terms of research but with a positive prospect ahead. The boundaries that have been found during its effectiveness trials are due to methodological impairments of many of the conducted studies, for not being randomized – due to either lack of relevant samples or the insufficiency of the researched features. Furthermore, the multifactorial clinical presentation and etiology hamper the reach of all the changeable factors. It's necessary to carry on the efforts to overcome the mental disorders stigma and achieve treatments that provide a safe and effective response.

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