Chapter 12

Non pharmacological treatments

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Abstract

In clinical psychiatry, we dispose of different non-pharmacological approaches, such as somatic treatments, chronobiological treatments, cognitive remediation and psychotherapy.

Somatic treatments include transcranial direct current stimulation (tDCS), transcranial magnetic stimulation (TMS) and electroconvulsive therapy (ECT). These techniques, which exert their function through the modulation of cortical excitability, find an application in many psychiatric disorders, but mainly in resistant depression.

Chronotherapies, a group of non-pharmacological therapeutic approaches to mood disorder treatment, are rooted in the hypothesis of chronobiology aetiopathogenesis of psychiatric disorders (mainly mood disorders). Chrono-biological treatments include light therapy (LT), sleep deprivation (SD) and dark therapy (DT). While LT and SD are mainly used in depression, DT finds a clinical application in mania.

Cognitive Remediation (CR) is a set of interventions based on behavioral training whose goal is to enhance neurocognitive abilities. This technique finds its main application in schizophrenia.

Psychotherapy approaches have a proved effectiveness for the treatment of various psychiatric conditions when combined to psychopharmacological treatment. The two main approaches are Cognitive-Behavioral Therapy and Psychodynamic Therapy.

Keywords: neurostimulation, somatic treatments, chronobiology, chronotheraputics, light therapy, sleep deprivations, cognitive remediation, psychotherapy.

12.1. SOMATIC TREATMENTS

Introduction

Different therapeutic approaches have been developed, both pharmacological and non-pharmacological, including chronobiologic, psychological interventions and neuro-stimulation techniques. Even when adequately effective, current antidepressants require several weeks to achieve at least a clinical response and, ideally, a complete remission of symptoms. The rate of response to antidepressant treatment is of 50-70% after one antidepressant monotherapy.

Unfortunately, it is estimated that up to 30% of depressed patients might fail to achieve clinical remission after multiple sequential pharmacological treatments, a condition named treatment resistant depression (TRD). Various TRD definitions have been proposed, according to the number of pharmacological and non-pharmacological trials failed. However, it is generally accepted to have tried at least two medications at an adequate dosage for an adequate duration without any response or with rapid loss of effectiveness, especially if the drugs belong to different pharmacological classes.

Lack of standardized definition of treatment failures and the absence of a standardized definition of the clinical entity treatment-resistant depression (TRD) has been shown to lead to confusion in clinical practice.

TRD is defined as MDD that does not respond or remit to one or more antidepressant trials of adequate dose and duration.

BOX 1. TRD risk factors

TRD risk factors are summarized in:

- Comorbid general and psychiatric medical disorders
- Severe intensity of depressive symptoms
- Suicidal thoughts and behaviour
- Adverse life events
- Personality disorders
- Early age of onset of major depression (eg, age <18 years)
- Recurrent depressive episodes
- Low socioeconomic status

There are two classification of TRD which are generally accepted**,** the first is Thase & Rush (1997) Stadiation with five degrees of treatment resistance:

BOX 2. Thase & Rush (1997) Stadiation

0.	Pseudo-resistance. Wrong doses and/or timing.
I.	1 AD Trial
II.	2 AD Trials from different classes
III.	2 AD Trials, at least 1 TCA
IV.	3 AD Trials, at least 1 IMAO and 1 augmentation
V.	ECT

The second classification of TRD is Souery where the author introduced the criteria of duration of treatment not defined in Thase e Rush stadiation where they considered the different classes of compounds

BOX 3. Souery (1999) Stadiation

A. Treatment Resistant Depression

Not responder to at least 2 AD trials.

TRD1: 12-16 weeks

TRD2: 18-24 weeks

TRD3: 24-32 weeks

TRD4: 30-40 weeks

TRD5: 40-52 weeks

B. Chronic Resistant Depression

Period of 12 months.

After defining the clinical entity of treatment-resistant depression and above all after staging according to the two classifications described above, a neurostimulation treatment such as electroconvulsive therapy, rTMS or tDCS can be used.

Non-invasive brain stimulation

Introduction

Researchers have been trying to identify effective methods to modulate intra-cortical and sub-cortical excitability for almost a century. The purpose of these procedures was to find out non-invasive tools

that could act as brain stimulators aimed at specific cerebral targets in fully awake subjects without inducing generalized or partial convulsions. Different methods have been investigated, using either electrical or magnetic fields to modulate neuronal excitability and firing. Experiments on this field date back to the early 20th century, when electrodes directly placed over the exposed grey matter of animal models were first used to deliver electrical pulses. When applied at a threshold intensity over the primary motor area, these stimuli induced a twitch in the contralateral limb after a 1 to 2 ms latency, a process later defined as Motor Evoked Potential (MEP). Decades later, this research was translated in humans using an electrical circuit composed of two electrodes over the scalp attached to a battery to stimulate the underlying cortical neurons. Interestingly, this circuit elicited the same peripheral muscular twitching in conscious subjects in a non-invasive fashion, laying the background for modern neuro-stimulation techniques, such as Transcranial Electrical Stimulation (TES). Unfortunately, TES resulted poorly tolerated due to discomfort and pain in the stimulation area caused by direct stimulation of the superficial muscular structures via collateral circuits. In the search for alternative techniques, Transcranial Magnetic Stimulation (TMS) emerged as a viable option with comparable results and fewer adverse reactions in 1990, with an increasing number of applications in both clinical and research settings. On the other hand, TES safety and tolerability were improved using direct, low-intensity currents, identifying a more feasible device called transcranial Direct Current Stimulation (tDCS).

12.1.1. TRANSCRANIAL DIRECT CURRENT STIMULATION (tDCS)

Principles and mechanisms of action of transcranial direct current stimulation

Pathophysiology of many neuropsychiatric diseases concerns alterations of neuroplasticity and cortical excitability. Non-invasive brain stimulation (NIBS) is an effective and highly tolerated approach to act on those aspects and modify cortical activities; one of the most valuable therapeutic NIBS approach is transcranial direct current stimulation (tDCS). Since many decades it has been known that neural activity could be modulated by the direct application of current on nervous tissues, but in the late 1960s was demonstrated how that brain neural activity or cortical excitability could also be altered via transcranial application of a direct current.

Even if the discovery of tDCS dates back more than 60 years, only in the last 20 years have its effects and potential been studied. The main tDCS effect on neurons is a subthreshold modification of their resting membrane potentials (or resting voltage) in sense of depolarization or hyperpolarization; but it not only changes their membrane potential and firing rate but also reduces membrane resistance.

This excitability modulation persists for more than one hour after the end of a single stimulation of several minutes. If the “synaptic effect” of tDCS may last for hours, its “non-synaptic effect” might contribute to explain the long-lasting effects of tDCS through the hours, days and weeks. Repeated tDCS stimulations induce neural plasticity, acting on various neurotransmissions (NMDA and GABA), modulating transmembrane ion conductance, changing function and conformation of various axonal molecules, membrane structure, cytoskeleton, and axonal transport. tDCS has a local effect, but it also acts on functional connectivity, synchronization, and oscillatory activities modulating various neuronal networks, both at cortical and sub-cortical level. The effect of tDCS on cortical excitability (depolarization or hyperpolarization of resting membrane potentials) depends on the relation between the current flow direction and the axonal fibre orientation. So, by modifying the electrode polarity, it is possible to determine whether the tDCS field is excitatory or inhibitory (i.e., anodal tDCS excitatory, cathodal tDCS inhibitory). If it’s more understandable the relationship between stimulation polarity and type of modulation (excitatory or inhibitory), it’s unclear the relationship between other stimulation parameters: strength of stimulation, duration of stimulation, session repetition timing. For example, the relationship between intensity of stimulation and the biological effect produced appeared to be non-linear: doubling intensity from 1 mA to 2 mA appeared to reduce the inhibition produced by cathodal tDCS on primary motor cortex (M1). The clinical effect of tDCS is also strongly affected by to some technical and neuroanatomical aspects: electrode size, their shape and their placement primarily influence the diffusion of the current through the scalp and thus the induced electric field into the brain. Taking into account all the aspects seen above, many different stimulation protocols were designed and studied thorough the years.

tDCS is generally well-tolerated and it is associated with relatively minor side effects, including tingling and/or itching sensation at the stimulation site, moderate fatigue, headache, nausea, insomnia, induction of hypomania.

Therapeutic indications and clinical use

Even if tDCS is currently not FDA approved, in the lasts two decades tDCS was not only widely used as a tool for neuroscience research but was also applied as treatment of various neurological and psychiatric disorders with different results, including pain (neuropathic pain, migraine, fibromyalgia), Parkinson’s disease, stroke, Aphasia, Epilepsy, Alzheimer's disease, Depression, Schizophrenia, Substance abuse, addiction and craving.

BOX 3. Recommendation Level

Level B (probable efficacy)

- Anodal tDCS of the left primary motor cortex (M1) (with right orbitofrontal cathode) in fibromyalgia
- Anodal tDCS of the left dorsolateral prefrontal cortex (DLPFC) (with right orbitofrontal cathode) in major depressive episode without drug resistance
- Anodal tDCS of the right DLPFC (with left DLPFC cathode) in addiction/craving

Level B (probable inefficacy)

- Anodal tDCS of the left temporal cortex (with right orbitofrontal cathode) in tinnitus
- Anodal tDCS of the left DLPFC (with right orbitofrontal cathode) in drug-resistant major depressive episode.

Depression

The rationale about the efficacy of tDCS as treatment of depressive disorders is largely the same of rTMS therapy; it is based on the knowledge of interhemispheric imbalance of neuronal activity between left and right dorsolateral prefrontal cortex (DLPFC) and ventromedial prefrontal cortex areas, functional and structural abnormalities in the DLPFC, amygdala and hippocampus in depressed patients.

As for rTMS, high-frequency on left DLPFC or low-frequency on right DLPFC, the current tDCS antidepressant approach is to enhance neural activity in the left DLPFC or to reduce neural activity in the right DLPFC, with anodal and cathodal stimulations respectively.

One of the most effective protocol in the treatment of major depressive episode received a Level B of probable efficacy: 10 sessions of 20 minutes with 2 mA anodal stimulation of the left DLPFC with a right orbitofrontal cathode.

Many studies on healthy subjects have investigated the tDCS effect in the cognitive performance modulation showing a positive effect of tDCS on working memory, verbal fluency, language processing and more complex cognitive functions. In contrast, only few studies have investigated the

impact of tDCS on cognitive functions in depressed patients: in particular tDCS appeared to be effective in reducing both depressive symptoms and cognitive impairment when compared to sham in elderly depressed patients with cerebrovascular disease (vascular depression).

Schizophrenia

Many studies agree on the relation between some of the most drug-resistant symptoms of schizophrenia, as auditory verbal hallucinations and negative symptoms (e.g., avolition, alogia, or emotional withdrawal) and specific alterations in brain activity and connectivity.

Auditory verbal hallucinations and negative symptoms were linked to a frontotemporal connectivity alteration and hypo-activity of DLPFCs. Auditory verbal hallucinations were related to a hyperactivity in the left temporo-parietal region too.

Considering this neurophysiological background, different therapeutic protocols based on the concept of excitatory anodal stimulation versus inhibitory cathodal stimulation were hypothesized: anodal stimulation combined with a cathodal stimulation on the hyperactive left temporo-parietal region; a different montage consists in deliver a bilateral stimulation to both DLPFC regions: anodal stimulation to the left DLPFC and cathodal stimulation to the right one.

Anyway, the results obtained made no recommendation about the efficacy of tDCS to relieve schizophrenia symptoms, either positive or negative.

Substance abuse, addiction and craving

Dysfunction of inhibitory control mechanisms and reward mechanisms are the core of disturbances related to abuse, craving and addiction to different substances such as alcohol, drugs, food and nicotine. tDCS, acting on the DLPFCs, seems to regulate the activity of these systems in patients with various types of addiction.

Bi-hemispheric DLPFCs tDCS (anode on the right DLPFC and cathode on left DLPFC) received a Level B of probable efficacy in reducing craving in patients with various types of addiction.

A different montage with the anode over the right DLPFC and the cathode over the left supraorbital region appeared to be effective in reducing food craving since the first tDCS session; this effect seems to last for a month after a five-day protocol. Anyway, these results are preliminary and do not make a recommendation.

12.1.2. TRANSCRANIAL MAGNETIC STIMULATION (TMS)

Mechanism of action

Following the Maxwell-Faraday Equation, TMS relies on the fact that a time-varying magnetic field is always accompanied by a spatially varying electric field and vice versa. Hence, an electrical current flow through a wire TMS coil generates a concomitant magnetic field with a perpendicular orientation. Rapid changes in the magnetic field (as with brief single pulses) determine the induction of circular electrical currents in the underlying area, oriented on a plane parallel to the original current flow. When applying the coil tangential to the scalp at a threshold intensity, the resulting current reaches cortical neurons, lowering their firing threshold and ultimately inducing focal action potentials. The concomitant recruitment of a sufficient number of neurons beneath the stimulation area finally results in axons depolarization, consequently propagating the signal alongside all functionally connected neural networks involving both cortical and subcortical structures in the Central Nervous System (CNS) and Peripheral Nervous System (PNS).

The choice of the appropriate coil is crucial to the application of TMS. Changes in shape and positioning determine significant variations in the spatial distribution of the magnetic field, inducing different effects. Two factors should be taken into consideration: focality of action and depth of stimulation. Circular and figure-of-eight coils are the first introduced and most commonly used. The former generates a circular magnetic field encompassing larger areas with lower-intensity but widespread distribution; the latter, instead, allows for a focal and more powerful stimulation by combining two circular magnetic fields (eight-shaped) at their intersection point, with a resolution of approximately 1 cm^2 for commonly used coils. In both cases, the coils can be adapted to different cerebral areas by simply moving them along the skull. However, they show significant limitations in the spatial distribution of the magnetic field. Its intensity correlates inversely with the distance from the coil, showing a rapid decrease after few centimetres, with further interpersonal variations based on the attenuation by superficial structures (musculocutaneous layers, skull, and meninges). Therefore, the direct effects of these coils are limited to cortical stimulation; subcortical structures, instead, can only be consequently involved as part of functionally integrated networks. New coils have been introduced to overcome this limitation, with the capability to reach deeper regions within the CNS directly (e.g., limbic system). The double cone coil, for instance, is composed of two circular coils oriented in a conic structure, with the apex at their intersection. The resulting magnetic fields develop perpendicularly, interacting with each other more deeply than the classic figure-of-eight coil, allowing for a stimulation in areas located below the cortex. More recently, the same principle was applied to more sophisticated coils, namely H-coils, presented as helmets composed of multiple

radially oriented coil loops. The final effect derives from the contribution of each loop intersecting at deeper cerebral regions, which are stimulated directly. More than 14 H-coils exist, differing in shape and coils orientation according to the stimulation area. Even though highly effective at deeper regions, H-coils are more expensive than classical coils, with lower adaptability to the site of stimulation and reduced focality of action.

No coil is generally preferred over the others, but the choice varies according to their availability, cost-effectiveness, and the individual protocol of stimulation, which should be tailored to each patient.

Stimulation protocols

TMS is a versatile and multifaceted technique, allowing for both diagnostic and therapeutic uses. Since the identification of depolarizing properties of single, brief magnetic stimuli, TMS has appeared as a promising tool adapted to a large variety of situations. If single pulses exert immediate effects with a fast distribution through functional networks in CNS and PNS but a rapid resolution within milliseconds ("online" effect), repetitive patterns of stimulation can elicit a neuroplastic modulation of the cerebral activity ("offline" effect) through long-term potentiation (LTP) and long-term depression (LTD) mechanisms. Online effects proved highly useful for diagnostic purposes, especially in the neurological field. The application of single pulses over target cortical regions allows for assessing the integrity of neural pathways by eliciting immediate sensorimotor reactions (e.g., motor evoked potentials). On the other hand, offline effects opened to the chance of generating long-term modulations of the neuronal activity with therapeutic potentialities. Repetitively administered stimuli create patterns of activation or inhibition of functional networks that persist beyond the stimulation session. As a result, repetitive TMS (rTMS) can induce stable modifications of the neuronal activity, potentially regulating functional disruptions responsible for both neurological and psychiatric conditions. A specific combination of parameters determines the pattern of rTMS, which, in turn, defines its clinical effect. Virtually infinite stimulation protocols can be applied, each requiring careful validation of efficacy and safety. The following parameters define a complete rTMS protocol:

- Site of stimulation
- Intensity of stimulation (SI)
- Frequency of stimulation
- Train of repetitive stimuli and Inter-Train Interval (ITI)
- Total number of pulses per session

- Number of sessions and distribution over time

The site of stimulation is the main parameter to consider when establishing the proper rTMS protocol. Data gathered from functional imaging studies are crucial in determining neurobiological targets for each neuropsychiatric disorder. Areas of stimulation can be located both in cortical and subcortical regions that pertain to various functional networks in the brain, requiring an adequate choice of the coil type according to the depth and width of the site. Within the psychiatric field, prefrontal regions are among the most investigated, especially the left and right dorsolateral prefrontal cortex (DLPFC) implicated in depression, anxiety disorders, and addiction in association with overactive limbic structures. DLPFC is a small functional region located in the frontal cortex directly accessible with focal coils, such as the figure-of-eight one. Other areas investigated include the parietal and the motor cortex, usually targeted in neurological disorders.

After the stimulation site has been identified together with the most appropriate coil type, the proper intensity of stimulation should be assessed for each patient. SI depends on multiple biological variables, such as the thickness of the superficial structures (e.g., skin, skull, and meninges), the intrinsic neuronal reactivity, and possible pharmacological agents that modulate cortical excitability. SI is defined for each protocol as a proportion of the Motor Threshold (MT). MT is the measurement of the minimum intensity of the magnetic stimulus able to elicit neuronal depolarization over the primary motor cortex after a single pulse, observable as a muscular twitching in the contralateral hand. Based on the assumption that the same intensity to depolarize neurons in the motor cortex apply to the other cortical regions (e.g., DLPFC), SI is usually calculated within a range of 80-120% of MT, according to the specific protocol.

When the appropriate SI has been calculated for each subject, rTMS delivers repetitive trains of stimuli with variable frequency. The modulating effect of TMS depends on the frequency of stimulation by the induction of different patterns of glutamatergic receptors activation/deactivation. Low frequencies (<5 Hz) reduce the functional connection between neurons at the synaptic level, ultimately leading to LTD mechanisms, while high frequencies (>5 Hz) strengthen cerebral networks through LTP mechanisms. The proper frequency relies on functional imaging studies, revealing overactive or hypoactive brain regions that require rebalancing. Low-frequency rTMS is usually administered continuously for the whole session, while high-frequency rTMS necessitate intermittent stimulation, with trains of pulses alternating with resting periods (ITI) to avoid the spread of the depolarizing signal to other regions (e.g., convulsions). More recently, a new paradigm of rTMS called Theta Burst Stimulation (TBS) has been introduced. TBS consists of bursts of extreme high-frequency stimuli (50 Hz) instead of single pulses, continuously repeated at low frequencies with inhibition properties (cTBS) or intermittently at high frequencies with stimulating properties (iTBS).

If TBS proved as effective as rTMS in multiple non-inferiority trials, it dramatically reduced the duration of the session from 20-40 minutes to 1-3 minutes, improving time-management and feasibility of the technique.

Irrespective of the frequency applied, each TMS session is usually composed of a total number of pulses around 1500-3000. Overstimulation should be avoided to prevent (sub-) convulsive reactions, while under-stimulation could result in a lack of efficacy. The treatment of acute conditions typically requires 20-30 sessions, even though adjunctive maintenance session can be added. Historically, daily rTMS sessions have been recommended from Monday to Friday (5 days per week), leading to a global 4- to 6-week treatment. More recently, accelerated protocols (aTMS) have been proposed, consisting of multiple daily sessions with adequate resting intervals. However, further research is needed on efficacy and timing of aTMS compared to standard rTMS.

Clinical applications

Since its introduction, TMS has been extensively investigated in a wide range of neurological and psychiatric conditions. Researchers experimented a multitude of protocols worldwide, variably combining parameters of stimulation to achieve clinical effects. Even though far from conclusive, the evidence available led to the approval of TMS devices to treat many neuropsychiatric disorders both in the US and the EU. The FDA first approved rTMS in treatment-resistant depression (TRD) in 2008 and later approved deep TMS to treat Obsessive-Compulsive Disorder (OCD) in 2018. More recently, deep TMS was also approved as a short-term aid in smoke cessation in 2020. In the EU, TMS was cleared for many indications, including Alzheimer's disease, Autism Spectrum Disorders, Bipolar Disorder (BD), Major Depressive Disorder (MDD), neuropathic pain, Parkinson's disease, Post-Traumatic Stress Disorder (PTSD), negative symptoms of Schizophrenia, and smoke cessation.

Depression

Depression is the first condition that achieved clearance for clinical use of TMS, with the largest body of evidence. The classical rTMS protocol for depression, both in MDD and in BD, consists of a focal, high frequency (HF) stimulation at 120% of MT over the left DLPFC, with 4-second trains and 26-seconds ITIs, for a total of 3000 pulses per session delivered daily for 20-30 sessions (4-6 weeks). Alternatively, a low frequency (LF) rTMS protocol over the right DLPFC was proposed, consisting of 1500 pulses administered continuously at 1 Hz for 20-30 sessions. Both protocols showed consistent and comparable antidepressant effects, as monotherapies or in combination with pharmacological treatments. However, left DLPFC HF-rTMS has the best quality evidence, leading to the highest level of recommendation. Some Authors proposed LF-rTMS over the right DLPFC as

the second choice thanks to its more tolerable profile, while others tried to combine HF- and LF-rTMS using bilateral stimulation, with conflicting results. Globally, bilateral stimulation did not show clear superiority over unilateral stimulation due to low-quality evidence, being supported at a lower level of recommendation. Despite the efficacy of both left and right DLPFC rTMS compared to placebo, response rates resulted in the range between 30 and 50%. With the development of innovative TMS methods, newer protocols were tested on depression to improve outcomes. Deep TMS using H-coils to stimulate left DLPFC at high frequencies systematically showed better results than placebo with high-quality evidence, leading to the FDA approval of HF-deep TMS over DLPFC with the highest level of recommendations. Based on HF- and LF-rTMS outcomes, iTBS and cTBS protocols over the left and right DLPFC were evaluated, to significantly reduce the session duration and improve time management. Given the conflicting results, evidence supporting non-inferiority compared to standard rTMS requires further support. Finally, aTMS protocols were investigated. Despite positive findings and no adjunctive safety issues, no standardized accelerated protocol has been approved to date, making impossible the generalizability of the results.

Overall, standard HF-rTMS and HF-deep TMS over the left DLPFC are currently recommended in depression, as supported by the highest quality evidence, even though other protocols could be found at least as effective in the future. Given the recent evolution, it is still unclear when to propose TMS to a patient affected by a Major Depressive Episode. Considering the low response and remission rates, TMS is generally recommended as an add-on therapy to pharmacological treatments, especially in patients with mild to moderate treatment-resistant depression. However, no clear indications on the level of treatment resistance, clinical profiles, and preferred combinations are currently available, leaving the choice to the psychiatrist.

Schizophrenia

Both positive and negative symptoms of schizophrenia were targeted using TMS, with conflicting results. In particular, some studies investigated the effect of rTMS over the temporoparietal cortex (TPC), including the superior temporal gyrus and the temporoparietal junction, in the presence of auditory-verbal hallucinations. LF-rTMS on the left TPC showed some positive but not univocal findings, leading to a low level of recommendation for treatment-resistant hallucinations, especially for young patients and females. Alternative protocols using different locations, HF stimulation, or cTBS approaches showed promising results, but demand further research before approval.

Similarly to depressive disorders, negative symptoms seemed responsive to HF-rTMS protocols over the left DLPFC using a figure-of-eight coil in schizophrenia. Again, findings regarding this set of symptoms are far from being conclusive. Different factors should be considered, including the high

variability of clinical profiles and the need for larger samples to draw significant conclusions. However, the use of circular coils, deep-TMS approaches, bilateral DLPFC stimulation, or the choice of alternative sites such as the vermal part of the cerebellum showed promising results.

Despite encouraging evidence, no specific protocol or target population is currently recommended in the US and the EU for positive and negative symptoms of schizophrenia, leaving this approach to a research setting to date.

Substance abuse and craving

According to the dopaminergic hypothesis, craving and addiction depend on the hyperactivation of cerebral networks such as the nigrostriatal, mesolimbic, and mesocortical pathways in the presence of a substance or other substance-related cues. The whole system encompasses multiple cortical and subcortical structures such as the ventral tegmental area, the striatum, the substantia nigra, the anterior cingulate cortex, the insula, the amygdala, the lateral habenula, and the prefrontal cortex, which constitute the reward system. More in detail, the cortical structures lose their top-down regulation over the subcortical networks when these are hyperactivated, leading to the impulsive search for the addictive substance or behaviour. As a common denominator between a wide range of substances and other addictive behaviours such as gambling, rTMS has emerged as a promising tool in targeting DLPFC to regulate the cortical/subcortical activation imbalance. Different protocols, including HF-rTMS over the left DLPFC, LF-rTMS over the right DLPFC, deep-TMS using H-coils over the DLPFC, iTBS, and cTBS, provided positive results in various conditions, such as alcohol craving, methamphetamine and cocaine addiction, nicotine craving, and gambling. However, the findings were highly heterogeneous and controversial, making TMS generally recommended in the EU but without specific protocol approval in all these conditions. Instead, the FDA cleared the use of HF deep-TMS for smoking cessation in 2020 (10 Hz, 120% MT, 3s pulse trains, 15s inter-train interval, 60 trains, 1800 pulses per session, 15 sessions).

Obsessive-Compulsive Disorder

Non-pharmacological approaches have been investigated in Obsessive-compulsive Disorder (OCD), including TMS, considering low response rates after multiple pharmacotherapies either alone or in combination. Different protocols were proposed using HF- and LF-TMS over various brain regions such as the prefrontal cortex, without univocal results. Focal LF-rTMS over the right DLPFC is among the most studied, with 1200-2000 pulses for 10-15 sessions, although without approved protocol schemes. This procedure is recommended with a low level of evidence due to some negative findings, requiring further research. According to functional imaging studies in OCD, LF-TMS approaches have also been tested on other areas, such as the left and right orbitofrontal cortex and the

pre-supplementary motor area, with positive but limited findings that are insufficient to draw further conclusions to date.

On the other hand, HF protocols showed heterogeneous results. If focal HF-TMS over the left and the right DLPFC did not find significant improvements in OCD symptomatology, bilateral stimulation of both DLPFCs exerted promising results. More importantly, HF deep-TMS using H-coils targeted at the bihemispheric medial PFC- anterior cingulate cortex region led to more prominent positive findings, allowing for the FDA approval of this procedure in the treatment of OCD in 2018.

Post-traumatic Stress Disorder

Few studies addressed the treatment of Post-traumatic Stress Disorder (PTSD) using TMS. Most of these focused on the right DLPFC using HF (10 Hz) and LF (1 Hz) protocols with figure-of-eight coils. Even if both therapeutic schemes showed some positive findings, HF-rTMS determined a higher reduction in anxiety symptoms, even persisting three months after the end of the treatment. Even if recommended, HF-rTMS in PTSD is still without clear-cut indications approved by regulatory agencies. On the other hand, LF protocols (1200-1800 stimuli/session for 15-30 sessions) found improvements in PTSD and depressive symptoms, especially when combined with cognitive therapy, even if some findings showed faster relapses after rTMS cessation. Given the limited evidence on this protocol, no recommendations or approval can be made on LF-rTMS. Finally, a single study investigated the effect of deep-TMS over bilateral medial-PFC using an H-coil with promising results in PTSD, even though it requires further research.

Other disorders

Considering the versatility and the potential of the application of TMS in a multitude of neuropsychiatric disorders, we are still far from an exhaustive knowledge of the treatment protocols. Even if still not recommended, some evidence explored the efficacy of TMS on other disorders, requiring further investigation to understand its role in their treatment plan. LF- and HF-rTMS protocols over the right DLPFC achieved some positive results in anxiety disorders, especially generalized anxiety disorder and panic disorder, with a functional rebalance in the connectivity within the limbic system. Little evidence accumulated on Autism Spectrum Disorders, especially Asperger's disorder, using deep, 5Hz-TMS over the dorsomedial-PFC bilaterally or LF-rTMS over the left DLPFC, with positive results in social anxiety and other symptoms. HF-rTMS was also tested in mental retardation as an augmentation strategy for language training, targeting the left Broca's area,

with improvements compared to language training alone. Finally, some studies investigated the effect of deep HF-TMS in ADHD but without significant results.

Safety and tolerability of TMS

TMS is generally a low-risk, well-tolerated technique. However, TMS operators should be aware of possible risks for the patients and themselves. TMS can be performed both as an inpatients' and an outpatients' service. As a non-invasive procedure, no special precautions are required before or after other than the removal of eyeglasses, earrings, necklaces, piercings, and all metallic materials in the head. During the stimulation, the patient is fully awake without any pre-medication or anaesthesia. If no adverse event (AE) arises, the subject is free to leave without further assessments or precautions after the session.

Before being admitted to the treatment, every patient should undergo a general screening for contraindications. As TMS is based on magnetic pulses applied over the skull and extending for several centimetres, all non-paramagnetic materials around the stimulation area serve as an exclusion criterion. Operators should extensively review medical history to identify prior accidents, surgeries, leads, or implants in cerebral structures that might contain metallic components. Furthermore, medical conditions, pregnancy, known brain lesions, and medications should be carefully considered as risk factors, potentially leading to the exclusion from TMS. At the moment, non-paramagnetic metallic parts in the skull represent the only absolute contraindication, while all other conditions are relative contraindication requiring individual assessment of the risk/benefit ratio.

If the patient is eligible for the treatment, the operator should monitor for possible AEs throughout the sessions. Even though well-tolerated, some subjects might experience AEs that can lead to TMS termination, especially during the initial sessions. The following are the main AEs of TMS:

- *Epileptic seizures*. Even if TMS is considered a non-invasive neurostimulation technique, the stimulation can induce a disorganized propagation of the pulse in structures other than the original target, generating partial or generalized seizures. After the first reports of this AE, concerns about the procedure led to the development of safety guidelines. According to them, stimulating protocols should not exceed predefined combinations of parameters, including frequency, pulses/train, ITI, and SI related to the MT. Despite the diffusion of TMS on larger scales, the introduction of safety limits determined a consistent drop in seizures among patients undergoing TMS. However, few cases have been reported with all stimulation patterns, even if the risk is considered very low. Current estimates of seizures are globally around 5-10/100000 sessions, with a higher risk for HF protocols and H-coils. Moreover, the

combination of medications with TMS had been a major concern, given their modulating effect on the seizure threshold. However, most of the patients suffering from severe neuropsychiatric disorders were concomitantly taking psychopharmacological agents without any substantial increase in seizure incidence. Even if medications demand caution, currently, there are no recommendations against their combination with TMS. Finally, concomitant medical conditions should be evaluated as part of the risk algorithm for seizure induction. The most important disorder to rule out is prior epilepsy. Even if it does not act as an absolute contraindication, careful revision of the medical history is mandatory, requiring special precautions during the session. Other neurological diseases can lower the seizure threshold, such as stroke, multiple sclerosis, brain lesions, and neurodegenerative disorders. Medical comorbidities, including electrolyte imbalance, metabolic abnormalities, liver/kidney failure, fever, infections, and substance abuse/withdrawal (e.g., cocaine, MDMA, alcohol) may act as predisposing factors. It is advisable to correct any disorder before administering TMS.

- *Changes in the hearing threshold.* Each TMS pulse is associated with an acoustic signal estimated to reach the maximum noise exposure limits. Few reports indicated increases in the hearing threshold considering the position of the coil close to the ears and the propagation of vibrations through the skull. Such changes appeared transient in their nature, resolving approximately 1-2 hours after the session, but long-term dysfunctions of the nerve cannot be excluded. Some protocols showed consistent variations in the auditory threshold, including repetitive patterns, HF stimulation, higher SI, and longer sessions. However, ear protection devices (earplugs or earmuffs) could be offered to prevent even transient effects. After each session, the operator should evaluate the occurrence of hearing loss, tinnitus, or aural fullness.
- *Dysesthesia/headache.* If TMS delivers magnetic pulses at an intensity sufficient to elicit neuronal depolarization, superficial structures in the scalp can be stimulated as well. The direct application over nerves and muscles can result in involuntary twitches in the face, discomfort, dysesthesia, or headaches in up to 20-30% of subjects, especially during the initial sessions. In most cases, these symptoms arise during the stimulation, but few patients reported the occurrence of headaches a few hours after. Even though benign, they can be considered unbearable, requiring either a readjustment of the SI or a switch to more tolerable protocols, such as LF and low-intensity rTMS. Should the symptoms persist beyond the session, paracetamol is generally recommended as a first-line agent.
- *Burns.* The generation of a magnetic pulse depends on the flow of an electric current inside the coil. Repetitive patterns of pulses can induce progressive heating of the coil attached to the scalp, which can cause burns. Nowadays, all TMS devices incorporate air- or liquid-based

cooling systems with an automatic block of the stimulation should the coil reach damaging temperatures. After the optimization of the technique, burns are no longer considered TMS side effects.

Besides risks for the patient, operators should be aware of recommended precautions for themselves. Electromagnetism can interfere with electronic or other magnetic devices, so it is advisable to keep mobile phones and credit cards away from the TMS equipment during the session. Considering long-term, daily exposures to rapidly time-varying magnetic fields, operators might exceed the "Exposure Limit Values" set as safety issues. A distance of at least 40 cm should be kept from the coil during active stimulation to avoid this inconvenience. Last, noise pollution can affect operators as well due to chronic exposure. The use of earplugs or earmuffs is recommended to prevent hearing alterations.

12.1.3. ELECTORCONVULSIVE THERAPY (ECT)

Definition

Electroconvulsive therapy (ECT), commonly known as electroshock therapy, is a therapeutic technique based on inducing convulsions in the patients after passing an electric current through the brain. The therapy was developed and introduced in the 1930s by the Italian neurologists Ugo Cerletti and Lucio Bini.

History:

- First chemically induced convulsions were used as a treatment for schizophrenia in the 1930s
- Ugo Cerletti developed an experimental model for epilepsy and produced the first ECT device to induce convulsions in animals. The first treatment in humans was carried out in 1938. The patient underwent 11 treatments without any adverse events
- In 1960 the introduction of new anaesthesia techniques included neuromuscular blockade
- In the late 1970s square wave machines were developed
- The Royal College of Psychiatrists declared ECT effective in "depressed patients“
- Late 1970s and 1980s: seven controlled trials carried out in Britain, despite uncertainties
- To date, up to 50.000-100.000 people every year undergo ECT in the US

The approach was based on the Nobel Prize winner Julius Wagner-Jauregg's research on the use of malaria-induced convulsions to treat certain nervous and mental disorders (such as paralytic dementia caused by syphilis) as well as on the theories developed by J Meduna, according to whom schizophrenia and epilepsy were antagonistic disorders. These theories led M. Sakel to develop insulin coma therapy in psychiatry in 1933.

Cerletti used electroconvulsive therapy for the first time in April 1938, in collaboration with Lucio Bini, on a patient suffering from schizophrenia with delusions, hallucinations and confusion; a series of therapeutic electroshocks allowed the patient to return to a normal mental state. In the following years, Cerletti and his collaborators regularly carried out therapeutic electroshocks, both on animals and on neuropsychiatric patients, establishing the reliability of the therapy and its safety and usefulness in clinical practice, especially for the treatment of acute schizophrenia, manic-depressive psychosis, and the most severe cases of depression.

Initially, the therapy was carried out on conscious patients, without the use of anaesthesia or muscle relaxants. Patients lost consciousness during the session and suffered violent uncontrolled muscle

contractions, which could sometimes cause bone fractures (especially of the vertebrae) and muscle strains. Since 1960, electroconvulsive therapy has been carried out under general anaesthesia.

ECT: Mechanism of action

Even if the exact mechanism of action is yet to be fully elucidated, there is clinical evidence of anti-depressant, anti-psychotic, anti-catatonic, and anti-convulsing effects.

There are significant changes in neural activity in front-limbic brain regions

The neurotransmission is involved in the mechanism of action in terms of an enhanced serotonergic, noradrenergic and dopaminergic functions. It was also found an increase of cortical GABA concentrations and evidence of increased seizure threshold after ECT treatment.

Dopamine system: Several evidences show that ECT activates the dopamine system.

HPA axis function: Studies show that ECT can activate the HPA axis, as indicated by the increases of cortisol, ACTH, and arginine vasopressin after ECT sessions.

It is important to take into consideration that there is an inducing effect on neuroplasticity in terms of dose-dependent hippocampus dendritic arborisation and excitatory synapses in the amygdala.

Clinical indications for ECT

- Major depressive episode with psychotic symptoms

- Bipolar disorder, depressive episode

- Bipolar disorder, manic episode

- Schizoaffective disorder

- Schizophrenia - acute onset, with confusion

- Catatonia

- Parkinson's disease (bradykinesia, tremors, rigidity, gait disturbances, postural instability)

As we have seen in the previous section, the mechanism of action of ECT is not selective, so it is not aimed at treating a single syndrome, although patients with melancholic depression seem to benefit more than those with other pathologies.

Depression with both unipolar and bipolar psychotic manifestations respond to treatment after 6-8 sessions twice a week.

Manic syndromes require daily treatment until the episode is resolved, while schizophrenics benefit in a very limited way.

So we might consider that in major depression the effect of ECT is syndromic in the sense that all components of the syndrome improve in a parallel way, whereas in the treatment of schizophrenia only some symptoms respond while Schneider's first- rank symptoms do not change.

Predictors of response to ECT treatment in depressed patients are the presence of delusional ideation and psychomotor retardation. About 90% of depressed patients with psychotic manifestations respond to this therapy.

Finally, a further clarification is that candidates for ECT are those who need a faster response to treatment than conventional treatment, such as catatonic patients or those with significant suicidal ideation or those who do not respond to medication.

ECT and pharmacological treatments:

It is advisable to discontinue psychotropic drugs if not strictly necessary, especially anticonvulsants and benzodiazepines, as they inhibit convulsions, but also tricyclics/MAOs because they make the course of therapy less predictable and finally lithium, cause it can be associated to an increase in organic mental syndrome and may prolong neuromuscular blockade. On the contrary neuroleptics can be maintained.

Contraindications:

- Uncontrolled hypertension;
- Myocardial ischaemia;
- Valvular stenosis;
- Aortic aneurysm;
- Pheochromocytoma;
- Thrombophlebitis in patients not on anticoagulant therapy;
- Airway infection;
- Upper airway obstruction due to arthritis, dental abscesses, laryngeal tumours, myopathies, myasthenia gravis, muscular dystrophy;
- Recent strokes;
- Brain tumours with increased endocranial pressure;
- Acute angle glaucoma;
- Hb value < 10g/dl;
- Hepatic or renal failure

Adverse events with ECT

Mortality: 2:100,000 treatments

Seizures: prolonged over 3 minutes evoke confusion and memory impairment

Other: headache, muscle pain, nausea, drowsiness, weakness, anorexia, amenorrhoea.

Cognitive effects

Studies in the 1970s using a sine-wave machine identified side effects inherent in memory processes, both retrograde, for events very close to the treatment, and anterograde amnesia, up to 6 months post-treatment.

Seventy-five per cent of patients undergoing electroconvulsive therapy acknowledged memory loss as the most serious side effect of the treatment. 30% said their memory had not returned to normal.

These data must be interpreted with caution as most published studies consider the possibility that the self-assessment of a symptom by individuals with depressive illness is inevitably influenced by the affective state or cognitive distortions typical of these patients.

Side effects are more common with a bilateral electrode placement treatment and another variable is type of electrical stimulus and are higher with a sine waves. Sometimes, it may occur delirium, which is connected with the age of the patient. So in order to avoid this side effects it is needed a reduction of the frequency reduction and a unilateral electrode placement application. Electroconvulsive stimulation induces alterations in hippocampal synaptic plasticity in ECT rats and a NMDA antagonists counteract this effect, e.g. ketamine is a potent NMDA antagonist and when combined with treatment with bifrontal electrode placement prevents the risk of ECT-induced encephalopathy.

12.2. CHRONOBIOLOGICAL TREAMENTS

The use of chronotherapies, a group of non-pharmacological therapeutic approaches to mood disorder treatment, is rooted in the hypothesis of chronobiology aetiopathogenesis of psychiatric disorders (mainly mood disorders) which spans across several biomedical disciplines - from molecular biology to internal medicine and clinical psychology.

Introduction

Life on Earth is marked by rhythmic occurrence of many phenomena such as the succession of periods of light and darkness, the alternation of seasons, the repetition of changes in environmental temperature, rain, flowering and fruit production, lunar phases and tides. All organisms must swing in accordance with external environment in order to adapt and survive, and their nervous systems

have developed so. *"Whoever wishes to investigate medicine properly, should proceed thus: in the first place to consider the seasons of the year, and what effects each of them produces for they are not at all alike, but differ much from themselves in regard to their changes"* is a quote by Hippocrates, the founder of occidental medicine, who already in V century b.C. recognized the influence of environmental cycles on the human organism. In the case of humans, rhythmicity is an integral part of the functioning of our organism: bodily functions such as heart rate, respiratory rate, hormone secretions, sleep-wake cycle exhibit a periodicity that is influenced by exposure to environmental stimuli. This rhythm that regulates our daily living, is determined by a biological clock within our brain and is independent of sleep and wake.

BOX 4. Chronobiology terminology

Circadian: a cycle that lasts 24 hours (there is one cyclic event per day), e.g. sleep-wake cycle

Ultradian: a cycle that lasts less than 24 hours (there are many cycles in a single day), e.g. respiratory cycle

Infradian: a cycle that lasts more than 24 hours (there is less than 1 cycle per day), e.g. menstrual cycle

Biological clock

The endogenous rhythms are closely linked to the rhythmicity of the surrounding environment through the so-called *Zeitgeber* (from the German "time givers") like the light-dark cycle, variations in ambient temperature or noise; these are all signals that inform the person's biological clock of what is happening in the surrounding environment, leading them to adapt accordingly.

The human biological clock resides in the suprachiasmatic nucleus (SCN), which is made of 20.000 cells packed in less than 0.3 mmc in the hypothalamus. It produces a signal that paces the organism at a 24-hour periodicity. Environmental stimuli, ambient light in particular, act on biological clock synchronizing it with external world every morning at dawn. In fact there is direct connection from retina to SCN to neurons and their genetic material, the DNA. There are genes that are activated by sunlight in the morning, with a cascade of genetic and metabolic events, and feedback inhibition of other genes, so that a complete cycle takes exactly 24 hours to complete. From the SCN, there is a polysynaptic connection to the pineal gland: it goes from the SCN to the paraventricular nucleus (PVN) in the hypothalamus, than to medio-lateral cell in the spinal cord to the superior cervical ganglion (SCG) and, finally, to the pineal gland so that the biological clock synchronized melatonin secretion with photoperiod (that is, the season).

According to preference for rest and awakening earlier in the evening or later in the night, people can be grossly divided in two chronotypes called “larks” and “owls”, respectively, which rely on a complex origin: genetic vulnerability, environment, gender and age all are contributing factors. The magnitude of such circadian variation is genetically determined by the allelic variations that a subject carries, therefore some characteristics can be inherited or be altered by epigenetic factors. It is everyday life experience that children tend to wake up and go to sleep early, adolescents progressively delay their phases, and sleep-wake cycle gradually shows a phase advance with age.

Not only light is a biological clock determinant, but also the so-called “non-photic stimuli”, for example life events and habitual behaviours, which have a deep psychological significance, can act as internal circadian regulators or disruptors. This is why a regularity of lifestyle and sleep hygiene are strongly recommended at the basis of every therapeutic approach.

Examples of the close link between environmental periodicity and pathophysiology are:

- Body temperature: normally, the body temperature is lowest in the middle of the night and gradually rises during the day, with the maximum temperature about dinner time (7 pm)
- Hormonal secretion: melatonin and cortisol are the principal hormones affected by circadian rhythms. Melatonin production is affected not only by light intensity but also by the photoperiod, i.e. the hours of light to which we are exposed: in winter, with 7 hours of light, melatonin production starts at around 7 p.m., while in summer, with 12 hours of light, production begins at 10 p.m. Melatonin not only regulates the sleep-wake cycle, but via cytokines and second messengers regulates various body systems (e.g. neurotransmitter and receptor turnover, synaptic dynamics, immune system, blood pressure, metabolic organs). Typically, cortisol secretion shows a peak a couple of hours before awakening, with the goal of preparing the body to start a new day and lowers in the evening preparing the body to melatonin actions, but depressed patients have been demonstrated to have a compromised morning secretion of cortisol and a HPA hyper-activation.
- Sleep-wake cycle: according to the two-process model of sleep postulated by Borbély, somnolence and need for sleep depend both on tiredness and “sleep debt” that we accumulate for the mere sake of being awake (the homeostatic process), and biological clock that regulates day and night rhythm and sleep architecture (the circadian process). A commonly experienced phenomenon in flight travellers is induction of depression when travelling from east to west (phase delay) and induction of manic symptoms when travelling from west to east (phase advance).

- Cognitive functions: attention, concentration, memory, thought, executive speed (e.g. in videogames, using a language or formal logic thought process) follow the same circadian rhythm that regulates every other body function, with maximum cognitive performance in late morning to early afternoon.

The circadian clock affects multiple systems and pathways that are thought to underline mood disorders. There are reciprocal interaction among circadian rhythms, immune response and mood regulation.

Examples of the close link between biological rhythms and psychiatric illness are:

- Major Depressive Disorder: it typically recurs with seasonal pattern, mainly in spring and autumn. Successful antidepressant treatment is associated with a normalization of the melatonin production in depressed patients. During a depressive episode, there is drop in daily body temperature respect to healthy controls and patients themselves during euthymia.
- Bipolar Disorder: depressive episodes typically occur in winter, while manic episode in late spring-summer. Bipolar patients have a different pattern of melatonin secretion, and it is particularly sensitive to environmental light with respect to healthy controls: if awakened during night sleep, Bipolar patients fail to secrete melatonin again so that they cannot fall asleep again, triggering manic episodes.
- Seasonal Affective Disorder: patients are unable to adjust the amount of melatonin to the photoperiod. An observational study on the seasonal presentation of certain phenomena showed that Google searches for “depression”, “anxiety” and “insomnia” showed a rhythmic pattern with a marked increase in searches in spring and autumn.
- Mood fluctuations: depressed patients present a marked worsening of symptoms in the early morning, with a progressive improvement later in the day.
- Gonadal hormones modulate neurotransmitter mechanisms: the lowering of ovarian hormones in premenstrual phase, in postpartum and menopause jeopardizes the functioning of biological clock, predisposing ground for development of cyclic mood disorder manifestations (e.g. MDE, manic episode, PMDD).
- Sleep architecture in Mood Disorder patients: depressed patients have a markedly reduced REM sleep latency, a shorter first REM phase with an increment in duration and intensity of REM sleep in the following sleep cycles, frequent awakenings and terminal insomnia. On the other hand, manic episodes are characterized by markedly reduced need of sleep and in some cases complete insomnia. Moreover, patients exhibit persistent sleep architecture alteration

even during euthymia, and so do first degree relatives, so that these hallmarks have been proposed as *endophenotypes* of depression.

- Suicide: disrupted sleep and nocturnal wakefulness are evidence-based risk factors for suicidal thoughts and behaviours.
- Anxiety and OCD: alertness and reactivity to threatens, altered emotional processing and response, repetitive worries and intrusive thoughts correlate bi-directionally with sleep and circadian cycle alterations (e.g. delayed sleep phase advance, childhood insomnia).
- Schizophrenia: frequently, circadian cycle alteration are prodromal to SKZ onset and symptom severity has been associated with circadian rhythm alteration itself; data showed that auditory hallucination manifest a circadian pattern, with higher occurrence in the evening (6-9 pm). At molecular level, SKZ patients have distorted melatonin secretion curves (e.g. blunted peak, reduced rhythm amplitude, phase advance, altered response to darkness and sleep habits) and at a genetic level, post mortem studies showed disrupted rhythmicity in cortical neuron gene expression among.
- Genetic variants in clock genes, such as SNPs, have been associated with a variety of psychiatric and neurodevelopmental disorders (e.g. MDD, BD, schizophrenia, ASD…): a hypothesis is that such disorders reflect a defect in synchronization between ambient and internal rhythms, so that the body - both at cellular and as an organism - fails to adapt to environmental periodic changes.

Chronotherapies

In recent decades, based on developing knowledge in chronobiology system and multi-factorial aetiopathogenesis of Mood Disorders, specific therapeutics have been developed, aimed at treating Mood Disorders through the manipulation the biological clock. The main therapies are Sleep Deprivation, Light Therapy and Dark Therapy.

The therapeutic effect of chronobiological techniques in Mood Disorders can be seen at a neurobiological level. LT and SD act on the biological clock, with an increase in the production of serotonin and activation of numerous areas involved in the emotional circuitry that is compromised at various degrees in Mood Disorder patients. Interestingly, these neurobiological changes in functional connectivity and neurotransmitter communication is the same as in successful antidepressant treatment and somatic therapies (e.g. TMS, ECT), furtherly supporting the exquisite role of circadian rhythm disruption in Mood Disorders pathophysiology. The effect of chronobiology on functional brain activity is also correlated with the genetic profile. For example, subjects with the

s/s alleles in the SERT gene have a reduced function of the transporter and a reduced response to both pharmacological and chronobiological treatments.

Light therapy

Light therapy (LT) has a complex mechanism of action, not fully understood yet: based on the hypothesis of Seasonal Affective Disorder (SAD) aetiopathogenesis, it has been supposed that LT functions by resynchronizing the biological clock's phase delay in wintertime, or by augmentation of serotonin dynamics. However, the mainstay of its therapeutic effect is restoration of melatonin evening peak in depressed subjects.

LT has been developed as an antidepressant treatment for SAD; in successive studies, it has been demonstrated that LT combined with antidepressant medications hastens antidepressant effects in non-seasonal depression as well, with an effect comparable to that of antidepressant medications.

Given the extreme sensitivity of the biological clock to light stimuli and the endogenous alteration in overall circadian rhythm, it has been studied when LT exerted the most beneficial effects: the antidepressant effect is greater if the light is administered 2 hours earlier than the usual wake-up time, a time best individuated through the Morningness-Eveningness Questionnaire (MEQ), thus generating a phase advance.

As not all morning times are alike, so not all "lights" are therapeutics. A proper LT treatment sees the utilization in Bright Light sources (typically10.000 Lux) with an UV-ray filter. The patient sits in front of the LT source, at about 50-100 cm from the lamp, with open eyes but not directly staring at it (for example they can read a book or a magazine), for about 30 minutes. After LT session, patients should not go back to bed despite any trouble in night sleep or physical tiredness or activating effects of LT on neurotransmitters and mood symptoms would vanish.

Sleep deprivation

In 1966, Schulte firstly noted a possible correlation between reduction of sleep hours and improvement of depressive symptoms. In 1971, Pflug conducted the first therapeutic trial on Sleep Deprivation (SD) as antidepressant treatment: clinical improvement was transitory and patients relapsed the day after. In 1983 and 1987 Gillin and Wiegand proposed that sleep disorders could be of pivotal importance in depression physiopathology, with special regard to BD.

General indications for SD treatment are:

- Supporting diagnosis and prognosis (e.g. BD versus MDD)
- Alternative or potentiation to classical pharmacological treatments
- Treatment-Resistant Depression

- Rapid cycle patients

SD is a non-pharmacological intervention useful in Bipolar depression and other depressive episodes that has a rapid and striking effect in reducing depressive core symptoms, suicidal ideation included. It has the advantages of being quick, non-invasive, costless, well tolerated by most of patients. It was observed that the antidepressant effect of SD differs between the different categories of subjects suffering from depression.

Better effects have been observed in endogenous primary depression compared to reactive and/or secondary depression, and in the treatment of Bipolar Disorder (mean response rate 50-75%) compared to Major Depressive Disorder (mean response rate 33-66%). SD is used in the treatment of Bipolar depression, as an alternative or enhancement of antidepressant drugs. In fact, SD has been applied in drug-resistant depressed patients with good results: patients resistant to treatment with SSRIs had a positive response rate in 50% of cases, while patients resistant also to TCAs responded in 40% of cases.

BOX 5. Clinical indications for SD treatment

Unipolar depression (MDD)

Bipolar depression

Schizoaffective depression

Reactive depression

Secondary depression (e.g. Schizophrenia, Parkinson's disease…)

Depression in elderly and children

Depression associated with pregnancy and postpartum

Premenstrual Dysphoric Disorder

BOX 6. Clinical predictors of response to SD

Circadian mood oscillations

Pronounced cardiac frequency circadian variation

Increased motor activity

Clinical diagnosis (e.g. BD)

The development of treatment protocols was subjected to several considerations:

- One night of SD is effective in more than 60% of patients, but with a relapse rate is about 80-95%
- The antidepressant action of SD is higher and more stable is SD is for 36 consecutive hours (Total Sleep Deprivation, TSD)
- LT exposure in the middle of the awake night and in the morning after recovery sleep potentiates the chronobiological effects of SD
- Concomitant medication utilization potentiates and favour the maintenance of wellbeing after SD
- In BD patients, the use of lithium salts in combination with SD significantly improves clinical outcomes, compared with patients not taking lithium

BOX 7. SD Protocols

- Total SD
  - For three times in one week (see Fig. 1)
  - For two times in one week
  - Twice a week for three weeks
  - For two times in one week followed by partial SD
- Partial SD
  - Once a week for three weeks
  - For three times in one week
  - Twice a week for two weeks
  - Thrice a week for two weeks
  - For five times at five-days intervals
  - For six times at 4 days interval

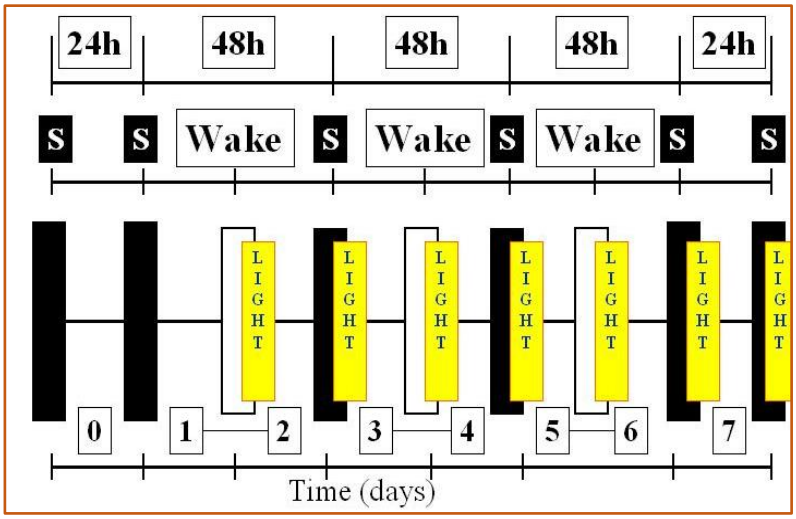

Fig. 1. Total Sleep Deprivation protocol: A robust treatment scheme consists of three forced vigils lasting 36 hours, alternating with nights of sleep recovery. LT is administered during the night of deprivation at 3 a.m. and on the awakening following the night of recovery.

Since sleep-wake rhythms are manipulated in bipolar patients and sleep deprivation is a trigger for the manic phase, the risk of shift into the manic phase has been worried and eventually observed. Numerous studies showed a switch rate of 6% after 3 cycles of TSD in BD type I non rapid-cyclers, definitely lower than drug-induced mania (15-29%), while rate peaked 78% in rapid-cycle patients. Restoration of nocturnal sleep with intravenous benzodiazepines results in a disappearance of manic symptoms in 30% of patients and recover into euthymia within 3-5 days.

Dark therapy

Environmental, psychological, and pharmacological factors that induce spontaneous SD can give rise to mania, with inverse correlation between the duration of sleep and the intensity of the manic symptoms at the beginning. As a matter of fact, SD is used in the animal model of mania (appearance of manifest behavioural changes in the rat, e.g. hypervigilance, hyperactivity, speed, irritability…): the replicability of inducing manic behaviours both in lower mammals and in humans with manipulations of the sleep-wake rhythm suggests the presence of a common and phylogenetically preserved biological substrate that might confer an evolutionary advantage.

In the 1990s Wehr and Wirz-Justice reported, separately, their successful experience in treating rapid-cycling bipolar manic patients with exposure to a prolonged ambient darkness and bedtime, the basis of Dark Therapy (DT) protocols, which might be added with mood stabilising and antipsychotic medications.

When it is impossible to reserve a quiet and isolated room for a manic patient, Virtual DT comes in help: it is carried out with the use of specific glasses with lenses that filter blue light waves (those light waves that mostly activate the SCN) in order to reduce the exposure to any awakening stimuli.

12.3. COGNITIVE REMEDIATION

Introduction

Cognition is one of the most relevant determinants of quality of life and daily functioning. Cognitive deficits may be observed in several psychiatric disorders such as schizophrenia, mood disorders, attention deficit/hyperactivity disorder (ADHD). Since neurocognitive impairment is associated with poor long-term global outcomes, including poorer quality of life and impairment in personal, occupational, and social functioning, early interventions targeting cognition are of crucial importance.

While antipsychotic treatments are usually highly effective in improving positive symptoms, they show scarce or null effects on cognitive deficits. To date, rehabilitation interventions are the best available and effective tools to treat cognitive impairment. Cognitive Remediation (CR) – a set of interventions based on behavioral training whose goal is to enhance neurocognitive abilities in a

generalized and durable manner – has thus become an essential component of the treatment for major psychiatric disorders.

Definition

CR has been defined as "an intervention targeting cognitive deficit (attention, memory, executive function, social cognition, or metacognition) using scientific principles of learning with the ultimate goal of improving functional outcomes". Such therapy aims to ameliorate the individual's everyday functioning, such as scholastic, professional, or social functioning, through the improvement of cognitive performance.

Originally, CR was designed and developed to target subjects with brain lesions and subsequently applied to other disorders that involve cognitive deterioration. Since then, interest in the effectiveness of CR has increasing grown, leading to the development of various types of CR therapies.

CR includes a range of approaches varying in the structure, intensity, and duration of treatment. However, all the approaches are typically based on the same main principles: Training, Strategy Monitoring, and Generalization.
Training consists of repetitive practice through the use of paper and pencil or computerized cognitive training exercises of increasing difficulty as patients progress through the program. The aim of the training is to promote neuroplasticity and improve information processing.
Strategy monitoring aims to promote a metacognitive comprehension of the problem-solving strategies used during the training. It is usually facilitated by therapists which assist the patients in developing awareness of the approaches they use, generating new strategies, and acquiring flexibility in shifting strategies depending on the specific situation.
Generalization refers to the process through which patients translate the abilities and strategies developed during the treatment into everyday life. Generalization is usually facilitated by therapists through activities that allow patients to identify areas of their daily life where they could apply the strategies acquired during the therapy.

CR strategies can be divided into two methods: "compensatory" and "restorative." The "compensatory" approach aims to bypass specific cognitive deficits, through the use of the patient's residual cognitive abilities.
Conversely, the "restorative" model aim at restoring cognitive function through repetitive practice based on brain plasticity and neurogenesis. Restorative strategies involve two different approaches: bottom-up or top-down. Bottom-up approaches start targeting basic cognitive domains, such as attention, and advance to more complex cognitive functions, such as problem-solving. On the other

hand, top-down approaches aim at improving specific neurocognitive functions through use of more complex skills. Therefore, while some restorative approaches involve the use of drill and practice exercises to enhance neuronal plasticity and restore cognitive functions, others involve the generation of new strategies and encourage the generalization in everyday life through the execution of activities that require their use.

CR techniques are highly variable, depending on the therapist's and the patient's characteristics, the therapy goals, and the program format. While early CR interventions consisted of paper and pencil exercises, nowadays, computer-assisted cognitive training programs are the most widely utilized. Computer-Assisted Cognitive Rehabilitation (CACR) represents a homogeneous subgroup of CR interventions, usually consisting of weekly sessions of drill and practice comprising both domain-specific exercises (such as verbal memory and fluency, attention, working memory psychomotor speed and coordination, executive functions) and non-specific exercises that require the simultaneous use of different cognitive functions. CogPack, CogRehab, and Circuits are among the most used types of computer-based CR programs.

CR for schizophrenia

Over the past decades, CR has been widely used in the treatment of schizophrenia, where cognitive dysfunction is prominent. Cognitive impairment represents a hallmark of schizophrenia: it occurs in about 75% of patients, and it is one of the main predictors of long-term outcomes, affecting quality of life, social relationships, independent living, and occupational functioning. Cognitive impairment appears prior to the onset of the disorder, predicts functional outcome even better than positive and negative symptoms and also limits recovery even when other support has been provided. Deficits are widespread and can be observed in attention, processing speed, memory, executive function, language, and social cognitive function.

Cognitive deficits progressively became the main target of rehabilitative interventions to achieve functional recovery.

In recent decades a wide range of cognitive remediation therapy (CRT) programs have been developed and their effectiveness on cognitive functions has been widely demonstrated. CR therapy (CRT) produces small to moderate effects on cognitive outcomes. CRT has been associated with improvement both in global cognition and in specific neuropsychological performances, as well as in psychiatric symptoms, especially negative ones. Finally, CRT has shown to produce improvements in general functioning, especially if the intervention is a part of a broader psychosocial rehabilitation

involving the learning of other communication, social, and self-control skills. Indeed, literature suggests that for CR to improve everyday functioning, the subject needs to be in an environment where active skill acquisition or development can take place. Moreover, while CRT effects on cognitive abilities seem to persist even after 5 years, a durable functional improvement requires an integrated rehabilitative approach.

Despite its documented efficacy, CRT is associated with highly heterogeneous outcomes, with some patients normalizing their performance to healthy control levels and others showing no improvement. Several patient's or treatment's variables could influence response or resistance to CRT. Overall, CR seems to be more effective in subjects with younger age, shorter duration of illness, greater pre-treatment cognitive reserve and fewer disorganized symptoms.

CR for other disorders

More recently, CR use has been broadened to other psychiatric disorders and the training has been successfully applied in the treatment of other psychiatric disorders, such as mood disorders, attention deficit/hyperactivity disorder, and anorexia nervosa.

Mood Disorders

Major depressive disorder (MDD) is associated with an impairment in neuropsychological functions such as attention, processing speed, learning and memory, and executive function. Cognitive decline is known to predict relapse of depressive episodes, treatment resistance and functional impairment, besides being associated to compromised quality of life. Moreover, cognitive functioning may continue to deteriorate, not only during the depressive episode, but also in euthymic states. Although literature is still scarce, the efficacy of CR in improving depressive symptom and psychosocial function suggest that CR could represent a promising treatment option for MDD.

Bipolar disorder has been associated with neurocognitive impairment as well, particularly in attention, executive functions, working memory, and social cognition domains. Such cognitive dysfunction affects quality of life, psychosocial functioning, and productivity. Only few studies investigating the effect of CR on neurocognitive and psychosocial function in bipolar disorder and results are inconclusive.

Attention deficit/hyperactivity disorder

Although ADHD is typically characterized by attention deficits, impairments in working memory, processing speed and executive functions have also been observed. CR studies conducted on ADHD

reported improvements in overall symptoms and neuropsychological performance, especially in working memory and executive functions.

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is characterized by impairment in social cognition and restricted and repetitive behaviours and interests. Moreover, subjects affected by ASD are known to experience deficits in cognitive domains such as memory and executive functions. These deficits may affect daily life and psychosocial functioning. Overall, studies investigating CR efficacy on ASD suggest CR interventions could be effective in improving social cognition and neurocognitive performance.

Substance Use Disorder

Deficits in cognitive domains such as attention, working memory and executive functions have also been observed in subjects with substance use disorders (SUD) and may contribute to poor treatment adherence and outcomes. Literature on CR efficacy on SUD showed improvements in neurocognitive domains, such as working memory, learning, processing speed and executive functions, but also in psychosocial outcomes such as depressive symptom, craving, and self-regulation. Overall, CR seems to be a promising approach in treating SUDs.

Anorexia Nervosa

Anorexia nervosa is not characterized by global cognitive dysfunction, but cognitive inflexibility and processing bias toward detail or local information have been reported and correlated with disease intensification and delayed recovery. CR has been used in subjects with anorexia nervosa, in addition to the usual treatment, with the aim of enhancing cognitive flexibility and central integration ability. Although studies showed mixed results, they suggest that CRT has potential as a supplementary treatment for anorexia nervosa.

Borderline Personality Disorder

Borderline personality disorder (BPD) is associated with cognitive deficits which may affect the outcome of this disorder. Few available data suggest the feasibility and potential effectiveness of CR on specific cognitive domains and psychosocial functioning measures.

CRT should not be a stand-alone therapy, but part of an integrated rehabilitation program. In this regard, most evidence suggests that an integrated rehabilitative approach seems to be more effective, in terms of both generalizability of results to daily functioning and also durability.

Regardless of the type of mental illness, cognitive impairment affects patients' quality of life, decreases vocational and social functioning and compromise the effectiveness of therapy. Cognitive rehabilitation is as an effective strategy for addressing these cognitive impairments, and has been linked to improvements in social adjustment, vocational functioning, and other functional domains.

12.4. PSYCHOTHERAPEUTIC APPROACHES

An increasing number of studies have highlighted the effectiveness of combined pharmacological and psychotherapeutic interventions for the treatment of different clinical conditions such as mood disorders, anxiety disorders, eating disorders and personality disorders. The definition of psychotherapy varies according to the theoretical model and the intervention model. In the following paragraph we briefly describe the two main approaches in psychotherapy: the cognitive-behavioural approach and the psychodynamic approach.

COGNITIVE-BEHAVIORAL THERAPIES:

Cognitive-behavioural therapies represent a class of pragmatic approaches for understanding and dealing effectively with a wide range of psychiatric disorders and problems. Cognitive Behavioural

Therapy (CBT) began during the 1970s when a large percentage of behaviour therapists shifted their focus to internal cognitive processes. This shift implied a central role for cognitive processes in the mediation of behaviour and therefore legitimized cognition as a viable target for clinical intervention. Specifically, cognitive-behavioural theories assume that cognition mediates emotional and behavioural responses and thereby it may influence the acquisition and maintenance of psychopathology.

Cognitive-behavioural therapies can be represented along a continuum in terms of how much cognition is included in the formulation: on the one end we find behaviour therapies that focus on behaviour and environmental determinants in terms of elementary learning theory, and at the other end of the continuum we find therapies that formulate therapy only in cognitive terms, leaving no space for behavioural intervention. Most cognitive-behavioural approaches fall somewhere in between since they emphasize the behavioural and cognitive interventions to differing extents.

Although there is much diversity among these treatments, they are all problem focused, goal directed, future oriented, time limited, and empirically based. Moreover, cognitive-behavioural therapies rely on psychoeducation whose goal is to improve quality of life through an adequate knowledge of the disorder, the capacity to recognize early symptoms of relapse and a strong compliance with the pharmacological treatment.

Principles of CBT:

Dobson (2001) has identified some basic principles that cut across the variety of treatment approaches in Cognitive Behavioural Therapy (CBT).

1. Cognitive activity affects behaviour and emotions
2. Cognitive activity may be monitored and altered
3. Desired emotional and behaviour change may be obtained through cognitive change.

Techniques of CBT: integrating cognitive and behavioural techniques

In order to give an overview of the features shared by cognitive-behavioural therapies, we briefly describe some basic methods and techniques that are commonly used to help patients dealing with their symptoms and problems.

Within the cognitive-behavioural framework, maladaptive thinking is both a symptom and a critical maintenance factor. Therefore, patients can overcome their problems by identifying and modifying their negative thoughts. Patients learn to recognize their automatic thoughts and they are encouraged to view them as hypothesis rather than manifest facts. The therapist induces *cognitive restructuring* by asking leading questions that guide the patient to question and alter his faulty cognition.

Another cognitive and practical technique is *problem solving*: a self-directed process by which a person attempts to identify and implement effective solutions for a specific problem faced in everyday

life. Problem solving has been applied to a wide range of situations commonly encountered in psychiatric practice: difficulties associated with anxiety, mood, stress, substance abuse.

Moving to more behavioural techniques the use of *activity schedules* serves to counteract the patient's loss of motivation and inactivity. Since inactivity is associated with negative emotional states, the therapist and the patient may use a schedule in order to plan activities in advance.

Exposure techniques are used to treat fear, anxiety and other intense emotional reactions. Because of the centrality of avoidance mechanisms in anxiety disorders, exposure techniques represent a major component of CBT for these clinical conditions. Exposure methods are usually graded: the patient begins to face situations or stimuli that trigger lower anxiety's levels and then is progressively confronted with stimuli that may produce higher levels of anxiety. Exposure to these feared or avoided situations allows the patient to gather data that are inconsistent with the beliefs that produce his anxiety. Exposure can be implemented *in vivo* or in imaginal mode.

Applications of CBT to specific disorders:

CBT has received a considerable attention in recent years because of its strong evidence base. There is an extensive literature supporting the efficacy of cognitive-behavioural therapy for many psychiatric disorders. Cognitive and behavioural therapies were first applied to mood and anxiety disorders and then they were extended to eating disorders, somatoform disorders, substance abuse, personality disorders and, recently, even to schizophrenia in conjunction with medication. Therefore, the efficacy of CBT has been studied taking into consideration for a wide variety of clinical conditions.

- ***MOOD DISORDERS:***

There is a growing evidence supporting the efficacy of CBT in combination with pharmacotherapy in the treatment of mood disorders.

Depression:

CBT of depression focuses on the cognitive restructuring of the major cognitive patterns that induce the patient to see himself, his future and his experiences in an idiosyncratic manner. At the same time, it involves behavioural strategies, such as weekly activity schedule, that are used not only to change the behaviour but also to elicit cognitions associated with specific behaviours. Different studies have demonstrated the efficacy of CBT in reducing the symptoms of depression and patients maintain their treatment gains at 3 and 6 months follow-up.

Bipolar disorder:

CBT in conjunction with mood stabilizers and regular psychiatric follow-up reduces relapse rates in the short term and improves symptoms and social functioning in the long term.

- ***ANXIETY DISORDERS:***

CBT is considered the gold standard psychotherapy for anxiety disorders. Recent meta-analyses have demonstrated that CBT is efficacious in treating anxiety disorders and there is some evidence suggesting its long-term efficacy. CBT is associated with greater improvement on measures of anxiety, panic, fear, avoidance, depression and quality of life. Moreover, CBT reduces the risk of relapse relative to pharmacotherapy alone.

Panic disorder:

Several studies showed the important therapeutic role of cognitive techniques through which the patient identifies maladaptive beliefs with regard to bodily sensations and then modifies them with more adaptive beliefs.

Social phobia:

Treatments for social phobia include exposure, social skills training and cognitive restructuring. Therefore, on the one hand, cognitive-behavioural therapists employ exposure methods to habituate anxiety and, thereby, enable the patient to function in the presence of other people. On the other hand, cognitive interventions target the negative beliefs about the self, helping the patient construct a more accurate image about himself as a social actor.

Specific phobia:

Exposure-based treatments represent the treatment of choice for specific phobia, however, adding cognitive restructuring appears to produce better outcomes than exposure alone.

Generalized anxiety disorder:

CBT therapists help patient to recognize anxious thoughts, seeking helpful alternatives and taking action to test these alternatives. At the same time, interventions include psychoeducation, applied relaxation and imaginal and in vivo exposure.

CBT has been found to produce better outcomes for patients with GAD than psychodynamic therapy.

- ***OBSESSIVE-COMPULSIVE DISORDER:***

Most behavioural and cognitive-behavioural treatments for OCD induce change via exposure and ritual prevention. Exposure and response prevention (ERP) is considered to be the first-line psychotherapy for the disorder. ERP aims to break this cycle of symptoms by eliminating rituals and avoidance, thereby teaching patients how to tolerate distress without engaging in counterproductive behaviours and providing "corrective information" that challenges people's existing fear response. More cognitively approaches to OCD help the patient to identify, evaluate and alter problematic beliefs.

- ***POST TRAUMATIC STRESS DISORDER (PTSD):***

Trauma-focused cognitive-behavioural methods, such as stimulus confrontation and cognitive restructuring, have proved to be efficacious and are often the treatments of choice for individuals with PTSD.

However, EMDR, an evidence-based treatment, has become one of the most used treatment for PTSD and its effectiveness has undergone the scrutiny of several meta-analyses. EMDR consists of a standard protocol which includes eight phases and bilateral stimulation (usually horizontal saccadic eye movements) to desensitize the discomfort caused by traumatic memories and the aim of the therapy is to achieve their reprocessing and integration within the patient's standard biographical memories.

- ***EATING DISORDERS:***

Eating disorders provide one of the strongest indications for CBT since their core psychopathology, the over-evaluation of shape and weight, is cognitive in nature.

CBT is the treatment of choice for bulimia nervosa and for binge-eating disorder. Regarding to anorexia nervosa CBT has made great advances over the last ten years appearing to be a viable and promising treatment for patients with AN, with about 40 % of adults and almost 60 % of adolescents reaching and maintaining a normal weight range. The increase in weight is accompanied by a decrease in eating disorder psychopathology and over half of adult and about 80 % of adolescent patients reaches and maintains minimal residual psychopathology.

- ***PERSONALITY DISORDERS:***

There is a strong support for the use of cognitive-behavioural psychotherapy for personality disorders in terms of efficacy and effectiveness. The intervention typically includes clinical assessment, cognitive conceptualization, technical interventions and building and using the therapeutic

relationship. Among the empirically investigated evidence-based therapies we can mention Dialectical Behaviour Therapy (DBT), Schema Therapy (ST), Acceptance and Commitment Therapy (ACT) and Rational-Emotive Behaviour Therapy (REBT). The majority of the studies focused on Borderline Personality Disorder (BPD) and DBT has been studied the most and is currently considered the most effective treatment for BPD. DBT conceptualizes BPD with the Biosocial Theory which suggests that BPD is primarily a dysfunction of the emotional regulation system and BPD arises from a transaction between biological vulnerability and invalidating environments. Since the DBT model assumes that individuals with BPD lack key interpersonal, self-regulation and distress tolerance skills, the therapy is designed to facilitate the learning of these skills through individual therapy and group therapy.

PSYCHODYNAMIC PSYCHOTHERAPY:

Psychodynamic therapy derives from psychoanalysis whose origins date back to Sigmund Freud in the late 1890s and the early 1900s. However, today psychodynamic therapy differs dramatically from the original approach.

Gabbard, in order to describe contemporary long term psychodynamic therapy, proposed the following definition which is partly based on Fonagy's conceptualization: a set of psychotherapeutic treatments, some specifically tailored to disorders and others more general that are based on a thoroughgoing understanding of human subjectivity and how it interacts with the individual's relationship with both the external and internal environments.

In order to distinguish psychodynamic therapy from CBT, seven distinctive features of technique have been identified by Blagys e Hilsenroth (2000):

1. Focus on affect and expression of emotion
2. Exploration of attempts to avoid aspects of experience
3. Identification of recurring themes and patterns
4. Discussion of past experience
5. Focus on therapeutic relationship
6. Exploration of wishes, dreams and fantasies.

Another distinctive feature of psychodynamic psychotherapy is that it focuses on the unique characteristics of the individual, therefore the strategies and the techniques are tailored to the patient. The duration of the therapy represents a feature that has always distinguished psychodynamic psychotherapy from other form of psychotherapy such as the cognitive-behavioural psychotherapy.

However, this aspect has changed over time and time-limited psychodynamic psychotherapies have arisen. Therefore, psychodynamic psychotherapy can be carried out both as a:

- Short-term (time-limited) treatment: the number of sessions is predetermined (STPP)
- Long-term open-ended treatment: the end of therapy is designed naturalistically.

More specifically, short-term treatments (STPP) usually last between 7 and 24 sessions, whereas Gabbard (2004) uses the term long-term psychodynamic psychotherapy (LTPP) when the treatment is longer than 24 sessions or 6 months.

Interventions:

With regard to the interventions used, psychodynamic therapy operates on a continuum from the expressive or interpretative pole, on the one hand, to supportive and emphatic pole, on the other hand. Thus, the therapist may be more expressive or exploratory at some time while shifting to a more supportive style at another, depending on the patient's needs. The more severely disturbed a patient is or the more acute his or her problem is, the more supportive and the less expressive interventions are required and vice versa.

On the expressive pole, the type of interventions that characterize psychodynamic psychotherapy consist in statements made by the therapist to explain the patient's feelings, thoughts, behaviours and symptoms linking them to unconscious fantasies, meanings or childhood origins. On the supportive pole of the continuum, therapist's interventions may include specific advice to patients on how they should live their lives, how they should behave in certain situations of their life.

Applications of psychodynamic psychotherapy to specific disorders:

Research on the outcomes of psychodynamic treatments has been relatively scares for years. However, in the last years, there is a growing body of efficacy research. We have now empirical evidence that supports the efficacy of psychodynamic psychotherapy. In addition, he pointed out that patients maintain therapeutic gains and often continue to improve after treatment has ended when the research involves follow-up measures.

- ***MOOD DISORDERS:***

The efficacy of short-term psychodynamic psychotherapy (STPP) for depression is debated. However, in the last years, a number of large-scale and high-quality studies have been conducted.

Depression:

Psychodynamic approaches to the treatment of depression focus on the patient's internal world, emphasizing "how (unconscious) motivational factors lead the patient to (mis)perceive and

(mis)interpret external reality and experiences and to create, unwillingly, problems that maintain depressive symptoms, particularly in interpersonal relationships". Recently, there has been an increasing number of studies supporting the efficacy of STPP for depression. STPP results in symptom reduction and function improvement during treatment and the gains are either maintained or further improved at follow-up.

- ***ANXIETY DISORDERS:***

Panic disorder:

Panic-focused psychodynamic psychotherapy consists in 24 sessions, twice a week. It uses substantially different techniques from CBT since it does not involve homework or exposure protocol. The therapy explores the personal meanings of panic symptoms in the light of common psychodynamic conflicts in panic disorders such as separation and autonomy.

Social phobia:

The study of Knijnik and colleagues (2004) aimed to assess the effectiveness of psychodynamic group therapy (PGT) in patients with generalized social phobia. PGT resulted superior to a placebo control group as shown by the significant changes in the anxiety's scales used.

Generalized Anxiety Disorder:

In a randomized controlled trial (Leichsenring et al., 2009) short-term psychodynamic psychotherapy (30-session treatment), which focuses on the therapeutic alliance as a corrective emotional experience that allows the patient to approach the feared situations, was associated with significant improvements in measures of anxiety.

- ***POST TRAUMATIC STRESS DISORDER:***

Psychodynamic therapy delves into the construed meanings of the traumatic event, the individual's response to it and the behaviours that developed after it, in the hope of helping patients develop insights into the factors that activate traumatic re-experiencing and gain mastery over their internal experiences through more effective coping.

Empirical and clinical evidence suggests that psychodynamic approaches may result in improved self–esteem, increased ability to resolve reactions to trauma through improved reflective functioning, increased reliance on mature defences and decreased reliance on immature defences and improved social functioning. In addition, psychodynamic psychotherapy results in further improvement after treatment ends.

- ***EATING DISORDERS:***

Psychodynamic therapists focus on the meaning of the symptom in terms of the patient's history and of their experience with their family and also on the effects of the symptom and its influence upon the patient's current relationship. Psychodynamic psychotherapy produces significant improvements in symptomatology, however some improvements, such as gain weight, are not always maintained after treatment's end.

- ***PERSONALITY DISORDERS:***

Dynamic therapist working with patients with personality disorders utilize models of personality pathology that emphasize developmental distortions and anomalies in cognitive and affective processes in the understanding of self and others. These underdeveloped or distorted internalized representations are the object of assessment and change.

Transference-Focused Psychotherapy (TFP), a form of LTPP, has proved to be an efficacious treatment for BPD through a significant diminution of the symptom criteria and significant changes in the levels of impulsivity, irritability and verbal and physical aggression.

A noteworthy psychoanalytically oriented and fully manualized treatment for BPD, is the *Mentalization-Based Treatment* (MBT). MBT was founded on the specific theoretical basis that vulnerability to frequent loss of metalizing is the underlying pathology that gives rise to these characteristic symptoms. Therefore, the treatment focuses on increasing mentalization that entails making sense of the actions of oneself and others on the basis of intentional mental states, such as desires, feelings, and beliefs.

Overall, psychodynamically-orientated psychotherapy reduces personality pathology, reduces symptoms and improves social functioning in patients presenting with a mixture of PD clusters A, B, C, and NOS (Not Otherwise Specified).

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