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Manifesto for an ECNP Neuromodulation Thematic Working Group (TWG): Non-invasive brain stimulation as a new Super-subspecialty

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Abstract
Non-Invasive Brain Stimulation (NIBS) techniques and in particular, repetitive Transcranial Magnetic Stimulation (rTMS), are developing beyond mere clinical application. Although originally purposed for the treatment of resistant neuropsychiatric disorders, NIBS is also contributing to a deeper understanding of psychiatric disorders.
rTMS is also changing the model of the disorder itself, from “mental” to one of neural connectivity. TMS allows the assessment of brain circuit excitability and eventually, of plastic changes affecting these circuits. While a clinical translational approach is, at the present time, the most adequate to meet the dimensional-circuit base model of the disorder, it refines the standard categorical classification of psychiatric disorders.
The discovery of the fundamental importance of the balance between neuroplasticity and inflammation is also now explored through neuro-modulation findings consistently with the evidence of anti-inflammatory actions of the magnetic pulses.
rTMS may activate, inhibit, or otherwise interfere with the activity of neuronal cortical networks, depending on stimulus frequency and intensity of brain-induced electric field. Of particular interest, yet still unclear, is how the relatively unspecific nature of TMS stimulation may lead to specific neuronal reorganization, as well as a definition of the TMS-triggered reorganization of functional brain modules, raising attention on the importance of the active participation of the patient to the treatment..
Configuration and state of consciousness of the subject have made subjective experience under treatment regain importance in the neuro-scientific Psychiatry based on the requirement of United States National Institute of Health (NIH) and the substantial importance of the consciousness state in the efficacy of the TMS treatment. By focusing on the subjective experience, a renaissance of the phenomenology offers Psychiatry an opportunity to become proficient and to distinguish itself from other disciplines.
For all these reasons, TMS should be included in the cluster of the sub-specialties as a new “Super-Specialty” and an appropriate training course has to be inaugurated. Psychiatrists are nowadays multi-specialists, moving from a specialty to another, vs super-specialist. The cultivation of a properly trained cohort of TMS psychiatrists will better meet the challenges of treatment-resistant psychiatric conditions (disorders of connectivity), through appropriate and ethical practice, meanwhile facilitating an informed development and integration of additional emerging neuro-modulation techniques. The aim of this consensus paper is to underline the interdisciplinary nature of NIBS, that also encompasses the subjective experience and to point out the necessity of a neuroscience-applied approach to NIBS in the context of the European College of Neuro-psychopharmacology (ECNP).

1. Introduction

There is a growing concern regarding the treatment of resistant depression and other psychiatric conditions with traditional therapeutic approaches (McLachlan, 2018; Voineskos et al., 2020). Indeed, advances in technology and emerging knowledge about the dysfunctional brain circuits underlying depression but also other mental disorders, have led to the development of different neuro-modulation techniques and, among non-invasive ones, repetitive Transcranial Magnetic Stimulation (rTMS) has become both popular and acceptable due to its tolerability. As neuroscience is unraveling circuit-specific alterations in a variety of brain diseases, we are now entering an era where treatments directed towards correcting the activity of specific neural circuits become feasible.

The idea of focally stimulating the brain to treat neuropsychiatric disorders is not new, but it is only in recent years that it has become increasingly used in clinical contexts. During the past decades, the idea of stimulating the brain has shifted from the “shock model” related to convulsivity – as for electroconvulsive therapy (ECT) – to a “connectivity model”, related to a targeting circuit-based approach. This paradigm shift is also spreading in the field of pharmacotherapy where, for instance, the use of esketamine is offered as a treatment that aims to restore prefrontal cortex functioning glutamate receptors (Abdallah et al., 2017). Connectivity changes have a key role in understanding the relationships – commonalities and differences – across neuropsychiatric disorders and in providing a framework to understand the evolution and the trajectory of a disorder (van den Heuvel & Sporns, 2019). A circuit-based paradigm has changed our approach to the therapy of several neuropsychiatric disorders, including depression, the disorder on which there is higher empirical evidence for TMS. Early 2000s studies from Helen Mayberg showed that depression is unlikely to be a disease of a single brain region or neurotransmitter system. Rather, it has been progressively viewed as a systems-level disorder affecting integrated pathways linking select cortical, subcortical, and limbic sites and their related neurotransmitter and molecular mediators (Mayberg et al., 2005), even though the causal defect could reside in one specific neuronal subset. This researcher's work has also highlighted the central role of Brodmann Area 25 (BA25 - subgenual cingulate) in depression, postulating that different interventions with varying primary mechanisms of action should be equally effective, if there is preserved compensatory capacity in the obligatory depression circuit overall (Mayberg, 2003). Changes in cortical, limbic-paralimbic and subcortical areas – especially in the subgenual cingulate – have been described following various treatments including medication, psychotherapy, sleep deprivation, ECT, rTMS and ablative surgery, as well as placebo treatments (ibidem), suggesting a common pathway of treatment efficacy and symptoms remission in depression.

The approach shift from mental disorders to brain diseases to disorders of connectivity has led to a change of focus in neuropsychiatric research: the reference point in research orientation is not the brain neither the mental anymore, but connectivity itself.

1.1. Transcranial Magnetic Stimulation: mechanisms of action

While invasive procedures, such as ECT and deep brain stimulation (DBS) are currently in mainstream clinical use, the field of non-invasive brain stimulation (NIBS), or non-invasive neuromodulation, has emerged as a promising investigational, diagnostic and therapeutic modality (Boes et al., 2018, Dell'Osso and Di Lorenzo 2020). NIBS refers to a set of technologies and techniques which allow transcranial (i.e., non-invasive) modulation of the excitability of specific brain areas and the large-scale networks to which they contribute (Boes et al., 2018). TMS is the most widely used non-invasive neuro-modulation technique in clinical neuropsychiatry: its therapeutic form, rTMS, has a modulatory effect that can persist for longer periods of time (i.e., months, if repeated daily) and has the capacity to exert its effects not only on the stimulated area but also at distant sites, involving interconnected brain networks. Therefore, by modifying brain functions, with after-effects lasting beyond the time of stimulation, rTMS opens exciting perspectives for therapeutic applications.

TMS involves the use of alternating magnetic fields to stimulate neurons in the brain. Its principle of action is based on Faraday's law, which states that "an alternating and rapidly changing magnetic field produces electric currents in an adjacent conductor". In the case of TMS, an electric current runs through a wire coil and generates a magnetic field that induces an electric current in a conducting medium, such as the brain and the nervous tissue. In 1985, this principle was successfully demonstrated in the human cerebral cortex (Barker et al.,1985) and effects of rTMS were investigated for their modulatory effects and spread in a variety of clinical neurology settings.

One of the most acknowledged evidence in regard to rTMS effects is the differential effects of low- and high-frequency stimulation: whereas low-frequency protocols ($\leq$1 Hz) are known to have an inhibitory effect on cortical excitability, high-frequency protocols ($\geq$ 5 Hz) are excitatory (Casula et al. 2014). Several studies, however, have reported increased brain activity with functional magnetic resonance imaging (fMRI) after 1 Hz stimulation. It seems that the inhibitory effect of rTMS cannot be fully generalized from motor to other functional areas of the brain. It is yet unclear why identical stimulation protocols have partly led to paradoxical effects, such as cortical excitation after inhibitory TMS. One of the most accounted hypotheses is that the direction of modulation critically depends on the target's connectivity profile and its underlying cellular composition (Castrillon et al., 2020). rTMS modulates excitability of both γ-aminobutyric acid (GABA-) and glutamatergic neurons and thereby has region-specific effects depending on the local cellular composition. As the electromagnetic field of TMS applied to the cortex spans several square centimeters "identical stimulation protocols induce different early gene expression and not all brain regions respond equally to the magnetic stimulation" (ibidem). In regard to the biological duration of pulses after-effects, current research has highlighted that the duration of the after-effects seems to vary in parallel with the length of the stimulation: a longer stimulation induces a longer duration of after-effects (Klomjai et al., 2015). For example, for Theta Burst Stimulation (TBS), intermittent stimulation (iTBS) applied for a total of 190 s increases motor evoked potential (MEP) for at least 15 min, whereas 40 s of continuous stimulation (cTBS) depresses MEP for approximately 60 minutes (ibidem). More research is needed to investigate the precise temporal dynamics of TMS pulses, in order to also specify the optimal inter-session interval between TMS sessions. Thus, it is unclear if the conventional 5-7 days treatment per week is optimal or whether the frequency of the sessions should be daily, or two or three times weekly.

1.2. Safety

The first approval for a TMS device is dated 2008, when the Food and Drug Administration (FDA) cleared the first device (Neuronetics, Pennsylvania, US) for the treatment of resistant depression. For patients with treatment-resistant depression, rTMS has been approved in Canada, Australia, New Zealand, the European Union, and Israel in addition to in the United States. Thereafter, other devices were approved, such as Brainsway (Jerusalem, Israel), Magstim (Whitland, UK), Magventure (Farum, Denmark). TMS safety guidelines have long been established: guidance regarding safety stimulation parameters can be found in the international consensus guidelines from 1998 (Wassermann, 1998) with an update in 2009 (Rossi et al., 2009). A panel of international experts developed safety guidelines, which address the undesired effects and risks of emerging TMS interventions, the applications of TMS in patients with implanted electrodes in the brain, and safety aspects of TMS in neuroimaging environments. The guidelines also recommend limits of stimulation parameters and other important precautions, such as patient monitoring, expertise of the rTMS team and ethical issues (ibidem). The overall safety profile of NIBS is excellent when the safety guidelines (as outlined by an international panel of experts in 2009) are adhered to closely (Boes et al., 2018).

1.3. Target and dose

The mechanism of action of TMS has yet to be fully elucidated. While one of the preliminary and most robust findings is its ability to modulate cortical excitability in the brain regions directly targeted by the coil, nowadays the concept of focality is evolving. Brain targets and optimal dosing are two of the most important and discussed parameters of rTMS stimulation.

1.3.1. Target

The use of TMS and neuro-modulation techniques in clinical practice has a solid neuro-scientific basis. The Research Domain Criteria (RDoC) approach has been launched by the United States National Institute of Mental Health with the purpose of implementing the awareness of clinicians that what they assess and treat clinically represents a visible expression of a circuitry dysfunction with a disorder of connectivity. It aims to inform a future classification scheme, conceptualizing mental disorders as disorders of brain circuitry and assuming that the dysfunctions characteristic of mental illness can be identified with the tools of clinical neuroscience (Insel, 2010). The RDoC project is based upon the idea that psychiatric disorders result from underlying neural circuits alterations, and that these dysfunctions can/will be identified by current or future tools of neuroscience: its ultimate goal is “precision medicine” for psychiatry or, in other words, a diagnostic refinement based on a deeper understanding of the circuitries and networks of psychiatric disorders considered to be brain diseases (Insel, 2014). As every research model, RDoC exhibits shortcomings and has not been formalized as unique reference model for brain research. Nevertheless, it deserves credit for generating data to inform research on neuro-circuitry.

The idea of a ‘map of neural connections’ is a long-known inspiring idea that led to the production of a myriad of “protoconnectome maps” throughout the centuries, each one reflecting the theory and method of investigation that prevailed at the time (Catani et al., 2013). The evolution of technologies runs parallel to the evolution of the concept of connectivity and connectivity maps.

Historically, a number of approaches have followed over the years: from lesion-specific methods to colorimetrics as in Brodmann Areas, to surgical brain exploration as in Penfield’s research, to tractography and neuroimaging. We are now oriented toward the latest innovations such as functional connectivity and anticorrelation between brain regions. The development of TMS is redesigning connectivity maps and is overtaking MRI and neuroimaging due to its direct relationship with the clinical picture. TMS is therefore becoming the neuro-scientific basis of connectivity research and clearing the way to personalized treatment based on individual differences in brain connectivity.

Consistently, current identification of targets for rTMS treatment is increasingly personalized and based on individual morphology and connectivity. Among these, connectivity is the most intrinsically complex concept, since there are two main types of brain connectivity: structural and functional. Analysis of functional connectivity may estimate functional connectivity (correlation or coherence between two regions, with no directionality) or effective connectivity (estimating the directionality of the connectivity) Functional brain connectivity has become one of the most influential concepts in modern cognitive neuroscience, with the identification of complex brain functions that involve synchronous processing in a wide-spread network (Fingelkurts et al., 2005). It has long since been posited that TMS can impact upon brain activity in regions that are distant from the stimulation site as well as modulating functional connectivity between pairs of brain regions that are not directly stimulated. The development of new TMS interventions should take into account the propagation of stimulation effects beyond the immediate stimulation vicinity. The idea of the ability of pulse propagation limited to “one synapsis away” has been progressively dismissed in favor of a more extended network propagation, supported by studies demonstrating that TMS-induced activity evoked by TMS of the left dorsolateral prefrontal cortex (DLPFC) has the ability to, directly or indirectly, propagate from the DLPFC to the subgenual anterior cingulate cortex (sgACC) (Vink et al., 2018).

Choosing stimulation targets based only on local cortical abnormalities may result in unknown and potentially detrimental downstream effects (Cocchi et al., 2018). Connectivity maps can be used to infer the brain-wide effects of stimulation relative to a local stimulation site. Therefore, therapeutic TMS should be evaluated in light of the network of brain regions in which the targeted cortical area belongs (ibidem). Brain connectivity can be measured or inferred at multiple levels: structural (or anatomical) connectivity refers to the existence and structural integrity of tracts connecting different brain areas (i.e. white matter tracts connecting cortical areas/nuclei), effective connectivity is the causal influence that neural populations exert over each other, and can be inferred from functional imaging data (fMRI, EEG); functional connectivity refers to the consequences of these causal interactions; for example, correlations between region- or source-specific time series. TMS techniques can make a contribution to the study of brain networks. For example, concurrent transcranial magnetic stimulation and electroencephalography (TMS-EEG) has emerged as a powerful tool to non-invasively probe brain circuits in humans, allowing for the assessment of several cortical properties such as excitability and connectivity. While techniques such as EEG, fMRI and Positron Emission Tomography (PET) are able to evaluate functional connectivity, defined as the temporal correlations between spatially remote neurophysiological events: the integration of TMS with the above mentioned neuroimaging methodologies could be a potential tool to reveal the effective connectivity, defined as the influence one neural system exerts over another through causal or non-causal effects (Hallett et al., 2017). The relevance of intrinsic functional connectivity for rTMS has been highlighted by Fox and colleagues (2012) suggesting that it is more clinically effective in treating depression when targeted specifically to Brodmann area 46, because this area has intrinsic functional connectivity (negative correlation) with area 25. Some authors argued that anticorrelation with the subgenual is related to antidepressant response and used resting-state functional connectivity MRI (fcMRI) to individually target the region of left DLPFC most anti-correlated with the sgACC(Cole et al., 2019; Williams et al., 2018). On the other hand, a recent review summarizes that rTMS reliably induces changes in resting-state functional connectivity, but that the direction of these changes is not totally consistent with the common frequency-dependent heuristic observed for proximal effects (Beynel et al., 2020). This relatively new field with disparate studies still displays high variability between results and therefore findings should be taken in the context of several important limitations that should be taken into account in future studies. At this time, no recommendations can be provided regarding optimal stimulation parameters as well as for optimal resting state data collection (e.g. eyes open, eyes closed, maintain central fixation) and the type of analysis (e.g. seed-based or data-driven).

The recognition of high levels of treatment resistance led to a critical revision of a non-circuit-based approach in target identification. The cortical stimulation target is perhaps the parameter that is most commonly considered for personalization. Nonetheless, other parameters (such as frequency, intensity, and number of pulses) also require optimization. For example, the stimulation intensity can be adjusted as a function of the scalp-neuropil distance, which can vary markedly between the motor cortex and other regions: not taking this variability into consideration may result in suboptimal stimulation protocols that generate heterogeneous effects across sites (Cocchi et al., 2018). Imaging-guided neuro-navigation to target a given cortical region has been shown to increase the response to rTMS treatment in psychiatric disorders including depression. Recent evidence suggests to extend this basic form of personalization to include interindividual variability in relation to gender, age, clinical symptoms, brain connectivity, brain chemistry, and genomic information. In addition to improving treatment efficacy, this level of personalization may lead to a better understanding of heterogeneity in neuropathology across patients and provide a deeper understanding of the biological mechanisms of action underpinning TMS (ibidem).

Recent methodological advances suggest that the current theta-burst protocols might be improved through precision targeting of the left DLPFC to sgACC circuit. Resting-state functional connectivity might be helpful to increase the targeting precision by performing functional connectivity magnetic resonance imaging (fc-MRI) guided TMS (Cole et al., 2020).

Also, TMS can directly probe the excitability of neocortical networks, as reflected for instance in fluctuations of EEG alpha activity, while bypassing the afferent sensory pathways that are subject to thalamic gating (Romei et al., 2008a, 2008b; Sauseng et al., 2009).

1.3.2. Dosing

It is increasingly recognized that a higher overall number of stimuli dose is associated with higher efficacy of rTMS treatment (Kaster et al., 2018), consistent with DBS studies, where up to 500,000 pulses are delivered each day. In the case of depression, it is possible that individuals with a higher degree of treatment resistance display neuroplasticity impairments. Thus, highly treatment-resistant individuals may require a higher amount of stimuli to obtain a clinical response, and individuals with the highest degree of treatment resistance may require maintenance iTBS therapy (Cole et al., 2020). This is a more efficient form of rTMS and it has been recently approved by the FDA. iTBS can deliver a massive amount of stimuli in only 3 minutes and produces equivalent antidepressant responses to traditional TMS. Finally, recent studies have implemented an accelerated treatment protocol, in which multiple sessions (10/day) are, for instance, delivered every day with an inter-session interval of 50 minutes for 5 consecutive days (Cole et al., 2020; Williams et al., 2018), with optimal tolerability and promising results in terms of clinical efficacy.

1.4. EFFICACY

rTMS can produce significant clinical improvement in various neurological and psychiatric disorders (Lefaucheur et al., 2020) and the latest evidence-based guidelines from 2020 also summarize the specific effectiveness in a number of neuropsychiatric disorders. Specifically, Level A evidence (definite efficacy) was reached for neuropathic pain, depression and post-acute stage of stroke. Level B evidence (probable efficacy) was reached for improving quality of life or pain and in fibromyalgia, for improving motor impairment or depression in Parkinson's disease, motor recovery at the post-acute stage of stroke, lower limb spasticity in multiple sclerosis, posttraumatic stress disorder, chronic post-stroke non-fluent aphasia, depression and bihemispheric stimulation of the DLPFC combining right-sided LF-rTMS (or continuous theta burst stimulation) and left-sided HF-rTMS (or intermittent theta burst stimulation) in depression. Level A/B evidence is not reached concerning efficacy of rTMS in any other condition (ibidem).

Diagnosis	rTMS protocol/s	Level of evidence
Neuropathic Pain	HF-rTMS of M1 contralateral to pain side	Level A
	LF-rTMS of M1 contralateral to pain side	Level B
Fibromyalgia	HF-rTMS of the left M1	Level B
	HF-rTMS of the left DLPFC	Level B
Parkinson's Disease	HF-rTMS of bilateral M1 regions	Level B
Motor Stroke	LF-rTMS of contralesional M1	Level A
	HF-rTMS of ipsilesional M1	Level B
	LF-rTMS of contralesional M1	Level C
	LF-rTMS of right IFG	Level B

(*continued on next page*)

Diagnosis	rTMS protocol/s	Level of evidence
Multiple sclerosis	iTBS of the leg area of M1 contralateral to the most affected limb (or both M1)	Level B
Alzheimer's Disease	Multisite rTMS-COG	Level C
Depression	Deep HF-rTMS over the left DLPFC	Level A
	Bilateral right-sided LF-rTMS and left-sided HF-rTMS of the DLPFC	Level B
	right-sided cTBS and left-sided iTBS of the DLPFC	Level C
Post-traumatic stress disorder	HF-rTMS of the right DLPFC i	Level B
Obsessive-compulsive disorder	LF-rTMS of the right DLPFC	Level C
Schizophrenia negative symptoms	HF-rTMS of the left DLPFC	Level C

1.5. TMS beyond the clinical application: a new culture

The application of neuro-modulation techniques, particularly rTMS, is developing beyond clinical applications. Recent evidence suggests that it contributes to a deeper understanding of psychiatric disorders that benefit from rTMS. This is allowed by the embedding of rTMS in a digital ecosystem (including mobile EEG, machine learning, big data analysis, etc.) that allows for assessment of individual and inter-individual neural connectivity dynamics over longer periods of time. As a first step, the identification of neural connectivity features in psychiatric disorders is of crucial importance. Recent research highlighted the heterogeneity of neural connectivity patterns in major depressive disorder (MDD): Helm and colleagues (2018) demonstrated that brain regions that are most consistently affected across connectivity studies in depression are the orbit-medial prefrontal cortex, anterior cingulate cortex, amygdala, hippocampus, cerebellum and the basal ganglia, therefore extending the involved circuitries beyond the cortico-limbic network (Helm et al., 2018). This kind of evidence may also account for the differential effects of scientifically proven effective antidepressants. Antidepressants support the reorganization of pathological connectivity and changes in the concentrations of neurotransmitters or neuromodulators could have long-term effects on the neuronal organization of the brain and, by this, on depressive symptoms (Kozel et al., 2011; Li et al., 2013).

The identification of neuropsychological subtypes (or biotypes) of depression represents an example in this direction. This type of approach has already given some insights into how differing biological mechanisms may give rise to overlapping, heterogeneous clinical presentations of psychotic disorders and neuroimaging biomarkers of abnormal brain function have proven utility in the assessment of pain and have also shown promise for depression, both for the prediction of treatment response and for treatment selection.

Drysdale and colleagues (2015) showed that patients with depression can be subdivided into four biotypes defined by distinct patterns of dysfunctional connectivity in limbic and frontostriatal networks. These biotypes cannot be differentiated solely on the basis of clinical features, but they are associated with differing clinical-symptom profiles defined by distinct patterns of dysfunctional connectivity in limbic and frontostriatal networks (ibidem). It is posited that they also predict responsiveness to TMS therapy, since connectivity features predicted individual differences in the rTMS responsiveness with 78.3% accuracy. In addition, classification according to connectivity features plus biotype diagnosis yielded the highest predictive accuracy (89.6%). By contrast, clinical symptoms alone were not strong predictors of rTMS treatment responsiveness at an individual level: they were only modestly (62.6%) predictive of treatment responsiveness (Drysdale et al., 2015). Nevertheless, these results have been recently criticized due to the methods employed in the study. In a few attempts to replicate the results, other research groups found non statistically significant results after rigorous statistical tests (Dinga et al., 2019; Mihalik et al., 2020).

Whereas the identification of response trajectories to rTMS may be important to: a) enable individualized prediction of fast response, slow response, and non-response to rTMS using baseline clinical characteristics; b) help determine whether the optimal treatment duration to achieve remission varies among individuals, as does pharmacotherapy; and c) offer clues regarding the biological heterogeneity of major depression itself, based on pace of response (Kaster et al., 2019), studies on this topic are still scarce. A recent study (Kaster et al., 2019) found four distinct trajectories to an acute course of dorsolateral prefrontal rTMS in depression: nonresponse, rapid response, and two intermediate response trajectories. Greater age, absence of benzodiazepine use, and lower baseline depression severity were associated with the rapid response trajectory, and greater baseline depression severity was associated with the non-response trajectory.

In summary, the optimal approach towards rTMS is to encompass a translational clinical neuroscience view, consistent with the goal of the European College of Neuropsychopharmacology (ECNP) and should not be considered as just another treatment to be added to the therapeutic arsenal.

1.5.1. NIMH requirements

As rTMS is increasingly been considered as a technology applied to Psychiatry or a neuro-scientific tool to redefine the field, recently the NIMH underlined the requirements and core parameters to be considered in the use of rTMS. NIMH pays special attention to research in neuro-modulation and suggest lines of research, whereas European countries largely differ one to another in regard to approvals of protocols, insurance covering and seem to have a less univocal policies. Three main features should be investigated:

A) the waveform of electric field (E-field modeling),
B) the precise localization of target, and

C) the consciousness state before and after stimulation (NIMH Non-Invasive Brain Stimulation E-Field Modeling Workshop; 2017).

Summarizing the specific guidance regarding meeting the requirements to specify the spatial, temporal, and contextual aspects of dosing for devices, the NIMH underlined that all aspects of delivered dose should be thoroughly defined, modeled, and where appropriate, measured. This mainly includes: a) Spatial aspects (realistic head modeling simulates electric field induced, amplitude, and spatial distribution, evaluate degree of target to non-target stimulation, demarcate threshold for neuronal activation, show reached at target and not at non-targets, toolsets for neuro-navigation); b) Temporal elements (pulse shape, pulse direction, frequency, train duration, inter-train interval); c) Context (temporal correspondence to underlying neural oscillations in open or closed-loop fashion, brain state at time of administration, on-line or off-line cognitive/behavioral therapies, social context of device delivery, concomitant pharmacological intervention, interest in multi-modal strategies). In particular, the critical elements of target engagement include: (i) the ability to reach the target, (ii) the ability to modulate the target (mechanism of action); and (iii) dose-dependence. The consciousness state has been recently measured by Transcranial Magnetic Stimulation combined with electroencephalography (TMS/EEG) to quantify brain complexity in wakefulness and during physiological (sleep), pharmacological (anesthesia) and pathological (brain injury) loss of consciousness (Sarasso et al., 2014). Usually, high definition EEG (hd-EEG) is combined with TMS to measure with good spatiotemporal resolution the brain response to the direct perturbation of different subsets of cortical areas..

2. Assessment

The administration of rTMS within a translational approach should include a careful and comprehensive assessment of the patient before undergoing treatment. This includes not only collecting his/her recent and past history, clinical symptoms and current medications, but also encompasses more neuro-psychologically-oriented tools. While the variables to consider before commencing rTMS treatment have been well-described in a recent Consensus Recommendation (McClintock et al., 2018) including patient's personal or family history of epilepsy, seizure, head trauma, loss of consciousness, stroke, brain tumor, traumatic brain injury, any implanted medical devices, any metal in the head and current use of medications that lower seizure threshold and of alcohol/substances, there are other neuropsychological data to be collected. For example, EEG can detect the response of a cortical area to the TMS pulse (i.e., cerebral reactivity) based on the related electric markers of its activity, namely TMS-evoked potentials (TEPs). The analysis of TEP characteristics such as latency, amplitude, polarity, and waveform can offer an insight into the physiological state of the stimulated brain area, allowing researchers to tackle inference with TMS mechanisms. On the other hand, neuroimaging techniques such as fMRI, PET, single photon emission computed tomography (SPECT), and near-infrared spectroscopy (NIRS), which provide better spatial resolution than basic forms of EEG, offer a detailed picture of responses to TMS throughout the brain. One of the most direct exemplifications of a neuroimaging contribution is the demonstration of the spread dynamics of TMS-evoked activity from the stimulated area to the connected regions (Casula et al., 2013).

2.1. Neuro-modulation and Psychotherapy

The idea of coupling neuro-modulation with current established psychotherapeutic interventions for psychiatric disorders is increasingly spreading, as the potential synergistic rather than additive effects are intriguing. This evolves from the recognition of the importance of the 'state' of the targeted cortical region during the stimulation, which greatly influences its effects (Luber and Lisanby 2014). The concept of "state dependency" has led to re-conceptualizing neuromodulation as an interaction between external stimulus and the underlying state of the stimulated region or network. Given that TMS effects are state dependent, methods to control ongoing neural activity in the targeted region and associated networks during stimulation may improve outcomes and reduce inter-individual variability in response. One potential way of achieving the goal of state-control is to combine neuro-modulation with targeted, cognitive-behavioral techniques. Such a combination is a potentially promising approach to maximize the benefits to be gained from either intervention (Sathappan et al., 2018).

A recent implementation of coupled rTMS with cognitive behavioral therapy (CBT) is the use of personalized symptom provocation (to determine arousal in the involved neurocircuitry) during deep TMS (dTMS) in obsessive-compulsive disorder (Carmi et al., 2019). The provocation procedure was administrated by a certified and trained staff member before each treatment session, with the aim of achieving a self-reported distress score between 4 and 7 on a visual analogue scale ranging from 1 to 10. The staff guided the patient through the hierarchical list and chose the item that triggered the required distress score. Once the score was achieved, the patient was asked to keep thinking about this specific obsession during the treatment. This method was also examined in smoking cessation studies (Dinur-Klein et al., 2014), stating that the level of arousal of the circuitry is not less important than the area in which the circuitry is stimulated.

One of the leading ideas underlying the conjunct use of rTMS and psychotherapy is the possibility to reinforce the effects of psychotherapy by inducing neural plasticity, therefore amplifying learning phenomena through Long-Term Potentiation (LTP). Notably LTP and Long Term Depression (LTD) are thought to be key mechanisms supporting the long-term changes in synaptic strength following exposure to TMS. LTP enhances synaptic strength and can persist for several days, weeks, or months, whereas LTD results in the long-term reduction of synaptic strength. LTP is induced by high-frequency, or theta-burst, stimulation or a situation in which the stimulation of a presynaptic neuron is followed by the stimulation of a postsynaptic neuron within several tens of milliseconds. On the other hand, LTD is caused by low-frequency stimulation or the stimulation of a post- synaptic neuron that is followed by the stimulation of a presynaptic neuron within several tens of milliseconds (Chervyakov et al., 2015).

2.2. Pharmacotherapy and neuro-modulation

The combination of pharmacotherapy and TMS to study the effects of drugs on TMS has considerably improved our understanding of the effects of TMS on the human brain. Also, since in the clinical practice most of TMS interventions are carried out in subjects undergoing concomitant pharmacological therapy, the importance of clear insights on the mutual effects of the treatments is mandatory. While it has long since been known that some drugs may alter cortical excitability and increase the risk of seizure, the link between pharmacological and neuro-modulation-induced synaptic plasticity has yet to be fully elucidated. A recent contribution helps to highlight the acute effects of centrally-active drugs on TMS measures of human motor cortical plasticity as well as the effects of CNS active drugs on several well-explored TMS-EMG measures of corticospinal and motor cortical excitability (Ziemann et al., 2015). For example, it is noteworthy that: a) lamotrigine is able to increase resting motor threshold; b) diazepam and lorazepam are able to decrease silent period duration; c) haloperidol, methylphenidate and atomoxetine increase intra-cortical facilitation (ibidem).

There is a need for a TMS oriented pharmacotherapy: specific strategies for TMS in combination with pharmacotherapy for acute treatment, sequentially when transitioning from acute TMS therapy to maintenance medication therapy, and again in combination if TMS reintroduction is needed during the maintenance period. In combining TMS and pharmacotherapy, some clinical considerations are to be made. First, all concomitant psychotropic medications should be carefully categorized as partially helpful or not helpful. Medications that are not at least partially helpful should be sequentially tapered and stopped. Medications that contribute to adverse effects (e.g., weight gain) and have not been helpful should be tapered first. Ideally, a patient's medication regimen should be stable for at least 2-4 weeks prior to starting TMS: this preparation allows the physician to specifically assess the adverse effects and response to TMS (Janicak & Dokucu, 2015). Also, the risk for symptoms worsening with medication changes during TMS is to be carefully considered. A plan about any medication changes to be performed during TMS therapy should be formulated, in accordance with the with patient's psychiatrist if this is not the TMS clinician. One important consideration to be made for bupropion is that it carries a more prominent warning regarding its seizure-inducing potential (ibidem).

2.3. Education of future generations

The dissemination of a novel culture of neuro-modulation inevitably relies on a revision of the academic background of Psychiatry residents. We here took TMS as example neuro-modulation treatment strategy. DBS and transcutaneous direct current stimulation are other currently available brain-directed treatment options. But there are more at the horizon. Now that gene therapy has been approved for the treatment of spinal muscular atrophy (Mendell et al., 2017) and certain retina diseases (Campa et al., 2017), genetic modulation of neural circuit function comes in reach. One promising future therapeutic strategy is chemo-genetics, where specific neural circuit activity can be controlled by an otherwise inert drug (Sternson et al., 2014). Specialized training in neuro-modulation should include a thorough consideration of neuro-circuitry and neuro-anatomy (reflecting the paradigm shift from brain disorders and Brodmann Areas to disorders of connectivity) with consideration on state-dependent effects of neuro-modulation and their integration with neuroimaging methods to understand coupling between brain networks deputed to specific functions, as well as neural plasticity, in order to understand the physiological properties of neuro-modulation-induced plasticity and the mechanisms of LTP and LTD which are responsible for learning phenomena. Also, evidence of the impact of inflammation in psychiatric disorders, where abnormal profile of circulating pro- and anti-inflammatory cytokines is often observed, should be part of the residency topics since future psychiatrists are required to be fully aware of inflammation and plasticity mechanisms. In fact, an increasing number of studies show that both inflammation and neural plasticity act as key players in the vulnerability and recovery from psychiatric disorders and neurodegenerative diseases and the interplay between these two, although limitedly explored, seems to support the notion of a range of "optimal inflammation" with acute treatment with pro- and anti-inflammatory agents impair neural plasticity in a dose dependent manner (Golia et al., 2019). Neuro-inflammation is also is one of the possible targets for TMS effects: TMS seems to exert neuro-protective effects on remote degenerative mechanisms, such as apoptotic cell death and glial activation (Sasso et al., 2016). This could support an anti-inflammatory effect, and, subsequently, a possible anti-oxidant one of some paradigms of TMS (Yang et al., 2010; Pena-Philipides et al., 2014; Medina-Fernadez et al., 2017; for a review Medina-Fernardez et al., 2018). Whereas all treatments, both neuro-modulation (DBS (Perez-Caballero et al., 2014), transcranial direct current stimulation (tDCS), ECT (van Buel et al., 2015), transcranial vagal nerve stimulation (tVNS) and pharmacological (SSRIs)) have anti-inflammatory effects, rTMS has been shown to exert specific effects. These include an increase in serum levels of brain-derived neurotrophic factor (BDNF), interleukin (IL)-1β, and tumor necrosis factor (TNF)-α in elderly patients with refractory depression (Zhao et al., 2019). The effects of magnetic stimulation influence a variety of factors including neuronal morphology; glial cells; neurogenesis; cell differentiation and proliferation; apoptotic mechanisms; the concentrations of neuro-mediators, ATP, and neuro-trophic factors; glucose metabolism; and the expression of certain genes. The clinical significance and positive therapeutic effects of rTMS are likely determined by various combinations of these factors (Chervyakov, 2015).

3. Conclusions

Over the last two decades, TMS has become an innovative tool for neurophysiologic research, psychological and cognitive investigation, and, ultimately, clinical treatment of a wide spectrum of neuropsychiatric conditions. Many reasons justify the unprecedented growth of preclinical and clinical investigation with NIBS techniques, and TMS in particular. Among these, its accessibility and possibility to be associated with other research methodologies and clinical devices, including structural and functional neuroimaging, electroencephalography and biological investigation. Indeed, this has permitted an unprecedented understanding of the network activity underlying both healthy human brain functions as well as connectivity changes associated with dysfunctional states, which are characteristic of neuropsychiatric disorders. Ultimately, the adoption of this circuit-based approach is modifying the subject of Psychiatry as it goes beyond the diagnostic categories as we know them in the Diagnostic and Statistical Manual of mental disorders (DSM). Its application in the field of neuro-modulation represents an extension of what is currently applied for pharmacology (i.e. ketamine), entering the era of disruptive treatments in psychiatry after a long period of "me too" therapies (Vieta, 2019).

In this context, there is a major need for psychiatrists and clinical neuroscientists to learn and be trained on TMS, NIBS and, more in general, brain stimulation under European educational initiative. Furthermore, NIBS should be included as a Psychiatry subspecialty, currently subspecialities in Psychiatry comprise the following ones included in the table.

Subspecialty	Description
General adult psychiatry	Hospital based and covers all mental disorders in the age group 18-65 years
Social and community psychiatry (includes rehabilitation)	Same age group as above, but focus is on managing people so that they are able to remain in their own homes. Broader multidisciplinary approach
Old age psychiatry	Both hospital and community based, but more focused on the latter
Child and adolescent psychiatry	Specialisation in disorders occurring during development, such as conduct disorders or depression. May be either hospital or community based
Liaison psychiatry	Hospital based service that covers inpatient wards and the accident and emergency department
Forensic psychiatry	Based in hospital, community, or prison settings and concerned with mental disorders in offenders
Substance misuse (also called addiction psychiatry)	Either hospital or community based and covers a range of addictions, the bulk of which concern alcohol and opiate misuse
Learning disability	Strong community focus and concerned with both inherited and perinatally acquired mental disorders such as Down's syndrome and cerebral palsy which affect intellectual and social function
Psychotherapy—" talking therapy"	Covers both "here and now" (for example, cognitive behavior) and "interpretive" therapies that relate to early life (for example, psychodynamic).

TMS: what a clinician should know
State of the approval; indication
Protocol and devices
Level of evidence
Standards of care (prescriber, administrator)
Covering insurance

Key research priorities
Target brain region based on functional connectivity
Biological effects and duration of pulses after-effects
Waveform of electric field
State of consciousness before and after TMS session
Relationship between plasticity and immune activation
Learning processes related to TMS

Other subspecialties which may be classified as "super specialised" (in that they are either part of a tertiary referral service or have strong academic links) are eating disorders and neuropsychiatry. For TMS the proposal would be to consider it as a super-subspecialty: the question on where and how it should be classified remains open, whereas some core elements are to be considered and assessed. Particularly, the clinical, translational, inflammatory dimensions, the combination and interaction with pharmacotherapies also considering the close relationship and coupling with psychotherapy (with symptom provocation protocols during stimulation). It is still unclear how the relatively unspecific nature of TMS stimulation leads to specific neuronal reorganization, through mechanisms implied in LTP and LTD, as well as the definition of the TMS-triggered reorganization of functional brain modules (Kozyrev et al., 2018). Two are the main principles that lead from the unspecific effects of TMS to its specificity of action: on one side, the research of the a more precisely localized stimulation target, through optogenetics and chemo-genetics, in order to optimize treatment and identify the most suitable brain area for stimulation due to its functional connectivity and subparcellation of Brodmann Areas. On the other side, an increased participation and involvement of the patient to the treatment process, with arousal and symptom provocation procedure before and during the TMS session. What is to be underlined is that recovery is in any way a learning process, namely a "re-learning" that takes place in light of neuronal re-organization following plasticity processes and that these are the main features that could orient to the development of a Clinical neuropsychiatry subspecialty comprising TMS and other neuro-modulation techniques for tertiary referral treatment center. Table 1, Table 2

Declaration of Competing Interest

SP has received grant from NIH outside the current work. AM has no conflicts of interest. PFP has received grant fees from Lundbeck LTD and honoraria from Angelini, Menarini, Lundbeck, Boehringer Ingelheim outside the current work. AML has received consultant fees from: Boehringer

Ingelheim, Elsevier, Brainsway, Lundbeck Int. Neuroscience Foundation, Lundbeck A/S, The Wolfson Foundation, Bloomfield Holding Ltd, Shanghai Research Center for Brain Science, Thieme Verlag, Sage Therapeutics, v Behring Röntgen Stiftung, Fondation FondaMental, Janssen-Cilag GmbH, MedinCell, Brain Mind Institute, Agence Nationale de la Recherche, CISSN (Catania Internat. Summer School of Neuroscience), Daimler und Benz Stiftung, American Association for the Advancement of Science, Servier International. Additionally AML has received speaker fees from: Italian Society of Biological Psychiatry, Merz-Stiftung, Forum Werkstatt Karlsruhe, Lundbeck SAS France, BAG Psychiatrie Oberbayern, Klinik für Psychiatrie und Psychotherapie Ingolstadt, med Update GmbH, Society of Biological Psychiatry, Siemens Healthineers, Biotest AG. EV has received grants and served as consultant, advisor or CME speaker for the following entities (unrelated to the present work): AB-Biotics, Abbott, Allergan, Angelini, Dainippon Sumitomo Pharma, Ferrer, Gedeon Richter, Janssen, Lundbeck, Otsuka, Sage, Sanofi-Aventis, and Takeda. CSM has no conflicts of interest. RAHA has no conflicts of interest. SD has no conflicts of interest. BD in the last three years, has received lecture honoraria from Angelini, Lundbeck, Janssen, Pfizer, Otsuka, Neuraxpharm, Arcapharma and Livanova. CA has been a consultant to or has received honoraria or grants from Acadia, Angelini, Boehringer, Gedeon Richter, Janssen Cilag, Lundbeck, Minerva, Otsuka, Roche, Sage, Servier, Shire, Schering Plough, Sumitomo Dainippon Pharma, Sunovion and Takeda; CA has received funding from the Spanish Ministry of Science and Innovation. Instituto de Salud Carlos III (SAM16PE07CP1, PI16/02012, PI19/024), co-financed by ERDF Funds from the European Commission, "A way of making Europe", CIBERSAM. Madrid Regional Government (B2017/BMD-3740 AGES-CM-2), European Union Structural Funds. European Union Seventh Framework Program under grant agreements FP7-4-HEALTH-2009-2.2.1-2-241909 (Project EU-GEI), FP7- HEALTH-2013-2.2.1-2-603196 (Project PSYSCAN) and FP7- HEALTH-2013-2.2.1-2-602478 (Project METSY); and European Union H2020 Program under the Innovative Medicines Initiative 2 Joint Undertaking (grant agreement No 115916, Project PRISM, and grant agreement No 777394, Project AIMS-2-TRIALS), Fundación Familia Alonso and Fundación Alicia Koplowitz. JZ Received grants / research supports from Lundbeck, Servier, Brainsway & Pfizer, received honoraria or consultation fees from Servier, Pfizer, Abbott, Lilly, Actelion, AstraZeneca, SunPharma, Roche and Brainsway and participated in company sponsored Lundbeck, Roche, Lilly, Servier, Pfizer, Speaker's bureau: Abbott, SunPharma and Brainsway, Stock shareholder: Nil, Spouse/partner: Nil. LC has no conflicts of interest.

Author disclosure

SP, AM, PFP, AML, EV, CA, CSM, RAHA, SD, BD, LC, JZ have nothing to disclose.

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Contributors

SP contributed to the idea of the paper, the interpretation of results, the writing of the manuscript and approved the final version, AM contributed to the writing of the manuscript, PFP contributed the interpretation of the results and writing of the manuscript and has approved the final version. AML contributed to the writing of the manuscript and approved the final version. EV contributed to the writing of the manuscript and approved the final version, CSM contributed to the drafting and writing of the manuscript and approved the final version, RAHA contributed to the early editing of the paper and approved the final version, CA contributed to the editing of the manuscript and approved the final version, SD contributed to the editing of the manuscript and approved the final version, BD contributed in the editing and writing of the manuscript and approved the final version, LC contributed to the editing of the manuscript in its first and final forms and approved the final version. JZ overlooked the development of the manuscript, reviewed the draft and gave some suggestions and reviewed it in its final form.

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