INTERNATIONAL JOURNAL OF
CLINICAL NEUROSCIENCES
AND MENTAL HEALTH

REVIEW

Neuromodulation in Psychiatric disorders: recent findings and clinical implications

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Special Issue on the Neurobiology of Mental Illness

Abstract

The potential therapeutic value of electricity to treat neuropsychiatric disorders has been known for a long time. However, it is only recently that it has been successfully applied to these clinical conditions. Two of the most promising neuromodulation techniques are the deep brain stimulation (DBS) and the transcranial magnetic stimulation (TMS). DBS uses a high-frequency stimulation that causes a "reversible lesion" and is increasingly becoming an alternative for lesional surgery for its better balance between efficacy, tolerability and safety, and has consistently been shown to improve depressive and obsessive symptoms. TMS is a non-invasive and safe approach that has been approved for the treatment of major depressive disorder and for auditory-verbal hallucinations in schizophrenia and is being studied in several other psychiatric disorders, such as obsessive-compulsive disorder, eating disorders and negative symptoms of schizophrenia.

In the current paper, we will review recent evidence of these two neuromodulation techniques, its main psychiatric indications and present two brief case reports to further illustrate its clinical applicability.

Keywords: Neuromodulation, Deep brain stimulation, Transcranial magnetic stimulation, Depression, Obsessive-compulsive disorder, Schizophrenia.

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Citation: Andrade et al. Neuromodulation in Psychiatric disorders: recent findings and clinical implications. International Journal of Clinical Neurosciences and Mental Health 2017; 4(Suppl. 3):S07

DOI: https://doi.org/10.21035/ijcnmh.2017.4(Suppl.3).S07

Published: 15 Nov 2017

Introduction

Since ancient times the therapeutic potential of electricity has been known and acknowledged. The electrical ray was named *Torpedo nobiliana* by the Romans and narke by the Greeks for its ability to subdue its preys and defend itself against predators numbing them with a 220v electrical discharge. In 46 BC this fish was used to improve severe headache, and due to its remarkable efficacy in pain relief, it was widely used until the 18th century in several diseases as gout, depression and epilepsy [1].

In the beginning of the 19th century, following Faraday's work and with the development of an electrical generator, the use of electricity became progressively more common and the dogma of the "inexcitable cortex" was questioned in 1870 by Fritsch and Hitzig. In fact, the results of their research showed different types of responses, from small arm movements to seizures, depending on the intensity of electrical current applied to the brain cortex [2]. However, only 80 years later, the development of stereotaxy in 1947 by Spiegel et al. led to a true revolution in neurosurgical techniques, and conditions for brain placement of electrodes emerged [1]. With this new tool and brain mapping, mortality drops to 1%.

In the middle of the 20th century, the first reports of temporary electrode placement in different brain regions for pain control are published, and in the early 1970s chronic deep brain stimulation (DBS) begins with electrode placement in the thalamus for the treatment of chronic pain [1]. Good results that this new therapeutic strategy accomplished in the field of chronic pain, but also in movement disorders led to its application in several other clinical conditions, namely psychiatric disorders. In addition, new neuroimaging techniques (CT scan and MRI), and software brought an outstanding accuracy and, therefore, more safety to the procedure, making it a promising tool for the treatment of psychiatric illnesses like major depressive disorder (MDD) and obsessive-compulsive disorder (OCD).

On the other hand, the potential of non-invasive neurostimulation for improving psychiatric disorders has been increasingly studied over the past two decades. This is especially the case for repetitive transcranial magnetic stimulation (rTMS) that has been approved for the treatment of MDD and for auditory-verbal hallucinations in schizophrenia. Despite the limited research in other psychiatric disorders, initial evidence suggests that rTMS seems to have potential in the treatment of negative symptoms in schizophrenia, OCD and post-traumatic stress disorder.

Deep brain stimulation

Deep brain stimulation (DBS) is a recently approved neuromodulation technique as an alternative to brain surgery that offers the possibility of telemetric adjustment of different parameters individually tailored for each patient. Its high-frequency stimulation leads functionally to a "reversible lesion" through the inhibition of activity in the target region [3]. Therefore, it is an attractive therapeutic strategy for different neuropsychiatric disorders in which dysregulation of the cortico-limbic connections seems to have a major pathophysiological impact, such as OCD, MDD, addiction and anorexia.

Despite initial assumptions that DBS and lesional surgery act with similar mechanisms of action, working through the local inhibition of a pathological hyperactivity in the target region, recent findings point in a different direction. Improving signal transduction seems to be fundamental, leading to a paradigm shift that focuses more in connectivity than local effects. In fact, the combination of excitatory and inhibitory, as well as proximal and distal effects is the most likely way of inducing neuronal changes in DBS procedure [4].

DBS at high frequencies (approximately 100 Hz or greater) has been proposed to inhibit transmission by one or more of the following actions: 1) depolarization blockade, 2) synaptic fatigue, or 3) "neural jamming" (imposing a physiologically meaningless pattern of activity within the affected circuits). Any of these phenomena would produce a "functional lesion", mimicking the effect of an actual therapeutic lesion through a nondestructive mechanism [5]. Alternatively, DBS can activate neuronal networks, depending on stimulation parameters. Moreover, the intensity of the electric field is exponentially reduced with the distance to the electrode, so it might be possible that DBS inhibits neuronal activity in the centre of the stimulation area and activates the axons in the periphery [5].

The surgical procedure is initiated by mounting a stereotactic frame on the head of the patient, then a MRI is performed, and a computerized navigational system is used to the target structure identified on the MRI and a design for the trajectory is completed. A burr hole is made on each side of the midline for the implantation of two electrodes (about 1.3 mm in diameter with several contacts at their distal end) and an extension cable is tunneled under the skin, connecting the electrodes with a neuropacemaker placed below the clavicle in a subcutaneous pocket. The hospitalization duration after surgery depends on time needed for programming the device, but usually patients are discharged within 3–5 days [6].

Comparing with ablative techniques, the DBS advantages are: 1) versatility—stimulation parameters can be adjusted in each patient; 2) reversibility—with device switch off and removal. These features result in a much lower incidence of side effects with the possibility of an individualized treatment and therefore a better balance in risk-benefit. Still, DBS is not risk-free. The major risk in the operative procedure consists of intra-cerebral haemorrhages. Large studies have estimated the risk to be 1–2% with minor intracerebral haemorrhages taken into account [7]. In addition, some studies also report infection (4.3%) and seizures (0.9%) as potential risks related to the surgical procedure [8]. Implant-related complications may occur,

but they do not normally pose a serious health risk. They include fracture, displacement, disconnection and technical problems. When DBS is effective, battery failure can lead to symptom worsening, although with the increasing use of rechargeable devices this limitation is reduced with the need of replacement only every ten years. Stimulation-induced side effects in DBS are the most frequent ones and vary depending on target area and may include symptoms such as ocular disturbances, dysarthria, paresthesia, sweating and hypomania (20%). However, these side effects are reversible and can be removed changing the stimulation parameters or turning off the neuropacemaker. The stimulation does not seem to result in any residual physiological changes when the treatment is discontinued [6].

Because of it demonstrated tolerability, as well as encouraging clinical outcomes, DBS has qualified under the FDAs Humanitarian Device Exception (HDE) for a number of neurologically rooted disorders including stimulation of GPi and STN for dystonia in 2003, stimulation of the anterior limb of the internal capsule (ALIC) for obsessive-compulsive disorder (OCD) in 2009, and closed-loop stimulation for epileptic indications in 2013 [9]. This means that it is acknowledged that the health benefits surpass the potential risks and that no other available alternative is comparable, and permission to its use is given under strict supervision.

DBS in OCD

Studies in animal models and electrophysiologyical and neuroimaging studies in humans consistently report that DBS can be effective in resistant OCD patients through a hyperconnectivity reduction between prefrontal cortex (CPF) and nucleus accumbens (NAc). This is achieved through reduction of top-down-directed synchrony and reduction of frontal low-frequency oscillations. DBS appears to counteract striatal dysfunction through an increase in striatal dopamine and through improvement of reward processing. DBS affects anxiety levels through reduction of stress hormones and improvement of fear extinction [4].

All the studies published to date report very promising and consistent results on the efficacy of DBS in refractory OCD. A review of 31 studies, including 116 patients with severe OCD, shows global response rates of 60% with a 45.1% decrease in Y-BOCS score [8]. Similarly, a meta-analysis that included 10 studies with 64 OCD patients reported some heterogeneity in the response, but an overall significant clinical improvement, with a 2.77 SP reduction in Y-BOCS score [10]. Another meta-analysis also shows a partial symptom remission (mean Y-BOCS reduction of 9 points), but no significant impact in comorbid anxiety or depression [11].

The degree of effectiveness varies with the target (ranging from 52–54% for nucleus accumbens or anterior capsula/ventral striatum and 41% for subthalamic nucleus), electrode design, stimulation protocol and patient's individual clinical characteristics. For example, "just right" experiences or order-symmetry clinical symptom subtype, seem to show a poorer response when compared to other OCD symptom subtypes, even though samples are still too limited [12]. In contrast, OCD patients with a late-onset or with religious/sexual clinical symptom subtype have been associated with better response rates [8].

Another very important clinical outcome that has shown to be significantly improved is quality of life. This result is not related to symptom improvement and was reported even by non-responders. In addition, this quality of life improvement continues to rise even years after stimulation onset and when no additional clinical gain is reported, suggesting that specific factors unrelated to OCD symptoms (anxiety reduction, reward and motivation processing, affective component) influence quality of life perception, showing that patients need time to adjust and benefit from a new reality [8].

Comparing to the classic lesional surgery in OCD patients, DBS seems to have a similar, and in some studies, a superior clinical response. Approximately one third of patients show clinical improvement (reduction of over 35% in the Y-BOCS score) after one or more surgical interventions [13-15]. DBS seems to have a similar or even better response rate. According to some authors, around 60% of resistant OCD patients benefit from OCD [8, 16]. Given its safety and reversibility it is likely that it might surpass lesional surgery. However, DBS should not be seen as a first-line treatment, but as an alternative reserved for cases in which drug and psychological treatments were not effective.

The optimal target for resistant OCD is yet to be defined. The most studied targets include the anterior limb of the internal capsule (ALIC), nucleus accumbens (NAc), subthalamic nucleus (STN), ventral capsule/ventral striatum (VC/VS), the inferior thalamic peduncle (ITP) and, more recently, the bed nucleus of the stria terminalis (BST). In a recent systematic review, 25 studies reporting five DBS target structures to treat OCD were analyzed: five studies including 14 patients for ALIC, eight studies including 37 patients for NAc, four studies including 29 patients for VC/VS, five studies including 23 patients for STN and two studies including 6 patients for ITP. Despite the anatomical diversity, results showed similar response rates for the first four target structures. As for ITP, findings show a higher response rate but these results must be interpreted with caution because of the very small number of cases [17].

In Coimbra University Hospitals, 6 refractory OCD patients have been submitted to DBS using BST as the target and the first preliminary results are quite promising, showing an average improvement rate of 38.6% (**Table 1**).

DBS for MDD

DBS is a promising but still experimental therapy for patients with treatment-resistant depression. Open label studies with small samples of 6 to 20 subjects show re-

Table 1. Sociodemographic, clinical and psychometric data of OCD patients submitted to DBS in Coimbra University Hospitals.

Patient	Date	Target	Y-BOCS / DY-BOCS baseline	Y-BOCS / DY-BOCS 6 months	Rate of improvement
JR, ♂, 45y	2006	BST	38/40	16/40	55%
JGC, ♂, 46y	2008	BST	23/30	13/30	33%
MT, ♂, 47y	2010	BST	28/30	14/30	47%
AM, ♂, 42y	2013	BST	28/30	25/30	10%
AC, ♂, 36y	2015	NST	27/30	16/30	37%
FO, ♂, 38y	2016	BST	25/30	10/30	50%

sponse rates (the percentage of patients with > 50 % reduction of Hamilton Depression Rating Scale (HAMD) score) ranging from 40 to 70%, with an overall effect on all HAMD subscales, including anxiety symptoms [18]. An extended follow-up of 20 patients with treatment-resistant depression who received DBS in the subcallosal cingulate gyrus (SCC) reported progressive improvement over time and that patients who achieved remission did not show spontaneous relapses [19].

Albeit the mechanism of action of DBS on MDD remains unclear, studies using fMRI and postmortem anatomical studies indicated that abnormalities in the prefrontal cortex, the ventromedial frontal cortex, the ventral cingulum and the hippocampus appeared to be involved, namely changed patterns of activation [20]. SCC, also known as Brodmann area 25, is a critical brain hub for emotional regulation that constitutes a crossroad of path connections in the cortex [21]. SCC also plays an important role as DBS stimulation site because hyperactivity of this area has been linked with core clinical features of MDD, such as the retrieval of sad memories [22].

In a recent systematic review paper [23], 22 studies were analyzed, reporting six different anatomical sites of stimulation for MDD: three studies including 24 patients for nucleus accumbens (NAcc), three studies including 33 pacients for ventral capsule/ventral striatum (VC/VS), 12 studies including 122 patients for SCC, one case report for lateral habenula, one case report for inferior thalamic peduncle (ITP), and one study including seven patients for medial forebrain bundle (MFB). Although the results have been encouraging and consistent across studies, there are several limitations such as the small sample size and the heterogeneous inclusion criteria and outcome measures. Also, three controlled trials with sham stimulation periods found conflicting results concerning placebo effects.

Two multicentre prospective randomized trials targeting VC/VS [24] and SCC (letter from St. Jude Medical Clinical Study Management) were discontinued after the results of a preliminary analysis. It is possible that optimization of target selection and technique (e.g., higher energy delivery), modifications of inclusion criteria, and longer follow up periods might result in more reliable clinical benefit from DBS in patients with MDD. The development of new neuroimaging techniques such as diffusion tensor imaging has made possible the identification of new pathways linked with depression, which is relevant to electrode placement and programming.

Further investigation is required to confirm the therapeutic outcomes of DBS for MDD, particularly multicenter randomized and blind trials.

Case report

A 37 years old male patient was proposed for deep brain stimulation (DBS) after many years struggling with a severe obsessive-compulsive disorder (OCD). The patient presented obsessive-compulsive symptoms (mostly obsessive doubts and compulsive checking) since his childhood and the symptoms aggravated in his youth. The clinical presentation of his condition interfered with both personal and professional aspects of his life and caused significant impairment in his daily activities. He had a history of multiple hospitalizations and It was verified that the clinical condition was refractory to the combination of multiple treatments: drug treatment, cognitive behavioural therapy (CBT), and transcranial magnetic stimulation (TMS). A Dimensional Yale-Brown Obsessive-Compulsive Scale (DY-BOCS) filled before the surgical intervention showed the presence of numerous symptoms within all the six dimensions. The global severity scores for frequency (5 out of 5), distress (4 out of 5) and interference (4 out of 5) illustrated the severity and impairment of the condition. This patient spent more than 8 hours per day dealing with his obsessions and related compulsions, which was perceived as very disturbing and highly interfering.

DBS of the bed nucleus of the stria terminalis was successfully performed. Clinical follow-up has been carried out by a multidisciplinary team every two months, and drug therapy and DBS parameters have been adjusted according to the patient's feedback. The follow-up DY-BOCS global severity scores for frequency (2 out of 5), distress (1 out of 5) and interference (1 out of 5), obtained six months after surgery, were lower than those obtained before the procedure.

Transcranial magnetic stimulation (TMS)

Transcranial magnetic stimulation (TMS) is a non-invasive therapy option which can be applied to outpatients with several treatment resistant psychiatric disorders. The principle of brain stimulation with TMS is based on Faraday's law of induction for time-varying currents. Repetitive TMS mechanism of action is based on the magnetic field generated at the coil which passes unimpeded through the scalp and skull and produces changes in neuronal excitability. An electrical current is induced in the underlying tissue which modulates neural activity, and depending on the parameters of stimulation, namely choosing high or low frequencies, cortical excitability can be increased or decreased [25] and change regional brain blood flow [26]. During repetitive TMS, a fast series of brief pulses of strong magnetic stimuli are applied to the brain, leading to a more prolonged effect [27]. The diameter of the induced field is of approximately 2–3 cm, the same figure holds for the depth of stimulation, thus only cortical regions can be stimulated directly.

Although the exact mechanism of action of rTMS remains to be elucidated, there is evidence that dopaminergic neurotransmission is involved, at least for rTMS over prefrontal and motor areas. Studies have shown increased dopamine transmission in subcortical areas, but also in medial prefrontal areas, after TMS [28].

Intensity of stimulation is usually set at a certain percentage of the individual motor threshold. Motor threshold refers to the strength of the stimulus provided, which is the percentage of the total machine output that is required to produce movement of thumb or fingers. After the identification of the motor threshold, the coil is moved from the motor cortex to the specific target cortical region [28]. In contrast to ECT, no general anesthesia is required and as magnetic fields pass through scalp and skull, less energy is transferred to the brain and, therefore, less adverse effects are expected.

In fact, no long-term neurological, cognitive, or cardiovascular side effects are reported. Transient headache is the most common side effect after repetitive TMS. Scalp discomfort, transient headache and dizziness, insomnia, perceiving an odd smell, numbness in the right temporal and right cervical zone, and (in single cases) generalized seizures have been reported. There is no long-term evidence for repetitive TMS because most studies are limited to 6–12 weeks [29].

Contraindications for TMS are pacemaker, aneurysm clip, heart/vascular clip, prosthetic valve, intracranial metal prosthesis, personal or familial history of epilepsy, medications that reduce the threshold for seizure, and high alcohol or drug consumption [28].

TMS in MDD

Repetitive TMS (rTMS) was first proposed as a treatment for depression in the early 1990's and its formal approval by the United States Food and Drug Administration happened in 2008. Moreover, there is evidence for repetitive TMS either as a mono- or add-on therapy for the treatment of moderate treatment-resistant depression (evidence level I).

In a recent systematic review and meta-analysis of randomized, double-blind and sham-controlled trials, data from 29 randomized controlled trials (RCTs), totaling 1,371 patients was included. It was reported that, after approximately 13 sessions, 29.3% and 18.6% of subjects receiving rTMS were classified as responders and remitters, respectively. This was threefold of those receiving sham rTMS [30].

Regarding frequency and area of stimulation, the majority of RCTs suggest that MDD can be effectively treated by applying either high- (HF) or low-frequency (LF) rTMS to the left and right dorsolateral prefrontal cortex (DLPFC), respectively. In fact, a systematic review and meta-analysis that included eight RCTs composed of 249 patients that compared the therapeutic effects of both approaches reported that they were similar (odds ratio (OR) = 1.15; 95% confidence interval = 0.65–2.03). However, considering that LF right-sided rTMS produces fewer side effects and is more protective against seizures, its clinical applicability shows greater promise [31]. Despite the largely reported good results, the exact mechanism is still to be determined. A convergence of findings suggest that rTMS exerts its therapeutic effects by altering levels of various neurochemicals, electrophysiology as well as blood flow and activity in the brain in a frequency-dependent manner [32]. Given that abnormalities in two large-scale neuronal networks—the frontoparietal central executive network (CEN) and the medial prefrontal-medial parietal default mode network (DMN)—are consistent findings in depression and potential therapeutic targets for TMS, Liston and colleagues underwent a study using resting state functional magnetic resonance imaging to measure functional connectivity within and between the DMN and CEN in 17 depressed patients before and after a 5-week course of TMS. It was reported that TMS selectively modulates functional connectivity both within and between the CEN and DMN and modulation of subgenual cingulate connectivity may play an important mechanistic role in alleviating depression [33].

Moreover, evidence of hypometabolism of the left DLPFC was hypothesized to underlie reduced cognitive control of emotion, which has been confirmed by neuroimaging studies. In fact, a study that applied rTMS to the left DLPFC in healthy subjects found less positive affect and more monotonous speech, as it is characteristic in depression [34]. This suggests that stimulation of the left DLPFC does not merely improve positive mood indistinctively, but concerns a key node of the emotion regulation network.

TMS in other psychiatric disorders

Given its versatility and mode of action, TMS use has now been extended to other psychiatric disorders including post-traumatic stress disorder, obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, atten-

tion-deficit/hyperactivity disorder, catatonia, schizophrenia, and bipolar disorder. However, available evidence is still limited and there is a lack of RCTs that allow more definite conclusions. In Coimbra University Hospitals we are undertaking several research protocols to assess the efficacy of TMS in different psychiatric disorders such as OCD, schizophrenia (negative symptoms), and anorexia nervosa. We are also planning to extend the use of TMS to painful conditions that are highly comorbid with psychiatric disorders such as tension headaches and fibromyalgia .

In this topic we will summarize the available evidence in two of the most promising psychiatric disorders for the use of TMS: OCD and Schizophrenia.

TMS in OCD

As stated above, the depth of penetration of the magnetic field is very shallow and therefore the main target for neuromodulation is the brain cortex [35]. This led to some skepticism regarding the real efficacy in psychiatric disorders that involve subcortical circuits, like OCD. However, several studies have reported functional changes in areas that are distant from the chosen target [36].

In fact, in 1997 Greenberg and colleagues enrolled 12 patients with OCD and administered active HF-rTMS to the right and the left DLPFC (experimental condition) or to the mid-occipital cortex (control condition) for 20 min. Compulsions and depressive symptoms significantly decreased immediately after right and left DLPFC stimulation, whereas obsessions were not affected [37]. Since this initial study, several open label and randomized and sham-controlled trials (RCTs) have investigated the clinical utility of rTMS in resistant OCD patients, using different targets (DLPFC, Supplementary Motor Area and Orbitofrontal Cortex).

It remains unclear as to whether rTMS is effective for OCD, because the available data from RCTs to date have produced conflicting results [38]. Gomes et al. assigned 22 patients with OCD to either rTMS or sham over the SMA bilaterally, for two weeks, with a 3-month follow-up. At follow-up, patients receiving active rTMS showed, on average, a 35% reduction on the Y-BOCS, as compared with a 6.2% reduction in those receiving sham treatment [39]. On the other hand, a review that included 12 RCTs of rTMS on resistant OCD patients, reports no difference in OCD symptoms between the active and the control group, regardless of the chosen target [40]. Another review that included 10 RCTs with similar study design reports a significant difference between groups, with response rates of 35% in the active group against 13% in the control group. It also states that SMA and OFC seem to be the most promising target areas for OCD [41].

TMS in schizophrenia

Regarding schizophrenia, rTMS was mainly tested for the treatment of auditory hallucinations and negative symptoms, while experiences with catatonic symptoms are limited.

A recent literature review of the past 15 years, concluded that the use of TMS in schizophrenia has its greatest efficacy in treating auditory hallucinations. The frequency and severity of auditory hallucinations, in particular, may be decreased by targeting low frequency TMS stimuli to Wernicke's area in the left temporo-parietal cortex [42]. Moreover, a systematic review that compared 25 randomized, control trials using the severity of the hallucinations or psychosis as the primary outcome measure, reported that although no differences were seen with the severity of psychosis, severity of hallucinations was significantly reduced with paradigm of left temporo-parietal TMS at 1hz [43].

In which concerns negative symptoms, it has been suggested that they may be related with the so-called hypofrontality and a lack of dopamine in the prefrontal cortex [44]. It has been found that high frequency rTMS may be able to increase cortical excitability and modulate dopamine release [45, 46]. A meta-analysis of nine trials, involving 213 patients with schizophrenia, revealed a significant improvement in negative symptoms that was stronger for rTMS, than for sham. Typically, these studies involved the stimulation of the left DLPFC, as it has been done in depression, although one could argue that the right DLPFC is also of relevance as it has been implicated in negative symptoms. Thus, future studies may also include the right DLPFC as a target of neurostimulation [47].

Another meta-analysis of prospective studies on the therapeutic application of rTMS in schizophrenia assessing the effects of both low-frequency and high-frequency rTMS on negative symptoms, reported that rTMS is effective in alleviating negative symptoms in schizophrenia and a longer duration of illness was associated with poorer efficacy of rTMS on negative symptoms. The results of this meta-analysis suggest that rTMS is an effective treatment option for negative symptoms in schizophrenia. The moderators of rTMS on negative symptoms included duration of illness, stimulus frequency, duration of illness, position and intensity of treatment as well as the type of outcome measures used [48].

Case report

P is a male, Caucasian, 43-year old patient diagnosed with schizophrenia since his early 20's. He has only one hospital admission in his past history. Presently, P is a patient with residual positive symptoms (residual persecutory delusions, no hallucinatory activity) and is being followed-up regularly in the outpatient clinic. Since 2014, he is following a regime with paliperidone palmitate 150 mg monthly. Before, he was treated with haloperidol decanoate for several years. Although drug treatment has been effective in positive symptoms control, the patient has been suffering from prominent negative symptoms since at least five years (emotional blunting, apathy, lack of initiative and

motivation, anhedonia, and psychomotor retardation). A significant social withdrawal has also been evident. This patient does not have any socio-professional occupation and has been practically confined to his home, just leaving for medical appointments.

On May 2015, P accepted to participate in a pilot study of rTMS for Schizophrenia's negative and neurocognitive symptoms [49]. In this study, outcome measures were scores from Clinical Assessment Interview for Negative Symptoms (CAINS), Positive and Negative Symptoms Scale (PANSS), Personal and Social Performance (PSP), Logic Memory I and II, Digit Span, Reading the Mind in the Eyes Test (RMET) and Trail Making Test. rTMS was administered daily, five times a week, during two weeks. The patient received in each session a 10 Hz stimulus, at 110% of motor threshold, in 20 trains of 10 seconds (a total amount of 2000 pulses per day), on dorsolateral prefrontal cortex (DLPFC).

After the treatment, the patient improved many of his negative and neurocognitive symptoms (**Table 2** and **3**; **Figures 1–3**). He showed an increasing in his spontaneous movements and a better facial expression, and motivation to social and occupational tasks. He indeed showed more cordiality in social interactions, less blunted emotions, apathy and psychomotor retardation. Additionally we observed an improvement of his abstraction, memory and learning, executive function and theory of mind, abilities as well as a reduction of stereotyped thought [49].

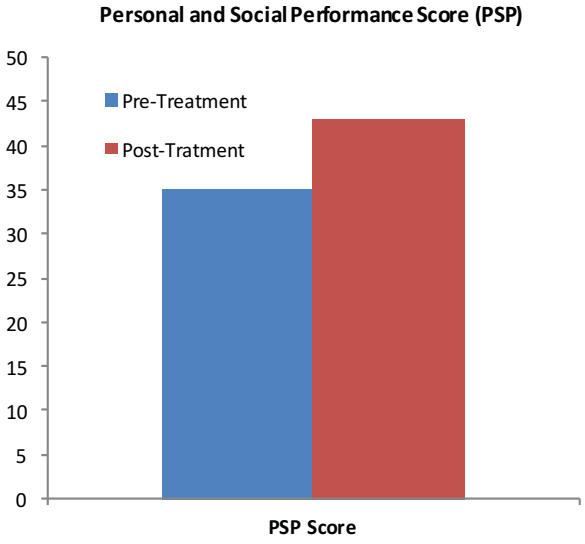

Figure 1. Personal and Social Performance score, comparing before and after treatment.

Concluding remarks

In conclusion, neuromodulation therapeutic approaches, both DBS and rTMS, are becoming progressively more accurate and, therefore, safer and more effective. In fact, DBS has proven to be a valid treatment option for several psychiatric conditions, namely MDD and OCD, and

Table 2. Clinical Assessment Interview for Negative Symptoms Scores.

	Before Treatment	After Treatment
Social Items		
1. Motivation for Close Family/Spouse/Partner Relationships	2	1
2. Motivation for Close Friendships/Romantic Relationships	3	2
3. Frequency of Pleasurable Social Activities - Past Week	3	1
4. Frequency of Expected Pleasurable Social Activities – Next Week	4	2
Work and School Items		
5. Motivation for Work and School Activities	2	1
6. Expected Pleasurable Work and School Activities – Next Week	4	2
Recreation Items		
7. Motivation for Recreational Activities	1	0
8. Frequency of Pleasurable Recreational Activities - Past Week	1	1
9. Frequency of Expected Pleasure from Recreational Activities – Next Week	2	1
Expression Items		
10. Facial Expression	1	0
11. Vocal Expression	1	0
12. Expressive Gestures	3	0
13. Quantity of Speech	0	0

(0 – no impairment; 1 – mild deficit; 2 - moderate deficit; 3 – moderately severe deficit; 4 – severe deficit)

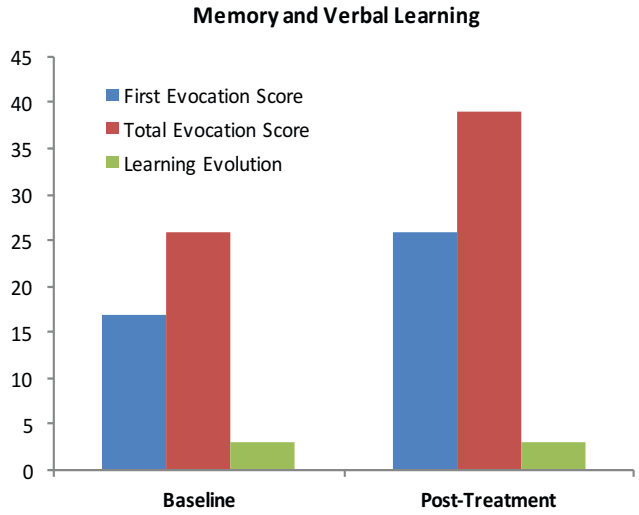

Figure 2. Memory and verbal learning score, comparing before and after treatment.

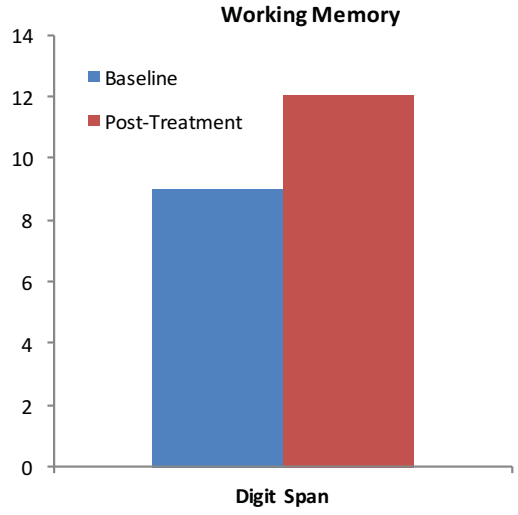

Figure 3. Working memory score, comparing before and after treatment.

research is heading towards other disorders with cortico-limbic dysfunctions, such as addiction and anorexia. On the other hand, rTMS, a non-invasive neuromodulation technique, has also shown very consistent results in treatment-resistant MDD and formal approval by the United States Food and Drug Administration happened in 2008. Although TMS is also a very promising therapeutic approach, results regarding other psychiatric conditions, such as OCD and schizophrenia, are still conflicting and further studies with more robust sample sizes are warranted to reach formal conclusions.

Abbreviations

ALIC: Anterior limb of the internal capsule; BST: Bed nucleus of the stria terminalis; CAINS: Clinical Assessment Interview for Negative Symptoms; CBT: Cognitive behavioural therapy; CEN: Central executive network; CPF: Prefrontal cortex; CT: Computed tomography; DBS: Deep brain stimulation; DLPFC: Dorsolateral prefrontal cortex; DMN: Default mode network; DY-BOCS: Dimensional Yale-Brown Obsessive-Compulsive Scale; ECT: Electroconvulsive therapy; FDA: Food and Drug Administration; fMRI: Functional magnetic resonance imaging; GPi: Globus pallidus internus; HAMD: Hamilton Depression Rating Scale; HDE: Humanitarian Device Exception; HF: High-frequency; ITP: Inferior thalamic peduncle; LF: Low-frequency; MDD: Major depressive disorder; MFB: Medial forebrain bundle; MRI: Magnetic resonance imaging; NAc: Nucleus accumbens; OCD: Obsessive compulsive disorder; OFC: Orbitofrontal cortex; OR: Odds ratio; PANSS: Positive and Negative Symptoms Scale; PSP: Personal and Social Performance; RCTs: Randomized controlled trials; RMET: Reading the Mind in the Eyes Test; rTMS: Repetitive transcranial magnetic stimulation; SCC: Subcallosal cingulate gyrus; SD: Standard deviation; SMA: Supplementary motor area; STN: Subthalamic nucleus; TMS: Transcranial magnetic stimulation; VC/VS: Ventral capsule/ventral striatum; Y-BOCS: Yale-Brown Obsessive-Compulsive Scale

Competing interests

The authors declare no conflict of interest.

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Table 3. Positive and Negative Symptoms Scale (PANSS).

	Before Treatment	After Treatment
Positive Symptoms		
P1. Delusions	1	1
P2. Conceptual disorganization	2	2
P3. Hallucinatory behaviour	2	1
P4. Excitement	2	1
P5. Grandiosity	1	1
P6.Suspiciousness/persecution	2	2
P7. Hostility	1	1
Negative Symptoms		
N1. Blunted affect	3	2
N2. Emotional withdrawal	3	2
N3. Poor rapport	2	1
N4. Passive/apathetic social withdrawal	5	3
N5. Difficulty in abstract thinking	3	2
N6. Lack of spontaneity and flow of conversation	3	1
N7. Stereotyped thinking	2	1
General Psychopathology		
G1. Somatic concern	4	1
G2. Anxiety	2	1
G3. Guiltfeelings	1	1
G4. Tension	1	1
G5. Mannerisms and posturing	1	1
G6. Depression	1	1
G7. Motor retardation	2	1
G8. Uncooperativeness	1	1
G9. Unusual thought content	2	1
G10. Disorientation	1	1
G11. Poor attention	1	1
G12. Lack of judgment and insight	2	2
G13. Disturbance of volition	2	2
G14. Poor impulse control	4	1
G15. Preoccupation	1	1
G16. Active social avoidance	2	1

(1 – absent; 2 – minimal; 3 - mild; 4 – moderate; 5 – severe moderate; 6 – severe; 7 - extreme)

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