The Use of Transcranial Magnetic Stimulation (TMS) for Obsessive-Compulsive Disorder (OCD)

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Abstract

We here describe a case of major depressive disorder in comorbidity with a hoarding disorder, treated with repetitive transcranial magnetic stimulation (rTMS). The patient was a 59-year-old woman with a treatment-resistant depression and a history of hoarding disorder. She had been treated with several antidepressants, belonging to different classes, with a partial or none response. The patient underwent a protocol of stimulation with high-frequency rTMS (10 Hz, 20 sessions, 1 session per day), on the left dorsolateral prefrontal cortex, 750 stimuli per session, in augmentation to the pharmacological treatment. We observed an improvement in both OCD and depressive symptoms. The rTMS had been well tolerated by the patient who did not report any side effects. In conclusion, the present clinical report shows the efficacy of rTMS in a patient with OCD in comorbidity with treatment-resistant depression.

Keywords

Repetitive transcranial magnetic stimulation · Treatment resistant depression · Obsessive-compulsive disorder · Hoarding

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16.1 Introduction

16.1.1 Obsessive-Compulsive Disorder: Epidemiology, Clinical Presentation and State of the Art

Obsessive-compulsive disorder (OCD) is an early onset and highly disabling condition, with a lifetime prevalence ranging between 1.5% and 3.5% of the general population and an equal gender distribution [1]. Prevalence rates seem to decrease with age, ranging up to 0.8% among people aged over 60 years and around 5–6% within the OCD elderly population [2–4]. Moreover, it has been reported a bimodal distribution for age at onset, with one peak at 12–14 years and another at 20–22 years [5, 6]. When compared to patients with generalized anxiety disorder and panic disorder, patients with OCD showed the earliest age at onset, suggesting a strong link between early onset, positive family history, and genetic load [7, 8].

OCD has been traditionally considered a condition with similar gender prevalence. However, some authors found that late-onset OCD was more likely to occur in females and that a significant rate of late-onset patients had a history of recent pregnancy [9]. In addition, peripartum and postpartum onsets were found to occur in 2–40% and 7–21% of OCD patients, respectively [10], the birth of a child and infant care, in fact, representing a potential source of psychological stress that may contribute to the development of OC symptoms and possibly OCD [11].

OCD symptoms are remarkably diverse, regarding both clinical presentation and severity, with patients reporting only one or, more often, many symptoms belonging to different phenotypes [12]. Studies are, however, conflicting about whether any particular phenotype of OCD is easier to treat or more likely to benefit from a particular treatment [13]. For instance, symptom presentation has received growing empirical attention, as studies have revealed that specific phenotypes exhibit different treatment response rates [14]. Checking and washing compulsions are the most common forms of ritualistic behavior in clinical samples of OCD in several different countries [15]. With respect to sociodemographic characteristics, Khanna and Mukherjee reported that patients with aggression/checking symptoms were more often young, single, and male, as well as more likely to have an early and insidious onset [16]. On the other hand, patients with contamination/washing symptoms were more frequently women and homemakers and more likely to experience OCD onset after marriage [16].

Hoarding disorder (HD) was associated with OCD, a finding supported by factor analytic studies, highlighting the prominence of hoarding behavior as a distinct symptom subtype of OCD [17]. However, in 2013, HD was classified as a distinct diagnostic entity in the last version of DSM [18], and currently it is no longer considered a symptom of OCD or obsessive-compulsive personality disorder. The prevalence of HD has been estimated at 2–5% of the general population [19].

Box 16.1 Hoarding

HD is characterized by acquiring and failing to discard a large number of objects along with difficulty in relation to keeping them organized. The resulting clutter inhibits the use of living spaces and leads to significant distress and/or impairment in day-to-day functioning [20, 21].

Before DSM-5, it was considered as an obsessive-compulsive subtype in which the accumulation was seen as a compulsive ritual. With the DSM-5, a new chapter titled "OCD and Related Disorder" has been introduced, and hoarding had been listed as a related disorder. This choice reflects the growing evidence of a link between these disorders, now separated from anxiety disorders.

DSM-5 Criteria

(A) Persistent difficulty discarding or parting with possessions, regardless of their actual value.
(B) This difficulty is due to a perceived need to save the items and to distress associated with discarding them.
(C) The difficulty discarding possessions results in the accumulation of possessions that congest and clutter active living areas and substantially compromises their intended use. If living areas are uncluttered, it is only because of the interventions of third parties (e.g., family members, cleaners, authorities).
(D) The hoarding causes clinically significant distress of impairment in social, occupational, or other important areas of functioning (including maintaining a safe environment for self and others).
(E) The hoarding is not attributable to another medical condition (e.g., brain injury, cerebrovascular disease, Prader-Willi syndrome).
(F) The hoarding is not better explained by the symptoms of another mental disorder (e.g., obsessions in obsessive-compulsive disorder, decreased energy in major depressive disorder, delusions in schizophrenia or another psychotic disorder, cognitive deficits in major neurocognitive disorder, restricted interests in autism spectrum disorder).

Specify if:

With excessive acquisition: If difficulty discarding possessions is accompanied by excessive acquisition of items that are not needed or for which there is no available space

Specify if:

With good or fair insight: The individual recognizes that hoarding-related beliefs and behaviors (pertaining to difficulty discarding items, clutter, or excessive acquisition) are problematic.

(continued)

Box 16.1 (continued)

With poor insight: The individual is mostly convinced that hoarding-related beliefs and behaviors (pertaining to difficulty discarding items, clutter, or excessive acquisition) are not problematic despite evidence to the contrary.

With absent insight/delusional beliefs: The individual is completely convinced that hoarding-related beliefs and behaviors (pertaining to difficulty discarding items, clutter, or excessive acquisition) are not problematic despite the evidence to the contrary.

16.1.2 Obsessive Compulsive and Related Disorders Treatment Guidelines

Selective serotonin reuptake inhibitors (SSRIs) are recommended first-line pharmacological interventions for OCD, while selective noradrenaline reuptake inhibitors (SNRIs), clomipramine, and other antidepressants are considered second- and third-line treatments [22]. Risperidone, olanzapine, haloperidol, and aripiprazole are considered as first-line adjunctive therapies for patients with poor response to SSRIs [22, 23].

Meta-analyses support the beneficial effects of psychological treatment for OCD, mainly cognitive behavioral therapy (CBT), generally including exposure with response prevention (ERP) [22, 24]. The combination of psychological and pharmacological treatment has been shown to be superior to medication alone, but not to CBT alone [25, 26]. These findings suggest that if pharmacotherapy is required or preferred, adding CBT to pharmacological treatment of OCD may enhance response rates and reduce relapse rates [22].

With respect to somatic therapies, a growing interest has been expressed over the last years toward brain stimulation interventions. These include noninvasive and more invasive interventions. For instance, several open trials have suggested that repetitive transcranial magnetic stimulation (rTMS) may be a promising adjunctive therapy in patients with treatment-refractory OCD [27–29]. However, results of sham-controlled trials are not univocal, and larger samples are needed to provide additional controlled evidence for the efficacy of TMS in treatment-resistant OCD [30–32]. In 2007 and 2010, two different research groups supported the efficacy of rTMS in improving comorbid depressive symptoms in patients with OCD [33, 34]. Moreover, several studies with small samples suggested that deep brain stimulation (DBS) may improve symptoms and functionality in up to two-thirds of patients with highly treatment-refractory OCD (fourth level of recommendation) [35, 36].

16.1.3 Transcranial Magnetic Stimulation: Mechanism of Action and Applications in Psychiatry

TMS is a brain stimulation technique, based on electromagnetic principles, in which magnetic fields are used to electrically stimulate targeted cortical brain areas [37].

The mechanism of action consists of an electrical flow generated into a coil with the production of a pulsating high-intensity (1.5–3 Tesla) magnetic field into targeted brain areas. The magnetic field penetrates within the different tissues at variable depths, usually no more than 2–3 cm below the stimulating coil, and reaches the brain cortex, where it is reconverted into an electrical flow [37]. Therefore, electricity interferes with the neuronal depolarization processes, enhancing or reducing cortical excitability, depending on stimulation parameters [37]. Modern devices are able to generate repetitive trains of stimuli, and this kind of stimulation is known as repetitive TMS (rTMS), commonly used for the treatment of psychiatric disorders [38].

In the last decade, TMS has been used in a wide range of neurological diseases such as migraine, tinnitus, and poststroke rehabilitation [39, 40]. Moreover, TMS has shown consistent positive results in the treatment of psychiatric disorders, such as major depression, anxiety disorders, and schizophrenia [41, 42]. However, major depressive disorder represents the only psychiatric indication approved by the International Guidelines and major International Regulatory Agencies, such as the US Food and Drug Administration [43].

Currently, two major international guidelines for the treatment of psychiatric disorders—the CANMAT [44] and the WFSBP [45]—include a section specifically dedicated to TMS. Another useful tool is represented by "TMS guidelines," published in 2009 by an international group of experts, specifically focused on the safety of TMS in psychiatric disorders [46]. Moreover, it is worth mentioning a recent publication about the first evidence-based guidelines that focuses on the clinical application of TMS on different psychiatric disorders [47]. Currently, rTMS, both at high and low frequency, applied on the dorsolateral prefrontal cortex (DLPFC) is the most commonly used protocol for treatment-resistant depression [48, 49].

With respect to the OCD treatment, a recent meta-analysis by Trevizol and colleagues including 15 RCTs (483 patients) showed heterogeneous results, in light of the different protocols of stimulation used. However, comparing active versus sham TMS, the active stimulation was found to be significantly superior for OCD symptoms [50]. These results are consistent with a previous meta-analysis by Berlim and colleagues [51] comparing 10 sham-controlled rTMS trials in OCD patients (282 patients). They concluded that low-frequency rTMS protocols targeting the orbitofrontal cortex or the supplementary motor area (SMA) seem to be the most efficacious; in addition, the efficacy of active rTMS for OCD seems to be comparable to second- or third-line pharmacological strategies for OCD without the long-term metabolic adverse effects [51].

Additionally, preliminary results showed that targeting the supplementary motor area with fMRI-guided navigation improves rTMS efficacy in patients with OCD [31]. Only 1 randomized sham-controlled study performed in 21 patients showed the potential value of this approach. In fact, after 4 weeks of treatment, the response rate

in the completer sample was 67% with active and 22% with sham rTMS [52]. The clinical effects of low-frequency rTMS applied to the supplementary motor area on patients with OCD were related to an inhibitory modulation of dysfunctional motor circuits in this cortical area [53].

It should be noticed that a recent sham-controlled trial of rTMS of the DLPFC reported a significant improvement in obsessions but not in compulsions, with Y-BOCS scores reduction, as well as relief in depressive and anxiety symptoms [54].

More recently, a Canadian group published a study targeting the medial prefrontal cortex (mPFC) and applied low-frequency deep rTMS to ten patients with OCD; all patients showed a significant symptom improvement after ten sessions of rTMS that persisted 1 month following the last session of rTMS [55].

Future placebo-controlled rTMS studies in OCD patients should include larger sample sizes and be more homogeneous in terms of demographic and clinical variables, stimulation parameters, and cortical target to provide definitive evidence for the efficacy of this technique in the treatment of drug-resistant OCD.

16.2 Case Presentation

A 59-year-old woman was referred to the outpatient service of our hospital suffering from treatment-resistant major depressive disorder with a severe comorbid hoarding disorder.

There was no certainty about her psychiatric family history: she described a probable depressive episode of her father immediately after his retirement, neither diagnosed nor treated by any psychiatrist.

Patient's medical history was characterized by poliomyelitis when she was 18 months old, with a consequent delay in the acquisition of common motor skills and a residual lameness due to the shortness of the left leg.

Box 16.2 Poliomyelitis
In some pediatric patients, the poliovirus can cause a delay in the growth of a limb, while the contralateral continues growing regularly. Patients can develop a shorter leg, which forces them to limp, determining, over time, some spinal deformities, scoliosis in particular.

Moreover, when the patient was 39 years old, she developed a postpartum thyroiditis, treated with methimazole for about 18 months. This treatment led to an iatrogenic hypothyroidism, controlled by a currently ongoing therapy with levothyroxine.

Box 16.3 Postpartum Thyroiditis

The incidence of postpartum thyroiditis affects approximately 4.1% to 7% of women. This disease is characterized by autoimmune dysfunction often occurring during the first 6 months after childbirth. The disease ranges from postpartum hyperthyroidism to hyperthyroidism followed by hypothyroidism and hypothyroidism in isolation.

In this condition, lymphocytes cause destruction of the thyroid, with an initial release of thyroid hormone as the thyroid follicles are attacked, followed by hypothyroidism.

Women, in the hyperthyroid phase of postpartum thyroiditis, generally do not have severe agitation, exophthalmos, or significant vital sign changes but may have palpitations, fatigue, and **mood changes**. Postpartum thyroiditis is typically present initially as a hyperthyroid episode, followed by hypothyroidism. The thyrotoxic state (hyperthyroidism) usually occurs 2–6 months postpartum. Symptoms are mild because of the limited elevation of thyroid hormone and are usually 2–12 months in duration. Approximately 30–50% of women will remain in a hypothyroid condition and require continuous levothyroxine treatment.

Patient's psychiatric history started in childhood, with cleansing, order, and symmetry rituals, limited to her bedroom: the patient used to organize her clothes in the closet according to colors, dimension, and type of fabric. At home, she spent most of the time in her bedroom, cleaning and tidying clothes, objects, and books.

Despite the aforementioned OC symptoms, no specialist was consulted by her parents. Nevertheless, the patient kept an acceptable level of functioning and overall good quality of life. In fact, she graduated high school and then started a job as schoolteacher. When she was 30 years old, she got married and had two children when she was 36 and 39 years old. No significant worsening of the OCD symptomatology was observed in the postpartum even though, after the marriage, the compulsive rituals extended from only one bedroom to the entire home.

On the occasion of her second pregnancy, the death of her mother and the postpartum thyroiditis occurred in a short space of time. In this period, the patient developed her first major depressive episode, characterized by symptoms such as asthenia, apathy, anhedonia, guilt, and feelings of ruin. The patient started treatment with methimazole, with a simultaneous rapid improvement of her depression. However, a worsening of OC symptoms occurred, with a change in compulsive themes. In fact, the patient started accumulating an increasing number of objects, filling the entire house. She wasted a lot of money buying unnecessary things, also purchasing in multiple copies, without any logical purpose. At the same time, she could not throw away anything.

When she was 41 years old, the patient experienced an important worsening in the quality of life, given the increasing amount of accumulated objects and number of depressive recurrences. For this reason, she referred to her general practitioner who

prescribed fluoxetine at an initial dosage of 20 mg/day, subsequently increased to 40 mg/day, due to lack of response.

After an initial improvement, which lasted about 3 months, the patient had several depressive recurrences, with short periods of partial remission. The depressive symptomatology progressively conditioned patient's quality of life, until she quit her job and divorced at 47 years.

When the patient was 49 years old, she had her first contact with a psychiatrist, and she was diagnosed with major depressive disorder (MDD) and obsessive-compulsive disorder (OCD). She started a treatment with venlafaxine at 75 mg/day and a cognitive behavioral therapy (CBT) specifically focused on OC symptoms. Psychotherapy, however, was soon interrupted (it lasted about 3 months) by the patient due to lack of efficacy. On the other hand, the psychopharmacological treatment was maintained for about 10 years, but the psychopathological history revealed a poor response to several first-line antidepressants, belonging to different classes—SSRIs, SNRIs, NDRIs, and tricyclics—such as venlafaxine, sertraline, escitalopram, paroxetine, and bupropion, both in monotherapy and in augmentation with olanzapine and amisulpride. Only clomipramine, up to 200 mg day, showed partial efficacy, especially on OCD symptoms.

Therefore, in light of the treatment-resistant depressive symptoms, an augmentation strategy with TMS was proposed to the patient, and, for this reason, she came to the attention of our clinic.

Box 16.4 Depression and Response to Treatment

Responder: Hamilton Depression Rating Scale (HAM-D) score reduction $\geq$ 50% compared to baseline

Partial responder: Reduction in HAM-D score between 25% and 50% compared to baseline

Absent response: Reduction in HAM-D score $<$ 25% compared to baseline

Remitter: HAM-D score $\leq$ 8

Treatment-resistant depression: Failure to $\geq$ 2 trials with antidepressants belonging to different pharmacological classes, given for an appropriate period of time, at standard dosages, and with compliance monitoring

During the first screening clinical interview, the patient reported several depressive symptoms, such as anhedonia, apathy, clinophilia, and terminal insomnia. Moreover, the hoarding symptoms were present and highly disabling. She was taking clomipramine 75 mg/day, zolpidem 10 mg/day, and levothyroxine 75 mcg/day. Blood tests and thyroid function were within the limit. A computed tomography (CT) of the brain was performed, in order to evaluate central nervous system (CNS) morphology. The imaging did not show any relevant abnormality (Fig. 16.1).

The screening assessment included questions about exclusion and inclusion criteria of the TMS protocol approved by the local ethical committee, and she was enrolled in a protocol of stimulation at high-frequency rTMS (10 Hz), 80% motor

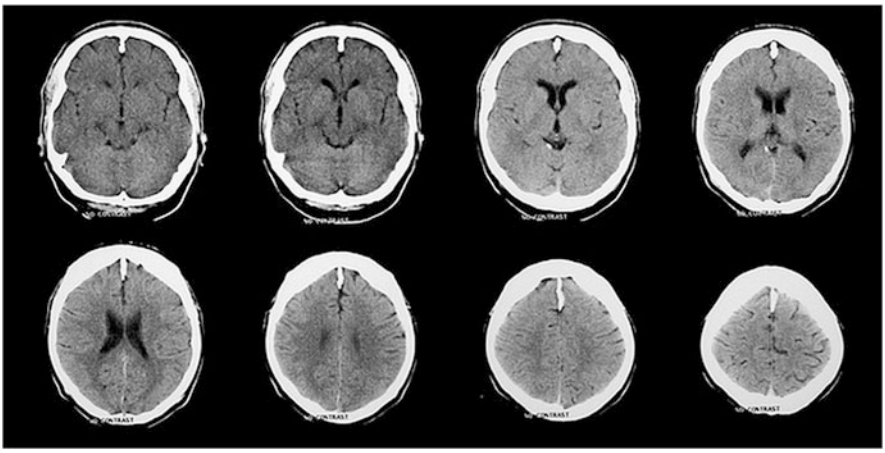

Fig. 16.1 CT showing no alteration in the posterior cranial fossa. Regular and symmetrical fourth ventricle. Normal supratentorial ventricular system. No expansive lesions in supratentorial regions. Normal cortical tropism

	HAM-D	MADRS	Y-BOCS	HAM-A
T0	24	30	23	16
T1	21	25	23	13
T2	16	20	21	10
T3	10	10	17	8
T4	7	6	15	12

Fig. 16.2 Patient's scores of psychometric scales at different time points (T0–T4)

threshold, of the left DLPFC with 5 s trains, with an interval of 25 s, 750 stimuli per session.

The pharmacological treatment remained unchanged throughout the entire duration of TMS treatment.

In Fig. 16.2, total scores of the psychometric scales at different time-points are reported.

Box 16.5 TMS Protocol (20 Applications, 4 Weeks of Treatment)

T0 (before treatment): – Clinical interview for inclusion and exclusion criteria

– Psychometric scales: Hamilton Depression Rating Scale (HAM-D), Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Scale (HAM-A), and Yale-Brown Obsessive Compulsive Scale (Y-BOCS)

Assessment during the stimulation:

T1 (after 1 week of treatment)
T2 (after 2 weeks of treatment)
T3 (after 3 weeks of treatment)
T4 (after 4 weeks of treatment)

Phase 1: screening
Phase 2: randomization to one of the three different protocols of stimulation (high and low frequency)
Phase 3: motor threshold measuring
Phase 4: TMS application on left or right dorsolateral prefrontal cortex (depending on the type of protocol)

From T0 to T4, a global score reduction of the different psychometric scales was observed. In particular, an improvement in the depressive and obsessive scores, particularly relevant from the third week of stimulation (T2–T3), was observed. The obsessive-compulsive symptoms were initially rated as moderately severe (Y-BOCS = 23), and, at the end of the stimulation, they turned into mild (Y-BOCS = 15).

The HAM-D and MADRS scores decreased from a situation of moderate depression (T0 = 24 and 30, respectively) to remission (T4 = 7 and 6, respectively).

The treatment was well tolerated by the patient, who did not show any side effect during the stimulation and at the end of the treatment.

Figure 16.3 shows a timeline of the patient's psychiatric history.

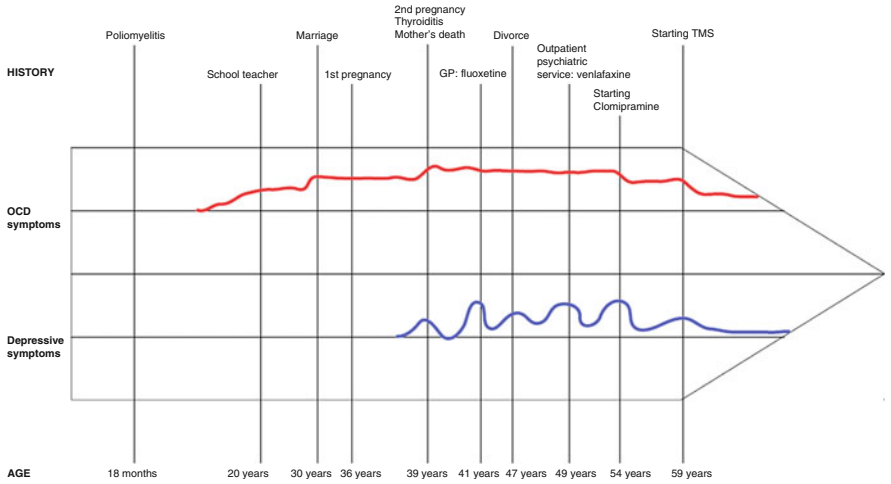

Fig. 16.3 Timeline of the psychiatric history

16.3 Discussion

The present clinical report describes the efficacy of rTMS in a complex clinical case characterized by OCD in comorbidity with treatment-resistant depression and previous hypothyroidism.

OCD symptoms began during the patient's childhood; however the full onset of the disorder, along with a significant functional impairment and reduced quality of life, manifested at the age of 30. These characteristics are consistent with the available literature about female OCD, describing a later onset compared to males although apparently not linked, in the present case, to the peripartum period [9].

OCD association with other psychiatric comorbidities has been frequently described in the literature, and major depressive disorder represents one of the most common comorbidities, both co-occurring and starting as a consequence of OCD symptoms [56].

In the clinical case set forth, patient's OCD was comorbid with a chronic depressive symptomatology. In fact, first depressive symptoms started in a context of OCD full symptomatology but were, at least initially, related to a concomitant hypothyroidism, which had been just discovered. This medical condition has been frequently linked to psychiatric disorders [57]. In the present case, even though hypothyroidism was successfully treated, the depressive disorder developed an independent course, and persisted showing a chronic relapsing course, ultimately characterized by treatment-resistance features. It should be noticed that the patient's father likely experienced at least one sub-threshold depressive episode during his life, so the family history may have played a role in the chronicization of the patient's depressive disorder [58].

In the present case, the course of OCD and depression showed an opposite trend at the beginning: while depressive symptoms were initially improved by the treatment with methimazole, OCD got worse, and symptoms increased in frequency and shifted from a cleaning/contamination subtype to a hoarding subtype. It is quite common for patients with OCD to progressively experience different or multiple obsessions/compulsions, resulting in a mixed clinical picture; in particular hoarding symptoms are frequently associated with other OCD phenotypes [59, 60].

It should be noticed, however, that after the 4-week treatment with TMS, the patient showed a progressive improvement of both depressive and OC symptomatology, with HAM-D and MADRS scores reduced from a moderate severity of illness (T0 = 24 and 30, respectively) to remission (T4 = 7 and 6, respectively) and Y-BOCS scores initially depicting a moderately severe OCD (T0 = 23) turning, at the end of the stimulation, into a mild severity. As previously mentioned, TMS has already been considered as a promising adjunctive therapy in patients with treatment-refractory OCD [27, 28], and the current clinical case seemed to support previous studies.

Comprehensively, we considered the reported case of clinical interest for different reasons. First, considering a longitudinal perspective, patient's OCD seemed to occur before the comorbid major depressive onset. Secondly, OCD symptoms were profoundly linked with hoarding manifestations which, according to the DSM-5, have been included in the chapter of obsessive-compulsive and related disorders. This is particularly relevant, as hoarding subtype of OCD or hoarding disorder "per se" has been traditionally considered a difficult-to-treat condition (either with pharmaco- or psychotherapy) [61]. In this perspective, the efficacy of TMS in such a particular OCD subtype seems to be of great clinical interest and needs further investigation. It is also important to mention that the stimulation protocol applied targeted the DLPFC which is, as already mentioned, one of the different targets implicated in the treatment with TMS of OCD patients. In fact, if this is a well-established target for the treatment of major depression, the hypothesis that it may be also a preferential target for OCD vs the SMA is still debated. Therefore, it is possible that in the clinical case, different features eventually contributed to the overall acute response to TMS, for example, the depressive comorbidity itself.

Although the whole case had many original issues that we deemed worthy of publication, we need to acknowledge that the reported TMS results were merely referred to the acute treatment and were obtained in an open setting, without any sham control. Therefore, further sham-controlled studies are warranted to specifically investigate the role of TMS in OCD treatment.

Key Points

- The association of OCD with other psychiatric comorbidities has been frequently described in the literature, and major depressive disorder represents one of the most common comorbidities.
- TMS has already been considered as a promising adjunctive therapy in patients with treatment-refractory OCD.

Self-Assessment Questionnaire

1. What is the prevalence of hoarding disorder in the general population?
   (A) 10–12%
   (B) 9%
   (C) **2–5%**
   (D) 22%
2. What kind of drugs are considered as first-line pharmacological treatment for OCD?
   (A) SNRI
   (B) Benzodiazepines
   (C) Mood stabilizers
   (D) **SSRI**
3. How could a partial responder depression be defined?
   (A) **A reduction of HAM-D scores between 25% and 50% compared to baseline**
   (B) A reduction of MADRS scores between 25% and 50% compared to baseline
   (C) HAM-D scores < 8
   (D) HAM-D score reduction $> 50\%$ compared to baseline
4. What brain area is the target for TMS in treatment-resistant depression?
   (A) Orbitofrontal cortex
   (B) **Dorsolateral prefrontal cortex**
   (C) Occipital cortex
   (D) Premotor area
5. What brain area is the target for TMS in OCD?
   (A) Dorsolateral prefrontal cortex
   (B) **Orbitofrontal cortex and supplementary motor area**
   (C) Occipital cortex
   (D) Cerebellum

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