Peer-Reviewed Article | Review Article

Treatment of Depersonalization Disorder

Safety and Possible Efficacy of Repetitive Transcranial Magnetic Stimulation (rTMS)

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Abstract

Background: Depersonalization/derealization disorder is an understudied debilitating condition characterized by subjective experiences of unreality, emotional numbness, and the feeling of the body being disconnected. Its etiology has been linked to emotional abuse and psychoactive substance abuse. The pathophysiology might involve dysfunction of the frontal, insula/limbic and the temporoparietal areas of the brain, amongst others. Most pharmacological and psychotherapeutic treatments do not lead to sufficient clinical improvement in patients. Alternative therapeutic approaches such as repetitive transcranial magnetic stimulation (rTMS) might be able to treat the condition but needs to be well researched first.

Methods: One randomized study, one open-label study and five case series on rTMS for the treatment of depersonalization disorder were retrieved.

Results: Studies were heterogeneous in terms of design and methodology with small sample sizes and short follow-ups, and with different stimulus parameters. The studies demonstrated a response to rTMS particularly to the right temporo-parietal junction in most of the subjects. There were no major adverse effects except for some cases of mild headache, labile affect, and pain above the eye. Future sham-controlled studies of 1 Hz rTMS particularly to the right temporo-parietal junction with increased statistical power, rigorous standards of randomization and optimal stimulus parameters are needed to confirm the short- and long-term safety, and efficacy of rTMS in the treatment of this condition.

Keywords: Depersonalization; rTMS; temporo-parietal junction

Introduction

Depersonalization/derealization disorder (DPD) is a debilitating dissociative condition characterized by persistent or recurrent subjective experiences of unreality, emotional numbness, feeling detached from one's mind (depersonalization) or from one's surroundings (derealization), disturbing sensations, the feeling that the self and the body are somehow disconnected and as if one is an outside observer with alterations in one's sense of self and the world (dreamlike state), anxiety and depression (table 1) [1, 2]. DPD causes distress and/or functional impairment [1] even though most patients might still maintain the insight that these feelings and sensations are not true and are pathological symptoms. DPD can be diagnosed with a thorough psychiatric evaluation along with the use of specialized rating scales, such as the Cambridge Depersonalization Scale (CDS) [3] and the Depersonalization Severity Scale [4], and medical evaluations after having ruled out physical illnesses or medication side effects. No laboratory or neuroimaging tests can diagnose DPD. Lifetime comorbidities are elevated for unipolar depressive disorder, anxiety disorders, avoidant, borderline and obsessive-compulsive disorders, and less frequently post-traumatic stress disorder [1]. Epilepsy and migraine seem to be commonly associated with DPD [5]. Its incidence rate is around 1% of the population [3–5]; the lifetime prevalence of DPD worldwide is approximately 2% [5–8]. It commonly begins between the ages of 16 and 23 years, with fewer than 20% having an onset after the age of twenty [9, 10], and it tends to become chronic [10]. Its etiology has been linked to emotional abuse but also to psychoactive substance abuse (such as marijuana, cocaine, hallucinogens, ketamine, or ecstasy), or certain medications, prolonged stress, or sleep deprivation over many days in a row amongst others [7, 11]. There is a genetic predisposition in 25 to 50% of cases [7, 11]. Depersonalization and derealization can also appear as symptoms of other psychiatric disorders [12], including approximately 12% of cases with panic disorder [10].

The syndrome of depersonalization is commonly described in patients with neurological conditions, especially those characterized by dysregulations in serotonergic neurotransmission and increased glucose metabolism, such as in temporal, parietal, and temporal lobe epilepsy [13].

Although the pathophysiology of DPD is poorly understood, there are reports of cortical asymmetry with increased excitability of the prefrontal cortex (energization, task setting, monitoring, behavioral/emotional regulation, meta-cognition understanding and distinguishing between different mental phenomena) in patients with this condition, along with reduced insula, limbic and visual association cortical activation in response to emotive pictures, and increased ventrolateral prefrontal cortex (VLPFC) activation; all areas involved in the processes of integrated body schemas [14–17]. Patients with severe dissociation have been found to have significantly lower left hemispheric excitability than right hemispheric excitability (i.e., lack of right hemispheric integration) [18]. Neuroimaging and neurophysiological findings suggest that the right temporo-parietal junction (TPJ) plays a crucial role in the spatial unity of the normal self and body, and the conscious experience of the normal embodied self; a process impaired in DPD. An altered structural connectivity in patients with DPD was demonstrated between the right middle temporal gyrus and the right supramarginal gyrus, as well as higher connectivity strength between the orbitofrontal cortex and

Table 1: Summarized DSM-5 and ICD-10 criteria for depersonalization/derealization disorder (DPD)

DSM-5	Persistent or recurrent experiences of depersonalization, derealization, or both	Reality testing intact	Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Disturbance is not attributable to the physiological effects of a substance or another medical condition
ICD-10	Either depersonalization symptoms or derealization or both + acceptance of a subjective and spontaneous change and clear sensorium	Disturbance is not better explained by another mental disorder		

the amygdala [19]. Excitation of the right TPJ by electrical stimulation has been shown to induce out-of-body experiences [20]. Based on these studies, it seems that the TPJ, the prefrontal cortex and the VLPFC are at least partially involved in the neurobiology of DPD and may therefore be potential targets for repetitive transcranial magnetic stimulation (rTMS).

Currently, no definitive treatments for DPD exist and research into pharmacological and psychological treatments are still lacking. However, a variety of pharmacological and psychotherapeutic treatments have been tried [21] but for the most part these have not led to sufficient clinical improvement in patients suffering from DPD [9, 10]. Some patients have responded to naltrexone, naloxone clonazepam with or without selective serotonin reuptake inhibitors, lamotrigine or aripiprazole, or to cognitive behavioral therapy [21–25].

In general, some of these studies were of good quality and open-label, but with negative outcomes. There have not been any more recent studies available concerning the treatment of DPD, which remains understudied and underdiagnosed. Alternative therapeutic approaches, such rTMS might be able to treat such a condition but needs to be well researched first.

Transcranial magnetic stimulation (TMS) is a non-invasive neurostimulation technique that is capable of modulating cortical excitability using electromagnetic pulses of high intensity administered through a coil [26–28]. The fast passage of electric current in the coil induces a transient, high intensity magnetic field that penetrates almost unimpeded through the scalp and reaches the underlying cortex. In the targeted cortex, this field can generate an electric current of sufficient intensity to induce depolarization of superficial cortical neurons and interconnected areas beneath the coil [27]. In repetitive TMS, trains of several pulses are delivered through repeated stimulation of the same area with frequencies ranging from 1 to 20 Hz. Adverse effects of rTMS include neck muscle contractions, lightheadedness, headache, tinnitus, syncope, very rarely seizures, as well as psychotic symptoms, anxiety, agitation and insomnia [29, 30]. Mania has been described in patients with uni- and bipolar depression [31, 32]. The safety of rTMS has been reported in several studies and the most recent guideline for their use has been published in 2009 [30]. In this review, I describe then discuss the studies that assessed the safety and efficacy of rTMS in the treatment of DPD.

Materials and Method

Using the search terms "transcranial magnetic stimulation", "repetitive transcranial magnetic stimulation", "rTMS", "dissociation", and "depersonalization disorder", I selected the publications that addressed the use of rTMS in the treatment of DPD. As a result, one randomized study, one open-label study and five case reports and case series on rTMS for the treatment of DPD involving humans published in English until July 2022 were retrieved through NCBI, PubMed, Embase and Science Direct searches [33–39]. Included were studies in which at least several sessions of rTMS were administered over one to a limited number of days with stimulus parameters comparable to those of conventional rTMS, and studies with well-defined outcome measures such as valid rating scales, well-described stimulus parameters, response rates as well as appropriate statistical analyses. Given that there was only one open-label study and otherwise single cases and small case series with heterogeneous methodology, it was impossible to perform a systematic review or a meta-analysis. Therefore, this is a narrative review of the literature.

Results

All seven studies, one randomized study, one open-label study and five case series, pertaining to rTMS treatment of DPD were identified through the review process.

The first study was the first case report in which the authors applied one session of 1 Hz rTMS to the right dorsolateral prefrontal cortex (RDLPFC) in one female patient with DPD and major depressive disorder (MDD) resulting in the reduction of depersonalization symptoms [33].

In a case report of a 25 year-old male with comorbid DPD and MDD who had not responded to two months of pharmacotherapy with fluoxetine, Jiménez-Genchi described the application of six sessions thrice weekly (for two weeks) of 20 Hz rTMS to the left dorsolateral prefrontal cortex (LDLPFC) for two weeks which resulted in a slight reduction in depersonalization symptoms with a 28% reduction on the CDS [3] but not in depressive symptoms [34]. Interestingly, his depersonalization symptoms continued to improve noticeably with clomipramine along with his depressive symptoms. For this case, the choice of HF rTMS to the LDLPFC was based on the patient's single photon emission tomography results which showed a left hypofrontality.

The only randomized study in which 22 patients with DPD and 21 healthy control subjects were randomized to receive two weekly sessions (total of 17–20 sessions) of right-sided low-frequency rTMS to the VLPFC and to the right TPJ showed significant reduction of depersonalization scores in DPD patients [35]. Patients received two sessions weekly, evenly spaced throughout the week for participants' convenience. At each session, symptoms of depersonalization were measured using the self-report version of the CDS-S immediately before and after rTMS, as well as a safety checklist after rTMS. At the last session, participants completed a CDS-T, Beck Anxiety Inventory, Beck Depression Inventory, and Dissociative Experiences Scale as final outcome measures. The CDS-S was defined as primary outcome measure.

A case series demonstrated, that 20 sessions (two sessions weekly) of right-sided, neuro-navigated 1 Hz rTMS to the VLPFC (Brodmann Area 47) for ten weeks in seven patients with medication-resistant DPD (score on the CDS of 70, 3 medicated) was associated with a reduction in CDS scores by an average of 44% (range: 2–83.5%) and an increase in physiological arousal [36]. Seven patients completed the full course of treatment (17–20 sessions). Two patients were full responders, four partial and one did not respond at all. Response usually occurred within the first six

sessions. There were no significant adverse events except for two patients who had a mild headache and one, who experienced pain above the left eye. Some patients displayed a labile affect.

Karris and colleagues reported a case of a 30-year-old medicated man with DPD (score of 149 on the CDS) and MDD who had not responded to pharmacotherapy but who had a significant reduction in his depersonalization symptoms after undergoing low-frequency (LF) rTMS to the RDLPFC followed by high-frequency (HF) rTMS to the LDLPFC [37]. The patient tolerated the procedure well and after 31 sessions, both his mood and his depersonalization symptoms were reduced (43.1% reduction on the CDS score). He then underwent 32 sessions of 10 Hz rTMS to the LDLPFC, which further improved his depersonalization symptoms.

The case of a right-handed 26-year-old medicated (paroxetine, trazodone, lamotrigine) man with a six month history of DPD (feeling detached from himself, previously familiar places looked unfamiliar, detached from memories of things) was reported [38]. The patient had developed depersonalization symptoms along with depressive symptoms and suicidal thoughts a few days after he was prescribed cyamemazine (phenothiazine antipsychotic) while he was hospitalized for the evaluation of insomnia. These symptoms persisted even after cyamemazine was discontinued, whereas his depressive symptoms and the suicidal thoughts abated. He responded safely and significantly to 29 weeks (29 sessions) of once-daily sessions (on weekdays) over six weeks of 1 Hz rTMS to the right TPJ. His CDS score dropped from 96 at baseline to 44 at week six (52.2% improvement, a full response). At week six, his symptoms consisted of feeling detached from reality and from his thoughts less frequently. He also felt that his surroundings were unreal much less often and he started to fully feel his emotions. The treatment was well tolerated with no major side effects reported by the patient except for mild headaches that lasted for two days after the first rTMS session.

In an open-label, cross-over study of rTMS in DPD, LF rTMS was applied for three weeks to the right TPJ (area between T4/P4, 10-20 International EEG System) in twelve right-handed outpatients (ten medicated) with DPD [39]. Partial responders (at least 25% improvement on the CDS) received three additional weeks of rTMS to the right or left TPJ and non-responders three additional weeks of rTMS to the left TPJ. For responders (at least 50% improvement on the CDS), three more weeks of rTMS were applied to the right TPJ. All patients completed the first phase, however four patients dropped out afterwards because of perceived lack of benefit from rTMS. At week three, six patients responded, four with a full response and two with a partial response. The five out of the six responders, who received three more weeks of rTMS to the right TPJ, showed a 68% reduction in symptoms of DPD symptoms after a total of six weeks of treatment. After three additional weeks of rTMS, only 50% of those who underwent rTMS to the right TPJ were full responders. Of the three patients who were switched to the left TPJ, one remained a partial responder and two were non-responders. Right TPJ rTMS was safe and effective. After six weeks of rTMS, there was a significant reduction in depressive (measured with the Hamilton Depression Rating Scale [HDRS]) and anxiety symptoms. In this trial, the domains that improved the most were alienation from surroundings, anomalous subjective recall, emotional numbing, and anomalous body experiences [40].

Discussion

The scientific literature on rTMS for the treatment of DPD is limited to very few case series, one randomized study and one open-label study. These studies were heterogeneous in terms of design with rather small sample sizes and short follow-ups, were either open-label, randomized or consisted of case series that investigated the safety and efficacy of rTMS alone or in combination with pharmacotherapy on DPD. In most of these studies, patients had comorbid psychiatric conditions such as MDD. Studies used different stimulus parameter as well as different number of sessions per unit of time (range of 6 to 63 sessions of rTMS over two to ten weeks).

The only randomized study [35] showed that one session of right-sided LF rTMS to the VLPFC and to the right TPJ significantly reduced depersonalization scores in DPD patients. Right-sided neuro-navigated 1 Hz rTMS to the VLPFC resulted in a moderate reduction in depersonalization symptoms [3].

An open-label study [39] included a limited number of medicated or unmedicated DPD patients (N=12) and showed that LF rTMS to the right TPJ was more effective than LF rTMS to the left TPJ.

Concerning the case series [33, 34, 36] in which rTMS targeted the prefrontal cortex, 20 Hz rTMS to the LDLPFC [32, 35] and 1 Hz rTMS to the RDLPFC followed by 10 Hz rTMS to the LDLPFC resulted in a slight [33] to significant [36] reduction of depersonalization symptoms. Another case study [38] demonstrated a significant response in a patient treated with rTMS to the right TPJ.

This review contains many limitations making it difficult to draw major conclusions about the efficacy of rTMS in the treatment of DPD. Given the different stimulus parameters and methodologies, the rather small number of studies and sample sizes, the open-label nature of one study, the absence of sham-controlled studies and the absence of blinding, as well as the lack of a clear description of comorbidities in certain studies, it is quite difficult to compare the relative efficacies of these protocols.

This being said, there were better results for rTMS of the right TPJ with seven full responders and a response rate of 58.3% compared to rTMS of the right VLPFC (two responders, 28.6% response rate). A placebo effect has to be taken into consideration. rTMS to the dorsolateral prefrontal cortex was mildly to moderately efficacious for the treatment of DPD with no apparent responders. It is worth mentioning, that a 31-year-old woman with a treatment-resistant depression (TRD) and generalized anxiety disorder developed troublesome depersonalization symptoms with accelerated HF rTMS of the LDLPFC [42]. rTMS to the LDLPFC might thus paradoxically worsen depersonalization symptoms and should therefore be more thoroughly investigated.

Studies have not reported major adverse effects with rTMS except for some cases of mild headache, labile affect and pain above the eye.

To summarize, the randomized study, the open study and some case series have shown a response to rTMS, particularly to the right TPJ. There has been some improvement of DPD symptoms with rTMS over the VLPFC, RDLPFC and LDLPFC. It is important to note that there was no sham control in most of these studies. Therefore, the responses might have been related to a placebo effect, the concomitant use of antidepressants or to the combination of rTMS and antidepressants, even though DPD responds poorly to such medications. DPD patients tend to have a low placebo response [39], suggesting that the observed clinical changes were probably the effect of stimulation by rTMS, although there was only a small number of studies with rather low quality available.

Conclusions

DPD is underresearched, and therefore good quality treatment studies are highly needed in general and for rTMS.

rTMS seems to have psychological effects in DPD symptoms although it is still unknown how this technique triggers this psychological effect. There are no published studies investigating psychotherapy and rTMS for the treatment of DPD.

Several reviewed studies claimed promising DPD results and none raised safety concerns. To date, although the data are limited because of small samples sizes and because of the nature of the studies, 1 Hz rTMS to the right TPJ appears to be the most efficacious in the treatment of DPD symptoms compared with rTMS to the right VLPFC or to the LDLPFC/RDLPFC.

To avoid limitations like the small number of studies, small samples sizes, the nature of the studies, their diverse methodologies as well as the absence of sham-controlled studies, future sham-controlled studies of 1 Hz rTMS particularly to the right TPJ or one of the other targets described above, with increased statistical power, rigorous standards of randomization, blinding procedures, optimal and safe stimulus parameters, potentially longer treatment durations, and better clinical outcome as well as global functioning measures are needed to confirm the short- and long-term safety and efficacy of rTMS in the treatment of DPD.

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You will find the full list of references online at https://doi.org/10.4414/sanp.2023.1156261901.