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Repetitive transcranial magnetic stimulation in the treatment of eating disorders: A review of safety and efficacy

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ABSTRACT

Eating disorders are a significant public health concern accounting for significant morbidity and mortality. Therapeutic approaches are available to treat eating disorders but less than half of the patients recover. Therapeutic alternatives are needed such as repetitive transcranial magnetic stimulation. I reviewed studies that evaluated the safety and efficacy of this technique for the treatment of eating disorders. The electronic literature on repetitive transcranial magnetic stimulation, theta burst and deep transcranial magnetic stimulation in the treatment of eating disorders was retrieved. The findings were quite heterogeneous in results with some studies showing relatively positive results with reduction of both craving and eating behaviors with active stimulation versus sham. Repetitive transcranial magnetic stimulation was safe. Research in this field was limited by the small number of studies and sample sizes, diversity of stimulation parameters, questionable placebo conditions, the lack of a sham-controlled design and the use of subjective scales lacking in sensitivity. The evidence supporting rTMS for eating disorders is somewhat promising. Future studies on high frequency rTMS of the LDLPFC/DMPFC with increased statistical power, rigorous randomization, outcome measures and optimal parameters are needed to confirm the short- and long-term safety and efficacy of rTMS for the treatment of eating disorders.

1. Introduction

Transcranial magnetic stimulation (TMS) is a non-invasive neurostimulation technique that is able to modulate cortical excitability (Wagner et al., 2007; Hallett, 2007; Wassermann and Lisanby, 2001). It consists of focused electromagnetic pulses of high intensity administered through a coil. The fast passage of electric current in the coil induces a transient, high intensity magnetic pulse that unimpededly crosses the scalp and reaches the underlying cortex. In the targeted cortex, the magnetic pulse generates an electric current which can induce depolarization of superficial cortical neurons and interconnected areas beneath the coil.

In repetitive TMS (rTMS), several pulses in repeated trains of stimulation are delivered through the same area with frequencies ranging from 1 to 20 Hz. The effects of rTMS lead to long-term changes in cortical functioning which vary depending on the frequency of stimulation. Generally, high frequency (HF) rTMS (>5 Hz) transiently increases cortical excitability whereas low frequency (LF) rTMS (≤1 Hz) decreases it (Daskalakis et al., 2006; Fitzgerald et al., 2006). The side effects of rTMS include sometimes mild headaches, local pain at the stimulation site, neck pains, dizziness and rarely syncopal vagal episodes, mania and very rarely seizures during the session (Rossi et al., 2009; Loo et al., 2008; Rachid, 2017).

The safety of rTMS has been reported in a number of studies and the most recent guidelines for their use have been published in 2009 by Rossi and colleagues. This technique appears to be safe when administered according to recommended guidelines and its safety record supports its further development as a clinical treatment (Rossi et al., 2009; Loo et al., 2008).

Eating disorders (EDs) are characterized by chronically and severely impaired eating behaviors and are amongst the most common health problems afflicting female adolescents and young women worldwide (Chen and Jackson, 2008). They have a lifetime prevalence of 4–6% (5.7% for females and 1.2% for males) (Hudson et al., 2007). EDs include anorexia nervosa (AN), bulimia nervosa (BN) and binge-eating disorder (BED).

AN is a severe psychiatric disorder with high rates of morbidity and impaired quality of life, sometimes with life-threatening consequences (Sullivan, 1995; Fichter et al., 2008; Klump et al., 2009). It is characterized by an intense fear of eating and gaining weight combined with a failure to maintain a minimally normal body weight for one's developmental stage. Patients with AN have a misperceptions of their body weight or shape, are obsessed with it (Arcelus et al., 2011) and are in a state of denial regarding their low body weight and its adverse impact on health (Diagnostic and Statistical Manual of Mental Disorders, (APA, 1994).

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AN is associated with one of the highest mortality rates of any psychiatric condition (10–15%), often as a consequence of medical complications resulting from starvation, purging and/or over-exercising (Katzman, 2005) or because of suicide (Berkman et al., 2007; Herzog et al., 2000).

BN is a condition characterized by recurrent episodes of binge eating with inappropriate compensatory behaviors in order to avoid weight gain such as vomiting, excessive exercise, laxative or diuretic misuse and a strong sense of losing control. It is associated with substantial functional impairment and an increased risk of mortality very often by suicide (Arcelus et al., 2011).

BED is a clinically significant disorder characterized by recurrent episodes of uncontrolled excessive food consumption or binging typically during marked distress which are not regularly followed by compensatory behaviors to avoid weight gain.

Conventional treatments for eating disorders include individual behavioral, cognitive-behavioral (CBT), psychodynamic, group, family therapies and inpatient treatments. Antidepressants are the most commonly used medications in eating disorders. However, selective serotonin reuptake inhibitors (SSRIs) have been shown to be ineffective in reducing AN symptoms or restoring weight (Bulik et al., 2007). Tricyclic antidepressants seem ineffective on weight gain or on AN symptoms (Biederman et al., 1985). However, 30–50% of patients show substantial rates of limited treatment response, dropout and relapse (Hay et al., 2012; Olmsted et al., 2005; Brownley et al., 2007; Shapiro et al., 2007; Wilson, 2010). For example, less than half (46.9%) of the patients recover on average from AN and one-third (33.5%) improve partially even with the best available psychotherapies (Schmidt et al., 2012).

The etiology of eating disorders is probably multifactorial with involvement of genetic factors (Scherag et al., 2010; Slof-Op't Landt et al., 2005; Klump et al., 2002; Pinheiro et al., 2009), neurobiological factors and temperamental vulnerabilities such as negative emotionality, perfectionism and obsessive-compulsive personality traits (Scherag et al., 2010; Stice, 2002) that may interact with environmental factors resulting in an increased risk (Kaye et al., 2011).

The brain reward system is a relatively well-characterized brain circuitry that plays a central role in the drive to eat and individuals with current or past eating disorders showed alterations in those pathways compared to controls.

In AN, there is a dysfunction in the reward-related neuro-circuitries primarily involving dopamine pathways, between the limbic and the cortical systems, such as the nucleus accumbens (NAc) and the anterior cingulate (emotional processing, body image, self-monitoring, reward based decision-making) and insula (Kampe et al., 2009) leading to abnormally low body weight. Functional neuro-imaging studies in eating disorders suggest over-representation of limbic drives from the insula (taste, interoceptive awareness, fear) and amygdala, together with altered prefrontal activity, structural and functional abnormalities in the anterior cingulate cortex and the dorsomedial prefrontal cortex (DMPFC) (Schäfer et al., 2010).

The dorsolateral prefrontal cortex (DLPFC), particularly the left DLPFC (LDLPFC) plays a key role in self-regulatory control mechanisms such as eating behavior, impaired inhibitory control (binge eating and purging) and poor cognitive flexibility (body checking, exercising, obsessive pre-occupation with eating, weight and shape)(Ochsner and Gross, 2007). Hypo-activity of prefrontal cor0tex (PFC) regions during response inhibition (Oberndorfer et al., 2011; Wierenga et al., 2014) and set-shifting tasks (Sato et al., 2013) have been reported in AN. Since set-shifting is assumed to involve the inhibition of a behavioral response (Monsell, 2003), poor inhibitory control may play a key role in set-shifting difficulties in AN that might contribute to both impaired inhibitory control and poor cognitive flexibility and to the maintenance of the disorder.

In BN, neuroimaging data have shown both hyper- and hypo-responsivity in the neural networks that sub-serve anticipatory and food reward processing within ventral limbic and dorsal cognitive fronto-striatal neural networks (Berner and Marsh, 2014) and hypo-activity in circuits that support self-regulatory capacities (Friederich et al., 2013; Marsh et al., 2009; Connan et al., 2007; Berner and Marsh, 2014), thus increasing instability and erratic responding to rewarding stimuli (Wierenga et al., 2014).

Based on the limited efficacy of pharmacotherapy and psychotherapies for the treatment of eating disorders, new approaches are highly needed such as rTMS. This paper reviewed the literature on the safety and efficacy of repetitive transcranial magnetic stimulation and its modified stimulation paradigms (deep TMS and theta-burst stimulation) as a treatment for eating disorders and discussed results and future directions for research in this growing area of attention.

2. Method

Using the search terms “eating disorders”, “anorexia nervosa”, “bulimia nervosa”, “binge eating disorder”, “transcranial magnetic stimulation”, “repetitive transcranial magnetic stimulation”, “rTMS”, “TMS”, “deep transcranial magnetic stimulation”, “dTMS”, theta burst stimulation”, “TBS”, the English literature on controlled (McClelland et al., 2016a, 2016b; Walpoth et al., 2008; Van den Eynde et al., 2010; Gay et al., 2016; Uher et al., 2005; Barth et al., 2011; Lowe et al., 2014), open-label studies (Van den Eynde et al., 2013; Van den Eynde et al., 2012; Dunlop et al., 2015; Sutoh et al., 2016) as well as case series (McClelland et al., 2013a, 2013b; McClelland et al., 2016a, 2016b; Choudhary et al., 2017; Hausmann et al., 2004; Downar et al., 2012; Baczynski et al., 2014) on humans published from 1966 to September 2017 were retrieved through NCBI Pubmed search. Overall, clinical studies and reviews were identified that involved the safety and clinical effects of rTMS on eating disorders published to date (see Tables 1–3). No studies of deep transcranial magnetic stimulation for the treatment of eating disorders could be retrieved in this search.

3. Results

3.1. rTMS and anorexia nervosa

A simple-blind study (Van den Eynde et al., 2013) investigated whether one session of 10 Hz rTMS to the LDLPFC reduces ED symptoms following exposure to visual and real food stimuli in ten female patients with AN on antidepressants. Patients were informed that they would be randomized to sham or active rTMS. However, they all received active rTMS, this procedure being unveiled at the end of the study. All patients reported some levels of discomfort, but rTMS was overall safe and well-tolerated and resulted in significant reductions in the levels of feeling full, feeling fat and anxious in nine patients. No changes were observed on urges to restrict, urge to eat, mood, tension and hunger. There were no changes in cortisol concentrations or in blood pressure and pulse rate contrary to the findings of another double-blind, randomized, sham-controlled trial (Claudino et al., 2011) in which one session of rTMS significantly lowered cortisol concentration compared with sham rTMS.

A randomized, double-blind, sham-controlled, parallel group study (McClelland et al., 2016) investigated the effects of one session of active or sham neuro-navigated 10 Hz rTMS to the LDLPFC on core AN symptoms and cortisol concentrations in sixty patients with AN on stable psychotropic medications. A food exposure task was administered before and after the procedure to elicit AN-related symptoms. Although rTMS was safe and well-tolerated, active rTMS was experienced as more uncomfortable by patients than sham but there were no significant differences between active and sham groups in the number of physical complaints (dizziness, headache). Patients who received active rTMS had a non-significant reduction in symptoms post-rTMS and at 24-h follow-up with a trend for increased urge to eat compared with those who received sham stimulation. Active versus sham rTMS