Eat Weight Disord (2014) 19:403–407
DOI 10.1007/s40519-013-0088-x

BRIEF REPORT

Potential role of repetitive transcranial magnetic stimulation in obesity

Rami Bou Khalil · Charline El Hachem

Received: 15 September 2013 / Accepted: 28 November 2013 / Published online: 11 December 2013

Abstract
Background Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique with mild side effects. Some forms of obesity may arise from eating disorders and recent data suggest that rTMS treatment could have beneficial effects in eating disorders.
Purpose The purpose of this comprehensive review is to hypothesize that rTMS may play a role in obesity.
Materials and methods Articles were selected based on a search on medline using the terms "rTMS", "food craving", "eating disorders", "addiction", and "obesity". They were published between 1995 and 2013.
Results Repetitive transcranial magnetic stimulation has been evaluated in the treatment of bulimia nervosa. It appears that it exerts its effect via the reduction of the level of craving for food. Obesity is being recognized as one of the endpoints of food addiction and craving. Besides, rTMS and transcranial direct current stimulation are brain stimulation techniques being used in the treatment of psychoactive substance addiction.
Conclusions Repetitive transcranial magnetic stimulation, through the reduction of food craving may be a potential treatment for a subset of individuals suffering from obesity. Further studies with a higher number of subjects are still needed to confirm the effects of rTMS on obesity.

R. Bou Khalil (✉)
Psychiatric Hospital of the Cross, Jalledib, Lebanon
e-mail: ramiboukhalil@hotmail.com

R. Bou Khalil · C. El Hachem
Department of Psychiatry, Saint Joseph University, Beirut, Lebanon

Keywords Obesity · Repetitive transcranial magnetic stimulation · Craving · Bulimia nervosa · Eating disorders

Introduction

Repetitive transcranial magnetic stimulation (rTMS), a non-invasive technique with mild side effects, is based on the principle of electromagnetic induction. It discharges a very large current, which results in the induction of a brief and pulsed magnetic field and delivers a repeated single magnetic pulse of the same intensity to a discrete area of the brain [1]. It is a novel tool in psychiatry and controlled studies over the left dorsolateral prefrontal cortex (LDLPFC) have shown antidepressive effects in humans [2]. Over the last several decades, obesity has become a problem of major concern across the developed world and efforts are being made to elucidate its potential causes and to discover new efficient treatments. Some forms of obesity may arise from eating disorders and recent data suggest that rTMS treatment could have beneficial effects in eating disorders. In fact, disturbances in the serotonin system and low levels of brain derived neurotrophic factor (BDNF) may be implicated in the pathogenesis of eating disorders. Knowing that rTMS modulates presynaptic serotonergic activity and increases BDNF levels, it can be speculated that rTMS may improve eating disorders [3]. Besides, cholecystokinin can inhibit food intake in humans and its levels may be increased by rTMS. Moreover, rTMS may have an important role in the treatment of addictions and therefore be of benefit in the treatment of obesity forms associated with food addiction [1]. In fact, rTMS over the prefrontal region has been shown to increase endogenous dopamine release in the striatum which is associated with reward learning [4]. We can thus predict phenomenological

and neurobiological overlaps between obesity and addiction on the basis that drugs of abuse tap into the same neuronal mechanisms that modulate the motivation and drive to seek and consume food [5]. In addition, both in abuse/addiction and in obesity, we can see an enhanced value of one type of reinforcer (drugs and food, respectively) at the expense of other reinforcers, and this appears to be a consequence of conditioned learning and resetting of reward thresholds secondary to repeated stimulation by drugs (abuse/addiction) and by large quantities of palatable food (obesity) in vulnerable individuals (which is affected by genetic factors) [6]. Accordingly, this manuscript has the objective of reviewing the relevant studies that supports the hypothesis that rTMS may be efficient in the treatment of obesity through its direct efficacy in reducing food craving.

Materials and methods

This is a comprehensive non-exhaustive overview of relevant studies evaluating the effects of rTMS on eating disorders and food addiction. Articles were selected based on a search on Medline using the terms "rTMS", "food craving", "eating disorders", "addiction", and "obesity". They were published between 1995 and 2013.

Results

Food craving in obesity

Food addiction has been found to be a major culprit for weight gain. In their study, Pedram et al. recruited 652 adults from the general population. The results showed that obesity measurements (body mass index, weight, body fat and trunk fat) were significantly higher in food addicts when compared to the control group. Therefore, it seems that food addiction indeed accounts for the increasing prevalence of human obesity [7]. Food addiction can be defined as a chronic, relapsing problem caused by various fundamental factors that encourage craving for food or food-substances so as to obtain a state of heightened pleasure, energy or excitement [8]. Most food addiction may be caused by the loss of control of neural signals, and by the impulsive and/or compulsive behavior, which results from environmental conditions and a psychological dependence on food [9]. Besides, compulsivity, a core feature in drug addiction and obesity, may arise, to some degree, from common underlying neurobiological mechanisms such as diminished striatal dopamine D2 receptor availability [10]. In addition, eating disorders tend to be clustered with drug addiction in individuals, and common neural circuits are thought to underlie food and drug rewards, especially dopaminergic pathways. Dopamine, the key neurotransmitter of addiction, plays a significant role in regulating the intake of food and reinforces its effects [11]. The prefrontal cortex is a key player to understand why obese subjects consume more food. Variable functioning of certain regions of the prefrontal cortex induce a decreased ability to cease eating in obese people as compared to lean people [12]. Moreover, in a study by Scharmuller et al. [13], 12 obese women and 14 normal weight right-handed women were exposed to a total of 60 pictures: 30 eating-related scenes with high-caloric food and 30 neutral scenes consisting of non-food items. The participants were asked to either passively look at the pictures or to regulate their appetite. They were then evaluated by functional MRI sessions. In obese women, the insula and the medial orbitofrontal cortex were activated; these regions are involved in food reward processing. Obese women displayed greater insula involvement when passively viewing food cues and stronger dorsolateral prefrontal cortex involvement when trying to attenuate food-elicited craving. Moreover, in a study by Filbey et al., 26 persons with high BMI (>25) and moderate binge-eating behavior, were evaluated by functional MRI (fMRI) scans when exposed to personally relevant high-calories cues. They found that exposure to high-calorie taste cues induced fMRI response in the reward system of individuals with high BMI [14]. As for the adolescent population, one study of 150 participants showed that older school children have experience with food craving symptoms and that intensity of these symptoms is significantly associated with BMI value [15]. Among food, sugar has been found to be an addictive substance since it releases dopamine, a characteristic shared by many addiction neurochemicals and sugar craving as an example of food addiction makes the consumers improve their mood caused by a drop in serotonin levels [16, 17]. Finally, as with drug and alcohol addiction, abstinence from sucrose can cause craving and withdrawal symptoms [18]. In conclusion, obesity may be explained, in many obese subjects, by addiction to some kinds of food, which impose food seeking behavior and food craving at a distance from food intake.

rTMS in bulimia nervosa (BN)

Some studies have supported the efficacy of rTMS in the treatment of patients suffering from BN. In a case report, a 28-year-old patient suffering from BN and major depressive episode as defined by the diagnostic and statistical manual of mental disorders, fourth edition (DSM-IV) was treated with daily rTMS over the LDLPFC during 2 weeks. The patient had a baseline of two binge attacks and vomited twice a day. After 10 sessions of rTMS the patient

recovered completely from binge and purge symptoms and in addition to that her mood improved) [19]. In another study, thirty-eight patients with bulimic-type eating disorders were randomly allocated to receive one session of real or sham high frequency rTMS to the LDLPFC in a double-blind procedure. Compared with sham control, real rTMS was associated with decreased self-reported urge to eat and fewer binge-eating episodes over the 24 h following stimulation [20].

Other studies did not demonstrate that rTMS is superior to placebo in treating patients with BN. One 3-week sham-controlled, randomized, double-blind trial studied the effects of five rTMS sessions per week in patients with BN. Bingeing, vomiting, and self-rated depressive and obsessive–compulsive symptoms improved in both groups but with no significant difference between the two groups over time. It should be noticed that the small sample ($n = 14$) and the large nonspecific improvement in the control group may explain these negative findings [21]. Handedness was taken into consideration in a study that compared the effects of rTMS between 7 left-handed females with BN or Eating Disorder Not Otherwise Specified (EDNOS) and 14 right-handed females with bulimic disorder [22]. Both of the groups received real rTMS. No difference was found between the two groups on the change score for the urge to eat, hunger or urge to binge-eat. However, the change in mood differed significantly between the two groups, with left-handed participants showing a worsening in mood scores. This highlights the importance of handedness in rTMS and the urge to do more studies taking into consideration this factor. Finally, one double-blind randomized sham-controlled trial tested the hypothesis that rTMS reduces salivary cortisol concentrations after exposure to food cues in people with a bulimic disorder. 11 patients received one session of real rTMS while eleven others received sham rTMS [23]. It showed that salivary cortisol concentrations in people with a bulimic eating disorder can be reduced by rTMS. This suggests a possible role of rTMS in reducing the stress response associated to BN.

rTMS in food craving

Craving, defined as an "irresistible urge to consume" and underpinned by abnormalities in frontostriatal circuits, appears to play a role in both substance abuse and overeating. Repetitive transcranial magnetic stimulation (rTMS) at high frequency has the potential to activate directly the immediately underlying cortex (e.g. dorsolateral prefrontal), while inhibiting neural activity in more remote areas (e.g., orbitofrontal and anterior cingulate cortex) [1]. Some studies evaluated the efficacy of rTMS in patients presenting cues of food craving. In a randomized double-blind parallel group study, 28 women, who reported frequent cravings for food were exposed to foods that typically elicit strong cravings before and after a single session of real or sham 10-Hz rTMS to the left dorsolateral prefrontal cortex. Self-reported food craving during exposure to the experimental foods remained stable before and after real stimulation compared with sham stimulation in which cravings increased over the experimental session. Consumption of snack foods within a 5-min period after stimulation did not differ between groups [24]. Another study investigated the effects of left prefrontal rTMS stimulation using an improved sham condition, in 10 healthy women. Each participant received both real and sham rTMS in random order and was blind to the condition. There was a significant drop in cravings in both the real- and sham-TMS groups, with no difference between conditions before and after controlling for hours since last meal. However, the prefrontal rTMS did not inhibit food cravings better than sham rTMS [25].

rTMS in addiction

Electromagnetic brain stimulation techniques such as rTMS and transcranial direct current stimulation (tDCS), are capable of externally modulating cortical activity [1]. rTMS inhibitory paradigms were administered as an investigative tool to index the pathophysiology of addiction in human subjects. This technique uncovered altered cortical excitability in the motor, prefrontal and occipital cortex of individuals exposed to addictive drugs. Administration of rTMS to frontal brain regions in both animal and human studies enhanced dopamine release in the mesocorticolimbic circuitry. Animal studies indicate the potential of brain stimulation in attenuating addictive behaviors. Application of rTMS to the DLPFC within substance dependent populations transiently reduced levels of craving and consumption of addictive substances. Anodal tDCS administered to the DLPFC was also found to attenuate levels of cue-induced cravings [26]. Nicotine and cocaine addictions have been investigated as possible indications for rTMS treatment. rTMS is the most well-studied technique of brain stimulation for the treatment of tobacco addiction. rTMS and tDCS targeted to the DLPFC are so far the most efficacious in reducing tobacco cravings, an effect that may be mediated through the brain reward system involved in tobacco addiction [26, 27]. Besides, alcohol craving could be temporarily suppressed by rTMS directed to the anterior cingulate [28]. The results of a review concerning rTMS and drug addiction show that rTMS is effective in reducing the degree of cravings for smoking, alcohol and cocaine when applied at high frequencies to the DLPFC [29]. It also suggests that repeated sessions of rTMS over the DLPFC may play a role in reducing smoking and alcohol consumption.

Discussion and conclusions

The studies reviewed in this paper provide some positive support for the potential efficacy of rTMS in the treatment of obesity through symptom-alleviation of food craving. However, in the study by Barth et al., in which an improved sham condition was used, both sham and real rTMS inhibited food craving without a difference [25]. This is in contradiction with the results of the work of Uher et al. [24] where real rTMS was better than sham rTMS. This difference may be due to the improved sham condition in Barth et al. study. Therefore, the mild pain induced by real and sham rTMS may inhibit food craving and the decreased craving may not be caused by the effect of rTMS itself. Further studies are needed to determine if rTMS exerts a direct effect on food craving or if it exerts an indirect effect through the pain stimuli it induces. Moreover, food craving and addiction are important factors for the development of obesity in predisposed persons but not all obese people suffer from these problems. Besides, there are many other factors incriminated in the occurrence of obesity, so it seems that rTMS could be beneficial in a subset of obese people. The studies reviewed also show that rTMS is of benefit in the treatment of drug, nicotine and alcohol addiction. However, despite the similarities between food and drug addiction, there are still many differences. In fact, in contrast to drugs whose actions are triggered by their direct pharmacological effects in the brain reward dopamine pathway (ventral tegmental area, nucleus accumbens, and ventral pallidum), the regulation of eating behaviors is modulated by multiple peripheral and central mechanisms that directly or indirectly converge into the brain's reward pathways [5]. If it reduces food craving, rTMS could be an important treatment for patients suffering from obesity especially those presenting features of food addiction. Further studies with a higher number of subjects are still needed to confirm the effects of rTMS on obesity.

Conflict of interest None.

References

1. Mishra BR, Sarkar S, Praharaj SK et al (2011) Repetitive transcranial magnetic stimulation in psychiatry. Ann Indian Acad Neurol 14(4):245–251
2. Fitzgerald PB, Brown TL, Marston NAU et al (2003) Transcranial magnetic stimulation in the treatment of depression. Arch Gen Psychiatry 60:1002–1008
3. Tsai SJ (2005) Repetitive transcranial magnetic stimulation: a possible novel therapeutic approach to eating disorders. Med Hypotheses 65:1176–1178
4. Ahn HM, Kim SE, Kim SH (2013) The effects of high-frequency rTMS over the left dorsolateral prefrontal cortex on reward responsiveness. Brain Stimul 6(3):310–314
5. Volkow N, Wang G, Tomasi D, Baler R (2013) The addictive dimensionality of obesity. Biol Psychiatry 73(9):811–818
6. Volkow N, Wang G, Fowler J et al (2008) Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. Philos Trans R Soc Lond B Biol Sci 363(1507): 3191–3200
7. Pedram P, Wadden D, Amini P et al (2013) Food addiction: its prevalence and significant association with obesity in the general population. PLoS One 8(9):e74832
8. Gold MS, Byars JA, Frost-Pineda K (2004) Occupational exposure and addictions for physicians: case studies and theoretical implications. Psychiatr Clin North Am 27:745–753
9. Warren MW, Gold MS (2007) The relationship between obesity and drug use. Am J Psychiatry 164:1268–1269
10. Kenny PJ, Voren G, Johnson PM (2013) Dopamine D2 receptors and striatopallidal transmission in addiction and obesity. Curr Opin Neurobiol 23(4):535–538
11. Salamone JD, Cousins MS, Snyder BJ (1997) Behavioral functions of nucleus accumbens dopamine: empirical and conceptual problems with the anhedonia hypothesis. Neurosci Biobehav Rev 21:341–359
12. Von Deneen KM, Liu Y (2011) Obesity as an addiction: why do the obese eat more? Maturitas 68:342–345
13. Scharmuller W, Ubel S, Ebner F, Schienle A (2012) Appetite regulation during food cue exposure: a comparison of normal-weight and obese women. Neurosci Lett 518(2):106–110
14. Filbey FM, Myers US, Dewitt S (2012) Reward circuit function in high BMI individuals with compulsive overeating: similarities with addiction. Neuroimage 63(4):1800–1806
15. Svetlak M, Psenicova K (2012) Food craving symptoms in older school age children and its relation to body-mass index. Vnitr Lek 58(2):110–117
16. Avena NM, Rada P, Hoebel BG (2008) Evidence for sugar addiction: behavioral and neurochemical effects of intermittent, excessive sugar intake. Neurosci Biobehav Rev 32:20–39
17. Wurtman RJ, Wurtman JJ (1995) Brain serotonin, carbohydrate-craving, obesity and depression. Obes Res 3:477S–480S
18. Berthoud HR, Lenard NR, Shin AC (2011) Food reward, hyperphagia, and obesity. Am J Physiol Regul Integr Comp Physiol 300(6):R1266–R1277
19. Hausmann A, Mangweth B, Walpoth M et al (2004) Repetitive transcranial magnetic stimulation (rTMS) in the double-blind treatment of a depressed patient suffering from bulimia nervosa: a case report. Int J Neuropsychopharmacol 7:371–373
20. Van den Eynde F, Claudino AM, Mogg A et al (2010) Repetitive transcranial magnetic stimulation reduces cue-induced food craving in bulimic disorders. Biol Psychiatry 67:793–795
21. Walpoth M, Hoertnagl C, Mangweth-Matzek B et al (2008) Repetitive transcranial magnetic stimulation in bulimia nervosa: preliminary results of a single-centre, randomised, double-blind, sham-controlled trial in female outpatients. Psychother Psychosom 77:57–60
22. Van den Eynde F, Broadbent H, Guillaume S et al (2012) Handedness, repetitive transcranial magnetic stimulation and bulimic disorders. Eur Psychiatry 27(4):290–293
23. Claudino AM, Van den Eynde F, Stahl D et al (2011) Repetitive transcranial magnetic stimulation reduces cortisol concentrations in bulimic disorders. Psychol Med 41(6):1329–1336
24. Uher R, Yoganathan D, Mogg A et al (2005) Effect of left prefrontal repetitive transcranial magnetic stimulation on food craving. Biol Psychiatry 58:840–842
25. Barth KS, Rydin-Gray S, Kose S et al (2011) Food cravings and the effects of left prefrontal repetitive transcranial magnetic stimulation using an improved sham condition. Front Psychiatry 2:9
26. Feil J, Zangen A (2010) Brain stimulation in the study and treatment of addiction. Neurosci Biobehav Rev 34:559–574
27. Wing VC, Barr MS, Wass CE et al (2013) Brain stimulation methods to treat tobacco addiction. Brain Stimul 6(3):221–230

28. De Ridder D, Vanneste S, Kovacs S et al (2011) Transient alcohol craving suppression by rTMS of dorsal anterior cingulate: an fMRI and LORETA EEG study. Neurosci Lett 496(1):5–10

29. Barr MS, Farzan F, Wing VC et al (2011) Repetitive transcranial magnetic stimulation and drug addiction. Int Rev Psychiatry 23(5):454–466