BRIEF REPORT

Repetitive Transcranial Magnetic Stimulation Changes Cerebral Oxygenation on the Left Dorsolateral Prefrontal Cortex in Bulimia Nervosa: A Near-Infrared Spectroscopy Pilot Study

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Abstract

Previous studies showed that food craving in eating disorders can be weakened with high-frequency repetitive transcranial magnetic stimulation (rTMS) on the left dorsolateral prefrontal cortex (DLPFC). The aims of this study were to assess cerebral oxygenation change induced with rTMS and to assess the short-term impact of rTMS on food craving and other bulimic symptoms in patients with bulimia nervosa (BN). Eight women diagnosed with BN according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision criteria participated in this study. We measured haemoglobin concentration changes in the DLPFC with near-infrared spectroscopy during cognitive tasks measuring self-regulatory control in response to food photo stimuli, both at baseline and after a single session of rTMS. Subjective ratings for food cravings demonstrated significant reduction. A significant decrease in cerebral oxygenation of the left DLPFC was also observed after a single session of rTMS. Measurement with NIRS after rTMS intervention may be applicable for discussing the mechanisms underlying rTMS modulation in patients with BN.

Keywords

bulimia nervosa; repetitive transcranial magnetic stimulation; near-infrared spectroscopy; dorsolateral prefrontal cortex; craving

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Introduction

Bulimia nervosa (BN) is an eating disorder (ED) characterised by recurrent binge eating and irrelevant compensatory purging behaviours. Treatment options for BN include psychotherapy such as cognitive behavioural therapy, interpersonal therapy, and pharmacotherapy (National Institute for Health and Clinical Excellence, 2004). These available treatments are only moderately effective, as the efficacy of pharmacotherapy is limited (Aigner, Treasure, Kaye, & Kasper, 2011), and psychotherapy is not so successful, with 40–60% of sufferers from BN not fully recovering following a well-conducted course of cognitive behavioural therapy (Wilson, 1999). Relapse rates are high, and refractory symptoms of illness persist longer, impairing the quality of life. Therefore, more effective, non-invasive treatments are needed for the poor responders to current therapies. Craving is thought to precipitate binging, sometimes followed by purging (Waters, Hill, & Waller, 2001). Neuroimaging data have shown that food craving includes hyperactivity in the orbitofrontal and anterior cingulate brain circuits in addiction, BN, and obesity (Goldstein et al., 2002; Uher et al., 2004). These data suggest that changes of activity in the frontal area are critical for bulimic disorders (Nozoe et al., 1995).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive brain stimulation technique using electromagnetic induction. Recently, a meta-analysis showed that rTMS is a safe strategy with relatively few adverse events, suggesting that augmentative rTMS is an effective intervention for treatment-resistant depression (Fitzgerald, et al., 2012). Positive effects of rTMS on EDs are now expected because of suggestive evidences that rTMS shows favourable effects on craving for substance dependence and craving for food (Jansen, et al., 2013; Grall-Bronnec & Sauvaget, 2014; McClelland, Bozhilova, Campbell & Schmidt, 2013). In EDs, a few studies using a randomised controlled trial design for BN have reported favourable effects (Walpoth et al., 2008; Van den Eynde et al., 2010). Van den Eynde, et al. (2010) demonstrated reduced frequencies of binge eating episodes of cue-induced food cravings, 'urge to eat', as assessed by a self-reported visual analogue scale (VAS). A few pilot studies in anorexia nervosa (AN) have shown that high-frequency rTMS

on the left dorsolateral prefrontal cortex (DLPFC) reduced food cravings in cases with severe enduring AN (Van den Eynde, Guillaume, Broadbent, Campbell, & Schmidt, 2013; McClelland et al., 2013). In these studies with BN as well as AN, the optimal parameters of rTMS for clinical efficacy were determined only on the basis of VAS.

Near-infrared spectroscopy (NIRS) is a noninvasive technique for measuring changes in blood oxygen concentration ([oxyHb]) that combines high temporal resolution, therefore meeting the requirements for monitoring the cortical response to TMS. Studies for blood oxygenation responses using NIRS and functional magnetic resonance imaging have revealed prefrontal hyperactivity patterns to food stimuli in BN (Kim, Ku, Lee, Lee, & Jung 2012; Schienle, Schafer, Hermann, & Vaitl, 2009) and self-regulatory function (Sutoh et al., 2013). rTMS generally leads to an initial increase and subsequent longer-lasting decrease in tissue oxygenation and haemoglobin concentration (Allen, Pasley, Duong & Freeman, 2007); however, its precise neural effect specific to BN has not yet been revealed.

The aims of this study were to assess the cerebral oxygenation change induced with rTMS and to assess the short-term impact of high-frequency rTMS to the left DLPFC on food craving and other bulimic symptoms in patients with BN. Prefrontal functions were assessed before and after one session of rTMS intervention using an intentional loss task performance and [oxyHb] measured during both a food-photo task and the intentional loss task.

Methods

Participants

Eight female subjects with BN participated in this study. They were recruited from the outpatient unit of Chiba University Hospital. The participants met the current diagnosis of BN according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria (American Psychiatric Association, 2000). Diagnosis was established with the ED module of the Structured Clinical Interview for DSM-IV-TR, Axis I Disorder/Patient Version Structured Clinical Interview for DSM-VI-TR Axis I Disorders, Research Version, Patient Edition (First, Spizer, Gibbon, & Williams, 2002).

Exclusion criteria were left-handedness, personal, and close family history of seizure, neurological disorders, brain injury, suicidal ideation, pregnancy, substance abuse, severe depressive disorders, BMI $< 17.5\,kg/m^2$, and use of medical equipment considered to be subject to the influence of magnetic stimulation (intracranial metal product). This study was approved by the institutional ethics committee of Chiba University, and all participants provided informed consent.

Examination schedule

As the baseline measurement [visit 0 (v0)], participants completed the assessments of clinical symptoms and cognitive tasks under prefrontal NIRS measurement. On the day at 1 week after v0 (v1), they underwent a single session of rTMS, and at 4 h after the rTMS intervention, they completed clinical assessments and cognitive tasks with NIRS the same as v0. They were asked to have breakfast before undergoing rTMS at 10 AM. They were asked to have lunch by 1 PM and not eat thereafter, and had NIRS measurement with cognitive tasks at 2 PM. They were also asked to abstain from smoking or drinking caffeinated beverages after 9 AM until the end of the NIRS measurement. The examination schedule is presented in Figure S1.

Cognitive tasks

As cognitive tasks to evoke prefrontal cortical activity, a food photo task and a rock-paper-scissors task with intentional loss (RPST) (Sutoh et al., 2013) were performed by all participants, in that order.

Food photo task

In the food photo task, 15 photographs were presented to participant, with five photographs of each of three categories: high-calorie food, low-calorie food, and neutral (scenery). Details are shown in the Supporting Information. Thus, participants experienced a total of 15 trials during each of which they viewed and responded to a single photograph in turn. Each trial consisted of a 15-s fixation, a 15-s photograph presentation, and a 50-s questionnaire consisting of 5 items (10 s each) scored on a VAS of 0 to 10. The VAS items for the food photographs were 'want to eat', 'urge to eat', 'sense of hunger', 'level of tension', and 'level of disgust' whereas those for neutral photos were 'want to visit', 'urge to visit', 'ought to visit', 'level of tension', and 'level of disgust'.

RPST

Our group previously designed a RPST based on an ordinary rock-paper-scissors game to assess self-regulatory control (Sutoh et al., 2013). The ordinary rock-paper-scissors game uses three hand shapes that are in a three-sided impasse relationship. It is a simple and easy method to divide two or more players into a winner and loser. Because it is familiar and frequently played by most Japanese, to lose quickly and intentionally in response to a presented hand gesture requires inhibitory self-regulation for habitual behaviour and emotion.

The RPST consisted of sequential presentations of pictures of a hand clenched in a fist (rock), held out flat (paper), or with two fingers splayed (scissors), shown one by one in a random order. Participants were instructed to respond by hitting any one of three buttons corresponding to each of three hand shapes. The task sequence consisted of five task periods, in which the goal was 'to intentionally lose' with inter-trial baseline periods in which the goal was to win. As the task performance, we assessed the rates of correct responses ('accuracy') and the mean reaction time. Please see the Supporting Information for details (Figure S1).

NIRS measurements

During both of the tasks, the left and right prefrontal [oxyHb] changes were measured with two-channel NIRS. Detailed information about probe placement and data processing are described in the Supporting Information.

rTMS setting

The stimulations were performed by trained psychiatrists with a figure-of-eight coil [Magstim Rapid System (MRS1000, Magstim Company Ltd, Wales, UK)] placed at 5 cm anterior in the same

parasagittal plane from the site of maximal abductor pollicis brevis stimulation, which was projected on the left DLPFC (Brodmann area 9). Stimulation was delivered at a frequency of 10 Hz and an intensity of 110% of the individual motor threshold. Fifteen trains of 5 s, with 55-s inter-train intervals, were performed. A total of 1000 pulses were provided over 20 min. These parameters were determined according to the previous studies, in which the stimulations were delivered with comparable rTMS instruments with that in the present study (Uher et al., 2005; Van den Eynde et al., 2010).

Assessments of clinical symptoms

All participants were assessed using Eating Disorder Inventory (Garner, 1991; Shimura, Horie, Kumano, Sakano & Suematsu, 2003), Eating Disorder Examination Questionnaire (Fairburn & Beglin, 1994), Bulimic Investigatory Test, Edinburgh (Henderson & Freeman, 1987), Hospital Anxiety and Depression Scale (HADS) (Zigmond & Snaith, 1983; Kitamura, Zigmond, & Snaith, 1993), Clinical Global Impression of disease severity (Guy, 1976), Food Craving Questionnaire-State Score (Cepeda-Benito, Gleaves, Williams, & Erath, 2000), and Global Assessment of Functioning (GAF) (American Psychiatric Association, 2000). These assessments were completed before (v0) and after (v1) rTMS.

Statistical analysis

The experimental values were statistically analysed using SPSS 12.0 (SPSS, Inc., Chicago, IL). Repeated measures of analysis of variances and Bonferroni's comparisons were performed for task performances and [oxyHb] data respectively. Exploratory correlation analysis was performed among [oxyHb] data, task performances, and symptom scales. Paired *t*-tests comparing v0 and v1 were used for scores of symptoms, VAS, and RPST (accuracy and reaction time). Values at $p < 0.05$ were considered statistically significant.

Results

Participants' characteristics and clinical assessments

Eight women (24.8 ± 2.5 years; range, 19–33 years) diagnosed with BN participated in this study. None of the participants had comorbidities such as depression, anxiety disorders, or substance addiction. Their demographics and symptom scale scores are listed in Table 1. Comparison between the symptom scales at v0 and v1 showed a significant reduction in the scores of HADS anxiety and a significant elevation in GAF. All participants safely underwent the NIRS measurements and rTMS intervention without side effects.

Task performance and NIRS measurement: food photo task

A significant reduction in the subjective ratings of want to eat, urge to eat, and sense of hunger for the high-calorie food stimuli was found at post-rTMS session (Table 2). On the other hand, no significant change was found in the subjective ratings for the low-calorie food and the neutral (scenery) stimuli. The NIRS measurement revealed a significant reduction in the left prefrontal [oxyHb] activation for the neutral photo stimuli at 4 h after following rTMS to the left DLPFC compared with the activation before the rTMS session. This [oxyHb] decrease took place during the last half of the photo task period. For each of two food stimuli, comparisons between the prefrontal activations at pre-rTMS and post-rTMS found no significant change. There was no significant difference between the [oxyHb] activations for the three picture sets within each measurement occasion.

Table 1 Demographic data and clinical symptoms

		Pre-rTMS		Post-rTMS			
		Mean	SEM	Mean	SEM	*p*	
Age		24.80	2.54				
BMI		19.54	1.54				
EDI-2		111.20	19.30	102.60	22.37	0.273	
EDEQ	Global	5.54	0.99	5.52	1.29	0.960	
	Restraint	3.20	0.81	2.96	1.02	0.509	
	Eating	3.52	0.64	3.68	0.71	0.675	
	Weight	3.44	0.70	3.44	1.04	1.000	
	Shape	3.71	0.77	3.73	0.82	0.912	
BITE	Severity	10.20	3.22	9.40	2.62	0.814	
	Symptom	17.40	1.69	18.60	0.87	0.535	
HADS	Anxiety	12.00	1.58	10.20	1.88	0.088	*
	Depression	8.80	1.91	8.60	2.54	0.828	
CGI-S		4.60	0.51	4.00	0.63	0.208	
FCQ		140.60	9.71	131.20	13.20	0.076	*
GAF		57.00	3.00	59.40	3.50	0.042	**

SEM, standard error of mean; BMI, body mass index; EDI-2, Eating Disorder Incentery-2; EDEQ, Eating Disorder Examination Questionnaire; BITE, Bulimic Investigatory Test, Edinburgh; HADS, Hospital Anxiety and Depression Scale; CGI-S, Clinical Global Impression of disease severity; FCQ, Food Craving Questionnaire-State Score; GAF, Global Assessment of Functioning.
*$p < 0.10$. **$p < 0.05$.

Table 2 Subjective ratings for three photograph categories at pre-rTMS and post-rTMS sessions

			Pre-rTMS		Post-rTMS			
			Mean	SEM	Mean	SEM	*p*	
Neutral	Q1	Want to visit	3.50	0.49	2.83	0.39	0.103	
	Q2	Urge to visit	1.68	0.35	1.25	0.26	0.139	
	Q3	Ought to visit	0.68	0.30	0.83	0.33	0.183	
	Q4	Level of tension	1.30	0.37	0.78	0.23	0.068	
	Q5	Level of disgust	1.23	0.35	0.70	0.20	0.068	
Low	Q1	Want to eat	4.18	0.43	3.38	0.39	0.078	
	Q2	Urge to eat	1.93	0.38	1.53	0.33	0.232	
	Q3	Sense of hunger	2.28	0.37	1.45	0.25	0.059	
	Q4	Level of tension	1.15	0.31	0.85	0.25	0.340	
	Q5	Level of disgust	1.10	0.21	0.83	0.21	0.102	
High	Q1	Want to eat	6.10	0.34	4.55	0.35	0.000	*
	Q2	Urge to eat	3.60	0.42	2.53	0.35	0.001	*
	Q3	Sense of hunger	3.28	0.35	2.10	0.28	0.009	*
	Q4	Level of tension	2.00	0.41	1.38	0.31	0.130	
	Q5	Level of disgust	1.55	0.29	1.13	0.33	0.169	

rTMS, repetitive transcranial magnetic stimulation; SEM, standard error of mean.
*$p < 0.05$.

Task performance and NIRS measurement: RPST

The results in the performance of RPST and the prefrontal [oxyHb] activities are shown in Table 3 and Figure 1 respectively. Surprisingly, rates of accuracy for the trials that required participants to lose showed a significant reduction at the post-rTMS session compared with those at the pre-rTMS session. There was no significant change in reaction time between the pre-rTMS and post-rTMS sessions. The NIRS measurements in the frontal regions during RPST revealed a significant decrease in [oxyHb] in the left DLPFC.

Discussion

To our knowledge, this is the first study to demonstrate changes in NIRS-measured modulation in blood oxygenation in the frontal region after rTMS intervention in BN participants. Previous research suggested that rTMS over the DLPFC reduced food craving and frequencies of binging (Uher et al., 2005; Van den Eynde et al., 2010). The findings in the present study, namely significant reductions in the subjective ratings for want to eat, urge to eat, and sense of hunger to the food stimuli, were consistent with those in the previous studies. Such decreases were shown only for the high-calorie food stimuli. This difference in sensitivity to rTMS might be because of the high-calorie food photos requiring greater cost for processing craving in the DLPFC than the low-calorie food and neutral photos. In other words, high craving intensity prior to rTMS might be required to distinguish the rTMS effect.

The causal mechanism of prefrontal rTMS for decreasing craving could be strengthening the inhibitory control for craving or weakening the craving itself. The results from the NIRS measurements provide a hint. According to the prefrontal activities to the neutral stimuli, the rTMS session seemed to induce a suppressive change in the prefrontal [oxyHb] activity to the photo stimuli. On the other hand, the prefrontal activities in response to high-calorie food stimuli showed no significant change between pre-rTMS and post-rTMS sessions, even though craving for foods were weakened. To explain these results, we hypothesise that lower and inefficient self-regulatory function of PFC in BN (Sutoh et al., 2013) was improved by rTMS. First, the changes in the responses to the neutral stimuli could be explained by saying that the self-regulatory prefrontal activation, which was 'indiscriminant' and not very necessary to the neutral stimuli, was reasonably suppressed with rTMS. That also explains the responses to the high-calorie food stimuli as follows: rTMS increased the efficiency of the self-regulatory function of the PFC to sufficiently decrease craving, while the PFC showed comparable [oxyHb] activation before and after rTMS.

RPST and the prefrontal measurement revealed a decrease in [oxyHb] during the RPST trials. There are inconsistent results of how high-frequency (>10 Hz) rTMS modulates task-related brain blood response. One study reported the absence of a task-related increase of total haemoglobin concentrations (Eschweiler et al., 2000) along with the present result; however, another reported no change (Guse et al., 2013). The hypothesis of inefficient prefrontal function in BN might also be an explanation: that is, lower and inefficient self-regulatory function of PFC (Sutoh et al., 2013) was modulated by the rTMS session to consequently require less blood in response to the same task load.

RPST also revealed a decline of accuracy in participants with BN from the pre-rTMS to post-rTMS intentional loss trials. This could be explained by visual attention which is known to depend on the frontal and parietal networks in the right hemisphere dominantly. A previous investigation showed laterality of the rTMS effect on prefrontal areas in attentional control such that a delay in reaction time in an attention task was induced by left prefrontal stimulation while not by right stimulation (Rounis, Yarrow & Rothwell, 2007). The present rTMS on the left prefrontal area might have affected the right hemisphere-dominant attentional control with interhemispheric inhibition and resulted in the decreased accuracy.

Table 3 Task performance of RPST loss

		Pre-rTMS		Post-rTMS			
	Correct response	Mean	SEM	Mean	SEM	*p*	
Accuracy (%)	Win	96.81	0.98	95.05	1.41	0.167	
	Lose	95.00	2.23	90.00	3.48	0.044	*
Reaction time (m s)	Win	1090.93	67.68	1027.84	45.64	0.254	
	Lose	1436.18	91.17	1417.67	123.54	0.848	

rTMS, repetitive transcranial magnetic stimulation; SEM, standard error of mean.
*$p < 0.05$.

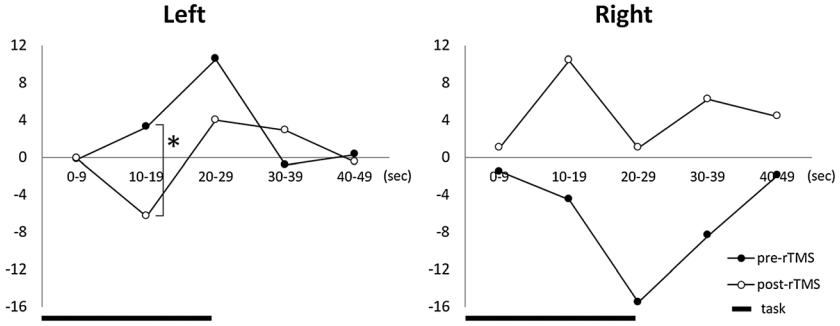

Figure 1. Standardised waveforms of prefrontal oxyhemoglobin concentrations during the rock-paper-scissors intentional loss task. A significant decrease was found in the [oxyHb] of the left prefrontal region during the task period. Note the repeated measures of analysis of variances and Bonferroni's comparisons; *$p < 0.05$

A significant reduction in the scores of HADS anxiety and a significant elevation in GAF were observed after the rTMS session. In a previous case report, levels of anxiety were decreased after rTMS stimulation in panic disorder comorbid with major depressive disorder (Machado et al., 2014). In this study, the levels of anxiety in the BN group were significantly elevated compared with those of healthy controls. Those suffering from EDs have traits of high anxiety, which are thought to affect the persistence of binge eating and purging behaviours. After the stimulation, the levels of anxiety fell; in practice, this may bring about a reduction in the levels of craving.

There are several methodological limitations to this study. The number of participants was relatively small and recruited without any justification. There was no control group and no sham rTMS. The brain region assumed to be stimulated by rTMS was narrowly localised to part of the left DLPFC. In addition, NIRS is methodologically limited in terms of the assessment of brain function, as has been described the previously (Sutoh et al., 2013).

In conclusion, the decrease in cerebral oxygenation in the frontal lobe during the RPST suggests that this measurement is applicable for efficiently monitoring the efficacy of neural-based treatment. Further studies are required with more subjects and with a controlled setting, in which we consider whether measuring NIRS in the brain region is applicable for measuring response to brain-directed treatment for the sufferers of EDs.

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