

Repetitive transcranial magnetic stimulation: A potential therapeutic option for obesity in a patient with Prader-Willi syndrome

To the Editor:

Hyperphagia and, consequently, obesity, are the most serious problems in patients with Prader-Willi syndrome (PWS), leading to decreased quality of life, increased morbidity, and even mortality. An aberrant activation in the following brain areas (i.e. hypothalamus, insula, dorsolateral prefrontal cortex [DLPFC], specifically, the orbito-frontal cortex [OFC] and midbrain reward system) has been shown in patients with PWS both after eating,¹ and in the fasting condition.² Recently, a lack of food-anticipatory cerebellar activity has also been described in individuals with PWS,³ with consequent impairment of the facilitating effects of cerebellar output on striatal dopamine release.³

Through a functional magnetic resonance imaging study, we showed that a 5-week treatment with high-frequency repetitive transcranial magnetic stimulation (rTMS), targeted to the DLPFC and the insula bilaterally, can enhance the functional connectivity of the OFC in patients with obesity, by reflecting an increased inhibitory activity of the PFC, specifically of the OFC, on eating behaviour.⁴ This mechanism is thought to mainly underlie the effectiveness of rTMS in controlling food craving and promoting long-term weight loss in individuals with obesity, as first shown in our previous clinical trial,⁵ and replicated by other studies.⁶

Whereas rTMS seems to promote the control of food craving by acting on the same brain areas that have been shown to be dysfunctional in patients with PWS, we hypothesized that rTMS may represent an effective treatment for the control of hyperphagia in PWS. Moreover, rTMS has been proposed as a non-invasive and well-tolerated treatment.⁷

Repetitive TMS was also shown to improve the cognitive functions in patients with cognitive disorders.⁸

We now present our experience in the first application of rTMS to treat hyperphagia and severe obesity in a patient with PWS, with combined monitoring of body weight and cognitive status.

The patient undergoing rTMS treatment was a 23-year-old man. He had received a diagnosis of PWS after birth. Severe hyperphagia and obesity had developed by the eighth year of life. Extreme body weight gain (about 25 kg) occurred in the last 3-4 years (body weight 127.4 kg, height 159 cm, body mass index [BMI] 50.4 kg/m²). Frequent episodes of 'binge eating' have been reported by the patient and by his caregiver familiar. Despite enormous efforts by the patient and his family, his weight gain could not be controlled after any period of short-term weight loss, and weight regain occurred immediately.

His obesity resulted in metabolic disorders (e.g. hyperinsulinaemia and type 2 diabetes), arterial hypertension, hypogonadism and obstructive sleep apnoea syndrome. The patient was also taking therapy with metformin 500 mg three times a day (stable dose for at least 6 months), amlodipine 10 mg per day and testosterone enanthate 250 mg every 15 days by injection. The patient had never received growth hormone replacement therapy.

Screening assessments included taking a blood sample for metabolic variables, and indirect calorimetry (resting energy expenditure, respiratory quotient).

Evaluation of cognitive status was performed through the Mini-Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MOCA) tests, at the baseline, at the end of rTMS treatment, and at the 3-month follow-up visit. Other specific questionnaires were administered at beginning and at the end of the rTMS intervention (Food Craving Questionnaire-Trait, Barratt Impulsiveness Scale, Rosenberg's Self-Esteem Scale, Short Form-36 Health Survey), to quantify the patient's desire for food, impulsiveness and behaviour, self-esteem and quality of life (Table 1).⁹⁻¹⁵

The protocol was approved by IRCCS Multimedica hospital's ethics committee as 'compassionate treatment'. The patient was fully informed of potential risks and benefits of the treatment and gave his full consent.

The deep rTMS was performed using a Neuro-MS/D magnetic stimulator (Neurosoft Ltd). Neurostimulation was addressed to bilaterally stimulate the PFC and the insula, according to our previous protocol for obesity.⁵

During the rTMS treatment, the patient lost about 1 kg per week, with a total weight loss of 4.4 kg (3.5%) at the end of the 5-week intervention, and of 5.9 kg (4.6%) at the 3-month follow-up. BMI changed from 50.4 to 48.6 kg/m² at the end of the 5-week intervention, and to 48.0 kg/m² at the 3-month follow-up (Figure 1).

A robust improvement in the MMSE score (corrected for age and scholarization) was found compared with baseline (from 22 [severe impairment] to 27 [moderate impairment] at the end of the 5-week rTMS treatment, and to 29, at the 3-month follow-up). The improvement in the cognitive status assessed through the MOCA test was confirmed, although perceptually weaker (17/30 to 19/30 at the end of the 5-week rTMS treatment and to 20/30 at the 3-month follow-up).

The patient regularly completed all the rTMS planned sessions and underwent the follow-up visit. The patient did not experience severe adverse events throughout the duration of the study.

TABLE 1 Body weight, energy expenditure, metabolic variables, psychological and cognitive assessments before and after the 5-week repetitive transcranial magnetic stimulation (rTMS) treatment and at the 3-month follow-up, in an adult patient with Prader-Willi syndrome

	Prestudy	5 weeks (end of rTMS treatment)	3-month follow-up
Body weight			
Value (kg)	127.4	123	121.5
Change from prestudy (kg)		-4.4	-5.9
BMI			
Value (kg/m ²)	50.4	48.6	48
Change from prestudy		-1.79	-2.33
WHR			
Value (waist-to-hip cm)	1.02 (148/145)	1.12 (143/128)	1.12 (144/128)
Change from prestudy		+0.1	+0.1
REE			
Value (kcal/day)	2736	2617	-
Change from prestudy		-119	-
RQ			
Value (kcal/day)	0.74	0.71	-
Change from prestudy		-0.03	-
HbA1c (%)	6.2	6.1	-
Fasting glucose (mg/dl)	90	90	-
Cholesterol (mg/dl)	212	190	-
HDL (mg/dl)	40	40	-
LDL (mg/dl)	142	124	-
Triglycerides (mg/dl)	152	131	-
FCQ-T score ^{9,10}			
Value	72	95	50
SF-36 s ¹¹			
Value	106	98	-
BIS score ¹²			
Value	72	73	-
RSES score ¹³			
Value	28	27	-
MOCA score ¹⁴			
Value	17	19	20
MMSE s ¹⁵			
Value	22	27	29

Abbreviations: BIS, Barratt Impulsiveness Scale; BMI, body mass index; FCQ-T, Food Craving Questionnaire-Trait; MMSE, Mini-Mental State Examination; MOCA, Montreal Cognitive Assessment; REE, resting energy expenditure; RQ, respiratory quotient; RSES, Rosenberg's Self-Esteem Scale; SF-36, Short Form-36 Health Survey; WHR, waist-to-hip ratio.

To the best of our knowledge, this is the first reported case of the application of high-frequency rTMS over two brain target regions (PFC and insula) to treat hyperphagia in a patient affected by PWs, in whom repeated interventions aimed at inducing weight loss had failed. After 15 treatment sessions, the patient exhibited a significant body weight loss up to 3 months from the end of intervention. Surprisingly, an improvement in the cognitive performance assessed by both MMSE and MOCA was shown along with the body weight loss.

Obesity is a major cause of premature morbidity and mortality in PWs, therefore improvement in weight control remains the main goal of any PWs treatment programme, but the management of obesity in these patients is very difficult. Pharmacotherapy options in patients with PWs are very limited, and currently, no medications have shown long-term effectiveness in controlling appetite in PWs patients; on the other hand, other investigated drugs, although fairly effective, have significant side effects or contraindications.

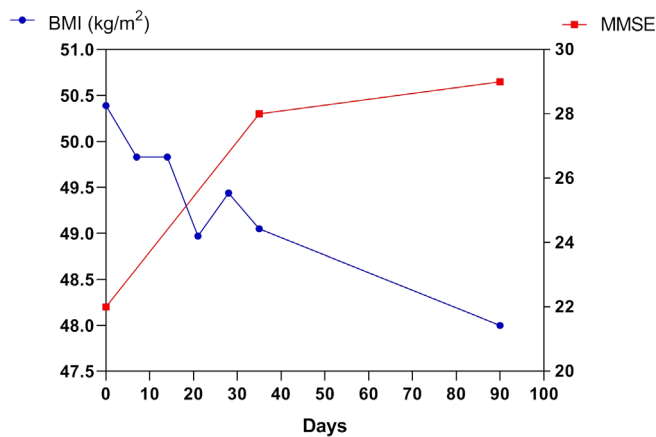


FIGURE 1 Changes in body mass index (BMI) and in mini-mental state examination (MMSE) score during repetitive transcranial magnetic stimulation (rTMS) treatment and follow-up, in an adult patient with Prader-Willi syndrome (PWs). The figure shows weekly decreasing changes of BMI (blue line) in the patient with PWs during the 5 weeks of high-frequency rTMS treatment and at the 3-month follow-up visit; benchmark values of the BMI are shown on the left ordinate axis. Values of MMSE score were assessed at baseline, at the end of the 5-week rTMS treatment and at the 3-month follow-up visit; increasing variations are highlighted by the red line and benchmark values of the MMSE are shown on the right ordinate axis

In a recent retrospective analysis evaluating intensive more effective medical weight loss interventions in adults with PWs (very-low-energy diet, phentermine/topiramate, glucagon-like peptide-1 receptor agonists), although most (93%) individuals were able to achieve an average weight loss of approximately 10% during treatment, non-adherence resulted in substantial weight regain at the follow-up.¹⁶ Adverse effects were ascribed mostly to phentermine and topiramate and resulted in discontinuation, whereas liraglutide was well-tolerated in this population, although the pre-existing risk for delayed gastric emptying and gastric rupture remains in the PWs population.¹⁷

Although the mechanisms underlying hyperphagic behaviour in PWs remain to be fully understood, it is well known that a hypoactivity of the PFC, specifically of the DLPFC, a key structure involved in the decision-making process, occurs in the PWs. Recently, a possible involvement of cerebellar activity, and thus of the cerebellum-induced dopamine release in response to food, has been hypothesized.³

Repetitive TMS was revealed to be a promising treatment for controlling overeating and body weight in individuals with obesity, specifically by targeting the PFC (and potentially, other brain areas). For this reason, we hypothesized that rTMS might be a more suitable treatment also in individuals with PWs. Preliminary evidence of efficacy was obtained by a pilot, double-blinded, sham-controlled, multicentre study in which a milder neurostimulation technique, the transcranial direct current stimulation addressed to the right DLPFC (applied for five sessions), had a persistent modulatory impact on food drive and behaviour, impacting hyperphagia in PWs.¹⁸

Furthermore, individuals with PWs display a lower cortical complexity in frontal, temporal and parietal lobes compared with healthy controls, irrespective of their specific genotype, which partially underlies cognitive impairment and developmental delay.¹⁹

Recent evidence emphasizes the application of rTMS also for cognitive enhancement: specifically, high-frequency rTMS is the most widely used technique for improving the overall cognitive task performance, especially if applied to the DLPFC.

In view of the urgent need of novel effective and safe interventions to treat obesity and improve quality of life in PWs, these findings support a potential role of rTMS in reducing food drive and behaviours impacting hyperphagia and obesity in PWs, with a possible positive impact also on cognitive functions.

AUTHOR CONTRIBUTIONS

LL conceptualized the paper; AF, LL, DC and CM conducted the experiment; LL and AF provided research conduct oversight; AF and DC drafted the first version of the manuscript. LL and AF revised it and contributed significantly with intellectual content. All the authors read and revised the manuscript and approved the final version. As corresponding author, LL confirms that he had full access to all the data in the study and had final responsibility for the decision to submit for publication.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analysed during the current study are available from the corresponding author on reasonable request.

KEYWORDS

cognitive deficit, hyperphagia, obesity, Prader-Willi syndrome, transcranial magnetic stimulation

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