TITLE: **Repetitive Transcranial Magnetic Stimulation (rTMS) in Anorexia Nervosa (AN): clinical, cognitive and functional correlates of dorsal and medial prefrontal stimulation.**

ABSTRACT:

Anorexia Nervosa (AN) is a severe psychiatric disorder characterized by an intense fear of weight gain and a pervasive disturbance of the body image. Affected people show alterations in cognitive and emotional dimensions, with frequent psychiatric and medical comorbidity (Zipfel, Giel, Bulik, Hay, & Schmidt, 2015). The high relapse rate of the disorder and its protracted course, often lead to poor quality of life and high levels of disability and mortality.

Many brain regions which are considered to have a role in the aetiology and mantainence of AN involve part of the ventral/limbic circuit and of the dorsal/cognitive one, causing alterations of emotional processing and behavioral response selection. A dysregulation of the prefrontal cortex activity could be implicated in the failure of integrative functions of these neural circuits and seems to be particularly relevant in the worsening of cognitive flexibility and inhibitory control abilities in AN (Collantoni et al., 2016; Tenconi et al., 2010).

New therapeutic strategies are highly necessary in adults with AN, as none of the current treatments showed a superior efficacy over others.

The possibility to use, in addition to current interventions, more targeted and brain directed treatment approaches, such as non-invasive neuromodulation strategies, would allow to modify the connectivity of specific neural circuits, leading to an improvement of specific psychopathology and cognitive dimensions.

The modulatory activity of Repetitive Transcranial Magnetic Stimulation (rTMS) on brain network connectivity depend on long term potentiation or long-term depression mechanisms, which allow long lasting after-effects (Polanía, Nitsche, & Ruff, n.d.).

To date, both dorsal and medial prefrontal regions (dlPFC and dmPFC) have been targeted with rTMS in different psychiatric conditions. While dlPFC stimulation is shown to modulate mainly cognitive control processing, dmPFC stimulation is demonstrated to be effective in the modulation of cortical-striatal loops connectivity, with a beneficial effect on habits formation and in obsessive-compulsive symptomatology (Dunlop et al., 2015).

Since both dorsal and medial prefrontal areas are involved in the psychopathology of AN, the aim of this study is to compare the effectiveness of rTMS on l-DLPFC and on dm-PFC in improving the core symptoms of the disorder and its cognitive correlates. Functional and structural neural correlates will be also examined.

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EXPERIMENTAL DATA:

To be acquired	x
Already acquired (ready to be used)	

Participants' eligibility will be established with a pre-randomisation assessment: 1) demographic and medical history 2) diagnostic, 3) psychiatric comorbidity.
An independent researcher will randomise eligible participants (n = 90) in a parallel design stratifying by AN-subtypes. Subjects: Inclusion criteria for patients were female gender, a current DSM-5 diagnosis of AN, a body mass index (BMI) between 14.0-18.5 kg/m2 and an age between 16 and 35 years. Neuropsychological assessment: All subjects will undergo a series of neuropsychological tests to investigate executive functioning and decision-making.
General assessment: Clinical and neuropsychological characteristics will be assessed at baseline, at the end of treatment and at a three-month follow-up in the two groups. Patients will also complete several visual analog scales before and after stimulation. These will assess perceived levels of anxiety, feeling fat, urges to restrict, to exercise, to binge/purge and mood.
At the end of each week, ED and mood symptomatology will be assessed using specific questionnaires, such as the Hopkins Symptoms Checklist and the Eating Disorders Examination Questionnaire.
rTMS protocol on l-DLPFC: 15 Hz, 110% rMT, 20 trains (5 s on, 55 s off, 1000 pulses per session), 20 daily sessions.
rTMS protocol on dmPFC: lateral coil orientation, 10Hz, 120 % rMT, 60 trains (5 s on, 10 s off, 3000 pulses per hemisphere and session), 20 daily sessions.
Magnetic Resonance Imaging study: All participants will undergo MRI scan: 1) a high-resolution T1 structural sequence 2) a BOLD sequence for exploring functional connectivity at rest; 3) a diffusion tensor imaging (DTI) for measurement of structural connectivity in a week before the first rTMS session and in a week after the end of the full session.
EEG study: All participants will undergo a 128 EEG before and at the end of the treatment to test the presence of any functional connectivity change at rest.

ETHICS COMMITTEE:

Obtained	
Conditioned submission*	Expected time response (in months): 2
Not required	