From Reward Circuit to Clinical Outcome: Piloting DLPFC-TMS Modulation of the Nucleus Accumbens in Adolescent Anorexia Nervosa

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1 Introduction

Anorexia nervosa (AN) carries the highest mortality rate of any psychiatric disorder, yet adolescent treatment options remain limited. The nucleus accumbens (NAcc), a reward and motivation hub, exhibits elevated responses in AN that correlate with harm avoidance and poor weight gain, making it a logical therapeutic target. Transcranial magnetic stimulation (TMS) has shown promise in adults with depression and AN, but its neural mechanisms and efficacy in youth are unknown. To measure NAcc function, we selected a monetary incentive delay (MID) task, as monetary stimuli reliably engage the NAcc in AN. However, standard TMS cannot directly reach the deep NAcc, but the NAcc is functionally connected to the dorsolateral prefrontal cortex (DLPFC), allowing for potential indirect modulation. This pilot study validates the task and protocol in healthy controls (HC) before an AN feasibility trial, investigating:

1. whether the MID task **optimally engages** the NAcc,
2. **NAcc response differences** between AN and healthy controls (HC),
3. whether DLPFC TMS **modulates NAcc reactivity** as a pathway to **clinical improvement**.

2 Methods

	Stage 1: Validation in HC	**Stage 2: Feasibility in AN**
Sample	10 healthy adults	10 adolescents with AN + 10 HC
Task	MID task during fMRI	MID task during fMRI
TMS	One session left DLPFC TMS (10 Hz) during fMRI	Active (n=5) or sham (placebo, n=5) TMS (10 Hz)
Outcomes	Acute NAcc and sgACC modulation	Pre/post NAcc/sgACC BOLD, Eating Disorder Examination (EDE) score, BMI
Additional	–	Semi-structured interview

Tab. 1: Study design overview.

The MID task was selected based on prior evidence that monetary stimuli reliably engage the NAcc in adolescent AN (Peel et al., 2025). Stage 1 TMS replicates Grosshagauer et al. (2024), who showed left DLPFC stimulation downregulates sgACC (functionally connected to NAcc). Table 1 summarizes the design.

3 Expected Outcomes

1. MID task elicits significant **NAcc activation** in both groups.
2. Active TMS acutely downregulates **sgACC/NAcc in HC** (stage 1).
3. In AN (stage 2), **NAcc/sgACC activation differs** vs. HC, and active TMS modulates these regions, predicting **improved BMI** and **reduced EDE scores**.

Stage 2 is a feasibility pilot. Therefore, analyses in stage 2 are exploratory and not powered for efficacy.

4 Discussion

The MID task is expected to robustly engage NAcc/sgACC. Prior monetary fMRI studies show consistent findings in AN, including altered prediction error signaling and noisier reward coding (Peel et al., 2025). Grosshagauer et al. (2024) showed left DLPFC TMS downregulates sgACC state-dependently. Reviews report modest BMI benefits via frontostriatal modulation (Wu et al., 2024). Several factors limit this pilot: small sample size (n=5/arm; feasibility only), generalizability from healthy adults to AN adolescents, ecological validity of monetary stimuli, and potential unblinding due to sham TMS somatosensory differences. Despite limitations, this study provides a critical first step toward a mechanism-driven TMS protocol for adolescent AN.

References

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