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Correspondence: Prognostic potential of the cortisol response to therapeutic rTMS

Dear Editor,

In a recent *Psychiatry Research* article, See et al. (2021) investigated whether neuroendocrine hormones indicative of hypothalamic-pituitary-adrenal (HPA) axis function informs the prognosis of major depression disorder (MDD) patients receiving bilateral repetitive transcranial magnetic stimulation (rTMS) over dorsolateral prefrontal cortex (DLPFC). The authors compared stimulation effects on depression severity, measured by the Beck Depression Inventory (BDI), with effects on salivary cortisol levels, as well as other neuroendocrine markers. These measures were probed at six timepoints: before and after the first, sixth, and thirtieth treatments.

Although this study lacked a proper control group, results replicated previous works, finding that DLPFC rTMS had an overall antidepressant effect (Lefaucheur et al., 2020) while no corresponding effects were observed in the hormone data (e.g., Baeken et al., 2010, where the effects on cortisol levels were more nuanced). See et al. concluded that the antidepressant effects of rTMS are not predicted by changes to hormone levels under investigation, including cortisol, dehydroepiandrosterone (DHEA), DHEA sulfate, and α-amylase.

Contrary to this conclusion, we believe these data can elucidate the hypothesis that HPA sensitivity, approximated by cortisol level fluctuations, predicts the efficacy of therapeutic rTMS. To wit, Baeken et al. (2010) found significant drops in cortisol levels in non-responders to the first high frequency (HF)-rTMS treatment – note, while this protocol is different from bilateral rTMS, it has a higher probability of treating MDD (Lefaucheur et al., 2020). Put these results another way, patients who responded to treatment (50% reduction on the Hamilton Depression Rating Scale score after ten treatments) did not present significant changes to salivary cortisol levels in response to the first rTMS session. Based on these results, Baeken et al. hypothesized that a highly sensitive (i.e., "hyper-responsive") HPA system may predict a poor response to therapeutic rTMS in depression. A similar pattern is suggested by See et al.'s Figure 2 (top left): a reduction of cortisol from pre- to post-rTMS treatment is observed across timepoints and patients. While trends were not significant, See et al. did not report responsive and non-responsive rates to rTMS and whether these cortisol level effects differ between these sub-groups.

This sub-group analysis would test Baeken et al.'s hypothesis, which predicts that an antidepressant response to rTMS would lack an effect on cortisol levels; conversely, non-responders are predicted to have significant drops in cortisol after every rTMS treatment (compared to levels right before treatment). Although there are several differences between these two studies, including rTMS protocols, parameters, number of treatments, and inclusion of a control group, a similar analysis as Baeken et al.'s is possible.

Since See et al. did not have a control group, this analysis could run a repeated measures one-way ANOVA, or a respective mixed effects model if too much data is missing. For the dependent variable, Baeken et al. used cortisol measures to compute the area under the curve emphasizing change in cortisol (AUC_i), as this is a simple measure of sensitivity of the HPA

response (Fekedulegn et al., 2007). These measures before and after rTMS treatment can be sub-divided further by patient responsivity to rTMS, e.g., whether or not a 50% reduction in BDI score occurred after 10 or 30 treatments. Should main or interaction effects justify further analysis, the authors could conduct an independent t-test between the AUC_i of responders and non-responders to rTMS. A lack of statistical significance would confirm See et al.'s conclusion, whereas significance would support Baeken et al.'s hypothesis. In either outcome, findings would better inform the prognostic potential of the HPA response.

Future efforts on this topic should consider that MDD patients are not a homogenous group. For instance, HPA responsivity may be downregulated in some patients due to sex differences (Chopra et al., 2009) – change in cortisol levels before and after an rTMS session may not provide usable prognostic information for such patients. Another consideration is sampling timepoints must be clearly reported and standardized as cortisol measurements vary throughout the day, e.g., measured always in the morning.

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