



## Modifications of cognitive performance in the stroop task following deep rTMS treatment course in OCD patients



Dear editor,

Adaptive decision making requires the adjustment of behavior following an error in order to improve future performance, but obsessive compulsive disorder (OCD) patients are characterized by abnormal error monitoring [1,2]. For example, in cognitive tasks like Flanker or Stroop, reaction time (RT) following commission of an error (post-error; PE) is often longer than that of RT following a correct response (post-correct; PC), but this phenomenon, known as PE slowing (PES), is inordinate in OCD patients (e.g. [1]). PES is associated with increased theta activity over the medial prefrontal cortex (mPFC) [3], and PES of OCD patients was shown to be mainly driven by abnormally slow PC RTs rather than a failure to slow down after errors [1]. Notably, a recent study [4] has demonstrated that acute theta transcranial alternating current stimulation over the mPFC of healthy volunteers induced short-term reductions of PES without compromising post-error accuracy (PEA) in the Flanker task. Given the notion that the effects of stimulation may accumulate over repeated sessions [5], it is plausible that multiple stimulation sessions of the mPFC may induce long-term modifications to cognitive functions associated with error monitoring [5].

To test this notion, we revisited data from a study recently published in *Brain Stimulation* [6], which compared the efficacy of 5 weeks of high-frequency active or sham deep transcranial magnetic stimulation (dTMS) over the mPFC as a treatment for OCD. The study included a Stroop task and electrophysiological recording administered before the first and before the last treatment sessions. The Stroop task was specifically designed to probe Error Response Negativity (ERN) in the clinical setting (i.e., short duration, but promoting sufficient errors rates in repeated tests). The task was divided into 10 blocks of alternating stimulus-response mapping (10 practice + 80 test trials each), making response selection less-automatic. Participants were requested to respond as accurate but as fast as possible and limited (1200 ms) catch trials were scattered randomly (10% of trials) to impose this instruction. Pre- and Post-treatment Stroop data was available for 12 patients of the active group (7 females) and 10 patients of the sham group (7 females). Gender was used as a covariate in all analyses due to earlier reports on gender differences in brain responses to errors and post-error adjustments [7] as well as gender differences in responses to dTMS observed in the original study [6].

First, analysis of total RT distribution (PC + PE) was conducted using extraction of percentiles (5, 25, 50, 75, 95) from the RT distribution of each individual during incongruent trials (where response selection is most challenging) [7]. These were subjected to ANOVA with Percentiles X Time (pre/post treatment) X

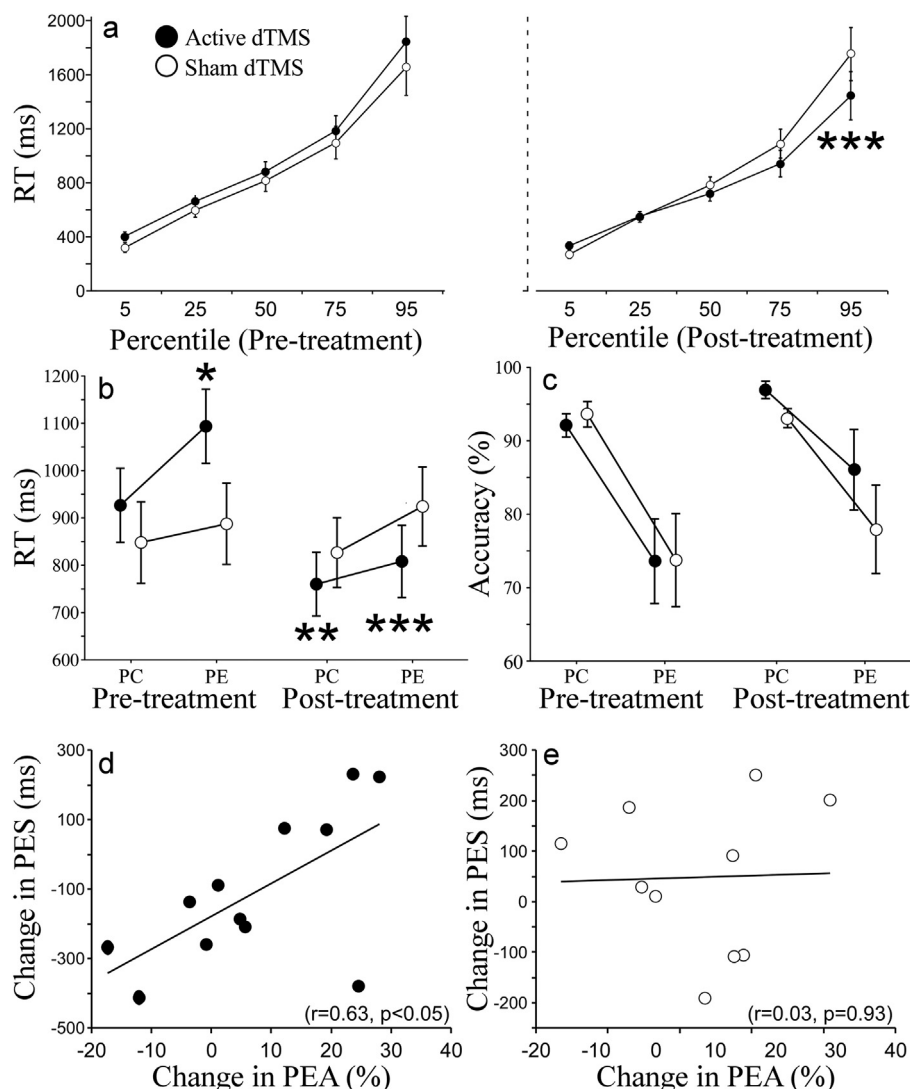
Treatment (active/sham), which revealed a significant 3-way interaction ( $F_{4, 76} = 2.51, p < 0.05$ ). A follow-up Bonferroni corrected post-hoc test revealed that only active dTMS significantly reduced RTs in Percentile 95 ( $p = 0.0008$ ), suggesting active dTMS-induced reduction of the slowest RTs regardless of condition (PC/PE) (Fig. 1a). When the condition was added to the analysis, error rate did not permit percentiles' analysis, but ANOVA of RTs revealed a three-way Time X Condition X Treatment interaction ( $F_{1, 19} = 5.38, p < 0.05$ ; Fig. 1b), and a follow-up Bonferroni corrected post-hoc analysis revealed that active dTMS significantly reduced RTs in both task conditions (PC:  $p < 0.005$ , PE:  $p < 0.00001$ ). Finally, a direct comparison between conditions revealed that PES was reduced in the active ( $F_{1,19} = 5.39, p < 0.05$ ) but not the sham ( $F_{1,19} = 1.06, p < 0.32$ ) group (Fig. 1b).

Comparable analysis of PEA revealed robust reduction of accuracy following errors ( $F_{1, 19} = 16.4, p < 0.001$ ) but without an interaction effect with treatment or time ( $F_{1, 19} = 0.04, p = 0.83$ ; Fig. 1c). These results indicate that PEA was not influenced by treatment and that accuracy levels were probably reduced following errors due to the contradiction between PES and task requirements (i.e., time limits). Moreover, the treatment-induced changes in PES and PEA were significantly correlated with each other in the active ( $r = 0.63, p < 0.05$ ; Fig. 1d), but not in the sham ( $r = 0.03, p = 0.93$ ; Fig. 1e) group. That is, shorter PES following active treatment was associated with reduced PEA, as ascribed in healthy population, suggesting treatment-induced beneficial recalibration of the speed–accuracy trade-off [8].

Taken together, these results indicate that patients receiving the active dTMS course improved their performance in the Stroop task in accordance with task requirements. They have adjusted their behavior in a constructive manner by reducing the rates of sluggish (slow) responses and by shortening of PES without losing accuracy.

Although deducing mechanism of action is beyond the scope of this report, these effects are probably due to the ability of this specific dTMS coil (the H7-coil) to affect both the mPFC and the anterior cingulate cortex (ACC) [6]. Both the mPFC and ACC play key role in the pathophysiology of OCD and error monitoring, and thus modifications to their excitability by multiple sessions of high-frequency dTMS combined with daily clinical meetings and symptom provocation [6] can induce alterations in these pathological circuitries.

This study includes limitations of relative medium sample sizes and the analysis method of PC and PE, which may be subject to potential drift bias (although alternative methods suffer from other pitfalls [9,10]). Nevertheless, this behavioral analysis of objective measures derived from a computerized cognitive task, further



**Fig. 1.** Effect of the treatment course on task performances. (a) Percentiles distribution of RTs, (b) average RTs following correct and erroneous responses, and (c) accuracy following correct and erroneous responses. (d) Correlation between changes in PEA and PES following active treatment and (e) correlation between changes in PEA and PES following sham treatment. Data are presented as Mean  $\pm$  SEM. \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .

supports the clinical improvements observed [6] and suggests that dTMS of the mPFC and ACC can induce long-term modifications to cognitive functioning associated with error monitoring.

#### Author contribution statement

**Uri Alyagon:** Formal analysis, Writing - original draft, Writing - review & editing. **Noam Barnea-Ygaël:** Formal analysis, Writing - original draft, Writing - review & editing. **Lior Carmi:** Methodology; Formal analysis, Writing - review & editing. **Abraham Zangen:** Conceptualization, Methodology, Writing - review & editing, Supervision

#### Declaration of competing interest

AZ is inventor of deep TMS technology and has financial interest in Brainsway Ltd., a company that develops and commercialize deep TMS devices. UA and NBY are partial employees in Brainsway. LC declare no competing interest.

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