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Cortical inhibition in major depression: Investigating the acute effect of single-session yoga versus walking

While the etiology of depressive disorders is multifactorial, spanning diverse polygenic origins and environmental exposures, its impact on an aberrant cortical inhibition-excitation balance is one of the final common pathophysiological processes [1–3]. Gamma-aminobutyric acid (GABA) – an abundant inhibitory neurotransmitter in the nervous system, along with glutamate – an excitatory neurotransmitter, is vital in maintaining an optimal balance required for healthy brain functions. One of the contributing factors to the cortical excitation-inhibition imbalance in depression is GABAergic dysfunction [4]. This is evident from observations of significantly lower cerebrospinal fluid GABA levels [5], reduced magnetic resonance spectroscopy-measured GABA concentrations in the anterior cingulate [6], and reduced Transcranial Magnetic Stimulation (TMS)-measured short interval intracortical inhibition – a measure of $GABA_A$ neurotransmission and cortical silent period – a measure of $GABA_B$ neurotransmission – in the motor cortex of patients with depressive disorders [7].

In vivo clinical experiments have demonstrated cortical GABA-enhancement with serotonin reuptake inhibitors [8,9], repetitive-TMS therapy [10], and electroconvulsive therapy [11] – all well-established treatments of depression. Yoga, a multi-dimensional practice of harmonized physical postures, respiratory control techniques, deep relaxation, and meditation has been used to augment the effects of antidepressant therapies [12]. The effects of yoga on GABA-enhancement have been demonstrated in yoga practitioners [13–16]. However, this engagement of cortical inhibition by yoga in depression is poorly documented. We examined TMS-measured cortical reactivity (excitation and inhibition) in patients with depressive disorder (n = 56) and healthy (n = 34) comparison subjects (experiment-1). In a proportion of these patients (experiment-2), we examined cortical reactivity changes in patients with depression after randomly assigning them to receive a single-session of yoga (n = 20) or intermittent-walking (n = 20). We hypothesized that patients would have reduced $GABA_A$ and $GABA_B$ mediated cortical inhibition. Based on our earlier observations in healthy yoga practitioners [15,16], we also hypothesized that yoga therapy will result in greater enhancement of $GABA_B$ mediated cortical inhibition compared to intermittent-walking.

We recruited patients from a tertiary care centre in Southern India and healthy volunteers from among acquaintances of the research staff and members from the community. All diagnoses were established independently by two qualified psychiatrists as per the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR) and confirmed using the Mini International Neuropsychiatric Interview (MINI) [17]. Healthy subjects were screened to rule out any Axis-1 psychiatric disorders using the MINI-Screening instrument [17]. The institute's human ethics committee reviewed and approved the study protocol. All study participants provided written informed consent. We excluded patients with co-morbid neurological disorders, substance dependence in the previous six months (except nicotine), intellectual disabilities, history of electroconvulsive therapy in the past three months, and current pregnant/postpartum states. Depression severity was assessed using the 17-item-Hamilton Depression Rating Scale [18]. The TMS-investigation was performed on day-0 as part of experiment-1, and following intermittent-walking as part of experiment-2. Participants randomized to receive yoga underwent two days of orientation to yoga, and then underwent the TMS-investigation on day-3 as part of experiment-2, before and after the yoga intervention. During the TMS-investigation, we obtained twenty-recordings each of cortical silent period (CSP), short (SICI) and long (LICI) interval intracortical-inhibition, and intracortical-facilitation (ICF).

Further details of the TMS-investigation and the interventions are provided in the supplementary material. Independent samples *t*-test was used to compare cortical reactivity between depression and healthy groups. We performed RMANOVA, with pre (day-0 recordings for the walking group and day-3 recordings for the yoga-group) and post-intervention cortical reactivity measures as within-group variables and intervention status as the between-group variable.

In experiment-1, the two groups were comparable on age, gender, marital status, and monthly income, but not years of education (Table S2). We found the patient group to have significantly shorter CSP compared to healthy subjects, with an effect size of 1.18 (Fig. 1). This difference persisted even after controlling for the years of education [F (df) = 29.43 (2, 87); $P < 0.001$]. There was no significant between-group difference in the other TMS-measures (Table S3); benzodiazepine prescription did not alter cortical reactivity (Table S5).

In experiment-2, the two patient-groups were comparable on baseline parameters (Table S5). We found a significant group × time interaction effect indicating a greater lengthening of the CSP in the yoga-group as compared to the intermittent-walking group following the intervention (Fig. 1; Table S6). We also compared the post-yoga intervention CSP recordings in the patient group (n = 20) with the CSP recordings of the healthy subjects (n = 34). While there was still a significantly shortened CSP in the patient group, the magnitude of its effect had reduced from 1.18 before yoga-intervention to 0.77 after the single-session of yoga – a net improvement of 34.3% (t = 2.64; $P = 0.01$; $d = 0.77$).

Results from experiment-1 revealed a significantly diminished CSP – a marker of $GABA_B$ mediated neurotransmission – in the

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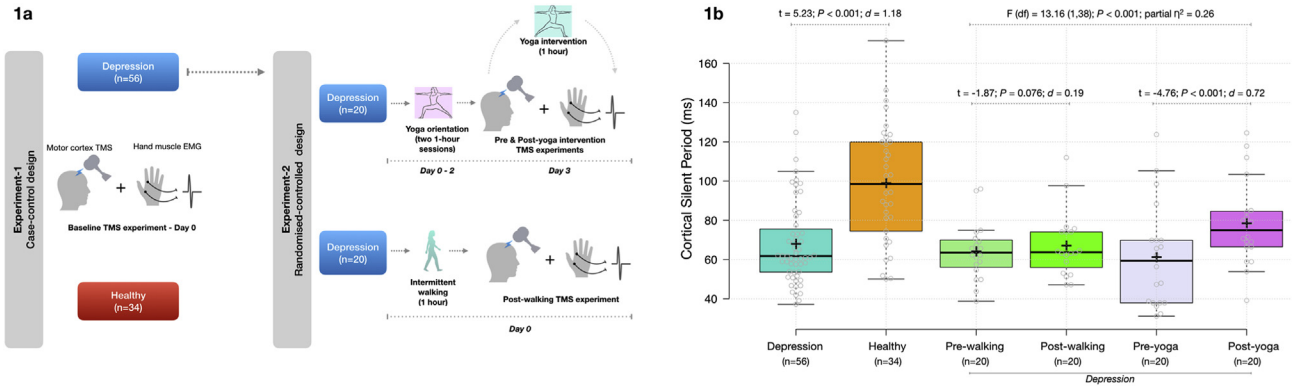

Fig. 1. (title): Experiment workflow and key results Figure-1 (legend): (1a) In experiment-1 a case-control design was employed and TMS experiment was conducted on the day of subject recruitment (day-0). In experiment-2, forty consenting subjects from the depression group of experiment-1 consented to be randomized to receive a single session of yoga or intermittent-walking. The intermittent-walking group subjects completed their intervention and post-intervention TMS-experiment on the day of recruitment (day-0). The yoga-group subjects attended two yoga orientation sessions before coming for the active intervention on day-3 when pre-and post yoga intervention TMS experiment was conducted; **(1b)** In the boxplots that represent cortical silent period duration within and between groups, the central lines and crosses represent medians and means respectively; box-limits are at 25th and 75th percentiles; whiskers extend 1.5 times the interquartile range from the 25th and 75th percentiles; black open circles represent outliers; data points are plotted as grey open circles; F-statistic is that of group × time interaction effect; T-statistic between depression and healthy groups is from comparing between-subjects group means (independent *t*-test) and that for pre- and post yoga and walking is from comparing within-subjects means (paired *t*-test); Cohen's *d* represents the effect size. We also examined if there was any significant change between day-0 and day-3 cortical reactivity measures in the yoga-group (i.e., change following the yoga orientation). There was no significant difference across all the measures on the paired *t*-test (Table S7); in addition, there was an average Pearson's correlation coefficient of 0.69 (range 0.3–0.99) between day-0 and day-3 (post yoga-orientation) cortical reactivity measurements, which demonstrated stability of cortical reactivity following yoga orientation.

patient group. This is a replication of findings from a meta-analysis, which had demonstrated a significantly shortened CSP (Hedge's $g = 1.23$) in depression. The magnitude of CSP deficit we found (1.18) was similar to that reported in a recent meta-analysis [7] (1.23). The post-hoc computation of achieved power for our study was 90% [19]. Nevertheless, it remains to be ascertained if this deficit is illness- or medication-related.

In experiment-2, we could demonstrate a significant lengthening of CSP in the yoga-group as compared to intermittent-walking. This provides validation within a clinical sample, of previous studies [13–16] that had demonstrated an enhancement of cortical GABA-tone following yoga among healthy subjects. To the best of our knowledge, this is the first such demonstration of yoga, specifically engaging the $GABA_B$ interneuron system in patients with depression. This provides an impetus for examining longer-term effects of yoga therapy within an experimental-medicine framework of evaluating newer therapies [20] by expanding on its target engagement with $GABA_B$ neurotransmission. Future studies may also examine if individuals with shorter CSP respond better to yoga, as has been recently demonstrated for electroconvulsive therapy [21]. Important caveats that need to be considered are the lack of longer-term effects following multiple yoga therapy sessions and the lack of blinding of the TMS-rater.

Disclosures

UMM is one of the Associate Editors at Schizophrenia Research and receives an honorarium from Elsevier for this service. This in no way influenced the findings of this study. JJ, AE, PDV, SV, JT and BNG reported no biomedical financial interests or potential conflicts of interest.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2019.07.029.

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Jitender Jakhar, Urvakhsh Meherwan Mehta*, Aboli Ektare, Pilli Devi Vidyasagar, Shivarama Varambally, Jagadisha Thirthalli, Bangalore N. Gangadhar
Department of Psychiatry, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, 560029, India

* Corresponding author. Department of Psychiatry, National Institute of Mental Health & Neurosciences (NIMHANS), Bangalore, 560029, India.
E-mail address: urvakhsh@nimhans.ac.in (U.M. Mehta).

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