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Probing the effects of single-session iTBS on associative memory: A prospective, randomized, controlled cross-over study

Dear Editor,

A large corpus of research demonstrated that high-frequency (HF) repetitive transcranial magnetic stimulation (rTMS) of the human cortex exhibits neuroplastic effects similar to long-term potentiation (LTP) induced by electrical stimulation in animal experiments. Intermittent theta burst stimulation (iTBS), a potent form of patterned rTMS, was also shown to have excitatory effects akin to LTP [1], although probably via a different cellular mechanism compared to standard rTMS [2]. However, recent evidence provides a crucial extension to the proposed mechanism of action of rTMS. In a study by Kozyrev et al. [3], authors investigated the effect of 30 minutes of HF rTMS over the primary visual cortex of anesthetized cats. Using voltage-sensitive dye imaging, they measured visual orientation maps in the submillimeter range. Before stimulation, these maps exhibited a regular preference of different orientation angles. Directly after the stimulation, the authors observed a reduction of orientation preferences and increased response variability. In addition, prolonged visual exposure to a single orientation following the stimulation led to a reorganization of maps, showing the domination of the newly acquired orientation preference. These results indicate that rTMS destabilizes previously acquired representations and opens a time window of increased permissiveness to change and remodeling neural representations. However, whether findings can be translated to the realm of human cognition awaits to be investigated.

We therefore set out to conduct an experiment that probes stimulation induced destabilization of acquired representations, followed by a remodeling of neural representations corresponding to newly acquired information in the context of associative memory. Associative memory is a function of a distributed neural network including prefrontal, medial temporal, and parietal cortices. Especially left lateralized frontal and parietal regions have been targeted with rTMS and iTBS in recent studies, demonstrating significant effects on face-cued word recall [4,5]. We hypothesized that 1) active iTBS compared to control stimulation will reduce recall capacity directly after the stimulation due to increased neural excitability and loosening of neural associations, as evidenced by Kozyrev et al. [3]. We further hypothesized that 2) active iTBS compared to control stimulation will increase recall capacity of the newly learned associations after the stimulation, due to facilitated neural reorganization and an associated reduction in proactive interference.

We performed a randomized, parallel, counterbalanced cross-over study including 75 healthy right-handed volunteers (see details in the supplementary content). Briefly, the study was divided into three phases. In phases I and II, 30 participants each received either active or control (vertex) iTBS stimulation in a counterbalanced, cross-over design. Active stimulation in phase I was targeted at the left lateral parietal cortex (lPC) at Montreal Neurological Institute (MNI) coordinate [-47, −68, +36] whereas the left dorsolateral prefrontal cortex (DLPFC) at [-38, +44, +26] was target in phase II. Phase III consisted of the same experimental setup as in phases I and II, except that participants (n = 15) were not subjected to any stimulation (for details, see Fig. S1). On each visit in all study phases, participants performed an associative memory test consisting of encoding and recall periods in which they had to memorize and recall face-word associations (face-cued word recall, Fig. 1B), respectively. Before the stimulation, participants underwent a first encoding period (E1), followed by a first recall period (R1). Immediately after stimulation, they underwent a second recall period (R2). This was followed by a resting period of about 5 mins. Participants viewed a distraction video and were told that no retention of the associations learned in E1 was required. Following the resting period, participants underwent another encoding period (New-E2) which consisted of new combinations of associations assembled using the same stimuli as in E1. The new encoding period was followed by a new recall period (New-R3) (Fig. 1C). ITBS stimulation consisted of 20 repeated trains with a total number of 600 pulses at an intensity of 100% of the individual resting motor threshold.

Results indicated an increase in recall performance for New-R3 compared to R1 and R2 in all study arms ($P < 0.05$, mixed models analyses). However, performance increases for New-R3 were significantly lower after lPC stimulation compared to control stimulation. Moreover, performance after DLPFC stimulation at R2 was significantly lower than performance after lPC stimulation at R2 (see Fig. 1D, for non-standardized values, see Table S2).

Hence, our study does not support the notion that stimulation-induced loosening of neural associations and permissiveness for change, as observed in animals, translates to human association learning. Our study differs in various aspects to Kozyrev et al. (2018) including the applied stimulation protocol, the stimulated brain region, and the species investigated, which may explain the diverging results. Moreover, Kozyrev et al. measured orientation selectivity in the cat visual cortex, whereas we studied human association learning retrieval, two functions associated with very different neurophysiological processes [6,7]. Hence, stimulation effects on these processes may likely differ as well.

We observed an impediment of newly acquired association memory following lPC stimulation. This indicates that lPC stimulation modulates recall performance contrary to our expectations.

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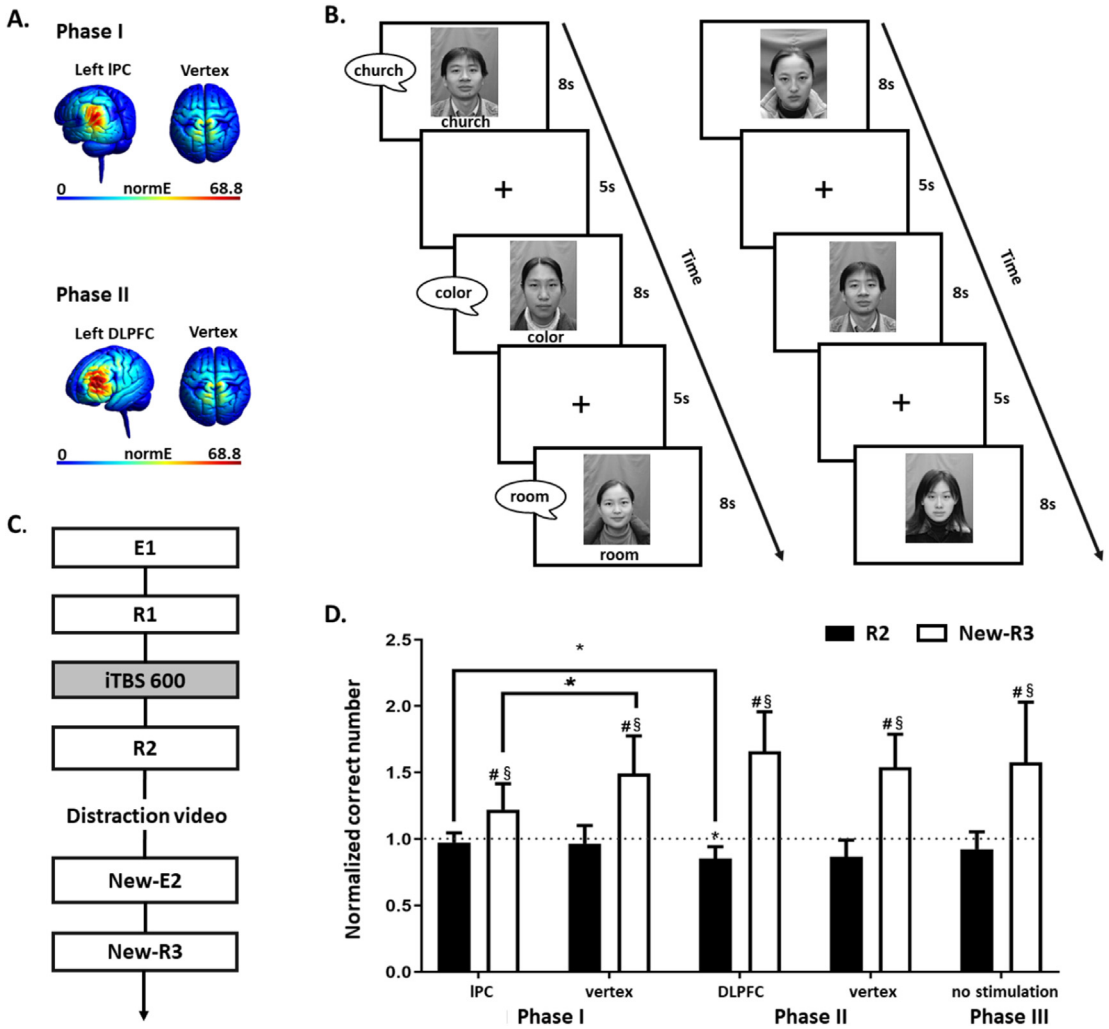

Fig. 1. iTBS on associative memory.
(A) Electric Fields (E-fields) for active and control stimulation locations, with red indicating peak intensity. lPC, lateral parietal cortex; DLPFC, dorsolateral prefrontal cortex.
(B) Overview of the associative memory test.
(C) Sequence of consecutive phases of the experiment. E1, first encoding period; R1, first recall period; iTBS 600, intermittent theta-burst stimulation; R2, second recall period; New-E2, new encoding period; New-R3, new recall period.
(D) Overall memory performance for the three study phases. Depicted are means and standard deviations for R2 and New-R3, normalized to baseline values (Recall 1, dashed line). # and § indicate a significant increase in New-R3 compared to baseline and R2, respectively. The large asterisk indicates a significant difference for the comparison of lPC versus vertex stimulation in Phase I (corrected for multiple comparisons). Small asterisks indicate a significant reduction for R2 after DLPFC stimulation and a difference to R2 after lPC stimulation (uncorrected). lPC, lateral parietal cortex; DLPFC, dorsolateral prefrontal cortex. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Our results show that lPC stimulation hinders, rather than facilitates reorganization and permissiveness to new encoding. This can be explained by an increased proactive interference from previously encoded associations. That is, iTBS facilitated the encoding of associations presented just before stimulation. Hence, stronger encoding of previously learned associations by iTBS may hinder encoding of new associations after stimulation.

Regarding DLPFC stimulation, we observed a lower recall capacity directly after stimulation compared to before stimulation, and compared to lPC stimulation. Although this effect was observed only on an exploratory basis and with an uncorrected level of significance (see supplementary information), this finding is in line with the results from Kozyrev et al. [3] indicating that excitatory stimulation increases response variability directly after stimulation. Despite being involved in episodic memory, the DLPFC is not part of the cortical networks interacting with the hippocampus [8]. Studies postulate a specific role of the DLPFC for controlling memory retrieval by suppressing irrelevant information [9]. Hence, our result indicates that neural reorganization after rTMS observed by Kosyrev et al. [3] is transferable only to the DLPFC due to its specific function to suppress irrelevant information during memory retrieval. However, our findings are only limited to short-term memory performance, further studies are needed to investigate the effects of iTBS on long-term memory performance and memory consolidation.

In conclusion, our results indicate that lPC stimulation with iTBS strengthens previously encoded associations, thereby hindering neural reorganization and permissiveness to new encoding. Conversely, DLPFC stimulation lowers recall capacity of previously encoded associations, possibly due to an increase in response variability directly after stimulation.

Author contributions

Bella B.B. Zhang: Methodology, Software, Investigation, Data Curation, Formal analysis, Writing-Original Draft, Writing-Review & Editing, Visualization; **Rebecca L.D. Kan:** Investigation, Data Curation, Software, Writing-Review & Editing, Visualization; **Tsz-Fung Woo:** Methodology, Software, Writing-Review & Editing; **Chetwyn C.H. Chan:** Resources, Methodology, Writing-Review & Editing; **Kenneth N.K. Fong:** Resources, Methodology, Writing-Review & Editing; **Georg S. Kranz:** Conceptualization, Methodology, Writing-Original Draft, Writing-Review & Editing, Supervision, Project administration.

Declaration of competing interest

None. Without any relevance to this work, G.S. Kranz declares that he received conference speaker honorarium from Roche, AOP Orphan and Pfizer.

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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.2021.05.017.

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