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High-definition transcranial direct current stimulation modulates neural activities in patients with prolonged disorders of consciousness

Despite accumulating evidence about its possible treatment effects on disorders of consciousness (DOC) patients [1,2], conventional transcranial direct current stimulation (tDCS) has encountered a bottleneck, with little progress as a treatment modality in DOC patients. Multi-channel high-definition tDCS (HD-tDCS), a modification of conventional tDCS, offers enhanced neuromodulation. As compared with conventional tDCS, HD-tDCS offers improved spatial targeting (focality) of stimulation [3,4]. Previous studies confirmed that HD-tDCS increased the intensity of the stimulus and prolonged its after-effects [5–7]. Moreover, HD-tDCS has been demonstrated able to improve humans' motor function [8], learning [9] and working memory [9,10], all of which are components of human conscious behaviors. Therefore, considering its outstanding performance in neural modulation, investigating the effects of HD-tDCS in patients with DOC is worthwhile.

Twenty-eight patients with DOC were enrolled in this study. None of the patients had severe cerebral atrophy or injuries of the parietal region on magnetic resonance imaging scans. They also had no history of epilepsy, pacemakers, aneurysm clips, neurostimulators or brain/subdural electrodes. All the patients had received routine medications and rehabilitation courses but had shown no improvement in consciousness for at least 1 week. Written informed consent to participate in the study was obtained from the patients' caregivers.

All the patients received HD-tDCS (Model 4x1-C2; Soterix Medical Inc., New York, NY), with 2 mA for 20 min. The 4×1 ring configuration of the HD-tDCS used Ag/AgCl ring electrodes to deliver a direct current to the scalp. The anode was placed over the Pz according, corresponding to the approximate location of the parietal region. Four return cathodal electrodes were placed approximately 3.5 cm radially from the Pz, corresponding roughly to locations Cz, P3, P4 and POz.

All the patients received one stimulation session each day in the afternoon for 14 days consecutively. No parenteral nutrition was provided at least 1 h before each session. A resting-state electroencephalogram (EEG) and the CRS-R were administered four times during the experiment: before the first session (T0) and 1 day (T1), 1 week (T2) and 2 weeks (T3) post-treatment.

Relative power was calculated at the following frequency bands for each electrode: delta (1–4 Hz), theta (4–8 Hz) and alpha (8–13 Hz). The Kolmogorov–Smirnov (KS) test was used to explore the existence of significant differences in relative power between T1-T3 and T0. A Bonferroni correction was conducted after multiple comparisons. The false discovery rate (FDR) correction was used to correct the p values after multi-comparisons at the electrode level. Correlational analyses of variations in CRS-R and relative power were measured using Kendall's tau coefficient.

After 2 weeks (T3), the total CRS-R scores of 85.7% (24/28) of the patients had increased. Among the study group, the CRS-R scores of 94.4% (17/18) of the MCS patients increased. At T3, the CRS-R scores of the MCS patients were significantly improved ($p = 0.009$) as compared with those at T0 (Fig. 1A). The consciousness state was altered in seven patients (MCS, $n = 6$; VS, $n = 1$) after HD-tDCS (defined as responders). Six patients who were classified as in a MCS- at T0 were classified as in a MCS + at T3. One patient in a VS at T0 was classified as in a MCS- at T3. The patients who showed no change in consciousness were defined as non-responders.

Among the responders, there was a gradual decrease in the delta band during the experiment, with a significant difference between T3 and T0 ($p = 0.02$). In addition, the responders showed distinct enhancement of the alpha band, with significance at T2 ($p = 0.03$) and T3 ($p = 0.01$) when compared with that at T0 (Fig. 1B). Among the non-responders, there were no significant alterations in relative power during the treatment.

At the single electrode level, when the data on the responders were averaged, HD-tDCS resulted in a global decrease in the delta band and an increase in the alpha band at T3. In particular, the electrodes at the posterior brain showed a distinctly different relative power between T3 and T0 (Fig. 1C). The relative power of delta significantly decreased between T3 and T0 at P3, P4, Pz, POz, Oz, O1 and O2 in the responders ($p < 0.05$). The relative power of alpha significantly increased between T3 and T0 at P3, P6, Pz, POz, Oz, O1 and O2 in the responders ($p < 0.05$). The Pz electrode, where exactly the location of the anode of HD-tDCS, showed a distinctly gradual decrease of power in the delta band and an increase in the alpha band, with significance between T3 and T0 (delta: $p = 0.009$, alpha: $p < 0.001$).

Fig. 1D shows the scatter plots of the △CRS-R scores and △relative power at the delta and alpha band for all the patients, where △ denotes the difference between T2/T3 and T0. When compared with T0, the increases in the CRS-R at T3 (△CRS-R) showed a significantly negative correlation with △relative power of delta ($r = -0.482$, $p < 0.001$) and a positive correlation ($r = 0.435$, $p = 0.003$) with △relative power of alpha.

The present study pioneered the application of HD-tDCS as a treatment for patients with DOC. The results of behavioural assessments and a resting-state EEG indicated that a protocol consisting of stimulation each day for 2 weeks effectively improved the patients' consciousness scores. Among the responders, modulation of neural activities at delta and alpha bands was accompanied by changes in consciousness states. These results indicate that HD-

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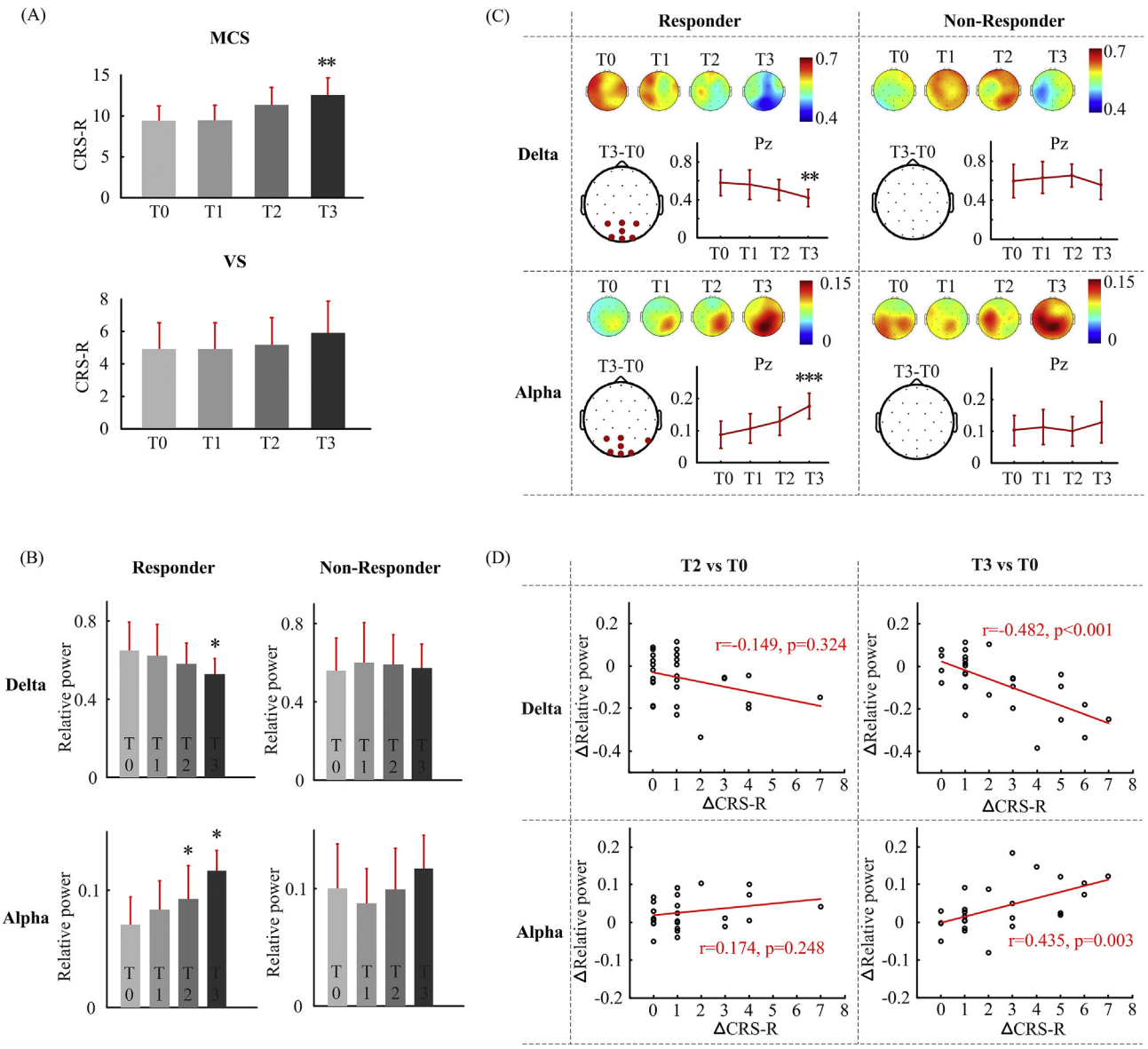

Fig. 1. Treatment of high-definition tDCS in patients with disorders of consciousness. (A) CRS-R bar plots of the patients at the four time points. **Denotes a significant difference ($p < 0.01$) in the CRS-R scores as compared with those prior to the treatment (T0). (B) Relative power of delta and alpha bands at the four time points for responders and non-responders. *$p < 0.05$ means a significant difference as compared with T0. (C) Average topography of relative power of delta and alpha bands at the four time points for responders and non-responders. The red circles indicate the electrodes in which there was a significant difference in the delta/alpha relative power between T3 and T0 ($p < 0.05$). The bar plots show the relative power of delta/alpha at the electrode placed over the Pz at the four time points for the responders and non-responders. **$p < 0.01$ and ***$p < 0.001$ mean a significant difference as compared with the relative power at T0. (D) Scatter plots of △CRS-R and △relative power of delta and alpha at T2 and T3 for all the patients. △ means a difference as compared with T0. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

tDCS could be a new promising non-invasive neuromodulation approach for DOC patients. Furthermore, the findings hint that the underlying mechanism of HD-tDCS in DOC patients may be related to delta and alpha activities. Despite the lack of a comprehensive comparison study, these results point to an enhanced treatment effect of HD-tDCS on DOC patients as compared with that achieved using conventional tDCS. Finally, the present results provide fundamental evidence for the use of HD-tDCS in DOC treatment.

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Conflicts of interest

The authors declare that they have no conflict of interest.

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