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Original article

Effect of multichannel transcranial direct current stimulation to reduce hypertonia in individuals with prolonged disorders of consciousness: A randomized controlled pilot study☆

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ABSTRACT

Background: Spasticity management in severely brain-injured patients with disorders of consciousness (DOC) is a major challenge because it leads to complications and severe pain that can seriously affect quality of life.
Objectives: We aimed to determine the feasibility of a single session of transcranial direct current stimulations (tDCS) to reduce spasticity in chronic patients with DOC.
Methods: We enrolled 14 patients in this double-blind, sham-controlled randomized crossover pilot study. Two cathodes were placed over the left and right primary motor cortex and 2 anodes over the left and right prefrontal cortex. Hypertonia of the upper limbs and level of consciousness were assessed by the Modified Ashworth Scale (MAS) and the Coma Recovery Scale-Revised (CRS-R). Resting state electroencephalography was also performed.
Results: At the group level, spasticity was reduced in only finger flexors. Four responders (29%) showed reduced hypertonicity in at least 2 joints after active but not sham stimulation. We found no behavioural changes by the CRS-R total score. At the group level, connectivity values in beta2 were higher with active versus sham stimulation. Relative power in the theta band and connectivity in the beta band were higher for responders than non-responders after the active stimulation.
Conclusion: This pilot study highlights the potential benefit of using tDCS for reducing upper-limb hypertonia in patients with chronic DOC. Large-sample clinical trials are needed to optimize and validate the technique.

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1. Introduction

Many patients with severe brain injury and disorders of consciousness (DOC) are affected by spasticity, whose treatment is a challenge [1,2]. Voluntary movements and collaboration are usually minimal if not absent in this population [3,4]. Treatments are often limited to passive physical therapy (e.g., conventional stretching or tilt table [5]) or pharmacological interventions such as anti-spastic drugs (e.g., baclofen, rivotril, sirdalud) or botulinum toxin injections, as prescribed for other neurological conditions such as stroke (for review see [6]). In addition, the patients' condition aggravates the symptoms because of inactivity and positioning; hence, a high proportion of patients with DOC have severe hypertonia: 89% present signs of hypertonia on a least one segment, and 61.5% have severe hypertonia (i.e., score of 3 or more on the Modified Ashworth Scale [MAS]) [1].

Transcranial direct-current stimulation (tDCS) involves using a weak electrical current to modulate the threshold for action potential generation [7]. Positive (anodal) or negative (cathodal) current facilitate the depolarization or hyperpolarization of neurons, respectively [8]. In both cases, tDCS seems to have a long-term effect in terms of long-term potentiation- or long-term

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depression-like plasticity [9,10]. Several studies involving tDCS have assessed the effect of this technique on reducing hypertonia in stroke patients, showing improved strength or reduced spasticity, among other effects [11–13].

From a pathophysiological point of view, brain lesions affect tracts in both pyramidal and extrapyramidal systems. Increased muscle tone results from neuroplastic changes (e.g., collateral sprouting) and/or release effects (disinhibition) as a result of the lesion [14]. In a 1-year longitudinal functional MRI (fMRI) study, the authors demonstrated an evolution in sensorimotor cortex (S1M1) activation from early (20 days after stroke) contralesional hyperactivation to later (4 months after stroke) ipsilesional hyperactivation concomitant with recovery [15]. Another electromyography-fMRI study of 10 chronic stroke survivors with upper-limb dysfunction demonstrated wide bilateral activation in the S1M1, supplementary motor area, and cerebellum while subjects moved the paretic hand [16]. These data suggest that ipsilesional S1M1 hyperactivation plays an important role in hypertonia caused by upper motor-neuron syndromes such as stroke. This finding could explain why a decrease, via cathodal stimulation, could reduce this hyperactivation and decrease the hypertonia.

In this study, we evaluated the effect of multifocal tDCS of the primary motor cortex (M1) on hypertonia of the arms, wrists, and finger flexors in individuals with chronic DOC. Our secondary outcomes were the effect of tDCS on the level of consciousness and motor function and on cortical activity.

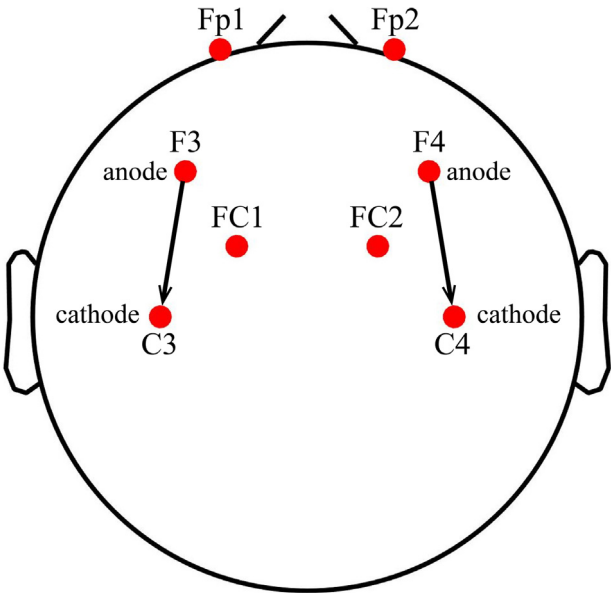

Fig. 1. The placement of the 8 electrodes used for stimulation and electroencephalography (EEG) recording. Anodes: F3-F4; cathodes: C3-C4. Recording electrodes: Fp1, Fp2, F3, F4, C1, C2, C3, C4.

2. Methods

2.1. Design

This was a double-blind sham-controlled randomized crossover pilot study.

2.2. Participants

All participants were recruited from the University Hospital of Liege during a week of assessments involving behavioral evaluations and neuroimaging acquisitions. Inclusion criteria were age $\geq$ 18 years; diagnosis of unresponsive wakefulness syndrome, minimally conscious state (MCS), emergence from MCS or locked-in syndrome; signs of pyramidal syndrome with upper-extremity hypertonicity in flexion as documented by the MAS; $>$ 3 months post-insult; stability of vital signs; and obtaining informed consent from the participant's legal representative. Exclusion criteria were premorbid neurological condition and contraindication to tDCS (e.g., metallic cerebral implant, pacemaker, uncontrolled epilepsy). We included individuals who were not taking sedative drugs or Na+ or Ca++ channel blockers (e.g., carbamazepine) or NMDA receptor antagonists (e.g., dextromethorphan). Medications, physical therapy and rehabilitation remained unchanged throughout the experiment. The study was approved by the ethics committee of the university and university hospital of Liège, Belgium.

2.3. Procedures

Direct current was applied by a battery-driven constant current stimulator via 2 cathodes placed over the left and right M1 (C3 and C4 according to the 10–20 international system [17] for electroencephalography [EEG] placement) and 2 anodes positioned over the left and right dorsolateral prefrontal cortex (F3 and F4 according to the 10–20 international system for EEG placement; Fig. 1). During active tDCS, the current was increased to 1 mA from the onset of stimulation and applied for 20 min. The sham tDCS session was preceded by 15-sec ramp-up and ramp-down periods at the beginning and the end of the 20-min session to mimic active stimulation. Electrode impedance was maintained at $<$ 10 kΩ and voltage $<$ 26 V. tDCS and sham stimulation were tested in random order in 2 separate sessions separated by a minimum of 2 days.

Hypertonia was assessed by the MAS in upper extremities bilaterally (arms, wrists, and finger flexors) and level of consciousness was evaluated by the Coma Recovery Scale-Revised (CRS-R) [0 (worst) and 23 (best)]. Both scales were administered directly before and after the tDCS and sham sessions by an examiner who was blinded to treatment.

The tDCS device allows for recording EEG activity, including the sites of stimulation. Therefore, we collected data from 6-min EEG (resting state) before and after the 2 sessions at the sites of stimulation in addition to 4 other electrode sites (Fig. 1).

2.4. Study outcomes

Our primary outcome was the effect of active tDCS as compared with sham stimulation on decreasing hypertonia of the upper limbs. Secondary outcomes were the effect of tDCS on level of consciousness, as measured by the CRS-R total score, and on motor function, as measured by the motor subscale of the CRS-R. We also recorded EEG (8 channels) and compared the difference between active and sham sessions (see 2.7 EEG analyses).

To assess the effect on hypertonia, we took the highest difference (post- minus pre-intervention) of both joints (left and right) and analyzed the data for the arm flexors, wrist flexors and finger flexors, separately.

2.5. Randomization and masking

Each patient received both anodal and sham stimulations in a randomized order. A computer-generated randomization sequence was used to assign the first session as anodal or sham tDCS in a 1:1 ratio. For sham tDCS, the tDCS device (8channels Startsim, Neuroelectrics, Barcelona) offers a built-in placebo mode. Thus, both the operator who administered tDCS and the participants could not identify the sham tDCS.

Table 1
Demographic characteristics and structural brain lesions for each individual included in the study.

ID	Diagnosis	Age (sex)	Etiology	Time since injury	Baseline CRS-R score	MRI lesions
1	UWS	50 F	TBI	378 days (>1 year)	3	Temporal and frontal lobes, temporo-occipital areas (R>L), hippocampi, thalami, cerebellum
2	MCS	26 F	TBI	1397 days (>3 years)	4	Hippocampi, temporal lobes, sensorimotor cortices
3	MCS	27 F	TBI	1012 days (>2 years)	5	Major hydrocephalus, corpus callosum, thalami, hippocampi (R>L)
4	MCS	39 M	Hemorrhagic stroke	253 days (>8 months)	12	R: perirolandic, frontolateral and insular regions L: pallidum, putamen
5	MCS	39 M	Cardiac arrest	2806 days (>7 years)	6	Diffuse axonal injury with global atrophy
6	MCS	73 M	Hemorrhagic stroke	3065 days (>8 years)	8	R frontal region, basal nuclei, anterior mesial frontal and temporo-parietal regions bilaterally
7	UWS	40 M	TBI	315 days (>10 months)	6	Temporal lobes, hippocampi, thalami, left pallidum, R caudate nucleus
8	UWS	25 F	TBI	233 days (>7 months)	3	R basal ganglia, frontal lobes, mesiotemporal regions, anterior periventricular regions
9	LIS	35 F	Hemorrhagic stroke	1143 days (>3 years)	22	Protuberance
10	MCS	27 F	Hemorrhagic stroke	90 days (>3 months)	4	R parietal lobe, right thalamus, temporo-parietal and occipital regions
11	MCS	39 F	TBI	1292 days (>3 years)	9	R lenticular capsule, R insula, R corona radiata, corpus callosum, L thalamus
12	EMCS	61 M	Hemorrhagic stroke	409 days (>1 year)	22	Thalami, L posterior pons
13	UWS	62 M	Cardiac arrest	318 days	6	Diffuse axonal injury with global atrophy
14	UWS	46 F	Cardiac arrest	170 days	5	Diffuse axonal injury with global atrophy

L: left; R: right; TBI: traumatic brain injury; CRS-R: Coma Recovery Scale-Revised [0 (worst) and 23 (best)]; UWS: unresponsive wakefulness syndrome; MCS: minimally conscious state; EMCS: emergence from MCS.

2.6. Statistical analysis

Because the MAS and the CRS-R are non-normally distributed and our sample size was small, treatment effects (post-active minus pre-active tDCS compared to post-sham minus pre-sham tDCS scores) were calculated by using the Wilcoxon rank sum test for MAS assessments (arm, wrist and finger flexors) and the CRS-R. Effect sizes were calculated as $r = z/\sqrt{2n}$, where z is the statistic of the Wilcoxon signed rank test. We used Spearman correlation to evaluate correlations between ordinal variables. As an exploratory analysis, we examined differences in proportion of responders (i.e., decrease in hypertonia in at least 2 joints after active but not sham tDCS) between the 2 groups by a proportional test.

2.7. EEG analysis

All recordings were band-pass–filtered between 0.7 and 45 Hz, with 5 bands of interest chosen: delta (1–4 Hz), theta (4–8 Hz), alpha (8–12 Hz), beta1 (12–18 Hz) and beta2 (18–30 Hz). Both sham and active stimulation pre- and post-recordings were visually inspected, and noisy epochs were discarded. Independent Component Analysis [18] was used to detect and discard components related to nearly stationary artifacts (i.e., eye-blinks, electrocardiography effects). For each participant, the session (active/sham) and electrode for each period (pre/post) was divided into 4-sec epochs, with a 50% overlap between contiguous epochs. Two sets of features were estimated for each band and period: 1) relative band power (RBP), defined for each electrode as the ratio between the total power in the band and total power in the 1- to 30-Hz range (Supplementary Materials section 1 [SM1]), and 2) weighted phase lag index (WPLI [19]) between each pair of electrodes (SM1). For each participant, session, band and electrode (RBP) or electrode pairs (WPLI), the difference between post- and pre-intervention was then estimated (ΔRBP and ΔWPLI).

For each band and electrode (or couple of electrodes; ΔWPLI), paired *t* test was used to compare active and sham stimulation, extracting the t-statistics. The t-statistic significance was assessed by a non-parametric permutation test (Supplementary Materials section 2 [SM2]).

Differences between groups (responders vs. non-responders) for each band and electrode (or couple of electrodes; ΔWPLI) were assessed by unpaired *t* test, extracting related *t* values. Analogously to the between-condition comparisons, the significance of each t-statistic was assessed by a non-parametric permutation test (69 randomizations, see SM2). Between-group comparisons were assessed for the active session and, as a control, the sham session. For all tests, the significance threshold was set at $P = 0.05$. All offline analyses were conducted using tailored Matlab codes

Table 2
Demographic characteristics and level of spasticity of the 4 responders.

		Change in MAS–active treatment			Change in MAS–sham treatment		
Age (sex)	Etiology/time since onset (days)	Arm flexors	Wrist flexors	Finger flexors	Arm flexors	Wrist flexors	Finger flexors
73 M	Stroke/3065	-1	-1	-3	0	0	0
39 F	TBI/1292	1	-1	-1	2	1	1
61 M	Stroke/409	1	-2	-2	0	-1	1
62 M	Cardiac arrest/318	−1	−1	0	0	1	1
Median (IQR)		0 (−1–1)	−1 (−1.75–−1)	−1.5 (−2.75–−0.25)	0 (0–1.5)	0.5 (−0.75–1)	1 (0.25–1)

M: male; F: female; MAS: Modified Ashworth Scale; TBI: traumatic brain injury; IQR: interquartile range.

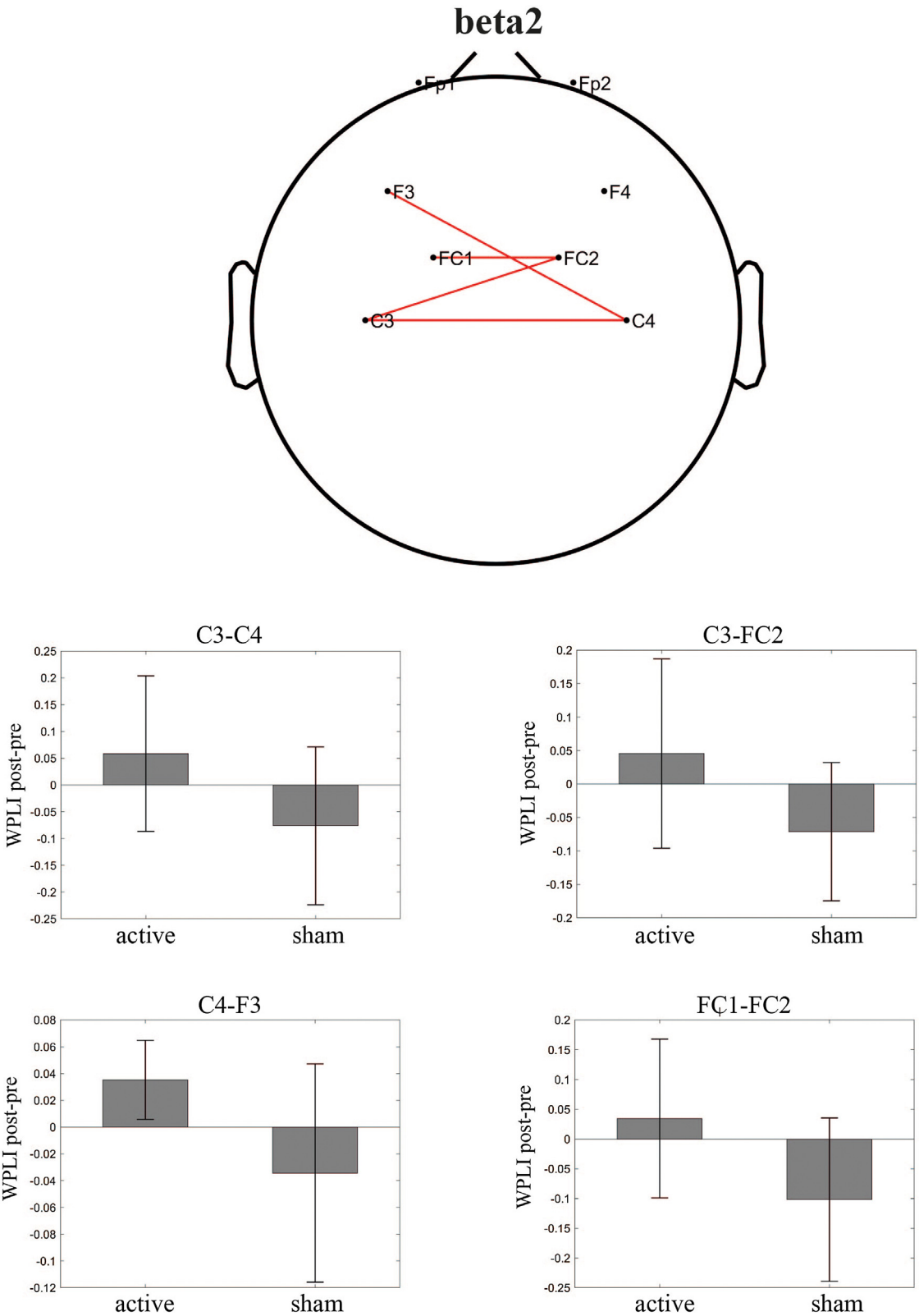

Fig. 2. Electrode pairs with higher difference in weighted phase lag index (ΔWPLI) between the active versus sham stimulation for the beta2 band at the scalp level (upper panel, red lines). Data are mean (SD) interval for each significant pair for active and sham stimulation.

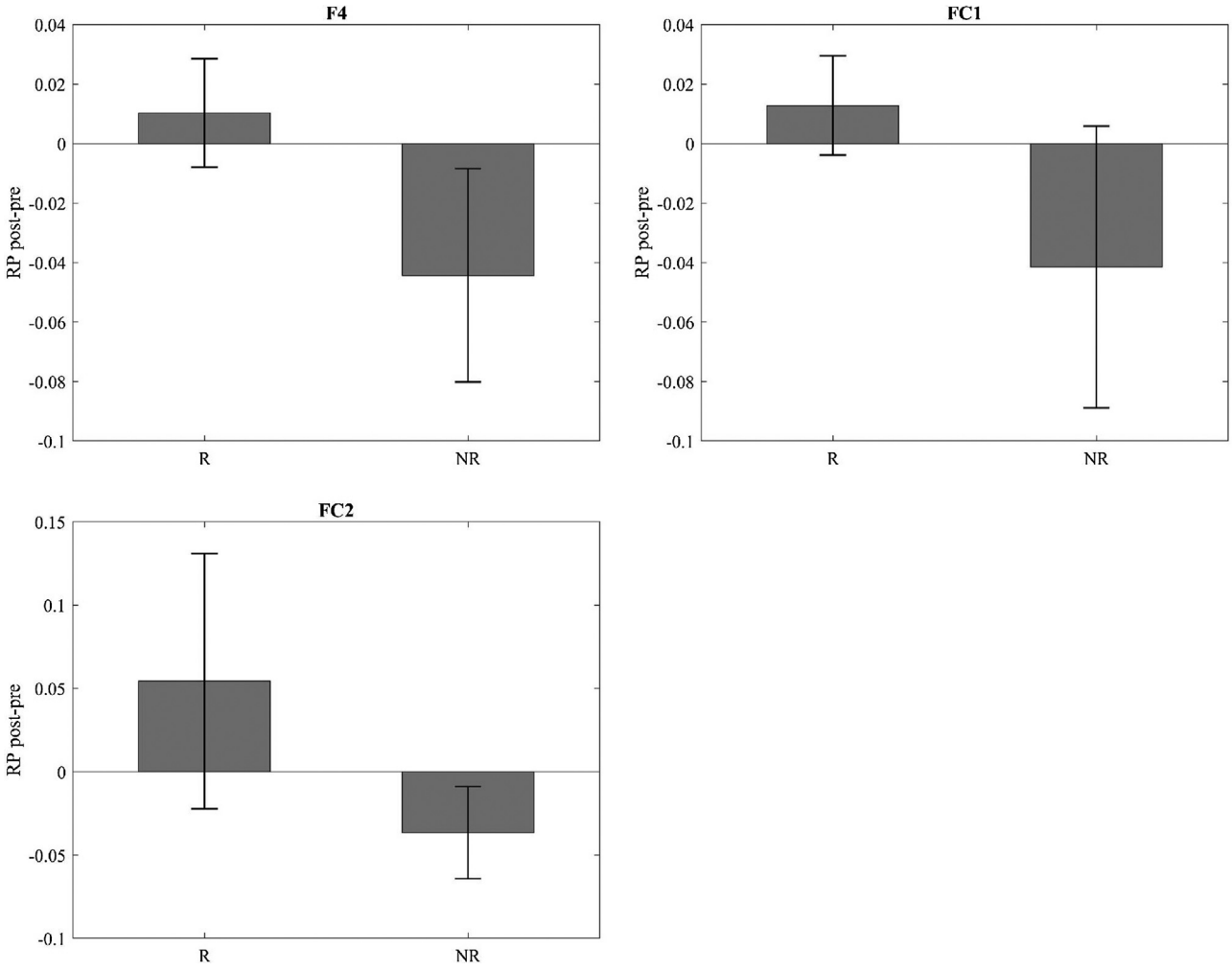

Fig. 3. Electrodes with higher difference in relative band power (ΔRBP) between responders (R) and non-responders (NR) for the theta band. Data are mean (SD) interval.

(MathWorks, Natick, MA, USA), and when dealing with Independent Component Analysis, taking advantage of EEGLAB toolbox functions [20].

3. Results

Between January 2014 and December 2017, we screened 17 patients, and 14 (mean [SD] age 47 [19], range 25–73 years; 7 women) were enrolled in the study (mean [SD] time since injury 30 [32], range 3–102 months, 6 with traumatic brain injury). No patients dropped out. Individual demographic information is in Table 1.

At the group level, we did not observe any treatment effect by the MAS for the arm flexors (z = 1.500; $P = 0.134$; r = 0.28) or wrist flexors (z = -1.341; $P = 0.180$; r = 0.25). We identified a treatment effect for the finger flexors (z = -2.344; $P = 0.019$; r = 0.44); however, post-hoc analyses did not demonstrate a difference in MAS scores after the active treatment (decrease of 0.25 points, z = 1.102; $P = 0.270$; r = 0.21) or sham treatment (increase of 0.75 points, z = -1.781; $P = 0.075$; r = 0.34).

We did not observe any treatment effect in terms of CRS-R total scores (z = 1.223; $P = 0.221$; r = 0.23) or the motor subscale of the CRS-R (z = 0.169; $P = 0.865$; r = 0.03) or any effect of etiology (R = 0.166; $P = 0.616$), time since insult (R = -0.397; $P = 0.200$) or diagnosis (R = -0.031; $P = 0.924$).

At the individual level, 4 participants showed a decrease in hypertonia in at least 2 joints after active but not sham tDCS (i.e., tDCS-responders), but none showed a decrease in MAS score on more than one joint with sham tDCS (Table 2). The proportion of responders was higher with active than sham treatment (z = -2179; $P = 0.029$).

For EEG results, because this was a pilot study, no correction for multiple comparisons was applied. Nevertheless, to ensure a certain robustness of the findings, when dealing with ΔRBP comparisons, we considered only bands showing significance for at least 2 electrodes and when dealing with ΔWPLI, only bands showing more than 3 significant comparisons.

Eight participants (4 responders) were retained for the analyses (6/14 were rejected because of noisy recordings in the sham or active stimulation session). We found no between-condition difference for any band when considering ΔRBP (Supplementary Materials section 3 [SM3], Table A). ΔWPLI values were higher with active than sham stimulation for 4 electrode pairs in beta2 (all $P < 0.05$; Fig. 2; SM3, Table B). When considering the active session, mean ΔWPLI was positive for all 4 pairs, which indicates higher synchronization in post-stimulation than pre-stimulation (Fig. 2). In the active session, ΔRBP values were higher for 3 electrode pairs in theta when comparing responders and non-responders (all $P < 0.05$; Fig. 3; Supplementary Materials section 4 [SM4], Table C). No significant difference was found when considering the sham session for ΔRBP or ΔWPLI (Supplementary Materials section 5 [SM5], Tables E–F). ΔWPLI values were higher for responders than non-responders for 4 electrode pairs in beta1 during the active session (all $P < 0.05$; Fig. 4; SM4, Table D).

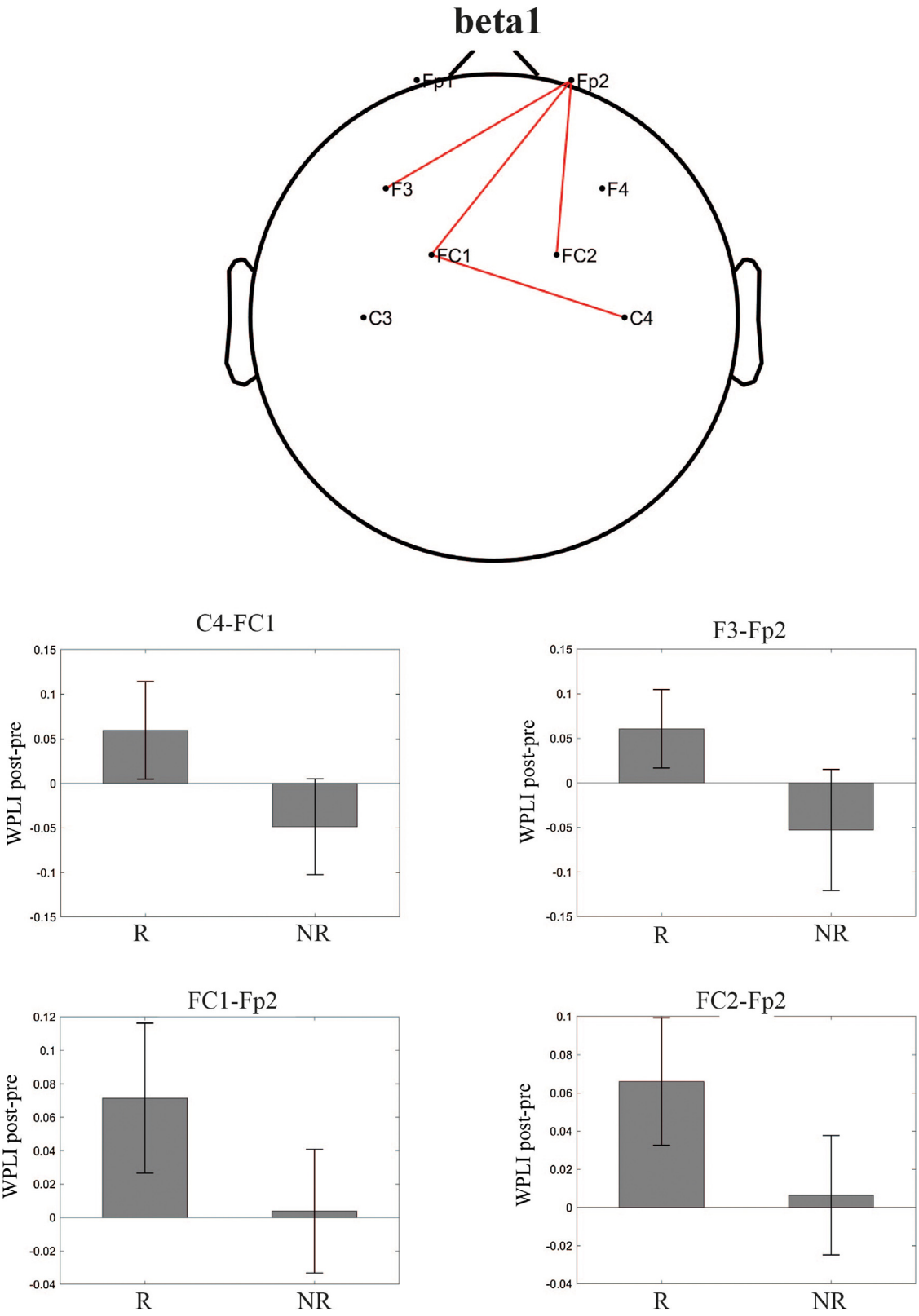

Fig. 4. Electrode pairs with higher ΔWPLI for responders versus non-responders for the beta1 band at the scalp level (upper panel, red lines). Data are mean (SD) interval.

4. Discussion

Here we report pilot data from a randomized sham-controlled double-blind study assessing the effect of a single session of bilateral cathodal tDCS over M1 on reducing hypertonia in individuals with DOC. We did not find an effect of tDCS at the group level, but at the individual level, 4 participants showed a clinically relevant decrease in spasticity after the active session (i.e., tDCS-responders: decrease in spasticity in at least 2 joints after the active but not sham session). We found no effects on signs of consciousness.

Regarding EEG analysis, an increase in beta2 band connectivity between motor areas and frontal areas has been identified after active tDCS. Beta connectivity in the central (or M1) and frontal regions are widely considered linked to movement and decision making. For instance, degree of beta-frequency resting-state functional connectivity between M1 and the anterior prefrontal cortex were found to predict subsequent degree of motor adaptation in healthy volunteers, which suggests that the resting-state synchronization dynamics can predict the degree of motor adaptation in a healthy population [21]. In stroke, beta coherence in the somatosensory areas is increased during movement planning and associated with velocity of movement [22]. In addition, central inter-hemispheric beta coherence was found linked to motor function recovery, patients with higher interhemispheric coherence presenting higher motor function recovery after stroke [23]. Our preliminary results highlight the possible effects of tDCS on motor function in patients with DOC.

For the 4 patients with clinical response (i.e., reduced hypertonia after active tDCS), we found a similar pattern of connectivity in the beta band (here beta1) between the motor and frontal areas, as identified at the group level. In addition, these patients demonstrated an increase in connectivity after the active stimulation in beta1 between the frontal, prefrontal and fronto-polar areas. Previous studies found similar increased beta power after a single stimulation session over the prefrontal cortex [24] or primary motor cortex [25]. The authors concluded that tDCS could prime brain activity to a "ready state" to perform cognitive tasks (prefrontal tDCS) or motor-related tasks (M1 tDCS). On the basis of this hypothesis, we could have expected behavioural changes more than reduced muscle overactivity. In this scenario, repeated sessions of tDCS may be needed to induce motor-related clinical improvement. Besides modulation of beta power, our responders showed increased power in the theta band for the frontal and fronto-central electrodes after active stimulation. Increase in theta power is mainly linked to memory functions and hippocampal activity [26,27]. However, theta oscillations have also been associated with sensorimotor integration arising from the hippocampal formation [28] and can be modulated after a motor task [29]. In this context, the reduced muscle hypertonia observed in responders together with increased theta activity in the fronto-central regions could result from a normalization of brain activity or reduced cortical maladaptive plasticity, leading to spasticity.

Although with a small sample size, this pilot study could help in the development of new trials aimed at managing hypertonia in patients with DOC by using non-invasive brain stimulation. Repeated tDCS sessions are considered required to induce clinically relevant and long-lasting effects in different neurological conditions [30–34]. Although we had a few responders, they represented 30% of our small sample. In this context, repeated stimulation sessions would increase the number of responders and could induce lasting clinical effects due to mechanisms thought to be related to long-term potentiation and long-term depression [35,36].

Regarding evaluation of consciousness (i.e., CRS-R), we did not observe any significant effect of tDCS on patients' responsiveness. In previous studies targeting the left prefrontal cortex, clinical improvements (i.e., responsiveness assessed by the CRS-R) were noted in patients with MCS, even after a single stimulation session of 20 min of tDCS at 2 mA [37]. Several factors could explain why we did not reproduce such behavioural effects. First, the sample size was relatively small, with only 14 individuals included, 7 with MCS, a subgroup for which tDCS seems to be more efficient. Second, we stimulated the left prefrontal cortex at 1 mA, which may not be sufficient to induce relevant clinical improvement after a single session of tDCS. Third, by placing cathodes over the M1, we may have also reduced the ability of participants to initiate the motor-mediate responses as assessed by the CRS-R. However, at the group level, patients' behavioural responses did not worsen as compared to baseline.

tDCS represents an interesting tool, especially for patients with DOC, because it does not require their participation. In addition, it is safe, with few side effects, which is also an essential factor for this population of individuals unable to communicate their feelings. Finally, the device is relatively inexpensive, portable, and user-friendly, so it is a good technique to be used in rehabilitation centers and in nursing facilities or even at home.

In conclusion, we report 4 individuals with DOC showing a significant reduction in muscle tone after tDCS, which highlights the potential clinical effect of cathodal tDCS applied over M1 for managing spastic symptoms in DOC. This finding is also supported by the increase in EEG connectivity within the motor and frontal regions in beta after tDCS. Muscle overactivity affects many individuals with severe brain injury, who have limited treatment options; therefore, tDCS represents a valuable tool to help manage hypertonia in this critical population. Future clinical trials including repeated sessions might confirm the effects of tDCS as a therapeutic option for treating hypertonia in individuals with chronic DOC. In addition, although low-intensity stimulation protocols were previously recommended [38], a recent study of stroke patients demonstrated the safety and tolerability of applying a current as high as 4 mA over the M1 [39]; therefore, increasing the current intensity of our protocol, for a total of 4 mA of injected current, could lead to stronger clinical effects. Studies should also assess participants' level of pain, known to be linked to hypertonia and may be related to quality of life (e.g., by means of the Nociception Coma Scale Revised) [40]. Excitatory tDCS (anodes applied over M1) could also be tested to reduce hypertonia, as was previously observed in stroke patients receiving intermittent excitatory theta burst stimulation [41].

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.rehab.2019.05.009.

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