Clinical Response to tDCS Depends on Residual Brain Metabolism and Grey Matter Integrity in Patients With Minimally Conscious State

Aurore Thibaut, Carol Di Perri, Camille Chatelle, Marie-Aurélie Bruno, Mohamed Ali Bahri, Sarah Wannez, Andrea Piarulli, Claire Bernard, Charlotte Martial, Lizette Heine, Roland Hustinx, Steven Laureys

Coma Science Group, GIGA Research, Cyclotron Research Centre and Neurology Department, University and University Hospital of Liège, Belgium
Neurorehabilitation Lab, Department of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Harvard Medical School, Boston, MA, USA
Laboratory for NeuroImaging of Coma and Consciousness, Massachusetts General Hospital, Boston, MA, USA
Cyclotron Research Centre, University of Liège, Liège, Belgium
PERCRO Laboratory, Scuola Superiore Sant'Anna, Pisa, Italy
Nuclear Medicine Department, University Hospital of Liège, Belgium

Background: Transcranial direct current stimulation (tDCS) was recently shown to promote recovery of voluntary signs of consciousness in some patients in minimally conscious state (MCS). However, it remains unclear why clinical improvement is only observed in a subgroup of patients.

Objectives: In this retrospective study, we investigated the relationship between tDCS responsiveness and neuroimaging data from MCS patients.

Methods: Structural Magnetic Resonance Imaging (MRI), Fluorodeoxyglucose Positron emission tomography (FDG-PET) and clinical electroencephalography (EEG) were acquired in 21 sub-acute and chronic MCS patients (8 tDCS responders) who subsequently received left dorsolateral prefrontal (DLPF) tDCS in a double-blind randomized cross-over trial. The behavioral data have been published elsewhere (Thibaut et al., Neurology, 2014).

Results: Grey matter atrophy was observed in non-responders as compared with responders in the left DLPF cortex, the medial-prefrontal cortex, the cingulate cortex, the hippocampi, part of the rolandic regions, and the left thalamus. FDG-PET showed hypometabolism in non-responders as compared with responders in the left DLPF cortex, the medial-prefrontal cortex, the precuneal, and the thalamus. EEG did not show any difference between the two groups.

Conclusion: Our findings suggest that the transient increase of signs of consciousness following left DLPF tDCS in patients in MCS require grey matter preservation and residual metabolic activity in cortical and subcortical brain areas known to be involved in attention and working memory. These results further underline the critical role of long-range cortico-thalamic connections in consciousness recovery, providing important information for guidelines on the use of tDCS in disorders of consciousness.

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Keywords: Transcranial direct current stimulation; Disorders of consciousness; Treatment; Magnetic resonance imaging; Voxel based morphometry; Positron emission tomography; Minimally conscious state

Abbreviations: tDCS, transcranial direct current stimulation; MCS, minimally conscious state; CRS-R, Coma Recovery Scale-Revised; PET, Positron emission tomography; EEG, Electroencephalography; MRI, Magnetic Resonance Imaging; DLPFC, dorsolateral prefrontal cortex; VBM, voxel based morphometry.

This study was supported by the National Funds for Scientific Research (FNSR), Action de Recherche Concertée (ARC), Fonds Léon Fredericq, James S. McDonnell Foundation, Mind Science Foundation, University of Liège, the Belgian American Educational Foundation (BAEF), the Fédération Wallonie Bruxelles International (WBI) and the Belgian interuniversity attraction pole.

* Corresponding author. Coma Science Group, GIGA Research, Cyclotron Research Centre and Neurology Department, Avenue de l’Hôpital, 1, 4000 Liège, Belgium. Tel.: +32 4 366 80 69.
E-mail address: athibaut@ulg.ac.be (A. Thibaut).

Both authors equally contributed to this work.

http://dx.doi.org/10.1016/j.brs.2015.07.024
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Introduction

Transcranial direct current stimulation (tDCS) is a form of noninvasive cortical stimulation modulating cortical excitability at stimulation sites via weak polarizing currents [1]. Anodal tDCS enhances excitability, whereas cathodal tDCS reduces it, by decreasing or increasing the action potential threshold [2]. The establishment of its long-lasting after-effects depend on membrane potential changes as well as modulations of N-methyl-D-aspartate (NMDA) receptor efficacy [3]. In another word, tDCS does not induce the firing of otherwise resting neurons, but it modulates the spontaneous firing rate of neurons by acting on the membrane potential. Nevertheless, the underlying mechanisms of tDCS remain only partly understood (for a recent review see Ref. [4]). This technique is being increasingly studied as a potential treatment for several neuropsychiatric diseases and symptoms including depression [5], pain [6], and tinnitus [7]. A number of recent studies has used tDCS on the motor cortex for motor rehabilitation after stroke [8] and for decreasing motor symptoms in Parkinson’s disease [9]. Additionally, stimulation of the left dorsolateral prefrontal cortex (DLPFC) was shown to improve cognitive abilities in patients with stroke [10], Alzheimer’s disease [11] and severe brain injury [12].

Many studies showed an improvement of motor and cognitive functions or pain after a stimulation over the motor or prefrontal cortices (for review see Refs. [13,14]), but only a few reported the number of responders. The proportion of tDCS responders may vary from 40% for patients with tinnitus [15], to 60% for patients with multiple sclerosis [16] or event 80% for patients with chronic pain [17]. In a recent sham-controlled randomized cross-over trial, we reported that 20 min tDCS on the left DLPFC could improve signs of consciousness in 15 out of 35 studied patients (43%) in a minimally conscious state (MCS) [12]. On the other hand, a recent meta-analysis on healthy subjects concluded that tDCS over the prefrontal cortex does not induce a significant effect on working memory outcome nor on language production tasks [18]. Nevertheless, a recent re-evaluation of this meta-analysis highlighted some problems with their data selection and statistical approach [19]. Therefore, they suggested to take Horvath and colleagues’ conclusions with caution. Furthermore, it is also possible that several sessions of tDCS may be required in order to achieve the desired effect. A study of repeated tDCS over the primary motor cortex in healthy volunteers highlighted a consolidation mechanism which lasted up to 3 months after 5 tDCS sessions [20].

If the findings of our recent study on patients with DOC suggest the potential interest of tDCS as a treatment for this population of severely brain injured patient, they also highlight the lack of a clinical improvement following tDCS in more than half of the patient population. The natural step is to deimprove following tDCS in more than half of the patient population. The natural step is to determine the structural and functional brain features of those patients that are likely to respond to tDCS [21].

The aim of this retrospective study is to characterize the previously described [12] subgroup of tDCS responders by means of multi-modal neuroimaging analyses, including fluorodeoxyglucose positron emission tomography (FDG-PET), structural magnetic resonance imaging (MRI) and electroencephalography (EEG). Effects of tDCS [4]. Exclusion criteria for healthy controls were a clinical history of chronic diseases, psychiatric and/or neurological impairments, loss of consciousness, drug and alcohol addiction and use of medication.

Out of the 30 MCS patients included in our previous study [12], 24 patients underwent a brain FDG-PET acquisition, MRI acquisition and EEG registration on clinical demand as part of their diagnostic and prognostic work in our tertiary expert unit [24]. The FDG-PET and MRI scans of three patients (non-responders 2, 6, 14 – see Fig. 1 and Table 1 in Supplementary Material) were excluded from the statistical analysis due to suboptimal normalization. FDG-PET and EEG recording were performed in resting-state conditions 24–48 h prior to tDCS (except in one patient who had undergone PET imaging 6 weeks before and did not redo the examination for radioprotection issues). MRI was acquired within one week prior to tDCS. Medication, physiotherapy and rehabilitation were kept unchanged throughout the tDCS experiment. The study was approved by the ethics committee of the University and University Hospital of Liège, Belgium and written informed consent was obtained by the legal representative.

Active and sham tDCS were applied for 20 min and tested in randomized order in two separate sessions separated by 48 h. The effects of a single session of anodal tDCS are expected to last for a maximum of 2 h [25]. Direct current was applied using a constant current stimulator and surface electrodes with the anode (increasing cortical excitability) positioned over the left DLPFC (F3 according to the 10–20 international system [26]) and the cathode (i.e., reference electrode) placed over the right supraorbital region (Fig. 3D). During active tDCS, the current was increased to 2 mA. For the sham condition the current was applied for 5 s and was then ramped down. Impedances were kept <10 kΩ and voltage <26 V. tDCS responders were defined as patients who presented at least one additional sign of consciousness after tDCS that was never present before real tDCS, nor before or after the sham tDCS session (i.e., command following; visual pursuit; recognition, manipulation, localization or functional use of objects; orientation to pain; intentional or functional communication [27]). Behavioral signs of consciousness were assessed by means of standardized Coma Recovery Scale Revised (CRS-R) assessments [27], performed directly before and after the anodal tDCS and sham tDCS sessions (Fig. 1).

A group of age-matched healthy controls (n = 17; mean age 47 ± 13 years; 9 men) underwent both MRI and FDG-PET scans acquisition within the same week. Note that controls did not received tDCS.

Magnetic resonance imaging

Data acquisition

Structural MRI T1 data (T1-weighted 3D gradient echo images using 120 slices, repetition time = 2300 ms, echo time = 2.47 ms, voxel size = 1 × 1 × 1.2 mm³; flip angle = 9°, field of view 24 × 24 × 20 cm³) and t1-weighted spin-echo images (T2-weighted images with inter-slice gap = 1 mm) were acquired in the double-blind randomized cross-over tDCS trial. tDCS responders were defined as those patients who presented a sign of consciousness (as assessed by means of Coma Recovery Scale Revised (CRS-R) assessments [27]) after tDCS that was never present before real nor before or after sham tDCS sessions.

Figure 1. Schematic representation of the study protocol. Electroencephalogram (EEG), Magnetic resonance imaging (MRI) and Fluorodeoxyglucose positron emission tomography (PET) was performed in resting-state conditions 24–48 h prior to inclusion in the double-blind randomized cross-over tDCS trial. tDCS responders were defined as those patients who presented a sign of consciousness (as assessed by means of Coma Recovery Scale Revised (CRS-R) assessments [27]) after tDCS that was never present before real nor before or after sham tDCS sessions.
view = 256 × 256 mm²) were acquired on a 3T scanner (Siemens Trio Tim, Munich, Germany). A T1-based voxel-based morphometry (VBM) analysis of brain structure (http://dbm.neuro.uni-jena.de/vbm/) was applied to search for potential morphological differences in grey matter volume between the two patient groups. For this analysis, we used DARTEL-based spatial normalization [29] to allow the high-dimensional spatial normalization in order to increase the chance of correct normalization of the severely damaged brain of patients with disorders of consciousness [30]. A study template made from the average of T1 images from our patients and control subjects was used to facilitate the normalization procedure [29,31,32]. The design matrix separately modeled patients’ (responders and non-responders) and healthy controls’ grey matter density. Results were considered significant at family-wise whole-brain volume-corrected for multiple comparisons (FWE) P < 0.05.

**Positron emission tomography**

Brain metabolism was measured during rest using PET-CT (Gemini Big Bore TF, Philips Medical Systems) after intravenous injection of 300 MBq FDG (as previously reported Ref. [33]). In order to reduce the influence of the surrounding structures on the radiotracer concentration, phenomenon known as partial volume effect (PVE) – particularly critical when the relative proportion of brain tissue components is altered a partial volume effect correction (PVEc) was applied to the PET images [34]. PET data were then preprocessed as previously published [35–37], including spatial normalization, smoothing (using a Gaussian kernel of 14 mm full width at a half maximum) and proportional scaling, implemented in Statistical Parametric Mapping toolbox (SPM8; www.fil.ion.ucl.ac.uk/spm). The design matrix separately modeled patients’ (responders and non-responders) and healthy controls’ PET scans. Results were considered significant at family-wise whole-brain volume-corrected for multiple comparisons (FWE) P < 0.05.

We finally compared the metabolic pattern with the structural patterns in responders and non-responders. The design matrix separately modeled patients’ (responders and non-responders) and healthy controls’ grey matter, and patients’ (responders and non-responders) and healthy controls’ PET scans. Results were considered significant at family-wise whole-brain volume-corrected for multiple comparisons (FWE) P < 0.05.

**Electroencephalography**

EEG was recorded with a 16 channels cap (using the 10–20 positioning system Fp1, Fp2, Fz, F3, F4, Cz, C3, C4, T7, T8, Pz, P3, P4, Oz, O1, O2), referenced to the mastoid for 10 min. Basic rhythms were visually inspected by an EEG expert in order to discard artifacts and retained epochs. The remaining epochs were filtered between 0.75 and 40 Hz. For each subject and electrode the normalized power in each frequency bands was estimated (delta: 1–4 Hz; theta: 4–7 Hz; alpha: 8–12 Hz; and beta: 12–25 Hz, as used in Ref. [28]). Then, we calculated the mean of all the electrodes rhythms together during the recording time. After checking for the normality of powers series, student unpaired t tests were performed to compare the mean power averaged of each rhythms of interest (i.e., bands) between responders and non-responders. Results were corrected for multiple comparisons.

**Clinical data**

Statistical comparisons of clinical data between the two groups (patients’ age, time since onset, etiology — trauma vs non-trauma — CRS-R total score changes) were performed using student t tests implemented in Stata (Stata Statistical Software 11.2 StataCorp, College Station, TX) and considered significant at P < 0.05 corrected for multiple comparisons.

**Results**

**Clinical**

Out of the 21 patients in sub-acute or chronic MCS that were included in the analyses, 8 were tDCS responder (4 post-traumatic, 4 non-traumatic, 4 men) and 13 were non-responder (8 post-traumatic, 5 non-traumatic, 10 men). The responders and non-responders did not show a significant difference in age (mean ± SD; 38 ± 19 vs 36 ± 14y respectively; p = 0.84), time since onset (6 ± 8 vs 4 ± 3y; P = 0.45), or baseline CRS-R total score (median (IQR); 9(3) vs 9(7); P = 0.29). At the group level, CRS-R total scores improvement (obtained before and after active tDCS) were higher in responders as compared to non-responders (Fig. 4A).

**Voxel based morphometry**

Statistical analyses identified: A) reduced grey matter areas (as compared with healthy controls) in the subgroup of tDCS non-responders, and B) reduced grey matter areas in the subgroup of tDCS responders (as compared with healthy controls). Based on the voxel-based morphometry analysis (VBM), responders showed decreased grey matter volume in the lateral temporal cortex, the thalamus, the lenticular nuclei, the left caudatum, the right amygdala and parahippocampal gyrus and to a certain extent the right dorsolateral prefrontal cortex and the cingulate cortex. Non-responders showed decreased grey matter volume in the same regions observed in the tDCS responders (except for part of the temporal poles) but more extensively in the precuneus/cuneus and the cingulate cortex and additionally in the left medium/inferior gyrus, the superior temporal gyr, the hippocampi, the left amygdala and to some extent the rolandic areas (see Fig. 2).

**FDG-PET**

Statistical analyses identified: A) brain areas showing hypometabolism (as compared with healthy control) in the subgroup of tDCS responders, B) brain areas showing hypometabolism in the subgroup of tDCS non-responders, and C) brain areas showing a relatively preserved metabolism in tDCS responders as compared to tDCS non-responders. Findings from FGD-PET in tDCS responders showed regional hypometabolism (as compared with healthy control) in the medial-prefrontal cortex/anterior cingulate cortex, the medial thalamus bilaterally and the caudate. tDCS non-responders showed impaired metabolism in similar areas (albeit relatively more preserved in the medial-prefrontal cortex, the caudate and left thalamus) and additionally in the precuneus and the left DLPFC. Areas showing preserved metabolism in responders as compared with non-responders were in the left DLPFC, the medial-prefrontal cortex, the precuneus, the caudate and the left thalamus (Table 1 and Fig. 3). Inversely, no brain areas appeared more extended in the medial-prefrontal cortex, the caudate and the left thalamus.
EEG

EEG findings failed to detect significant differences in the mean frequency bands (i.e., delta, theta, alpha, and beta) between the two groups.

VMB-FDG-PET comparison

When looking at the relationship between the brain structural and metabolic patterns in responders (when compared with healthy controls), the right DLPCF, the temporal cortex, the lenticular nuclei and partially the thalami and the cingulate cortex showed grey matter atrophy not associated with hypometabolism. The medial-prefrontal/anterior cingulate cortex, the right caudatum and to some extent the thalami showed hypometabolism not associated with grey matter atrophy. The left caudatum and part of the thalami displayed both grey matter atrophy and hypometabolism (Fig. 2 in Supplementary Material).

Table 1: Coordinates of peak voxels (in standardized stereotaxic MNI space) hypometabolic areas in responders and non-responders as well as less impaired metabolism in tDCS responders as compared to non-responders

<table>
<thead>
<tr>
<th>Region (Brodmann area)</th>
<th>X (mm)</th>
<th>Y (mm)</th>
<th>Z (mm)</th>
<th>Z-value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thalamus</td>
<td>0</td>
<td>–13</td>
<td>7</td>
<td>6.29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Caudate body</td>
<td>15</td>
<td>14</td>
<td>12</td>
<td>5.32</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Medial frontal gyrus B9</td>
<td>2</td>
<td>48</td>
<td>15</td>
<td>5.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Left angular gyrus B39</td>
<td>–54</td>
<td>–72</td>
<td>30</td>
<td>4.63</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Inula</td>
<td>–45</td>
<td>–18</td>
<td>12</td>
<td>4.60</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
| Hypometabolic areas in responders
| Caudate body           | 15     | 12     | 13     | 6.59    | <0.0001 |
| Left thalamus           | –2     | –16    | 10     | 6.31    | <0.0001 |
| Medial frontal gyrus B9 | –2     | 48     | 21     | 5.83    | <0.0001 |
| Precuneus B7            | 5      | –76    | 51     | 5.31    | <0.0001 |
| Precuneus B31           | –2     | –46    | 34     | 5.13    | <0.0001 |
| Posterior cingulate B23 | –2     | –58    | 19     | 5.12    | <0.0001 |
| Left superior frontal gyrus B6 | –15 | 20      | 67     | 5.04    | <0.0001 |
| Left superior frontal gyrus B8 | –12 | 47      | 48     | 4.78    | <0.0001 |
| Cingulate gyrus B31     | –2     | –45    | 34     | 4.62    | <0.0001 |
| Less hypometabolic in responders
| Medial frontal gyrus B9 | 0      | 38     | 33     | 6.04    | <0.0001 |
| Caudate body           | –12    | 12     | 13     | 5.59    | <0.0001 |
| Left thalamus           | –14    | 6      | 15     | 5.53    | <0.0001 |
| Precuneus B7            | 5      | –76    | 51     | 5.48    | <0.0001 |
| Cingulate gyrus B31     | –2     | –45    | 34     | 5.47    | <0.0001 |
| Superior frontal gyrus   | –30    | 24     | 57     | 5.12    | <0.0001 |
| Posterior cingulate B23 | –2     | –58    | 34     | 4.91    | <0.0001 |
| Superior frontal gyrus B8 | –14 | 45      | 49     | 4.88    | <0.0001 |
| Superior frontal gyrus B6 | –15 | 20      | 67     | 4.84    | <0.0001 |
| Left thalamus           | –9     | –9     | 9      | 4.22    | <0.0001 |
| Ventral lateral nucleus  |        |        |        |         |         |

4 Whole-brain family wise corrected for multiple comparisons.

Discussion

In this retrospective study, we aimed at characterizing tDCS responders in severely brain-injured patients with sub-acute and chronic MCS. We investigated the relationship between tDCS behavioral responsiveness and structural MRI and FDG-PET. As in our previous study [12], no specific behavioral patterns of improvement among the 8 patients who showed clinical improvement following left DLPCF tDCS could be observed. These findings are seemingly related to the high heterogeneity and variability of brain damage often detected in this patient population. One might suggest that the behavioral effects observed in our first study are due to an improvement of wakefulness and may not be related to consciousness. Nevertheless, when we looked at the arousal subscale differences between responders and non-responders (see Table 1 in Supplementary Material), we observed that not a single responder had an increase of arousal. These data suggest the idea that tDCS effects were not the consequence of a higher arousal level. Moreover, an increase of CRS-R score was not sufficient to consider a patient as responder. Indeed, according to the definition of responders (i.e., patient who presented at least one additional sign of consciousness after tDCS that was never present before real tDCS, nor before or after the sham tDCS session), only the increase of score related to improvement of consciousness (e.g., command following, visual pursuit) was taking into account when considering patients as responders.

In contrast with the clinical findings, we here observed a common pattern of metabolic preservation (as detected by FDG-PET) and grey matter preservation (as detected by MRI), in tDCS responders as compared with non-responders. The areas metabolically preserved in responders as compared with non-responders included the left DLPCF cortex, the medial-prefrontal cortex, the precuneus, and the thalamus. The areas of preserved grey matter observed in responders as compared with non-responders involved the medial-prefrontal cortex, the precuneus, part of thalamus, the temporal cortex, the cingulate cortex, the hippocampi, the left amygdala, the left posterior middle gyrus and to some extent the Rolandic areas.
The residual brain metabolism in the left DLPFC, where the anode of the tDCS was positioned, suggests that, independently from the variability of the cortical damage, a residual brain activity in the stimulated area is necessary for an effective stimulation. These results are in agreement with a previous study on patients with stroke showing that tDCS effects upon stimulation on motor area are limited when the pyramidal tract is damaged (as detected by diffusion tensor imaging) [38]. Moreover, a study using transcranial magnetic stimulation coupled with EEG on patients with DOC further showed that cortical responses can be detectable only upon stimulation of a preserved cortical tissue [39].

The DLPFC is connected to a variety of brain areas such as the orbitofrontal cortex, the basal ganglia, the thalamus and the associative cortical areas. The DLPFC receives multisensory information from the parietal associative cortices and projects to subcortical monoaminergic and cholinergic sources, and therefore it is thought to play a key integrating role in the motor and behavioral functions and to be a critical component in the executive functions, such as planning, working memory, inhibition and cognitive flexibility [40–42]. Apart from the executive functions, the additional cortical and subcortical circuits with which the DLPFC is connected are more generally required for all complex mental activity. Indeed, the DLPFC is part of the functional executive control network, known to be related to external awareness [43]. It could be hypothesized that, in relation to its critical integrating role and its relatively superficial brain location, DLPFC integrity might represent a necessary substrate for the effectiveness of the tDCS.

Our results regarding the residual brain metabolism and preserved grey matter in the medial-prefrontal cortex, posterior cingulate/precuneus and thalamus in responders rather than...
non-responders, highlight the role played by these structures in the recovery of consciousness. PET studies on unresponsive patients versus control subjects have previously identified metabolic impairment in regions involving the medial-prefrontal cortex and the posterior cingulate/precuneus, also known as default mode network, and the lateral fronto-parietal regions including the DLPFC, also known as executive control network, suggesting their crucial role in the emergence of consciousness [36,44,45]. The default mode network and the executive control network have further been functionally related respectively to internal awareness (i.e., awareness of self) and external awareness (i.e., awareness of the environment). Moreover, their metabolism has shown to be gradually restored going from a lower to a higher degree of consciousness [36,46]. In particular, the residual metabolic and structural integrity of the medial-prefrontal cortex and the thalamus observed in responders rather than non-responders seem to support the key role of these structures in the disturbances of consciousness, in the setting of widespread deafferentation and neuronal cell loss as observed after severe brain injuries [47,48]. The observed residual metabolic and structural integrity of the posterior cingulate/precuneus corroborates a large amount of literature indicating this structure as a key component of the internal awareness network, namely the default mode network, and a critical hub for consciousness recovery [36,44,46,49–51].

The circumstance that the metabolic and structural integrity of structures belonging to the default mode network seems to be necessary for the clinical improvement of MCS patients upon tDCS stimulation is consistent with recent studies showing that tDCS enhances diffusively brain functional connectivity, especially targeting the default mode network and the executive control network [52–56]. In fact, recent studies combining prefrontal tDCS and resting-state fMRI have shown that prefrontal tDCS modulates large-scale patterns of resting-state connectivity in the human brain by increasing coactivation patterns both in regions close to anode and cathode stimulation sites and in more widespread and distant brain regions. Additionally, these effects appeared to be more pronounced for the default mode network [54–56]. These studies further suggest the extensive and widespread action of the tDCS and therefore the importance of intra and inter-network connectivity for its efficacy.

The residual metabolic and structural preservation of the thalamus observed in responders rather than non-responders corroborates previous literature indicating that the thalamus and the cortico-thalamic loop hold a critical role in consciousness recovery. Indeed, the regain of a connectivity between thalamus and medial-prefrontal cortex has shown to be associated with the spontaneous recovery of consciousness [57]. The critical role of the thalamus in consciousness recovery has been further supported by the observed clinical improvement of an MCS patient following deep brain stimulation in the thalamus [58].

Our results regarding areas of atrophy and hypometabolism observed in patients versus healthy controls show some overlapping of the two patterns but also a mismatch with globally more atrophy than hypometabolism, especially in the non-responders group. Studies looking at the metabolic and structural patterns in degenerative chronic diseases such as Alzheimer, fibromyalgia, lateral amyotrophic sclerosis and fronto-temporal dementia also report a mismatch between hypometabolism and grey matter atrophy [59–63]. In particular, a recent study showed globally more extended hypometabolism than atrophy in patients with Parkinson [64]. However, patients with more severe cognitive decline exhibited more regions with atrophy non-associated with hypometabolism than those patients with lower cognitive decline. Therefore, the authors suggested that hypometabolism and atrophy are two steps of the same process initiated with a reduction of cortical glucose uptake evolving towards a decrease in grey matter volume seemingly expanding in an exocentric pattern [64]. Based on this hypothesis, we would expect in our chronic patients following severe acute brain injury extensively more atrophy than hypometabolism as an expression of their severe brain damage [65,66]. The presence of more extended areas showing atrophy not associated with hypometabolism in the non-responders as compared with responders suggests a more severe degenerative process in the non-responders patients.

With regards to EEG, it has been shown that left DLPFC cortex tDCS on healthy controls and patients with moderate traumatic brain injury can either improve EEG high frequency activity or decrease low frequency activity, both at rest and during cognitive tasks [67–69]. The routine clinical EEG data hereby collected did not show any statistically significant difference between the two patient groups. However, this might be explained by the suboptimal quality (small number of electrodes, analysis on whole brain) and accuracy of EEG as acquired in clinical setting. Actually, a limitation (at an electrophysiological level) to the present study is the lack of information regarding both single electrodes power spectra and connectivity analyses between channels. This limitation was inherent to the clinical EEG used for the recording, which did not allow either for the export of raw data or for online high-level EEG analyses. Future studies on tDCS effects will be conducted using a high density EEG system, allowing thus more accurate and higher level EEG analyses.
Finally, our findings must be read taking into account some caveats. Firstly, the study lacks of a direct comparison (responders versus non-responders) between the two patient groups. This is related to the limited size of the population and the high degree of variability within the groups including both neuroimaging and etiology. Secondly, we cannot use the findings of the present study to predict the clinical improvement upon tDCS at single subject level. In fact, our results could effectively be applied only at a group level. Further studies might be warranted to detect specific features to predict the outcome at the individual level. Thirdly, the exact stimulation area might be considered so far only theoretical since patients had widespread brain lesion and functional reorganization and/or development of atrophy and/or scars under the site of stimulation might have occurred, modifying the exact site of stimulation. Therefore, a single subject head model of the current field is needed in order to detect the trajectory of the current in this severely brain-injured population. Finally, other acquired neuroimaging data, such as functional MRI and diffusion tensor imaging, were not analyzed. In fact, functional MRI and diffusion imaging tensor are extremely sensitive to motion and metal artifacts. This resulted in the availability of a too small sample of good quality data to be included in a statistical analysis. Furthermore, when patients were sedated the fMRI data were excluded from the analysis by default, as sedation might have affected the results.

In conclusion, the present study shows that the transient improvement of signs of consciousness following left DLPFC tDCS in patients in sub-acute and chronic MCS seems to require grey matter integrity and/or residual metabolic activity in three brain regions: (i) the presumed stimulated area (i.e., left DLPFC), (ii) long distance cortical areas such as the precuneus, and (iii) subcortical brain areas known to be involved conscious processes (i.e., thalamus).

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brjs.2015.07.024.

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