Journal of the Neurological Sciences 368 (2016) 178–183

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Towards a method to differentiate chronic disorder of consciousness patients' awareness: The Low-Resolution Brain Electromagnetic Tomography Analysis

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ARTICLE INFO

Article history:
Received 23 May 2016
Received in revised form 1 July 2016
Accepted 8 July 2016
Available online 9 July 2016

Keywords:
LORETA
Minimally Conscious State
Resting state
Unresponsive Wakefulness Syndrome

ABSTRACT

Assessing residual signs of awareness in patients suffering from chronic disorders of consciousness (DOC) is a challenging issue. DOC patient behavioral assessment is often doubtful since some individuals may retain covert traces of awareness; thus, some Unresponsive Wakefulness Syndrome (UWS) patients may be misdiagnosed. The aim of our study was to explore possible differences between the source powers within poly-modal cortices to differentiate Minimally Conscious State (MCS) from UWS. To this end, we recorded an electroencephalogram (EEG) during awake resting state and performed a Low-Resolution Brain Electromagnetic Tomography (LORETA), which is a 3D source localization method allowing the visualization of the most probable neuroanatomical generators of EEG differences. MCS and UWS patients showed significant variations concerning the frontal source power of delta-band, frontal and parietal of theta, parietal and occipital of alpha, central of beta, and parietal of gamma, in correlation with the Coma Recovery Scale-Revised (CRS-R) score. The alpha-band was the most significant LORETA data correlating with the consciousness level. In addition, we observed a significant correlation between central beta-peaks and the motor abilities and a dissociation between theta and gamma bands within parietal regions. Our findings suggest that LORETA analysis may be useful in DOC differential diagnosis since distinct neurophysiological correlates in some UWS patients could be used to assess deeper the residual cerebral activity of brain areas responsible for covert awareness.

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1. Introduction

Consciousness depends on two interacting main components, the wakefulness (i.e. the level of arousal) and the awareness (i.e. the purposefulness of the patient's response) [1,2]. Patients in Minimally Conscious State (MCS) and Unresponsive Wakefulness Syndrome (UWS), both belonging to Chronic Disorders of Consciousness (DOC), show, respectively, a partial or a complete dissociation between awareness and wakefulness, owing to a broad cortico-thalamocortical disconnectivity syndrome [3].

In clinical practice, awareness assessment is a demanding task, and the misdiagnosis rate is significantly high [4]. Indeed, the patients affected by Functional Locked-in Syndrome (FLIS) are unable to show purposeful behaviors but have a partially preserved cortico-thalamocortical connectivity able to sustain awareness at a covert level. To this end, only neuroimaging and neurophysiological approaches can help clinicians in differentiating between UWS and FLIS patients [5–8]. In fact, UWS patients suffer from a global cortical metabolism drop and an evident dissociation between primary and polymodal cortices [9–12], whereas FLIS individuals show a partially preserved metabolism and large-scale connectivity [5–8,13,14].

Among the neurophysiologic approaches, electroencephalography (EEG) offers accurate information on the level of cortical information processing and integration and the changes occurring during different states of awareness [15]. In particular, 3D source localization methods have been applied to enable visualization of the most probable neuroanatomical generators of such EEG differences. To this regard, Low-Resolution Brain Electromagnetic Tomography (LORETA) is a functional imaging technique that belongs to a family of linear inverse solution procedures [16] and allows modeling 3D distributions of EEG sources [17]. LORETA in DOC patients has been validated independently by some studies showing a delta power increase and high amplitudes of posterior sources of delta and theta frequencies, paralleled by low values of posterior alpha and frontotemporal beta frequencies [18,19]. Altogether, these findings further confirm the importance of frontal-temporoparietal associative cortices concerning awareness generation and maintenance [18,19]. Nonetheless, the usefulness of LORETA analysis in differentiating DOC conditions has not been completely shown so

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http://dx.doi.org/10.1016/j.jns.2016.07.016
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far. In particular, the role of gamma oscillations, which are thought to be of importance concerning sensory-motor information processing at a conscious level [20], has been barely assessed. Therefore, our LORETA source analysis study was aimed at finding cortical sources within different frequency bands and the poly-modal cortices subtending awareness, helping in differentiating DOC patients. In particular, we hypothesized that FLIS and MCS patients might show greater activity in the gamma-range band within poly-modal cortices than UWS individuals. To this end, we opted for a bottom-up approach, looking for patterns in the EEG data discernible using LORETA.

2. Methods

2.1. Subjects

We enrolled 13 severe DOC patients (seven MCS and six UWS), following hypoxic-ischemic or traumatic brain damage, who met the criteria for vegetative state/UWS and MCS diagnosis [21–23]. As a control group, ten healthy individuals (HC) were included in the study. Detailed clinic-demographic characteristics are summarized in Table 1. Exclusion criteria were: pre-existing severe neurological or systemic diseases; actual critical conditions; administration of other modifying cortical-excitability drugs than L-Dopa, baclofen, and antiepileptic drugs; actual EEG epileptiform activity and suppression-burst patterns; a presence of skull discontinuities. The Local Ethics Committee approved the present study, and written informed consent was obtained from either HC or legal guardian of each patient.

2.2. Clinical assessment

Two neurologists skilled in DOC diagnosis evaluated independently the DOC patients every day for one month, through the JFK Coma Recovery Scale-Revised (CRS-R) [24]. CRS-R is a reliable and standardized tool, which integrates neuropsychological and clinical assessment, and includes the current diagnostic criteria for coma, vegetative state/UWS, and MCS, allowing clinicians to assign the patient to the most appropriate diagnostic category. The scale appears as a suitable measure for characterizing the level of consciousness and for monitoring the neurobehavioral function recovery [25].

2.3. Data pre-processing

Thirty minutes after the CRS-R administration, we recorded an EEG for 5 min in resting state (with eyes closed by eyepatches) from 19 electrodes positioned according to the International 10–20 system (Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, O2). An electrooculogram was also collected to monitor eye movements (0.3–70 Hz). Signals were sampled at 256 Hz, filtered at 0.3–70 Hz + 50 Hz-notch, referenced to Cz (even though LORETA solutions is a reference-free method of EEG analysis and it is possible to obtain the same LORETA source distribution for EEG data referenced to any reference electrode, including common average), and segmented into 1 s epochs. A 75% of overlapping 256-point segments were produced to minimize windowing effects. This format is applicable when using LORETA solutions [25,26]. We checked for possible EEG signs of drowsiness and sleep onset (an increase of tonic theta rhythms, K complexes, and sleep spindles), and applied the CRS-R arousal to keep constant the level of vigilance [23]. Data were preprocessed through a free release of EEGLAB under MATLAB [27]. Artifacts (ocular movement in frontal electrodes and muscular tension in temporal derivations) were removed using an independent component analysis. Power spectra of the selected artifact-free EEG epochs were calculated using a Fast Fourier Transformation (FFT) (employing Welch technique, Hanning windowing function, and no phase shift) with 1 Hz frequency resolution. The power spectra were averaged across frequency bands (delta, 1–3 Hz, theta 4–7 Hz, alpha 8–12 Hz, beta 13–30 Hz, gamma 31–70 Hz, and full band, 1–70 Hz) and scalp locations (frontal -F3, Fz, F4, F7, F8- central -C3, Cz, C4- parietal -P3, Pz, P4- occipital -O1, O2- and temporal regions -T3, T4, T5, T6). Thus, artifact-free data were analyzed to identify EEG sources by LORETA.

2.4. EEG sources by LORETA

EEG data were analyzed by a free release of LORETA-KEY alpha-software [28,29]. The LORETA version employed uses a three-shell spherical head model that includes the scalp, skull, and brain compartment. The latter was restricted to cortical gray matter, was co-registered to the Talairach probability atlas [30], and included 2394 voxels (7 mm resolution), each voxel containing an equivalent current dipole. LORETA images represent the electrical activity at each voxel as squared magnitude (i.e., power) of the computed current density. Of note, EEG electrode positions were not co-registered to individual brain source

Table 1
shows the clinical and demographic characteristics of DOC patients at the day of EEG examination. The variability index (R) of monthly CRS-R score is also reported (not relevant <0.1, small <0.3, medium <0.5, and large >0.5).

DOC		etiology	gender	age	BI	MRI	treatment	CRS-R							
								total	A	V	M	OM	C	Ar	R
MCS	1	T	F	70	33	Fb_h	LD(300)	18	3	4	4	3	1	3	<0.1
	2	A	M	57	9	WMH	LD(350),B(100)	17	3	4	5	2	1	2	<0.3
	3	T	F	72	6	FP_h	LD(300)	16	3	4	3	2	1	3	<0.3
	4	T	M	47	12	FP_h		16	3	3	3	3	1	3	<0.5
	5	T	M	33	18	multiple_h	B(75)	16	3	3	3	3	1	3	>0.5
	6	T	F	44	3	F_h		15	2	3	3	3	1	3	<0.5
	7	A	M	51	18	WMH		15	3	4	3	2	1	2	>0.5
mean ± SD				53 ± 14	14 ± 10			16 ± 1.1	3 ± 0.4	4 ± 0.5	3 ± 0.8	3 ± 0.5	1	3 ± 0.5	<0.5
UWS	1	A	F	62	19	WMH		6	0	1	1	1	0	2	>0.5
	2	A	F	43	6	WMH	LD(400)	6	1	1	2	0	0	2	>0.5
	3	T	F	54	40	DAI, F_h	B(100)	5	0	1	1	0	0	3	>0.5
	4	T	F	48	11	multiple_h		7	1	1	2	1	0	2	<0.3
	5	T	F	38	12	DAI, FP_h		6	1	1	2	0	0	2	>0.5
	6	T	M	45	3	DAI	LD(350)	5	1	1	1	0	0	2	>0.5
Mean ± SD				48 ± 9	15 ± 13			6 ± 0.7	1 ± 0.5	1 ± 0.2	2 ± 0.5	0.4 ± 0.6	0	2 ± 0.4	>0.5
t-test				NS	NS			<0.001	0.001	<0.001	0.003	<0.001		0.03	0.04

Legend: B baclofen with dosages in mg/24hh; BI brain injury onset; CRS-R coma recovery scale-revised (A auditory, V visual, M motor, OM oro-motor, C communication, Ar arousal); MRI magnetic resonance imaging pattern (DAI diffuse axonal injury; DOC disorder of consciousness; F frontal; Fb fronto-basal; FP frontoparietal; h hemorrhagic lesion); LD L-Dopa with dosages in mg/24hh; NS non-significant; WMH white matter hyperintensity; R variability index of monthly CRS-R score.

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