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Repetitive transcranial magnetic stimulation induced slow wave activity modification: A possible role in disorder of consciousness differential diagnosis?

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ABSTRACT

Slow wave activity (SWA) generation depends on cortico–thalamo-cortical loops that are disrupted in patients with chronic Disorders of Consciousness (DOC), including the Unresponsive Wakefulness Syndrome (UWS) and the Minimally Conscious State (MCS). We hypothesized that the modulation of SWA by means of a repetitive transcranial magnetic stimulation (rTMS) could reveal residual patterns of connectivity, thus supporting the DOC clinical differential diagnosis. We enrolled 10 DOC individuals who underwent a 24 hh polysomnography followed by a real or sham 5 Hz-rTMS over left primary motor area, and a second polysomnographic recording. A preserved sleep-wake cycle, a standard temporal progression of sleep stages, and a SWA perturbation were found in all of the MCS patients and in none of the UWS individuals, only following the real-rTMS. In conclusion, our combined approach may improve the differential diagnosis between MCS patients, who show a partial preservation of cortical plasticity, and UWS individuals, who lack such properties.

1. Introduction

The sleep-wake cycle (SWC), the sleep architecture, and the homoeostatic regulation of slow wave activity (SWA) (i.e. the 1–4.5 Hz EEG band power) have been put in relation to the global functional connectivity within the cortico-cortical and thalamo-cortical networks supporting consciousness generation and maintenance (Bassetti & Aldrich, 2001; Gottselig, Bassetti, & Achermann, 2002; Massimini, Tononi, & Huber, 2009). In particular, the amount of SWA can be as: (i) a measure of sleep pressure; (ii) a marker of plasticity phenomena subtending sleep-related restorative, learning, and memory functions (Bliss & Collingridge, 1993; Bliss & Lomo, 1973; Whitlock, Heynen, Shuler, & Bear, 2006); and (iii) a sign of homeostatic plasticity phenomena within short- and long-range cortical networks (Esser et al., 2006; Tononi & Cirelli, 2006). In addition, SWA generation and regulation depend on multiple cortico-cortical and thalamo-cortical loops (Bellesi, Riedner, Garcia-Molina, Cirelli, & Tononi, 2014; Massimini, Huber, Ferrarelli, Hill, & Tononi, 2004; Spoormaker, Czisch, Maquet, & Jäncke, 2011; Steriade, 2004; Steriade, McCormick, & Sejnowski, 1993). To this end, it has been shown that motor and cognitive tasks (Borbély, 1982, 2001; Huber, Ghilardi, Massimini, & Tononi, 2004; Tononi & Cirelli, 2006), as well as repetitive transcranial

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magnetic stimulation (rTMS) during sleep or wakefulness (Huber et al., 2007; Massimini et al., 2009, 2007) are capable to modulate the amount of SWA through long term potentiation/depression(LTP/LTD)-like synaptic plasticity mechanisms (Huber et al., 2007).

Interestingly, it has been shown that the degree of cortico–thalamo-cortical functional disconnectivity and of sleep architecture impairment are proportionally related to the consciousness deterioration level in patients suffering from chronic Disorders of Consciousness (DOC), such as the Unresponsive Wakefulness Syndrome (UWS) (formerly, Vegetative State) and the Minimally Conscious States (MCS) (Boly et al., 2008; Cologan et al., 2010; de Biase et al., 2014). Therefore, the assessment of sleep architecture and SWA modulability in DOC individuals could support either the differential diagnosis or the prognosis establishment.

Hence, we hypothesized that the modulation of SWA induced by an rTMS paradigm, delivered during wakefulness, could unmask residual patterns of cortico–thalamo-cortical connectivity in DOC patients, thus supporting the differential diagnosis beside a polysomnographic assessment of sleep architecture.

2. Materials and methods

2.1. Patients

Out of the 28 eligible DOC patients attending the long-term Neurorehabilitative Unit of the IRCCS Centro Neurolesi "Bonino-Pulejo" (Messina, Italy), we enrolled 10 individuals who met the international criteria for Vegetative State and MCS diagnosis (Giacino et al., 2002; Multi-Society Task Force on PVS, 1994a, 1994b), and the following exclusion criteria: DOC condition lasting less than 3 months after BI; other severe neurological or systemic diseases; critical conditions (i.e. inability to breathe independently, hemodynamic instability); administration of cortical excitability modifying drugs, beyond L-DOPA and baclofen; safety contra-indications to TMS; MRI focal lesions within left motor area (M1). The clinical and demographic characteristics are reported in Table 1. The patients were clinically monitored, every day, for one month, through the JFK Coma Recovery Scale-Revised (CRS-R) (Giacino & Kalmar, 2005; Giacino, Kalmar, & Whyte, 2004; Kalmar & Giacino, 2005), independently by two DOC-diagnosis skilled neurologists. The present study was approved by the local Ethics Committee and written informed consent was obtained from the legal guardian of each patient.

2.2. Study design

Each patient practiced a real- and sham-rTMS treatment in two separate experimental sessions that were carried out in random order with, at least, 2 days' interval. In the real experimental session, all the subjects underwent a first day EEG-cap adaptation (*i.e.* they simply wore the EEG-cap for 24 hh, from 7 am of day_1 to 7 am of day_2). Thus, they underwent a 24 hh polysomnography in order to assess the sleep pattern (from 7 am of day_2 to 7 am of day_3), then a 5 Hz-rTMS treatment over left M1 (~7.30 am of day_3), and thereafter a second 24 hh polysomnographyc recording (from 8 am of day_3 to 8 am of day_4). The sham session was carried out in the same way as the real one, but adopting a sham coil for 5Hz-rTMS.

2.3. 24 hh polysomnography

Polysomnographic registration was performed at bedside. The recording started at 7 or 8 am and ended at 7 or 8 am the next morning. Night-time was considered as the time when the patient was left alone with lights off (from 10 ± 1 pm to

Table 1
Shows the clinical and demographic characteristics. Data are reported as individual and mean ± standard deviation (sd) (in italic).

DOC	Etiology	Gender	Age	dd	CRS-R						
					Total	a	v	m	om	c	ar
MCS	A	F	72	5	17	3	4	4	2	1	3
	A	M	32	4	16	3	3	5	1	1	3
	A	F	66	23	12	1	3	2	2	1	3
	T	M	48	15	9	1	2	1	2	1	3
Mean ± sd			*54 ± 18*	*12 ± 9*	*13 ± 4*	*2 ± 1*	*3 ± 1*	*2 ± 2*	*1.6 ± 0.5*	*1*	*3*
UWS	A	F	53	21	5	1	1	1	1	0	1
	T	F	26	10	5	1	1	1	0	0	2
	A	F	62	9	4	1	1	1	0	0	1
	T	M	45	7	6	1	1	1	1	0	2
	T	F	48	5	4	1	1	1	0	0	1
	T	M	51	21	5	1	1	1	1	0	1
Mean ± sd			*48 ± 12*	*12 ± 7*	*5 ± 1*	*1*	*1*	*1*	*0.5 ± 0.5*	*0*	*1.3 ± 0.5*

Legend: dd: disease duration; CRS-R: Coma Recovery Scale-Revised; a: auditory function; v: visual function; m: motor function; om: oromotor function; c: communication function; ar: arousal level.