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Do you see me? The role of visual fixation in chronic disorders of consciousness differential diagnosis

Antonino Naro, Antonino Leo, Antonio Buda, Alfredo Manuli, Alessia Bramanti, Placido Bramanti, Rocco Salvatore Calabrò*

IRCCS Centro Neurolesi "Bonino-Pulejo" Messina, Italy

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ABSTRACT

Visual fixation (VF) of a target is a possible, although atypical, feature of the Unresponsive Wakefulness Syndrome (UWS). Whether VF may indicate residual awareness in these patients is debatable, since it may simply subtend a series of reflex processes. Objective tools should therefore be used to identify aware VF, which depends on the integrity of visuomotor networks encompassing frontal-parietal-occipital areas. The aim of our study was to detect residual visuomotor network functionality potentially sustaining aware VF. To this end, we evaluated the visuomotor integration (VMI) and visual P300 patterns in a chronic Disorder of Consciousness (DOC) sample and a control group of healthy individuals (HC), using an associative stimulation protocol combining transcranial magnetic stimulation (TMS) with visual stimulation through transorbital alternating current stimulation. The Minimally Conscious State (MCS) patients showed preserved patterns of VMI and P300, whereas nearly all the UWS patients showed no significant VMI. Notably, the electrophysiological findings were correlated with the visual domain of the Coma Recovery Scale-Revised. Nonetheless, two fixating UWS individuals had a VMI similar to MCS patients. Our data suggest that some UWS patients showing VF could be aware, but unable to manifest it clearly, probably because of a severe motor output impairment, which is a condition compatible with the Functional Locked-In Syndrome.

1. Introduction

The JFK Coma Recovery Scale-Revised (CRS-R) is considered the gold standard for the behavioral assessment and differential diagnosis of patients with chronic Disorder of Consciousness (DOC) (Cortese et al., 2015; Bodien et al., 2016), including the Unresponsive Wakefulness Syndrome (UWS), previously known as Vegetative State (VS), and the Minimally Conscious State (MCS) (Laureys et al., 2010; Giacino et al., 2002; Royal College of Physicians, 2003,2013). Patients with UWS/VS are characterized by a complete unawareness of the self and the environment, thus showing no evidence of sustained, reproducible, purposeful, and voluntary behavioral responses to many extrinsic stimuli and of language comprehension or expression. In addition, there is a preservation, at least partial, of the sleep-wake cycle, cranial-nerve and spinal reflexes, and hypothalamic and brainstem autonomic functions (The Multi-Society Task Force on PVS on PVS, 1994). On the contrary, patients in MCS show inconsistent but clearly discernible behavioral evidence of consciousness and can be distinguished from UWS by documenting the presence of specific behavioral features (Giacino et al., 2002).

CRS-R is based on six sub-items, including visual functions. Visual fixation (VF), i.e., the ability to fix on a target for at least 2 s in two of four trials, is considered an aware behavior, belonging to the MCS category (Giacino et al., 2002; Giacino and Kalmar, 2005). Nonetheless, VF can sometimes be observed in UWS subjects (~20–30%) (Laureys et al., 2010; Royal College of Physicians, 2013; The Multi-Society Task Force on PVS on PVS, 1994). Indeed, the response to the VF test may depend on the stimuli employed. In fact, it has been shown that some patients fix their gaze when using a mirror, but not when employing the other stimuli commonly used in clinical scales, including the CRS-R (Di et al., 2014; Thonnard et al., 2014; Vanhaudenhuyse et al., 2008). In addition, DOC patients may have hidden brainstem lesions or ocular trauma affecting ocular movements, thus challenging VF assessment. Finally, ocular movement ability can show a significant within- and between-day variability (Candelieri et al., 2011). However, it has been proposed that VF in UWS subjects would be entirely a reflex mediated by brainstem structures and automatic subcortical processes; instead, aware VF needs the functional preservation of a broad visuomotor frontal-parietooccipital network (FPON) (Bruno et al., 2010; Monti et al., 2010, 2013; Owen

* Correspondence to: IRCCS Centro Neurolesi "Bonino-Pulejo" Messina, S.S. 113, Contrada Casazza, 98124 Messina, Italy.
E-mail address: salbro77@tiscali.it (R.S. Calabrò).

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Table 1
Shows the clinical and demographic characteristics of DOC patients. We reported the individual CRS-R ± standard deviation (SD). The CRS-R was daily administered for 30 consecutive days before the protocol enrollment. Mean (M) ± SD values and t-tests are reported as well (in italic).

DOC	gender	etiology	age	BI	MRI	CRS-R						
						total	A	V	M	OM	C	Ar
MCS (n=7)	F	A	72	6	WMH	18 ± 3	4 ± 1.4	4 ± 6	5 ± 1.9	1 ± 1.8	1	3 ± 1.3
	M	T	51	13	WMH^{R}BG_h	15 ± 1	3 ± 1.5	3 ± 9	4 ± 1.7	1 ± 1.2	1	3 ± .8
	F	A	66	9	WMH	12 ± 3	1 ± .9	3 ± 1.2	2 ± .8	2 ± .7	1	3 ± .9
	F	T	70	12	^{L}Fb_h	16 ± 3	3 ± 1.6	3 ± 7	5 ± .5	1 ± .6	1	3 ± 1.9
	M	T	33	8	multiple h	13 ± 1	2 ± 1	3 ± .5	2 ± .7	2 ± 1.2	1	3 ± 1.4
	F	A	41	15	WMH	11 ± 4	2 ± .5	2 ± .5	1 ± .6	2 ± .3	1	3 ± 1.9
	M	T	35	12	WMH^{R}BG_h	10 ± 3	1 ± 1.8	2 ± .3	1 ± 1.7	2 ± 1.8	1	3 ± .1
M ± SD			*53 ± 17*	*11 ± 3*		*14 ± 3*	*2 ± 1*	*3 ± 1*	*3 ± 2*	*2 ± 1*	*1*	*3*
UWS (n=7)	M	A	53	8	WMH	4 ± 2	1 ± 1.1	.4 ± .2	1 ± 1.1	1 ± .6	0	1 ± 1.5
	F	T	26	5	DAI SAH	5 ± 1	1 ± .7	1 ± 1.4	.5 ± .7	.6 ± .4	0	2 ± .6
	F	T	66	8	^{R}FP_h	7 ± 2	.6 ± .3	2 ± 1.5	1 ± 1.4	1 ± 1.4	0	2 ± 2
	F	A	62	11	WMH	6 ± 2	1 ± 1.3	2 ± .6	1 ± 1.2	.4 ± .2	0	2 ± .4
	M	T	61	9	SAH	3 ± 1	.5 ± 1	1 ± .2	.4 ± .2	.5 ± .4	0	1 ± 1.6
	M	A	69	11	WMH	7 ± 2	1 ± .1	2 ± .7	1 ± .7	1 ± 1.1	0	2 ± .9
	F	T	74	12	DAI SAH	3 ± 3	.2 ± .4	1 ± .8	.2 ± .4	.3 ± .2	0	1 ± 1.4
M ± SD			*59 ± 14*	*9 ± 3*		*5 ± 2*	*1 ± .3*	*1 ± 1*	*1 ± .03*	*1 ± .3*	*0*	*2 ± 1*
t-test			*.5*	*.3*		*< .001*	*.007*	*< .001*	*.002*	*.004*		*< .001*

Etiology (A, post-anoxic; T, post-traumatic brain injury); BI: brain injury onset in months; age in years; MRI: structural patterns, including WMH (white matter hyperintensity), h (hemorrhagic lesion), ^{R}FP (right fronto-polar), ^{R}BG (basal ganglia), ^{L}Fb (left fronto-basal), SAH (subarachnoid hemorrhage), DAI (diffuse axonal injury); CRS-R: Coma Recovery Scale-Revised, including auditory (A), visual (V), motor (M), oro-motor (OM), communication domain (C), and arousal induction (Ar).

et al., 2006). In fact, UWS patients with or without VF show an extended metabolic dysfunction and a functional connectivity breakdown within such FPON, thus suggesting that VF does not necessarily reflect awareness (Bruno et al., 2010).

Hence, the association between awareness and VF seems debatable (Bruno et al., 2010; Monti et al., 2010, 2013; Owen et al., 2006). The presence of aware VF in DOC individuals needs to be carefully assessed since sustained VF and purposeful ocular movements predict rather accurately a favorable outcome (Riganello et al., 2013; Bagnato et al., 2016). To this end, objective tools should be used to demonstrate aware VF (Bosco et al., 2010). Using a coupled visual (toACS) and transcranial magnetic stimulation (TMS) (delivered over the primary motor area -M1) in a DOC sample, we previously investigated primary visuomotor integration (VMI^I). The latter reflects basic sensory-motor integration processes sustained by primary visual and M1 areas (Naro et al., 2015), and a transient cortical deafferentation, i.e., a motor evoked potential (MEP) amplitude decrease, allowing the elicitation of subcortical defensive reflex responses (in analogy to other sensory-motor integration processes) (Tinazzi et al., 1997). We found that some UWS individuals showing VF had a preserved VMI^I, which was similar to MCS patients, who showed more complex visuomotor behaviors (Naro et al., 2015). Therefore, some UWS individuals could have a covert awareness but can show no more than reflex VF. This condition is known as Functional Locked-In Syndrome (FLIS), in which patients have a preserved awareness but are unable to communicate, owing to a severe or complete motor output impairment (Formisano et al., 2011a, 2011b, 2013; Bruno et al., 2011, 2013).

Even though the VMI^I is essential for visuomotor behavior (Iacoboni, 2006), it does not necessarily indicate visual awareness per se. In fact, visual awareness relies on the preserved connectivity of large-scale visuomotor FPON (Sergent and Dehaene, 2004). This can be studied through event-related potentials, including the P300, which is a component of the information processing hierarchy up to conscious perception. Unlike earlier potentials, P300 is supposed to be an endogenous component that reflects the stimulus context and levels of attention and arousal (Bekinschtein and Manes, 2008; Faugeras et al., 2011; Rohaut et al., 2015). In addition, the connectivity of large-scale FPON can be studied through more complex VMI paradigms involving secondary sensory-motor areas, i.e., the secondary VMI (VMI^{II}). To this end, TMS stimuli over M1 can be paired to a visual oddball paradigm; this protocol would not modify MEP amplitude but it may perturb the P300 γ-power within parietooccipital, temporal, and prefrontal areas (Jing et al., 2001; Sokhadze et al., 2010). In particular, the narrowband γ-power (35–50 Hz) changes within those areas may be a marker of multiple cognitive processes related to visual information processing and proper behavioral output generation (Machado et al., 2014), given that narrowband γ-power changes: (i) occur only in response to specific stimulus features; (ii) occur within temporal and prefrontal areas when visual awareness is required (Panagiotaropoulos et al., 2012);.(iii) have a pure cognitive causality (Herrmann et al., 2004);.and (iv) represent a more accurate functional measure than the γ-power per se, given that the latter is affected by individual variations in non-physiological variables, including the convolution of cortical tissue generating an electromagnetic signal or degree of electroencephalographic (EEG) signal contamination by muscle activity (Whitham et al., 2007; Shaw et al., 2013).

The aim of our study was to verify the preservation of FPON sustaining aware VF in DOC patients by studying more complex visuomotor processes. To this end, we employed an electrophysiological approach combining TMS with visual stimulation delivered by toACS in a simple and oddball paradigm.

2. Results

There were no differences between the two DOC samples concerning disease etiology and demographic characteristics, whereas CRS-R scores were significantly different. In this regard, a score of two at visual CRS-R (i.e., VF) was achieved by two MCS (n.6 and 7) and three UWS patients (n. 3, 4, and 6), who otherwise showed all the remaining clinical features of UWS (Table 1).

We did not observe any adverse effects in patients and HC, either during or after the entire experimental procedure. The HC subjects reported a sensation of intermittent small flashing spots during the toACS procedure. During the oddball paradigm, the HC subjects reported that the small flashing spot sometimes slid up, down, or laterally; this occurred accordingly to the pair of stimulating electrodes and corresponded to the target stimulus (Fig. 1).

In the HC sample, toACS induced a clear positive deflection at MO electrode peaking at ~120 ms, with an amplitude of ~15μV. Such wave was present but delayed in latency and smaller in amplitude in DOC individuals (more in UWS than MCS subjects) (Fig. 2).

In the HC sample, the oddball paradigm induced a clear P300 (from