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OUTCOME PREDICTION OF CONSCIOUSNESS DISORDERS AND AWARENESS DETECTION IN THE ACUTE STAGE BASED ON BEHAVIOURAL RESPONSES OF EXISTING COMA SCALES

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1. Abstract

In patients with disorder of consciousness (DOC), awareness preservation is related to a better outcome prognosis (34). The dissociation of identified signs of awareness by laboratory assessment while undetected by bedside behavioural examination, is defined as cognitive motor dissociation (CMD) (1, 22-27). The rate of misdiagnosis is about 30% (18-21). Current researches emphasize enlarged bedside evaluation as it is easily administered and more economical (26). The Motor Behavioural Tool (MBT) had provided accurate insight into the content of consciousness, and had improved significantly the correlation with the outcome prediction during the acute stage, while the CRS-R sub-scores per se did not (1). We propose to further the exploration of supplementary motor behavioural signs by studying the predictability of the emergence defined by the CRS-R as well as the ability to detect CMD of the clinical items of three existing scales: The FOUR, the GCS and the NCS.

We enrolled 35 patients with first CRS-R, MBT and the 3 aforementioned scales evaluation performed within 28 days post-injury. One evaluation of each scale was selected for every patient. The FOUR has 4 items, the GCS 3, and the NCS 4, that means 11 items, all rated with a sub-score which were the analysed variables.

A first class of 8 group and 4 comparisons were made depending on the first and last CRS-R assessment, the latter defining the emergence: DOC patient emerging (1a) vs not emerged (1b), UWS (1c) and MCS (1e) emerging vs not emerged (1d) and (1f), and patients showing no CRS-R change (1g) vs those showing upper class of CRS-R (1h).
A second class of 5 groups with 3 comparisons were made according to the MBT assessment at the admission and the last CRS-R evaluation : CMD patients (2a) vs true DOC (2b) at the entry in the unit, true DOC with DOC at last CRS-R (2c) vs CMD with emergence at last CRS-R (2e), and CMD with DOC at last CRS-R (2d) vs CMD with emergence at last CRS-R (2e).
The statistical testing was based on a non-parametric Mann-Whitney U test to see whether there is a difference of sub-scores when comparing two groups for the same item.

The p-value was > 0.05 for all comparisons; in other word, none item enables to predict the outcome defined by the last CRS-S classification or to make the CMD diagnosis according to the MBT.
Moreover, 26% of CMD patients were classified as DOC on the last CRS-R which can be related to the rate of misdiagnosis found in the literature.
Those findings address explicitly the issue of how performing the clinical evaluation to overcome this underestimation of the degree and level of consciousness, and how essential it is to develop and render more accurate the bedside evaluation of awareness.

Keywords: Disorders of consciousness, cognitive motor dissociation, awareness, behavioural examination

2. Introduction

2.1 Background and knowledge

Consciousness is a complex entity which was extensively discussed over time and across scientific fields. This concept is practically approached in the clinical neurosciences, which proposes the nosology of disorders of consciousness (DOC). Such nosological classification is fundamental, since DOC occur in nearly 20% of the patients (1,2) who underwent a brain injury whether traumatic or not (strokes, anoxia, infections, poisoning, drug overdoses, etc.) (3).

Consciousness should be understood from two dimensions: wakefulness (level of consciousness) and awareness (content of consciousness). Wakefulness is manifested in the eye-opening, depending on sleep-wake cycle and is sustained by the brain stem and the thalami (4). Awareness includes the ability to perceive, think, remind, feel emotions and to have intentions and wills in relation to the environment and the self (5). Clinically, intentional behaviour and non-reflex movements such as command following and oriented response to noxious stimulation allows to deduce the presence of awareness. It is related to the inner connectivity within a network containing the associative cortices in the frontoparietal area and to the connectivity between this network and the thalami (6,7). In general, wakefulness is the indispensable condition to be aware, while awareness isn't essential to be awake (4).

Awareness preservation is related to a better outcome prognosis. That is why, a classification of different states according to the presence or absence of awareness has been established. The following described states are not diagnosis but they allow to presume the outcome prognosis and therefore, to consider an adequate therapeutic management (34). Coma is the most severe level of consciousness impairment, as the patients cannot be awoken, keep persistently their eyes closed, and must be intubated because of the diminution of the vegetative functions. Only reflex motor responses are discernible (4). The unresponsive wakefulness syndrome (UWS) is characterized by, under stimulation, or, spontaneously, opening the eyes and regaining the autonomous nervous system activity. However, they still only show reflex movements without following given tasks (8). The minimally conscious state (MCS), occurs when the first indications of awareness, such as a coherent verbal and emotional response or the objects manipulation, are noticeable at the bed side, despite being unable to communicate properly (9). The presence or absence of command following led to specify the subcategories of MCS+ and MCS- respectively (10,11). Finally, the emergence from disorder of consciousness is defined by a functional communication and employment of object (9).

Assessing the level and the contain of consciousness in patients with brain injury (BI) is crucial in the acute phase to render an accurate prognosis and, in turn, an appropriate care decision. The main way to assess these levels of consciousness so far is the behavioural evaluation at the bedside with different tools encompassing

several clinical signs revealing or not awareness, as it is easily administered and economical. These tools are used to classify the severity of awareness impairment, which is correlated with the outcome prognosis (34).

The Coma recovery scale revised (CRS-R) allows to discriminate between MCS and UWS, but also defines the emergence of disorder of consciousness by criterions which showed a better home return (34). It includes six items, each rated with a sub-score, according to the complexity of the clinical signs the patient manifests. The possible numerical values for the item's sub-scores are ordered from the least elaborate behaviour, such as the reflexes, to the one with the highest level of complexity, which require awareness. This takes between 10 and 60 minutes to apply and is the gold standard to evaluate severely brain injured patients (4,12). The Glasgow Coma Scale (GCS) is a quickly-done evaluation scale applied internationally mostly in the acute stage to assess the severity of the brain damage using eye, verbal and motor behaviours. Yet, if the patient is intubated or tracheostomised, the verbal response is unassessable. The total score varies between 3 and 15 (4). The Full Outline of UnResponsiveness (FOUR) scale has also been devised to assess severely brain-injured patient in intensive care, and It includes four subscales evaluating motor, ocular responses, brainstem reflexes and breathing, and, as it doesn't comprise a verbal subscale, it can be used in the case of tracheostomy or intubation. This scale is appropriate to distinguish UWS from MCS as it assesses the visual pursuit and also allows to diagnose the locked-in syndrome and brain death. (4,13,14). The nociception coma scale has been created to assess pain in noncommunicative patient, to adapt the analgesic treatment. It consists in four items (motor response, verbal response, facial expression and visual response to nociceptive stimuli) sub-scoring from 1 to 3 (15).

However, the detection of awareness is often difficult as it can be easily missed due to ambiguous and rapidly exhausted response or the rater's lack of experience but also to several pitfalls which conceal awareness that would otherwise be assessable at the bedside, such as motor deficit, impaired cognition, sensory impairment, etc. (4, 6, 7 13). Nowadays, imagery and electrophysiological biomarkers provide a new evidence of covert consciousness which is objectified by a modulation of the brain activity visible on the functional magnetic resonance and on the electroencephalogram when task instruction are given (16,17). Until now, the rate of aware patients among the ones who are classified as unaware is estimated at more than one third compared to a diagnosis made with one of these laboratory assessments or a more accurate behavioural evaluation (18-21).

The dissociation of identified signs of consciousness by laboratory assessment while undetected by bedside behavioural examination, is defined as cognitive motor dissociation (CMD) (1, 22-27). However, intensive care unit's environment imposes strong constraints that may restrict functional neuroimagery and electroencephalographic recording, and those laboratory investigations do not deliver strong sensitivity (26). Therefore, current researches emphasize enlarged bedside evaluation. In this scope, the Motor Behavioural Tool was designed to identify subtle

and non-reflexive motor behaviour; in complement to the CRS-R, it had provided accurate insight into the amount and the content of consciousness, and had improved significantly the correlation with the outcome prediction during the acute stage, while the CRS-R sub-scores per se did not. It encompasses positive motor signs, that the CRS-R may neglect, pitfalls such as medical conditions hiding awareness and negative signs including pyramidal signs inconsistent with preserved awareness as it conveys that, if the brain stem is intact, there is a bilateral lesion of the pyramidal tract, which means a severe disconnection between the cortex and the subcortical region. The principle is to increment the score of the CRS-R when quoted as a reflex behaviour. We also found that each subitems of first CRS-R wasn't predictive of the emergence according to the last CRS-R, but making CRS-R over time was only predictive after 19-22 days (1). Recently, the MBT was revised (MBT-r) to allow specifically the early detection of CMD patients (28).

2.2 Purpose of the study

We propose to further the exploration of supplementary motor behavioural signs by studying the predictability of the emergence defined by the CRS-R as well as the ability to detect CMD according to the MBT of the clinical items of three existing scales gradating the severity of brain injury in the acute phase: The Nociceptive Coma Scale (NCS) (15), the FOUR score (14) and the Glascow Coma Scale (GCS) (29). NCS was developed to manage pain in non-communicative patients with DOC (30), while FOUR and GCS provide a classification of the severity of awareness impairment with the aim of associating it with an outcome prognosis (31). By assessing the predictability of the emergence according to the CRS-R of each item and their ability to detect CMD depending on their MBT diagnosis, we might extend the number of clinical signs that could demonstrate awareness and be added to the evaluation of the outcome in the acute phase. This could lessen the rate of misdiagnosis and help the therapeutic management during the acute stage.

3. Methodology

3.1 Patient Demography

We enrolled 35 patients out of 88 who were admitted to our Unit of Acute Neuro-Rehabilitation (Department of Clinical Neurosciences at the University Hospital of Lausanne, Switzerland) between October 2011 and December 2017 for acute neuro-rehabilitation and whose data were collected by two members of the research team, including a physician, a neuropsychologist, and a nurse. They conducted the CRS-R, NCS, FOUR, GCS and MBT assessments using video recordings. Discrepant sub-scores within evaluators have been removed. We gathered all their assessments

over time as well as general patient information: sex, age, localization of brain lesions from routine neuro-imaging, brain damage etiology, delay between occurrence of brain lesion and the first CRS-R/MBT assessment, as between occurrence of brain lesion and the last CRS-R score.

3.2 Ethical approval

The local Lausanne Ethics Committee approved this study and the legal surrogates of all of the participants provided written informed consent.

3.3 Inclusion and exclusion criteria

Inclusion criteria

a) an initial diagnosis of disorder of consciousness (DOC), including Unresponsive Wakefulness Syndrome (UWS) or Minimally Conscious State, according to CRS-R criteria, within 28 days of BI – a short cut-off time was applied to exclude patients with prolonged DOC for whom recovery probability is low skewing the outcome assessment (32).

b) an outcome diagnosis of UWS, MCS+, MCS- or emergence, according to CRS-R criteria (33), at least 31 days after BI (unless the patient emerged before 31 days).

c) a clinical assessment using the MBT evaluation at time of the DOC diagnosis.

d) a clinical assessment using the NCS, the FOUR and the GCS (holding respectively four, four and three sub-scores) at time of the DOC diagnosis within 28 days post-injury.

e) a standardised intensive programme of rehabilitation, including physical, occupational, neuropsychological and speech therapies, at least 3 hours per day.

Exclusion criteria

a) a current neuromuscular function blockers or sedation.

b) a premorbid history of developmental, psychiatric or neurological illness at the time of BI.

c) persistent acute illness or progressive systemic or neurological disease.

d) missing data.

e) data not fitting within the 28 days post injury.

f) a last CRS-R assessed as DOC before 31 days post-injury.

3.4 Study design

We selected, for every patient, the earliest evaluation of NCS, FOUR and GCS after the Brain injury, so that we had one evaluation of the three scales for all of them. That

means 11 items, each rated with one sub-score (see figure 1 for the possible values according to the clinical sign), per patient.

Figure 1: The Full Outline of UnResponsiveness (FOUR), the Glasgow Coma Scale (GCS) and the Nociception Coma Scale with theirs items and sub-scores describing the behavioural signs.

Scale/ Score	Item/ subscale	Behavioural sign	Sub-score
FOUR	Eye Response	Opens spontaneously and tracks to command	4
		Opens to command, doesn't track	3
		Opens to loud voice	2
		Opens to painful stimulation	1
		Eyes closed following painful stimulation	0
	Motor Response	Obeys, make sign to command	4
		Localises painful stimulus	3
		Flexes to painful stimulus	2
		Extends to painful stimulus	1
		None or myoclonic status epilepticus	0
	Intubation	Not intubated, normal respirations	4
		Not intubated, Cheyne-Stoke respirations	3
		Not intubated irregular respirations	2
		Intubated, breathes above ventilator settings	1
		Intubated, breathes below ventilator settings, or apnoeic	0
	Brain stem reflexes	Pupils +, corneals+, cough+	4
		1 pupil unreactive, corneals +, cough+	3
		Pupillary or corneals absent	2
		Pupils -, corneals -, cough+	1
		Pupils-, corneals-, cough-	0
	Total		16

Scale/ Score	Item/ subscale	Behavioural sign	Sub-score
GCS	Eye opening response	Spontaneously	4
		Opens on command	3
		On painful stimulation	2
		No response	1
	Motor response	Obeys commands	6
		Localises pain	5
		Flex to withdraw from pain	4
		Abnormal flexion (decorticate)	3
		Abnormal extension (decerebrate)	2
		No response	1
	Verbal response	Oriented to time person and place	5
		Confused	4
		Inappropriate words	3
		Incomprehensible sounds	2
		No response	1
	Total		15

Scale/ Score	Item/ subscale	Behavioural sign	Sub-score
NCS	Visual response	Fixation	3
		Eye movements	2
		Startle	1
		None	0
	Motor response	Localization to noxious stimulation	3
		Flexion withdrawal	2
		Abnormal posturing	1
		None/flaccid	0
	Verbal response	Intelligible verbalization	3
		Vocalization	2
		Groaning	1
		None	0
	Facial expression	Cry	3
		Grimace	2
		Oral reflexive movements/ startle	1
		None	0
	Total		12

Glasgow Coma Scale (GCS, Teasdale and Jennett 1974)
Full Outline of UnResponsiveness (FOUR, Wijdicks and Bamlet, 2005)
Nociception Coma Scale (NCS, Schnakers and al. 2010)

A two-stage classification procedure was designed to define the various sample classes as proposed, in part, by the study of Pignat & all (1).

First, initial and outcome classification based on the first and last CRS-R, were used to define two primary outcome classes and six outcome subclasses, according to the consistency of sample size provided by patient demography (see Results):

1a) DOC patients (encompassing UWS, MCS- and MCS+) recovering consciousness, labelled “emerged/OUT” at the last CRS-R

1b) DOC patients remaining in DOC (encompassing UWS, MCS- and MCS+) at the last CRS-R.

1c) UWS patients emerging

1d) UWS patients remaining with DOC

1e) MCS (joined MCS- and MCS+) patients emerging

1f) MCS remaining in DOC

1g) DOC patients without recovery (UWS, MCS- and MCS+ patients remaining in UWS, MCS- and MCS+, respectively)

1h) DOC patients showing part (e.g. upper change of state) or complete recovery by CRS-R classification improvement.

Emergence was defined by a score of 2 in communication or of 6 in motor response according to the last CRS-R. MCS was defined if one of the items of the CRS-R had one of the following sub-score: At least 3 in audition, 2 in visual, 3 in motor, 3 in verbal response or 1 in communication.

Second, MBT was used in the acute phase to identify CMD patients among the ones who were initially classified as DOC according to the CRS-R. The second classification was therefore made depending on the MBT diagnosis at the time of entry in the unit, and the last CRS-R evaluation, providing 2 primary diagnosis classes and 4 outcome subclasses according to the consistency of sample size provided by patient demography (see Results):

2a) CMD patients

2b) true DOC patients (UWS, MCS- and MCS+).

2c) true DOC patients with a DOC classification according to the last CRS-R (UWS, MCS- and MCS+)

2d) CMD patients with a DOC classification at the last CRS-R assessment

2e) CMD patients with a last CRS-R classification of emergence

2f) true DOC patients with a last CRS-R classification of emergence.

For the true DOC patients, the classification of UWS, MCS- and MCS+ was kept in accordance with the first CRS-R

Considering the MBT property of outcome predictability defined by the CRS-R classification of emergence, subclasses 2c, 2d, 2e and 2f represent the number of true negatives, false positives, true positives and false negatives.

3.5 Statistical analysis

The variables for the statistical analysis were the item's sub-scores (see table 1 for the different possible values), which were inferred across all possible combinations. More formally, all sub-scores were pooled and we determined all possible k-combinations of progressive sub-scores subsets (k going from 1 to 11, 11 being the number of all item's sub-score provided by NCS, FOUR et GCS) on which we performed the statistical prediction of patients' outcome and ability to detect CMD by comparing all classes and subclasses. The aim is to see whether there is a difference of sub-scores when comparing two groups for the same item. For the classification based on the CRS-R, the following classes and subclasses were compared: classes 1a and 1b, 1c and 1d, 1e and 1f, 1g and 1h; for the classification based on MBT, 2a and 2b, 2d and 2e classes were compared; we performed an additional comparison between emerging CMD patients (2e) and true DOC patients remaining with DOC at the last CRS-R (2c). No comparison was made with the class 2f because only 1 false negative was found.

Figure 2: Comparisons and groups according to CRS-R evaluation

Comparisons and groups according to CRS-R evaluation						
Class	**First CRS**	**Last CRS**		**Class**	**First CRS**	**Last CRS**
1a	DOC	OUT	compared with	1b	DOC	DOC
1c	UWS	OUT	compared with	1d	UWS	DOC
1e	MCS	OUT	compared with	1f	MCS	DOC
1g	UWS	UWS	compared with	1h	UWS	MCS-
	MCS-	MCS-			UWS	MCS+
	MCS+	MCS+			MCS-	MCS+
					UWS	OUT
					MCS-	OUT
					MCS+	OUT

Figure 3: Comparisons and groups according to MBT diagnosis and last CRS-R assessment

Comparisons and groups according to MBT diagnosis and last CRS assessment						
Class	**MBT diagnosis**	**Last CRS**		**Class**	**MBT diagnosis**	**Last CRS**
2a	CMD		compared with	2b	true DOC	
2c	true DOC	DOC	compared with	2e	CMD	OUT
2d	CMD	DOC	compared with	2e	CMD	OUT

The statistical testing was based on a non-parametric Mann-Whitney U test because of the multinomial distribution of each sub-score which are categorical ordinal variables. P-values were corrected for multiple comparison with the Holm-Bonferroni method. Besides, we measured the sensitivity and the specificity of MBT with regard to the outcome predictability defined by the emergence according to the CRS-R.

4. Results

4.1 Patient's demographic

Among the 35 enrolled patients, 13 (37%) were females and 22 (63%) were males. The average age was 51 years old. 16 (45%) had a non-traumatic brain injury (mainly intraparenchymal or subarachnoid haemorrhage on hypertensive crisis, aneurysm rupture and anticoagulation, and post-anoxic encephalopathy) with an average age of 57 years old and 19 (58%) had a traumatic brain injury with an average age of 46 years old. Globally, 21 patients (60%) recovered consciousness according to the CRS-R (class 1a) and 14 patients (40%) remained with DOC (class 1b). The shortest and longest time of following to state the outcome of emergence were 23 and 71 days respectively, as well as 31 and 79 respectively to classify DOC patients.

Table 1: details information about individual patient demographics for patient with an outcome of emergence according to the last CRS-R (class 1a).

Patient n°	age	Sex	date of injury	injury localisation	Aetiology	limit date	1st CRS	last CRS	Lesion vs CRS 1	Lesion vs CRS 2	initial CRS-R	initial MBT	outcome CRS-R
1	76	F	17.01.12	rT,rP,rO	IPH on hypertensive crisis	14.02.12	01.02.12	27.03.12	15	70	UWS	CMD	OUT
2	52	M	03.06.12	rT,lT,lP, rF	TBI with IPH	01.07.12	12.06.12	28.06.12	9	25	MCS-	CMD	OUT
3	69	M	13.11.12	rP,rT, rF, lF, lP	TBI with right SDH, bifrontal IPH and SAH of left precentral sulcus	11.12.12	20.11.12	09.12.12	7	26	MCS-	CMD	OUT
4	24	M	10.03.13	rT,lT,rP,lP	TBI with bilateral temporoparietal SAH and right temporal IPH.	07.04.13	14.03.13	05.04.13	4	26	MCS-	CMD	OUT
5	73	M	20.05.13	ventricles, DAI	anticoagulation induced tetraventricular hemorrhage and hydrocephalus	17.06.13	27.05.13	15.07.13	7	56	UWS	CMD	OUT
6	66	F	23.06.13	rC, rF, lF	TBI with right cerebellar and bifrontal IPH, bifrontal SAH and SDH, cerebellar tentotium SDH, 4th ventricle hemorrhage, right transverse sinus thrombosis	21.07.13	25.06.13	16.07.13	2	23	UWS	CMD	OUT
7	66	M	16.11.13	lF,lO,rO,lP, rT, lT	TBI with left frontal and cerebellar tentorium SDH, parietal SAH, bitemporal IPH	14.12.13	25.11.13	11.12.13	9	25	MCS+	CMD	OUT
8	59	M	20.12.13	lF,rF, lP	TBI with bifrontal IPH and left convexity SDH	17.01.14	31.12.13	20.01.14	11	31	UWS	CMD	OUT
9	63	M	13.02.14	lP	right sylvian SAH	13.03.14	03.03.14	25.04.14	18	71	UWS	CMD	OUT
10	65	M	13.04.14	lthal, rF,rP, lF,lP	IPH on hypertensive crisis	11.05.14	14.04.14	05.06.14	1	53	MCS+	CMD	OUT
11	41	M	26.04.14	lBG	TBI with left lenticular hematoma	24.05.14	12.05.14	05.06.14	16	40	UWS	CMD	OUT
12	46	M	06.12.14	rP, rT, rF, lF	TBI with right convexity SDH, right temporal and bifrontal IPH	03.01.15	24.12.14	28.01.15	18	53	UWS	CMD	OUT
13	65	F	31.01.15	rF,rP,rT,lF,lP	TBI with right frontal SDH, falx cerebri SAH, bifrontal and right temporal IPH	28.02.15	04.02.15	23.03.15	4	51	UWS	CMD	OUT
14	20	M	06.02.15	DAI, rT, licap, ventricles	TBI with SAH, bilateral ventricle hemorrhage and IPH	06.03.15	11.02.15	03.03.15	5	25	UWS	CMD	OUT
15	39	F	13.02.15	rThal, ricap	hemorragic stroke in the context of Moya-Moya disease	13.03.15	16.02.15	02.04.15	3	48	UWS	Coma	OUT
16	71	M	05.03.15	rBG, lBG	Post anoxic encephalopathy after CO intoxication	02.04.15	17.03.15	13.05.15	12	69	MCS-	CMD	OUT
17	43	M	11.12.15	lF, lP, lT, rmes	TBI with IPH, SDH and SAH	08.01.16	21.12.15	01.02.16	10	52	UWS	CMD	OUT
18	56	M	04.06.16	rT,rP, rF, lT, lP, lmes	TBI with IPH	02.07.16	27.06.16	05.07.16	23	31	MCS-	CMD	OUT
19	43	M	10.06.16	lF, lT, rmes, lthal	SAH on aneurysm rupture	08.07.16	30.06.16	21.07.16	20	41	UWS	CMD	OUT
20	73	F	08.12.17	rT, rP, rF	hypertensive SAH	05.01.18	13.12.17	30.01.18	5	53	UWS	CMD	OUT
21	59	M	30.10.17	lF	SAH on aneurysm rupture	27.11.17	07.11.17	21.12.17	8	52	UWS	CMD	OUT

Table 2: details information about individual patient demographics for patient with an outcome of DOC according to the last CRS-R (class 1b).

Patient n°	age	Sex	date of injury	injury localisation	Aetiology	limit date	1st CRS	last CRS	Lesion vs CRS 1	Lesion vs CRS 2	initial CRS-R	initial MBT	outcome CRS-R
22	50	M	04.02.12	lF	TBI with SDH, IPH and SAH	03.03.12	09.02.12	16.03.12	5	41	MCS-	CMD	MCS-
23	36	M	14.07.13	DAI, rBG, lBG	Post-anoxic encephalopathy	11.08.13	22.07.13	17.09.13	8	65	UWS	Coma	UWS
24	35	F	27.07.13	bF,bP,bT, DAI, pons	TBI with IPH and SDH	24.08.13	14.08.13	30.09.13	18	65	UWS	UWS	UWS
25	27	F	04.12.13	thal, mes, hydrocéphalie	hemorrhage on cavernoma and intra-opérative bithalamic ischemic stroke.	01.01.14	09.12.13	21.01.14	5	48	UWS	CMD	MCS-
26	22	F	17.01.14	lF, lP, lT, rP, rT	TBI with left frontoparietal SDH, left parietotemporal and right parietal SAH, right temporal IPH	14.02.14	28.01.14	17.02.14	11	31	UWS	Coma	UWS
27	53	F	03.02.14	rP	SAH on aneurysm rupture	03.03.14	11.02.14	08.04.14	8	64	UWS	UWS	UWS
28	42	M	24.05.14	lBG	intraparenchymatous hemorrhagic stroke	21.06.14	10.06.14	07.07.14	17	44	MCS-	CMD	MCS+
29	45	M	18.07.14	rP, lP	TBI with left SAH and right SDH	15.08.14	29.07.14	26.08.14	11	39	UWS	CMD	MCS-
30	37	F	19.11.14	rT,rO, rP, thal, pons	TBI with IPH and left carotid dissection	17.12.14	27.11.14	06.02.15	8	79	UWS	Coma	MCS-
31	24	M	07.08.15	rF,rT,lT,lP,lF, DAI	TBI with IPH and bifrontal SDH	04.09.15	27.08.15	12.10.15	20	66	UWS	CMD	MCS+
32	60	F	16.01.16	lF,lT,lP	SAH on aneurysm rupture and IPH	13.02.16	26.01.16	29.02.16	10	44	UWS	CMD	MCS-
33	53	F	19.04.16	mes,pons, DAI, lO,rO,lP, lT, rP	TBI with IPH and SAH	17.05.16	29.04.16	10.06.16	10	52	UWS	Coma	UWS
34	78	F	13.10.16	rP,rF	SAH on aneurysm rupture	10.11.16	19.10.16	28.11.16	6	46	MCS+	CMD	MCS+
35	58	M	23.11.17	lP,rP,lO,rO	post anoxic encephalopathy on STEMI	21.12.17	13.12.17	05.01.18	20	43	UWS	UWS	MCS-

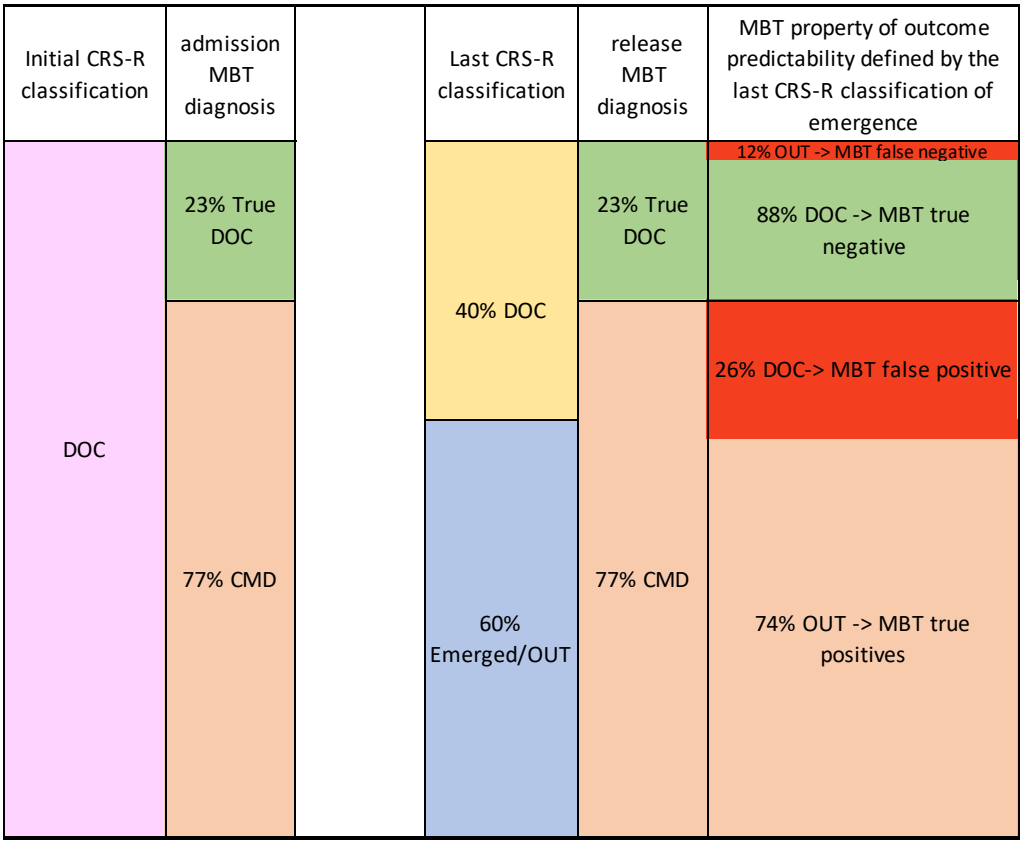
Legend for table 1 and 2:

TBI : Traumatic Brain Injury, IPH : Intraparenchymal hemorrhage, SDH: subdural hematoma, SAH : subarachnoid hemorrhage, rT/lT/bT : right/left/bitemporal, rP/lP/bP: right/left/biparietal, rF/lF/bF: right/left/bifrontal, rO/lO/bO: right/left/bioccipital, rC/lC: right/left carotid, DAI: diffuse axonal injury, rthal/lthal/bthal: right/left/bithalamic, rBG/lBG: right/left basal ganglia, ricap/licap: right/left internal capsule, rmes/lmes : right/left mesencephalus

25 patients (71%) were classified as being in UWS, 7 patients (20%) as being in an MCS-, and 3 patients as MCS+ (9%), at the first evaluation with the CRS-R. According to the subclassification, 14 out of 25 UWS patients (56%) emerged from DOC (subclass 1c) while 11 patients remained with DOC (44%) (1d); among the joined MCS- and MCS+ patients, 7 out of 10 patients (70%) emerged from DOC (subclass 1e), while 3 patients (30%) remained in MCS- or MCS+, and none of them worsened to UWS (1f). Finally, 7 patients (20%) (5 UWS, 1 MCS- and 1 MCS+) remained with their initial category (subclass 1g), while 28 patients (80%) improved their CRS-R classification (5 UWS patients evolved to MCS-, 1 to MCS+ and 14 UWS patients emerged; 1 MCS- patients evolved to MCS+ and 5 emerged; 2 MCS+ patients emerged) (1h).

According to the MBT evaluation, 27 patients (77%) were considered as CMD (class 2a) and 8 patients (2b) (23%) were diagnosed as being true DOC. Among the CMD patients, 20 out of 27 patients (74%) had a last CRS-R assessment of emergence (class 2e, true positives), while the remaining 7 patients (26%) were in DOC at the last CRS-R (4 in MCS- and 3 in MCS+) (class 2d, false positive). Among the 8 patients being true DOC, 7 (88%) remained in DOC at the last CRS-R (2c, true negatives) and 1 (12%) emerged (2f, false negative).

Figure 4: percentage of initial and last CRS-R assessment and MBT diagnosis.



4.2 Item's analysis

Table 3: Patient's value for each variable (item's sub-score). In 10 patients, one or more values were removed due to discrepancy within evaluators.

Scale	FOUR				GCS			NCS			
Patient n°	Eye	Motor	Resp	Brain stem	Eye	Motor	Verbal	Visual	Motor	Verbal	Facial
1	0	2	4	4	1	4	1	0	2	0	0
2	3	4	4	4	4	6	3	3	3	2	3
3	3	2	4	1	4	5	1	2	3	0	2
4	1	4	4	1	2	6	2	1	3	1	2
5	1	2	4	2	2	4	x	1	2	0	2
6	1	2	4	4	2	4	1	1	2	0	1
7	4	2	1	4	3	4	x	3	2	x	2
8	0	2	1	4	1	4	1	0	2	0	2
9	0	2	1	4	1	3	x	0	2	x	2
10	0	2	1	4	1	3	1	2	0	0	0
11	0	0	2	4	1	1	1	0	0	0	1
12	2	3	1	4	3	4	1	1	2	0	0
13	0	2	1	2	1	3	1	0	2	0	0
14	3	3	1	3	4	3	1	1	3	0	2
15	0	2	1	0	1	4	1	0	2	0	0
16	4	0	0	4	4	1	1	3	0	0	2
17	0	2	4	1	1	4	1	0	2	0	0
18	4	0	4	1	4	1	1	3	0	0	1
19	x	0	x	4	2	1	1	1	0	0	x
20	2	2	4	4	3	4	1	3	2	0	2
21	1	3	1	4	2	5	1	1	3	0	2
22	4	2	x	4	4	4	1	3	2	0	2
23	0	1	4	2	1	2	1	0	1	0	1
24	3	1	4	3	3	2	1	1	1	0	1
25	x	2	x	2	x	4	1	1	2	0	3
26	0	0	0	0	1	1	x	0	0	0	0
27	3	2	4	4	4	4	1	1	2	0	1
28	1	3	0	2	2	5	1	2	3	0	2
29	0	0	0	2	1	1	1	0	0	0	0
30	0	0	0	0	1	1	1	0	0	0	0
31	0	0	3	1	1	1	1	0	0	0	0
32	0	2	4	1	1	4	1	0	2	0	1
33	0	x	x	x	1	2	1	x	x	0	x
34	4	4	0	4	4	6	1	3	3	0	2
35	1	2	X	4	4	3	1	1	2	0	2

Statistical analysis of all scales' item for both CRS-R and MBT classification exhibited negative results after correction for multiple comparison; in other words, none of the items taken individually or in combination enable to predict the outcome of DOC patients defined by the last CRS-S classification whether considering the first CRS-R assessment or integrating the CMD nosology as a starting point. Also, not any exposed the CMD diagnosis. In a previous study (1), it had already been demonstrated that the first CRS-R items weren't correlated with the last CRS-R outcome, but if complemented by the MBT-tool, it could. By these analyses we can add that these three common scales items aren't predictive of the emergence defined by the CRS-R either and that they don't reveal awareness.

However, assessment of MBT performance provided a very high sensitivity (95%), while specificity was moderate (50%): true positive (or positive predictive value) 74%, false positive 26%, true negative (or negative predictive value) 88% and false negative 12%.

Table 4: CRS-R classification analysis

CRS-R classification analysis		FOUR								GCS						NCS							
Patient's class		EYE		MOTOR		RESP		BRAIN STEM		EYE		MOTOR		VERBAL		VISUAL		MOTOR		VERBAL		FACIAL	
1a	1b	1a	1b	1a	1b	1a	1b	1a	1b	1a	1b	1a	1b	1a	1b	1a	1b	1a	1b	1a	1b	1a	1b
1	22	0	4	2	2	4	x	4	4	1	4	4	4	1	1	0	3	2	2	0	0	0	2
2	23	3	0	4	1	4	4	4	2	4	1	6	2	3	1	3	0	3	1	2	0	3	1
3	24	3	3	2	1	4	4	1	3	4	3	5	2	1	1	2	1	3	1	0	0	2	1
4	25	1	x	4	2	4	x	1	2	2	x	6	4	2	1	1	1	3	2	1	0	2	3
5	26	1	0	2	0	4	0	2	0	2	1	4	1	x	x	1	0	2	0	0	0	2	0
6	27	1	3	2	2	4	4	4	4	2	4	4	4	1	1	1	1	2	2	0	0	1	1
7	28	4	1	2	3	1	0	4	2	3	2	4	5	x	1	3	2	2	3	x	0	2	2
8	29	0	0	2	0	1	0	4	2	1	1	4	1	1	1	0	0	2	0	0	0	2	0
9	30	0	0	2	0	1	0	4	0	1	1	3	1	x	1	0	0	2	0	x	0	2	0
10	31	0	0	2	0	1	3	4	1	1	1	3	1	1	1	2	0	0	0	0	0	0	0
11	32	0	0	0	2	2	4	4	1	1	1	1	4	1	1	0	0	0	2	0	0	1	1
12	33	2	0	3	x	1	x	4	x	3	1	4	2	1	1	1	x	2	x	0	0	0	x
13	34	0	4	2	4	1	0	2	4	1	4	3	6	1	1	0	3	2	3	0	0	0	2
14	35	3	1	3	2	1	X	3	4	4	4	3	3	1	1	1	1	3	2	0	0	2	2
15		0		2		1		0		1		4		1		0		2		0		0	
16		4		0		0		4		4		1		1		3		0		0		2	
17		0		2		4		1		1		4		1		0		2		0		0	
18		4		0		4		1		4		1		1		3		0		0		1	
19		x		0		x		4		2		1		1		1		0		0		x	
20		2		2		4		4		3		4		1		3		2		0		2	
21		1		3		1		4		2		5		1		1		3		0		2	
p-value		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05	

1c	1d	1c	1d	1c	1d	1c	1d	1c	1d	1c	1d	1c	1d	1c	1d	1c	1d	1c	1d	1c	1d	1c	1d
1	23	0	0	2	1	4	4	4	2	1	1	4	2	1	1	0	0	2	1	0	0	0	1
5	24	1	3	2	1	4	4	2	3	2	3	4	2	x	1	1	1	2	1	0	0	2	1
6	25	1	x	2	2	4	x	4	2	2	x	4	4	1	1	1	1	2	2	0	0	1	3
8	26	0	0	2	0	1	0	4	0	1	1	4	1	1	x	0	0	2	0	0	0	2	0
9	27	0	3	2	2	1	4	4	4	1	4	3	4	x	1	0	1	2	2	x	0	2	1
11	29	0	0	0	0	2	0	4	2	1	1	1	1	1	1	0	0	0	0	0	0	1	0
12	30	2	0	3	0	1	0	4	0	3	1	4	1	1	1	1	0	2	0	0	0	0	0
13	31	0	0	2	0	1	3	2	1	1	1	3	1	1	1	0	0	2	0	0	0	0	0
14	32	3	0	3	2	1	4	3	1	4	1	3	4	1	1	1	0	3	2	0	0	2	1
15	33	0	0	2	x	1	x	0	x	1	1	4	2	1	1	0	x	2	x	0	0	0	x
17	35	0	1	2	2	4	X	1	4	1	4	4	3	1	1	0	1	2	2	0	0	0	2
19		x		0		x		4		2		1		1		1		0		0		x	
21		1		3		1		4		2		5		1		1		3		0		2	
p-value		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05	

1e	1f	1e	1f	1e	1f	1e	1f	1e	1f	1e	1f	1e	1f	1e	1f	1e	1f	1e	1f	1e	1f	1e	1f
2	22	3	4	4	2	4	x	4	4	4	4	6	4	3	1	3	3	3	2	2	0	3	2
3	28	3	1	2	3	4	0	1	2	4	2	5	5	1	1	2	2	3	3	0	0	2	2
4	34	1	4	4	4	4	0	1	4	2	4	6	6	2	1	1	3	3	3	1	0	2	2
7		4		2		1		4		3		4		x		3		2		x		2	
10		0		2		1		4		1		3		1		2		0		0		0	
16		4		0		0		4		4		1		1		3		0		0		2	
18		4		0		4		1		4		1		1		3		0		0		1	
p-value		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05	

1g	1h	1g	1h	1g	1h	1g	1h	1g	1h	1g	1h	1g	1h	1g	1h	1g	1h	1g	1h	1g	1h	1g	1h
22	1	4	0	2	2	x	4	4	4	4	1	4	4	1	1	3	0	2	2	0	0	2	0
23	2	0	3	1	4	4	4	2	4	1	4	2	6	1	3	0	3	1	3	0	2	1	3
24	3	3	3	1	2	4	4	3	1	3	4	2	5	1	1	1	2	1	3	0	0	1	2
26	4	0	1	0	4	0	4	0	1	1	2	1	6	x	2	0	1	0	3	0	1	0	2
27	5	3	1	2	2	4	4	4	2	4	2	4	4	1	x	1	1	2	2	0	0	1	2
33	6	0	1	x	2	x	4	x	4	1	2	2	4	1	1	x	1	x	2	0	0	x	1
34	7	4	4	4	2	0	1	4	4	4	3	6	4	1	x	3	3	3	2	0	x	2	2
	8		0		2		1		4		1		4		1		0		2		0		2
	9		0		2		1		4		1		3		x		0		2		x		2
	10		0		2		1		4		1		3		1		2		0		0		0
	11		0		0		2		4		1		1		1		0		0		0		1
	12		2		3		1		4		3		4		1		1		2		0		0
	13		0		2		1		2		1		3		1		0		2		0		0
	14		3		3		1		3		4		3		1		1		3		0		2
	15		0		2		1		0		1		4		1		0		2		0		0
	16		4		0		0		4		4		1		1		3		0		0		2
	17		0		2		4		1		1		4		1		0		2		0		0
	18		4		0		4		1		4		1		1		3		0		0		1
	19		x		0		x		4		2		1		1		1		0		0		x
	20		2		2		4		4		3		4		1		3		2		0		2
	21		1		3		1		4		2		5		1		1		3		0		2
	25		x		2		x		2		x		4		1		1		2		0		3
	28		1		3		0		2		2		5		1		2		3		0		2
	29		0		0		0		2		1		1		1		0		0		0		0
	30		0		0		0		0		1		1		1		0		0		0		0
	31		0		0		3		1		1		1		1		0		0		0		0
	32		0		2		4		1		1		4		1		0		2		0		1
	35		1		2		X		4		4		3		1		1		2		0		2
p-value		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05	

Table 5: MBT/CRS-R classification analysis

MBT/CRS-R classification analysis		FOUR								GCS						NCS							
Patient's class		EYE		MOTOR		RESP		BRAIN		EYE		MOTOR		VERBAL		VISUAL		MOTOR		VERBAL		FACIAL	
2a	2b	2a	2b	2a	2b	2a	2b	2a	2b	2a	2b	2a	2b	2a	2b	2a	2b	2a	2b	2a	2b	2a	2b
1	15	0	0	2	2	4	1	4	0	1	1	4	4	1	1	0	0	2	2	0	0	0	0
2	23	3	0	4	1	4	4	4	2	4	1	6	2	3	1	3	0	3	1	2	0	3	1
3	24	3	3	2	1	4	4	1	3	4	3	5	2	1	1	2	1	3	1	0	0	2	1
4	26	1	0	4	0	4	0	1	0	2	1	6	1	2	x	1	0	3	0	1	0	2	0
5	27	1	3	2	2	4	4	2	4	2	4	4	4	x	1	1	1	2	2	0	0	2	1
6	30	1	0	2	0	4	0	4	0	2	1	4	1	1	1	1	0	2	0	0	0	1	0
7	33	4	0	2	x	1	x	4	x	3	1	4	2	x	1	3	x	2	x	x	0	2	x
8	35	0	1	2	2	1	X	4	4	1	4	4	3	1	1	0	1	2	2	0	0	2	2
9		0		2		1		4		1		3		x		0		2		x		2	
10		0		2		1		4		1		3		1		2		0		0		0	
11		0		0		2		4		1		1		1		0		0		0		1	
12		2		3		1		4		3		4		1		1		2		0		0	
13		0		2		1		2		1		3		1		0		2		0		0	
14		3		3		1		3		4		3		1		1		3		0		2	
16		4		0		0		4		4		1		1		3		0		0		2	
17		0		2		4		1		1		4		1		0		2		0		0	
18		4		0		4		1		4		1		1		3		0		0		1	
19		x		0		x		4		2		1		1		1		0		0		x	
20		2		2		4		4		3		4		1		3		2		0		2	
21		1		3		1		4		2		5		1		1		3		0		2	
22		4		2		x		4		4		4		1		3		2		0		2	
25		x		2		x		2		x		4		1		1		2		0		3	
28		1		3		0		2		2		5		1		2		3		0		2	
29		0		0		0		2		1		1		1		0		0		0		0	
31		0		0		3		1		1		1		1		0		0		0		0	
32		0		2		4		1		1		4		1		0		2		0		1	
34		4		4		0		4		4		6		1		3		3		0		2	
p-value		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05	

2c	2e	2c	2e	2c	2e	2c	2e	2c	2e	2c	2e	2c	2e	2c	2e	2c	2e	2c	2e	2c	2e	2c	2e
23	1	0	0	1	2	4	4	2	4	1	1	2	4	1	1	0	0	1	2	0	0	1	0
24	2	3	3	1	4	4	4	3	4	3	4	2	6	1	3	1	3	1	3	0	2	1	3
26	3	0	3	0	2	0	4	0	1	1	4	1	5	x	1	0	2	0	3	0	0	0	2
27	4	3	1	2	4	4	4	4	1	4	2	4	6	1	2	1	1	2	3	0	1	1	2
30	5	0	1	0	2	0	4	0	2	1	2	1	4	1	x	0	1	0	2	0	0	0	2
33	6	0	1	x	2	x	4	x	4	1	2	2	4	1	1	x	1	x	2	0	0	x	1
35	7	1	4	2	2	X	1	4	4	4	3	3	4	1	x	1	3	2	2	0	x	2	2
	8		0		2		1		4		1		4		1		0		2		0		2
	9		0		2		1		4		1		3		x		0		2		x		2
	10		0		2		1		4		1		3		1		2		0		0		0
	11		0		0		2		4		1		1		1		0		0		0		1
	12		2		3		1		4		3		4		1		1		2		0		0
	13		0		2		1		2		1		3		1		0		2		0		0
	14		3		3		1		3		4		3		1		1		3		0		2
	16		4		0		0		4		4		1		1		3		0		0		2
	17		0		2		4		1		1		4		1		1		2		0		0
	18		4		0		4		1		4		1		1		3		0		0		1
	19		x		0		x		4		2		1		1		1		0		0		x
	20		2		2		4		4		3		4		1		3		2		0		2
	21		1		3		1		4		2		5		1		1		3		0		2
p-value		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05	

2d	2e	2d	2e	2d	2e	2d	2e	2d	2e	2d	2e	2d	2e	2d	2e	2d	2e	2d	2e	2d	2e	2d	2e
22	1	4	0	2	2	x	4	4	4	4	1	4	4	1	1	3	0	2	2	0	0	2	0
25	2	x	3	2	4	x	4	2	4	x	4	4	6	1	3	1	3	2	3	0	2	3	3
28	3	1	3	3	2	0	4	2	1	2	4	5	5	1	1	2	2	3	3	0	0	2	2
29	4	0	1	0	4	0	4	2	1	1	2	1	6	1	2	0	1	0	3	0	1	0	2
31	5	0	1	0	2	3	4	1	2	1	2	1	4	1	x	0	1	0	2	0	0	0	2
32	6	0	1	2	2	4	4	1	4	1	2	4	4	1	1	0	1	2	2	0	0	1	1
34	7	4	4	4	2	0	1	4	4	4	3	6	4	1	x	3	3	3	2	0	x	2	2
	8		0		2		1		4		1		4		1		0		2		0		2
	9		0		2		1		4		1		3		x		0		2		x		2
	10		0		2		1		4		1		3		1		2		0		0		0
	11		0		0		2		4		1		1		1		0		0		0		1
	12		2		3		1		4		3		4		1		1		2		0		0
	13		0		2		1		2		1		3		1		0		2		0		0
	14		3		3		1		3		4		3		1		1		3		0		2
	16		4		0		0		4		4		1		1		3		0		0		2
	17		0		2		4		1		1		4		1		0		2		0		0
	18		4		0		4		1		4		1		1		3		0		0		1
	19		x		0		x		4		2		1		1		1		0		0		x
	20		2		2		4		4		3		4		1		3		2		0		2
	21		1		3		1		4		2		5		1		1		3		0		2
p-value		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05		>0,05	

5. Discussion

The identification of subtle motor behavioural signs in the acute phase of BI has provided new insight into the amount and the content of consciousness improving the outcome prediction (1). In this scope, the current study was designed to further the exploration of new clinical signs by evaluating each clinical item of three existing scales (NCS, FOUR and GCS) assessing consciousness.

Results emphasize the absence of predictive property of any item taken individually or in combination and support previous results outlining that any subscales of the CRS-R cannot promote DOC predictability, while more subtle motor behaviour, as provided by MBT, can [1]. It is worth noting that the NCS shares one clinical sign with MBT, the facial expression induced by noxious stimulation. In this current research, this item, the facial expression was not predictive for better outcome, while the accuracy of such motor sign was previously demonstrated (1). In this respect, the difference in the assessment modality between MBT and NCS may explain such discrepancy.

On the other hand, High sensitivity and moderate specificity of MBT were reproduced as assessed in the study of Pignat and all. (1). This moderate specificity, which is partly determined by a relatively high false positive (FP) rate (0.26), should be put into perspective, with regard to the fact that almost half of CMD patients with a DOC outcome according to the last CRS-R were considered as MCS+ at outcome evaluation, meaning being statistically close to emergence (34). The rate of 26% patients among the CMD ones who were classified as DOC on the last CRS-R, could also be put in relation with the literary rate of the behavioural scales inability to identify awareness (18-21), though, the rate of approximately 34% found in the literature concerns the patients who actually have awareness among the ones who are classified as unaware, that means, the behavioural scales false negatives.

Those findings do not dispute the accuracy validity of the bedside motor behavioural examination but address explicitly the issue of how performing the clinical evaluation to overcome this underestimation of the degree and level of consciousness.

First, examination criteria need to be adapted to the underlying medical conditions, including motor, verbal or drive deficits, which may cover the non-reflexive motor responses being explored (35). Current coma scales require too stringent criteria to identify such positive signs. Therefore, bedside evaluation should explore any form of subtle intentional movement at the body level arising spontaneously or induced by a sensitive stimulation; furthermore, how to stimulate plays a preponderant role in triggering a movement. Such observation is outlined by the example provided by the evaluation of facial expression; in the current study, the item of facial expression was not predictive, although the grimace induces by noxious stimulation was expected to, with regard to previous results (1). Such discrepancy may be explained by differences in assessment methods, since NCS requires a clear grimace (15), while MBT takes

into consideration subtler facial movements. Therefore, non-conservative rules for measuring motor behaviour may be emphasized.

Second, accounting for reflexive reaction should be also promoted as they inform about the integrity of some reflex loops within the brainstem. Besides, the persistence of reflexes may also suggest a disruption in higher level pathways involved in perception. However, a special attention should be drawn to the fact that the detection of a subtle motor reaction may be confused with a reflex. The closeness of both the subtle movement and the reflex may enlighten the relative high false positive rate and thus the limited specificity of MBT.

Then, positive and negative signs should be considered within the perspective of all current medical conditions, including brain lesion localisation, central and peripheral neuropathologies and oral or systemic diseases, which may participate to the inhibition of any motor behaviour.

Finally, those negative results raise the issue of the predictability property of the selected scores. Lacking prediction from NCS is explained by the fact that it was developed to evaluate pain intensity in DOC patients to control discomfort triggered by covert noxious stimuli. For the FOUR and GCS, global scores are considered to be predictive, despite some misclassifications, and not individual items.

Development of tools, such as the MBT, have to be emphasized, as they may economically identify covert consciousness allowing DOC nosology discrimination, including CMD, and outcome prediction.

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