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CHAPTER 3

BEHAVIORAL RESPONSIVENESS IN PATIENTS WITH DISORDERS OF CONSCIOUSNESS

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KEYWORDS: Vegetative state • Minimally conscious state • Consciousness • Assessment • Diagnosis • Sensory stimulation

ABSTRACT

Until now, the main way to assess whether a patient is conscious or not is to observe what he can do spontaneously or in response to stimulation. Although there is a growing body of research on the subject, detecting oriented/voluntary responses is still extremely challenging. Motor, verbal, and cognitive impairments; fluctuations of vigilance; and medications with impact on the central nervous system are among the factors complicating the diagnosis. Establishing a proper diagnosis is nevertheless of high clinical relevance when considering patients' prognosis and treatment. In this review, we will characterize the behavioral patterns of the various levels of consciousness, we will explain how challenging it is to detect signs of consciousness, and which tools currently exist to help in the assessment of those signs. Secondarily, we will present preliminary data investigating the interest of various sensory modalities in determining the diagnosis of patients with severe brain injury.

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3.1 Introduction

Some patients surviving extensive brain damage only regain limited levels of consciousness. Until now, the main way to assess whether a patient is conscious or not is to observe what he/she can do spontaneously or in response to stimulation. Although there is a growing body of research on the subject, detecting oriented/voluntary responses is still extremely challenging. Motor, verbal, and cognitive impairments; fluctuations of vigilance; and medications with impact on the central nervous system are among the factors complicating the diagnosis. Establishing a proper diagnosis is nevertheless of high clinical relevance. Conscious and unconscious patients have different outcomes. Patients in a minimally conscious state have a better long-term prognosis compared to those in a vegetative state [1]. Twelve months after brain injury, about half of the patients in minimally conscious state improve and show a good functional outcome, whereas only a very small percentage (3 %) of patients in vegetative state do so [2]. The diagnosis also has an impact on the patients' daily care and therapeutic choices when it comes to the administration of pharmacological interventions such as pain medication or new non-pharmacological interventions such as neurostimulation (deep brain stimulation or transcranial direct current stimulation) [3,4]. Finally, regarding end-of-life decisions, previous legal cases in several countries have established the right of the medical team to withdraw artificial nutrition and hydration in patients diagnosed as being in a vegetative state [5]. In such context, a correct diagnosis is therefore crucial. In this review, we will characterize the behavioral pattern of the various levels of consciousness, we will explain how challenging it is to detect signs of consciousness, and which tools currently exist to help in the assessment of those signs. Secondarily, we will also present preliminary data investigating the interest of various sensory modalities in determining the diagnosis of patients with severe brain injury.

3.2 Behavioral Pattern in Disorders of Consciousness

When the patient is in a coma, there is no arousal and no consciousness. During this transient condition, patients' eyes are continuously closed (even following stimulation), autonomic functions are reduced, and respiratory assistance is needed [6] (Table 3.1). Most patients recover from a coma within hours to weeks after injury. However, some patients can recover arousal (i.e., open their eyes spontaneously or in response to stimulation) without being conscious (no oriented/voluntary responses). These patients are in a state called "vegetative state" (VS) [7] (Table 3.1). In this state, breathing occurs without assistance since autonomic functions (e.g., cardiovascular regulation, thermoregulation) are preserved. The patients may also moan, demonstrate smiling, crying, or grimacing even though inappropriate and appearing out of context [7, 8]. This state can be either transient or persistent (when above a month post-injury). After a year for traumatic etiologies and 3 months for nontraumatic etiologies, the VS can be considered as permanent. These patients have, in that case, less than 5 % of chances to recover. Only then, the ethical and legal issues around withdrawal of hydration and nutrition may be discussed [9]. Note that, given the negative connotation of the term "vegetative state,"

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The European Task Force on Disorders of Consciousness has recently proposed to use the more neutral and descriptive term "unresponsive wakefulness syndrome" (VS/UWS) [10].

Consciousness recovery consists of regaining fluctuating but reproducible nonreflexive-oriented and/or voluntary behaviors. Such state is called the "minimally conscious state" (MCS) [11] (Table 3.1). Behaviors that suggest consciousness are, for example, command following, visual pursuit, object localization, or contingent responses to emotional stimuli. MCS has recently been divided into two categories, MCS+ (plus) and MCS- (minus), based on the complexity of behavioral responses. Patients in an MCS- show nonreflexive-oriented responses such as visual pursuit or localization to noxious stimuli, while MCS+ refers to patients showing nonreflexive voluntary responses such as command following, intelligible verbalization, and/or nonfunctional communication [12, 13]. When patients demonstrate reliable "functional communication" (i.e., accurate yes-no responses to situational orientation questions) or "functional object use" (i.e., appropriate use of different common objects) on two consecutive assessments, the patient is considered to have emerged from the MCS (EMCS) [11] (Table 3.1). After emerging from MCS, these patients are not considered as being in a disorder of consciousness anymore. However, they often remain confused, disoriented, and sometimes agitated. The term "acute confusional state" (ACS) has recently been used to describe these patients [14].

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***Table 3.1**: Summary of the behavioral features for coma, VS/UWS, MCS-, MCS+, and emergence from MCS*

Level of consciousness	Behavioral features
Coma	No arousal/eye opening
	Impaired spontaneous breathing/brainstem reflexes
	No oriented or purposeful behaviors
	No groans, vocalizations, or verbalizations
	No language comprehension/response to command
Vegetative state/unresponsive wakefulness syndrome	Arousal/spontaneous or stimulus-induced eye opening
	Preserved spontaneous breathing/brainstem reflexes
	No oriented or purposeful behaviors
	Groans and/or vocalizations but no verbalizations
	No language comprehension/response to command
Minimally conscious state	Fluctuation of vigilance (MCS-/+)
	Preserved spontaneous breathing/brainstem reflexes
	MCS-: object localization-reaching-manipulation and/or sustained visual fixation and/or visual pursuit and/or automatic motor behavior and/or localization to pain
	MCS+: command following and/or object recognition and/or intelligible verbalization and/or intentional communication Emergence: functional communication and/or functional object use on at least two consecutive assessments

3.3 Misdiagnosis

Differentiating MCS from VS/UWS can be challenging since voluntary and reflexive behaviors can be difficult to distinguish and subtle signs of consciousness may be missed. The development of diagnostic criteria for MCS [11] would reasonably be expected to reduce the incidence of misdiagnosis relative to the rates reported before these criteria were established [15, 16]. However, recent studies found that around 40 % of patients believed to be in VS/UWS were still misdiagnosed [17,18] (Fig. 3.1).

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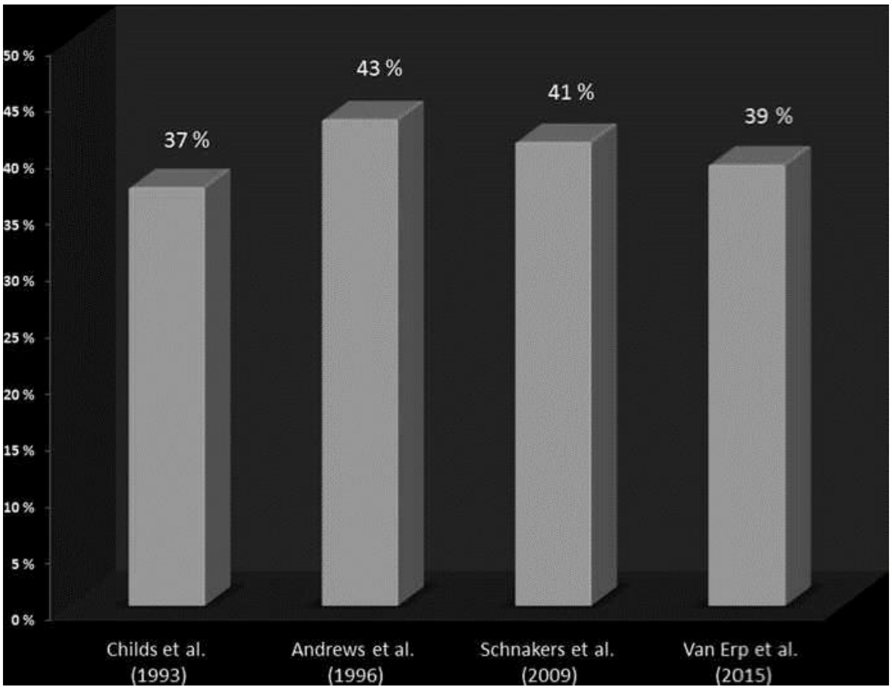
The high rate of misdiagnosis likely reflects different sources of variance. Variance in diagnostic accuracy may result from biases contributed by the examiner, the environment, and/or the patient. First, examiner errors may arise when the range of behaviors sampled is too narrow, response-time windows are over- or under- inclusive, criteria for judging purposeful responses are poorly defined, and exami-nations are conducted too infrequently to capture the full range of behavioral fluctuation. The use of standardized rating scales offers some protection from these errors, although failure to adhere to specific administration and scoring guidelines may jeopardize diagnostic accuracy. Second, the environment in which the patient is evaluated may bias assessment findings. Paralytic and sedative medications, restricted range of movement stemming from restraints and immobilization techniques, poor positioning, and excessive ambient noise/heat/light can decrease or distort voluntary behavioral responses. The last source of variance concerns the patient. Fluctuations in arousal level, fatigue, subclinical seizure activity, occult illness, pain, cortical sensory deficits (e.g., cortical blindness/deafness), motor impairment (e.g., generalized hypotonus, spasticity, or paralysis), or cognitive deficits (e.g., aphasia, apraxia, agnosia) constitute a bias to the behavioral assessment and therefore decrease the probability to observe signs of consciousness.

Some sources of error can be avoided, but this is not always possible or within the examiner's control. It is, however, particularly crucial to optimize the way consciousness assessments are performed as clinical management, from treatment of pain to end-of-life decision-making, often depends on behavioral observations. For this reason, the use of standardized and sensitive behavioral scales can substantially help clinicians to detect subtle signs of consciousness.

Fig. 3.1: *Previous findings on misdiagnosis rate in patients with severe brain injury*



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3.4 Clinical Assessment of Disorders of Consciousness

Behavioral assessment is based on two main components: wakefulness and awareness. Wakefulness refers to the patient's level of arousal and is assessed by observing eye opening. Awareness is related to subjective experiences and can be subdivided into awareness of the external world (i.e., perception of the environment or "consciousness") and awareness of the internal world (i.e., stimulus-independent thoughts such as mental imagery and inner speech or "self-awareness"). Raters assessing patients with severe brain injury will mainly assess consciousness of the environment, since self-awareness is difficult to evaluate when only based on bedside observations and not on patients' report. The assessment of consciousness can be done through repeated examinations revealing reproducible, oriented, or voluntary behavioral responses to various stimuli (the most common being auditory, verbal, and motor stimuli). The first scale widely used and known for assessing severely brain-injured patients recovering from coma is the Glasgow coma scale (GCS) [19]. This scale is short and can easily be incorporated into routine clinical care. Despite its widespread use, the GCS has been criticized for fluctuant inter-rater reliability and problems of scoring in patients with ocular trauma, tracheostomy, or ventilatory support [20]. The Full Outline of UnResponsiveness (FOUR) has been developed to replace the GCS for assessing severely brain-injured patients in intensive care [21]. The scale includes four subscales assessing motor and ocular responses, brainstem reflexes, and breathing. The total score ranges from 0 to 16. Unlike the GCS, the FOUR does not assess verbal functions to accommodate the high number of intubated patients in intensive care. It also assesses brainstem reflexes and breathing and, therefore, helps to better monitor comatose and VS/UWS patients. The FOUR also tracks emergence from VS/ UWS since it includes the assessment of early signs of consciousness such as visual pursuit. The scale is globally more sensitive than the GCS for diagnosing MCS but like the GCS is not adapted to a rehabilitation setting.

Since the 1970s, a high number of scales have been validated for being used in subacute and chronic patients with severe brain injury (Table 3.2). Recently, the American Congress of Rehabilitation Medicine (ACRM) has conducted a systematic evidence-based review of the available scales to provide recommendations for use according to validity, reliability, outcome prediction, and diagnostic sensitivity [22]. Among the scales evaluated, the Wessex Head Injury Matrix (WHIM) has been recommended with moderate reservations. The WHIM was developed to capture changes in patients in VS/UWS through emergence from post-traumatic amnesia [23]. This tool is particularly sensitive to detect changes in patients in MCS not captured by other scales such as the GCS. The WHIM has been structured according to the sequence of recovery observed in 88 patients recovering from traumatic brain injury. The scale assesses arousal level and concentration, visual pursuit, communication, cognition (i.e., memory and spatiotemporal orientation), and social behaviors. The WHIM score represents the rank of the most complex behavior observed. Despite a good validity, its reliability is still unproven, and, even though superior to the GCS, its diagnostic sensitivity is lower than other standardized scales such as the Coma Recovery Scale- Revised (CRS-R) [24]. In fact, according to the ACRM, the CRS-R is the most reliable tool for differentiating disorders of consciousness and received the strongest recommendation with minor reservations [22]. This scale was developed in 1991 and revised in 2004. Its primary purpose is to differentiate VS/UWS from MCS and MCS from EMCS. It

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measures auditory, visual, motor, and verbal functions as well as communication and arousal. Each of these subscales is hierarchically structured; the lowest scores reflect reflexive behaviors, while the highest scores indicate cognitively mediated behaviors. This scale has clear definitions for both the administration and the scoring of each item. The CRS-R can be administered reliably by trained examiners and produces reasonably stable scores over repeated assessments. Validity analyses have shown that the CRS-R is capable of discriminating patients in MCS from those in VS/UWS better than the GCS, the FOUR, and the WHIM [24].

Other scales such as the Western Neuro Sensory Stimulation Profile (WNSSP) [25], the Sensory Modality Assessment Technique (SMART) [26], and the Disorders of Consciousness Scale (DOCS) [27] have acceptable standardized administration and scoring procedures and have also been recommended with moderate reservations by the ACRM. On the contrary to the CRS-R whose main purpose is the diagnosis, the WNSSP, the SMART, and the DOCS are rather used when applying a sensory stimulation treatment to patients with severe brain injury. Sensory stimulation programs usually consist in presenting different types of environmental stimuli to the patient in order to optimize her/his consciousness level. These programs are supposed to constitute enriched environments which are supposed to enhance synaptic reinnervation, improve brain plasticity, and therefore accelerate the recovery from coma. However, even though numerous studies investigated the interest of these sensory stimulation programs, none of these studies has proven the efficacy of such treatment since the findings did not allow to differentiate spontaneous recovery from recovery due to treatment. Despite this, scales such as the WNSSP, the SMART, or the DOCS could still be interesting in a diagnostic context since they include the assessment of more sensory modalities than the CRS-R (i.e., tactile, olfactory, and gustatory modalities). The interest of those modalities for detecting signs of consciousness has nevertheless never been evaluated.

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Table 3.2: *Behavioral responses assessed by scales developed for patients with disorders of consciousness*

Name of the scale (Reference)	Response to command	Contingent emotional response	Object localization/ manipulation	Intelligible verbalizations	Oriented response to sensory stimulation				
					V	N	T	O	G
Coma Recovery Scale-Revised [4]	*		*	*	*	*			
Western Neuro Sensory Stimulation Profile [25]	*	*	*	*	*		*	*	
Sensory Modality Assessment & Rehabilitation Technique [34]	*	*	*	*	*		*	*	*
Wessex Head Injury Matrix [23]	*	*	*	*	*				
Disorder of Consciousness Scale [27]	*			*	*		*	*	
Sensory Stimulation Assessment Measure [35]	*		*	*	*		*	*	*
Glasgow Coma Scale [19]	*			*		*			
Reaction Level Scale [36]	*			*	*	*			
Innsbruck Coma Scale [37]						*			
Glasgow-Liège Scale [38]	*			*		*			
Full Outline of UnResponsiveness [21]	*				*	*			
Coma/Near-Coma Scale [39]	*			*	*		*	*	

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3.5 Can More Sensory Modalities Increase Diagnostic Sensitivity?

It has previously been shown that some sensory modalities are more sensitive to detect consciousness than others. In studies investigating misdiagnosis, oriented eye movements (i.e., visual pursuit and fixation) have been reported as the responses the most frequently missed during behavioral assessments [28, 17, 18]. In parallel, the visual modality of the CRS-R has been shown as the subscale allowing the highest detection of MCS as compared to the auditory, motor, or verbal modalities [29, 30]. Oriented visual responses are particularly interesting to detect since it is one of the first signs of consciousness appearing during patients' recovery and as it is associated with good outcome [31, 32, 2]. Until now, no study has investigated the interest of other sensory modalities (such as tactile, olfactory, and gustatory) when assessing consciousness, even though several scales recommended by the ACRM include such modalities (Table 3.2).

In a preliminary study, we therefore decided to investigate the interest of tactile, olfactory, and gustatory modalities in the assessment of consciousness. We assessed 38 patients (46 ± 16 years old, 17 traumatic, 21 chronic) diagnosed as being in a VS/ UWS ($n = 15$) or in a MCS ($n = 23$) by using the CRS-R. Tactile, olfactory, and gustatory stimuli used in the WNSSP, the SMART, and the DOCS have been administered in each patient in a randomized order. Tactile stimuli included tap on the shoulder, nasal swab, feather (applied on arms, fingers, and face), air into the neck, hair touching, vibration on the arm, scrub (i.e., kitchen scouring pad applied over the arm), and firm hand pressure on the arm. Each of these stimuli was applied for 10 s on both sides of the body on three consecutive trials. Olfactory stimuli included vinegar, syrup, and ammonia which were held under the patients' nose for 10 s (patient's mouth closed) on three consecutive trials. In case of tracheotomy, the entrance of the cannula was covered. Gustatory stimuli included vinegar and syrup. A stick soaked of this flavor was introduced into the patient's mouth for 10 s on three consecutive trials. Several recommendations had to be followed such as applying the treatment while the patients were in a wakeful state with eyes open in a setting with minimal ambient noise and respecting a 30 min rest before each session (i.e., absence of nursing care). Oriented responses (e.g., eyes/head toward or away from the stimulus, hand toward or pushes away the stimulus, congruent facial expression, mouth opening, or tongue pumping) were considered as present when it was clear and reproducible, meaning it was observed at least two times to exclude reflexive behaviors. The oriented responses obtained using those tactile, olfactory, and gustatory stimulations have then been compared to the diagnosis obtained using the CRS-R. Patients' outcome has also been collected at 1 year after assessment (n=27), using the Glasgow Outcome Scale (GOS) [33].

According to our results (Fig. 3.2), a minority of patients diagnosed as being in a VS/UWS by using the CRS-R showed oriented olfactory or gustatory responses (7 % and 14 %, respectively). The patient for whom we had outcome data (one missing data) did not recover consciousness a year after assessment. Additionally, oriented olfactory or gustatory responses were absent in a majority of patients diagnosed as being in a MCS by using the CRS-R (70 %) and in a majority of

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patients who showed oriented eye movements (61 %). Using tactile stimuli, a higher percentage of patients diagnosed as being in a VS/UWS showed oriented responses (40 %). Oriented tactile responses were present in a majority of patients diagnosed as being in an MCS by using the CRS-R (65 %) and in a majority of patients who showed oriented eye movements (83 %). When considering the stimulus leading to the most frequent oriented responses, the nasal swab helped to detect 80 % of the oriented tactile responses. However, only one of the VS/UWS patients showing oriented tactile responses recovered consciousness a year after assessment (17 %). The patient (50 years old, 50 days after nontraumatic injury) was able to localize a tactile stimulus using her hand. Repeated CRS-R assessments, at that time, showed only reflexive behaviors (i.e., auditory startle, blinking to threat, flexion to noxious stimulation, oral reflexive movements, and arousal with stimulation). Two years after our assessment, the CRS-R indicated an EMCS. Finally, to test whether the outcome measured by the GOS differs according to the presence or absence of an oriented response, U Mann-Whitney tests were performed. There was no statistical difference for olfactory ($U = 51.5$; $p = 0.61$), gustatory ($U = 49$; $p = 0.5$), and tactile ($U = 76.5$; $p = 0.51$) modalities.

Considering our data, oriented olfactory and gustatory responses do not seem to be linked to consciousness since they are not observed in the majority of significant proportion of conscious patients and since they are not associated with consciousness recovery. Oriented tactile responses seem to be observed in most conscious patients but are not clearly related to consciousness recovery and could be false positives. This preliminary study hence seems to indicate that adding sensory modalities such as olfactory, gustatory, or tactile modalities to the CRS-R does not constitute a further help for decreasing the level of misdiagnosis in patients with disorders of consciousness.

Fig. 3.2: *Percentage of oriented responses in VS/UWS and MCS patients (panel a) and outcome at 1 year (averaged Glasgow Outcome Score - GOS, with 95 % confidence intervals) according to the absence (0) or presence (1) of oriented responses (panel b) ("ns" indicates difference is nonsignificant (p >0.05))*

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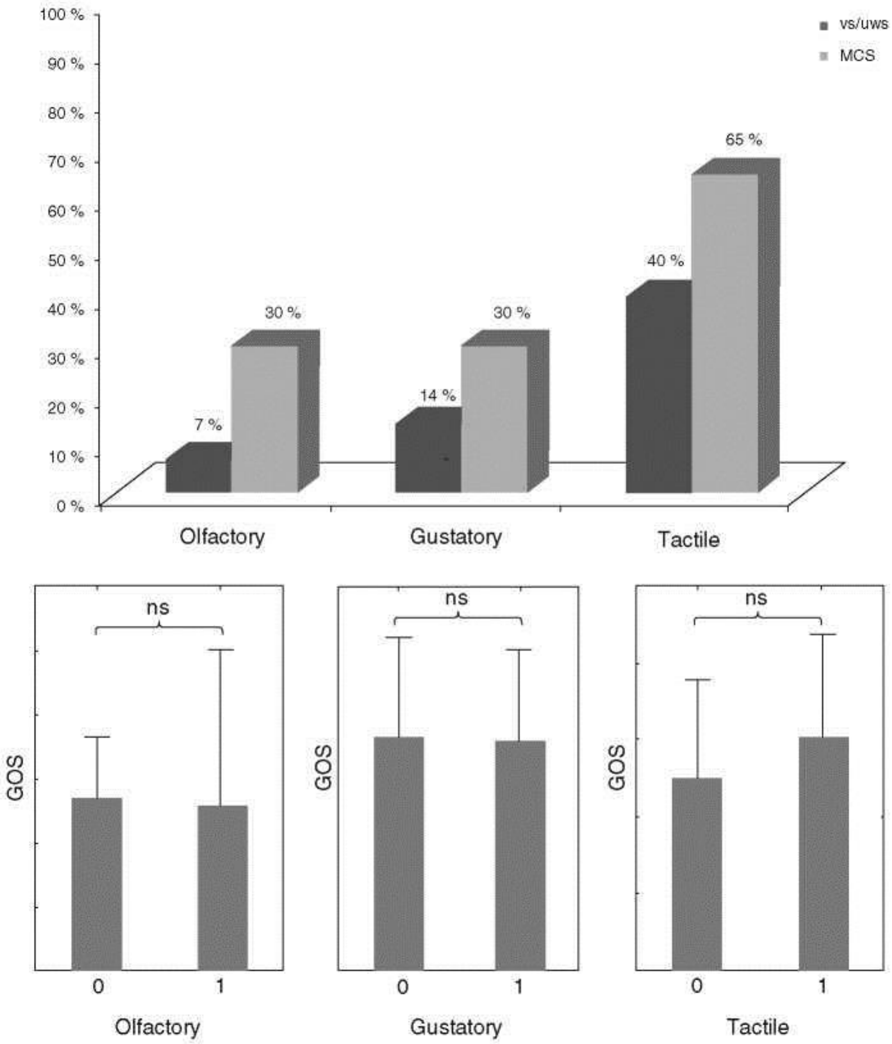

3.6 Conclusion

Establishing a proper diagnosis is very important in the care of patients with severe brain injury. However, clinical assessment is difficult and can often lead to a misdiagnosis of the level of consciousness. The use of sensitive standardized tools is therefore crucial when establishing the diagnosis. The CRS-R is currently the most reliable and valid scale available and constitutes a substantial help in the differentiation of conscious vs. unconscious patients. Finally, even though our findings need to be replicated in a bigger sample, using gustatory, olfactory, or tactile stimuli that are included in several behavioral scales for the assessment of disorders of consciousness do not seem to be of further help when detecting consciousness in patients with severe brain injury.

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