

This provisional PDF corresponds to the article as it appeared upon acceptance.  
A copyedited and fully formatted version will be made available soon.  
The final version may contain major or minor changes.

## **An Italian multicentre validation study of the Coma Recovery Scale-Revised**

anna ESTRANEO, Pasquale MORETTA, Antonio DE TANTI, Giordano GATTA,  
Joseph T GIACINO, Luigi TROJANO

Eur J Phys Rehabil Med 2014 Mar 06 [Epub ahead of print]

*EUROPEAN JOURNAL OF PHYSICAL AND REHABILITATION  
MEDICINE*

Rivista di Medicina Fisica e Riabilitativa dopo Eventi Patologici

pISSN 1973-9087 - eISSN 1973-9095

Article type: Original Article

The online version of this article is located at <http://www.minervamedica.it>

**Subscription: Information about subscribing to Minerva Medica journals is online at:**

<http://www.minervamedica.it/en/how-to-order-journals.php>

**Reprints and permissions: For information about reprints and permissions send an email to:**

[journals.dept@minervamedica.it](mailto:journals.dept@minervamedica.it) - [journals2.dept@minervamedica.it](mailto:journals2.dept@minervamedica.it) - [journals6.dept@minervamedica.it](mailto:journals6.dept@minervamedica.it)

## **An Italian Multicentre validation study of the Coma Recovery Scale-Revised**

**A. Estraneo<sup>1</sup>, P. Moretta<sup>1</sup>, A. De Tanti<sup>2</sup>, G. Gatta<sup>3</sup>, J.T. Giacino<sup>4,5</sup>, L. Trojano<sup>1,6</sup>, for the Italian CRS-R Multicentre Validation Group [Corporate Author].**

<sup>1</sup>Disorders of Consciousness Laboratory, Salvatore Maugeri Foundation, IRCCS, Scientific Institute, Telesse Terme (BN), Italy;

<sup>2</sup>Dept. of Rehabilitation, Cardinal Ferrari Hospital Fontanellato-Parma, Italy;

<sup>3</sup>Rehabilitation Medicine Unit, Ravenna Hospital, Ravenna, Italy;

<sup>4</sup>Dept of Physical Medicine and Rehabilitation, Spaulding Rehabilitation Hospital, Boston, MA, USA; <sup>5</sup> Dept of Physical Medicine and Rehabilitation, Harvard Medical School, Boston, MA, USA; <sup>6</sup>Neuropsychology Lab., Dept. of Psychology, Second University of Naples, Caserta, Italy.

**Running head:** Italian Multicentre validation of CRS-R

The study has been entirely supported from Salvatore Maugeri Foundation without external funding.

**Addresses for reprint requests:** Anna Estraneo, Salvatore Maugeri Foundation, IRCCS, Via Bagni Vecchi, 1, 82037, Telesse Terme (BN), Italy. Tel: 39 0824 909111. e-mail: [anna.estraneo@fsm.it](mailto:anna.estraneo@fsm.it)

**The Italian CRS-R Multicentre Validation Group [Corporate Author]:**

**Participating Centres:** Salvatore Maugeri Foundation, IRCCS, Scientific Institute of Telesse Terme, Benevento (V. Cardinale); Department of Rehabilitation, Cardinal Ferrari Hospital Fontanellato-Parma (I. Trioli, E. Mezzadri); Salvatore Maugeri Foundation, IRCCS, Scientific Institute of Pavia (C. Pistarini, B. Cazzulani); S.Lucia IRCCS Foundation, Roma (R. Formisano, P. Ciurli, G. Ferri, F. Rizza); Clinical Neurophysiology Unit, Neuroscience Department, Careggi Teaching Hospital and Don Gnocchi Rehabilitation Unit, Firenze (A. Grippo, A. Comanducci); Don Gnocchi Foundation, Sant'Angelo dei Lombardi, Avellino (M. Ebreo, G. Di Iasi); Rehabilitation Medicine, Severe Brain Lesions Unit, Caraglio, Cuneo (G. Lamberti, E. Giraud, A. Giaccardi); Institute of Santa Maria del Pozzo, Neurorehabilitation Unit, Somma Vesuviana, Napoli (V. Scarano, L. Nargi); Department of Rehabilitation, Motta di Livenza Hospital, Treviso (S. Bargellesi, A. Calabrese, A. Sartorato); S.Stefano Institute, Porto Potenza, Ascoli Piceno (R. Fortuna, D. Mogliani, L. Gironelli); S.Anna Institute, Crotona (L.F. Lucca, D. Cortese, F. Arcuri).

## Abstract

**Background:** Rate of misdiagnosis of Disorders of Consciousness (DoC) can be reduced by employing validated clinical diagnostic tools, such as the Coma Recovery Scale-Revised (CRS-R). An Italian version of the CRS-R has been recently developed, but its applicability across different clinical settings, and its concurrent validity and diagnostic sensitivity have not been estimated yet.

**Aim:** To perform a multicentre validation study of the Italian version of the Coma Recovery Scale–Revised (CRS-R).

**Design:** Analysis of inter-rater reliability, concurrent validity and diagnostic sensitivity of the scale.

**Setting:** One Intensive Care Unit, 8 Post-acute rehabilitation centres and 2 Long-term facilities

**Population:** Twenty-seven professionals (physicians, n= 11; psychologists, n= 5; physiotherapists, n= 3; speech therapists, n= 6; nurses, n= 2) from 11 Italian Centres

**Methods:** CRS-R and Disability Rating Scale (DRS) applied to 122 patients with clinical diagnosis of Vegetative State (VS) or Minimally Conscious State (MCS)

**Results:** CRS-R has good-to-excellent inter-rater reliability for all subscales, particularly for the communication subscale. The Italian version of the CRS-R showed a high sensitivity and specificity in detecting MCS with reference to clinical consensus diagnosis. The CRS-R showed good concurrent validity with the Disability Rating Scale, which had very low specificity with reference to clinical consensus diagnosis.

**Conclusions:** The Italian version of the CRS-R is a valid scale for use from the sub-acute to chronic stages of DoC. It can be administered reliably by all members of the rehabilitation team with different specialties, levels of experience and settings.

**Clinical Rehabilitation Impact:** The present study promote use of the Italian version of the CRS-R to improve diagnosis of DoC patients, and plan tailored rehabilitation treatment.

**Keywords:** Disorders of Consciousness; Coma Recovery Scale-Revised; Validation

## Introduction

Several survivors to severe acquired brain injury, after a variable period of coma, show eye opening (awakening) but nonetheless remain unable to intentionally react to environmental stimuli, i.e. they are considered to be in a Vegetative State (VS).<sup>1</sup> Some of these patients eventually regain minimal but reproducible sign of self- and environmental-awareness, thus entering in a Minimally Conscious State (MCS).<sup>2</sup> The distinction between these two conditions, based on assessment of responses to stimuli, is critical to define treatment and prognosis,<sup>3,4</sup> since a significantly more favourable outcome is associated to MCS with respect to VS.<sup>5-7</sup> Interpretation of patients' behavior (reflexive versus volitional) for differential diagnosis may be very difficult because of marked fluctuations of patients' conditions and may diverge among examiners.<sup>8</sup> Rate of misdiagnosis can be reduced by employing validated clinical diagnostic tools, such as the Coma Recovery Scale-Revised (CRS-R).<sup>2,7,9,10</sup>

The CRS-R takes into account the Aspen Workgroup criteria for MCS,<sup>2,11</sup> and consists of six subscales addressing auditory, visual, motor, oromotor/verbal, communication and arousal functions. The lowest score on each subscale represents reflexive activity, while the highest score means cognitively mediated behaviour. For each subscale specific operational criteria have been defined to distinguish VS from MCS, such that presence of intentional (non-reflexive) responses on a single subscale can suffice to identify patients in MCS; the CRS-R total score has no direct diagnostic implication. French, Norwegian and Spanish versions of the CRS-R have been developed, and show good levels of reliability and validity.<sup>12-14</sup>

The CRS-R has been recently adopted in clinical practice by Italian neurorehabilitation teams, thanks to availability of an Italian version.<sup>15</sup> A study in which two physicians independently evaluated a small sample of DoC patients admitted to one Rehabilitation Unit showed that the Italian version of CRS-R has good

inter-rater agreement and reliability.<sup>16</sup> A study on a larger sample of DoC patients demonstrated that the Italian CRS-R version has adequate internal validity and reliability under the Rasch analysis framework.<sup>17</sup>

On this basis, we aimed to assess applicability and inter-rater agreement of the Italian CRS-R across different clinical settings, and to ascertain its concurrent validity and diagnostic sensitivity, which have not been estimated yet. For these purposes, we performed a multicentre study in which professionals from different specialties, with different expertise, and working in different kinds of facilities took part.

To assess concurrent validity, we used the Disability Rating Scale (DRS),<sup>18</sup> adapted in the Italian language, as it is the most widely used tool for assessment of DoC patients in Italian Rehabilitation Centres for patients with severe acquired brain injuries.<sup>3</sup> The DRS provides a quantitative assessment of general functioning and outcome of severe head trauma patients during the recovery course, from coma to return to community.<sup>18</sup> The DRS consists of 8 items divided into 4 categories: 1. "Eye Opening", "Communication Ability" and "Motor Response" assessing arousal and awareness; 2. "Feeding", "Toileting" and "Grooming," evaluating cognitive ability to handle self-care functions; 3. "Level of Functioning," gauging physical dependence upon others and 4. "Employability," measuring psychosocial adaptability for work, housework, or school. A total DRS score is calculated by adding the score for each item of the scale. Although the DRS has not been devised for diagnostic purposes, in the original study the DRS total score was divided into nine functional categories, including VS.<sup>18</sup> More recently, DRS items assessing best verbal response, best motor responses and cognitive ability have been codified as indicative of MCS diagnosis, in order to evaluate the concurrent validity of two versions of the CRS-R.<sup>7,13</sup>

## Materials and methods

### *Study design*

The study was conducted in three distinct phases. In the first, professionals from several centres were recruited and participated in a single training session in which administration and scoring of the Italian version of the CRS-R were presented. In the second phase, participating professionals administered and scored CRS-R scales on three patients with disorders of consciousness. Professionals' scores were analysed to assess inter-rater reliability. In the third phase of the study, in each participating centre two of the recruited professionals evaluated a sample of inpatients at their institution to assess the concurrent validity and diagnostic sensitivity of the scale.

### *Participating centres and professionals*

Eleven centres, qualified by the Italian National Health System for care of DoC patients (1 Intensive Care Unit, 8 Post-acute rehabilitation centres and 2 Long-term facilities), participated to the study. Participating centres were recruited on the basis of an informal survey aimed to identify professional teams with variable expertise in use of both CRS-R and DRS. In each centre 2-3 professionals who were potential or actual caretakers of DoC patients were identified as participants. All recruited participants (n= 27) had prior experience in the administration of the Italian version of the CRS-R, with variable levels of expertise (12 to 60 months, more than 10 DoC patients evaluated before the study); they worked as physicians (n= 11), psychologists (n= 5), physiotherapists (n= 3), speech therapists (n= 6) or nurses (n= 2).

The study was conducted after approval by the local Ethic Committee of each centre and according to the Helsinki declaration.

## *Procedures*

First phase: training session. The recruited professionals took part to a training session in which administration and scoring procedures of each item of the Italian version of CRS-R scale were presented. For this purpose three videotapes showing assessment of three patients with DoC were used. One physician (G.G.) involved in the Italian translation of CRS-R<sup>15</sup> was responsible for this training phase. For the patients appearing in the videotapes, written informed consent had been obtained from each patient's legal guardian.

Second phase: inter-rater agreement. In a second session, all trained participants were shown three novel videotapes, each showing administration of all CRS-R items to a different patient with prolonged (>6 months post brain injury) DoC; one patient was affected by VS and two patients were affected by MCS, and all of them were severely disabled (DRS score 24-26). Videotapes were stopped after each item and each participant scored it on his/her score sheet.

Inter-rater reliability of the CRS-R total and subscale scores, and level of diagnostic agreement among raters, were evaluated by means of Fleiss Generalized kappa test<sup>19</sup> which determines reproducibility of measures. As in previous validation studies,<sup>12,13,16</sup> values of 0.4 or less can be considered poor, values between 0.4–0.6 fair-to-moderate, and values between 0.6–0.8 good, whereas values greater than 0.8 suggest excellent inter-observer agreement.

The Fleiss Generalized kappa test was also used to assess inter-rater agreement as a function of participants' profession, distinguishing three groups: physicians, psychologists and other professionals, and level of expertise in CRS-R administration, distinguishing professionals with low (about 12 months of

practice, 10-20 patients evaluated), medium (12 to 24 months of practice, 20-40 patients evaluated), or high (more than 24 months of practice, more than 40 patients evaluated) expertise.

Third phase: diagnostic sensitivity and concurrent validity. After the second session, in each centre, the CRS-R was administered by one of the trained professionals to a sample of patients meeting the following inclusion criteria: DoC due to severe acquired brain injury; established clinical diagnosis of VS or MCS according to international criteria,<sup>1,2</sup> based on daily behavioural observation by the clinical team until 24 hours before CRS-R administration; lack of severe organ insufficiency or acute illness. One-hundred and twenty-two post-comatose patients (80 males; mean age= 54.58; range= 14-88) were included in this phase of the study; eight centres recruited 10-11 patients, three centres recruited 12 patients or more. Aetiology of brain injury was traumatic (n= 47), post-anoxic (n= 29), vascular (n= 39) or other (n= 5). Thirty-eight patients were evaluated 25 to 90 days post-onset (sub-acute period), 51 were assessed from 91 days to 1 year post-onset (post-acute period) and 33 patients were assessed more than 1 year after disease onset (chronic period). Written informed consent was obtained by the legal guardians of all patients.

To ensure sufficient arousal level, centrally acting drugs, neuromuscular function blockers and sedation were discontinued within the 24 hours of the assessment, and the CRS-R was administered while patients had their eyes open. Patients who did not show spontaneous and continuous eye-opening underwent the Arousal Facilitation Protocol according to standard CRS-R administration procedures.<sup>20</sup> In the same day, and in the same day period, a second examiner administered the DRS scale to the same patient. The trained rater administering the CRS-R was blind to the clinical consensus diagnosis and to DRS findings.

Diagnostic sensitivity and specificity of CRS-R were calculated with clinical consensus-based diagnosis as the reference standard and VS as disorder of interest; confidence intervals for sensitivity and specificity were calculated by means of non-parametric methods. McNemar's test for paired categorical data was

used to check for systematic shifts. Diagnostic sensitivity and specificity of CRS-R were also calculated with DRS as the reference standard and VS as disorder of interest (Table 1).

--- please insert Table 1 (diagnostic criteria) about here ---

Concurrent validity was determined by computing Spearman rank correlation coefficient between CRS-R total score and DRS total score.

## Results

### *Inter-rater agreement*

Overall inter-rater agreement, as expressed by mean kappa values, was excellent for the communication subscale, and good for all the remaining sub-scales (Table 2). Agreement on single subscale was good to excellent across different professions, and even in the worst case (assessment of arousal scale among psychologists) kappa value was not lower than .60. Agreement was generally good among raters with low or medium level of expertise, and was good to excellent in the most skilled professionals.

Overall inter-rater agreement for diagnostic classification based on CRS-R was good (Table 2).

Agreement across professions and level of expertise was always good, but was excellent in physicians, and in the most skilled raters.

--- please insert Table 2 (Inter-rater agreement) about here ---

### *Diagnostic sensitivity*

Agreement between the CRS-R and clinical diagnosis was high: there were only 8 cases in which the CRS-R profile supported a diagnosis of MCS when the clinical diagnosis was VS, whereas in 5 cases the clinical diagnosis of MCS was not supported by the CRS-R profile (Figure 1). This resulted in high sensitivity (indicating the proportion of persons diagnosed as VS by clinical consensus diagnosis -the reference standard- and by the CRS-R: 91.9%, 95% confidence interval: 82.4-96.5) and high specificity

(indicating the proportion of persons classified as not being in VS by the CRS-R or by the clinical consensus diagnosis: 86.7 %, 95% confidence interval: 82.4-96.5).

--- Please insert Figure 1 (Diagnostic agreement) about here ---

A larger proportion of disagreement was observed between CRS-R and DRS: 29 patients classified as MCS by the CRS-R were considered to be in VS by the DRS, whereas only 1 disagreement was found for patient with a diagnosis of VS for CRS-R (Figure 1). As a consequence, sensitivity was quite high (95.1%, 95% confidence interval: 86.7-98.3), but specificity was low (51.7%, 95% confidence interval: 39.3-63.8).

### *Concurrent validity*

Raw data for CRS-R Total Score, CRS-R subscales, and DRS Total Score in VS and MCS patients are reported in Table 3. Spearman correlation coefficients between CRS-R and DRS total scores were significant for the total sample (Table 4) and also when considering different time periods of the observation (i.e., sub-acute, post-acute or chronic stages), or aetiology (i.e., traumatic, haemorrhagic or anoxic).

--please insert Table 3 (Raw scores) and Table 4 (Correlation between CRS-R and DRS) about here

## **Discussion**

This first multicentre validation study confirmed good inter-rater agreement of the Italian version of the CRS-R, in line with previous validation studies.<sup>7,12,13,16,17</sup> Results did not change as a function of professional specialties or level of expertise in CRS-R administration, indicating that this scale yields reproducible findings across examiners working in different rehabilitation settings. This novel finding supports use of the CRS-R, in its Italian version, across all rehabilitative stages, from the Intensive Care Unit to Long-term care facilities. In this sense, the CRS-R might provide a common language that enables optimization of continued care for DoC patients.<sup>3,4,21,22</sup> Moreover, to assess accurately the level of responsiveness is useful for making decisions about intensity and duration of treatment: the guidelines for care of disorders of consciousness, recently issued by the Italian Ministry of Health,<sup>4</sup> suggest different care levels as a function of patients' responsiveness.

Good-to-excellent inter-rater reliability was found for all subscales, particularly for the visual subscale. It is important to recognize that the use of videotaped assessment may have reduced inconsistencies among raters with respect to actual CRS-R administration at bedside, but this procedure allowed us to verify inter-rater agreement in a relatively high number of observers.

The Italian version of the CRS-R showed high sensitivity and specificity in detecting MCS with reference to clinical consensus diagnosis. In the present study we observed a very high correspondence between CRS-R and clinical consensus diagnosis, differently from that reported in previous studies on CRS-R.<sup>9</sup> This findings is likely explained by the fact that, differently from previous studies, here the clinical diagnosis was strictly grounded on the same Aspen Workgroup's criteria that informed the development of CRS-R. Nonetheless, a few discrepancies were present between CRS-R and clinical diagnosis. In some cases the CRS-R could identify as MCS patients who were considered in a VS by the clinical diagnosis; this finding has already been reported in literature, and has been ascribed to high effectiveness of standardized CRS-R administration in capturing behavioural signs of consciousness.<sup>7</sup> However, we also found 5 patients with the reverse pattern, i.e. those who were considered in a VS by the CRS-R and were in MCS according to the

clinical diagnosis; all these patients needed to be stimulated by the Arousal Facilitation Protocol before being examined,<sup>20</sup> because of fluctuations of their arousal level at the time of testing. We could thus suggest that this latter discrepancy between CRS-R and clinical diagnosis could be due to the fact that, because of the study design, CRS-R was applied only once to each patient, and this might lead to underestimation of intentional behaviours. In clinical practice CRS-R should be applied more than once for obtaining reliable diagnostic indications.<sup>7</sup>

Unlike the CRS-R, the DRS had very low specificity with reference to clinical consensus diagnosis, in line with the American and Norwegian validation studies.<sup>7,13</sup> In fact, the DRS total score has well-described psychometric characteristics, but it was not intended to provide clinical diagnostic information and is best suited for studies on functional outcome. Moreover, it is worth underlining that the DRS was developed before wide dissemination of the clinical diagnostic criteria for MCS,<sup>2</sup> and does not include items that assess visual behaviour specifically. Instead, assessment of visual behaviour is thought to provide key elements for differential diagnosis of DoC.<sup>2,12,23-25</sup> Thus, we believe the low specificity of the CRS-R in this analysis reflects the limitations of the gold standard for differential diagnosis. Nonetheless, we observed good concurrent validity between the CRS-R and DRS, in line with previous findings with the English and the Norwegian versions of CRS-R.<sup>7,13</sup> We were also able to verify that the correlation between CRS-R and DRS total scores is not influenced by disease duration or aetiology, suggesting that these scales can be used as complementary measures to evaluate responsiveness and functional autonomy, respectively. It should be emphasized that, by means of specific testing and scoring procedures, the CRS-R seems to be able to capture non-reflexive behaviour not detected by the DRS.

The present study has several limitations. First, the study included only professional examiners who already had previous experience in using the scale, and performed a training session before starting the study. This aspect could have biased measures of inter-rater agreement, but adequate knowledge and training in administration and scoring procedures are critical as they promote high reproducibility of CRS-R

assessments. Moreover, it is also possible that video presentation of assessment might have enhanced inter-rater agreement, but this allowed us to compare evaluations by a relatively high number of observers, as briefly mentioned above. A further limitation of the study, common to other validation studies, is the lack of comparison with independent instrumental assessment. However, it is widely accepted that at the moment, the gold standard for diagnosis of DoC rests on clinical observation.<sup>26</sup> Future validation studies might nonetheless consider correlating clinical-functional features with instrumental findings. A last possible limitation was related to the fact that we assessed concurrent validity using the DRS, and did not use other scales primarily designed to assess responsiveness in DoC patients and used in a previous validation study on CRS-R,<sup>9</sup> such as the Full Outline of Unresponsiveness Scale (FOUR)<sup>27</sup> and the Wessex Head Injury Matrix (WHIM).<sup>28</sup> However, this was a forced choice since no validated versions of such scales are currently available in Italy. We hope that the present study might prompt validation of other assessment tools for DoC patients. In this context, future studies might also investigate applicability, concurrent validity and diagnostic sensitivity of the CRS-R in the acute phase, to verify possible usefulness of a homogenous assessment tool for DoC patients during the entire care pathway and also to recognize early signs of responsiveness or sub-clinical behavioural responses with predictive value. In this perspective, it is worth mentioning that a recent report showed that the CRS-R total score (more effectively than DRS total score) had higher predictive value for recovery of responsiveness in patients in prolonged anoxic VS,<sup>22</sup> suggesting the prognostic usefulness of this scale.

To conclude, the present results show that the Italian version of the CRS-R is a valid scale suitable for use during the sub-acute through chronic stages of DoC. The CRS-R can be administered reliably by members of the rehabilitation team with different specialties, levels of experience and settings. Furthermore, the CRS-R identifies MCS patients more frequently than other behavioural scales, presumably because it is based on the precise diagnostic criteria developed by the Aspen workgroup<sup>2</sup> and uses effective administration methods. Therefore, the CRS-R is a useful tool for improving the diagnostic process for

DoC patients.<sup>7,9</sup> An accurate diagnosis is indeed crucial not only to guide clinical decision making,<sup>4,27</sup> but also to clarify the expected evolution of DoC.<sup>21,22,28</sup> However it must be underlined that to reach reliable diagnostic and prognostic conclusions, it is important that a multi-professional team integrates repeated administration of CRS-S with clinical and functional examination, with data about structural and functional integrity of the nervous system and with information about potential confounding variables such as medical complications and drug effects.

## References

1. The Multi-Society Task Force on the Persistent Vegetative State. Statement on medical aspects of the persistent vegetative state. *N Engl J Med* 1994;330:1499-508.
2. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, Kelly JP, Rosenberg JH, Whyte J, Zafonte RD, Zasler ND. The minimally conscious state: definition and diagnostic criteria. *Neurology* 2002;58:349-53.
3. Taricco M, De Tanti A, Boldrini P, Gatta G. National Consensus Conference. The rehabilitation management of traumatic brain injury patients during the acute phase: criteria for referral and transfer from intensive care units to rehabilitative facilities. *Europa Medicophysica* 2006;42:73-84.
4. Conferenza Stato-Regioni. Linee di indirizzo per l'assistenza alle persone in stato vegetativo e stato di minima coscienza. *Gazzetta Ufficiale della Repubblica Italiana, Serie Generale* 126, 1/6/2011.
5. Katz DI, Polyak M, Coughlan D, Nichols M, Roche A. Natural history of recovery from brain injury after prolonged disorders of consciousness: outcome of patients admitted to inpatient rehabilitation with 1–4 year follow-up. *Prog Brain Res* 2009;177:73-88.
6. Luauté J, Maucort-Boulch D, Tell L, Quelard F, Sarraf T, Iwaz J, Boisson D, Fischer C. Longterm outcomes of chronic minimally conscious and vegetative state. *Neurology* 2010;75:246-52.
7. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. *Arch Phys Med Rehabil* 2004;85:2020-9.
8. Majerus S, Gill-Thwaites H, Andrews K, Laureys S. Behavioral evaluation of consciousness in severe brain damage. *Prog Brain Res* 2005;150:397-413.

9. Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, Moonen G, Laureys S. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. *BMC Neurology* 2009;9:35.
10. American Congress of Rehabilitation Medicine, Brain Injury-Interdisciplinary Special Interest Group, Disorders of Consciousness Task Force, Seel RT, Sherer M, Whyte J, Katz DI, Giacino JT, Rosenbaum AM, Hammond FM, Kalmar K, Pape TL, Zafonte R, Biester RC, Kaelin D, Kean J, Zasler N. Assessment scales for disorders of consciousness: evidence-based recommendations for clinical practice and research. *Arch Phys Med Rehabil* 2010;91:1795-813.
11. Giacino JT. The vegetative and minimally conscious states: consensus-based criteria for establishing diagnosis and prognosis. *NeuroRehabilitation* 2004;19:293-8.
12. Schnakers C, Majerus S, Giacino J, Vanhaudenhuyse A, Bruno MA, Boly M, Moonen G, Damas P, Lambermont B, Lamy M, Damas F, Ventura M, Laureys S. [A French validation study of the Coma Recovery Scale-Revised \(CRS-R\)](#). *Brain Inj* 2008;22:786-92.
13. Løvstad M, Frøslie KF, Giacino JT, Skandsen T, Anke A, Schanke AK. Reliability and diagnostic characteristics of the JFK coma recovery scale-revised: exploring the influence of rater's level of experience. *J Head Trauma Rehabil* 2010;25:349-56.
14. Noé E, Olaya J, Navarro MD, Noguera P, Colomer C, García-Panach J, Rivero S, Moliner B, Ferri J. Behavioral recovery in disorders of consciousness: a prospective study with the Spanish version of the Coma Recovery Scale-Revised. *Arch Phys Med Rehabil* 2012;93:428-33.
15. Lombardi F, Gatta G, Sacco S, Muratori A, Carolei A. The Italian version of the Coma Recovery Scale-Revised (CRS-R). *Funct Neurol* 2007;22:47-61.
16. Sacco S, Altobelli E, Pistarini C, Cerone D, Cazzulani B, Carolei A. Validation of the Italian version of the Coma Recovery Scale-Revised (CRS-R). *Brain Inj* 2011;25:488-95.
17. La Porta F, Caselli S, Ianes AB, Cameli O, Lino M, Piperno R, Sighinolfi A, Lombardi F, Tennant A. Can we scientifically and reliably measure the level of consciousness in vegetative and minimally

- conscious states? Rasch analysis of the Coma Recovery Scale-Revised. *Arch Phys Med Rehabil* 2013;94:527-35.
18. Rappaport M, Hall KM, Hopkins K, Belleza T, Cope DN. Disability rating scale for severe head trauma: coma to community. *Arch Phys Med Rehabil* 1982;63:118-23.
  19. Fleiss JL, Cohen J. The equivalence of weighted kappa and the intraclass correlation coefficient as measures of reliability. *Education Psychol Measur* 1973;33:613-619.
  20. Kalmar K, Giacino JT. The JFK Coma Recovery Scale-Revised. *Neuropsychol Rehabil* 2004;15:454-60.
  21. Estraneo A, Moretta P, Loreto V, Lanzillo B, Santoro L, Trojano L. Late recovery after traumatic, anoxic, or hemorrhagic long-lasting vegetative state. *Neurology* 2010;75:239-45.
  22. Estraneo A, Moretta P, Loreto V, Lanzillo B, Cozzolino A, Saltalamacchia A, Lullo F, Santoro L, Trojano L. Predictors of recovery of responsiveness in prolonged anoxic vegetative state. *Neurology* 2013;80:464-70.
  23. Vanhauzenhuysse A, Schnakers C, Brédart S, Laureys S. Assessment of visual pursuit in post-comatose state: use a mirror. *J Neurol Neurosurg Psychiatry* 2008;79:223.
  24. Trojano L, Moretta P, Loreto V, Cozzolino A, Santoro L, Estraneo A. [Quantitative assessment of visual behavior in disorders of consciousness](#). *J Neurol* 2012;259:1888-95.
  25. Trojano L, Moretta P, Loreto V, Santoro L, Estraneo A. Affective saliency modifies visual tracking behavior in disorders of consciousness: a quantitative analysis. *J Neurol* 2013;260:306-8.
  26. Giacino JT, Schnakers C, Rodriguez-Moreno D, Kalmar K, Schiff N, Hirsch J. Behavioral assessment in patients with disorders of consciousness: gold standard or fool's gold? *Prog Brain Res* 2009;177:33-48.
  27. Wijndicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: the FOUR score. *Ann Neurol* 2005;58:585-93.

28. Shiel A, Horn SA, Wilson BA, Watson MJ, Campbell MJ, McLellan DL. The Wessex Head Injury Matrix (WHIM) main scale: a preliminary report on a scale to assess and monitor patient recovery after severe head injury. *Clin Rehabil* 2000;14:408-16.
29. Hirschberg R, Giacino JT. The vegetative and minimally conscious states: diagnosis, prognosis and treatment. *Neurol Clin* 2011;29:773-86.
30. Bernat JL. The natural history of chronic disorders of consciousness. *Neurology* 2010;75:206-7.

Figure legend.

Figure 1. Distribution of patients identified as VS or MCS by CRS-R with respect to classification based on clinical consensus diagnosis (left panel) and DRS (right panel): diagnostic agreement was higher between CRS-R and clinical consensus diagnosis, than between CRS-R and DRS, mainly because DRS underestimated the number of patients in MCS (see text).

Table 1. Criteria used in the current study for diagnostic classification based on Coma Recovery Scale-Revised (CRS-R)<sup>7</sup> or the Disability Rating Scale (DRS)<sup>18</sup>; table adapted from Løvstad et al.<sup>13</sup>)

	<b>VS</b>	<b>MCS</b>
<b>CRS-R</b>		
Auditory	$\leq 2$ and	3-4 or
Visual	$\leq 1$ and	2-5 or
Motor	$\leq 2$ and	3-5 or
Oromotor/verbal	$\leq 2$ and	3 or
Communication	0	1
<b>DRS</b>		
Best verbal response	$\geq 3$ and	0-1 or
Best motor response	$\geq 2$ and	0-1 or
Cognitive ability	3	0-2

Table 2. Inter-rater agreement on the single subscales of CRS-R and on the diagnostic classification based on CSR-R, expressed as Fleiss generalized Kappa statistic (and 95% Confidence interval), as a function of professional status and level of expertise.

Scale/Raters	All raters (n= 27)	Profession			Expertise		
		Physician (n= 11)	Psychologist (n= 5)	Other* (n= 11)	Low (n= 8)	Medium (n= 10)	High (n= 9)
Auditory	.76 (.66-.83)	.76 (.60-.86)	.83 (.59-.93)	.84 (.69-.92)	.83 (.66-.92)	.61 (.44-.75)	.81 (.64-.90)
Visual	.73 (.63-.81)	.81 (.66-.89)	.68 (.43-.84)	.73 (.57-.85)	.68 (.50-.82)	.62 (.45-.77)	.82 (.64-.91)
Motor	.76 (.66-.83)	.74 (.59-.85)	.76 (.52-.90)	.75 (.59-.86)	.78 (.60-.89)	.70 (.53-.83)	.82 (.65-.91)
Oromotor	.73 (.63-.81)	.78 (.63-.87)	.82 (.59-.92)	.67 (.51-.79)	.60 (.42-.75)	.75 (.58-.86)	.80 (.63-.89)
Communication	1	1	1	1	1	1	1
Arousal	.72 (.63-.80)	.68 (.53-.79)	.60 (.37-.78)	.81 (.67-.89)	.69 (.52-.81)	.64 (.48-.77)	.77 (.60-.87)
Diagnostic classification	.79 (.71-.84)	.88 (.76-.93)	.60 (.38-.77)	.78 (.64-.86)	.74 (.52-.83)	.68 (.53-.79)	1

\*Note: This group included physiotherapists (n= 3), speech therapists (n= 6) and nurses (n= 2).

Table 3. Median (and range) of the CRS-R Total Score, of CRS-R subscale scores, and of the DRS Total Score in patients affected by VS or MCS, as identified by CRS-R.

	VS (N= 62)	MCS (N= 60)
CRS-R Total Score	5 (1-8)	10 (6-17)
CRS-R subscales		
Auditory	1 (0-2)	2 (0-4)
Visual	0 (0-1)	3 (0-5)
Motor	2 (0-3)	3 (0-5)
Oromotor/verbal	1 (0-2)	1 (0-3)
Communication	0	0 (0-1)
Arousal	1.5 (02)	2 (1-3)
DRS Total Score	25 (22-29)	22 (19-26)



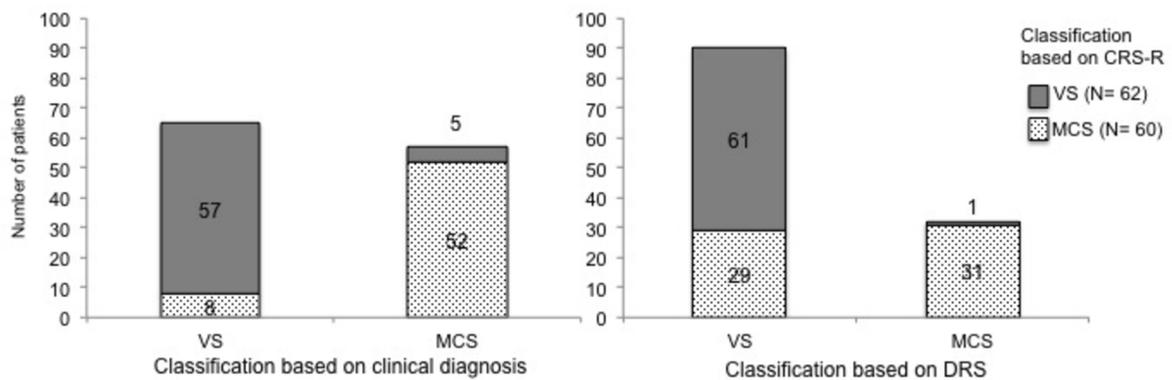


Figure 1