Published in : Journal of Neurology (2020), n° 267, pp. 1245–1254
DOI: 10.1007/s00415-019-09628-y
Status : Postprint (Author's version)

Minimally conscious state "plus": diagnostic criteria and relation to functional recovery

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Keywords: Minimally conscious state • Disorders of consciousness • Brain-injuries • Coma recovery scale-revised • Disability rating scale • Command-following • Intentional communication • Intelligible verbalization

Abbreviations:

CRS-R Coma recovery scale-revised
DoC Disorders of consciousness
DRS Disability rating scale
MCS Minimally conscious state
TBI Traumatic brain injury
UWS/VS Unresponsive wakefulness syndrome/vegetative state

Abstract

Background We investigated the relationship between three language-dependent behaviors (i.e., command-following, intelligible verbalization, and intentional communication) and the functional status of patients with disorders of consciousness (DoC). We hypothesized that patients in minimally conscious state (MCS) who retain behavioral evidence of preserved language function would have similar levels of functional disability, while patients who lack these behaviors would demonstrate significantly greater disability. We reasoned that these results could then be used to establish empirically-based diagnostic criteria for *MCS+*.

Methods In this retrospective cohort study we included rehabilitation inpatients diagnosed with DoC following severe- acquired brain injury (MCS = 57; vegetative state/unresponsive wakefulness syndrome [VS/UWS] = 63); women: 46; mean age: 47 ± 19 years; traumatic etiology: 68; time post-

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injury: 40 ± 23 days). We compared the scores of the Disability Rating Scale score (DRS) at time of transition from VS/UWS to MCS or from *MCS-* to *MCS+*, and at discharge between groups. Results Level of disability on the DRS was similar in patients with any combination of the three language-related behaviors. MCS patients with no behavioral evidence of language function (i.e., *MCS-*) were more functionally impaired than patients with *MCS+* at time of transition and at discharge.

Conclusions Command-following, intelligible verbalization, and intentional communication are not associated with different levels of functional disability. Thus, the *MCS+* syndrome can be diagnosed based on the presence of any one of these language-related behaviors. Patients in *MCS+* may evidence less functional disability compared to those in MCS who fail to demonstrate language function (i.e., *MCS-*).

Introduction

In patients with disorders of consciousness (DoC) caused by severe-acquired brain injury, clinical decisions regarding medical management, prognosis, and intensity of care hinge on establishing an accurate diagnosis [1]. Thus, diagnostic criteria must be able to distinguish states of consciousness associated with different trajectories of recovery and functional outcome. Behavioral assessment is currently the gold standard for establishing diagnosis and prognosis in patients with DoC. However, recent evidence from neuroimaging studies has elucidated pathophysiologic differences that have informed important nosological distinctions needed for appropriate clinical management [2-4]. The term, "vegetative state," was originally coined to highlight preserved vegetative (autonomous) nervous system functions (e.g., sleep-wake cycle, breathing, digestion or thermoregulation, and basic motor reflexes) in comatose patients who subsequently recover eye-opening but do not express any purposeful behavior [5]. The term, "unresponsive wakefulness syndrome (UWS)," has recently been introduced to describe this awake but behaviorally-unresponsive state, and to eliminate the pejorative connotations of the "vegetative state" [6]. In 2002, a case definition for the "minimally conscious state" (MCS) was published by a joint working group of neurologic specialties, differentiating unconscious patients (i.e., VS/UWS) from those retaining limited but clearly-discernible behavioral signs of consciousness (i.e., MCS [7]). Criteria were also established to mark emergence from MCS, centering on recovery of functional communication or object use [7]. Recognizing the clinical heterogeneity of MCS, two sub-categories, termed *MCS+* and *MCS-*, were proposed based on the presence or absence, respectively, of behavioral evidence of residual language function as measured by the Coma recovery scale-revised (CRS-R) [8]. *MCS+* was initially defined by the presence of (a) command-following, (b) intelligible verbalization, or (c) gestural or verbal yes/ no intentional communication [9] while *MCS-* included (a) automatic motor behaviors (e.g., nose-scratching), (b) object manipulation (e.g., grasping and holding a cup), (c) localizing objects in space (e.g., reaching for and grasping the examiner's hand), (d) localizing noxious stimuli (e.g.,

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rubbing an area that has just been pinched), (e) visual pursuit, and (f) visual fixation, but no evidence of receptive or expressive language function.

The subcategorization of MCS is further supported by functional neuroimaging data showing significantly greater preservation of metabolic activity and resting state functional connectivity in the language network of patients in *MCS+* as compared to those in *MCS-* [10]. It is important to note however that these data were acquired in a study that did not use the same criteria to define *MCS+* as those proposed in the original study. Specifically, only reproducible command-following was used to designate patients as *MCS+* (i.e., intelligible verbalization and intentional communication were not considered). Some recent structural and functional neuroimaging studies [11, 12] have relied on the same *MCS+* criteria as first proposed by Bruno et al. (i.e., command-following, intelligible verbalizations, or yes/no signaling [9]) while others refer generally to "preserved language functions" or "high-level behavioral interactions, such as command-following," without identifying the specific behaviors used to differentiate *MCS+* and - [13, 14]. In a recent review of MCS, Schnakers et al. proposed object recognition, reproducible command-following, and intelligible verbalization as defining features of *MCS+*, while excluding intentional communication [15]. Given the variability of the *MCS+*/- criteria proposed in the published literature, and the risks associated with definitional inconsistency, a standardized definition should be adopted to ensure consistent communication between clinicians, and to provide a more uniform approach to research in this population.

The aim of the current study is to develop empirically- driven, behaviorally-based diagnostic criteria for *MCS+*. To determine which behaviors should be included in the diagnostic criteria for *MCS+*, we investigated the relationship between three different language-related behaviors and the level of functional disability evident in patients transitioning from VS/UWS to *MCS+* or -, or from *MCS-* to *MCS+*. We hypothesized that patients in MCS who retain behavioral evidence of preserved language function (i.e., command following, intelligible verbalization, intentional communication) would have similar levels of functional disability, while patients who lack these behaviors would demonstrate significantly greater disability.

Methods

In this retrospective study, we used the CRS-R [8] to identify subjects who recovered at least one of the following behaviors representing preserved language function: command following, intelligible speech and intentional communication (i.e., *MCS+*). We also identified patients who recovered signs of consciousness not related to language function (i.e., *MCS-*). After identifying these cases, we determined their corresponding Disability Rating Scale (DRS) score [16] at transition from VS/UWS to MCS, or from *MCS-* to *MCS+* and at discharge from inpatient rehabilitation, to determine if there were significant differences in disability severity between patients demonstrating any of these three behaviors as compared to those without any evidence of preserved language function.

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Participants

Inclusion criteria were: (1) acquired brain injury; (2) at least 16 years old; (3) between 2 and 20 weeks post-injury; (4) evidence of recovery of at least one feature of *MCS*- or *MCS*+ on the CRS-R during the rehabilitation stay (i.e., patients admitted in VS/UWS who transitioned to *MCS*- or +, or patients admitted in *MCS*- who transitioned to *MCS*+); (5) DRSscore available within 7 days of the index CRS-R assessment. We excluded patients who presented with one or more signs of *MCS*+ at admission so that we could capture patients who transitioned to *MCS*+ while they were in rehabilitation. For patients who were readmitted due to an intervening acute hospitalization, we only used data from the first admission. We also included MCS patients who did not demonstrate any behavioral evidence of language function (i.e., *MCS*-) for comparative analyses.

Measures

CRS-R

The CRS-R consists of six subscales that assess auditory, visual, motor, verbal, communication, and arousal functions. Each subscale includes hierarchically-ordered items that progress from brain stem reflexes (e.g., auditory startle) to cognitively- mediated behaviors (e.g., command-following). Diagnosis is based on the presence of operationally-defined behavioral responses to standardized assessment procedures as described in the CRS-R Administration and Scoring Manual [17]. The CRS-R was designated as a Traumatic Brain Injury Common Data Element by the National Institute on Neurological Disorders and Stroke and is the top-ranked behavioral assessment scale for patients with DoC based on a systematic review conducted by American Congress of Rehabilitation Medicine [18].

Operational definitions of the three language-related behaviors are described below.

Consistent command-following: eight clearly-discernible behavioral responses are observed over sight consecutive trials of two different commands.

Reproducible command-following: three clearly-discernible behavioral responses are observed over four consecutive trials on at least one of two commands.

Intelligible verbalization: two different words are recognized, each consisting of a consonant-vowel-consonant (C-V-C) triad (words produced by writing or alphabet board are acceptable).

Intentional communication: at least two clearly-discernible verbal or gestural yes-no responses are observed within 10 s in response to six situational orientation questions. On the CRS-R, intentional communication is only administered if there is evidence of command-following or spontaneous communication.

DRS Level of disability was determined using the DRS [16]. This instrument assesses (1) eye-opening, verbalization, and motor responses (derived from the Glasgow Coma Scale), (2) cognitive

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ability for feeding, dressing, and grooming, (3) overall degree of assistance and supervision required, and (4) employability. Scores range from 0 to 29, with higher values indicating greater degree of disability [16]. The DRS measures function disability from across the spectrum of recovery after TBI ranging from coma to com-munity reintegration.

Procedure

We used data acquired from patients admitted to an inpatient DoC rehabilitation program. Data were extracted from a REDCap database (https://www.redcap.org) [19] that includes demographic and clinical data on 272 patients admitted approximately 1 month post-onset (35 ± 31 days). The REDCap database was approved by the local Institutional Review Board. Data were acquired during routine clinical care by trained clinicians.

We reviewed the REDCap DoC database to identify patients who met our inclusion/exclusion criteria and divided the sample into the following seven groups based on CRS-R performance: recovery of (1) command-following only (i.e., auditory subscale score ≥ 3 or visual subscale score = 5), (2) intelligible verbalization only (i.e., oromotor subscale score = 3), (3) intentional communication only (i.e., communication subscale score = 1), (4) command-following, and either intentional communication or intelligible verbalization observed during the same assessment, (5) intentional communication and intelligible verbalization without command-following observed during the same assessment (6) command-following, intentional communication, and intelligible verbalization observed during the same assessment, and (7) no evidence of language function but demonstrates at least one behavioral feature of MCS (i.e., visual pursuit, visual fixation, object localization, localization to noxious stimulation, object manipulation, automatic motor behavior). Participants in groups one through six meet the criteria for *MCS+* while those in group 7 meet criteria for *MCS-*. Operational definitions for each group are presented in Table 1.

Because the DRS was performed weekly, the corresponding DRSs were collected within 7 days of the CRS-R assessment. The average time between the CRS-R assessment at transition and the DRS assessment was 2.7 ± 2.0 days. Figure 1 summarizes the study protocol.

The primary outcome was degree of disability as measured by the DRS total score at the time of transition from VS/UWS to *MCS+* or -, or from *MCS-* to *MCS+*. The secondary outcome was the DRS total score at discharge from the DoC program. We also compared the DRS total score on admission to rehabilitation to determine whether level of disability was similar across groups at admission to the rehabilitation program.

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Table 1. *Operational criteria for minimally conscious state (MCS) plus and minus*

Group	Operational criteria
1. *MCS*+—A3	Response to command (score of 3 or 4 on the CRS-R auditory subscale)
2. *MCS*+—O3	Intelligible verbalization (score of 3 on the CRS-R verbal subscale)
3. *MCS*+—C1	Intentional communication (score of 1 on the CRS-R communication subscale)
4. *MCS*+—A3 & C1 or O3	Response to command and intentional communication or intelligible verbalization
5. *MCS*+—O3 & C1	Intelligible verbalization and intentional communication
6. *MCS*+—A3 & O3 & C1	Response to command and intelligible verbalization and intentional communication
7. *MCS*-	No evidence of language function but demonstrates at least one behavioral feature of MCS (i.e., visual pursuit, visual fixation, object localization, localization to noxious stimulation, object manipulation, automatic motor behavior)

A3 command-following, *O3* intelligible verbalization, *C1* intentional communication

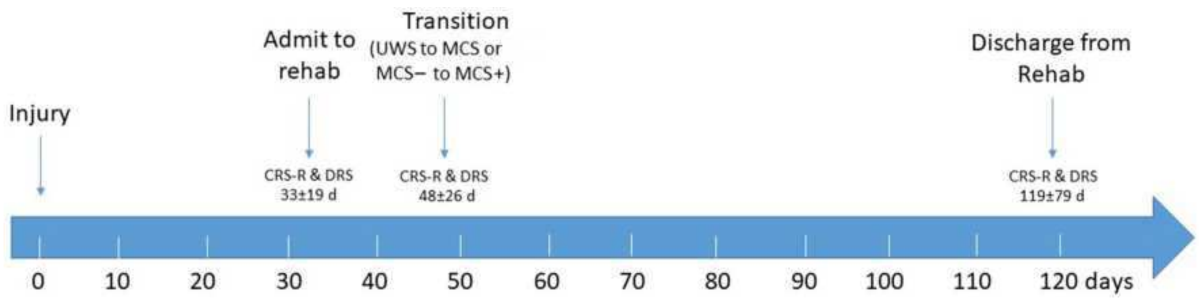

Fig. 1. *Study protocol. CRS-R coma recovery scale-revised, DRS disability rating scale, MCS minimally conscious state, UWS unresponsive wakefulness syndrome*

As exploratory analyses, we evaluated differences between the seven groups based on injury etiology (TBI vs non-TBI).

Finally, as the DRS includes one subscale that assesses communication, and this ability is a criterion for *MCS+*, to avoid a tautology of measurement, we subtracted the Communication subscale score from the total DRSscore (decreasing the maximum DRS total score to 25) and repeated the primary and exploratory analyses comparing disability level at the time of transition between groups.

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Statistical analyses

We used analysis of variance (ANOVA) models to compare the difference in DRS total scores between the seven groups at admission. We also compared the time interval between the injury and transition from UWS to MCS or from *MCS-* to *MCS+*, between the injury and admission to rehabilitation, and between the injury and discharge from rehabilitation between the seven groups to evaluate the influence of chronicity on outcomes.

We also used ANOVA models to compare the difference in DRS total scores between the seven groups at time of transition and at discharge.

We performed post-hoc analyses with Student's t test, and applied Bonferroni correction for multiple comparisons (*MCS-* vs the other six groups), to determine which groups contributed significantly to explaining the variance in the ANOVA findings. For all Bonferroni corrected results, significance was determined to be at $p < 0.0083$. Analyses within the six *MCS+* groups were conducted in an exploratory manner and were therefore not corrected for multiple comparisons. We also investigated differences between groups of patients with traumatic and non-traumatic etiologies, separately, in an exploratory analysis using Student's t tests after grouping the six *MCS+* groups (i.e., *MCS-* vs all *MCS+*). Descriptive statistics are reported as means with standard deviations (SD). All analyses were performed with Stata Statistical Software 13.2 (StataCorp, College Station, TX).

Results

We screened 272 patients and 120 met all inclusion criteria (40 ± 23 days post-onset at admission; 63 VS/UWS and 57 *MCS-* at admission; 68 TBI; 46 women, see supplementary figure S1 for reasons for exclusion and supplementary table S1 for demographic and clinical characteristics per etiology). Non-TBI etiologies included 34 hemorrhagic stroke, four ischemic stroke, 11 anoxia, one meningitis, one sepsis, and one brain tumor). Demographic data are presented in Table 2. While a significant group effect was found (F=2.95; p = 0.0129) for DRS score at admission, none of the post-hoc tests comparing the *MCS-* group with the six *MCS+* groups reached significance after Bonferroni correction. There were no between-group effects for time since injury (F= 1.91; p = 0.0846), time to admission (F= 1.28; p = 0.2737) or time to discharge (F = 1.42; p = 0.2138) so these variables were not included in subsequent analyses.

DRS at transition from VS/UWS to MCS or transition from MCS- to MCS+ DRS total scores differed between the seven groups at time of transition from VS/UWS to MCS or *MCS-* to *MCS+* (F = 5.61; p < 0.001). Post-hoc testing revealed that patients in *MCS-* had significantly higher DRS scores (i.e., more disability) than each of the other six groups (all p values < 0.001). The group that recovered all three language-related behaviors simultaneously (i.e., command following, intelligible verbalization, and intentional communication) had lower (i.e., better) DRS total scores than the

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groups presenting with command-following only *(p* < 0.001), verbalization only *(p* = 0.002) or intentional communication only *(p* < 0.001). There was no difference in DRS scores between the groups presenting with command-following only, intelligible verbalization only, and intentional communication only, at the time of transition from VS/UWS to *MCS+* or the transition from *MCS-* to *MCS+*. Results are presented in Table 3 and Fig. 2.

DRS at discharge

A significant group effect was found for DRS score at dis-charge *(F*=4.97; *p* <0.001). Post-hoc analysis revealed that patients in *MCS-* had significantly higher DRS (i.e., worse) scores at discharge than any other group (all *p* values < 0.001). No other group comparisons showed significant differences (see Fig. 3).

Subgroup analyses

Among the 68 patients with TBI, only three were in the *MCS-* group, therefore, we report only mean and standard deviations for each group. At the time of transition from *MCS-* to *MCS+*, patients in *MCS- (n* = 3) had DRS scores of 23.0 ±0.0, while patients in *MCS+ (n* = 65) had DRS scores of 18.9 ± 3.2. At discharge, patients in *MCS-* had DRS scores of 21.3 ± 1.1, while patients in *MCS+* had DRS scores of 12.9 ± 5.1 (see supplementary Fig. 1).

Among the 52 non-TBI patients, those in *MCS- (n* = 6) had significantly higher DRS scores at time of transition and at discharge relative to those in *MCS+ (n* = 46) *(t* = 3.57; p< 0.001 and *t* = 3.84; *p* < 0.001, respectively, supplementary figure S2).

Results remained significant after we re-ran the analysis comparing disability level between groups at the time of transition with the Communication subscale score subtracted from the total DRS score (F = 3.93; *p* = 0.001). The *MCS-* group had significantly lower (i.e., worse) DRS scores than all other groups (all *p* values < 0.05—supplementary figure S3).

Discussion

The results of this study support our primary hypothesis that patients in MCS who retain behavioral evidence of receptive or expressive language ability have less functional disability when assessed between 3 and 6 months post-injury than those who lack this ability. This finding was evident at both assessment points: time of transition to MCS and at discharge from rehabilitation. Although disability ratings were similar in patients with any combination of command following, intelligible verbalization, and intentional communication, those who demonstrated all three behaviors at the same time-point had significantly less disability than those with fewer language-related behaviors. For patients in *MCS-*, level of disability remained in the "extremely severe" range from the point of transition in consciousness to discharge. In contrast, patients in *MCS+* (all groups but those who recovered the three language-related behaviors simultaneously) improved from "extremely severe" disability at the time of transition to "severe" disability at discharge. Moreover,

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patients who recovered all three language-related behaviors simultaneously, improved from the "severe" to "moderately severe" disability range at discharge (see Table 2). The evidence from this study, acquired using well-established standardized assessment measures and empirically-based (vs consensus-based) diagnostic criteria, indicates that (1) command-following, intelligible verbalization and intentional communication (alone or in combination) are associated with the same level of functional disability, and (2) the absence of these behaviors is linked to significantly higher (i.e., worse) disability ratings during the first 3-6 months post-injury. These findings suggest that all three language- related behaviors-command-following, intelligible verbalization, and intentional communication, should be included in the diagnostic criteria for *MCS+*, as originally proposed by Bruno et al. [10] (see Fig. 4).

MCS is a heterogeneous condition that includes patients with various types and degrees of cognitive dysfunction. The original subcategorization of *MCS+* and - was based on the presence of behaviors indicating at least partial preservation of language function [9]. This subcategorization was later supported by a neuroimaging study evaluating regional brain metabolism of patients in *MCS-* and *MCS+*, showing that patients in *MCS-* demonstrated partially-preserved metabolism in the brainstem and right hemisphere, while the left hemisphere, including Broca's and Wernicke's regions, posterior parietal, supplementary motor, sensorimotor and premotor areas, was impaired. Conversely, patients diagnosed with *MCS+* showed preservation of the language network in the left hemisphere, as well as the premotor, supplementary motor, and sensorimotor areas [10].

Command-following requires preserved functional connectivity between neural networks responsible for mediating language comprehension, memory, volition, and motor execution. To understand spoken language, for example, a complex series of processing steps is required to translate sounds into meaningful linguistic content. The neural networks underlying this system include left- lateralized frontal and temporal cortices [20-22] and the cerebellum [23, 24]. Previous studies have identified various subprocesses of verbal working memory in structures of the left inferior frontal gyrus [25] while the capacity for voluntary action depends on the functional integrity of the pre-supplementary motor area, anterior prefrontal, and parietal cortices. These networks have been shown to be partially preserved in patients diagnosed with *MCS+* but not in those with *MCS-* [10, 12].

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Table 2. *Demographic characteristics and DRSs at admission, time of transition (from UWS to MCS—/+ or from MCS— to MCS+) and discharge*

Group	*N*	Diagnosis at admission/etiology	Age (gender-female)	DRS at admission (severity category)	Time at admission (days post-injury)	DRS at time of transition to MCS (severity category)	Days post-injury at transition from UWS to MCS or *MCS-* to MCS±	DRS at discharge (severity category)	Days post-injury at discharge
All	120	57 *MCS*-63 UWS 68 TBI-52 NTBI	46.68 ±18.85 (46 women)	21.83 ±2.79 (extremely severe)	32.23 ±18.98	19.21 ±3.21 (extremely severe)	48.20 ±25.95	14.06 ±5.07 (severe)	119.02±78.88
A3	39	18 *MCS*-21 UWS 25 TBI-14 NTBI	38 ± 17 years (16 women)	22.56±2.58 (vegetative state)	43.85±13.42	19.23± 3.13 (extremely severe)	43.28 ±13.43	13.23 ± 5.36 (severe)	118.615± 82.73
03	14	9 *MCS*-5 UWS 7 TBI-7 NTBI	52 ± 17 years (six women)	21.36±3.18 (extremely severe)	34.29±31.54	18.93 ±3.49 (extremely severe)	59.00±43.30	14.64±6.38 (severe)	157.71 ±113.123
Cl	12	4 *MCS*-8 UWS 6 TBI-7 NTBI	45 ± 24 years (seven women)	22.00±2.26 (vegetative state)	41.59±32.65	19.83±2.16 (extremely severe)	59.58±37.55	14.92 ±4.72 (severe)	145.58 ±92.59
A3 + C1 or 03	21	9*MCS*-12UWS 15 TBI-6 NTBI	54 ±21 years (five women)	21.57 ±3.20 (extremely severe)	26.29 ±22.57	19.81 ± 3.30 (extremely severe)	42.57±23.35	14.09 ±3.78 (severe)	118.95± 82.60
C1 + O3	13	7 *MCS*-6 UWS 4 TBI-9 NTBI	51 ± 16 years (six women)	20.80±2.80 (extremely severe)	38.78± 19.34	18.15±2.64 (extremely severe)	45.92 ± 18.48	13.08 ± 3.97 (severe)	85.85±27.51
A3 + C1+O3	12	9 *MCS*-3 UWS 7 TBI-5 NTBI	54 ± 10 (four women)	19.92±2.31 (extremely severe)	3O.O8± 13.52	16.08 ±2.27 (severe)	41.42 ± 14.59	10.83 ± 3.24 (moderately severe)	98.67 ±36.77
MCS-	9	2 *MCS*-7 UWS 3 TBI-6 NTBI	43 ±19 years (two women)	23.89 ±1.26 (vegetative state)	41.33 ±16.53	23.11 ±0.53 (extremely severe)	63.00±32.88	21.22±1.72 (extremely severe)	100.33 ±31.67

DRS disability rating scale, *MCS* minimally conscious state, UWS unresponsive wakefulness syndrome, *A3* command-following, *O3* intelligible verbalization, *C1* intentional communication, *TBI* traumatic brain injury, *NTBI* non-traumatic brain injury

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Table 3. *Comparison of DRSs between groups at time of transition to MCS and at discharge*

Subgroup comparison (*t* tests)	DRS at transition to MCS	DRS at discharge
MCS- vs command-following only	*t* =3.732; *p* <0.001	*t* =4.518;*p*< 0.001
MCS- vs intelligible speech only	*t* =3.505; *p* =0.002	*t*=3.002;*p* = 0.007
MCS- vs intentional communication only	*t* =4.308; *p* <0.001	*t*=3.804;*p* = 0.001
MCS- vs command-following + intentional communication or intelligible verbalization)	*t* = 2.942; *p* =0.006	*t*=5.382;*p* < 0.001
MCS- vs (intentional communication + intelligible verbalization)	*t* =5.432; *p* <0.001	*t*=5.763;*p* < 0.001
MCS- vs (command-following + intentional communication or intelligible verbalization)	*t* = 8.837; *p* <0.001	*t*=8.704;*p* < 0.001

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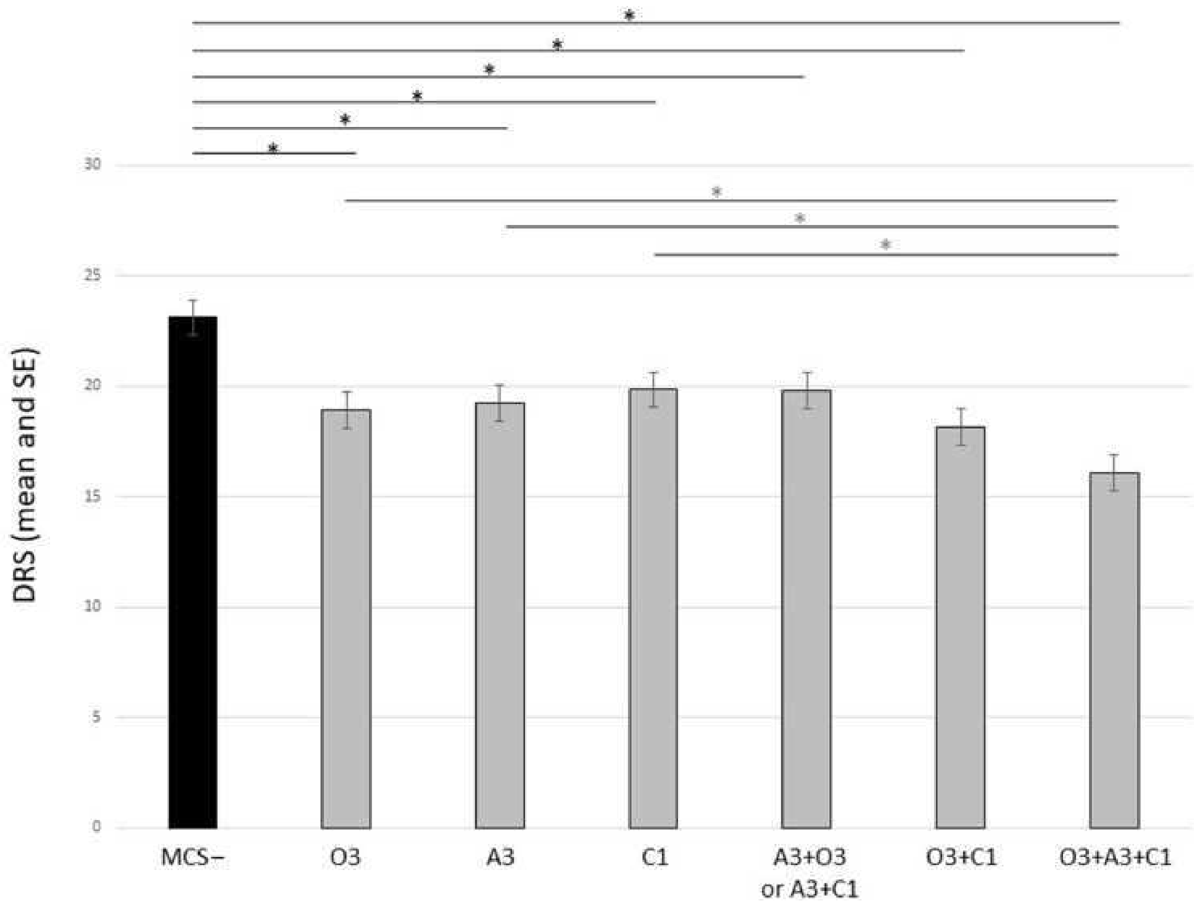

Fig. 2. *DRS total scores (means and SEs) for each group at transition from UWS to MCS- (black column) or at transition from UWS or MCS- to MCS+ (six grey columns). A3 command-following, C1 intentional communication, DRS disability rating scale, MCS minimally conscious state minus, O3 intelligible verbalization. Black asterisks represent statistical differences between groups corrected for multiple comparisons (Bonferroni corrected). Grey asterisks represent a significant difference uncorrected for multiple comparisons*

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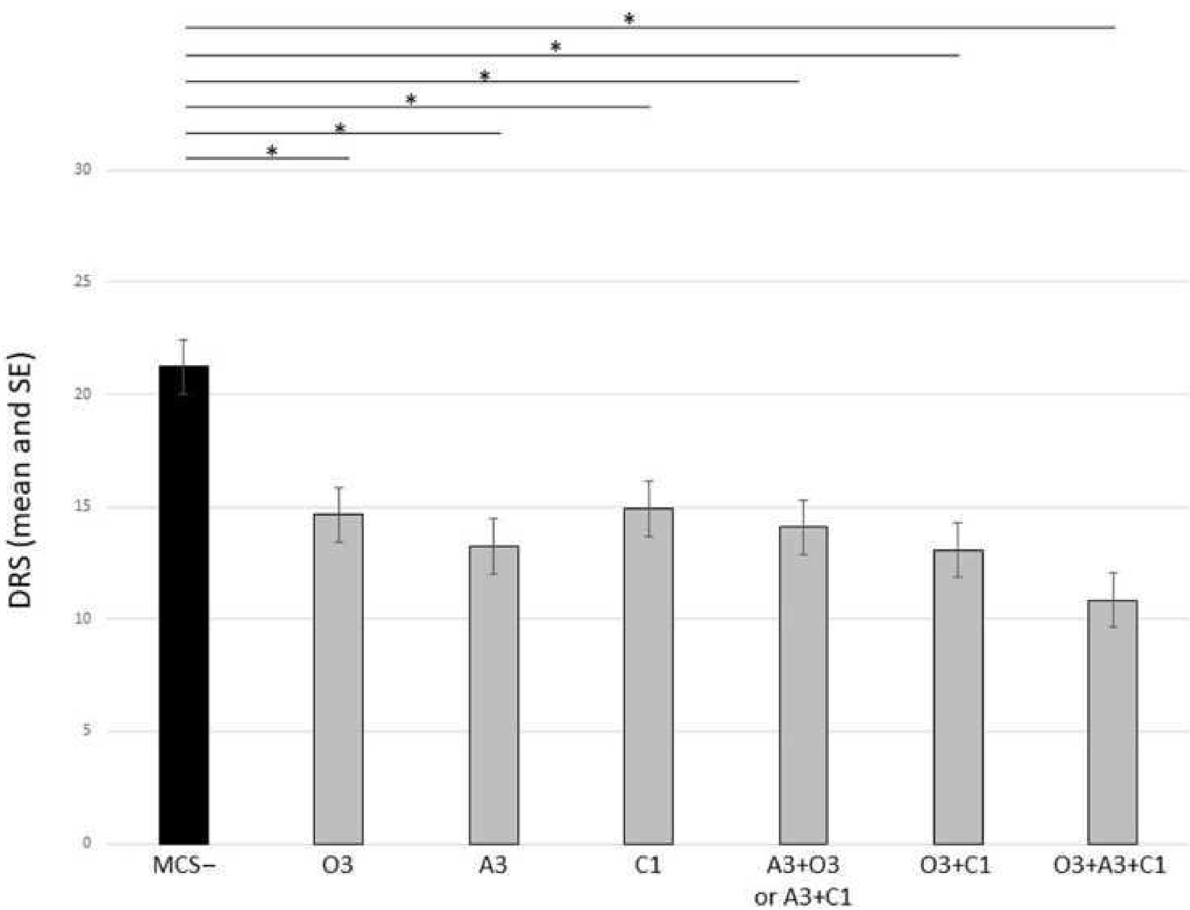

Fig. 3. *DRS* total scores (means and SEs) for each group group at discharge from rehabilitation. *A3* command-following, *C1* intentional communication, *DRS* disability rating scale, *MCS* minimally conscious state minus, *O3* intelligible verbalization. Black asterisks represent statistical differences between groups corrected for multiple comparisons (Bonferroni corrected). Grey asterisks represent a significant difference uncorrected for multiple comparisons

Command-following requires preserved functional connectivity between neural networks responsible for mediating language comprehension, memory, volition, and motor execution. To understand spoken language, for example, a complex series of processing steps is required to translate sounds into meaningful linguistic content. The neural networks underlying this system include left- lateralized frontal and temporal cortices [20-22] and the cerebellum [23, 24]. Previous studies have identified various subprocesses of verbal working memory in structures of the left inferior frontal gyrus [25] while the capacity for voluntary action depends on the functional integrity of the pre-supplementary motor area, anterior prefrontal, and parietal cortices. These networks have been shown to be partially preserved in patients diagnosed with *MCS+* but not in those with *MCS-* [10, 12].

A recent review addressing parcellation of language functions sought to determine whether language and communication are supported by distinct brain regions [26]. Relying on neuroimaging and neuropsychological studies, the authors concluded that language and

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DOI: 10.1007/s00415-019-09628-y
Status : Postprint (Author's version)

communication abilities are mediated by different cortical systems [27-30]. Studies of patients with lesions involving the language network indicate that some aphasic patients retain the ability to perform communicative tasks [31, 32]. The degree of functional disability evidenced by patients who can signal "yes" and "no," regardless of accuracy, is similar to the level of disability experienced by those who can verbalize intelligibly or follow commands. Patients who recover either receptive or expressive language function (i.e., *MCS+*), therefore, are likely to have less severe functional disability in the short-term than those who do not (i.e., *MCS-*). Early recovery of language function (i.e., *MCS+*) may also prove to be a predictor of more favorable long-term outcome, further justifying the need for clear diagnostic criteria for *MCS+*.

Study limitations

This study has some limitations that should be considered. First, our sample size did not permit us to perform subgroup analyses to account for differences related to etiology. Second, this is a retrospective study performed in a rehabilitation center with a specialized DOC program and the results may not be generalizable to patients cared for in other settings that do not provide the same intensity and type of care. Third, the interval between the DRS and CRS-R assessments was 7 days. While it would have been optimal if both measures were acquired concurrently, rate of recovery in this population reduces the likelihood that degree of disability would have changed substantially within a 1-week period. Finally, we do not know whether the outcome advantage in the *MCS+* group would be retained over a longer term as the observation period was limited to the inpatient rehabilitation stay. Nonetheless, a lower burden of disability during inpatient rehabilitation has implications for nursing acuity and treatment planning. A prospective multicenter study with a larger sample size and longer follow-up is required to address these issues.

Conclusions

The lower boundary of the *MCS+* syndrome should be marked by reproducible evidence of any one of the following behaviors: (1) command-following, (2) intelligible verbalization, or (3) intentional communication (i.e., discernible verbal or gestural yes-no responses, regardless of accuracy). Reproducible evidence of reliable yes-no communication and functional object should continue to establish the upper boundary of *MCS+*. Future prospective studies should investigate differences in long-term functional outcome (i.e., > 6 months) between patients in *MCS+* and *MCS-*.

Published in : Journal of Neurology (2020), n° 267, pp. 1245–1254
DOI: 10.1007/s00415-019-09628-y
Status : Postprint (Author's version)

COMA RECOVERY SCALE - REVISED
Record Form

Patient: **Date:**								
AUDITORY FUNCTION SCALE								
4 - Consistent Movement to Command ·								
3 - Reproducible Movement to Command ·								
2 - Localization to Sound								
1 - Auditory Startle								
0 - None								
VISUAL FUNCTION SCALE								
5 - Object Recognition								
4 - Object Localization: Reaching								
3 - Pursuit Eye Movements								
2 - Fixation *								
1 - Visual Startle								
0 - None								
MOTOR FUNCTION SCALE								
6 - Functional Object Use †								
5 - Automatic Motor Response *								
4 - Object Manipulation *								
3 - Localization to Noxious Stimulation *								
2 - Flexion Withdrawal								
1 - Abnormal Posturing								
0 - None/Flaccid								
OROMOTOR/VERBAL FUNCTION SCALE								
3 - Intelligible Verbalization ·								
2 - Vocalization/Oral Movement								
1 - Oral Reflexive Movement								
0 - None								
COMMUNICATION SCALE								
2 - Functional: Accurate †								
1 - Non-Functional: Intentional ·								
0 - None								
AROUSAL SCALE								
3 - Attention *								
2 - Eye Opening w/o Stimulation								
1 - Eye Opening with Stimulation								
0 - Unarousable								
TOTAL SCORE								

Denotes emergence from MCS †
Denotes *MCS-* *
Denotes *MCS+* ·

Fig. 4. *Coma recovery scale-revised (CRS-R) record form showing behavioral criteria for MCS-, MCS+ and MCS emergence.*

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Status : Postprint (Author's version)

Acknowledgements Dr. Aurore Thibaut is a FNRS is a post-doctoral research fellow and has been supported by the Wallonie Brussel International (WBI) scholarship, the Belgian American Educational Foundation (BAEF), and the Leon Fredericq Foundation. Dr. Bodien is supported by the National Institute on Disability, Independent Living and Rehabilitation Research (NIDILRR), Administration for Com-munity Living (90DP0039, Spaulding-Harvard TBI Model System). Dr. Giacino received support from NIDILRR (90DP0039, Spaulding- Harvard TBI Model System) and the James S. McDonnell Foundation (Understanding Human Cognition-Collaborative). The authors thank the clinical staff at Spaulding Hospital Cambridge and Spaulding Rehabilitation Hospital for acquiring the clinical metrics used in this study.

COMPLIANCE WITH ETHICAL STANDARDS

Conflicts of interest The authors report no conflict of interest.

Ethical standards The REDCap database was approved by the local Institutional Review Board. Data were acquired during routine clinical care by trained clinicians.

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