

ORIGINAL RESEARCH

# Behavioral Fluctuation in Disorders of Consciousness: A Retrospective Analysis



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## Abstract

**Objectives:** To assess the frequency of behavioral fluctuations in patients with prolonged disorders of consciousness (DoC), characterize the stability of consciousness ratings, and characterize the stability of behavioral signs of consciousness.

**Design:** Prospective observational analysis.

**Setting:** Specialized DoC program in an inpatient rehabilitation facility and a long-term acute care hospital.

**Participants:** Patients in a vegetative state/unresponsive wakefulness state, minimally conscious state, and emerging from a minimally conscious state followed weekly by the Coma Recovery Scale-Revised (CRS-R) between 28 and 90 days postinjury (N=241).

**Main Outcome Measures:** Change in CRS-R subscale scores and consciousness ratings.

**Results:** Behavioral fluctuation was observed in >80% of patients and was most common in the CRS-R motor subscale and least common in the communication subscale (83% and 54% of patients experienced  $\geq 1$  fluctuation over the 3wk study period, respectively, with a 1-point change observed most frequently). Among patients who were conscious at baseline assessment, 25% were subsequently rated as unconscious at least once. Localization to pain and object manipulation were the most stable signs of consciousness, recurring at least 3 times after the first occurrence in  $\geq 97\%$  of the sample. Reproducible command-following and intelligible verbalization were the least stable, recurring at least 3 times after the first occurrence in  $\leq 27\%$  of the sample.

**Conclusions:** Patients with prolonged DoC who undergo serial assessment demonstrate a high rate of fluctuation in behavioral signs of consciousness. These findings highlight that repeated assessments are essential in this population, both to capture the highest level of consciousness and to help distinguish spontaneous fluctuation from response to treatment in interventional studies.

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Disorders of consciousness (DoC) are common after severe acquired brain injury. The 3 major DoCs are coma, vegetative state (VS), also referred to as unresponsive wakefulness syndrome (UWS), and minimally conscious state (MCS). The defining feature of a coma is the complete loss of wakefulness.<sup>1</sup> The eyes are continuously closed, and the patient cannot be aroused. There are also no observable signs of cognition or purposeful motor activity. In VS/UWS, sleep-wake cycles return along with spontaneous eye-opening in the absence of behavioral signs of self or environmental awareness.<sup>2</sup> In MCS, there is minimal but definite behavioral evidence of self or environmental awareness demonstrated by simple command-following, intelligible verbalization, recognizable but unreliable verbal or gestural “yes/no” responses, or behaviors that selectively occur in the presence of specific environmental stimuli and cannot be attributed to reflexive activity (eg, visual tracking of a moving object).<sup>3</sup> MCS has been subcategorized into “MCS-plus (MCS+)” and “MCS-minus (MCS-)” based on the presence or absence, respectively, of receptive or expressive language function.<sup>4</sup> Emergence from MCS (eMCS) is signaled by the recovery of reliable communication or functional object use.<sup>3</sup> Patients who emerge from traumatic MCS typically transition into the posttraumatic confusional state.<sup>5</sup>

Diagnostic assessment of patients with DoC is complex. Prior studies suggest that approximately 40% of patients who are believed to be unconscious based on routine bedside examination actually retain conscious awareness.<sup>6,7</sup> Fluctuation in behavioral responsiveness, a hallmark feature of DoC, is among a myriad of confounding factors that can contribute to misdiagnosis. This phenomenon has been described in both acute and prolonged (ie, >28d postinjury) DoC.<sup>3,8</sup> Patients with DoC may demonstrate clear and convincing evidence of command-following in one examination and then fail to show this sign of consciousness when the examination is repeated shortly afterward. Although behavioral fluctuation in DoC is widely recognized by investigators and clinicians,<sup>9</sup> the frequency of these fluctuations and their effect on diagnostic assessment have not received adequate attention. Behavioral fluctuation can lead to significant consequences, including misdiagnosis and misattributing normal behavioral variability to treatment effects. Misdiagnosis in DoC is common,<sup>6</sup> even when using a standardized behavioral assessment instrument such as the Coma Recovery Scale-Revised (CRS-R),<sup>10</sup> which is considered the most reliable behavioral tool to evaluate patients with DoC.<sup>10,11</sup> Wannez et al<sup>12</sup> found that at least 5 CRS-R examinations were necessary to reduce the risk of misdiagnosing a conscious patient as unconscious to 5% or less. When a single examination was performed, consciousness was missed in 36% of the cases assessed. Cortese et al<sup>13</sup> found that signs of consciousness also fluctuate diurnally and are more likely to be observed in the morning than in the afternoon. Daily fluctuations in visual pursuit, which often marks the transition from an unconscious to conscious state,<sup>14</sup> have been noted in 38% of cases followed.<sup>15</sup> Given

the ubiquity of fluctuation in DoC<sup>16</sup> and the central role that diagnosis plays in clinical decision-making, a deeper understanding of the base rate of spontaneous behavioral fluctuation in DoC is needed.

In view of the knowledge gaps described above, the aims of this study were to (1) determine the frequency of spontaneous fluctuation in behaviors indexed by the CRS-R among adult patients with prolonged DoC, (2) characterize the stability of ratings of consciousness among patients diagnosed with MCS and eMCS, and (3) characterize the stability of specific behavioral signs of consciousness over repeated CRS-R assessments.

## Methods

### Participants

We enrolled a convenience sample comprised of patients admitted to a DoC neurorehabilitation program colocated in an inpatient rehabilitation facility and a long-term acute care hospital. We identified patients who met the following inclusion criteria: (1) at least 18 years old; (2) admitting diagnosis of VS (also known as VS/UWS, MCS, or eMCS) from either a traumatic or nontraumatic (ie, stroke, hemorrhage, hypoxic, ischemic, and metabolic) mechanism of injury; (3) assessed at least 6 times with the CRS-R over a maximum of 21 days; and (4) between 28 and 90 days postinjury at the time of initial assessment.

### Procedures

All participants underwent serial standardized behavioral assessments of their level of consciousness and received multidisciplinary rehabilitation provided by speech, physical, and occupational therapists in accordance with standard clinical procedures. Trained clinicians administered the CRS-R twice per week during regularly scheduled therapy sessions. Examinations were always performed between 8:00 AM and 3:00 PM, either in the patient's room or in a therapy room within the hospital. CRS-R scores were recorded in the electronic medical record by the clinician and then extracted and transferred by research staff to the Research Electronic Data Capture (REDCap).<sup>17,18</sup> The research protocol was approved by the local institutional review board, and written informed consent was waived because all data were collected as part of routine clinical care for the inpatient DoC program.

### Measures

The CRS-R served as the primary outcome measure. The CRS-R is a traumatic brain injury common data element recommended for monitoring the recovery of consciousness in patients with DoC. The 6 subscales of the CRS-R assess auditory, visual, motor, oromotor/verbal, communication, and arousal functions, and all administration and scoring procedures are manualized. Subscale items are hierarchically arranged and correspond to brainstem, subcortical, and cortically-mediated functions.<sup>19</sup> The highest score on each subscale represents a cortically based, cognitively-mediated behavior, whereas the lowest score represents reflexive brainstem-mediated responses. The subscale score profile obtained from each assessment is used to establish the DoC diagnosis (VS/UWS, MCS, and eMCS). The auditory subscale score ranges from 0-4, the visual score from 0-5, the motor score from 0-6, the

#### *List of abbreviations:*

|               |   |
|---------------|---|
| <b>CRS-R</b>  | <b>Coma Recovery Scale-Revised</b>              |
| <b>DoC</b>    | <b>disorders of consciousness</b>               |
| <b>eMCS</b>   | <b>emergence from minimally conscious state</b> |
| <b>MCS</b>    | <b>minimally conscious state</b>                |
| <b>REDCap</b> | <b>Research Electronic Data Capture</b>         |
| <b>TCC</b>    | <b>test completion code</b>                     |
| <b>UWS</b>    | <b>unresponsive wakefulness syndrome</b>        |
| <b>VS</b>     | <b>vegetative state</b>                         |

**Table 1** Simulated illustration of the approach used to calculate the frequency of fluctuation

| Simulated Patient Scores           | CRS-R Assessment |   |    |    |    |   | Frequency of Fluctuation |
|------------------------------------|------------------|---|----|----|----|---|--------------------------|
|                                    | 1                | 2 | 3  | 4  | 5  | 6 |                          |
| CRS-R visual subscale score        | 3                | 3 | 5* | 4* | 3* | 3 |                          |
| Fluctuation present (+)/absent (–) |                  | – | +  | +  | +  | – | 3                        |

NOTE. This example shows a patient with CRS-R visual subscale scores of 3, 3, 5, 4, 3, and 3 on assessments 1–6. Fluctuations in scores are marked with an asterisk (\*). A plus sign (+) is used to indicate the presence of a fluctuation in the score between consecutive assessments, and a minus sign (–) indicates the absence of fluctuations between assessments. As shown, fluctuations occurred between CRS-R assessments 2 and 3 (the score increased from 3 to 5), 3 and 4 (the score decreased from 5 to 4), and 4 and 5 (the score decreased from 4 to 3) for a total of 3 fluctuations across the 6 assessments performed. CRS-R: Coma Recovery Scale-Revised.

oromotor score from 0–3, the communication score from 0–2, and the arousal score from 0–2. Test completion codes (TCCs) were assigned to standardize validity ratings for each subscale administered. Performance was coded as *valid* if the measure was completed in full with no threats to validity, *attempted but not completed* if the measure was not completed or judged invalid, or *not attempted* if no attempt was made to administer the subscale. The TCCs also indicate why performance was judged invalid (eg, sensory impairment, language barrier).

We also collected data on demographic (ie, age and sex) and injury characteristics (ie, mechanism of injury and time since injury).

## Statistical analyses

Data analyses only included CRS-R assessments that were assigned a valid TCC (1.0) to eliminate the influence of confounding factors on subscale scores. For analytic purposes, we collapsed “consistent command-following” and “reproducible command-following” in the auditory subscale and “visual fixation” and “visual pursuit” in the visual subscale.

To evaluate the frequency of spontaneous fluctuations in CRS-R subscale scores for each participant (objective 1), we calculated the number of times a CRS-R subscale score changed across 6 consecutive assessments and the percentage of patients by the number of fluctuations in the subscale score captured (minimum=0, maximum=5) across the 6 assessments. Fluctuations in the arousal subscale score were excluded from this analysis because scores in this subscale, unlike the other 5 CRS-R subscales, are not used to establish DoC diagnosis. We defined fluctuation as a change (ie, increase or decrease) in a CRS-R subscale score between consecutive assessments. See [table 1](#) for a simulated illustration of the number of fluctuations in a single patient. We calculated the magnitude of behavioral fluctuations by identifying the absolute difference in the subscale score (increase or decrease) between consecutive examinations. See [table 2](#) for an

illustration of how the magnitude of fluctuation was calculated. We also explored whether the level of arousal, indexed by the arousal subscale score, was associated with fluctuations in other subscale scores and compared the directionality of the fluctuations and changes in arousal in a  $2 \times 2$  matrix showing the frequency with which a fluctuation was associated with an increase or decrease in the CRS-R arousal subscale score. We tested the distribution of the matrix with a chi-squared test.

To characterize the “stability of consciousness” (ie, unconscious vs conscious) (objective 2), we included only patients who were conscious (ie, diagnosed with MCS or eMCS) at the first (ie, baseline) CRS-R assessment. We evaluated the number of times each of these participants was rated as conscious over the 5 CRS-R examinations that followed the baseline assessment. We also explored the relationship between the stability of consciousness and arousal ratings. To determine whether the level of arousal was associated with stability of consciousness, we used a  $2 \times 2$  matrix to compare the frequency with which changes in consciousness were accompanied by changes in the CRS-R arousal subscale score. We tested the distribution of the matrix with Fischer exact test.

Lastly, to determine the stability of individual CRS-R behavioral signs of consciousness (objective 3), we calculated the frequency with which each of these behaviors recurred over the 5 evaluations that followed the first occurrence of the behavior. We operationally defined signs of consciousness as consistent or reproducible responses to a command, visual fixation or pursuit, object reaching, object recognition, localization to noxious stimulation, intelligible verbalization, intentional communication, and functional communication. We considered a behavioral sign of consciousness to have recurred any time the same behavior or a higher-scoring behavior was scored as present after the first occurrence. This approach aligns with the evidence-based hierarchical structure of the CRS-R in which higher-scoring behaviors have been shown to subsume lower-level behaviors.<sup>19,20</sup> We also report the percentage of the sample that showed each behavior 1–5 times after the first occurrence. This analysis included only participants showing at least 1 behavioral sign of consciousness. Most patients demonstrated more than 1 conscious behavior and were included in more than 1 analysis. For example, if a patient showed reproducible response to command, visual pursuit, and object recognition in the first CRS-R assessment, their data were included in the analyses for all 3 of these behaviors.

All data were analyzed using RStudio version 4.3.1.<sup>a</sup>

## Results

Of 361 patients included in the REDcap database, 241 met all eligibility criteria, 121 had traumatic brain injury, 96 were women, the mean age was 65.3 (SD=19.0) years, and the mean time since

**Table 2** Simulated illustration of the approach used to calculate the magnitude of fluctuations.

|                             | CRS-R Assessment |   |    |    |    |   |
|-----------------------------|------------------|---|----|----|----|---|
|                             | 1                | 2 | 3  | 4  | 5  | 6 |
| Patient 1                   |                  |   |    |    |    |   |
| CRS-R visual subscale score | 3                | 3 | 5* | 4* | 3* | 3 |
| Magnitude of fluctuation    | NA               | 0 | +2 | –1 | –1 | 0 |

NOTE. This example shows a patient with changes in the CRS-R visual subscale score (marked with an asterisk) between CRS-R assessments 2 and 3 (+2 points), 3 and 4 (–1 point), and 4 and 5 (–1 point). As indicated, the magnitude of fluctuation ranges from –1 to +2 points across the 6 assessments performed. Abbreviations: NA, not applicable.

**Table 3** Demographic and clinical characteristics of the sample.

| Variable           | n (%) <sup>*</sup> |
|--------------------|--------------------|
| Sample size, n     |                    |
| Screened           | 361                |
| Included           | 241                |
| Age (y), mean (SD) | 65.3 (19)          |
| TSI (d), mean (SD) | 35.8 (13)          |
| Sex                |                    |
| Female             | 96 (39.8)          |
| Male               | 145 (60.6)         |
| Etiology           |                    |
| TBI                | 121 (50.2)         |
| n-TBI              | 120 (49.7)         |

Abbreviations: n-TBI: nontraumatic brain injury; TSI: time since injury.

\* Unless otherwise specified.

injury was 35.4 (SD=13.0) days (see [table 3](#) for demographic and injury characteristics and [fig 1](#) for the study flowchart).

## Frequency and magnitude of fluctuation

Behavioral fluctuation occurred most frequently in the motor subscale and least often in the communication subscale (83% and 54% of patients with  $\geq 1$  fluctuation, respectively). In the auditory, visual, and oromotor/verbal subscales,  $\geq 1$  fluctuation was observed in 80%, 80%, and 74% of participants, respectively. The frequency of fluctuations by subscale is illustrated in [figure 2](#), and the proportion of participants by number of fluctuations (0-5) is shown in [supplemental table S1](#) (available online only at <http://www.archives-pmr.org/>). A 1-point fluctuation in the CRS-R subscale score was observed most frequently; however, fluctuations as high as 5 points (ie, motor and visual subscales) were observed. See [figure 3](#) for details on the magnitude of fluctuations. The direction of fluctuation (ie, increase vs decrease in the CRS-R subscale score) was not related to the direction of change in arousal (increased vs decreased arousal; see [table 4](#) for details). Changes in subscale scores were evenly distributed across increases and decreases in arousal, and the chi-squared test was not significant ( $P=.27$ ).

## Stability of ratings of consciousness

Among the 192 participants who were diagnosed as conscious at the first assessment, 25% had at least 1 subsequent assessment in

which consciousness was not detected. [Figure 4](#) shows the proportion of patients who were diagnosed as conscious 1-5 times after being diagnosed as conscious at the baseline examination.

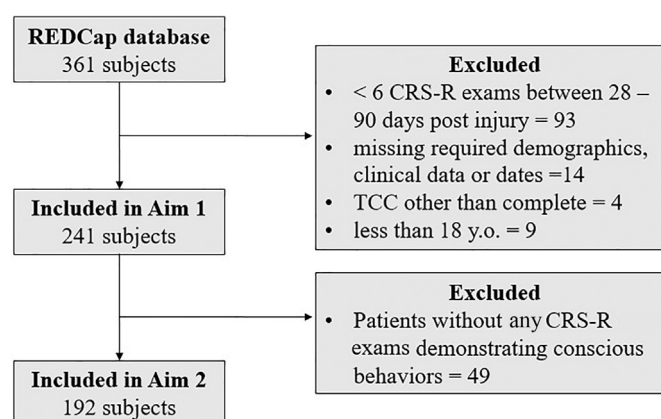
The results of Fisher exact test ( $P<.001$ ) indicate a significant association between ratings of the level of consciousness and the level of arousal. Ratings of the level of consciousness were associated with increases, but not decreases, in arousal level (see [table 5](#)). In 100% of the examinations in which arousal level was observed to increase, the consciousness rating also improved. However, in 86% of the examinations, when the level of arousal decreased, the consciousness rating remained unchanged.

## Stability of behavioral signs of consciousness

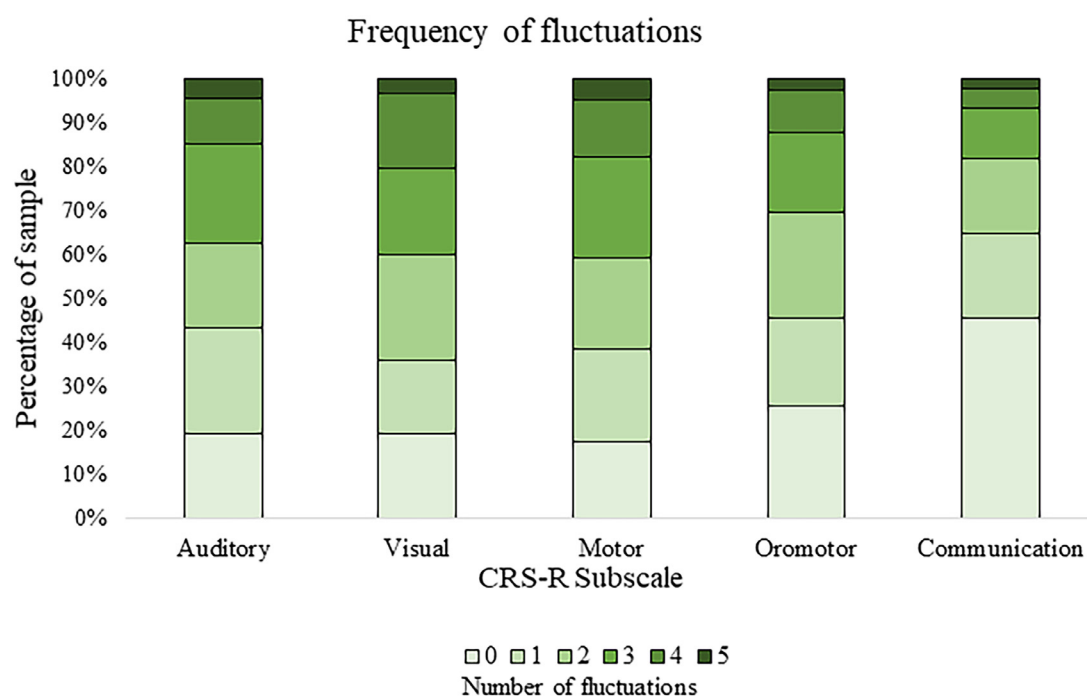
[Figure 5A-C](#) shows the frequency with which specific CRS-R behavioral signs of consciousness recurred across the 5 examinations that followed the baseline examination. Motor behaviors (ie, localization to pain and object manipulation) were the most stable signs of consciousness, recurring at least 3 times after the first occurrence in  $\geq 97\%$  of the sample. Language-related behaviors (ie, reproducible command-following and intelligible verbalization) were the least stable, recurring at least 3 times after the first occurrence in  $\leq 27\%$  of the sample. Approximately one-half of the sample demonstrated intentional (55%) or functional communication (51%) at least 3 times after the first occurrence. [Supplemental table S2](#) (available online only at <http://www.archives-pmr.org/>) shows the most stable behavioral signs of consciousness in rank order.

## Discussion

Behavioral fluctuation is commonly observed in patients with prolonged DoC.<sup>9</sup> Our objective was to systematically characterize the frequency and magnitude of behavioral fluctuation among patients with DoC and explore the effect of these fluctuations on diagnostic assessment. We found that behaviors indexed by CRS-R subscales fluctuated at least once across 6 consecutive examinations. The magnitude of fluctuation was typically 1 point, although up to 20% of participants showed a change of 2 or more points, depending on the CRS-R subscale. Among participants who were found to be conscious on the first examination, 1 in 4 failed to demonstrate consciousness on a subsequent examination. In line with this finding, most behavioral signs of consciousness fluctuated at



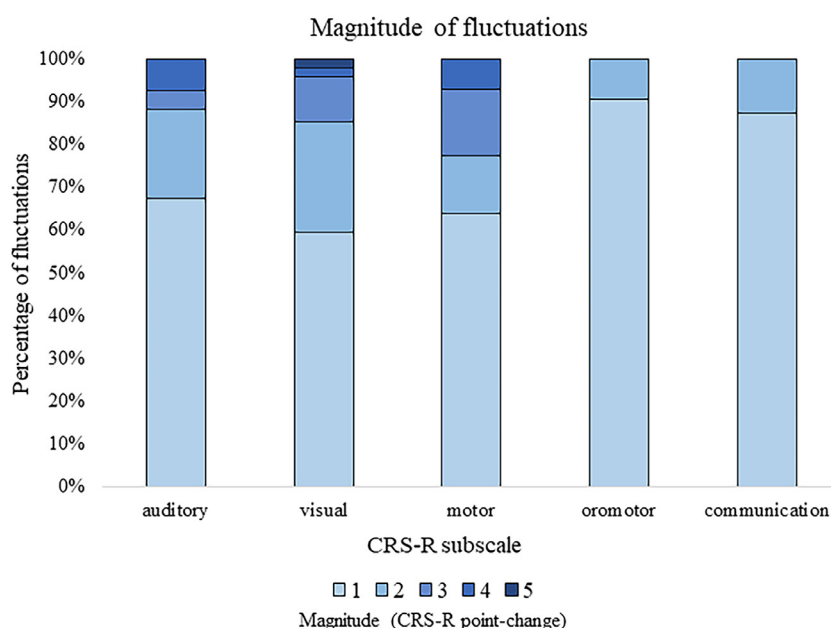
**Fig 1** Study flowchart.



**Fig 2** Frequency of fluctuation. Bars represent the proportion of the sample (N=241) demonstrating 0 to 5 fluctuations in CRS-R subscale scores over the course of the 6 evaluations, specified by color (ie, 0, 1, 2, 3, 4, and 5).

least once over the 5 examinations performed after the baseline assessment. Given the frequency with which behavioral signs of consciousness appear to fluctuate, our results support existing practice guidelines recommending serial assessment before establishing a DoC diagnosis.<sup>12,21</sup> Our findings also suggest that 1- to 2-point increases or decreases in CRS-R subscale scores commonly occur in the absence of treatment interventions, suggesting

that changes of this magnitude may reflect the base rate of fluctuation rather than true clinical improvement or decline. Serial monitoring provides a means to better understand the trajectory and clinical significance of CRS-R subscale changes, because many participants showed increases or decreases in scores that subsequently reverted back to the original score over the course of 21 days or less.



**Fig 3** Magnitude of fluctuation. Bars represent the proportion of CRS-R subscale score fluctuations among the full sample (N=241), that were between 1 and 5 points. Note that the range of possible score fluctuations varied by subscale (auditory: 0 to 4; visual: 0 to 5; motor: 0 to 6; oromotor/verbal: 0 to 3; communication: 0 to 2). While the modal fluctuation was 1 point, we observed fluctuations as high as 5 points, depending on the subscale.

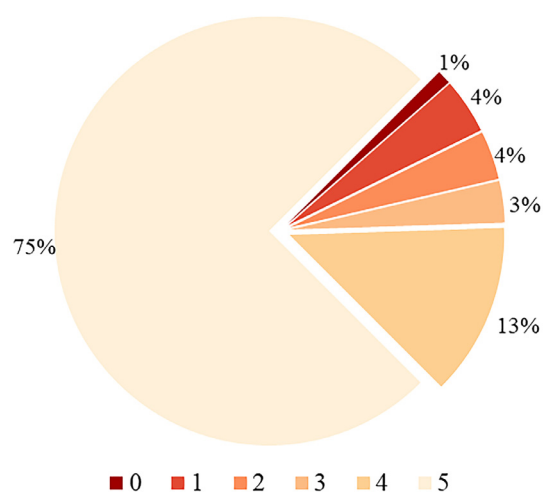


**Table 4** Relationship between arousal and behavioral fluctuation.

| CRS-R Subscale Score | Arousal Up | Arousal Down | No. of Observations |
|----------------------|------------|--------------|---------------------|
| Fluctuation up       | 333        | 434          | 767                 |
| Fluctuation down     | 290        | 336          | 626                 |
| No. of observations  | 623        | 770          | 1393                |

NOTE. Fluctuation up indicates that there was an increase in the CRS-R subscale score (ie, behavioral improvement), and fluctuation down indicates that there was a decrease in the CRS-R subscale score (ie, behavioral decline). Arousal up indicates an increase in the arousal subscale score (ie, improvement in arousal level), and arousal down indicates a decrease in the arousal subscale score (ie, a decline in arousal level). Increases and decreases in arousal level did not co-occur with improvement and decline in CRS-R subscale scores, respectively ( $\chi^2=1.1806$ ,  $P=.277224$ ).

The root cause of fluctuation in behavioral responsiveness in patients with DoC is unknown and likely multidetermined. Schiff and Purpura<sup>8</sup> have proposed a pathophysiological model, hypothesizing that when a lesioned brain area is unable to provide excitatory input to distant brain regions, a mechanism referred to as “disfacilitation,” the result may be diffuse neural network inhibition. This inhibitory state produces hyperpolarization of neuronal membranes that, together with generally lower global cerebral metabolism postinjury, may result in functional impairments that appear disproportionate to the extent of the structural injury. The combined effects of diffuse inhibition, hyperpolarization, and reduced cerebral metabolic rate are dynamic and may drive or contribute to behavioral fluctuation.



Number of CRS-R exams demonstrating consciousness

**Fig 4** Stability of ratings of consciousness. Colors depict the number of examinations in which the patient was rated as conscious after the first examination demonstrating consciousness (ie, 0, 1, 2, 3, 4, and 5). Among 192 subjects who demonstrated consciousness on at least 1 examination, 1 in 4 (25%) fluctuated from conscious to unconscious at least once over the 5 examinations. Thirteen percent of the sample was diagnosed as being in VS/UWS only once across the 5 examinations (4 conscious assessments), whereas the remaining 12% was diagnosed as being in VS/UWS in 2 to 5 instances.

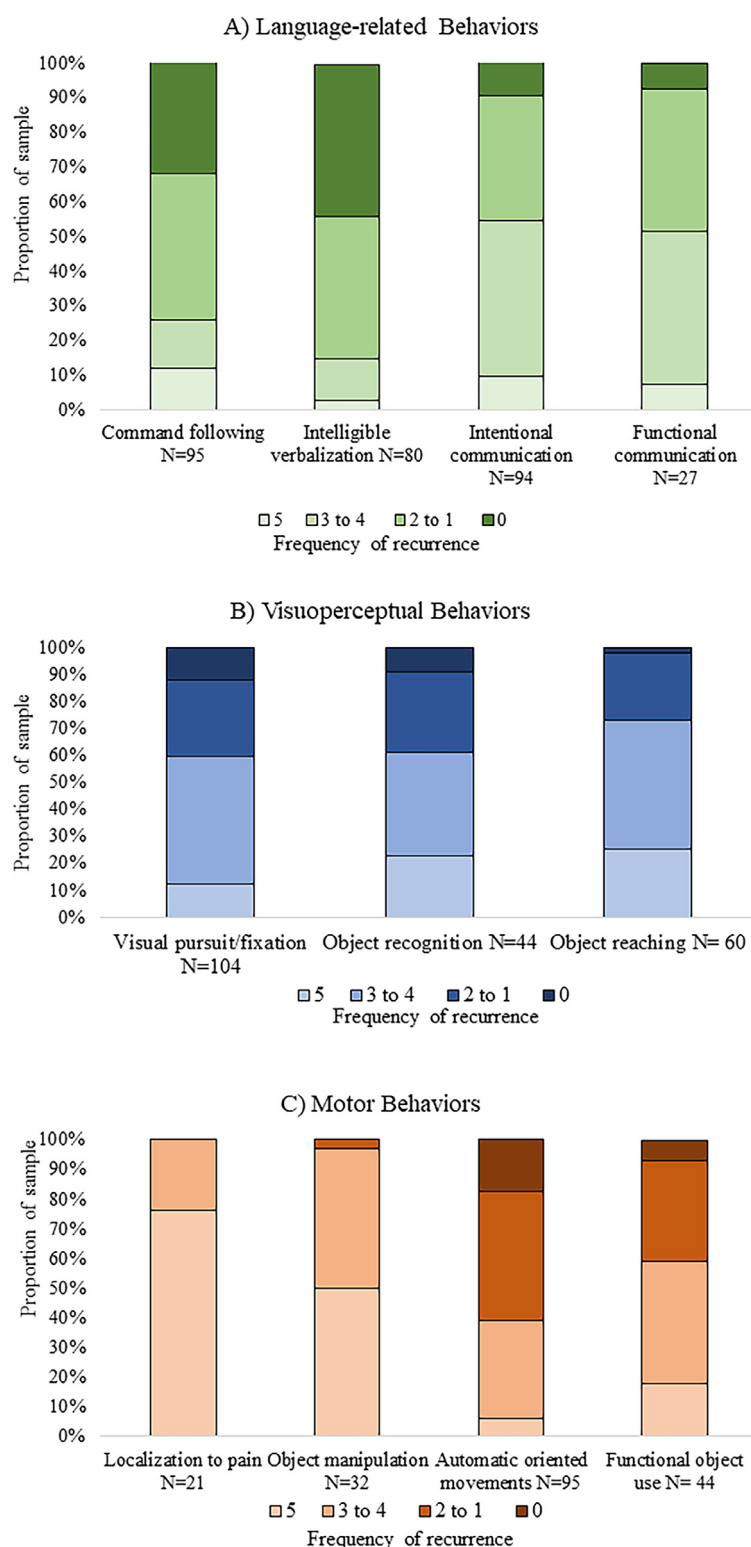
**Table 5** Relationship between arousal and ratings of consciousness.

| Level of Consciousness | Arousal Down | Arousal Up | No. of Observations |
|------------------------|--------------|------------|---------------------|
| Consciousness down     | 13           | 0          | 13                  |
| Consciousness up       | 10           | 35         | 45                  |
| No. of observations    | 23           | 35         | 58                  |

NOTE. Consciousness down indicates a decline in the level of consciousness (ie, change in diagnosis from MCS or eMCS to VS/UWS), and consciousness up indicates an improvement in the level of consciousness (ie, change in diagnosis from VS/UWS to MCS or eMCS). Arousal down indicates a decrease in the arousal subscale score (ie, a decline in arousal level), and arousal up indicates an increase in the arousal subscale score (ie, an improvement in arousal level). As indicated in the table, while increases in the arousal subscale score were associated with an improvement in the level of consciousness (ie, arousal up/consciousness up=35/35; arousal up/consciousness down=0/35), decreases in the arousal subscale score did not differentially affect the level of consciousness (ie, arousal down/consciousness down=13/23; arousal down/consciousness up=10/23) (Fisher exact test:  $P<.001$ ). Fluctuations in the level of consciousness that did not occur in association with changes in the level of arousal were excluded.

We found an association between fluctuations in arousal level and ratings of consciousness. While changes from an unconscious to a conscious state were always associated with increases in the level of arousal, consciousness ratings remained stable in nearly 90% of the examinations associated with a decline in arousal ratings. This finding suggests that declines in the level of consciousness are not necessarily driven by decreases in arousal level and may instead reflect naturally occurring oscillations in the resting brain state, as have previously been reported in cortical deafferentation, sleep, and anesthesia studies.<sup>8,22</sup> The absence of a consistent bidirectional relationship between arousal level and changes in the level of consciousness may also be because of the influence of potentially sedating medications, because their effect on behavioral responsiveness varies based on drug class, dosage, and time of administration. However, these effects are difficult to assess, given the variability in dosing and metabolism across patients. Additionally, this was a retrospective study, and the timing of CRS-R administration in relation to these data elements was not consistently available in the medical record. We are also unable to rule out that the absence of a relationship between decreased arousal and the level of consciousness is attributable to the lack of sensitivity of the arousal subscale, although the unidirectional nature of this finding makes this possibility less likely.<sup>22</sup>

One of the most important findings from this study is that 25% of participants failed to show any signs of consciousness in at least 1 examination performed after the initial detection of consciousness. This points to the importance of conducting regular, systematic assessments over the course of 2-3 weeks, especially during the acute to subacute phase of recovery, as originally recommended by Wannez.<sup>12</sup> We are unable to draw firm conclusions about the stability of specific behavioral signs of consciousness as small sample sizes for some behaviors prevented comparative analysis. Nevertheless, our study provides descriptive evidence that localization to pain and object manipulation in the CRS-R motor subscale and object reaching and object recognition in the visual subscale may be more stable than other behavioral signs of consciousness.



**Fig 5** (A-C) Stability of behavioral signs of consciousness. Bars represent the frequency with which specific CRS-R language (A), visuo-perceptual (B), and motor (C) signs of consciousness recurred across the 6 examinations. Sample sizes are indicated at the bottom of each bar and differ for each behavior, reflecting differences in the number of participants demonstrating the behavior at baseline. Color shading shows the proportion of participants who demonstrated each behavioral sign of consciousness 0 to 5 times after the first demonstration of the behavior. Localization to noxious stimulation ( $n=21$ ) was captured most consistently across examinations (75% of the sample showed this behavior in all 5 assessments after the first occurrence). In contrast, in 44% of the sample, intelligible verbalization was never captured after the first occurrence.

## Study limitations

This study has several important limitations that should be considered. First, we were unable to control for extraneous factors that may have influenced changes in CRS-R subscale scores. Many of these factors have been well-documented and include time of day, exposure to potentially sedating medications, seizure activity, occult medical complications, metabolic instability, and sleep disturbance.<sup>13,16</sup> Nonetheless, these circumstances are characteristic of the real-world conditions that clinicians must contend with. Future studies should incorporate study design features that control or adjust for these factors. Second, we included patients who were 28-90 days postinjury. The pattern of fluctuation preceding and following this time period may differ from what we observed here. Finally, it is important to recognize that our definition of fluctuation is deliberately agnostic as to whether the observed changes in behavior (and CRS-R subscale scores) reflect true clinical improvement or decline. For example, a participant whose motor subscale score continuously improved over the course of the 6 examinations was coded as having experienced 5 fluctuations. Although our data do not allow us to identify the underlying cause of these changes, this frequency was only observed in 2%-5% of the sample and, as such, may represent a nonrandom change in clinical status. Measures of CRS-R responsiveness have recently been developed<sup>23</sup> and are expected to help clinicians discern when changes in behavioral responsiveness exceed measurement error and reflect true change.

## Conclusions

Serial standardized assessment of the level of consciousness conducted over 21 days among patients with prolonged DoC suggests that behavioral fluctuation is frequently observed. When the CRS-R is used to monitor behavioral recovery, a 1-point change in subscale scores in either direction appears to be the norm, although larger changes (ie, 3 points) are not uncommon. Behavioral fluctuation does not appear to be closely tied to arousal level and may reflect injury-related pathophysiologic perturbations in corticothalamic connectivity. These findings suggest that it is essential to conduct repeated assessments in this population to capture the highest level of consciousness retained and to help distinguish spontaneous fluctuation from response to treatment in interventional studies.

## Supplier

a. RStudio, version 4.3.1; Posit; 2023

## Keywords

Assessment scale; Disorders of consciousness; Minimally conscious state; Rehabilitation; Traumatic brain injury; Unresponsive wakefulness syndrome; Vegetative state

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