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ORIGINAL ARTICLE

Family caregivers improve the diagnostic accuracy of disorders of consciousness: from remote to near-bed auditory stimulation

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ABSTRACT

BACKGROUND: Family caregivers (FC) contribute to reducing the misdiagnosis rate in patients with disorders of consciousness (DOC). Unfortunately, the recent pandemic of COVID-19 imposed drastic restrictions that limited the access of FC to the sensory/cognitive stimulation protocols. Telemedicine approaches have been implemented to avoid discontinuity in care pathways and to ensure caregivers involvement in rehabilitation programs.

AIM: The aim was to investigate whether the presence of FC remotely connected might help clinicians in eliciting higher cortically mediated behavioral responses in patients with DOC.

DESIGN: Cross-sectional study.

SETTING: Post-acute Unit of Neurorehabilitation.

POPULATION: DOC due to severe brain injury.

METHODS: Consecutive patients with DOC were assessed by means of the Coma Recovery Scale-Revised (CRS-R) by two expert examiners. Each patient underwent to five assessments in two weeks in three different conditions: 1) by the examiner only (standard); 2) with the verbal stimulation given by the FC remotely connected by PC tablet (caregiver in remote); and 3) with the verbal stimulation given by the FC physically present (caregiver in presence).

RESULTS: Thirty patients with DOC (VS/UWS=10; MCS=20; mean age: 51, range: 21-79; vascular: 16; anoxic: 6; TBI=8) and their FC were enrolled. Higher total scores of CRS-R were recorded both in "caregiver in remote" and in "caregiver in presence" than in standard condition (standard *vs.* remote, Z=2.942, P=0.003; standard *vs.* presence, Z=3.736, P<0.001). Furthermore, the administration of the CRS-R with a FC, elicited higher levels of behavioral responses in MCS patients, than CRS-R performed in standard condition. In particular, 2 patients out of 30 (6.66%) showed higher scores and better diagnosis when the CRS-R was administered with FC in remote. Similarly, 5 out of 30 patients (16.66%) showed better diagnoses when the CRS-R was administered with FC in presence. Five patients changed diagnosis between standard and presence conditions (3 MCS- were diagnosed as MCS+; 2 MCS+ were diagnosed as conscious).

CONCLUSIONS: Our findings add new evidence regarding the beneficial role of family members in the diagnosis of DOC, even mediated by telemedicine approach.

CLINICAL REHABILITATION IMPACT: In future guidelines, FC should have an active and supporting role in the diagnostic and rehabilitative process of DOC.

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KEY WORDS: Consciousness disorders; Wounds and injuries; Caregivers; Rehabilitation.

The differential diagnosis of disorders of consciousness (DOC) due to severe acquired brain injury (sABI) of different etiology is very challenging for clinicians.[1, 2] Currently, the behavioral assessment still represents the gold standard in the assessment of DOC.[3-5] Unfortunately, several confounding factors, such as extreme motor disability, spasticity, diffuse pain and cognitive deficits, arousal fluctuations, and iatrogenic effects (antiepileptic, sedative drugs, antispastic agents, etc.) may lead to a high rate of misdiagnosis.[2, 6, 7]

The use of validated tools, such as the Coma Recovery Scale-Revised[1] and the application of standardized protocols[4] may enhance diagnostic accuracy. However, the CRS-R might have some weaknesses, such as the neutral emotional nature of the stimuli used and the marginal role of caregivers in the assessment of the patients' level of responsiveness. In recent years, several studies have addressed this important issue by identifying factors that can reduce the rate of misdiagnosis.[8, 9] Specifically, a recent study demonstrated that the frequent use of CRS-R (at least 5 assessments in 2 weeks) allows enhancing diagnostic accuracy.[6, 8, 10] In addition, another important factor that may lead to an accurate diagnosis is reported to be the presence of family caregiver during the assessment, performed by using standardized tools.[9] In fact, Formisano *et al.* found that the presence of family-caregiver allowed obtaining higher scores on CRS-R, and Sattin *et al.* observed a change in diagnosis of DOC in 16% of patients by administrating CRS-R in presence of family caregivers. Moreover, the presence of family caregivers has been associated with better improvement in patients after sABI.[11, 12] Therefore, the abovementioned studies highlighted the importance of the participation of family caregivers in the diagnostic process and in rehabilitative programs.[6, 8-10, 13] Unfortunately, the recent pandemic of COVID-19 had a dramatic impact on neurorehabilitation of sABI, preventing family caregivers from participating in rehabilitation settings.[13]

The anti-COVID-19 measure drastically affected caregivers' participation in rehabilitative programs, limiting their important contribution to the sensory/cognitive stimulation protocols. Telemedicine approaches have been implemented and diffused to avoid discontinuity in care pathways and to ensure caregiver involvement in clinical and rehabilitation programmes.[14, 15]

The main aim of the present study was to investigate whether the presence of family caregivers remotely connected could elicit more complex behavioral responses in patients with DOC and lead to increase accuracy of diagnostic process of DOC. In particular, we aimed to verify if the assessment of the level of consciousness performed by means of the CRS-R in presence of the family caregivers remotely connected or physically present, could enhance diagnostic accuracy compared to the CRS-R assessment performed by the examiner alone.

Materials and methods

Participants

We enrolled consecutive patients admitted in the post-acute phase to the Neurorehabilitation Unit for Disorders of Consciousness of Istituti Clinici Scientifici Maugeri IRCCS, Institute of Telese Terme (Telese Terme, Italy), from September 2021 to December 2022. All patients had a clinical diagnosis of vegetative state/unresponsive wakefulness syndrome (VS/UWS) or of minimally conscious state (MCS) due to sABI of different etiology (traumatic and non-traumatic) satisfying the following inclusion criteria: established diagnosis of VS/UWS or MCS according to international criteria;[16] lack of severe organ insufficiency or acute illness (Supplementary Digital Material 1: Supplementary Figure 1). Patients were excluded if they had neurodegenerative or psychiatric diseases, or for the lack of a family caregiver available to participate in the study. Patients underwent the examinations in absence of infections or acute clinical complications. The informed consent was obtained from all patients' legally authorized representatives and informal caregivers. The study was conducted after approval by the local Ethic Committee (Istituto Nazionale Tumori Fondazione Pascale, Naples, Italy; with reference number ICS 8/21) and according to the Helsinki declaration. The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Procedures

All patients were assessed by means of the Coma Recovery Scale-Revised[1, 17] by two expert examiners who were blind to the aims and hypothesis of the study.

Each patient was enrolled at least one month after admission in Neurorehabilitation Unit and was assessed five times in two consecutive weeks. Each assessment was performed in three different conditions (3 conditions × 5 assessments): 1) CRS-R administered by the examiner alone (standard); 2) CRS-R administered by the examiner in presence of family caregiver connected on remote by PC tablet (caregiver in remote); and 3) CRS-R administered by the examiner in presence of family caregiver (caregiver in presence).

During the evaluative sessions of "caregiver in remote" and "caregiver in presence," the family caregivers were invited to verbally present all the verbal stimuli included in the CRS-R protocol.[1, 17]

In detail, family caregivers presented all the verbal instructions standardized in the CRS-R protocol, usually presented by the examiner (*e.g.*, instructions for command following and for communication protocol). Notably, visual stimulations and the object-based stimuli included in the CRS-R protocol were not performed by family caregivers when they were in presence, in order to not create a possible confounding difference between presence and remote conditions. Examiners presented the object-based stimuli (*e.g.*, two objects) and family caregiver verbalized the instructions (*e.g.*, "Look at [object name]").

All caregivers were previously trained to perform the verbal protocol of the CRS-R through a brief training session performed by an expert neuropsychologist. The three conditions have been randomized in each evaluative session. The time interval between each session was 10 minutes.

To ensure sufficient arousal level, centrally acting drugs, neuromuscular function blockers, and sedation were discontinued within 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.[1] Patients were classified as VS/UWS, MCS, and EMCS, according to the clinical diagnostic criteria.[18]

Moreover, patients in a minimally conscious state (MCS) were subcategorized into MCS plus (MCS+) and MCS minus (MCS-), based on command-following, intelligible verbalization, or intentional communication.[19]

Assessment of consciousness

The level of consciousness was assessed by means of the Italian version of the Coma Recovery Scale-Revised.[17] CRS-R is a 29 items scale, hierarchically structured and divided into 6 subscales assessing auditory, visual, motor, oromotor/verbal, communication, and arousal functions. The lowest score on each subscale represents reflexive behaviors, while the highest score represents cortically-mediated behaviors. Each subscale, alone, allows us to classify patients as VS/UWS or MCS, while the motor and communication subscales further distinguish VS/UWS, MCS, and patients that recover full consciousness (emergent from a minimally conscious state, EMCS). In detail, VS/UWS diagnosis was established if the following criteria were satisfied: auditory score ≤2 and/or visual score ≤1 and/or motor score ≤2 and/or oromotor/verbal score ≤2 and/or communication score =0; arousal score ≤2. Patients were considered in MCS if auditory score =3-4 and/or visual score =2-5 and/or motor =3-5 and/or oromotor/verbal =3 and/or communication =1. Last, patients were considered as EMCS if they obtained a motor score of 6 and/or a communication score of 2.

Statistical analysis

Score distribution and descriptive statistics were used to report data from patients and caregivers. Categorical variables were compared by means of the non-parametric χ^2 test. Means and medians were used for continuous variables. The level of diagnostic agreement of the CRSR total scores among raters was evaluated by means of the Fleiss Generalized Kappa Test, which determines the reproducibility of measures.[20] Moreover, to assess possible significant fluctuations of scores among five sessions of CRS-R assessments, we studied the reliability between CRS-R total scores as a function of condition, by means of Intraclass Correlation Coefficient. Values greater than 0.8 suggest excellent interobserver agreement.[2, 21] To calculate differences in CRS-R total scores between the three conditions of the research protocol (standard *vs.* caregiver in remote *vs.* caregiver in presence) we considered the best performance scores obtained among the five assessment sessions for each condition. We compared the total scores of CRS-R of the three conditions, by means of non-parametric Friedman Test, for k-related samples. *Post-hoc* comparisons were performed by means of non-parametric Wilcoxon Test. An alpha level set at P=0.05 was used for all the comparisons. To verify the diagnostic accuracy of the three conditions we compared the diagnosis obtained by means of CRS-R based on standard clinical criteria with the diagnosis obtained by CRS-R with caregivers in remote or in presence conditions. Diagnostic sensitivity and specificity of the diagnosis based on CRS-R performed with caregivers (in remote or in presence conditions) were calculated with CRS-R standard assessment condition as the reference and VS, MCS- or MCS+ as disorders 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. The number of diagnoses obtained from each of the three conditions was compared with the two-tailed marginal homogeneity test for categorical data. Significance was set at P<0.05 with the confidence interval estimated at the 95% level.

Results

Clinical and demographical characteristics of patients and family caregivers are shown in Table I, II.

Inter-rater agreement and reliability

Overall interrater agreement for diagnostic classification based on CRS-R, as expressed by mean of kappa values, was excellent in all three conditions (CRS-R standard condition: Kappa=0.910, P<0.001; CRS-R caregiver in remote: Kappa=0.950, P<0.001; CRS-R caregiver in presence: Kappa=0.952, P<0.001).

The reliability of CRS-R total scores recorded in the five sessions of assessments was high in all three conditions (all intraclass correlation coefficients were > 0.8; P<0.001) independently from the diagnosis of patients at study entry, based on diagnostic criteria. All results are shown in Supplementary Digital Material 2 (Supplementary Table I).

Comparisons between different conditions

The comparisons between total scores of CRS-R of the three conditions (standard *vs.* remote stimulation *vs.* caregiver in presence) showed significant differences (χ^2=24.800, df=2, P<0.001). In particular, *post-hoc* comparisons showed higher scores in both "caregiver in remote" and "caregiver in presence" conditions than in standard condition (standard *vs.* caregiver in remote, *Z*=2.942, P=0.003; standard *vs.* caregiver in presence, *Z*=3.736, P<0.001). Moreover, the CRS-R total score obtained with family caregivers in presence was higher than the CRS-R total score obtained in remote (remote *vs.* caregiver presence, *Z*=2.259, P=0.02). Considering diagnosis at study entry, the differences in CRS-R total scores of patients with VS/UWS were not statistically significant (P>0.05) in the three conditions. Instead, CRS-R total scores of MCS patients were different in the three conditions (χ^2=9.1; P=0.01). *Post-hoc* comparisons showed that the total scores of CRS-R administered with family caregivers in presence were higher than CRS-R total scores obtained by the expert alone (*Z*=2.456, P=0.01). No differences were observed between "standard" *versus* "caregiver in remote" and between "caregiver in remote" *versus* "caregiver in presence" (P>0.05).

TABLE I.—*Patients' sociodemographic and clinical information.*

Parameters	Patients (N.=30)
Age at onset, in years, median (range)	51 (21-79)
Gender (m/f)	18/12
Time since injury, in months, median (range)	3.8 (2-5)
Etiology, N. (%)	
Traumatic	8 (26.7)
Vascular	16 (53.3)
Anoxic	6 (20)
Diagnosis at study entry, N. (%)	
VS/UWS	10 (33.3)
MCS-	11 (36.7)
MCS+	9 (30)

VS/UWS: vegetative state/unresponsive wakefulness syndrome; MCS: minimally conscious state.

TABLE II.—*Caregivers' sociodemographic features.*

Parameters	Caregivers (N.=30)
Age at onset, years, median (range)	62.4 (19-72)
Gender (m/f)	9/21
Education, in years, median (range)	12.4 (8-17)
Type of relationship (patient is…), N. (%)	
Spouse	18 (60)
Parent	7 (23.3)
Son	5 (16.7)

Diagnostic accuracy

The CRS-R in standard condition confirmed the clinical diagnosis based on diagnostic criteria[21] in 25 patients on 30 (83.33%). More specifically, the CRS-R administered by the examiners revealed a change of diagnosis: 2 patients were diagnosed as MCS- when the clinical diagnosis was VS/UWS, and 3 patients were diagnosed as MCS+ when the clinical diagnosis was MCS-.

Instead, the administration of the CRS-R with a family caregiver both remotely connected and in presence elicited higher levels of behavioral responses in patients than CRS-R performed in standard condition. In particular, 2 patients out of 30 (6.66%) showed higher scores and different diagnosis when the CRS-R was administered with family caregivers in remote; moreover, we found a change of diagnosis in 16.66% of patients: 5 out of 30 patients showed different diagnoses when the CRS-R was administered with family caregivers in presence. In detail, the "caregiver in remote" condition revealed 2 patients with motor responses to verbal stimuli who satisfied criteria of MCS+ among 11 patients (18.1%) diagnosed as MCS- on standard condition.

In addition, the comparison between CRS-R in standard and in presence conditions revealed a change in diagnosis in 5 cases: 3 cases of 11 (27.3%) changed from MCS- when the CRS-R was administered in standard condition to MCS+ when the CRS-R was administered with caregivers in presence,; the diagnosis changed in 2 cases of 9 (22.2%) from MCS+ when the CRS-R was administered in standard condition to EMCS when the CRS-R was ad-

TABLE III.—*Scores of diagnostic accuracy of CRS-R in the two conditions with caregiver verbal stimulation with CRS-R standard as reference.*

CRS-R standard	Caregiver in remote		Caregiver in presence	
	MCS-	MCS+	MCS-	MCS+
Sen (CI %)	81.8 (52.3-94.9)	100 (70-100)	72.7 (43.4-90.2)	77.8 (45.3-93.7)
Spec (CI %)	100 (83.2-100)	90.5 (71.1-97.3)	100 (83.2-100)	85.7 (65.4-95)
PPV	100 (70-100)	81.8 (52.3-94.9)	100 (67.6-100)	70 (39.7-89.2)
NPV	90.5 (71.1-97.3)	100 (83.1-100)	83.4 (66.7-95.3)	90 (69.9-97.2)

CRS-R: Coma Recovery Scale-Revised; MCS: minimally conscious state.

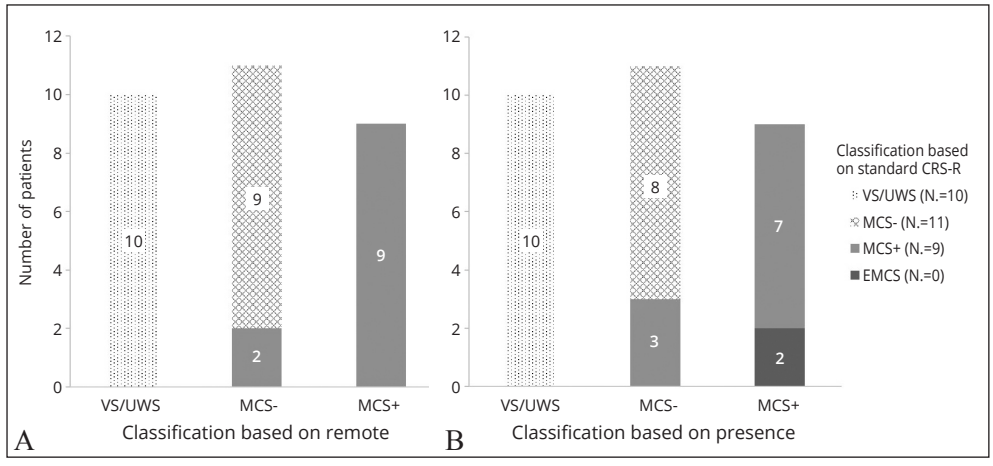

Figure 1.—A, B) Distribution of patients classified as VS/UWS or MCS- or MCS+ or EMCS by CRS-R with caregivers in presence or online with respect to diagnosis obtained by examiners performing clinical assessment by administering CRS-R in standard modality. VS/UWS: vegetative state/unresponsive wakefulness syndrome; MCS: minimally conscious state; EMCS: emergent from a minimally conscious state; CRS-R: Coma Recovery Scale-Revised.

ministered with caregivers in presence. The results of diagnostic accuracy are shown in Table III.

The number of patients diagnosed as VS/UWS was the same in all three conditions, although 2 patients showed responses of localization to sound in the "caregiver in presence" condition, a behavioral response associated with a diagnosis of VS/UWS. The results are shown in Figure 1.

Change of diagnoses in the three CRS-R conditions

The number of patients diagnosed as VS, MCS-, MCS+, or EMCS in the three different conditions is reported in Table IV.

Analyzing the distribution of the diagnoses in the three CRS-R conditions, the difference between CRS-R in standard and remote conditions regarded 2 patients (MH=-1.414, P=0.15): both patients diagnosed as MCS- by means of the CRS-R standard, were diagnosed as MCS+ in remote condition. Instead, the difference between CRS-R in standard and presence conditions regarded 5 patients (MH=-2.236, P=0.02): three patients diagnosed as MCS- by means of CRS-R standard, were diagnosed as MCS+ and two patients previously identified as MCS+ were diagnosed as EMCS in presence condition.

Furthermore, 3 patients represent the difference between the administration of CRS-R in remote and presence (MH=-1.732, P=0.83); specifically, one patient diagnosed as MCS- in remote condition, was diagnosed as MCS+.

TABLE IV.—*Distribution of the clinical diagnosis in the two assessment conditions of the CRS-R with caregivers compared to the diagnosis obtained by applying the standard CRS-R.*

Parameters	CRS-R standard	Caregiver in remote				Caregiver in presence			
	N.	VS/UWS	MCS-	MCS+	EMCS	VS/UWS	MCS-	MCS+	EMCS
VS/UWS	10	10	0	0	0	10	0	0	0
MCS-	11	0	9	2	0	0	8	3	0
MCS+	9	0	0	9	0	0	0	7	2

CRS-R: Coma Recovery Scale-Revised; VS/UWS: vegetative state/unresponsive wakefulness syndrome; MCS: minimally conscious state; EMCS: emergent from a minimally conscious state.

Nevertheless, the condition of family caregivers in presence was the only one that detected 2 patients as EMCS.

Finally, the facilitatory effect of verbal stimulation was not associated with age, sex, etiology and time from injury (P>0.05).

Discussion

The COVID-19 pandemic had a dramatic effect on the health system and partially interrupted the usual care pathways. This led to the rapid and extensive development of telemedicine in most care settings to continue providing care to patients and their family caregivers.[22] This process had positive effects on the treatment of different conditions, including chronic diseases, mental disorders, and oncologic diseases.[23] Telemedicine was also applied to the field of neuropsychological assessment.[24] Regarding the rehabilitation of sABI few experiences of telemedicine approach have been described.[25-27]

To the best of our knowledge, no studies investigated the effects of caregivers' involvement in the assessment of behavioral responses of patients with DOC by means of a telemedicine approach.

The main aim of our study was to examine whether the participation of family caregivers, even if remotely connected, could improve diagnostic accuracy during the behavioral assessment of patients with DOC. Specifically, we investigated if the presence of the family caregiver could influence the manifestation of behavioral responses assessed by means of CRS-R protocol, a gold standard tool for assessing levels of consciousness.[4, 16]

Unlike previous studies,[8, 9] we focused only on the auditory stimulation given by relatives during the administration of CRS-R performed by two expert clinicians. In addition, for the first time, we studied the effects of this stimulation carried out by family caregivers remotely connected by PC tablet.

Our findings showed that the CRS-R performed with contribution of family caregivers showed higher scores of CRS-R than those obtained by the examiner only and helped to detect more patients with verbal residual abilities, thus improving the diagnostic accuracy of disorder of consciousness.

Normally, the CRS-R does not include the use of salient emotional stimuli or the presence of family caregivers in the protocol.[4, 5] In contrast, our findings support the recommendation to use the CRS-R with the participation of family caregivers even in remote to reduce the risk of underestimating the level of responsiveness of patients with DOC. Moreover, the CRS-R guidelines suggest carrying out several administration sessions and using the best score as a reference for the degree of the level of consciousness.[4] Our results indicate that the best level of responsiveness always occurs in presence of the family caregiver. Thus, the CRS-R used by an expert examiner with the support (*i.e.*, the verbal stimulation) of family caregivers might improve the detection of cortically mediated behaviors and have important implications in decision-making about the intensity and duration of treatment.

In detail, our results showed that the CRS-R administered with the support of family caregivers remotely connected detected two more MCS+ patients than the CRS-R administered in standard condition. Instead, we detected one more MCS+ patient and two EMCS patients, with the family caregiver.

Therefore, we found that verbal stimulation given by family caregivers remotely connected or physically present allowed eliciting more complex and consistent behavioral responses in patients that did not show responses to verbal stimuli during standard assessment of CRS-R, thus previously classified as MCS-. Regarding the diagnosis of MCS+, CRS-R administered in the remote condition showed very high sensitivity: it was able to identify more patients diagnosed as MCS+ (2 more than standard CRS-R).

Furthermore, the CRS-R administered with auditory stimulation of the family caregiver in presence allowed to detect two patients with intentional and functional communication ability (satisfying criteria for EMCS diagnosis), previously diagnosed as MCS+ by professionals alone. Of paramount importance, only the administration with the family caregiver in presence was able to detect EMCS patients.

Noteworthy, both the conditions involving the presence of relatives (remotely connected or physically present) never scored lower than the standard condition. However, differences in the detection of more complex cortically mediated behaviors have been observed only in MCS patients. In fact, no significant effects of the presence of family caregivers, independently of modality, were observed in VS/UWS. A first possible explanation of this result could be based on the more severe degree of brain impairment of patients with VS/UWS, less sensible to the saliency of the stimuli.[1, 28-30] A further possible explanation depends on the characteristics of our study protocol. In fact, it was specifically focused on the verbal stimulation performed by family caregivers, that is associated with high levels of cortically mediated residual abilities. More likely, the auditory nature of our salient stimuli, did not help in detect-

ing the subtle signs of intentional behavior represented by visual responses (*e.g.*, visual pursuit), as well-described by several studies.[17, 28, 31, 32] As a possible consequence of the characteristics of our study protocol, we could underestimate patients with minimal signs of responsiveness, such as MCS-.

In general, DOC patients may exhibit individualized patterns of behavioral response related to the diffuse and variable nature of sustained damage.[33] Areas related to sensory, motor, and cognitive functions vary among patients depending on the location and extent of neurological damage. Some patients may have residue cognitive abilities and a good level of consciousness with extremely severe motor symptomatology, which does not allow them to manifest visible behavioral responses. Thus, differences in behavioral manifestations following salient stimuli might be influenced by a cognitive-motor dissociation as commonly reported in the literature.[34-36]

Taken together, our findings clearly indicated that the presence of the family caregiver elicits more complex intentional behavioral responses in MCS patients. However, this effect seems to be strictly connected to the modality of presentation of the salient stimuli (remote *versus* presence) and to the degree of impairment of the patient (MCS- *versus* MCS+). In fact, when the family caregivers were remotely connected, and the stimulation was mostly auditory, the MCS- showed more complex residual signs of intentional behaviors, but these responses were fluctuating and not sufficient to meet the criteria for EMCS. On the other hand, when the family caregivers were physically present, and the stimulation was more multisensory, some patients with a diagnosis of MCS- showed evidence of more complex behaviors and can be diagnosed as MCS+. Furthermore, some of those patients who were already classified as MCS+, showed signs of functional and appropriate communication abilities (*i.e.* diagnosis of EMCS).

These findings are in line with previous studies showing that multisensory stimulation has a greater enhancement effect than unimodal stimulation.[37] In addition, Zuo *et al.* demonstrated that early family-centered sensory and affective stimulation was more effective than routine care and nurse-implemented sensory stimulation in improving the level of consciousness and cognition of DOC patients, underlying the critical role of caregivers in all processes of care.

Moreover, our results confirmed the importance of family caregivers in the behavioral assessment of DOC patients:[8, 9] their active participation during CRS-R assessment appears to elicit more behavioral responses than neutral stimuli and could improve response detection and decrease the rate of misdiagnosis. We observed the diagnostic enhancement both when family caregivers were remotely connected and physically present, although the effect is greater in the latter.

Indeed, our results characterized by a high rate of diagnosis changed from lower levels of intentional responsiveness to higher behavioral responses to verbal commands, highlighting the important role of salient stimuli.[16] Certainly, the family caregiver represents a salient affective stimulus capable of eliciting more efficient cortical activation.[38] In this regard, the efficacy of salient auditory stimulation in patients with DOC has been demonstrated in several studies[27, 39, 40] and our results confirmed the important contribution of the familiar voice and its emotional valence.[41, 42] In addition, evidence suggests that familiar speakers can activate the appropriate brain areas in patients diagnosed as MCS.[43] In fact, patients with DOC may have the ability to recognize salient emotional and affective stimuli.

In contrast, there are some MCS patients unresponsive to salient stimuli. These differences could be due to fluctuations in the patients' level of arousal and to possible sensory-motor and cognitive impairments that might hamper the expression of a covert cognition state.[36, 44] Additionally, the severity of the brain injury and the different individual patient's condition could also play a crucial role in their ability to respond to stimuli.[28]

Limitations of the study

Our study had several limitations that need to be taken into account. First, the relatively small sample size suggests caution in the discussion of these findings. Second, the level of responsiveness was measured through behavioral responses so we could not exclude that diagnosis systematically reflect the residual brain or cognitive function.[45, 46] Moreover, in this study we did not perform a comparison with an instrumental assessment that could provide evidence of subtle signs of covert-cognition. Future research might consider correlating clinical-functional characteristics with instrumental findings.

Last, as already discussed above, our study protocol may have underestimated MCS- patients. In fact, visual behavior could play a key role in the differential diagnosis between VS/UWS and MCS.[29] However, the use of different stimuli changes the frequency of visual fixations occurred in patients, thereby possibly affecting the accuracy of the diagnosis.[32, 41] However, in the present study, we mainly focused on verbal stimulation, whereas visual

stimulation was indirect and was represented by the physical presence of the familiar caregiver (presence condition) or by the image of the caregiver on the tablet screen (remote condition). Future research should try to investigate the responses of patients using auditory-visual stimulation with the family caregiver remotely connected.

In general, future studies should be implemented with a larger sample size and with the support of neuroimaging functional data on the integrity and activation of brain structures involved in the emotional resonance of familiar voice recognition in disorders of consciousness.

Conclusions

Family caregivers play a crucial role in the care decision-making process,[47] in classifying the level of disability, and in the assessment of patients with DOC.[8] The presence of family caregivers can positively affect behavioral assessments of persons with DOC, thus contributing to the definition of the optimal setting for behavioral evaluation of patients and decreasing the misdiagnosis rate. Our findings add new evidence regarding the beneficial role of family members in the diagnosis and treatment of patients with DOC. In future guidelines, they should be considered an integral part of caregiving. We encourage the involvement of family members who are physically present because, according to our findings and those in the literature,[8, 9] in this modality patients may show more complex behaviors that correspond to a better diagnosis than in other conditions. If this is not possible, the presence of remotely connected caregivers can also provide the necessary stimuli for the patient to exhibit a greater degree of responsiveness. An important practical implication of our study regards the utility of telerehabilitation approach to the clinical practice with sABI. In this regard, our findings suggest the need and the possibility to develop protocols and tools that allow clinicians to follow-up patients even in home settings. In conclusion, we can state that the presence of the caregiver during the diagnostic process is crucial to ensure the best possible behavioral assessment. This has important implications for how patients with DOC should be evaluated.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

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Authors' contributions
Pasquale Moretta, Cinzia Femiano, Nicola D. Cavallo, Anna Lanzillo, Fabrizio Luciano, Cesario Ferrante, Antonio Maiorino, Gabriella Santangelo and Laura Marcuccio have given substantial contributions to study conception and design, Pasquale Moretta, Cinzia Femiano and Laura Marcuccio to study supervision, Nicola Davide Cavallo, Anna Lanzillo, Antonio Maiorino, Cesario Ferrante and Fabrizio Luciano to data acquisition, collection and analysis, Pasquale Moretta, Cinzia Femiano, Laura Marcuccio and Gabriella Santangelo to manuscript writing. All authors read and approved the final version of the manuscript.

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Supplementary data
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