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Can Salient Stimuli Enhance Responses in Disorders of Consciousness? A Systematic Review

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Abstract

Purpose of Review Diagnostic classification of patients with disorders of consciousness (DoC) is based on clinician's observation of volitional behaviours. However, patients' caregivers often report higher levels of responsiveness with respect to those observed during the clinical assessment. Thus, increasing efforts have been aimed at comprehending the effects of self-referential and emotional stimuli on patients' responsiveness. Here we systematically reviewed the original experimental studies that compared behavioural and electrophysiological responses with salient vs. neutral material in patients in vegetative state/unresponsive wakefulness syndrome or in minimally conscious state.

Recent Findings Most of the reviewed studies showed that salient stimuli (i.e. patient's own or familiar faces, patient's own name, and familiar voices) seem to elicit a higher amount of behavioural or electrophysiological responses with respect to neutral pictures or sounds. Importantly, a quite high percentage of patients seem to respond to salient stimuli only.

Summary The present review could foster use of personally salient stimuli in assessing DoC. However, the low overall quality of evidence and some limitations in the general reviewing process might induce caution in transferring these suggestions into clinical practice.

Keywords Disorders of consciousness · Vegetative state · Minimally conscious state · Clinical evaluation · Saliency-self-related stimuli

Introduction

After severe diffuse (e.g. anoxic) or multifocal (e.g. traumatic, vascular) brain injuries, patients may remain in an altered state of consciousness for weeks or longer. In such prolonged disorders of consciousness (DoC) [1••], spontaneous eye-opening in the lack of any sign of awareness defines vegetative state/unresponsive wakefulness syndrome (VS/UWS) [2, 3]. Inconsistent appearance of minimal but reproducible voluntary behaviours clinically classifies patients in minimally conscious state (MCS) [4].

Since a favourable outcome, namely regaining full consciousness, is more likely to occur for patients in MCS than for patients in VS/UWS [5], discriminating these clinical conditions accurately is critical for optimizing care pathways [6, 7]. However, to date, diagnostic evaluation of DoC is still a major challenge, as it rests on clinician's interpretation of patients' possible intentional responses to multisensory stimulation [8]. Moreover, fluctuations in the patients' level of vigilance and possible sensory-motor and cognitive impairments [9] might hamper behavioural responses and make actual level of responsiveness hard to detect. For these reasons, serial neurobehavioural assessments by standardized scales are strongly recommended [1••], and the Coma Recovery Scale-Revised (CRS-R) [10] is one of the most used [11] and accurate [12] of such scales.

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To reduce ambiguity about patients' conscious awareness, and to gather feasible and sensitive multimodal measures supporting clinical evaluation, different approaches have been proposed. Visual analysis of standard EEG background activity and reactivity to external stimuli could help in distinguishing patients in VS/UWS from those in MCS [13]. EEG recorded during an auditory oddball paradigm could reveal the presence of late cognitive event-related potentials (ERPs), such as P300 and mismatch negativity, more frequently in MCS than in VS/UWS [14, 15]. Otherwise, Trojano et al. [16] focused on visual pursuit of moving stimuli, a critical ability discriminating patients in MCS from patients in VS/UWS [17, 18]; by means of a computerized eye-tracking system, the authors found a significant difference in proportion of on-target and off-target fixations between patients in VS/UWS or in MCS.

Notwithstanding the diagnostic value of these approaches, the findings of multimodal formalized assessment might deviate from opinions of patients' relatives, who often report a higher level of responsiveness than that observed by clinicians [19, 20]. This discordance might reflect a justifiable optimistic bias in patients' family members, but could also be ascribed to a difference in the modality of interaction with patients. Clinical evaluations employ administration of standard neutral stimuli, whereas family caregivers ordinarily interact with patients by calling them by their own name, using their favourite objects, and referring to shared biographical experience. This might lead to higher probability of eliciting voluntary, non-reflexive behaviours. Indeed, the mere listening to a familiar voice or expression may result in an environmental enrichment able to raise arousal level and grab patients' attention [21]. On this basis, some studies introduced self-referential or emotional stimuli in clinical assessment of patients with DoC. For example, in administering the CRS-R, Vanhaudenhuyse et al. [22] and Di et al. [23•] proposed to use a mirror reflecting patients' own faces, instead of a light or common objects, to assess presence of visual pursuit and fixation, respectively. Likewise, Perrin et al. [24] devised an auditory oddball paradigm where rare sine tones were replaced with subject's own name (SON), whereas frequent sine tones were replaced with other first names, and observed a clear P300 wave after the SON in 6/6 patients in MCS and in 3/5 patients in VS/UWS. Presenting a similar paradigm to a sample of patients in MCS, Schnakers et al. [25] recorded a larger P300 amplitude in a condition of active counting with respect to passive listening. However, salient material with emotional value has been often used in experimental studies and rarely in clinical practice (with some exceptions; see [10]), and for this reason, its real effectiveness in boosting patients' responses, compared with neutral material, is still uncertain.

Here we systematically reviewed the studies that directly compared the effect of salient vs. neutral stimuli on the assessment of responsiveness in patients with DoC. By analyzing the studies' main features and findings (and possible limitations), our primary aim was to evaluate actual effectiveness of emotional salient stimuli in eliciting volitional responses, possibly supporting clinical diagnosis. The secondary aim of the present review was to identify stimuli's characteristics that could potentially support or hinder advantage of using salient material. We also discussed the possible neural correlates of this effect.

Methods

Search Strategy

We referred to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic literature reviews [26].

An online search was performed on PubMed and Cochrane Library databases until May 2019 using the following search terms: "disorders of consciousness" or "DoC" or "vegetative state" or "unresponsive wakefulness syndrome" or "minimally conscious state" and "salient" or "saliency" or "affective" or "emotionally" or "emotional" or "familiar". The search was restricted to papers: (i) available in full text; (ii) written in the English language; (iii) published in peer-reviewed journals; (iv) involving human participants only. Papers' references and a manual search conducted on Google Scholar were further sources of articles.

Inclusion Criteria

To be included in the present systematic review, the papers gathered via systematic search had to meet the following criteria: (i) reporting results of original experimental studies; (ii) including patients in VS/UWS and/or in MCS; (iii) comparing salient vs. neutral material in evaluation of responsiveness by means of behavioural or neurophysiological measures. These criteria were specifically tailored to address the primary and secondary aims of our review, and did not allow including functional neuroimaging studies (see below).

Study Selection

The primary search on the different databases provided a total pool of 1046 results, and further 6 studies were added manually. After duplicate exclusion, we screened 1044 unique articles. Out of these, 976 were excluded by checking title and abstract. We then reviewed the full text of the 68 articles left. Study selection procedure is reported in Fig. 1 (PRISMA flow diagram). It is worth underlining that 10 neuroimaging studies

assessed processing of emotional vs. neutral stimuli, but mainly provided information about the neural correlates of emotion processing in DoC and healthy individuals, without specifically addressing our primary and secondary aims (differences in responsiveness to emotional vs. neutral material). For this reason, the neuroimaging studies were not included in the review but were considered for discussing its findings.

Data Extraction

The following data were extracted from each selected article: authors, approach, patient sample, aetiology, setting, type of assessment, comparison, outcome, main findings, potential biases (Table 1).

Quality Assessment

Two independent judges rated the quality of evidence (QoE) for each included study through the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system [27]. In the GRADE system, randomized controlled trials (RCTs) are assigned the highest quality rank and observational studies the lowest rank; then, five factors (risk of bias, inconsistency, indirectness, imprecision, and publication bias) may lead to rating down the quality of evidence, whereas three factors (large effect, dose response, residual confounders) may lead to rating it higher [28]. When the two judges made discordant evaluations, they smoothed over their divergences until an agreement was reached. Summary of the GRADE scores is reported in Table 1.

Results

Characteristics of the Included Studies

Ten unique articles met the selection criteria and were included in the systematic review (Fig. 1). The study characteristics are summarized in Table 1 and reported in detail in the Supplementary material (Online resource).

Eight studies assessed behavioural responses [22, 23•, 29–33, 34•] and two studies assessed neurophysiological responses [35, 36] of patients with DoC. The included studies were published from 2008 to 2018. All but three studies ([22, 34•]: only MCS; [36]: only VS/UWS) included patients in VS/UWS and MCS with different aetiologies, and all studies

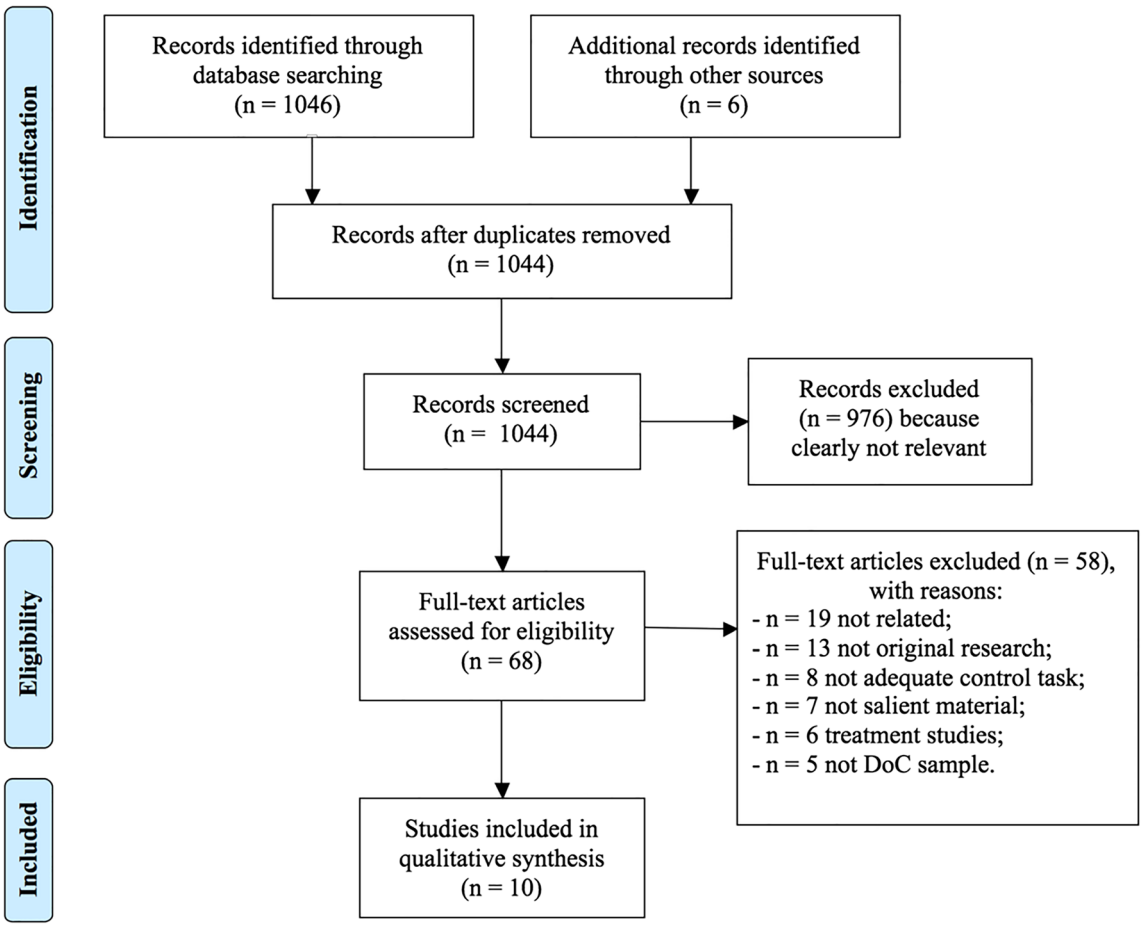

Fig. 1 PRISMA flow diagram of the selected studies. *DoC*, disorders of consciousness

Table 1 Main findings of the included studies (in chronological order)

Study	Approach	Patient sample	Aetiology	Setting	Assessment	Comparisons	Outcome	Main findings	Potential biases	GRADE QoE
Vanhaudenhuyse et al. 2008 [22]	Behavioural	51 MCS	TBI (24); Vascular (11); Anoxic (11); Metabolic (3); Toxic (2)	Acute (28); Post-acute (23)	CRS-R (mirror tracking); WHIM (person and object tracking)	Mirror vs. person vs. object	Presence of visual pursuit	Pts who successfully tracked a moving mirror were significantly more (36/38) than pts who tracked a moving person (25/38) or object (21/38)	Lack of blinding	Moderate
Formisano et al. 2011 [29]	Behavioural	9 VS/UWS; 2 MCS	TBI (5); Vascular (5); Anoxic (1)	Post-acute	CRS-R	Examiner + caregiver vs. neutral examiner	CRS-R subscores	In 4/5 pts, higher scores were recorded when a caregiver participated to the assessment.	No statistical comparisons; lack of randomization and blinding; small sample size	Very low
Di Stefano et al. 2012 [30]	Behavioural	6 VS/UWS; 6 MCS	TBI (10); Vascular (1); Anoxic (1)	Post-acute	WHIM	Personalized stimulation vs. hygienic care	Number of behaviours; best behaviour	Significantly more and more complex behaviours observed by using personalized stimuli	Variety of stimuli; lack of randomization and blinding; small sample size	Very low
Cheng et al. 2013 [31]	Behavioural	47 VS/UWS; 39 MCS	TBI (53); Vascular (21); Anoxic (12)	Post-acute	CRS-R (localization to sound)	Patient's own name vs. bell ringing	Presence of localization	More patients (33/37) showed localization to their own name compared with sound (20/37); this difference was statistically significant in MCS but not in VSUWS.	Lack of blinding	Moderate
Trojano et al. 2013 [32]	Behavioural	13 VS/UWS; 13 MCS	TBI (8); Vascular (4); Anoxic (14)	Post-acute	Eye tracking during visual pursuit	Familiar face vs. parrot vs. red circle	On-target fixations	In MCS pts, proportion of on-target and off-target fixations was significantly higher for the relative's face compared with the other two stimuli.	Lack of blinding; small sample size but large effect size	Moderate
Di et al. 2014 [23•]	Behavioural	38 VS/UWS; 43 MCS	TBI (59); Non-TBI (22)	Post-acute	CRS-R (visual fixation)	Mirror vs. ball vs. flashing light	Presence of visual fixation	Pts in MCS who showed fixation to a mirror (39/40) were significantly more than the pts who fixated a ball (23/40) or a light (20/40).		High
Thonnard et al. 2014 [34•]	Behavioural	88 MCS (including 51 from	TBI (43); Vascular (19); Anoxic (20);	Acute (38); Post-acute (50)	CRS-R (mirror tracking);	Mirror vs. person vs. object	Presence of visual pursuit	Significantly more pts (59/61) tracked the mirror, whereas 42/61 and 35/61 pts tracked a	Lack of blinding	Moderate

Table 1 (continued)

Study	Approach	Patient sample	Aetiology	Setting	Assessment	Comparisons	Outcome	Main findings	Potential biases	GRADE QoE
		Vanhaudenhuyse et al. 2008 [22])	Infection (3); Mixed (2); Intoxication (1)		WHIM (person and object tracking)			person or an object, respectively.		
Trojano et al. 2018 [33]	Behavioural	20 VS/UWS; 11 MCS *minus*; 13 MCS *plus*	TBI (7); Vascular (12); Anoxic (25)	Post-acute	Eye tracking during visual pursuit	Patient's own face vs. unfamiliar face vs. red circle	On-target fixations	Only in the MCS *plus* group, proportion of on-target and off-target fixations was significantly higher for both face conditions compared with the red circle.	Lack of randomization and blinding; small sample size	Very low
Cavinato et al. 2011 [35]	Neurophysiological	11 VS/UWS; 6 MCS	TBI (6); Vascular (6); Anoxic (4); Brain tumour (1)	Post-acute	EEG during an active auditory oddball task	Subject's own name (SON) vs. other first name (OFN) vs. sine tones (ST)	Amplitude and latency of P300 on ERPs	In MCS pts, significantly longer latency of the P3 in the SON and OFN conditions with respect to the ST	Lack of blinding; group assignation	Low
Del Giudice et al. 2016 [36]	Neurophysiological	4 VS/UWS	TBI (1); Anoxic (3)	Post-acute	EEG during a passive auditory oddball task	Familiar voice vs. unfamiliar voice	Alpha desynchronization	In 2 VS/UWS pts, differences in alpha desynchronization were found between familiar and unfamiliar voice conditions.	Lack of randomization; very small sample size; inconsistent results	Very low

QoE, quality of evidence; *VS/UWS*, vegetative state/unresponsive wakefulness syndrome; *MCS*, minimally conscious state; *TBI*, traumatic brain injury; *CRS-R*, Coma Recovery Scale-Revised; *WHIM*, Wessex Head Injury Matrix; *Pts*, patients; *ERPs*, event-related potentials

recruited patients in the post-acute phase (> 4 weeks after brain injury), except two [22, 34•] that recruited patients in both acute and post-acute phases. In all the studies, the diagnosis was made according to internationally established diagnostic criteria of VS/UWS and MCS [2, 4, 37]. In six studies [22, 23•, 31, 34•, 35, 36], the authors explicitly declared that sedative or psychotropic drugs were discontinued during data collection, whereas in the remaining studies, no indications about pharmacological treatment were provided. Some studies employed the whole CRS-R scale [29] or some of its items ([22, 34•]: visual pursuit; [31]: localization to sound; [23•]: visual fixation) to assess behavioural responses. Other studies used the Wessex Head Injury Matrix (WHIM [38]; [30]: number of behaviours and best behaviour; [22] and [34•]: person and object tracking) or the Post-Coma Scale (PCS [39]; [29]: total score). Trojano et al. [32, 33] performed a quantitative analysis of eye fixations during visual pursuit. Finally, Cavinato et al. [35] and Del Giudice et al. [36] recorded EEG during an auditory oddball task and investigated presence of ERPs and alpha desynchronization, respectively.

Quality Evaluation

Cumulative QoE for included studies resulted to be low (Table 1). No study qualified as RCT or observational, and nonetheless, we assigned high-quality ratings to all reviewed studies as a starting point. However, we had to downgrade most studies because of severe risk of bias and imprecision ($n = 4$) [29, 30, 33, 36], because of severe risk of bias ($n = 1$) [35] or because of minor risk of bias ($n = 3$) [22, 31, 32, 34•]. Even if Trojano et al.'s study [32] also suffered from imprecision, it reported a large magnitude effect despite the small sample size. For Di et al. [23•], we did not find any critical methodological issue.

In summary, out of 10 reviewed studies, 1 was judged to be a high-quality study, 4 were judged of moderate quality, 1 was judged of low quality, and 4 of very low quality.

Discussion

Here we aimed at systematically reviewing current literature on the effectiveness of emotionally salient and self-referential stimuli (compared with neutral stimuli) in boosting responses in VS/UWS and MCS. We gathered ten experimental studies that directly compared behavioural or neurophysiological effects of salient and neutral material. The overall quality of evidence was judged to be low.

Vanhaudenhuyse et al. [22] and (partially) Thonnard et al. [34•] demonstrated that a mirror is more effective than a neutral object or than a moving person in eliciting visual pursuit; indeed, 29% and 26% respectively of patients in MCS tracked the mirror only. Similarly, Di et al. [23•] reported that 35% patients in MCS responded to a mirror, rather than to a ball and to a light, when visual fixation was assessed. These findings are consistent with recent evidence showing that self-referential stimuli, such as the mirror and one's own face, are harder to neglect than other familiar faces in healthy subjects [40]. For instance, presentation of own face could cause a temporary shift of attention [41] and elicit earlier and wider P300 responses [42] with respect to familiar or unknown faces. Similar attentional facilitation has also been observed toward familiar faces, when compared with unfamiliar faces [43]. In this regard, by means of an eye-tracking system, Trojano et al. [32] found that a high proportion of patients in MCS exhibited more accurate visual pursuit when presented with their relatives' faces, compared with neutral stimuli. A further quantitative assessment of eye movements [33] reported a similar enhancement of visual pursuit accuracy during observation of own face or unfamiliar faces, compared with a neutral shape, in patients in MCS with high-level behavioural responses (MCS *plus* [44]). These observations seem to suggest that human faces in general definitely represent one of the most salient class of stimuli for both healthy individuals [41] and patients with DoC [32, 33]. Indeed, neuroimaging studies found that even some patients in VS/UWS, as well as healthy individuals, can show cortical activation in the right fusiform gyrus including the fusiform face area (FFA) [45, 46], and in anterior insula, and in the amygdala [47] during passive viewing of their own or familiar faces compared with unfamiliar faces or scrambled pictures. Presence of activity in FFA, a brain region in extrastriate cortex playing a widely accepted key-role in human face processing [48, 49], would mean that some patients clinically classified as in VS/UWS could be able not only to perceive primary features of visual stimuli such as the shape or the colour but also to process their content. Additionally, spread of this activation in the anterior insula and in the amygdala, two major nodes in the saliency neural network [50, 51], could allow merging emotional attributes of familiar faces into somatic interoceptive representations [47]. However, the activation of FFA, anterior insula, and the amygdala related to emotional and self-relevant features of human faces does not necessarily imply conscious processing in VS/UWS patients. Indeed, observation of pictures of relatives or friends would determine additional activation of a large-scale network including the occipital, parietal, temporal, prefrontal, and orbitofrontal cortices in most patients in MCS as in healthy individuals [52]. Notwithstanding the behavioural evidence of enhanced visual responses to the mirror or to pictures of human faces in DoC patients, it should be considered that these two kinds of stimuli are not equivalent. Indeed, when visual pursuit in response to mirror and to pictures of own or familiar faces was compared significantly, more patients in MCS tracked the mirror than the pictures, whereas no differences emerged between the two static face pictures [53]. The dynamic quality of one's own

face reflected in a mirror might provide, as compared with static human faces, additional information able to improve stimulus's saliency and to further enhance attentional focusing [54]. Future studies should take into account this issue.

A similar explanation could also account for the advantage toward the patient's own name reported by Cheng et al.'s study [31], in which a high percentage (45%) of patients localized the sound only when patient's proper name (instead of a ringing bell) was acoustically presented. One's own name is also a very salient stimulus, automatically catching attention. This phenomenon has been formalized in the early 1950s as the "cocktail party effect" [55] in healthy individuals and can be observed also in conditions of reduced arousal and awareness (sleep [56] and anaesthesia [57]). In DoC, the patient's own name (vs. other names or words) seems to elicit neural activity in regions believed to process self-related information, such as the precuneus and the anterior cingulate cortex [58–60], even if to a lesser degree compared with healthy individuals. These same brain regions, as well as the anterior insula and the amygdala, seem to be activated also by listening to familiar voices (vs. unfamiliar voices [59–61]), emotional sounds (vs. neutral [62]), or pain-related sounds (vs. neutral [63]). Despite neuroimaging studies revealed an activation of self-related brain areas by salient auditory stimuli such as the own name or a familiar voice, results from the neurophysiological studies included in this review did not totally agree with behavioural findings. Indeed, Cavinato et al. [35] found that P300 amplitude did not significantly differ when the patients heard their own names rather than sine tones during an active oddball paradigm, whereas P300 latency was delayed in response to own name or other names compared with sine tones, but only for patients in MCS. The authors argued that the increased P300 latency as a function of the stimulus complexity could reflect language processing, or could be related to different stimuli's duration (longer for the names with respect to the tones [35]). Moreover, in their study, Del Giudice et al. [36] reported conflicting results in the two patients who showed changes in alpha desynchronization after hearing a familiar voice compared with an unfamiliar voice. The inconsistency between results from behavioural and neurophysiological studies could likely be related to the difficulty in collecting good-quality EEG recordings in patients with DoC [36] and to differences in the experimental paradigms. Cheng et al. [31] investigated localization to sound uttering patient's name for a maximum of 4 times (2 for each side), whereas Cavinato et al. [35] averaged responses from 40 presentations of patients' own name, and Del Giudice et al. [36] used a total of 234 repetitions in which either patients' own name or other names were pronounced by familiar or unfamiliar voices. Although own name is a powerful stimulus, its effect on attention seems to be very sensitive to the number of presentations: when trials are repeated many times, the stimulus itself becomes less salient and its effect disappears in healthy individuals [64, 65]. The same could apply to the potential facilitatory effect of a familiar voice, as well. Moreover, it should be considered that more trials mean longer duration of the task and patients with DoC are very susceptible to arousal fluctuations and fatigue that might hinder changes of responsiveness. Fatigue should always be taken into account since a certain number of patients can paradoxically respond to neutral but not to salient stimulation when the salient stimulus is presented as the last one [22, 23•, 31] (see Supplementary material). Therefore, randomization or counter-balancing of trials seems to be mandatory in evaluation of patients with DoC.

Enriching environment by allowing patients to see familiar faces and hearing their own name uttered by a familiar voice [29] or by using familiar objects with an affective valence during assessment [30] provided promising results also when a whole clinical scale, rather than a single item, was administered. Indeed, the use of personally or emotionally salient stimuli had a relevant impact on the evaluation of outcome, compared with not relevant stimuli, and led to an increase in responsiveness in a relevant percentage of patients. This percentage (approximatively 35%) is close to the rate of misdiagnosis reported in previous investigations (30–40%) [8, 9, 66]. Importantly, in the reviewed studies, the facilitatory effect of personally salient stimuli seemed to be independent from patients' features, such as age, aetiology, and time from injury. However, these conclusions should be regarded with caution, since the overall methodological quality of the reviewed studies tended to be low, primarily due to lack of adequate randomization and blinding procedures. Since nowadays assessing level of consciousness is completely based on the clinical experience of the examiner, it is mandatory that future studies on this topic have a rigorous experimental control. Nevertheless, we believe that certain studies included in this review should receive more attention. Indeed, after Vanhaudenhuyse et al. [22], the use of a mirror for assessing visual pursuit has become part of common practice, but the same does not apply to the use of a mirror in the assessment of visual fixation or to the use of the patient's own name in the assessment of localization to sound, notwithstanding the studies by Di et al. [23•] and Cheng et al. [31] with high and moderate methodological quality, respectively.

This review has some limitations. First, we included ten papers, whereas we could not consider further studies that assessed the effect of emotional stimuli in patients with DoC because of the lack of adequate control task. For example, albeit a certain number of neurophysiological studies [24, 25, 67–70] used both salient and neutral material to investigate ERPs in patients with DoC, they compared responses with two kinds of stimuli in oddball paradigms where salient stimuli were always the rare stimuli and neutral stimuli were always frequent. Therefore, in these cases, the findings could reflect differences in the proportion of the two kinds of stimuli

and could not be ascribed to their content unambiguously. Riganello et al.'s study [71] also lacked an appropriate control task as it assessed variation in heart rate variability during listening to positively or negatively valenced music, compared with silence. Second, we could not include neuroimaging studies in our review since they provided information about which brain areas are activated by emotional and self-related stimuli and whether this activation could be also observed in patients with DoC, but they did not specifically compare effectiveness of salient vs. neutral material in eliciting patients' responses. Last, we could not explore the possibility that the included studies suffered from inconsistency (under-reporting of non-significant results) or publication bias (unpublished studies), since we complied with the GRADE guidelines using a single-study approach.

Conclusions

Current literature on the use of emotional and self-referential stimuli compared with neutral stimuli suggested that presenting own or familiar faces and own name or familiar voices could augment behavioural or electrophysiological responses in patients with DoC. However, the limited number of included studies and several methodological issues make it difficult to provide reliable recommendations. Further studies with strict experimental precision and larger sample sizes are needed to address this issue.

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Compliance with Ethical Standards

Conflict of Interest Alfonso Magliacano, Francesco De Bellis, Alejandro Galvao-Carmona, Anna Estraneo, and Luigi Trojano each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1.•• Giacino JT, Katz DI, Schiff ND, Whyte J, Ashman EJ, Ashwal S, et al. Practice guideline update recommendations summary: disorders of consciousness: report of the Guideline Development, Dissemination, and Implementation. Arch Phys Med Rehabil. 2018;99(9):1699–709. https://doi.org/10.1016/j.apmr.2018.07.001 **This paper provides the most recent practice recommendations for improving diagnostic and prognostic accuracy in patients with prolonged DoC.**

2. Multi-Society Task Force on PVS. Medical aspects of the persistent vegetative state. New Engl J Med. 1994;330(21):1499–508. https://doi.org/10.1056/nejm199507133330216.
3. Laureys S, Celesia GG, Cohadon F, Lavrijsen J, León-Carrión J, Sannita WG, et al. Unresponsive wakefulness syndrome: a new name for the vegetative state or apallic syndrome. BMC Med. 2010;8(1):68. https://doi.org/10.1186/1741-7015-8-68.
4. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The minimally conscious state: definition and diagnostic criteria. Neurology. 2002;58(3):349–53. https://doi.org/10.1212/wnl.58.3.349.
5. Giacino JT, Kalmar K. The vegetative and minimally conscious states: a comparison of clinical features and functional outcome. J Head Trauma Rehabil. 1997;12(4):36–51.
6. Bernat JL. Chronic disorders of consciousness. Lancet. 2006;367(9517):1181–92. https://doi.org/10.1016/S0140-6736(06)68508-5.
7. Estraneo A, Trojano L. Prognosis in disorders of consciousness. In: Schnakers C, Laureys S, editors. Coma and disorders of consciousness. Cham: Springer; 2018. p. 17–36.
8. Schnakers C, Vanhaudenhuyse A, Giacino J, Ventura M, Boly M, Majerus S, et al. Diagnostic accuracy of the vegetative and minimally conscious state: clinical consensus versus standardized neurobehavioral assessment. BMC Neurol. 2009;9(1):35. https://doi.org/10.1186/1471-2377-9-35.
9. Majerus S, Gill-Thwaites H, Andrews K, Laureys S. Behavioral evaluation of consciousness in severe brain damage. Prog Brain Res. 2005;150:397–413. https://doi.org/10.1016/S0079-6123(05)50028-1.
10. Giacino JT, Kalmar K, Whyte J. The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch Phys Med Rehabil. 2004;85(12):2020–9. https://doi.org/10.1016/j.apmr.2004.02.033.
11. Formisano R, Giustini M, Aloisi M, Contrada M, Schnakers C, Zasler N, et al. An International survey on diagnostic and prognostic protocols in patients with disorder of consciousness. Brain Inj. 2019:1–11. https://doi.org/10.1080/02699052.2019.1622785.
12. Estraneo A, Moretta P, Cardinale V, De Tanti A, Gatta G, Giacino JT, et al. A multicentre study of intentional behavioural responses measured using the Coma Recovery Scale–Revised in patients with minimally conscious state. Clin Rehabil. 2015;29(8):803–8. https://doi.org/10.1177/0269215514556002.
13. Estraneo A, Loreto V, Guarino I, Boemia V, Paone G, Moretta P, et al. Standard EEG in diagnostic process of prolonged disorders of consciousness. Neurophysiology. 2016;127(6):2379–85. https://doi.org/10.1016/j.clinph.2016.03.021.
14. Faugeras F, Rohaut B, Weiss N, Bekinschtein TA, Galanaud D, Puybasset L, et al. Probing consciousness with event-related potentials in the vegetative state. Neurology. 2011;77(3):264–8. https://doi.org/10.1212/WNL.0b013e3182217ee8.
15. Faugeras F, Rohaut B, Weiss N, Bekinschtein T, Galanaud D, Puybasset L, et al. Event related potentials elicited by violations of auditory regularities in patients with impaired consciousness. Neuropsychologia. 2012;50(3):403–18. https://doi.org/10.1016/j.neuropsychologia.2011.12.015.
16. Trojano L, Moretta P, Loreto V, Cozzolino A, Santoro L, Estraneo A. Quantitative assessment of visual behavior in disorders of consciousness. J Neurol. 2012;259(9):1888–95. https://doi.org/10.1007/s00415-012-6435-4.

17. Giacino JT. The vegetative and minimally conscious states: consensus-based criteria for establishing diagnosis and prognosis. Neurorehabilitation. 2004;19(4):293–8.
18. Estraneo A, Moretta P, De Tanti A, Gatta G, Giacino JT, Trojano L. An Italian multicentre validation study of the coma recovery scale-revised. Eur J Phys Rehabil Med. 2015;51(5):627–34.
19. Jox RJ, Kuehlmeyer K, Klein AM, Herzog J, Schaupp M, Nowak DA, et al. Diagnosis and decision making for patients with disorders of consciousness: a survey among family members. Arch Phys Med Rehabil. 2015;96(2):323–30. https://doi.org/10.1016/j.apmr.2014.09.030.
20. Moretta P, Trojano L, Masotta O, Cardinale V, Loreto V, Estraneo A. Family caregivers' opinions about interaction with the environment in consciousness disorders. Rehabil Psychol. 2017;62(2):208. https://doi.org/10.1037/rep0000144.
21. Mack A, Pappas Z, Silverman M, Gay R. What we see: inattention and the capture of attention by meaning. Conscious Cogn. 2002;11(4):488–506.
22. Vanhaudenhuyse A, Schnakers C, Brédart S, Laureys S. Assessment of visual pursuit in post-comatose states: use a mirror. J Neurol Neurosurg Psychiatry. 2008;79(2):223–3. https://doi.org/10.1136/jnnp.2007.121624.
23.• Di H, Nie Y, Hu X, Tong Y, Heine L, Wannez S, et al. Assessment of visual fixation in vegetative and minimally conscious states. BMC Neurol. 2014;14(1):147. https://doi.org/10.1186/1471-2377-14-147 **The authors investigated the effect of using a mirror, compared with an object or a flashing light, to elicit visual fixation, and turned out to be the study with higher methodological accuracy, as assessed by the GRADE system, in the present review.**
24. Perrin F, Schnakers C, Schabus M, Degueldre C, Goldman S, Brédart S, et al. Brain response to one's own name in vegetative state, minimally conscious state, and locked-in syndrome. Arch Neurol. 2006;63(4):562–9. https://doi.org/10.1001/archneur.63.4.562.
25. Schnakers C, Perrin F, Schabus M, Majerus S, Ledoux D, Damas P, et al. Voluntary brain processing in disorders of consciousness. Neurology. 2008;71(20):1614–20. https://doi.org/10.1212/01.wnl.0000334754.15330.69.
26. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med. 2009;151(4):264–9. https://doi.org/10.1016/j.ijsu.2010.02.007.
27. Schünemann H. The GRADE handbook. Cochrane Collaboration; 2013.
28. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, et al. GRADE guidelines: 1. Introduction—GRADE evidence profiles and summary of findings tables. J Clin Epidemiol. 2011;64(4):383–94. https://doi.org/10.1016/j.jclinepi.2010.04.026.
29. Formisano R, D'Ippolito M, Risetti M, Riccio A, Caravasso CF, Catani S, et al. Vegetative state, minimally conscious state, akinetic mutism and Parkinsonism as a continuum of recovery from disorders of consciousness: an exploratory and preliminary study. Funct Neurol. 2011;26(1):15.
30. Di Stefano C, Cortesi A, Masotti S, Simoncini L, Piperno R. Increased behavioural responsiveness with complex stimulation in VS and MCS: preliminary results. Brain Inj. 2012;26(10):1250–6. https://doi.org/10.3109/02699052.2012.667588.
31. Cheng L, Gosseries O, Ying L, Hu X, Yu D, Gao H, et al. Assessment of localisation to auditory stimulation in post-comatose states: use the patient's own name. BMC Neurol. 2013;13(1):27. https://doi.org/10.1186/1471-2377-13-27.
32. Trojano L, Moretta P, Loreto V, Santoro L, Estraneo A. Affective saliency modifies visual tracking behavior in disorders of consciousness: a quantitative analysis. J Neurol. 2013;260(1):306–8. https://doi.org/10.1007/s00415-012-6717-x.
33. Trojano L, Moretta P, Masotta O, Loreto V, Estraneo A. Visual pursuit of one's own face in disorders of consciousness: a quantitative analysis. Brain Inj. 2018;32(12):1549–55. https://doi.org/10.1080/02699052.2018.1504117.
34.• Thonnard M, Wannez S, Keen S, Brédart S, Brun MA, Gosseries O, et al. Detection of visual pursuit in patients in minimally conscious state: a matter of stimuli and visual plane? Brain Inj. 2014;28(9):1164–70. https://doi.org/10.3109/02699052.2014.920521 **The authors demonstrated on a very large sample of patients with DoC the importance of using a mirror, compared with an object or a moving person, when clinically evaluating visual pursuit, a critical marker discriminating VS/UWS and MCS.**
35. Cavinato M, Volpato C, Silvoni S, Sacchetto M, Merico A, Piccione F. Event-related brain potential modulation in patients with severe brain damage. Clin Neurophysiol. 2011;122(4):719–24. https://doi.org/10.1016/j.clinph.2010.08.024.
36. Del Giudice R, Blume C, Wislowska M, Lechinger J, Heib DP, Pichler G, et al. Can self-relevant stimuli help assessing patients with disorders of consciousness? Conscious Cogn. 2016;44:51–60. https://doi.org/10.1016/j.concog.2016.06.013.
37. Bates D. The vegetative state: guidance on diagnosis and management-a report of a working party of the Royal College of Physicians. Clin Med. 2003;3(3):249–54. https://doi.org/10.7861/clinmedicine.3-3-249.
38. Shiel A, Horn SA, Wilson BA, Watson MJ, Campbell MJ, McLellan DL. The Wessex Head Injury Matrix (WHIM) main scale: a preliminary report on a scale to assess and monitor patient recovery after severe head injury. Clin Rehabil. 2000;14(4):408–16. https://doi.org/10.1191/0269215500cr326oa.
39. Formisano R, Vinicola V, Carlesimo GA, Sabbadini M, Penta F. Assessment scale for patients with prolonged disturbances of consciousness (postcoma scale). Proceedings of the Fifth Conference of the International Association for the study of Traumatic Brain Injury and 20th Conference of the Australian Society for the Study of Brain Impairment. Melbourne: Australian Academic Press. 1996. p. 15-18.
40. Brédart S, Delchambre M, Laureys S. One's own face is hard to ignore. Q J Exp Psychol. 2006;59(1):46–52. https://doi.org/10.1080/17470210500343678.
41. Devue C, Brédart S. Attention to self-referential stimuli: can I ignore my own face? Acta Psychol (Amst). 2008;128(2):290–7. https://doi.org/10.1016/j.actpsy.2008.02.004.
42. Tacikowski P, Nowicka A. Allocation of attention to self-name and self-face: an ERP study. Biol Psychol. 2010;84(2):318–24. https://doi.org/10.1016/j.biopsycho.2010.03.009.
43. Tong F, Nakayama K. Robust representations for faces: evidence from visual search. J Exp Psychol Hum Percept Perform. 1999;25(4):1016. https://doi.org/10.1037//0096-1523.25.4.1016.
44. Bruno MA, Vanhaudenhuyse A, Thibaut A, Moonen G, Laureys S. From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. J Neurol. 2011;258(7):1373–84. https://doi.org/10.1007/s00415-011-6114-x.
45. Menon DK, Owen AM, Boniface SJ, Pickard JD. Cortical processing in persistent vegetative state. Lancet. 1998;352(9134):1148–9. https://doi.org/10.1016/s0140-6736(05)77805-3.
46. Owen AM, Menon DK, Johnsrude IS, Bor D, Scott SK, Manly T, et al. Detecting residual cognitive function in persistent vegetative state. Neurocase. 2002;8(5):394–403. https://doi.org/10.1076/neur.8.4.394.16184.
47. Sharon H, Pasternak Y, Simon EB, Gruberger M, Giladi N, Krimchanski BZ, et al. Emotional processing of personally familiar faces in the vegetative state. PLoS One. 2013;8(9):e74711. https://doi.org/10.1371/journal.pone.0074711.

48. Grill-Spector K, Knouf N, Kanwisher N. The fusiform face area subserves face perception, not generic within-category identification. Nat Neurosci. 2004;7(5):555. https://doi.org/10.1038/nn1224.
49. Kanwisher N, Yovel G. The fusiform face area: a cortical region specialized for the perception of faces. Philos Trans R Soc Lond B Biol Sci. 2006;361(1476):2109–28. https://doi.org/10.1098/rstb.2006.1934.
50. Menon V, Uddin LQ. Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct. 2010;214(5-6):655–67. https://doi.org/10.1007/s00429-010-0262-0.
51. Pessoa L, Adolphs R. Emotion processing and the amygdala: from a 'low road' to 'many roads' of evaluating biological significance. Nat Rev Neurosci. 2010;11(11):773. https://doi.org/10.1038/nrn2920.
52. Zhu J, Wu X, Gao L, Mao Y, Zhong P, Tang W, et al. Cortical activity after emotional visual stimulation in minimally conscious state patients. J Neurotrauma. 2009;26(5):677–88. https://doi.org/10.1089/neu.2008.0691.
53. Wannez S, Vanhaudenhuyse A, Laureys S, Brédart S. Mirror efficiency in the assessment of visual pursuit in patients in minimally conscious state. Brain Inj. 2017;31(11):1429–35. https://doi.org/10.1080/02699052.2017.1376755.
54. Xiao NG, Perrotta S, Quinn PC, Wang Z, Sun YHP, Lee K. On the facilitative effects of face motion on face recognition and its development. Front Psychol. 2014;5:633. https://doi.org/10.3389/fpsyg.2014.00633.
55. Cherry EC. Some experiments on the recognition of speech, with one and with two ears. J Acoust Soc Am. 1953;25(5):975–9.
56. Oswald I, Taylor AM, Treisman M. Discriminative responses to stimulation during human sleep. Brain. 1960;80:440–53. https://doi.org/10.1093/brain/83.3.440.
57. Kurtz D, Trapp C, Kieny MT, Wassmer JM, Mugnaioni MD, Pack A, et al. Study of recovery and the post-anaesthetic period (author's transl). Rev Electroencephalogr Neurophysiol Clin. 1977;7(1):62–9.
58. Staffen W, Kronbichler M, Aichhorn M, Mair A, Ladurner G. Selective brain activity in response to one's own name in the persistent vegetative state. J Neurol Neurosurg Psychiatry. 2006;77(12):1383–4. https://doi.org/10.1136/jnnp.2006.095166.
59. Bick AS, Leker RR, Ben-Hur T, Levin N. Implementing novel imaging methods for improved diagnosis of disorder of consciousness patients. J Neurol Sci. 2013;334(1-2):130–8. https://doi.org/10.1016/j.jns.2013.08.009.
60. Nicholas CR, McLaren DG, Gawrysiak MJ, Rogers BP, Dougherty JH, Nash MR. Functional neuroimaging of personally-relevant stimuli in a paediatric case of impaired awareness. Brain Inj. 2014;28(8):1135–8. https://doi.org/10.3109/02699052.2014.890745.
61. Bekinschtein T, Niklison J, Sigman L, Manes FRLJA, Leiguarda R, Armony J, et al. Emotion processing in the minimally conscious state. J Neurol Neurosurg Psychiatry. 2004;75(5):788–8. https://doi.org/10.1136/jnnp.2003.034876.
62. Kotchoubey B, Merz S, Lang S, Markl A, Mülle F, Yu T, et al. Global functional connectivity reveals highly significant differences between the vegetative and the minimally conscious state. J Neurol. 2013;260(4):975–83. https://doi.org/10.1007/s00415-012-6734-9.
63. Yu T, Lang S, Vogel D, Markl A, Müller F, Kotchoubey B. Patients with unresponsive wakefulness syndrome respond to the pain cries of other people. Neurology. 2013;80(4):345–52. https://doi.org/10.1212/WNL.0b013e31827f0846.
64. Harris CR, Pashler H. Attention and the processing of emotional words and names: not so special after all. Psychol Sci. 2004;15(3):171–8. https://doi.org/10.1111/j.0956-7976.2004.01503005.x.
65. Laureys S, Perrin F, Brédart S. Self-consciousness in non-communicative patients. Conscious Cogn. 2007;16(3):722–41. https://doi.org/10.1016/j.concog.2007.04.004.
66. Seel RT, Sherer M, Whyte J, Katz DI, Giacino JT, Rosenbaum AM, et al. Assessment scales for disorders of consciousness: evidence-based recommendations for clinical practice and research. Arch Phys Med Rehabil. 2010;91(12):1795–813. https://doi.org/10.1016/j.apmr.2010.07.218.
67. Laureys S, Perrin F, Faymonville ME, Schnakers C, Boly M, Bartsch V, et al. Cerebral processing in the minimally conscious state. Neurology. 2004;63(5):916–8. https://doi.org/10.1212/01.wnl.0000137421.30792.9b.
68. De Salvo S, Caminiti F, Bonanno L, De Cola MC, Corallo F, Caizzone A, et al. Neurophysiological assessment for evaluating residual cognition in vegetative and minimally conscious state patients: a pilot study. Funct Neurol. 2015;30(4):237.
69. Wang XY, Wu HY, Lu HT, Huang TT, Zhang H, Zhang T. Assessment of mismatch negativity and P300 response in patients with disorders of consciousness. Eur Rev Med Pharmacol Sci. 2017;21(21):4896–906.
70. Castro M, Tillmann B, Luauté J, Corneyllie A, Dailler F, André-Obadia N, et al. Boosting cognition with music in patients with disorders of consciousness. Neurorehab Neural Repair. 2015;29(8):734–42. https://doi.org/10.1177/1545968314565464.
71. Riganello F, Candelieri A, Quintieri M, Conforti D, Dolce G. Heart rate variability: an index of brain processing in vegetative state? An artificial intelligence, data mining study. Clin Neurophysiol. 2010;121(12):2024–34. https://doi.org/10.1016/j.clinph.2010.05.010.