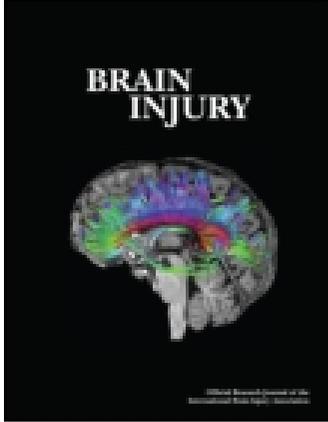


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Detection of visual pursuit in patients in minimally conscious state: A matter of stimuli and visual plane?

Marie Thonnard^{1*}, Sarah Wannez^{1*}, Shannan Keen², Serge Brédart³, Marie-Aurélié Bruno¹, Olivia Gosseries¹, Athena Demertzi¹, Aurore Thibaut¹, Camille Chatelle¹, Vanessa Charland-Verville¹, Lizette Heine¹, Dina Habbal¹, Steven Laureys¹, & Audrey Vanhauzenhuyse⁴

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Abstract

Objectives: The aim of this study was to determine whether the assessment of pursuit eye movements in patients in minimally conscious state (MCS) is influenced by the choice of the visual stimulus (study 1) and by the moving plane (study 2).

Methods: Patients with MCS (MCS– and MCS+) in the acute (<1 month post-injury) or chronic (>1 month) setting were assessed. The Coma Recovery Scale-Revised (CRS-R) procedure was used to test visual pursuit of a moving mirror, object and person (study 1, $n = 88$) and to test vertical and horizontal visual tracking (study 2, $n = 94$).

Results: Study 1: Patients with visual pursuit tracked preferentially the moving mirror over the moving person or object. Study 2: Patients displaying visual pursuit, especially in MCS– and in chronic setting, preferentially tracked on the horizontal rather than the vertical plane.

Conclusion: The findings confirm the importance of using a mirror to assess visual pursuit in patients in MCS and of initiating testing using the horizontal plane, specifically in patients in MCS– and those in chronic setting. Assessment should then be done on the vertical plane if visual pursuit is not detected on the horizontal plane.

Keywords

Behavioural assessment, disorders of consciousness, minimally conscious state, visual pursuit

History

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Introduction

The presence of visual pursuit occurring in direct response to moving or salient stimuli is one of the first clinical signs [1] differentiating the minimally conscious state (MCS) from the vegetative state/unresponsive wakefulness syndrome (VS/UWS). Patients in VS/UWS show preserved arousal with only reflexive behaviours [2], whereas patients in MCS are characterized by fluctuant but reproducible signs of consciousness without functional communication [3]. Visual pursuit assessment represents a real challenge. First, visual pursuit is one of the first sign of consciousness [1] and can easily be missed if not properly assessed [4]. Secondly, some patients are more likely to be misdiagnosed if visual pursuit is missed. Indeed, patients in MCS MINUS (MCS–) [5] only show low levels of non-reflexive behavioural interactions such as visual pursuit. This contrasts with patients in MCS PLUS (MCS+) who generally show a larger behavioural repertoire such as command following. Thirdly, because patients with MCS have a better prognosis than patients in

VS/UWS [6, 7], misdiagnosis can lead to grave consequences, especially in end-of-life decision-making [8].

Despite its importance in diagnosis, behavioural assessment of visual pursuit is still under debate. Depending on the scale used, stimuli differ: the Coma Recovery Scale-Revised (CRS-R [9]) and the Western Neuro-Sensory Stimulation Profile (WNSSP [10]) employ a moving mirror; the Coma/Near Coma Scale [11], the Wessex Head Injury Matrix (WHIM [12]) and the Sensory Modalities Assessment and Rehabilitation Technique (SMART [13]) use a moving person; the WNSSP, SMART and WHIM also use a moving object or finger, as does the Full Outline of Unresponsiveness Scale (FOUR [14]). The importance of using a mirror when evaluating visual pursuit in patients with disorders of consciousness has been emphasized previously [4]. However, because of the smaller sample size and because, to the best of the authors' knowledge, it is the only available study evaluating the efficiency of the stimulus used in the assessment of visual pursuit, the results are worth being confirmed in a bigger sample.

There is no consensus on which plane (horizontal or vertical) should be tested for visual pursuit assessment. Some scales, such as the WHIM [12], limit the assessment of visual pursuit to the horizontal plane. Other scales, for instance the CRS-R [9] or the SMART [13], assess visual pursuit in both horizontal and vertical planes. Similarly, the FOUR [14] assesses vertical plane only if there is no visual pursuit

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detected in the horizontal plane. In some scales, planes are not mentioned (e.g. Rancho Los Amigos–Revised Levels of Cognitive Functioning [15]). To date, no data are available concerning the assessment of vertical and horizontal planes and their differences in detecting visual pursuit. However, if assessment of planes can affect the detection of visual pursuit, then the scale used to assess patients with disorders of consciousness could also bias diagnosis and lead to diagnostic errors. Research is, therefore, needed to determine if the assessment of one plane instead of, or with, the other can make a difference to the efficiency of visual pursuit detection.

The aim of the present study is 2-fold. First it determines, on a larger cohort of patients, whether the assessment of pursuit eye movements in patients in MCS is influenced by the choice of the visual stimulus. Visual pursuit was prospectively evaluated using a standardized presentation of a moving mirror and this study compared the responses obtained with a moving person and a moving object. Second, it investigated whether the assessment of pursuit eye movements in patients in MCS is influenced by the choice of the visual plane (horizontal vs. vertical). This study prospectively studied visual pursuit using a standardized presentation of a moving mirror on the horizontal vs. the vertical planes.

Methods

Patients in MCS were studied free of sedative drugs in the acute (≤ 4 weeks) and chronic (>4 weeks after insult) settings. Patients were assessed with the CRS-R on the day of the visual pursuit assessment by experienced, skilled neuropsychologists. The diagnoses of MCS were established according to the Aspen workgroup criteria for MCS [3] and the diagnoses of MCS–/MCS+ were established in accordance with the recent sub-categorization proposed by Bruno et al. [5]. Each patient was assessed in the seated position and patient preparation employed a standardized arousal facilitation protocol, as defined in the CRS-R [9]. The study was approved by the Ethics Committee of the Medical School of the University of Liège. Informed consent to participate in the study was obtained from the legal surrogate of each patient.

Study 1: Evaluating the influence of the choice of stimulus

This study used the methodology previously described in Vanhauzenhuyse et al. [4]. A mirror or an object was held 4–6 inches in front of the patient's face and was moved slowly 45° to the right and left of the vertical midline. For visual pursuit assessment using a moving person, the examiner moved slowly 45° to the right and left of the vertical midline. Stimuli were presented twice for each direction using randomized order of presentation. Visual pursuit was defined as a full range (i.e. 45°) eye movement without loss of fixation on at least two occasions in any direction [9]. Differences between visual pursuit, as assessed by the mirror, person or object, were tested using a binomial test for comparison of proportions (i.e. exact test permitting computation of the level of significance of the difference between two proportions. For more details see Siegel and Castellan [16]). Results were considered significant at a p value less than 0.05. Bonferroni's correction for multiple comparisons was applied where appropriate.

Study 2: Evaluating the influence of the visual plane

A mirror was held in front of the patient's face and was moved slowly 45° to the right and left of the vertical midline and 45° above and below the horizontal midline. This procedure was repeated twice for each plane. The same CRS-R criteria for visual pursuit were applied for each plane separately [9]. Horizontal and vertical plane responses were tested using the mirror only, since it has been shown that a mirror was more efficient in detecting visual pursuit as compared to a moving person or object [4]. Differences between visual pursuit on the vertical and horizontal plane were assessed using binomial testing [16]. Results were considered significant at a p value under 0.05. Bonferroni's correction for multiple comparisons was applied where appropriate.

Results

Study 1: Influence of the choice of stimulus

Of 88 patients in MCS (51 previously published in Vanhauzenhuyse et al. [4], 26 women; mean age = 51, SD = 20 years), 38 were studied in the acute (mean interval = 16, SD = 7 days) and 50 in the chronic (mean = 2 years and 10 months, SD = 4 years 11 months) setting. Aetiology was traumatic in 43 patients and non-traumatic in 45 patients (i.e. anoxic encephalopathy ($n = 20$), ischaemic or haemorrhagic stroke ($n = 19$), mixed aetiology (i.e. trauma and anoxia, $n = 2$), infection ($n = 3$) or intoxication ($n = 1$)). Thirty-two patients were diagnosed as MCS– and 56 as MCS+ [5].

Sixty-one (69%) of the 88 patients in MCS showed pursuit eye movements occurring in response to moving salient stimuli. In the 61 patients in MCS showing pursuit eye movements, more patients tracked the moving mirror ($n = 59$; 97%; 30 traumatic; 33 chronic; 25 MCS–) than the moving person ($n = 42$; 69%; $p < 0.01$; 19 traumatic; 23 chronic, 15 MCS–) or the moving object ($n = 35$; 57%; $p < 0.01$; 14 traumatic; 18 chronic, 12 MCS–) (Figure 1, Table I). There was no statistical difference between responses obtained using a moving person or a moving object ($p = 0.51$).

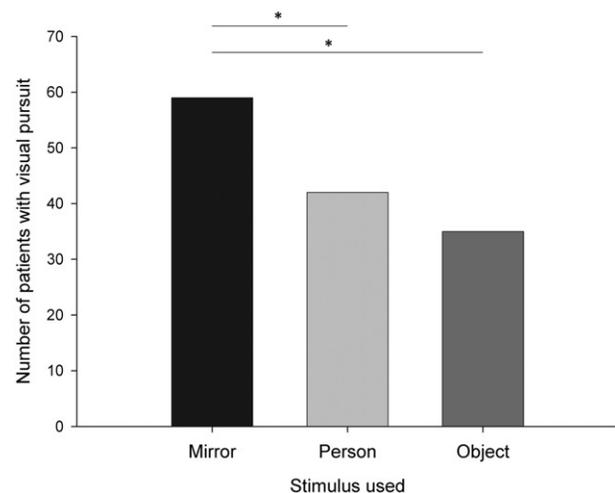


Figure 1. Number of patients showing visual pursuit in response to mirror, person or object as stimuli. * $p < 0.05$.

Table I. Numbers and percentages of patients showing visual pursuit in response to mirror, object or person as stimuli according to the clinical diagnosis, chronicity and aetiology.

Visual pursuit	Patients with visual pursuit					
	All (% , n = 61)	MCS- (% , n = 25)	MCS+ (% , n = 36)	Chronic (% , n = 34)	TBI (% , n = 31)	NTBI (% , n = 30)
Mirror	59 (97)* ⁺	25 (100)* ⁺	34 (94) ⁺	33 (97)* ⁺	30 (97)* ⁺	29 (97) ⁺
Person	42 (69)	15 (60)	27 (75)	23 (68)	19 (61)	23 (77)
Object	35 (57)	12 (48)	23 (64)	18 (53)	14 (45)	21 (70)
Mirror only	16 (26)* ⁺	10 (40)* ⁺	6 (17) ⁺	10 (29)* ⁺	11 (36)* ⁺	5 (17)
Person only	2 (3)	0	2 (5)	1 (3)	1 (3)	1 (3)
Object only	0	0	0	0	0	0
Mirror & person	8	3 (12)	5 (14)	5 (15)	5 (16)	3 (10)
Mirror & object	3	0	3 (8)	1 (3)	1 (3)	2 (7)
Person & object	0	0	0	0	0	0
Mirror & person & object	32	12 (48)	20 (56)	17 (50)	13 (42)	19 (63)

*Mirror (only) vs. person (only) and ⁺Mirror (only) vs. object (only) comparisons significant at $p < 0.05$ corrected for multiple comparisons; no comparison person (only) vs. object (only) was significant.

MCS-, minimally conscious state MINUS. MCS+, minimally conscious state PLUS; TBI, traumatic brain injury; NTBI, non-traumatic brain injury.

Between-group comparisons revealed that visual pursuits in response to a moving mirror, person or object did not differ in terms of aetiology (traumatic vs. non-traumatic, mirror: $p > 0.99$; person: $p = 0.53$; object: $p = 0.144$), chronicity (acute vs. chronic mirror: $p > 0.99$; person: $p > 0.99$; object: $p > 0.99$) or MCS sub-categorization (MCS- vs. MCS+, mirror: $p = 0.63$; person: $p = 0.63$; object: $p = 0.63$). There was no statistical difference in terms of age for each stimulus tested.

Since 51 patients were previously studied by Vanhauzenhuysse et al. [4], this study performed analysis of the sample of new patients only ($n = 37$, 24 (65%) showing visual pursuit). In patients showing visual pursuit, more patients tracked the moving mirror ($n = 23$; 96%; 11 traumatic; 19 chronic; seven MCS-) than the moving object ($n = 14$; 58%; $p = 0.005$; five traumatic; 13 chronic; four MCS-), but not than the moving person ($n = 18$; 75%, $p = 0.11$; seven traumatic; 14 chronic; six MCS-). There was no statistical difference between responses obtained using a moving person or a moving object ($p = 0.63$).

Study 2: Influence of the visual plane

Of 94 patients (25 also included in study 1, none from Vanhauzenhuysse et al. [4]; 28 women; mean age = 46, SD = 18 years), 25 were studied in the acute (mean interval = 19, SD = 6 days) and 69 in the chronic (mean = 2 years 11 months, SD = 4 years 6 months) setting. Aetiology was traumatic in 46 and non-traumatic in 48 patients (i.e. ischaemic or haemorrhagic stroke ($n = 22$), anoxic encephalopathy ($n = 13$), mixed aetiology (i.e. trauma and anoxia, $n = 3$) and other (e.g. infection, metabolic, tumour, etc.; $n = 10$)). Forty-seven patients were diagnosed as MCS- and 47 as MCS+ [5].

Of the 94 patients in MCS showing pursuit eye movements, patients tracked significantly more horizontally ($n = 80$; 85%; 40 traumatic; 61 chronic, 39 MCS-) than vertically ($n = 61$; 65%; $p < 0.01$; 30 traumatic; 46 chronic, 26 MCS-). There were more patients showing visual pursuit in the horizontal plane ($n = 31$; 33%; 15 traumatic; 21 chronic, 20 MCS-) than patients showing visual pursuit in the vertical

plane ($n = 12$; 13%; $p < 0.01$; five traumatic; six chronic, seven MCS-). Note that two patients (one MCS+ and one MCS-) failed to reach the criteria for both planes when considering planes independently (i.e. they only showed tracking once in each plane) (Table II).

In the 47 patients in MCS-, significantly more patients tracked horizontally ($n = 39$; 83%; 18 traumatic; 36 chronic) than vertically ($n = 26$; 55%; $p < 0.01$; 11 traumatic; 18 chronic). There were more patients showing visual pursuit in the horizontal plane only ($n = 20$; 43%; 10 traumatic; 13 chronic) than patients with visual pursuit in the vertical plane only ($n = 7$; 15%; $p < 0.01$; five traumatic; one chronic, Figure 2). In patients in MCS+ ($n = 47$), there was no statistical difference between the responses obtained in the horizontal plane ($n = 41$, 87%, 22 traumatic, 33 chronic) and the vertical plane ($n = 35$, 74%, $p = 0.21$, 19 traumatic, 28 chronic). There was also no difference between the number of patients showing visual pursuit only in the horizontal plane ($n = 11$, 23%, five traumatic, eight chronic) or only in the vertical plane ($n = 5$, 11%, $p = 0.24$, two traumatic, three chronic).

In the 69 chronic patients, significantly more patients tracked horizontally ($n = 61$; 88%; 40 traumatic) than vertically ($n = 47$; 67%; $p < 0.01$; 30 traumatic). More chronic patients showed only horizontal visual pursuit ($n = 21$; 30%; 15 traumatic) than only vertical visual pursuit ($n = 6$; 9%; $p < 0.01$; five traumatic). Visual pursuit plane preference was not significantly different in terms of aetiology (all $p > 0.05$). There was no statistical difference in terms of age for each stimulus tested.

Discussion

The findings highlight the importance of the assessment procedure for visual pursuit. In the first study on the influence of the choice of stimuli, it was shown, on an extended cohort of patients, that patients in MCS tend to track a moving mirror better as compared with tracking a moving person or object, independently of aetiology, chronicity or MCS sub-categorization. These data confirm the results previously reported by Vanhauzenhuysse et al. [4]. However, since data

Table II. Number of patients showing visual pursuit on horizontal and vertical planes according to the clinical diagnosis, duration and aetiology.

Visual pursuit	All (% , n = 94)	MCS- (% , n = 47)	Chronic (% , n = 69)	TBI (% , n = 46)	NTBI (% , n = 48)
Horizontal	80 (85)*	39 (83)*	61 (88)*	40 (87)*	40 (83)*
Vertical	61 (65)	26 (55)	46 (67)	30 (65)	31 (65)
Horizontal only	31 (33)*	20 (43)*	21 (30)*	15 (33)*	16 (33)*
Vertical only	12 (13)	7 (15)	6 (9)	5 (11)	7 (15)
Horizontal and Vertical	49 (52)	19 (40)	40 (58)	25 (54)	24 (50)

*Horizontal (only) vs. vertical (only) significant at $p < 0.05$ corrected for multiple comparisons.

MCS-, minimally conscious state MINUS; TBI, traumatic brain injury; NTBI, non-traumatic brain injury.

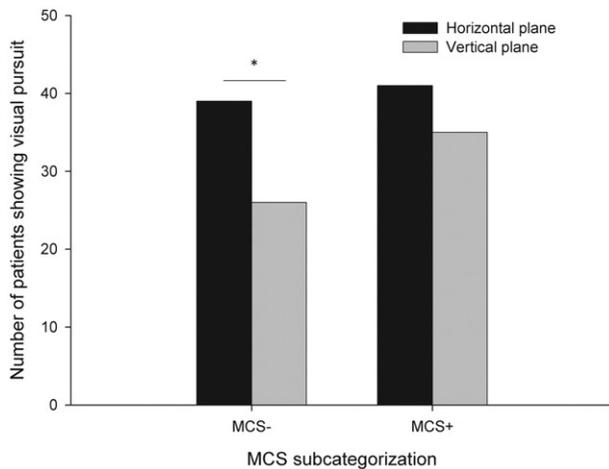


Figure 2. Number of patients showing visual pursuit on horizontal and vertical planes according to the clinical diagnosis of MCS- or MCS+. * $p < 0.05$.

from Vanhauzenhuysse et al. are included here, analysis on the new patients were performed and show relatively similar patterns of results, with the exception of an absence of statistical difference between the number of visual pursuits recorded for the moving mirror and the moving person. This absence of difference can be explained by the lower sample size of this sub-group (almost two-thirds less than in the entire sample), resulting in a loss of statistical power. In contrast, proportions of patients showing visual pursuit with each stimulus are similar to those obtained in the entire sample and to the proportions reported in Vanhauzenhuysse et al. [4].

Extended research is needed to understand attentional properties of seeing one's own face and its significance in terms of self-awareness perception. However, the use of the patient's own face/reflection as a stimulus seems promising for the study of residual self-awareness in non-communicative patients. Indeed, as demonstrated by the well-known 'cocktail party' phenomenon, auto-referential stimuli can particularly capture attention in everyday social interactions and give rise to a sense of self-awareness [17]. Several studies have previously demonstrated that faces constitute a class of stimuli that are especially prone to capturing one's attention (for a review, see Laureys et al. [18]). In healthy volunteers, studies have shown that one's own face can be easier to detect than other faces [19, 20]. However its 'distractive value' seems to vary according to the task used in the experiment. Indeed, whereas, in a visual search task, one's own face does not seem to be more distractive than other faces [19, 20], it could be so in a person classification task using names rather

than faces [21]. In patients with disorders of consciousness, the particularity of auto-referential stimuli and its usefulness in such patients has already been shown [4, 22, 23].

Despite the need to better understand the effect of one's own face/own reflection in patients with altered states of consciousness, the use of a mirror for clinical diagnosis could be useful. This is because a mirror seems to improve diagnostic accuracy in detecting more efficiently visual pursuit than does testing using an object or person. However, some could argue that the use of a mirror ought to be ethically discussed, particularly in cases of severely brain-injured patients, who are often intubated, sometimes with head or facial trauma. Indeed, in clinical settings in particular, clinicians do not know whether patients are conscious or not, nor to what extent. Hence, the vision of one's own face with apparatus such as intubation and/or injuries could potentially be traumatic. However, only patients with sufficient levels of consciousness and sufficiently spared memory are likely to be traumatized by the sight of their own reflection. Additionally, in such medical conditions, where clinical assessments are sometimes the only tool available to assess consciousness and since prognosis and life-sustaining treatment rely on diagnosis, the reliability of the diagnosis should be balanced with the psychological trauma that could potentially be caused by seeing their own injured face.

The second part of the study showed that the clinical assessment of visual pursuit depends on which plane (horizontal or vertical) is tested. The results highlighted that chronic patients in MCS showed preferential horizontal visual pursuit compared to vertical. The sub-group of patients in MCS- showed a similar preference (i.e. more visual pursuit on the horizontal plane). The functional neuroanatomy of horizontal and vertical pursuit is still only partially understood. In addition to afferent and efferent visual systems, both cortical and sub-cortical control centres are involved in these behaviours [24]. If patients are considered with locked-in syndrome, for example, they are known to show more preserved vertical visual pursuit than horizontal [25]. If these observations contrast with this finding, it should be emphasized that patients in MCS are characterized more by supra-tentorial brain lesions compared to patients with locked-in syndrome [26]. Different hypotheses can be drawn concerning horizontal plane preference. First, horizontal and vertical gazes rely on different brain pathways that separate in the cerebellum. Neural signals for horizontal and vertical visual pursuit are separately encoded by Purkinje cells in the cerebellar flocculus [27]. Projections from flocculus to the motoneurons take different directions for

horizontal and vertical pursuit: through superior vestibular nucleus for vertical pursuit [28] and through abducens nucleus via vestibular nucleus for horizontal pursuit [29]. Therefore, vertical eye movements can be affected independently from horizontal eye movements, resulting in this preference. This hypothesis could not be tested in this study and should be further investigated. Second, studies on smooth visual pursuit showed there is a better smooth pursuit performance along the horizontal rather than along the vertical axes [30–32] and, more recently, for downward than for upward motion [30]. This asymmetry for visual axes is considered to be an adaptive response to the requirements of the visual context in that preferred motion directions are more critical to survival than non-preferred ones [30]. In brain injured patients, this natural ease with the horizontal plane in normal conditions could allow them to track in a horizontal plane, while vertical eye movements are more demanding.

The clinical implications of these findings can be important. While 33% of the patients in MCS and 43% of the patients in MCS– only tracked on the horizontal plane, 15% of the patients in MCS and 15% of the patients in MCS– only tracked on the vertical plane. If assessed using a scale other than the CRS-R (e.g. the WHIM [12] or the extensively used Glasgow Coma Scale [33]), all these patients could be misdiagnosed as VS/UWS, since visual pursuit was not detected. Finally, chronic patients tend to track better on the horizontal plane (30% of visual pursuit would have been missed if tested only on the vertical plane). Horizontal and vertical eye movements can be differentially affected by lesions depending on their particular location. Vertical gaze palsies can result from rostral midbrain and/or paramedial thalamic injuries [34]. A lesion in these regions could, thus, explain the absence of vertical visual pursuit in these patients.

Patients in MCS– and MCS+ tend to differ in their patterns of results obtained for horizontal and vertical tracking. Whereas patients in MCS– show a preference for the horizontal plane, this preference was not observed in patients in MCS+ where both planes did not differ in terms of the number of visual pursuits detected. Patients in MCS+ are known to have more complex behaviours and more extended preserved brain networks than patients in MCS– [5, 35]. Therefore, patients in MCS+ could have been more able to perform the visual pursuit task in both the horizontal and the vertical planes, whereas patients in MCS–, with less cognitive abilities and resources, could experience more difficulty in reaching the criteria for vertical visual pursuit. On the other hand, the question of vigilance fluctuations in patients in both MCS– and MCS+ should be raised. Since patients in MCS+ tend to display more resource-demanding behaviours, it could be supposed that their attentional abilities allow them to complete the task more efficiently than patients in MCS–, as MCS– patients appear to have more difficulties focusing their attention and/or maintaining vigilance. Both hypotheses should be further investigated.

These results emphasize the importance of assessing both planes when evaluating visual pursuit in post-comatose states. It is proposed to first start with testing of the horizontal plane, adding vertical plane assessment if visual pursuit is not detected on the horizontal plane. This is especially important for chronic patients, since, as previously shown, misdiagnosis

is greater for chronic than for acute patients, meaning that signs of consciousness are easily missed in the former category of patients [36]. Indeed, visual pursuit can be missed through the use of misfitting or inappropriate protocol. However this behaviour can also reappear several months after the injury [6, 37].

Besides patients demonstrating visual pursuit in study 1, 22 patients (25% of patients assessed) did not show visual pursuit according to CRS-R criteria, whereas they did demonstrate other signs of consciousness (e.g. response to command, localization of noxious stimulations). This could be due to several confounding factors such as visual impairment or blindness, eye asymmetry resulting in difficulties in assessing ocular behaviours or the often reported fluctuating vigilance of patients in MCS [38]. Because of these fluctuations of vigilance, visual pursuit could have been missed in those patients. Moreover, unsettled vigilance could also have impacted both studies by negatively affecting both the patients' performance and diagnosis. Indeed, a recent study showed that visual pursuit is particularly sensitive to within-day fluctuations in patient with MCS [39].

Further research should aim to focus on the fluctuating vigilance problem by, for instance, performing repetitive assessments in order to improve diagnostic accuracy as previously recommended in the literature [3, 38, 40] and also to determine the prognostic value of visual pursuit. Some recent data show that, in the course of emerging from VS/UWS towards MCS, visual pursuit, along with or immediately preceded by head control and head turning, are associated with better outcome [41]. Because visual pursuit assessment relies on an examiner's observation of a patient's eye movements, which might not be obvious, the use of quantitative assessment systems, such as eye-tracking systems, should be useful. Recent research has notably shown that patients with VS/UWS and MCS patients differ in their visual behaviours. Indeed, patients in MCS tend to show more on-target fixation than patients in VS, as recorded with a quantitative eye tracking system [42]. Such a method applied along with stimuli used in most behavioural assessment scales (i.e. mirror, object, person) could permit clinicians to better identify visual pursuit in patients with disorders of consciousness and allow for better understanding of the visual patterns associated with each stimulus. Finally, since the re-appearance of visual pursuit is regarded as a reliable marker of favourable outcome [37, 43], the prognostic value of particular visual behaviours such as horizontal vs. vertical eye tracking movements or the preference or ability to complete visual pursuit tasks, depending on the stimulus used, should be further investigated.

In conclusion, since visual pursuit is one of the behavioural criteria allowing for differentiation between conscious and unconscious patients [40], the findings emphasize the importance of using a mirror and the importance of testing both horizontal and vertical planes, preferentially starting with the horizontal, when evaluating eye-tracking in patients in post-comatose states.

Declaration of interest

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