Finger or Light: Stimulation Sensitivity of Visual Startle in the Coma Recovery Scale-Revised for Disorders of Consciousness

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Dear Editor,

Coma, the vegetative state (VS), and the minimally-conscious state (MCS), often collectively referred to as disorders of consciousness (DOCs), typically occur after severe traumatic or non-traumatic brain injury [1]. The boundary between awareness and unawareness remains elusive, making it difficult to correctly distinguish MCS from VS patients. It is possible to employ noninvasive neuroimaging techniques, such as functional MRI (fMRI) [2] to assess residual cognitive processing as well as consciousness. However, the causal link between neural activity in specific brain areas and specific behavioral tasks is hard to dissect using fMRI [3]. Therefore, detecting residual cognitive function and consciousness in patients surviving severe brain injury remains extremely challenging.

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The Coma Recovery Scale-Revised (CRS-R) is an important diagnostic tool for diagnosing DOCs and a widely accepted tool for distinguishing MCS from VS [4–6]. The scale is designed to detect subtle changes in multiple neurobehavioral signs of awareness and has led to the development of standardized approaches for diagnostic assessment and predicting outcomes for DOC patients [7]. The visual function subscale accounts for a substantial extent of the global scale difference between VS and MCS patients. A primary part of this subscale, the response to a visual startle, is designed to elicit the blink reflex by suddenly thrusting a fingertip towards a patient's eyes from the periphery [4]. The visual startle response is considered intact if there is either partial or complete closure of the eyelids. In the bedside test of the visual startle response, we found that several VS and MCS patients produced a reflex blink to a flashlight (weak or bright light) rather than a fingertip. Here, we focused on the sensitivity of different stimulus conditions (bright light, weak light, and fingertip) to induce a visual startle response in patients with DOCs.

This study began in January 2012 and ended in August 2016. The study protocol was approved by the Clinical Research Ethics Committee of the General Hospital of Guangzhou Military Command and was conducted in accordance with the Declaration of Helsinki. All patients' guardians were informed about the experimental procedures and signed consent forms. All the DOC patients were recruited from the Coma Recovery Unit at the same hospital. The inclusion criteria were as follows: age > 18 years; diagnosed as DOC, including VS and MCS (mainly determined by the motor subscale) with spontaneous open eyes, but no blink to visual threats (i.e., visual subscale score = 0); and no sedative drugs during the test. The exclusion criteria were as follows: significant ophthalmic disease that impeded light detection; nuclear and

peripheral facial nerve lesions, as well as diseases of the neuromuscular junction, and myopathies involving the orbicularis oculi. We established a unified nursing schedule to guarantee the stability, repeatability, and accuracy of the test. Nursing, feeding, and treatment procedures, and time schedules were consistent for all patients. All were given daily basic nursing care before 09:00 and after 16:00. Mealtimes were set at 07:30, 12:30, and 17:30. Treatments were given after the test during the morning and afternoon to reduce the interference of confounding factors, in compliance with the unit schedule [8]. The visual startle reflex was tested at two predetermined times (10:00 and 15:00), as these times have previously shown to produce the most sensitive responses in patients [8].

In accordance with the CRS-R [7], a fingertip, a beam of bright light, and a beam of weak light were tested in random order, which was designed in advance using a statistical analysis system. Bright light was defined as a beam of LED light at an intensity of 4500–5000 lux, and weak light was defined as a beam of ordinary light at an intensity of 1500–1800 lux. To assess the visual startle reflex to an object, an examiner quickly passed a fingertip one inch in front of one of the patient's eyes, while avoiding the eyelashes or creating a breeze [7]. Each stimulus condition was tested four times for each eye; if at least two trials produced a positive response, we recorded “yes”, otherwise “no” was recorded. If a visual startle reflex stably occurred on each stimulus and consecutively for three successive days, the test protocol was terminated. The CRS-R global score was assessed by specially-trained professionals on admission and at the end of the protocol. One year after discharge, we called each patient's relatives to determine the outcomes according to the Glasgow outcome scale [9]. Randomized block analysis of variance was used to compare the three stimuli (bright light, weak light, and fingertip), and the time from DOC onset to the appearance of a positive reflex blink (in days) in response to the three stimuli were analyzed using the χ^2 test. All statistical calculations were performed using IBM SPSS 19.0. A two-tailed $P < 0.05$ was considered statistically significant.

We recruited a total of 21 DOC patients, whose demographic characteristics and CRS-R scores are shown in Table 1. Among the 21 patients, 16 (76.2%) were diagnosed as VS and 5 (23.8%) as MCS. At the beginning of the protocol, the visual startle reflexes were absent in 3 MCS and 12 VS patients; the other DOC patients had a blink reflex induced only by bright light. At the end of the following three months, 3 VS patients appeared to have a reflex blink only to bright light, while the other 2 VS patients had a reflex blink to bright and weak light but not to a fingertip passing across the eye. Each patient was followed up for one year after discharge. Seventeen

patients ultimately regained consciousness, while the others remained in a DOC state, although their Glasgow outcome scale and CRS-R improved. The time (in days) it took for a reflex blink to occur was considered as an independent variable, while the three stimuli were considered as three independent groups. The data were then analyzed by randomized block analysis of variance, and the results indicated significant differences ($F = 20.144$, $P < 0.05$) among the three stimuli. In addition, the mean time for a reflex blink to occur from the different stimuli also reached statistical significance ($P < 0.05$). The Student-Newman-Keuls (SNK) test showed that the time to the positive blink startle in the fingertip group was significantly longer than those in the other two groups ($P < 0.05$), and the time to a positive startle blink in the weak light group was significantly longer than that in the bright light group ($P < 0.05$). Ordinal logistic regression analysis showed that the time to the positive startle blink for different stimulus conditions predicted the Glasgow outcome scale ($P < 0.001$; Table 2).

Our results indicated that assessment of the visual startle response depends on the type of stimulus used. To the best of our knowledge, this is the first study to assess stimulation sensitivity for the visual startle response in the CRS-R. We found that a visual startle response in DOC patients occurred most frequently when a bright light was used, followed by a weak light, and then a fingertip.

It is known that the visual startle response to light or an object (a finger) requires an intact optic nerve and connection to the pretectum [10]. When light or an object signal stimulates retinal ganglion cells, the information is transmitted *via* the afferent pathway along the optic nerves to the optic chiasma, where it is then transmitted along the optic tracts to synapses in the pretectal nucleus in the midbrain, rather than in the superior colliculus. From there, fibers are sent *via* the tectospinal tracts to the facial nucleus, where the efferent pathway originates and where the facial nerve sends motor fibers to the orbicularis oculi muscles, leading to eyelid closure [11]. This process is called the protective blink reflex or blink to visual threat. If the afferent and efferent pathways are functioning properly, the eyelids should react equally to light or finger stimulation input to the retina. An absent blink to a threat reflex could result from a lesion in the afferent visual pathway by interrupting the presentation of a full array of visual information from the eye to the brainstem and cerebral cortex [12]. Alternatively, a defect in the efferent pathway to the orbicularis oculi may also abolish the ability to blink. An absence of all blink reflexes occurs when clinical signs of anatomical or functional disorders of the medullary of the pontine-medullary region are found. The pretectal nucleus in the midbrain is regarded as the neural regulation center participating in the visual startle response.

Table 1 Clinical characteristics, CRS-R, time to appearance of visual startle for different stimulus conditions, and Glasgow outcome scale scores of DOC patients.

Patients	Gender	Age (years)	Etiology	CRS-R		Visual startle (days*)			GOS
				A	D	Bright light	Weak light	Finger	
VS1	Female	67	Hypoglycemia	3	3	103	None	None	2
VS2	Male	40	TBI	6	13	96	108	121	3
VS3	Male	45	TBI	6	10	104	105	None	3
VS4	Female	66	TBI	2	8	66	71	81	3
VS5	Male	51	TBI	5	8	44	49	68	3
VS6	Male	23	TBI	5	14	19	21	23	3
VS7	Male	45	ICH	4	9	48	98	106	3
VS8	Male	19	TBI	4	4	57	70	78	2
VS9	Male	27	TBI	3	14	31	34	35	3
VS10	Female	56	TBI	7	17	8	16	19	3
VS11	Male	43	TBI	5	16	29	30	33	3
VS12	Male	49	TBI	5	8	23	30	46	3
VS13	Male	32	TBI	6	14	93	98	113	3
VS14	Male	37	TBI	6	14	121	None	None	3
VS15	Male	40	TBI	3	7	54	75	None	2
VS16	Male	45	TBI	7	8	806	None	None	2
MCS1	Male	16	TBI	8	10	150	190	223	3
MCS2	Male	21	TBI	8	9	40	58	65	3
MCS3	Male	25	Electrical injury	11	18	27	32	47	3
MCS4	Male	49	TBI	5	8	23	30	46	3
MCS5	Male	22	TBI	8	20	55	60	70	3

A on admission, *CRS-R* Coma Recovery Score-Revised (score range, 0–23), *D* on discharge, *GOS* Glasgow outcome scale (score range, 1–5; outcomes can be classified as VS (score: 2) or severe disability (score: 3) [8]), *ICH* intracerebral hemorrhage, *MCS* minimally-conscious state, *TBI* traumatic brain injury, *VS* vegetative state.

*Time from DOC onset to the appearance of a positive reflex blink.

Table 2 Association between different stimulus conditions and Glasgow outcome scale by ordinal logistic regression.

Variables	<i>b</i>	<i>S_b</i>	Wald χ^2	<i>P</i>
Threshold	− 3.121	0.108	830.524	< 0.001
X	1.557	0.062	630.476	< 0.001

b regression coefficient, *S_b* standard errors of regression coefficient, *X* visual startle stimulus (finger, 0; weak light, 1; bright light, 2).

Therefore, in DOC patients, the visual startle response should be distinguished from other reflex blinks, which are mostly brainstem-mediated, such as the orbicularis oculi reflex, the corneal blink reflex, and the cochleopalpebral reflex.

Of note, the visual startle response is not present in neonates, and does not emerge until 2–4 months of age. Therefore, the protective blink reflex is believed to be a learned response in non-DOC patients [12], and suggests that the visual startle response is not a primitive reflex, but one that requires higher-order cortical processing of a stimulus more complex than touching the cornea. Moreover, the parieto-occipital and parieto-temporal areas may

be necessary for the reflex blink to visual startle stimuli [13]. Several reported cases of cortical blindness and unilateral parietal lesions have also demonstrated the absence of blink to visual startle stimuli, suggesting that attentional mechanisms are important for this response. Besides, the posterior parietal lobe, frontal lobe, and cingulate gyrus are instrumental in the proposed cortical networks for directed attention. Certain PG (located in the lateral parietal region) neurons are responsive to visual startle stimuli and are capable of coupling perception of the threat in the striatal cortex with the motor pathway for blinking. Thus, the absence of a visual startle response in DOCs may not only indicate a visual field deficit, but also reflect a defect in visual attention.

Whether the visual startle response indicates “automatic” subcortical processing atypical for MCS, or a higher-order cortical activation and partially recovered consciousness remains unknown [12]. Yet, the responses, such as those to the stimulus conditions tested in the current study, are conventionally regarded as indicative of surviving modules of functional brainstem-cortex interactions that are thought to sustain consciousness in the

wakeful subject and are altered in the VS and MCS [14]. Ordinal logistic regression analysis showed that the time to the appearance of a positive blink startle for different stimulus conditions predicted the score on the Glasgow outcome scale. Nevertheless, the requisite visual modalities for the reflex blink to visual threat have not been thoroughly studied. Based on the current knowledge we infer that the properties (shape, brightness, or luminance) of a finger and a beam of light may be important for DOC patients. It is important to stress, however, that the results presented here should be taken as proof-of-concept, and do not allow any inference concerning the prevalence of this kind of “brain behavior” in the population in general [4].

This pilot study describes an interesting phenomenon that light is more effective than a finger to trigger a startle blink in DOC patients. This may be influenced by the etiology, injury severity, and the length of time post-injury. Nevertheless, due to the limited sample size, we did not stratify patients by etiology or stage of disease during data analysis, which may have biased the results. Therefore, cohort studies of larger samples are warranted. Systematic monitoring of these variables would supplement these preliminary findings, and identify correlations or cycles of possible relevance in the investigation of VS and MCS patients.

Overall, our findings emphasize the clinical importance of using light when performing bedside testing of localization to visual startle stimuli in patients with DOCs.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

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