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Probing consciousness in a sensory-disconnected paralyzed patient

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Keywords: disorder of consciousness; quantitative EEG; brain functional imagery; consciousness; locked-in syndrome.

Abstract:

Background: Diagnosis of consciousness can be very challenging in some clinical situations such as severe sensory-motor impairments.

Case study: We report the case study of a patient who presented a total “locked-in syndrome” associated with and a multi-sensory deafferentation (visual, auditory and tactile modalities) following a protuberantial infarction.

Result: In spite of this severe and extreme disconnection from the external world, we could detect reliable evidence of consciousness using a multivariate analysis of his high-density resting state electroencephalogram. This EEG-based diagnosis was eventually confirmed by the clinical evolution of the patient.

Conclusion: This approach illustrates the potential importance of functional brain-imaging data to improve diagnosis of consciousness and of cognitive abilities in critical situations in which the behavioral channel is compromised such as deafferented locked-in syndrome.

Introduction

Diagnosis of consciousness can be very challenging in some clinical situations such as severe sensory-motor or cognitive impairments ^[1]. When patients can neither communicate (verbally or non-verbally) nor exhibit any intentional behavior, clinicians have to rely on indirect cues collected through behavioral and functional brain-imaging methods ^[2]. During the last decade, several cognitively active tasks have been developed in this perspective while recording brain activity with fMRI or bedside EEG. For instance, putative neural signatures of conscious processing have been identified by asking a patient to perform a mental imagery task ^[3,4] or an explicit mental counting of rare stimuli delivered among frequent ones ^[5,6]. However, each of these measures require the patient to receive and perceive task instructions. Obviously, a sensory disconnected brain challenges this original approach given the impossibility to deliver instructions to the patient. In the present case study, we report how we could convincingly identify EEG neural signatures of consciousness in such a “sensory disconnected” and paralyzed patient.

Case study

The patient was 63 years old when he suffered from a brainstem infarction following a scheduled abdominal surgery that subsequently raised the question of the diagnosis of a locked-in syndrome. He had several medical conditions including arrhythmic cardiopathy, inherited thrombotic factor (factor V Leiden mutation), hypertension, dyslipidemia, atherosclerosis and a chronic renal disease which required kidney transplantation 3 years ago. After surgery (scheduled colic continuity reestablishment surgery following a Hartmann surgery for an acute colitis), the patient suffered from a

septic shock. Sedation was maintained at the minimum level and duration following international guidelines ^[7] and stopped after four days. Although the patient recovered wakefulness, he remained unable to express any intentional behaviour. MRI revealed an infarction of the median and transversal bulbo-protuberantial territory in relation with a basilar artery occlusion (Figure 1; Figure S1-B). Neurological examination revealed a spontaneous ocular bobbing (Video S1) with no visual pursuit, no blink to visual threat, and no startle reflex to loud noise. Pupillary light reflexes, corneal and cough reflexes were preserved. The patient did not show any movement of the limbs or of the face, even after nociceptive stimulation. According to the current behavioural and clinical scores, this patient was classified as being in a vegetative state/unresponsive wakefulness syndrome (VS/UWS; Table 1). This mismatch between a radiological pattern reminiscent of locked-in syndrome, and a much poorer behavioural evidence of conscious processing triggered the decision to transfer the patient to our “Disorders of Consciousness patients Team” two months after the diagnosis of the brainstem infraction.

Beyond behavior

A quantitative MRI analysis of the supra-tentorial white matter fractional anisotropy ^[8] revealed a normal pattern, and therefore invalidated the hypothesis of a per-surgery or post-surgery shock - related severe brain hypoperfusion (Figure 1, Figure S1-A).

Brainstem auditory evoked potentials (BAEP) revealed a severe peripheral and central deafness with a bilateral alteration of wave-I and III (110dB stimulation level) and the abolition of wave-V. This pattern explained the absence of startle reflex, and the potential inability to understand verbal commands. The auditory deficit resulted from the association of an otitis media, a cochlear dysfunction related to tacrolimus toxicity, and a possible VIIIth nucleus and intra-axial VIIIth nerve lesions (Figure 1).

We did not find any cerebral responses elicited by the auditory ‘Local Global’ evoked-related potentials paradigm. This paradigm developed by our team is usually able to probe neural signature of conscious processing in patients ^[5,6,9]. However, in this case, the patient’s deafness prevented a reliable interpretation of this negative result. SSEP revealed a preservation of bulbar responses (N14 and N18), but a severe alteration of cortical responses (abolition of N20 on the left side and severe alteration on the right side).

EEG background activity, - recorded at bedside with 8 electrodes -, consisted in a posterior and symmetrical theta band (4-6Hz) activity, slightly reactive to passive eye-opening/closing, but neither to auditory nor to nociceptive stimulation.

At this stage, we hypothesized that the patient was indeed in a particular form of locked-in syndrome (also called deafferentation syndrome) since associated with deafness and severe visual impairment that could be called a “deafferented locked-in syndrome”. Several attempts to deliver the patient with visual written instructions (asking to move his eyes) failed. However, the absence of horizontal eye mobility as well as the permanent bobbing could not rule out a patient’s inability to accurately read verbal commands.

To overcome this severe multi-sensory disconnection, we used an automatic classification algorithm we recently designed and trained to distinguish between VS/UWS and minimally conscious state (MCS) patients on the basis of a high-density EEG recording while stimulated under an auditory oddball paradigm ^[10,11]. This classifier combines several tens of putative EEG markers sensitive to conscious states such as event related potentials, signal complexity, long-range functional connectivity and spectral power patterns. Although the patient was deaf and thus, the event related potentials were absent, our classifier considered this patient as being most likely in a

condition of minimally or conscious state (71%), while a VS/UWS could not be ruled out (29%). We then analyzed in detail the univariate markers that are usually more contributive to the multivariate classifier by comparing the topographies from the previously recorded and diagnosed patients with this patient. Detailed analysis further revealed that patterns of spectral power of EEG (in delta and alpha band), complexity markers (spectral entropy, permutation entropy and Komolgorov-Chaitin complexity), and functional connectivity (weighted Symbolic Mutual Information, wSMI ^[12]) were strongly supportive of a conscious state, rather than of a VS/UWS or even MCS (Figure 2). As expected, univariate markers of auditory event-related potentials were not contributive given patient's deafness.

In summary, anatomical and electrophysiological brain data supported a diagnosis of “extreme locked-in syndrome” with major motor and multi-sensory deficits. After a week of systematical attempts to deliver visual instructions, - strongly encouraged by the results of our exploration supporting consciousness -, we eventually could observe a reproducible visual pursuit of a mirror, and then of any vertically moving target (bobbing was still present and vertical oculocephalic reflex still abolished suggesting a vestibular input impairment). According to this visual pursuit behaviour, the patient was now scored as MCS on the CRS-R ^[13]. However, and in spite of our efforts, the patient could not follow written commands (see Video S2). Three weeks after patient admission (one week after high-density EEG recording), we could finally detect a more complex behaviour: in response to a big contrasted arrow pointing either upward or downward, the patient was able to systematically orient his gaze toward the direction pointed by the arrow (see Video S3). These responses strongly suggested that the patient was able: i) to engage attention, ii) to understand the meaning of this symbol, iii) to use it as a cue to elicit an intentional behaviour meaningful for the

examiner, and iv) to actively maintain this intentional behaviour during long periods of time (tens of seconds). These characteristics are generally indicative of conscious behaviours ^[14].

Discussion

This case study demonstrates the utility of functional brain-imaging (here EEG), - in complement to detailed clinical, behavioural and structural imaging data -, to probe consciousness and cognition in such an extreme condition of severe motor and multi-sensory disconnection. In contrast to more classical approaches previously reported ^[3,15-19], because of his massive sensory impairment, we could not use any task instruction or stimulus processing correlates to probe consciousness in this patient.

The ability of automatized and quantitative EEG-based mathematical classifiers to capture putative markers of consciousness in the absence of any behavioural evidence and of sensory-motor pathway impairment is of potentially great importance. In the present case, our algorithm preceded behavioural evidence of consciousness by 7 days. Finally, preliminary reanalysis of our database showed that all these markers could also be computed from a standard bedside 21-electrodes EEG and provide very similar results (submitted). If confirmed, this method could be nicely complete the TMS/EEG method ^[20], which is also able to probe consciousness while bypassing the sensory-motor pathway, but needs a very highly complex acquisition setting.

Material and methods

The patient EEG was recorded in the very same condition as our patients' database ^[10] while being subject to the Local-Global paradigm ^[5]. Briefly, the Local-Global paradigm is characterized by two embedded levels of auditory regularities allowing to

identify the cortical response to sounds (P1), the automatic response to local novelty (MMN and P3a) and the conscious response to global novelty (P3b).

EEG was sampled at 250 Hz with a 256-electrode geodesic sensor net connected to a high impedance amplifier (EGI, Oregon, US) referenced to the vertex. Impedances were controlled inferior to 100 k Ω . Data were filtered from 0.5 Hz to 45 Hz. Trials were segmented from -200ms to 1300 ms relative to the onset of the Local-Global trials. Electrodes in which more than 50% of the trails exceeded a 100 μ V were marked for rejection. Trials where at least 10% of the electrodes exceeded the same threshold were discarded. Data was re-referenced to the average of all electrodes. Finally, electrodes marked for rejection were discarded and the information was reconstructed using interpolation.

Markers were then computed as described in the original publication supplementary material ^[10].

Structural Similarity Index Measure (SSIM) was computed according to the original formula ^[21] with modifications to apply it on EEG topographies: each electrode was assumed to be a pixel. Since the EEG montage is three-dimensional, the definition of neighbours was redefined as all the electrodes within an Euclidean norm of 1.0 from a normalized montage between -1.0 and 1.0 in all axes (X, Y and Z).

All processing stages and topographical maps were performed with MNE-python ^[22,23] and custom made python libraries. The Case Report guidelines were followed throughout ^[24].

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All the authors report no declarations of interest.

Patient Consent:

Authors have received the patient's spouse written consent for this publication.

However, as the patient's consent could not be obtained, details have been removed from this case description to ensure a maximal anonymity.

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Figures' legend:

Figure 1. MRI in sagittal T1-weighted (A) and axial T2-weighted acquisitions (B, C). There is a localized ischemic lesion at the upper part of the medulla oblongata and lower part of the pons, including the cortico spinal tracks and nuclei of the VIIIth nerves. Bilateral filling of the mastoids and middle ears and small ischemic infarction of the right cerebellar hemisphere are also present.

Figure 2. Topographical map of the patient's EEG markers. Scalp topographical 2D projection (top = front) of each measure [contingent negative variation (CNV), mismatch negativity (MMN), P300b (P3B), normalized power in delta ($||\delta||$) and alpha ($||\alpha||$) bands, spectral entropy (SE), permutation entropy in theta band ($PE\theta$), Komolgorov-Chaitin Complexity (K) and weighted symbolic mutual information in theta band ($wSMI\theta$)] obtained from the patient's EEG (first column, "Patient"). These topographies were compared to groups of Vegetative State /Unresponsive Wakefulness Syndrome (VS/UWS: n=76), Minimally Conscious State (MCS; n=68) and Conscious State patients (CS; n=23) as well as Healthy controls (H; n=14). The last column shows the topographical similarity of patient's topography compared to each of the groups (SSIM; z-score +/- 95%CI).

Supplementary Online Material:

Figure S1. Sagittal reconstructed FA map derived from diffusion tensor imaging (A) and angio MR acquisition of the circle of Willis (B). There is an interruption of the corticospinal track at the junction between the pons and the medulla oblongata (white arrow). The angio MRI discloses a persistent occlusion of the basilar artery at this level, with recirculation in its upper part through the posterior communicating arteries.

Video S1. Clinical examination revealed spontaneous vertical eyes movement (downward fast movement) corresponding to an eye bobbing. Horizontal and vertical oculocephalic reflexes were abolished.

Video S2. After several attempts, the patient became able to follow visual targets moving vertically (day 16). In this video we used a mirror, as visual pursuit of one's own gaze has been shown to be one of the most efficient visual target.

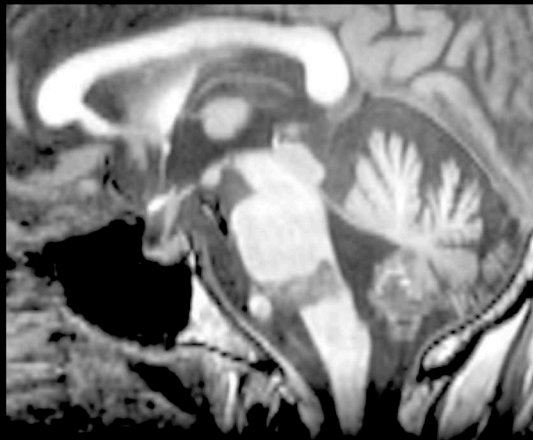
Video S3. The patient became able to follow symbolic instructions delivered implicitly through a large arrow drawn on a slate pointing downward or upward (day 20). The short reaction time and the consistency (12 successive trials with a 100% accuracy in this video) of this behaviour were in favour of intentional conscious behaviour (see text for discussion of this issue).

Table 1. Clinical scores across time.

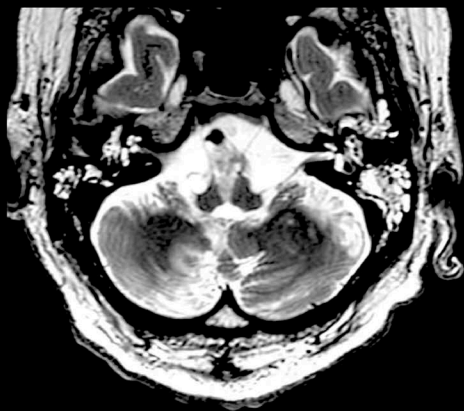
Day	D1	D1*	D2	D6	D13***	D16	D16*	D18	D19	D20*
Coma Recovery Scale (CRS-R)										
Auditory		0			0		0			0
Visual		2			2		4			4
Motor		0			2		2			2
Oromotor/verbal		0			0		0			0
Communication		0			0		0			0
Arousal		1			1		1			1
Total		3			5		7			7
FOUR-Score										
Eye response	0	3	0	0	0	0	4	0	2	4
Motor response	0	0	2	2	2	2	2	2	2	2
Brainstem reflexes	4	4	4	4	4	4	4	4	4	4
Respiration	1	0	1	1	1	0	1	1	1	1
Total	5	7	7	7	7	6	11	7	9	11
Glasgow Coma Scale										
Eye response	1	4	1	1	1	1	3	1	2	4
Motor response	1	1	3	3	3	3	3	3	3	3
Verbal response	1	1	1	1	1	1	1	1	1	1
Total	3	6	5	5	5	5	7	5	6	8
Clinical classification	Coma	VS/UWS	Coma	Coma	Coma	Coma	MCS	Coma	VS/UWS	CS***

Clinical scores obtained 2 months after the diagnosis of the brainstem infraction in our unit from day 1 (D1) to day 20 (D20). CRS-R: Coma Recovery Scale – Revised; FOUR-score: Full Outline Of Unresponsiveness; GCS: Glasgow Coma scale obtained during the 20 days observation span.

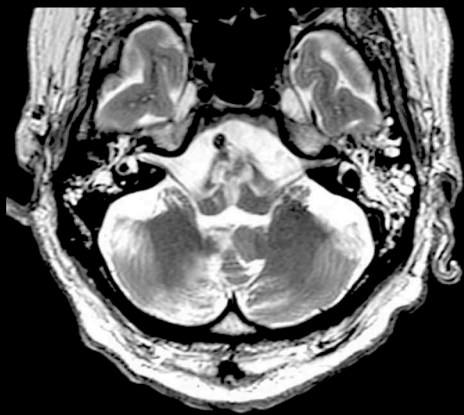
* Specialized medical examination (BR, LN); ** ERP; *** Based on the arrow command following, according to the CRS-R the patient was MCS (see Video S3); VS/UWS: Vegetative State/Unresponsive Wakefulness Syndrome; MCS: Minimally Conscious State; CS: Conscious State; FOUR: Full Outline of Unresponsiveness; CRS-R: Coma Recovery Scale – Revised.



A



B



C

