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## Neurology and Intensive Care

# Toward a coherent structuration of disorders of consciousness expertise at a country scale: A proposal for France

L. Naccache<sup>a,b,c,d,\*</sup>, J. Luauté<sup>e,f</sup>, S. Silva<sup>g,h</sup>, J.D. Sitt<sup>a,b</sup>, B. Rohaut<sup>a,b,d</sup>

<sup>a</sup> Sorbonne université, institut du cerveau - Paris Brain Institute - ICM, Inserm, CNRS, Paris, France

<sup>b</sup> Sorbonne université, UPMC Univ Paris 06, faculté de médecine Pitié-Salpêtrière, Paris, France

<sup>c</sup> AP-HP, hôpital groupe hospitalier Pitié-Salpêtrière, DMU neurosciences, department of clinical neurophysiology, Paris, France

<sup>d</sup> AP-HP, hôpital groupe hospitalier Pitié-Salpêtrière, DMU neurosciences, department of neurology, Neuro ICU, Paris, France

<sup>e</sup> Service de médecine physique et réadaptation, hôpital Henry-Gabrielle, Hospices Civils de Lyon, Saint-Genis Laval, France

<sup>f</sup> Équipe « Trajectoires », centre de recherche en neurosciences de Lyon, Inserm UMR-S 1028, CNRS UMR 5292, université de Lyon, université Lyon 1, Bron, France

<sup>g</sup> Intensive Care Unit, Purpan University Hospital, 31000 Toulouse, France

<sup>h</sup> Toulouse NeuroImaging Center (ToNIC lab) URM UPS/INSERM 1214, 31000 Toulouse, France

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### ABSTRACT

Probing consciousness and cognitive abilities in non-communicating patients is one of the most challenging diagnostic issues. A fast growing medical and scientific literature explores the various facets of this challenge, often coined under the generic expression of 'Disorders of Consciousness' (DoC). Crucially, a set of independent converging results demonstrated both (1) the diagnostic and prognostic importance of this expertise, and (2) the need to combine behavioural measures with brain structure and activity data to improve diagnostic and prognostication accuracy as well as potential therapeutic intervention. Thus, probing consciousness in DoC patients appears as a crucial activity rich of human, medical, economic and ethical consequences, but this activity needs to be organized in order to offer this expertise to each concerned patient. More precisely, diagnosis of consciousness differs in difficulty across patients: while a minimal set of data can be sufficient to reach a confident result, some patients need a higher level of expertise that relies on additional behavioural and brain activity and brain structure measures. In order to enable this service on a systematic mode, we present two complementary proposals in the present article. First, we sketch a structuration of DoC expertise at a country-scale, namely France. More precisely, we suggest that a 2-tiers network composed of local (Tier-1) and regional (Tier-2) centers backed by distant electronic databases and algorithmic centers could optimally

\* Corresponding author at: AP-HP, Hôpital Groupe hospitalier Pitié-Salpêtrière, DMU Neurosciences, Department of Neurology, Neuro ICU, Paris, France.

E-mail address: [lionel.naccache@gmail.com](mailto:lionel.naccache@gmail.com) (L. Naccache).

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enable the systematic implementation of DoC expertise in France. Second, we propose to create a national common register of DoC patients in order to better monitor this activity, to improve its performance on the basis of nation-wide collected evidence, and to promote rational decision-making.

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## 1. Introduction

Probing consciousness and cognitive abilities in non-communicating patients is one of the most challenging diagnostic issues. A fast growing medical and scientific literature continuously explores the various facets of this challenge, — often coined under the generic expression of “Disorders of Consciousness” (DoC) —, and converges to highlight the great medical importance of DoC expertise. Once aware of this evidence, it becomes an ethical obligation to make this expertise accessible to all concerned patients.

In this article, we expose two major proposals to improve accessibility and performance of DoC expertise at the country-scale of France. We build our rationale on three steps.

We first describe the type of patients who are concerned by this expertise.

Second, we then explain why this expertise appears as a mandatory stage in the management of these patients. An accurate diagnosis of the cognitive and conscious status of DoC patients enables to correct diagnostic errors up to 40% of cases, and conveys determinant prognostic value to predict consciousness recovery.

Third, we briefly list the main tools that can contribute to this DoC expertise, from neurological and expert behavioural examination, to the most used measures of brain structure and brain activity. We show that an optimal DoC expertise relies on the combination of several of these measures by expert clinicians, assisted by machine learning tools. According to case difficulty and incertitude, the optimal intensity of this expertise can vary from one patient to another.

We then expose our two proposals: (1) structuration of DoC expertise through a 2-tiers organization taking advantage of telemedicine and digital tools, (2) creation of a national registry of DoC patients.

## 2. Who are the concerned patients?

On purpose, we did not enlarge here the scope of this structuration proposal so to include comatose states. This project focuses primarily on DoC patients who regained some vigilance, and who are usually in one of the following states [1]: vegetative state also coined unresponsive wakefulness syndrome (VS/UWS) [2], minimally conscious state (MCS) [3] that includes MCS- and MCS+ [4], and conscious but cognitively impaired patients who often emerged from a MCS (EMCS and related states). Obviously, patients with severe motor (e.g.: locked-in syndrome [5]) or sensory or major attentional deficits that complicate the identification of consciousness also belong to the scope of this article [6].

A continuation of the present work could discuss the potential enlargement of this expertise structuration so to include comatose patients.

In clinical practice, patients concerned by DoC expertise can be split in two categories: acute phase patients ( $\leq 3$  month after brain injury), and chronic phase patients ( $> 3$  month after brain injury).

In the acute phase, patients concerned by this evaluation are the one who do not regain consciousness after awaking from coma resulting from an acquired brain lesion: traumatic brain injury (TBI), post-anoxic, stroke, hypoglycemia etc. It is difficult to have a clear and comprehensive picture of the corresponding current number of patients in France, as there is a lack of figures and statistic bringing together all these situations. Given the crucial importance of major ethical decisions that are often made of this acute stage (i.e. in particular withdrawal of life-sustaining therapy (WLST)), all acute brain-lesioned awake patients who did not regain consciousness after sedation withdrawal should benefit from a DoC expertise that relies on additional behavioural and brain assessments. Such an evaluation should be performed as soon as possible and within the first month after insult.

In the chronic phase (after 3 months), the prevalence of DoC is also difficult to estimate accurately. In France, around 1500 patients live with a persistent DoC in dedicated hospital units (‘Circulaire DHOS/02/DGS/SD5D/DGAS n° 2002-288 du 3 mai 2002 relative à la création d’unités de soins dédiées aux personnes en état végétatif chronique ou en état ‘paucirelationnel’). Before the admission in such dedicated and specialized units— and for all patients surviving with a DoC — an expertise should be provided in order to confirm and make an appropriate diagnosis of DoC. Obviously, such evaluations should also be accessible during the long-term follow-up of DoC patients.

## 3. Why is expertise of consciousness in non-communicating patients useful?

We identified three main converging and concurring reasons to claim that a systematic expertise of consciousness status is of prime importance for each awake but non-communicating patient.

First, a small fraction of these patients are actually conscious, such as exemplified by the seminal case of locked-in syndrome [5,7,8] and related clinical presentations [9].

Second, the crucial distinction between MCS and VS/UWS is predictive of consciousness recovery and cognitive outcome, beyond a self-fulfilling prophecy bias (i.e.: beyond a bias corresponding to less WLST for patients in MCS than for those

in VS/UWS) [6,10,11]. Moreover, even if MCS does not necessarily correspond to residual consciousness, it certainly demonstrates the contribution of cortical networks into the overt behaviour of the patient, and therefore probes a ‘Cortically Mediated State’ (CMS) that is more prone to evolve toward consciousness recovery than a VS/UWS condition that does not reflect the contribution of cortical activity in overt behaviour [12]. In the absence of an expert behavioural assessment, up to 40% patients are misdiagnosed as being in a VS/UWS whereas they are already in a MCS/MCS richer state, associated with an overall better outcome [13]. This strong prognosis value of DoC expertise is of prime importance for all patients, and in particular for acute patients in whom active care limitations are often discussed.

Third, a set of independent studies showed that a proportion of 10–30% VS/UWS patients who benefited from an expert behavioural evaluation of consciousness, actually show much richer than expected patterns of brain activity associated with MCS/CMS or even with a conscious state [14–22]. Interestingly, irrespective of the functional brain-imaging technique used (e.g.: fMRI, EEG, PET, EEG-TMS, . . .), and of the active/passive cognitive task versus resting state conditions,

this overall 10–30% proportion is invariably reported, and has been labelled as Cognitive Motor Dissociation (CMD) or Higher-order cortex Motor Dissociation (HMD) depending on the type of richer state (MCS/CMS, MCS+, conscious) revealed by brain-activity measurements. Several theoretical and expert panels studies pointed out the need to revise current DoC classifications in order to combine brain activity measurements to expert behavioural assessment [12,23–25].

In the light of these three main reasons, we consider the structuration of DoC patients expertise as a mandatory and necessary objective to reach, for both medical, ethical and socio-economic reasons.

#### 4. What are the ingredients of this expertise?

In the following section, we have listed main assessment tools which contribute to the diagnosis of DoC patients, according to their relevance, level of evidence, and feasibility. We classified these tools in four categories: behaviour, brain structural anatomy, brain functional anatomy and therapeutic tests (Table 1).

**Table 1 – Ingredients of DoC expertise.**

Type of data	Assessment tools	Modality	Current practice	Optimal practice
Behaviour	CRS-R	5 times	Tier-2	Tier-1
	DOC Feeling	Multidisciplinary	Tier-2	Tier-1
	hASR		Tier 2	Tier-1
	Eye tracker		R	Tier-2
Brain structure	MRI	T2*, SWI, Flair, Diffusion	Tier-1	Tier-1
	Quantified MRI	DTI (MD, FA); 3D T1 (brain volume, ventricle volume)	Tier-2	Tier-2
Brain activity	PET	FDG	Tier-2	Tier-2
	fMRI brain imaging	Resting state (DMN)	Tier-2	Tier-2
		Active cognitive task	Tier-2	Tier-2
	Electrophysiology	EEG (reactivity)	Tier-1	Tier-1
		SSEPs	Tier-2	Tier-1
		N100, MMN, P3, local-global	Tier-2	Tier-2
		Quantified EEG: complexity markers (wSML . . .)	Tier-2	Tier-1
	Multimodal integration	Multi-EEG features AI prediction	Tier-2	Tier-1
		Perturbing brain activity (TMS-EEG)	Tier-2	Tier-2
		Motor command decoding task with EEG	Tier-2	Tier-2
Multimodal features AI prediction		R	Tier-2	
Therapeutic test or intervention	Behavioural intervention	Standing position	Tier-1	Tier-1
		Sensory regulation	Tier-2	Tier-1
		Median nerve electrical stim	R	Tier-2*
	Brain stimulation	tDCS	Tier-2	Tier-1
		Low intensity focus ultrasound	R	Tier-2*
		Vagus nerve stimulation	R	Tier-2*
		Deep brain stimulation	R	Tier-2*
	Drugs	Amantadine	Tier-2	Tier-1
		Zolpidem	Tier-2	Tier-1
		Other drugs (MP, modafinil . . .)	R	Tier-2

CRS-R: Coma recovery scale revised; (DoC)-feeling: disorders of consciousness feeling; hASR: habituation of the auditory startle reflex; MD: mean diffusivity; FA: fractional anisotropy; FDG: fluorodesoxyglucose; DMN: default mode network; SWI: Susceptibility Weighted Imaging; SSEPs: somatosensory evoked potentials; AEPs: auditory evoked potentials; MMN: mismatch negativity; wSML: weighted Symbolic Mutual Information; tDCS: transcranial direct current stimulation; MP: methylphenidate; R: research; AI: artificial intelligence (i.e.: machine learning algorithms). Tiers-2\* refers to a global collective decision-making process gathering all existing Tier-2 centers.

#### 4.1. Behavioural assessment

First, rigorous neurological examination is of prime importance to provide a first description of patient's condition and deficits. As illustrated by the famous case of locked-in syndrome (LIS), — that corresponds to conscious but paralyzed patients with whom a communication code can (usually) be established through the preservation of voluntary eye movements —, neurological examination can detect conscious states that would otherwise be undetected. Beyond classical brainstem-injury LIS, many such complex states can be found in patients suffering for instance from severe Guillain-Barré syndrome or from ALS. Neurological examination also provides a first description of central nervous system functionality, disentangling the respective levels of brainstem, diencephalic and cortical structures.

Second, numerous scales have been developed to assess DoC. Among these the Glasgow coma scale, the coma Recovery Scale Revised (CRS-R), the Wessex Head injury Matrix (WHIM), the Sensory Stimulation Assessment Measure (SSAM), the Western Neuro Sensory Stimulation Profile (WNSSP), the Sensory Modality Assessment Technique (SMART), the Disorders of Consciousness Scale (DOCS), and Coma/Near-Coma Scale (CNC) have acceptable standardized administration and scoring procedures [26]. Both the European and American guidelines recommend performing serial standardized clinical assessments to improve the detection of consciousness and consider the CRS-R as the gold standard [23,24]. It has been shown that at least 5 repetitions of the CRS-R should be performed to increase the reliability of the diagnosis given the fluctuation of awakening and consciousness in many cases [27]. In this scale, behaviours that reflect voluntary or intentional responses are pinpointed by a star [28]. Items more frequently associated with MCS are visual fixation, visual pursuit, movement in response to order, and oriented response to noxious stimuli [29]. A simplified version of the test has been developed using these most frequent items: The Simplified Evaluation of CONsciousness Disorders (SECONDS) and is currently in the process of validation [30]. Moreover, visual fixation and visual pursuit are the most frequent first signs of emergence from VS/UWS [31,32]. Hence, eye-tracker based quantified measures of ocular movements and pupillometry are promising tools to improve sensitivity of diagnosis in DoC ([33]).

Three last points are of prime importance here: first, this behavioural expertise is not limited to neurologists or to other physicians, but should be also exerted at a large scale by nurses, nurse assistants, behavioural psychologists and other professionals involved in the rehabilitation of DoC patients like speech and language therapists. In a recent work, we showed that the use of analogic scales of consciousness by nurses and nurse assistants could substantially enrich and improve the power of behavioural observation in DoC patients [34].

Second, there is still a need to enrich the range of behavioural measures of cognitive and conscious processes. For instance, we recently showed that habituation of auditory startle response is one of the best signs of MCS/CMS, and that it can be tested using a simple but rigorous procedure [35]. Similarly, many teams explored new tests probing trace

conditioning [36], working memory or self-consciousness behaviours [37]. This is another reason why to open largely access to DoC patients bedside to researchers in behavioural cognitive science.

Third, for patients who are able to demonstrate a response to command (MCS+), a 'yes-no' code will be searched using all possible means, up to brain computer interfaces (BCI) [38].

#### 4.2. Brain structure

Although the exact neural structures subtending arousal and consciousness are not yet perfectly delineated, some key sub-cortical and cortical regions have now been identified within a 'meso-circuit' comprising the ascending reticular activating system, the striato-pallidal structures, the central part of the thalamus and associative cortical areas organized in cortico-striato-pallido-thalamo-cortical loops [39,40]. Several complementary models of the cortical organization subserving consciousness have been proposed such as the global neuronal workspace [41,42]. This model postulates that consciousness involves a brain-scale network of high-level interconnected cortical areas, encompassing notably frontoparietal associative cortices.

For some patients, the lesions pattern is coherent with the observed behavioural state. However, in many cases, this correspondence is at least not obvious, as the DoC may result both from anatomic lesions and from functional disturbances of partially preserved brain networks. Such a mismatch or doubtful situation between behaviour and gross brain anatomy description calls for additional explorations aiming at probing markers or signatures of consciousness. Today, such 'positive' information (i.e.: preservation of markers of conscious processing or of predictors of consciousness recovery) is most of the time absent from clinical reasoning, and this may negatively influence our decision-making processes [43]. In the following of this section, we will go through main medical tools developed to identify brain lesions affecting consciousness, as well as markers of preserved conscious processing.

Brain MRI is the gold standard imaging tool, and it should include at least 3D-T1 to explore lesions anatomy and patterns of brain atrophy, T2\* and Susceptibility weighted imaging (SWI) sequences to detect blood (including microbleeds), diffusion and Fluid-attenuated inversion recovery (FLAIR) sequences to detect ischemia and swelling, as well as Time-of-flight (TOF) in case of stroke for imaging the human vascular system. In case of contraindication to MRI, a brain CT-scan will provide basic information about brain structure and brain lesions pattern.

A quantified evaluation of white matter damage with diffusion tensor imaging (DTI), and especially the calculation of fractional anisotropy (FA), allows in vivo quantification of white matter injuries that occur in an acute, subacute, or delayed manner after global anoxia [44,45]. In post-cardiac arrest comatose patients, MRI methods allowing both in vivo quantification of white (diffuser tensor imaging [DTI]) and gray (voxel-based morphometry [VBM]) matter integrity have shown a high sensitivity and specificity of DTI [46] and VBM [47] measurements for predicting neurological recovery in anoxo-ischemic patients. For example, it has been shown that a normalized FA value lower than 0.91, had a positive



predictive value of 100% (90.0–100), with 89.7% sensitivity (75.8–97.1) and 100% specificity (69.1–100) for the prediction of unfavourable outcome on the Glasgow-Pittsburgh Cerebral Performance Categories (CPC) [46]. In severe TBI, diffuse axonal injuries (DAIs) and brain atrophy are common anatomical lesions difficult to visualize and quantify with standard MRI sequences [48,49]. Quantified MRI tools such as DTI (global mean diffusivity MD and global FA) and 3D T1 volumetric MR sequences have offered new opportunities to assess and quantify respectively DAI lesions and brain atrophy [50]. In a cohort of severe brain injured patients, a recent work showed that the global MD is the best radiological marker to discriminate good and bad outcome according to the Glasgow outcome scale (GOS) [51]. In the same perspective, Simeone et al. characterized and quantified atrophy of deep brain structures after severe TBI, and could show that DTI imaging performed in the subacute phase can predict the occurrence and localization of these tertiary lesions as well as long-term neurological outcome [52].

### 4.3. Brain activity

Several tools have been developed to assess brain activity, either at rest or during cognitive tasks, in order to probe residual cortical processing and most importantly neural signatures of conscious processing or predictors of consciousness recovery. These functional brain-imaging tools notably include FDG-PET, fMRI and electrophysiological techniques including EEG.

#### 4.3.1. FDG-PET brain imaging:

Glucose metabolism at the whole brain level or in specific regions can be measured at rest with 18F-Fluorodesoxyglucose or [18F] FDG radiotracer [53]. Although until now there is not a standardized way to quantify brain metabolism especially in brain-damaged patients, a global decrease in the estimated cerebral metabolic rate of glucose with visual or semi-quantified measures seems proportional to the degree of DoC [1]. Moreover, a modification of the glucose metabolism in specific regions of the consciousness network is correlated to the profile of DoC. In line with this assumption, a hypometabolism in the thalamus has been reported in chronic patients with DoC [54], and a relative preserved glucose metabolism in the fronto-parietal associative cortices has a high sensitivity to distinguish a MCS from a UWS [18] and leads to a better outcome [55]. Stender et al. developed an original and automatized quantification method coined the ‘Metabolic Index of the Best preserved Hemisphere’ (MIBH), that uses extra-brain head metabolism values to normalize PET values [20]. The diagnostic power of this promising method has been replicated confirmed by a distinct group in a recent study [56], and appears as a promising objective measure of consciousness with PET.

#### 4.3.2. fMRI brain imaging

Resting state functional magnetic resonance imaging (fMRI) can identify structured patterns of functional connectivity among defined neuroanatomical systems including the default mode network (DMN) [57,58]. Many studies have shown that the functional connectivity is globally decreased at

rest in DoC patients [59] and also in executive control (CEN), salience (SN), sensorimotor, auditory and visual networks [60]. Changes in connectivity within specific regions of the mesocircuit may account for the loss of consciousness such as connectivity centered in the posterior cingulate cortex [61] and connectivity between subcortical structures and cortical networks [62], or between distant cortical regions [63]. Analyzing resting state fMRI recordings as a dynamics of serial discrete states revealed very promising results. In a multicentric study, patients in conscious states of in MCS showed specific neural dynamics recruiting functional connectivity patterns between distant cortical structures that escaped the mere direct cortico-cortical ‘wiring’ measured with DTI connectome maps [64]. Such results are compatible with the idea of conscious states corresponding to complex functional states of brain-scale networks.

Rather than recording ‘resting state’ brain activity, one can also engage the patient in an active cognitive task that cannot be performed unconsciously. If a patient’s brain shows patterns of activity observed in conscious controls performing this task, one may infer he/she is conscious. The seminal ‘imagine play tennis/navigating in your home’ task conceived by Owen and colleagues illustrates this approach [65,66] and can even lead to brain cerebral interface in a limited proportion of DoC patients [14]. Another promising track, closer to ecological conditions than usual cognitive tasks, consists in recording brain activity (fMRI, EEG,...) or other physiological signals such as heart rate, while exposing the patient to a movie or to an audio narrative, and then to compare its dynamics to the one of conscious controls [67–69].

#### 4.3.3. Electrophysiology

Electrophysiological tools such as EEG and evoked potentials can also provide a direct and time-resolved measure of functional state of the brain in DoC patients. These tools are noninvasive, easy to perform at patient’s bedside, and inexpensive. Basic EEG can detect signs of cortical wakefulness with a posterior alpha rhythm and reactivity to stimulations. Evoked potentials (EPs) can provide the most direct indication of the functional state of sensory pathways through auditory evoked potentials (AEPs), visual evoked potentials (VEPs) and somato-sensory evoked potentials (SSEPs). The integrity of the motor pathway from the primary motor cortex to the muscle contraction can also be tested with motor evoked potentials (MEPs) [25,70].

Cognitive event-related potentials (ERPs) using oddball paradigms may elicit several electrical brain response to novelty (i.e.: contrasting deviant versus standard stimuli) such as the mismatch negativity (MMN) component and the P300 response or complex. Prior to these cognitive stages of processing, it has been shown that the bilateral absence of early cortical responses of SSEPs is a good predictor of poor coma outcome [71,72]. Moreover, the presence of later ERPs has proved a good marker of positive coma outcome such a MMN [73–76], and can be enhanced by the use of the patient’s own name [77,78] or music [79]. The ‘local-global’ auditory oddball paradigm also proved useful to probe conscious access to auditory stimuli. In this paradigm, 2 levels of auditory novelty are crossed: a ‘local’ in time, intra-trial novelty effect (local effect) that does not require conscious processing of the

stimulus, and a ‘global’ inter-trial novelty effect that requires conscious processing in working memory (global effect) [80]. Global effect is more likely to be observed in conscious patients than in DoC patients [6,81], and its presence is associated with a better prognosis of consciousness recovery [6]. Two clinically VS patients showed a global effect and recovered overt behavioural evidence of MCS and of consciousness several days after ERPs recording [82].

Autonomic respiratory or cardiac activity markers, — such as heart rate (HR) and HR variability (HRV), and cardiac cycle phase — or the brain evoked responses to cardiac activity, can be modulated by the cognitive processing of the auditory stimuli, and may therefore be used to better assess DoC patients using a body-brain approach [83,84]. Several active task paradigms using EEG signal proved useful to detect residual consciousness and to identify patients with CMD [85].

Quantified EEG metrics based on spectral power [85], signal complexity and functional connectivity of the EEG at rest have been found to be specific to conscious states [17,86,87]. The multivariate combination of these measures using machine-learning algorithms proved to add relevant information to probe conscious states and to predict conscious recovery [88]. These markers enabled for instance the detection of conscious state in a paralyzed and multisensory disconnected ‘locked-in syndrome’ patient [9].

A recent active paradigm using machine learning applied to EEG recordings to decode brain activity in response to verbal motor instructions (e.g. ‘move your right/left hand’ vs ‘stop moving your right/left hand’) could identify CMD in 15% (16/104) of DoC patients [22].

Another original TMS-EEG approach aims at disrupting brain activity with a focal and transient electromagnetic stimulation, while recording how it reacts to this stimulation. While early, transient and focal brain responses can be observed in unconscious states (such as: N3 deep sleep stage, coma, deep general anesthesia with different anesthetics, VS/UWS), whereas late, sustained, distant (in cortical space) and complex brain responses appeared as specific to conscious states [15,89–92].

#### 4.4. Maximizing detection of rich cognitive state and therapeutic tests

In order to maximise the probability to detect conscious processing in a DoC patient, several strategies are useful.

First, it is recommended that clinicians should identify and treat confounding medical conditions such as paroxysmal sympathetic hyperactivity, infection, muscle and tendon shortening, epileptic seizure, and a special attention should be allocated to pain [23], and probably also to circadian rhythms [93].

Second, clinicians should systematically attempt to increase arousal before assessing the level of consciousness [23], by using for instance the CRS-r arousal facilitation protocol. For chronic DoC patient, a multi-disciplinary evaluation by an expert rehabilitation team involving the family should be systematically proposed given the care complexity typically associated to this chronic condition (neuro-orthopedic disorders, swallowing evaluation, nutrition issues, . . .).

During the last decades, several therapeutic interventions have been evaluated with the aim to enhance the detection of consciousness as well as the time course of recovery [94]. We will briefly explore some of these interventions that may facilitate the detection of consciousness in a clinical ward. We will consider subsequently: (i) behavioural interventions, (ii) brain stimulation techniques, and (iii) pharmacological drugs.

##### 4.4.1. Behavioural interventions

Based on the rationale that sensory stimulation prevents sensory deprivation and enhance experience-dependent plasticity, it is widely accepted that DoC patients should be intensively stimulated in order to speed-up recovery. However, contrary to a general belief, there is not any proof favouring a beneficial effect of multi-sensory intensive stimulation program [95]. The concept of sensory regulation should be preferred given the importance of fatigue in DoC patients [96]. This approach is based on the following principles: low ambient noise level; appropriate interstimulus intervals; regular rest intervals; observational period to determine the type of stimulus and sensory modality that elicit the most obvious and frequent response. Among others, preferred music is an easy to use personalized and salient stimulus, which can enhance arousal and consciousness [97]. The beneficial effect of right median nerve electrical stimulation observed in small controlled trials [98] remains to be demonstrated in a future study conducted at a larger scale, but this non-invasive technique may represent an interesting method to hasten awakening through a stimulation of ascending reticular activating system. Aside from sensory stimulation, awakening and consciousness is increased when a DoC patient is standing rather than supine [99]. Hence, clinical examination should be performed when the patient is comfortably settled in a chair rather than lying in a bed.

##### 4.4.2. Brain stimulation

Several methods aiming at delivering electro-magnetic stimulations to patient’s brain to improve and foster its functioning have emerged within the last decades [100]. The less invasive of these methods are transcranial current stimulation (tCS), that can use continuous or alternate current (tDCS and tACS respectively), and transcranial magnetic stimulation (TMS). Given a potential risk of epilepsy after TMS, tDCS is generally preferred as a therapeutic tool. In randomized controlled trials, a transient improvement of the CRS-R (+ 1,5 point) has been shown in MCS patients with a single session of 20 minutes of tDCS (2 mA) over the left prefrontal cortex [101]. It has been shown that this behavioural effect of tDCS coincided with an enhancement of EEG markers of consciousness suggestive of a direct causal effect of tDCS [102]. A lasting effect, albeit moderate, can be obtained with repeated sessions (during a 4 weeks program), which can be performed at home, by patients’ relatives or caregivers [103] (and see [104] for a similar approach). Altogether, given the absence of side effects, inexpensiveness, easiness and potential effectiveness of this tool, we recommend that at least a single 20 minutes session of tDCS (2 mA) on the left prefrontal cortex should be performed in DoC patient, and if possible daily sessions over a 4 weeks program.

In addition to electromagnetic tools, low intensity focused ultrasound appears as a new potential alternative for restorative intervention in DoC by allowing reversible modulation of subcortical brain regions. A first application of thalamic ultrasound stimulation has been reported in three patients with chronic DoC. This pilot study, — part of a larger clinical trial —, showed encouraging results and may represent a new therapeutic option in the future given the non-invasive character of this tool [105].

Vagus nerve stimulation may improve conscious processing in chronic DoC patients, through a diffuse brain activation mediated by brain-stem nuclei, as shown in a pilot single-case study [106]. The beneficial effect has to be confirmed in a larger sample, and the potential risk for sleep apnea that was observed in the first patient has to be evaluated in future studies. This technique may be of particular interest in DoC patients with an active epilepsy corresponding to a classical and longstanding indication for VNS.

Deep brain stimulation (DBS) is a more invasive technique to activate brain regions of the meso-circuit to enhance recovery of consciousness in DoC patients, but it may provide a unique way to target with a very high precision brain regions preserved by the lesion in some patients. After the remarkable results obtained in one chronic patient [107], series of cases showed heterogenous results suggesting that some patients are more likely to be responders than others [108,109]. Previous studies performed before the rise of the MCS/Vs distinction and of the CRS-r scale also reported mitigated results [110]. In a close future, DBS could be proposed to specific chronic patients with spared cortical networks and delineated lesions of sub-cortical regions affecting the meso-circuit. Such very targets and tailored indication may improve the efficacy of DBS in DoC patients.

#### 4.4.3. Pharmacological drugs

Many psycho-active pharmacological agents (dopamine agonists, NMDA antagonists, GABA agonists) have been used to enhance recovery of DoC patients [94]. Among these, amantadine and zolpidem show a very interesting risk-benefit ratio, and should be systematically proposed in DoC patients in the absence of contraindication.

In the acute or sub-acute phase, amantadine has demonstrated a functional gain in DoC patients in a large randomized controlled trial [111]. It is now recommended that clinicians should prescribe amantadine (100–200 mg bid) for adults with traumatic VS/UWS or MCS (4–16 weeks post injury) to hasten functional recovery and reduce disability early in recovery [23], in the absence of contraindications.

Improvements of consciousness and other neurological functions have been repeatedly reported in single-cases with zolpidem — a classical sleeping drug — in patients with sub-acute or chronic disorders of consciousness [112]. This paradoxical effect of zolpidem has been demonstrated in ~5% a placebo-controlled study conducted in eighty-four participants with traumatic and non-traumatic disorders of consciousness [113]. Although responders concern a small proportion of DoC patients, the beneficial/risk ratio appears very favorable, and we recommend that a therapeutic test should be performed in all patients showing a delayed awakening after coma at least with a single dose of 10 mg

given the potential spectacular ‘on-off’ effect within the 45 first minutes following drug ingestion.

## 5. A 2-tiers proposal

Currently, clinicians confronted to diagnostic and prognostic issues regarding a DoC patient rely almost exclusively on their own local strategies, knowledge and on their access, — usually very limited —, to some of the explorations listed above. In the best-case scenario, they have the possibility to transfer this patient to one of the very few expert teams (around 5 in France) who master some of these diagnostic and prognostic tools and who practice them on a regular basis. Obviously, this present situation is not optimal given: (i) that most recommendations converge toward a minimal observation period of about 1 week, and that (ii) the number of acute, subacute and chronic DoC patients far exceeds the capacity of these few expert teams. The COVID19 pandemics made this problem even worse by preventing DoC expertise to proceed on a regular way because most expert teams use intensive care units beds.

In order to improve this situation, we propose here a 2-tiers structuration of DoC expertise that could provide a systematic coverage of all DoC patients with an optimal performance for each concerned individual.

This structuration goal combines two hierarchical levels (Tier 1 and Tier 2), and takes advantage of digital networks and resources in order to organize distant meetings with video and multimedia channels, and to allow distant processing of brain structure and brain activity datasets.

At a first level (Tier 1), any medical structure in charge of DoC patients should be able to perform the following tests (Fig. 1a):

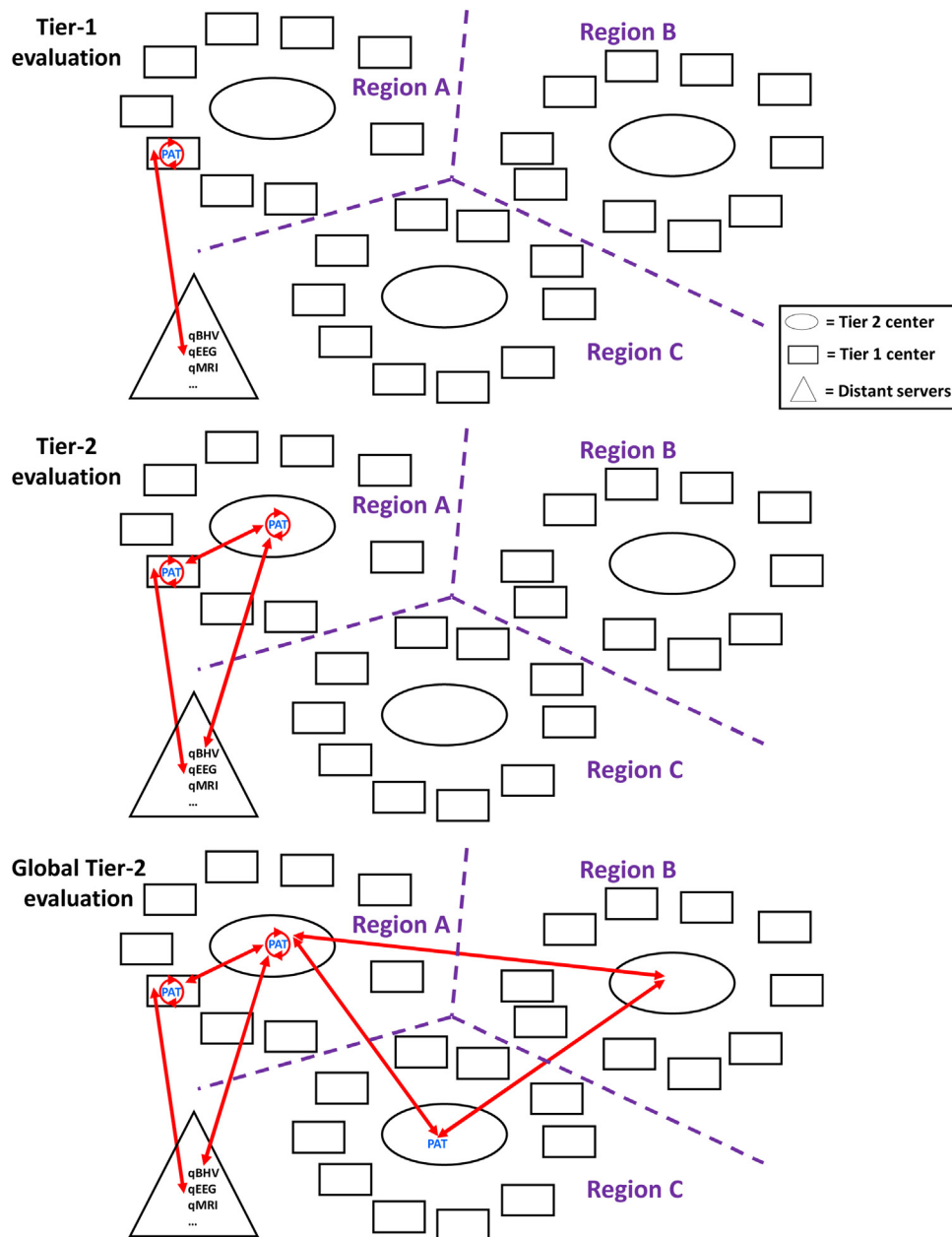
- neurological examination;
- CRS-R scorings;
- resting state or automatically delivered task-related quantified EEG with automatic analysis and classification scores of DoC state (diagnosis and prognosis), after uploading the acquired data to a common distant server;
- standard encephalic MRI in the absence of contraindication, or encephalic CT-scan;
- single-shot pharmacological test such as zolpidem test in the absence of contraindication.

This Tier-1 level should be able to provide clinicians and families with an objective and reliable description of patient’s state. This Tier-1 level evaluation should be sufficient in the majority of cases to provide reliable diagnostic and prognostic data.

However, several red flags should encourage local Tier-1 clinicians to contact a regional Tier-2 expert team. We list here some of these triggers:

- unusual etiologies of DoC;
- complex neurological examination;
- doubts about patient’s condition;
- mismatches between behavioural and brain activity data;
- mismatches between behavioural and brain structure data;





**Fig. 1 – Sketch of the proposed 2-Tiers network of DoC expertise.** Tessellation of France in regional ensembles, - that are already used to interact locally for the management of DoC patients -, would be the easiest and more convenient way to start with this structuration of the DoC expertise network. In each region (A, B, C, ...), the various Tier-1 centers are represented by black rectangles, whereas the regional Tier-2 center is shown as an ellipse. All centers would interact, - at various intensities and levels -, with distant digital servers enabling uploading, analysis and back-reporting of various datatypes (including behavior, EEG, MRI, ... data). A Tier-1 level expertise (see upper panel) would be fully executed in a Tier-1 center examining the concerned patient, with the aid of digital tools. If a doubt or a red-flag is still present at this stage, the expertise would require a Tier-2 level evaluation (see middle and lower panels). Such Tier-2 level expertises include various modalities including the following 5 progressive options, depending of case-difficulty: (i) distant telemedicine from the regional Tier-2 center to local Tier-1 center in charge of the patient, (ii) physical visit of regional Tier-2 experts to examine the patient in the Tier-1 center, (iii) physical transfer of the patient to the regional Tier-2 center where new exams will be performed, (iv) global Tier-2 level evaluation that will use telemedicine tools to enable a dedicated virtual meeting between all Tier-2 centers and the concerned Tier-1 center, (v) a similar global evaluation across all Tier-2 centers and the local Tier-1 center, with a physical transfer of the DoC patient from one Tier-2 center to another one in case crucial key explorations accessible only there would be considered as necessary.

- mismatches between brain structure and brain activity patterns;
- mismatches among caregivers, or between professionals and patient's relatives.

A Tier-2 level should be proposed to all chronic DoC patients who survive after the acute stage. Ideally such an evaluation should be performed before admission in one of the various types of rehabilitation or care centers.

In such situations requiring a Tier-2 level expertise, the Tier-1 to Tier-2 interaction could lead to one of the 3 following solutions (Fig. 1b):

- a telemedicine virtual meeting to discuss the case;
- a physical visit of Tier-2 experts to the local Tier-1 team in order to enrich behavioural and neurological examination;
- a transfer of the concerned patient to a Tier-2 structure.

This Tier-2 level evaluation of the concerned DoC patient would then include part of the following and non-exhaustive explorations:

- additional behavioural measures;
- quantified MRI DTI or similar measures with DoC classification scores;
- resting state and task-related quantified EEG with classification scores of DoC;
- EEG monitoring (sleep/wake cycles; REM sleep; ...);
- etiological investigations (e.g.: lumbar puncture with anti-neuronal antibodies, ...);
- TMS/EEG;
- FDG-PET;
- fMRI;
- tDCS tests;
- Other pharmacological or stimulation tests.

This Tier-2 level evaluation should be able to address many of the complex cases still unsolved after Tier-1 level evaluation.

However, the most complex cases may still call for a higher-level of expertise made possible through the global networking of all Tier-2 expert centers with the local Tier-1 team in charge of the patient (Fig. 1c). Again, various modalities of this global Tier-2 networking (Tier-2\* in Table 1) will be possible from distant meeting and distant processing of patient datasets only, to transfer of the patient in one of the distinct Tier-2 level centers in charge of specific explorations that are not accessible in other Tier-2 structures.

In addition to its primary goal aiming at offering every DoC patient an optimal evaluation, such a systematic, hierarchically structured and coherent organization of DoC expertise should also carry additional positive collateral effects. First, if adopted such a model will drive and foster an improvement of DoC expertise of all actors intervening in Tier-1 and Tier-2 centers. For instance, reliable behavioural examination should be improved at all levels (e.g.: CRS-r use that can be estimated by detecting impossible scores [114]). In its present form, this project includes explorations that are not yet fully accessible (e.g.: easy distant processing of resting state or active task EEG datasets), but it delineates the expected improvements we should tend towards. Similarly, new tools will emerge we are

ignorant of while writing this opinion paper, and one should mostly focus on the general dimension of this project than on its necessary limited and imperfect form.

Second, the coordination of local and distant actors could favor collective reasoning and should take advantage of 'wisdom of the crowds' effects, in particular when such 'crowds' are particularly educated on the concerned topics (i.e.: DoC expertise). One should therefore develop and use modern tools to take advantage of the cognitive diversity of experts, rather than impoverishing it by hierarchical effects such as argument from authority effects [115,116].

Third, the exchange of skills across Tier-1 and Tier-2 centers should provide a rich emulation for clinical and research projects. Indeed, such an organization would facilitate top-level, original and multidisciplinary clinical and more fundamental research in the field of consciousness and its disorders. In particular, this network would be ideally suited to the evaluation of disruptive therapeutics approaches such as the use of deep-brain stimulation, vagus nerve stimulation, original tDCS/tACS and pharmacological trials to improve patients with a DoC.

Fourth, we conducted this exercise at a country scale (France) for many reasons including our familiarity with the national care system, but it could obviously be adapted to other countries and continents (e.g.: Europe) beyond states frontiers (see for instance the 'Curing Coma Campaign' initiated by the Neurocritical Care Society [116]), as we informally do in research projects with our colleagues disseminated all over the globe. As far as we know, such a proposal has not been proposed, and it could therefore stimulate discussions and developments in the DoC expertise community.

## 6. A digital national registry of DoC patients

In close logical proximity with our 2-Tiers proposal, we also suggest that a national registry of DoC patients should be created, in strict compliance with medical legal regulations and with general data protection regulation (GDPR).

Such a national registry will allow the following key goals:

- active and sustained monitoring of DoC patients population and of its dynamics in France, with medical, epidemiological, sociologic, psychological and health economy impact;
- evaluation of the impact of Tier-1 level evaluation;
- evaluation of the impact of Tier-2 level evaluation;
- fine exploration of DoC patients trajectories;
- suggest new initiatives in terms of needs for DoC patients and their relatives;
- enrich clinical research in the field of DoC patients;
- homogenization of DoC expertise guided by rational and evidence-based decisions;
- allow large-scale therapeutic trials for DoC patients.

## 7. Conclusion

We hope this article will stimulate thinking and brainstorming about the optimal way to improve accessibility and

performance of DoC expertise at a country-scale. Our two proposals could be considered as a sketch or framework of a more fine-grained project that would require the contribution of the whole community of actors involved in DoC patients care and expertise, including patients and patients' relatives associations. We tried to imagine the minimal requirements so to reach what appears as an univocal evidence: we have to offer each DoC patient the optimal expertise required to guide his or her medical management. Finally, and as mentioned above, we focused this exercise at the scale of France, but these proposals could be implemented in other countries and at a larger-scale that is not necessarily constrained by geographical frontiers.

### Disclosure of interest

The authors declare that they have no competing interest.

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