Unconsciousness or unresponsiveness in Akinetic Mutism? Insights from a multimodal longitudinal exploration

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Abstract

The clinical assessment of patients with disorders of consciousness (DoC) relies on the observation of behavioral responses to standardized sensory stimulation. However, several medical comorbidities may directly impair the production of reproducible and appropriate responses, thus reducing the sensitivity of behavior-based diagnoses. One of these is Akinetic Mutism (AM), a rare neurological syndrome characterized by the inability to initiate volitional motor responses, sometimes associated with clinical presentations overlapping with those of DoC. Here we describe the case of a patient with large bilateral mesial frontal lesions showing a prolonged behavioral unresponsiveness and a severe disorganization of electroencephalographic (EEG) background, compatible with a vegetative state/unresponsive wakefulness syndrome (VS/UWS). By applying an unprecedented battery of multimodal longitudinal measurements encompassing spontaneous EEG, evoked potentials, event-related potentials, transcranial magnetic stimulation-evoked potentials, and structural and functional MRI, we provide (i) a demonstration of the preservation of consciousness despite unresponsiveness in the context of a complete AM, (ii) a plausible neurophysiological explanation of behavioral unresponsiveness and of its subsequent recovery during rehabilitation stay and (iii) novel insights into the relationships between DoC, AM and parkinsonism. The present case provides proof-of-principle evidence supporting the clinical utility of a multimodal hierarchical workflow combining conventional and advanced techniques to detect covert signs of consciousness in unresponsive patients.

Keywords

disorders of consciousness; akinetic mutism; EEG; TMS-EEG; fMRI

Abbreviations

ABR, auditory brainstem responses; ACoA, anterior communicating artery; AM, akinetic mutism; CaN, caudate nucleus; CMD, cognitive-motor dissociation; CRS-R, Coma Recovery Scale-Revised; CT, computed tomography; DAR, delta-alpha ratio; DTI, diffusion tensor imaging; DoC, disorder of consciousness; EEG, electroencephalography; EMG, electromyography; EP, evoked potentials; ERP event-related potentials; FLAIR, fluid attenuated inversion recovery; fMRI, functional magnetic resonance imaging; GCS, Glasgow Coma Scale; GM, gray matter; ICU, intensive care unit; IRU, intensive rehabilitation unit; MEP, motor evoked potentials; MPRAGE, magnetization-prepared rapid acquisition with gradient echo; NeMo, Network Modification Tool; PCI, perturbational complexity index; PET, positron emission tomography; SEP, somatosensory evoked potentials; sMRI, structural magnetic resonance imaging; SPIDER-NET, Software Package Ideal for Deriving Enhanced Representations of Brain NETworks; VS/UWS, vegetative state/unresponsive wakeful-

ness syndrome; TEP, TMS-evoked potentials; TMS-EEG transcranial magnetic stimulation combined with electroencephalography; WM, white matter.

Introduction

Detecting recovery of consciousness in severely brain-injured patients relies on the observation of their motor behavior and responsiveness to sensory stimuli according to standardized scales. Although structured behavioral examinations, such as the Coma Recovery Scale-Revised (CRS-R) (Giacino *et al.* , 2004), represent the gold standard for diagnosing recovery of consciousness (American Congress of Rehabilitation Medicine, Brain Injury-Interdisciplinary Special Interest Group, Disorders of Consciousness Task Force *et al.* , 2010), impairment of sensory, executive and motor function may result in false-negatives. Indeed, several neurological conditions, such as cranial nerve palsies, lesions affecting afferent sensory and efferent motor pathways, cortical blindness, aphasia or frontal akinetic syndrome can directly interfere with the production of reproducible and appropriate behavioral responses to external stimuli, thus reducing the sensitivity of standard clinical tests (Pincherle *et al.* , 2019, 2021).

To address these limitations, the last American (Giacino *et al.* , 2018) and European (Kondziella *et al.* , 2020) guidelines on diagnosis of disorders of consciousness (DoC) recommended the integration of advanced diagnostic technologies with clinical evaluation whenever behavioral evidence for consciousness is inconclusive. These strategies complement bedside clinical testing by employing tools such as functional magnetic resonance imaging (fMRI), electroencephalography (EEG), sensory-motor evoked potentials (EP), event-related potentials (ERPs), transcranial magnetic stimulation-evoked potentials (TEP), or positron emission tomography (PET), to derive brain-based markers of consciousness that are independent of overt behavior. Collectively, studies employing these approaches both in the intensive care unit (ICU) and rehabilitation settings have provided evidence that up to 20% of patients may retain a capacity for consciousness that may not be expressed in behavior (Monti *et al.* , 2010; Sitt *et al.* , 2014; Casarotto *et al.* , 2016; Claassen *et al.* , 2019; Edlow*et al.* , 2021). Given the complexity of this emerging landscape, operational workflows designed to hierarchically combine conventional and advanced multimodal techniques and systematize their use at the patient's bedside along the course of disease have been recently proposed (Comanducci *et al.* , 2020; Monti & Schnakers, 2022).

The present case-report represents a practical implementation of such a proposal in an intensive rehabilitation unit (IRU) setting. We present the trajectory of a patient with a large bilateral fronto-subcortical vascular injury who was initially diagnosed as being in a vegetative state/unresponsive wakefulness syndrome (VS/UWS) on repeated CRS-R assessments. The patient underwent an unprecedented multimodal battery encompassing currently recommended paraclinical tests for DoC diagnosis, including EEG, EP, ERP, TMS-EEG measures of complexity, advanced structural MRI (sMRI) as well as fMRI with an active task-based paradigm. Furthermore, the assessment was repeated at multiple time points along the clinical evolution of the patient from the sub-acute to the chronic phase.

Overall, the multimodal paraclinical tests, subsequently confirmed by the clinical evolution, provided complementary and compelling evidence that the patient was not unconscious but rather unresponsive, due to a complete akinetic mutism (AM) syndrome. This exploration, combining state-of-the-art sMRI, EEG, EP, ERP, TMS-EEG and fMRI approaches, confirms that, in some presentations, AM, which may occur when bilateral fronto-subcortical circuits are massively disrupted, can mimic an unconscious VS/UWS state, whereby the patient is unresponsive, albeit awake. More generally, the present case provides an opportunity to reflect on the significance of multiple evidence of dissociations between clinical and paraclinical markers of consciousness.

Description of clinical and multimodal paraclinical assessments

1. Phase 1: from ICU to prolonged unresponsiveness in IRU (week 1 to 5)

1.1 *Clinical history and structural neuroimaging*

Eight weeks prior to admission at our IRU, the patient (female, 65 years old, right-handed, without relevant

medical history) was hospitalized due to a sudden series of seizures associated with an altered state of consciousness. Head computed tomography (CT) scan and angiography revealed a bi-hemispheric subarachnoid hemorrhage with intraventricular hemorrhage and severe brain swelling due to the rupture of an aneurysm of the anterior communicating artery (ACoA). The patient soon became comatose (with a Glasgow Coma Scale, GCS, of 6) and an urgent endovascular coiling treatment was performed on the same day. In a few days, the neurological status further deteriorated (GCS decreased from 6 to 4) in ICU due to a re-bleeding of the ACoA aneurysm, requiring an additional endovascular treatment. A left cortical-subcortical parieto-occipital infarct due to diffuse cerebral vasospasm was also revealed by serial CT-scans. Apart from the GCS, no clinical or paraclinical assessments of consciousness were collected during the patient's ICU stay.

Upon sufficient stabilization of vital signs, the patient was admitted at our IRU with a diagnosis of a prolonged VS/UWS requiring artificial hydration and feeding, as well as total nursing care (Figure 1). Here, a first neurological examination showed spontaneous eye opening, a severe diffuse hypertonia with combined extrapyramidal and pyramidal features (rigidity and spasticity were predominant in both lower limb and the left upper limb), grasp and palmo-mental reflexes, Myerson's sign (not-extinguishable glabellar tap reflex), hypomimia after painful stimuli and a lack of any consistent command following, visual fixation or tracking. She did not initiate any spontaneous motor behavior.

A multimodal investigation was conducted within the multicentric "Perbrain" project (Willacker *et al.* , 2022), approved by the ethics section "IRCCS Fondazione Don Carlo Gnocchi " of ethics committee IRCCS Regione Lombardia (Prot. n. 32/2021/CE FdG/FC/SA) and a written informed consent was provided by the patient's legal guardian at admission.

On week 1, sMRI protocol was acquired on a 3 Tesla Siemens Prisma scanner equipped with a 64channels head/neck coil. The MRI protocol included a 3D sagittal magnetization-prepared rapid acquisition with gradient echo (MPRAGE) as anatomical reference (1mm3; 256x256;TR/TE: 2300/2,98ms; TI:919ms), a 3D sagittal fluid-attenuated inversion recovery (FLAIR) for lesion detection (0,8x0,8x1mm; 320x320; TR/TE:5000/394ms; TI:1800ms) and a diffusion weighted imaging (DWI) sequence for quantifying the white matter microstructural status (2mm3; 104x104; including short and long phase-encoding reversed data; TR/TE:3600/92ms 5 b0 images, 50 diffusion-encoding directions with b = 1000 s/mm2 and 50 diffusion directions with b = 2000s/mm2).

Neuroradiologist's visual analysis of sMRI sequences revealed extensive bilateral cortico-subcortical encephalomalacia (associated with hemosiderin deposits) at frontal and parietal median parasagittal locations and corpus callosum thinning throughout its extent (Figure 2). In addition, there was a cortico-subcortical ischemia at the left parieto-occipital region as well as a bilateral enlargement of the ventricles at the frontal and temporal horns. Due to the aneurysm clip in the anterior communicating artery territory, a partial magnetic distortion in the median fronto-basal area and in the region of the basal nuclei was also observed.

The lesions were segmented on the FLAIR images by an expert radiologist using the Jim software package (http://www.xinapse.com). Then, in order to map which gray matter (GM) and white matter (WM) areas were involved by the lesion, the lesion mask was non-linearly registered to the MNI space (resolution 1x1x1mm3) using FMRIB's Software Library (FSL,*http://www.fmrib.ox.ac.uk/fsl*).

1.2 *Serial standardized behavioral assessment is consistent with a VS/UWS*

In view of the clinical presentation and of the pattern of anatomical injury, involving the bilateral mesial frontal territory of the anterior cerebral arteries, a differential diagnosis between a complete AM and a VS/UWS was considered (Freemon, 1971). To minimize the possibility of missing minimal signs of volitional motor activity such as gaze tracking or reproducible responses to stimuli, a standardized clinical assessment with serial CRS-R was applied weekly, along the IRU stay (at least 3-5 times/week for 20 weeks). Multiple behavioral evaluations were performed by expert examiners (neurologist and neuropsychologist) at different times of the day, with similar environmental conditions. The clinical trajectory as well as the best CRS-R total score per week is detailed in Figure 1. During the first five weeks of standardized clinical monitoring,

the patient was repeatedly diagnosed as VS/UWS since only reflexive responses (such as auditory startle, visual startle, abnormal posturing, and oral reflexive movement) could be detected in the absence of any reproducible behavioral sign of minimal consciousness. During this period, the patient appeared fully awake, but she was not able to consistently follow moving objects with the gaze or fixate. No verbal contact was possible and no motor response on request was produced (CRS-R total score ranging from 5 to 7).

1.3 *Resting EEG shows a severe background disorganization*

During week 2, a comprehensive neurophysiological battery including visual and spectral analysis of spontaneous EEG (Figure 3) was performed to complement the behavioral evaluation. The visual analysis of clinical standard EEG demonstrated a diffuse slowing of the background activity with high-amplitude frontally-dominant slow-waves (>75μV) and sporadic lateralized epileptiform discharges on the left parietal sites, without a reproducible reactivity to exogenous stimuli (Figure 3, upper left panel). In accordance with recent review and specific recommendations (Curley *et al.* , 2022), these findings were interpreted as a severely abnormal EEG, a pattern more often found in VS/UWS patients and not suggestive of covert consciousness (Forgacs*et al.* , 2014; Curley *et al.* , 2018). The severity of EEG slowing was confirmed by the quantification of Delta-Alpha Ratio (DAR) spectral power (Leon-Carrion *et al.* , 2008; Bai *et al.* , 2021; Wutzl *et al.* , 2021) showing values above the 95th percentiles of the distribution previously obtained in a reference population of 40 patients with a minimally conscious state (MCS) (Figure 3, upper right panel).

1.4 *Sensory-motor EP and EMG reveal a partial sensory and motor functional disconnection*

To characterize the functional status of afferent sensory and efferent motor systems, sensory-motor EP and EMG were then applied as a second-level assessment (Figure 3 middle panel). Auditory brainstem responses (ABR) indicated a mild alteration of transmission along the central pathway at the midbrain level (increase of the III-V interpeak), however, not sufficient to significantly affect the CRS-R auditory function subscale. There was no alteration in visual transmission detected with flash visual EP, suggesting that the absence of visual fixation and tracking was not due to cortical blindness.

Somatosensory EP (SEP) showed the absence of the cortical N20 in the left hemisphere along with a preserved subcortical P14, suggesting an alteration of central somatosensory transmission from the right upper limb. Moreover, motor EP (MEP) elicited by TMS over primary motor cortex indicated a severe functional disconnection along the cortico-spinal tracts for both lower limbs and the left upper limb. Electromyography and electroneurography revealed a diffuse combined peripheral neuropathy and myopathy (compatible with an ICU-acquired weakness) further complicated by a left upper-trunk brachial plexopathy. Finally, a significant lack of habituation of the blink reflex reflecting the increased excitability typical of a hypo-dopaminergic state was detected (Formisano *et al.* , 2009).

This comprehensive neurophysiological battery, demonstrated the coexistence of multiple partial sensory and motor sites of functional disconnections, both at the central and peripheral levels, possibly confounding an accurate assessment of reflexes and volitional motor responses.

1.5 *ERP analysis shows preserved P100 but lack of higher-level cognitive processing*

To characterize residual sensory-cognitive abilities at a higher level, we recorded ERP by applying a binaural acoustic stimulation with a classical oddball task following the technical guidelines for clinical research previously described in (Duncan *et al.* , 2009). This third-level bed-side neurophysiological evaluation (Figure 3, lower panel) with a cognitive paradigm only showed a stable N1 component in response to the acoustic stimuli indicating a residual preserved activation of primary and peri-primary acoustic areas. However, we did not identify higher-level neurophysiological correlates of cognitive processing, such as the pre-attentional mismatch negativity or the late positive P3 component.

The partial sensory-motor disconnection highlighted by the multimodal EP-EMG examination and the inconclusive ERP results obtained with a clinical visual analysis, in conjunction with the marked slowing of

EEG background, called for a deeper-level investigation; indeed, consciousness can be preserved even in conditions of disconnection from the sensory-motor periphery (Rohaut *et al.* , 2017; Bayne *et al.* , 2020), in the absence of a P3 (Faugeras *et al.* , 2012) as well as in the presence of a severely abnormal EEG pattern (Frohlich*et al.* , 2021).

1.6 *The complexity of TEP indicates a capacity for consciousness*

TMS-evoked potentials (TEP) allow probing neuronal dynamics within thalamocortical networks without engaging sensory, motor and executive functions and can be used to assess by a causal perspective to what extent distributed and differentiated groups of neurons interact as a whole to produce complex dynamics (Massimini *et al.* , 2005, 2009; Rosanova *et al.* , 2009). The Perturbational Complexity Index (PCI), has been specifically developed to quantify this form of brain complexity (Casali *et al.* , 2013; Sarasso *et al.* , 2021), and has been validated as an index of consciousness in healthy controls and brain injured patients (Casarotto *et al.* , 2016; Sarasso*et al.* , 2020). Based on this benchmark calibration, finding a maximum PCI value across stimulation sites (PCI_{max}) higher than 0.31 indicates a capacity for consciousness irrespective of behavioral responsiveness and of the dominant EEG background pattern.

TEP were recorded on week 3, with a 62-channel TMS-compatible EEG amplifier (Brainamp DC, Brain Products GmbH, Germany) following the same procedure reported in (Casarotto *et al.* , 2016) and using a customized software for real-time evaluation of TEP (Casarotto *et al.* , 2022). Specifically, EEG responses to TMS were obtained by targeting three cortical sites: the left and right superior parietal lobule as well as the right superior frontal gyrus (Figure 4, panel A). This exam revealed high PCI values for both right (PCI=0.34, Figure 4 panel B, blue square) and left (PCI=0.33, Figure 4 panel B, blue circle; panel C", blue TEP) parietal stimulation sites, indicating a capacity for consciousness according to published norms (Casali *et al.* , 2013; Casarotto *et al.* , 2016; Sinitsyn *et al.* , 2020). Interestingly and in contrast with parietal stimulation, frontal stimulation only elicited a slow, stereotypical wave resembling those typically obtained in sleeping healthy subjects (Figure 4, panel C', blue TEP) that was associated with low complexity (PCI=0.25) (Figure 4, panel B, blue diamond). This mixed pattern whereby high-complexity brain responses can coexist with local sleep-like reactivity, especially in areas surrounding lesions, is typically found in conscious patients with (multi)-focal lesions (Sarasso *et al.* , 2020). Overall, the analysis of TEP documented high brain complexity (PCI_{max}=0.34) and a substantial impairment of the reactivity of frontal circuits, consistent with a preserved capacity for consciousness in a clinical context of impaired executive and motor function.

2. Phase 2: the emergence of fluctuating signs of consciousness (weeks 6-13)

2.1. *Emergence of behavioral responsiveness and TMS-EEG changes*

Starting at week 6 the patient showed the first reproducible, albeit fluctuating, signs of consciousness, such as object manipulation followed by the appearance of visual tracking at week 8, consistent with a diagnosis of low-behavioral MCS, or MCS "minus" (MCS-) (Figure 1). During this transition period (week 7), the patient underwent a second TMS-EEG measurement to assess possible changes in cortical reactivity and complexity related to the behavioral evolution. Brain complexity remained above the threshold (PCI_{max}>0.31) for consciousness detection and increased for both left and right parietal stimulation (PCI from 0.33 to 0.40 and from 0.34 to 0.35 respectively; Figure 4 panel B, red circle and red square); in the case of right frontal stimulation PCI slightly increased but remained below threshold (PCI from 0.25 to 0.27; Figure 4 panel B, red diamond).

2.2 *fMRI demonstrates covert consciousness despite fluctuations in responsiveness*

In the following period (weeks 9-10-11) the patient continued to show significant variations in behavioral responsiveness (CRS-R total score ranging from 5 to 9) corresponding to transitions between a VS/UWS and a MCS- diagnosis. However, the clinical evolution and the consistently high values of brain complexity, suggested the possibility of an underlying state of covert consciousness amidst large fluctuations in behavioral responsiveness. To test this hypothesis, we evaluated the patient during a period of unresponsiveness (week 6, CRS-R=6; diagnosis VS/UWS) employing a fMRI paradigm whereby covert consciousness can be

demonstrated with high specificity based on the patient's ability to modulate brain activity in response to verbal commands (Owen *et al.* , 2006; Monti *et al.* , 2010; Owen, 2013). In particular, the fMRI paradigm (ABAB block design) consisted of a simple command-following task (Bekinschtein *et al.* , 2011; Curley*et al.* , 2018) that prompted the patient to actually perform the motoric action of opening and closing the left or the right hand, even if incapable of doing so. The fMRI EPI* sequence was acquired on the same 3T Siemens Prisma scanner (resolution:3x3x3mm3; matrix:80x80; TR/TE: 2000ms/30ms). As shown in Figure 5, when comparing right-hand commands vs rest, a consistent blood-oxygen-level-dependent (BOLD) activation of left superior temporal and premotor cortices was revealed.

3. Phase 3: Diagnostic hypothesis and recovery of overt command following (week 14 to discharge)

3.1. *A pattern of structural dysconnectivity suggestive of AM and mesocircuit disruption*

In light of converging TMS-EEG and fMRI evidence of consciousness in the face of a severe impairment of motor initiation and execution, the lesional pattern was re-analyzed on a finer grain to support a diagnosis within the AM spectrum. To this aim, we performed a second-level sMRI analysis utilizing the Network Modification Tool (NeMo) (Kuceyeski*et al.* , 2013). Based on a large reference set of tractography data, NeMo associates changes in WM integrity to expected changes in GM connectivity. This allows the characterization of the effects of lesions on cortical-subcortical connectivity and thus the assessment of the structural underpinnings of AM. NeMo does not require tractography and the most disconnected GM regions, were visualized through an easy-to-use, flexible toolbox (SPIDER-NET, Software Package Ideal for Deriving Enhanced Representations of Brain NETworks) for connectogram generation (Coluzzi *et al.* , 2022). Such representation highlighted a significant disconnection between frontal regions and subcortical ventral basal ganglia, dorsal striatum and thalamus as well as between bilateral frontal areas (Figure 6). Interestingly, this pattern of dysconnectivity involving both frontal and anterior basal forebrain not only was consistent with an AM diagnosis but also matched the model of deafferentation proposed with the mesocircuit hypothesis (Schiff, 2010; Fridman *et al.* , 2014; Edlow *et al.* , 2021).

3.2. *Treatment, recovery of command following and improvement of frontal reactivity*

Considering the dysconnectivity pattern, involving the bilateral mesial frontal cortex and the basal ganglia (Figure 6) and consistent with a mesocircuit hypothesis, a treatment with amantadine, a pro-dopaminergic drug with antiglutamatergic and anticholinergic properties, was attempted (Kraus & Maki, 1997; Thibaut *et al.* , 2019). Amantadine was administered according to the following schedule: 50mg once daily in week 13, 100 mg once daily in week 14, 100 mg twice daily in week 15, 150 mg twice daily up to the discharge (week 20) (Figure 1).

Increasing doses of amantadine were paralleled by a gradual recovery of responsiveness from a fluctuating low-level MCS- to a stable high-behavioral MCS "plus" (MCS+) diagnosis (week 17), due to the appearance of subtle but reproducible movement to command with CRS- R assessments (Figure 1). Notably, motor execution was finally achieved by the recovery of voluntary motility of the right hand, corresponding to the side where MEP, EMG and fMRI findings previously converged in predicting a residual preservation of the central and peripheral motor pathway.

Before IRU discharge (week 20), the patient underwent a final TMS-EEG exam (week 19) to reassess the state of cortical circuits. TEP revealed an increase of brain complexity not only when targeting the left parietal site (PCI from 0.40 to 0.47, Figure 4 panel B, green circle; panel C", green TEP) but notably also over the right superior frontal gyrus; here, the recovery of fast oscillations and late component both locally and bilaterally, far from the stimulation site resulted in higher complexity responses (PCI from 0.27 to 0.32, Figure 4 panel B, green diamond; panel C', green TEP), This change paralleled the recovery of executive functions suggesting that TMS-EEG may represent an interesting read-out of regional changes in cortical circuits that are relevant for functional recovery during the IRU stay.

Discussion

This case-report demonstrates the challenges and the opportunities that clinicians face when they are called to assess consciousness in patients in whom brain injury results in inconsistent responsiveness and motor behavior. The trajectory we describe here clearly highlights the problem of discriminating between unconsciousness and unresponsiveness and shows how a comprehensive hierarchical assessment, combining clinical and advanced paraclinical markers, can help minimizing diagnostic error. At the same time, the comprehensive multimodal exploration performed here prompts an interesting pathophysiological reflection on the relationships between DoC, AM and extreme parkinsonism.

Consciousness beyond unresponsiveness

After admission at the IRU for a multifocal brain injury of vascular origin, the patient remained unresponsive for five weeks during which repeated CRS-R examinations resulted in a VS/UWS diagnosis. According to recent recommendations (Giacino *et al.* , 2018; Comanducci *et al.* , 2020; Kondziella *et al.* , 2020), the patient underwent a series of paraclinical exams, including visual and quantitative assessment of the resting EEG background, multimodal EP and EMG to explore sensory and motor pathways as well as ERP to investigate residual cognitive functions. Finding a preserved EEG background or evidence of late cognitive ERP, such as the late P3, would have provided a specific indication of a condition of clinical-paraclinical dissociation, such as those previously described as covert awareness (Owen *et al.* , 2006), cognitive-motor dissociations (CMD) (Schiff, 2015), functional LIS (Giacino *et al.* , 2009), MCS* (Gosseries*et al.* , 2014), covert cortical processing (Edlow *et al.* , 2021). However, this possibility was apparently inconsistent with the finding of a severely disorganized EEG background and the absence of a P3. The novelty of the present report is that these negative results were followed by a deeper level of investigation, involving TMS-EEG and eventually by a fMRI active paradigm. As described in a recent expert review (Comanducci *et al.* , 2020), the rationale for such a hierarchical evaluation is that while EEG and ERP can provide a specific indication of preserved consciousness when they are positive, they are inconclusive in case of a negative result due to their low sensitivity. Indeed, a direct assessment of the complexity of causal interactions within the thalamocortical system, revealed a preserved capacity for consciousness according to published norms, i.e. complexity values that are only found in conscious subjects (Casali *et al.* , 2013; Sarasso *et al.* , 2015; Casarotto *et al.* , 2016; Sinitsyn*et al.* , 2020). In the absence of behavioral responsiveness and lack of communication, the question of what it means for a particular patient to have high brain complexity is hard to resolve. In general, inferring an actual instance of preserved experience is based on the evidence that control subjects who show $PCI_{max}>0.31$ during unresponsiveness in sleep or under ketamine anesthesia regularly report dream experiences upon awakening. In the present case, two additional elements strongly support this conclusion. The first element is the fMRI evidence that the patient was able to engage in volitional activity in response to verbal commands during periods of unresponsiveness. The second element is the convergent evidence (bilateral mesial-frontal lesional pattern, abnormal EEG frontal slowing, altered EEG frontal response to TMS, MEP and EMG showing a severe disconnection along the central and peripheral motor pathway) that unresponsiveness could be explained by a fundamental impairment of executive/motor circuits and pathways, rather than by unconsciousness.

Akinetic mutism, parkinsonism and the mesocircuit hypothesis

Syndromes in the AM spectrum are among the clinical conditions that may hamper the bedside detection of consciousness (Pincherle *et al.* , 2021). AM causes a specific impairment of initiating motor responses even after prompting, despite a preserved intrinsic capacity to move (Freemon, 1971). As such, the spectrum of clinical presentation may range from a total unresponsiveness (complete variant) to a sporadic production of words and volitional movements, though with a delay in the initiation and poor reproducibility (Arnts *et al.* , 2020).

Although AM is often discussed under the umbrella of "DoC" (Németh*et al.* , 1986; Wijdicks & Cranford, 2005; Shetty *et al.* , 2009), there are only few studies specifically aimed at disentangling the impairment of responsiveness from the impairment of consciousness in these patients (Kotchoubey *et al.* , 2003; Naccache *et al.* , 2004). In fact, a comprehensive multimodal assessment including the currently recommended conventional and advanced tools for DoC diagnosis has not been systematically conducted so far.

Due to the low incidence of AM, the majority of studies were single-case reports, mostly with CT-scan (Ure *et al.* , 1998; Nagaratnam*et al.* , 2004; Shetty *et al.* , 2009), and more advanced techniques, such as TMS-EEG to longitudinally track capacity for consciousness or fMRI to identify residual volitional abilities have not been employed before this case.

An intriguing aspect of the present exploration is the remarkable degree of overlap, both at the anatomical and at the clinical level, between the unresponsiveness typical of a DoC and the severe akinesia related to a dopamine depletion of an advanced parkinsonism (Formisano *et al.* , 2011; Formisano & Zasler, 2014; Comanducci *et al.* , 2022). Indeed, "akinetic" symptoms represent the end point on a clinical continuum including abulia (i.e., lack of will and motor initiative) and apathy (i.e. lack of emotional involvement) (Niedermeyer, 2008). This is perhaps not surprising as the neural circuits most affected in AM intersect both with those often involved in DoC (activating projections from the midbrain to the thalamus) and with those typically accounting for parkinsonism (mesolimbic, mesocortical and nigrostriatal dopaminergic projections) (Mega & Cohenour, 1997; Arnts *et al.* , 2020).

In this case, despite the behavioral unresponsiveness, clinical extrapyramidal symptoms such as the diffuse rigidity, Myerson's sign and hypomimia after painful stimuli suggest a shared mechanism with parkinsonism based on dopaminergic dysfunction. Moreover, the role of amantadine in promoting recovery of consciousness further corroborated the hypothesis of a critical pathophysiological dysfunction within the dopaminergic projections (Spindler et al., 2021) and the midbrain(substantia nigra)-striatal-thalamic-frontal pattern of dysconnectivity which well matched the network proposed by the mesocircuit model (Schiff, 2010)

In this vein, the covert (fMRI-based) and then overt improvements in motor control and response initiative could be explained by a progressive restoration of function within the anterior forebrain mesocircuit network reflecting a spontaneous and amantadine-related re-activation of fronto-thalamic and basal ganglia outflow (Kraus & Maki, 1997; Thibaut et al., 2019; Formisano & Zasler, 2014).

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Conflict of interest

Marcello Massimini is co-founder and share-holder of Intrinsic Powers, a spin-off of the University of Milan. The other authors declare no conflict of interest.

Author contributions

All authors contributed to the study conception and design. Patients' selection and neurophysiological data collection were performed by AC, CD, SC, MR. MRI data collection, analyses and interpretation: CM, AP, FB, VB. The first draft of the manuscript was written by AC and MM. All authors read and approved the final version of the manuscript.

Data Availability

The dataset used during the current study is available upon reasonable request.

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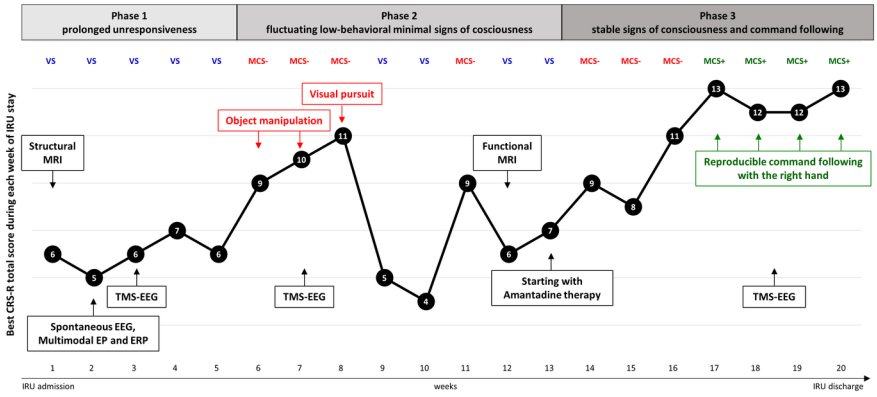

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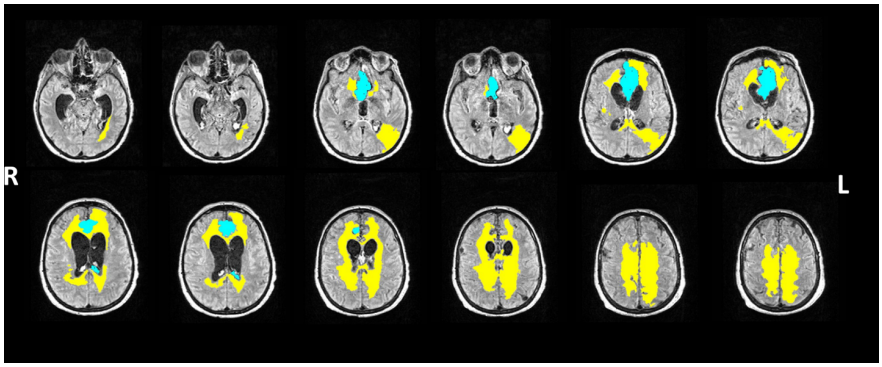

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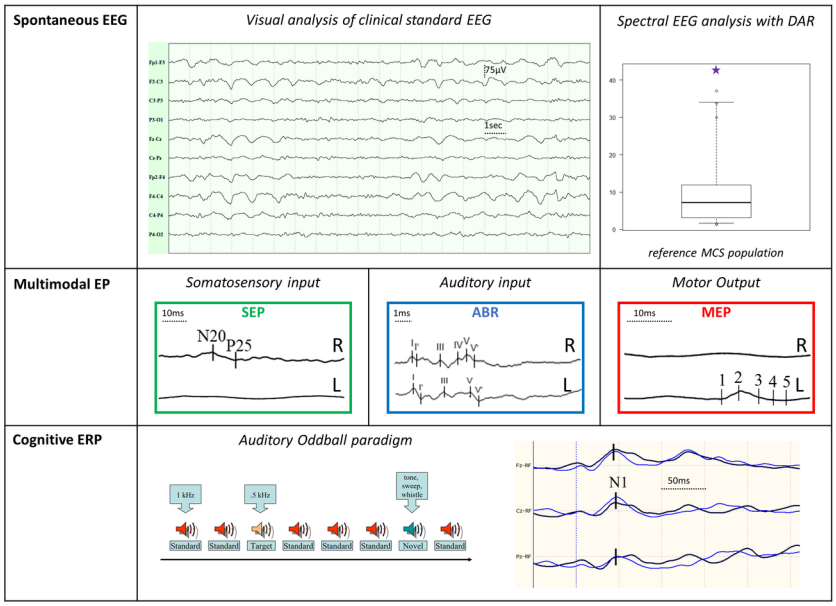

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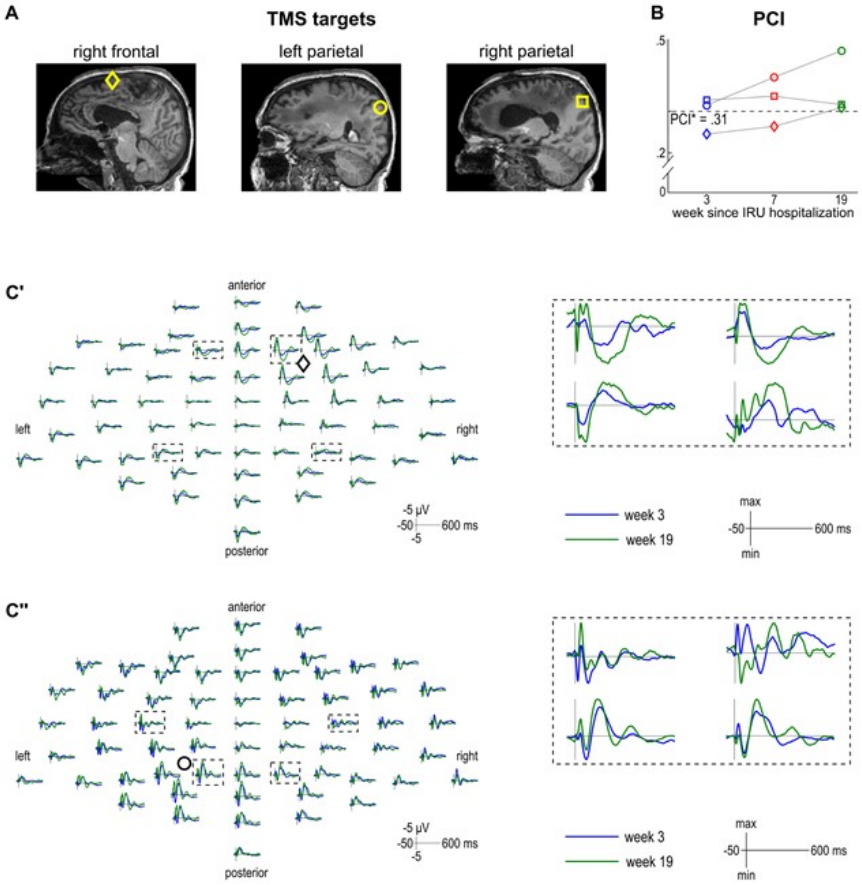

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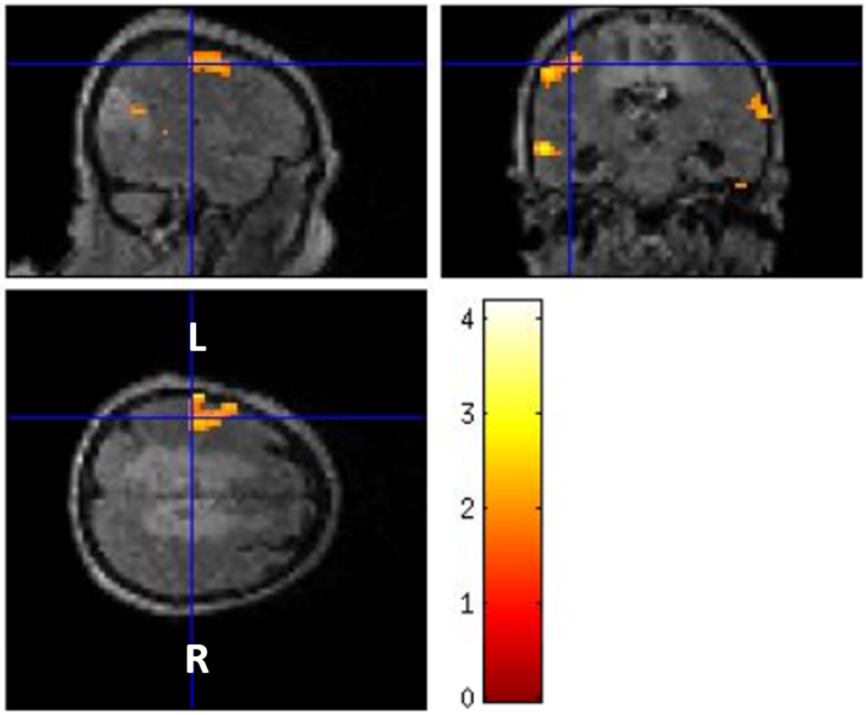

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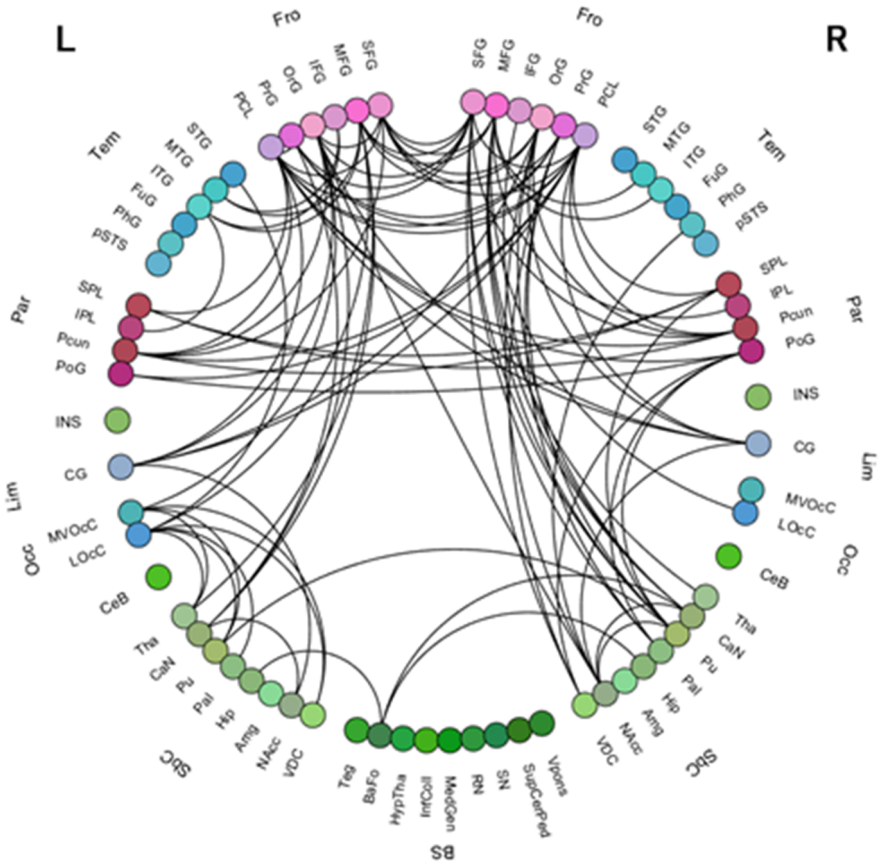

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