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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 behavioural responses to standardised sensory stimulation. However, several medical comorbidities may directly impair the production of reproducible and appropriate responses, thus reducing the sensitivity of behaviour-based diagnoses. One such comorbidity is akinetic mutism (AM), a rare neurological syndrome characterised by the inability to initiate volitional motor responses, sometimes associated with clinical presentations that overlap with those of DoC. In this paper, we describe the case of a patient with large bilateral mesial frontal lesions, showing prolonged behavioural unresponsiveness and severe disorganisation of electroencephalographic (EEG) background, compatible with a vegetative state/unresponsive wakefulness syndrome (VS/UWS). By applying an unprecedented multimodal battery of advanced imaging and electrophysiology-based techniques (AIE) encompassing spontaneous EEG, evoked potentials, event-related potentials, transcranial magnetic stimulation combined with EEG and structural and functional MRI, we provide the following: (i) a demonstration of the preservation of consciousness despite unresponsiveness in the context of AM, (ii) a plausible neurophysiological explanation for behavioural unresponsiveness and its subsequent recovery during rehabilitation stay and (iii) novel insights into the relationships between DoC, AM and parkinsonism. The present case offers proof-of-principle evidence supporting the clinical utility of a

Abbreviations: AIE, advanced imaging and electrophysiology-based technique; AM, akinetic mutism; CRS-R, Coma Recovery Scale-Revised; 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; ICU, intensive care unit; IRU, intensive rehabilitation unit; MEP, motor evoked potentials; PCI, Perturbational Complexity Index; SEP, somatosensory evoked potentials; sMRI, structural magnetic resonance imaging; TEP, TMS-evoked potentials; TMS-EEG, transcranial magnetic stimulation combined with electroencephalography; VS/UWS, vegetative state/unresponsive wakefulness syndrome.

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multimodal hierarchical workflow that combines AIEs to detect covert signs of consciousness in unresponsive patients.

KEYWORDS
akinetic mutism, cognitive–motor dissociation, covert consciousness, disorder of consciousness, TMS-EEG

1 | INTRODUCTION

Detecting recovery of consciousness in severely brain-injured patients relies on the observation of their motor behaviour and responsiveness to sensory stimuli according to standardised scales. Although structured behavioural 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 behavioural 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 for diagnosis of disorders of consciousness (DoC) recommended the integration of advanced imaging and electrophysiology-based techniques (AIE) with clinical evaluation whenever behavioural 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) and transcranial magnetic stimulation-evoked potentials (TEP), to derive brain-based markers of consciousness that are independent of overt behaviour. 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 behaviour (Casarotto et al., 2016; Claassen et al., 2019; Edlow et al., 2021; Monti et al., 2010; Sitt et al., 2014). Given the complexity of this emerging landscape, operational workflows designed to hierarchically combine conventional and advanced multimodal techniques and systematise their use at the patient's bedside along the course of disease have been recently proposed (Comanducci et al., 2020; Monti & Schnakers, 2022).

This case report represents a practical implementation of such a proposal in an intensive rehabilitation unit (IRU). We describe 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 behavioural assessments. The patient underwent an unprecedented multimodal battery of AIEs 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 during the rehabilitation stay, provided complementary and compelling evidence that the patient was not unconscious but rather unresponsive, due to an akinetic mutism (AM) syndrome. AM is a rare neurological syndrome which may occur when bilateral fronto-subcortical circuits are massively disrupted resulting in a global inability to initiate volitional responses. This exploration, combining state-of-the-art AIEs, confirms that AM 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.

2 | DESCRIPTION OF CLINICAL AND MULTIMODAL PARACLINICAL ASSESSMENTS

2.1 | Phase 1: From ICU to prolonged unresponsiveness in IRU (weeks 1 to 5)

2.1.1 | Clinical history and structural neuroimaging

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

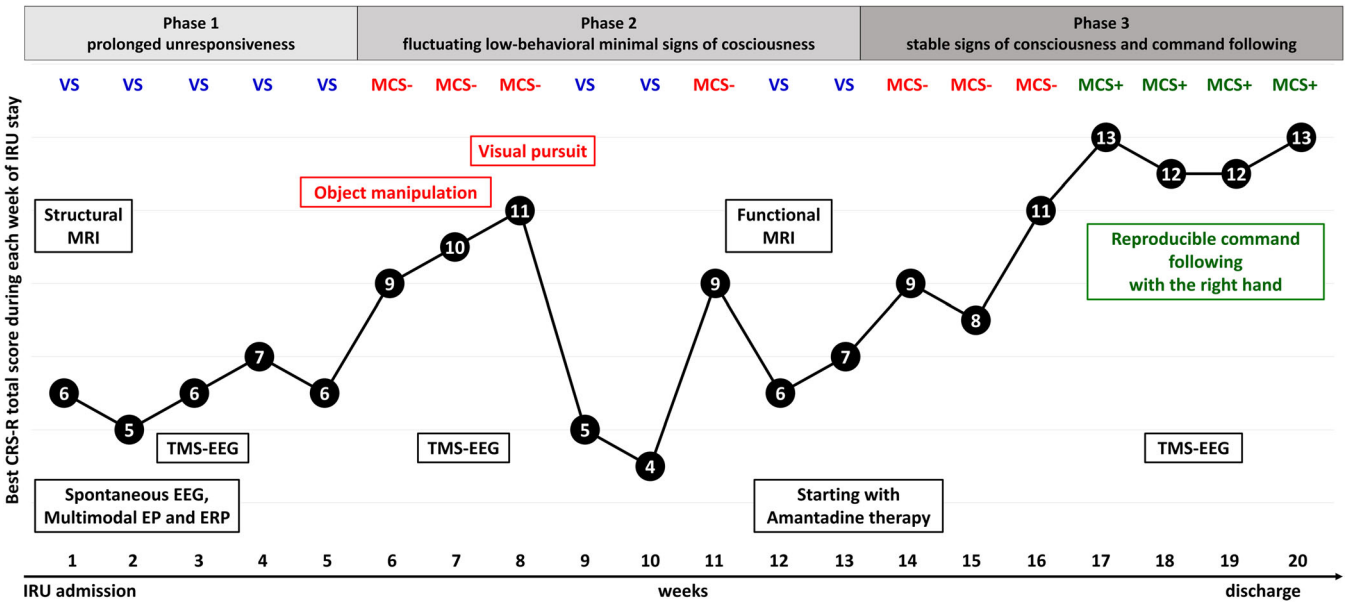

FIGURE 1 Timeline of standardised behavioural evaluations using CRS-R (black dots indicate the best total score out of five evaluations per week) and advanced imaging and electrophysiological techniques during the 20-week IRU stay. The upper bar displays the three main phases of clinical evolution and their corresponding weekly changes in clinical diagnosis: minimally conscious state 'minus' (in red) and 'plus' (in green), as well as the vegetative state (in blue). CRS-R, Coma Recovery Scale-Revised; EEG, electroencephalography; EP, evoked potentials; ERP, event-related potentials; IRU, intensive rehabilitation unit; MCS, minimally conscious state; MRI, magnetic resonance imaging; TMS-EEG, transcranial magnetic stimulation combined with EEG; VS, vegetative state.

medical history) was hospitalised due to seizures associated with an altered state of consciousness. Head computed tomography and angiography revealed a bi-hemispheric subarachnoid haemorrhage and severe brain swelling due to the rupture of an aneurysm of the anterior communicating artery. 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 aneurysm, requiring an additional endovascular treatment. Apart from the GCS, no clinical or paraclinical assessments of consciousness were collected during the patient's ICU stay.

Upon sufficient stabilisation of vital signs, the patient was admitted at our IRU with a diagnosis of a prolonged VS/UWS (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 lower limbs and the left upper limb), grasp and palmo-mental reflexes, a not-extinguishable glabellar reflex, hypomimia (i.e., a reduced degree of facial expression) after painful stimuli and a lack of any consistent command-following, visual fixation or tracking. She was not able to initiate any spontaneous motor behaviour.

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 64 channels head/neck coil. The MRI protocol included a 3D sagittal magnetisation-prepared rapid acquisition with gradient echo as anatomical reference (1 mm^3; 256 × 256;TR/TE: 2300/2.98 ms; TI: 919 ms), a 3D sagittal fluid-attenuated inversion recovery (FLAIR) for lesion detection (0.8 × 0.8 × 1 mm; 320 × 320; TR/TE: 5000/394 ms; TI: 1800 ms) and a diffusion weighted imaging sequence for quantifying the white matter microstructural status (2 mm^3; 104 × 104; including short and long phase-encoding reversed data; TR/TE: 3600/92 ms 5 b0 images, 50 diffusion-encoding directions with b = 1000 s/mm^2 and 50 diffusion directions with b = 2000 s/mm^2).

Neuroradiologist's visual analysis of sMRI sequences revealed extensive bilateral cerebral softening at frontal and parietal median parasagittal locations and a corpus callosum thinning throughout its extent (Figure 2). Due to the aneurysm clip in the anterior communicating artery territory, a partial magnetic distortion in the

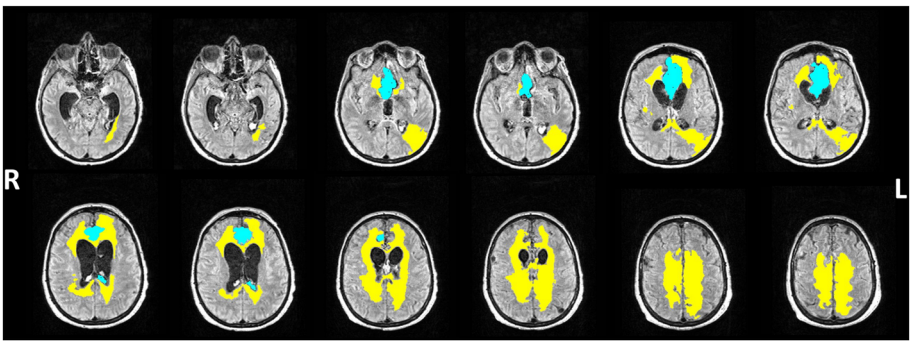

FIGURE 2 Lesion segmentation and characterisation were performed using the 3D-FLAIR MRI sequence, which revealed an almost complete destruction of brain tissue in the territory of the bilateral anterior cerebral arteries. Additionally, significant gliotic–malacic changes were highlighted in yellow, while post-hemorrhagic sequelae were indicated in light blue. R, right and L, left, refer to the hemispheric side. 3D-FLAIR, three-dimensional fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

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 grey and white matter areas were involved by the lesion, the lesion mask was nonlinearly registered to the Montreal Neurological Institute space (resolution $1 \times 1 \times 1$ mm^3) using FMRIB's Software Library (http://www.fmrib.ox.ac.uk/fsl).

2.1.2 | Serial standardised behavioural 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 detect even minimal signs of volitional motor activity such as gaze tracking or reproducible responses to stimuli, a standardised clinical assessment with serial CRS-R was applied weekly, along the IRU stay (at least 3–5 times/week for 20 weeks). The clinical trajectory as well as the best CRS-R total score per week is detailed in Figure 1. During the first 5 weeks of standardised clinical monitoring, the patient was repeatedly diagnosed as VS/UWS since only reflexive responses (such as auditory and visual startle, abnormal posturing and oral reflexive movement) could be detected in the absence of any reproducible behavioural 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). Notably, the patient did not receive any medications, such as benzodiazepines or antipsychotics, that could potentially explain the profound alteration of consciousness.

2.1.3 | Resting EEG shows a severe background disorganisation

During week 2, a comprehensive neurophysiological assessment including visual and spectral analysis of spontaneous EEG (Figure 3) was performed to complement the behavioural evaluation. The visual analysis of clinical standard EEG demonstrated a diffuse slowing of the background activity with high-amplitude frontally dominant slow-waves (>75 μV) without a reproducible reactivity to 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 (Curley et al., 2018; Forgacs et al., 2014). The severity of EEG slowing was confirmed by the quantification of Delta-Alpha Ratio spectral power (Bai et al., 2021; Leon-Carrion et al., 2008; 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).

2.1.4 | Sensory-motor EP and EMG reveal a partial sensory and motor functional disconnection

To characterise the functional status of afferent and efferent pathways, sensory-motor EP and

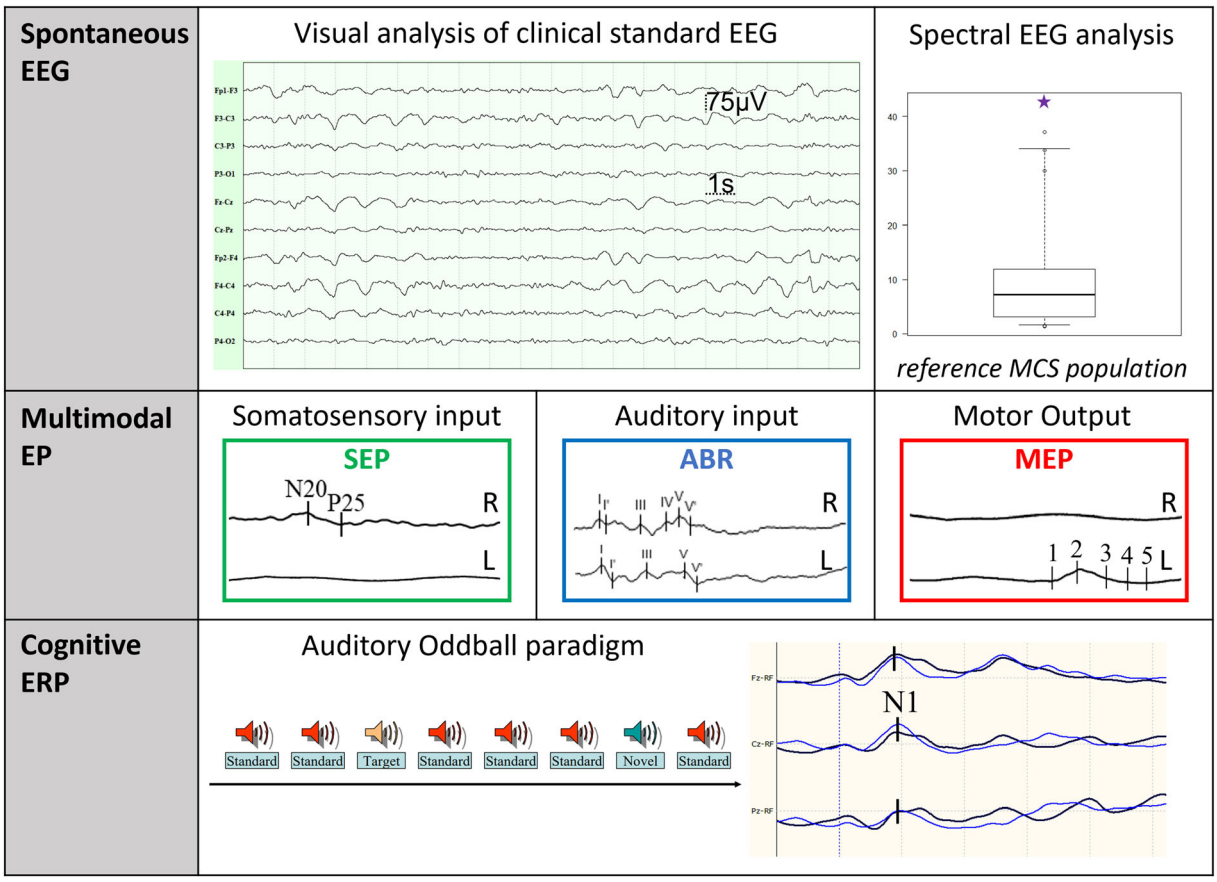

FIGURE 3 A hierarchical workflow of conventional electrophysiological techniques was employed, including spontaneous EEG (in the upper panel) with a clinical standard visual representation of 20 s according to a bipolar montage and spectral EEG analysis (on the right) that included the patient's individual delta-alpha ratio, indicated by a purple star, and a box plot distribution of reference values collected in a sample of MCS patients. A second-level assessment (middle panel) was performed with sensory-motor EP, while a third-level assessment (lower panel) was conducted with cognitive ERP using an auditory oddball protocol. Notably, ABR revealed an increase of the III-V interpeak. Furthermore, no reproducible cortical SEP from the left primary sensory cortex were observed after right median nerve stimulation, and no peripheral MEP were recorded from the intrinsic muscle of the left hand after single-pulse TMS applied to the right motor cortex (middle panel). R, right and L, left, refer to the hemispheric side. ABR, auditory brainstem responses; DAR, delta-alpha ratio; EEG, electroencephalography; EP, evoked potentials; ERP, event-related potentials; MEP, motor evoked potentials; SEP, somatosensory evoked potentials; TMS, transcranial magnetic stimulation.

electromyography (EMG) were applied as a second-level assessment (Figure 3, middle panel). Auditory brainstem responses indicated a mild alteration of transmission along the central pathway at the midbrain level, but 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 severe functional disconnections along the cortico-spinal tracts for both lower limbs and the left upper limb. EMG revealed a diffuse combined peripheral neuropathy and myopathy (compatible with an ICU-acquired weakness) further complicated by a damage of multiple nerves of the left brachial plexus. Finally, a significant lack of habituation of the blink reflex was detected, which is indicative of increased excitability typical of a hypo-dopaminergic state (Formisano et al., 2009).

This comprehensive neurophysiological workflow 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.

2.1.5 | ERP analysis shows preserved P100 but lack of higher-level cognitive processing

To characterise residual sensory-cognitive abilities at a higher level, we recorded ERP by applying a binaural acoustic stimulation with a classical oddball task following the guidelines previously described in Duncan et al. (2009). This third-level evaluation (Figure 3, lower panel) 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 P3 component.

The partial sensory–motor disconnections highlighted by the multimodal EP-EMG examination and the inconclusive ERP results, 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 (Bayne et al., 2020; Rohaut et al., 2017), in the absence of a P3 (Faugeras et al., 2012) as well as in the presence of a severe EEG slowing (Frohlich et al., 2021).

2.1.6 | The complexity of TEP indicates a capacity for consciousness

TEP allow for 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). According to this benchmark calibration, a maximum PCI value across stimulation sites (PCI_{max}) higher than 0.31 indicates a capacity for consciousness, irrespective of behavioural responsiveness.

On week 3, TEP were recorded 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 customised 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 4a). This exam revealed high PCI values for both right (PCI = 0.34, Figure 4b, blue square) and left (PCI = 0.33, Figure 4b, blue circle; Figure 4c″, 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 4c′, blue TEP) that was associated with low complexity (PCI = 0.25) (Figure 4b, 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 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.

2.2 | Phase 2: The emergence of fluctuating signs of consciousness (weeks 6–13)

2.2.1 | Emergence of behavioural 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-behavioural 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 behavioural 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 4b, 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 4b, red diamond).

2.2.2 | fMRI demonstrates covert consciousness despite fluctuations in responsiveness

In the following period (weeks 9, 10, and 11), the patient continued to show significant variations in behavioural

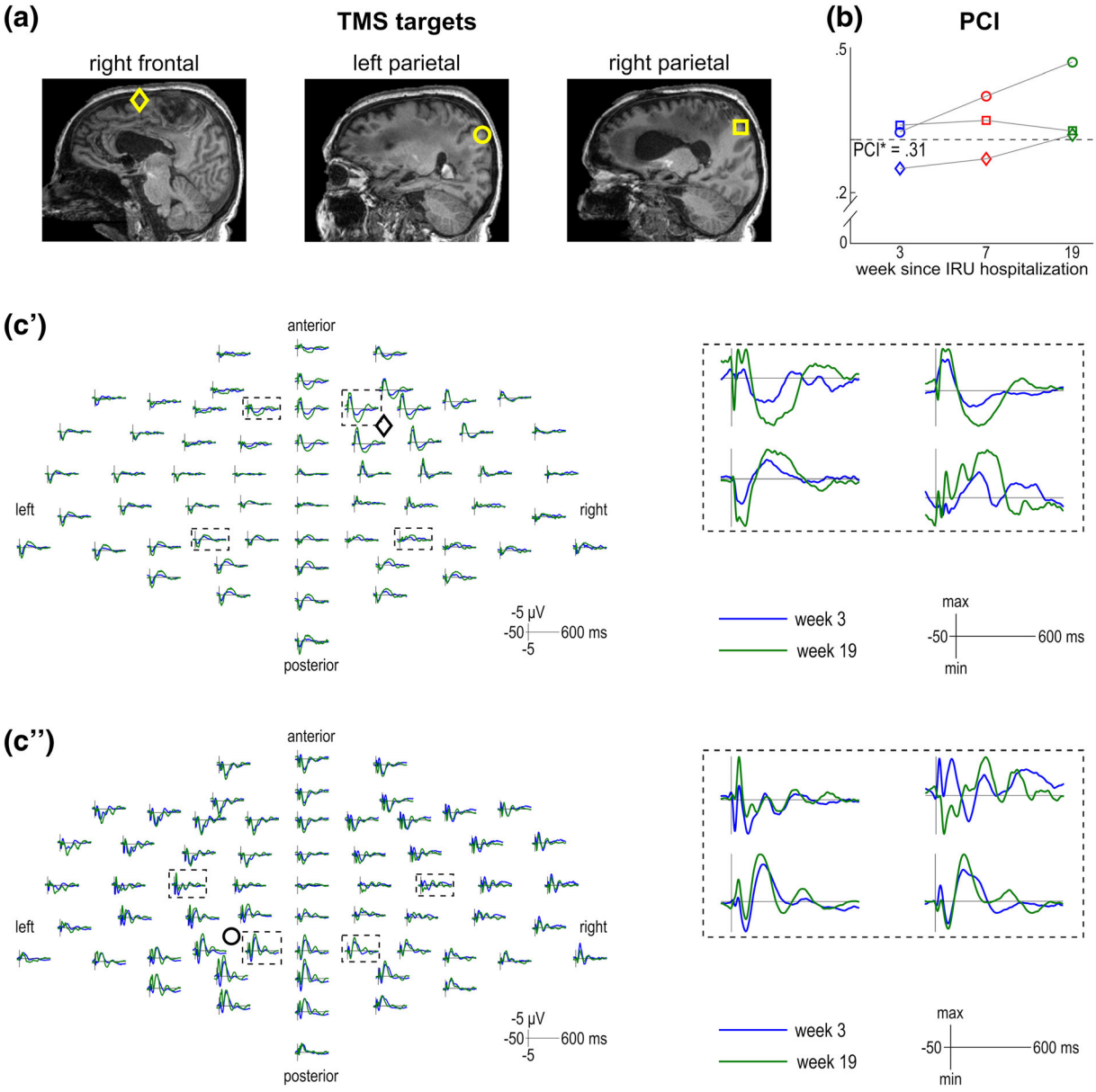

FIGURE 4 (a) Location of three TMS targets on T1-weighted structural MRI of the patient (sagittal view): right frontal (yellow diamond), left parietal (yellow circle) and right parietal (yellow square). (b) Changes in PCI over time (at week 3 (blue), week 7 (red) and week 19 (green) during the IRU stay by stimulating the three cortical targets. The value PCI* = 0.31, which represents the previously validated empirical cutoff for detecting the capacity for consciousness, is indicated by a horizontal dashed line. (c) Average TEP recorded from 62 scalp electrodes at week 3 (blue) and at week 19 (green) of IRU stay by stimulating the right frontal (diamond) (panel c′) and the left parietal (circle) (panel c″) targets. On the right side of panels c' and c″, TEP obtained from a selection of representative EEG channels (for right frontal target, F1, F2, P3, P4; for left parietal target, C3, C4, P1, P2) are shown. EEG, electroencephalography; IRU, intensive rehabilitation unit; MRI, magnetic resonance imaging; PCI, perturbational complexity index; TEP, TMS-evoked potentials; TMS, transcranial magnetic stimulation.

responsiveness (CRS-R total score ranging from 5 to 9) corresponding to fluctuations between a VS/UWS and 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 behavioural 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 (Monti et al., 2010; Owen, 2013; Owen et al., 2006). In particular, the fMRI paradigm (ABAB block design) consisted of a

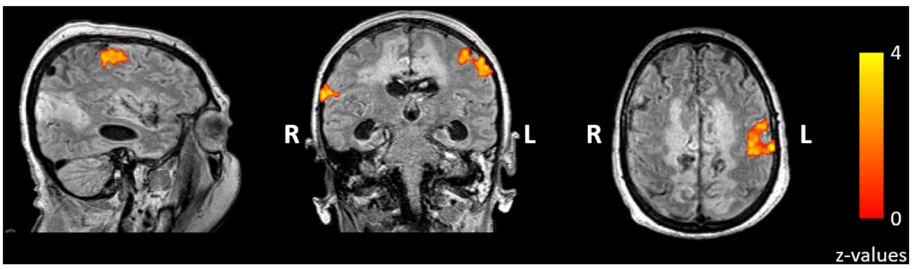

FIGURE 5 fMRI revealed the BOLD activation on the left premotor cortex in response to a simple command-following task ('move your right hand'). BOLD activity maps were superimposed on the individual's structural image, with 'L' indicating left and 'R' indicating right sides. *Z*-scores were used as a measure of effect size, and the statistical threshold level was set at $p < 0.05$. BOLD, blood-oxygen-level-dependent; fMRI, functional magnetic resonance imaging.

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 3 T Siemens Prisma scanner (resolution: $3 \times 3 \times 3$ mm^3; matrix: 80×80; TR/TE: 2000 ms/30 ms). As shown in Figure 5, when comparing right-hand commands versus rest, a consistent blood-oxygen-level-dependent (BOLD) activation of left superior temporal and premotor cortices was revealed.

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

2.3.1 | A pattern of structural disconnectivity 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-analysed at a finer grain to support a diagnosis of unresponsiveness within the AM spectrum. For this purpose, we performed a second-level sMRI analysis utilising the Network Modification Tool (Kuceyeski et al., 2013). Based on a large reference set of tractography data, the tool associates changes in white matter integrity with those expected in grey matter connectivity. This allows for the characterisation of the effects of lesions on cortical–subcortical connectivity and, thus, the assessment of the structural underpinnings of AM. This approach did not require tractography and the disconnected grey matter regions, were visualised through an easy-to-use, flexible toolbox for connectogram generation (Coluzzi et al., 2022). This 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 disconnectivity involving both frontal and anterior basal forebrain was not only consistent with an AM diagnosis but also matched the model of deafferentation proposed with the mesocircuit hypothesis (i.e. a model to explain clinical recovery of consciousness with an emphasis on cortical–subcortical anterior forebrain circuits) (Edlow et al., 2021; Fridman et al., 2014; Schiff, 2010).

2.3.2 | Treatment, recovery of command following and improvement of frontal reactivity

Considering the disconnectivity 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: 50 mg once daily in week 13, 100 mg once daily in week 14, 100 mg twice daily in week 15 and 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-behavioural 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

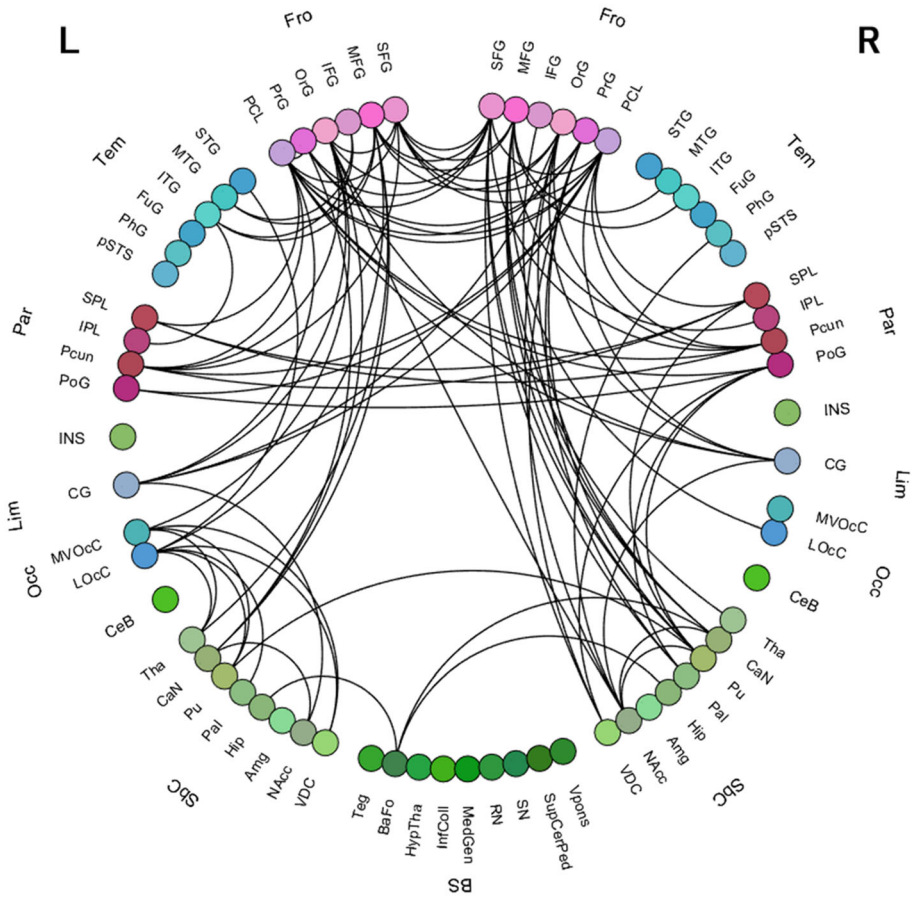

FIGURE 6 Disconnectivity predictions obtained with the Network Modification Tool and shown with a toolbox for connectogram generation. The circular plot illustrates the connectivity matrix related to the streamlines passing through the patient's pattern of lesions. Only disconnections having a value higher than 0.90 are shown (represented by black lines). Notably, the most functionally disconnected grey matter areas were the bilateral frontal cortical areas (represented by pink dots) and the bilateral subcortical nuclei (represented by light green dots), such as the dorsal striatum, ventral striatum and thalamus, particularly on the right side. R, right and L, left, refer to the hemispheric side. Fro:Frontal (IFG, inferior frontal gyrus; MFG, middle frontal gyrus; OrG, orbital gyrus; PCL, paracentral lobule; PrG, precentral gyrus; SFG, superior frontal gyrus); Tem:Temporal (FuG, fusiform gyrus; ITG, inferior temporal gyrus; MTG, middle temporal gyrus; PhG, parahippocampal gyrus; pSTS, posterior superior temporal sulcus; STG, superior temporal gyrus); Par:Parietal (IPL, inferior parietal lobule; Pcun, Precuneus; PoG, postcentral gyrus; SPL, superior parietal lobule); INS, insular gyrus; Lim:limbic (CG, cingulate gyrus); Occ:Occipital (LOcC, lateral occipital cortex; MVOcC, MedioVentral occipital cortex); CeB, cerebellum-cortex; SbC:Subcortical structures (Amg, amygdala; CaN, caudate; hip, hippocampus; NAcc, Accumbens-area; pal, pallidum; Pu, putamen; Tha, thalamus-proper; VDC, ventral diencephalon); BS:Brainstem (BaFo, basal forebrain; HypTha, hypothalamus; InfColl, inferior colliculi; MedGen, medial geniculate body; RN, red nucleus; SN, substantia nigra; SupCerPed, superior cerebellar peduncle; Teg, tegmentum; Vpons, ventral pons).

brain complexity not only when targeting the left parietal site (PCI from 0.40 to 0.47, Figure 4b, green circle; Figure 4c″, 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 4b, green diamond; Figure 4c′, 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.

3 | 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 behaviour. The trajectory we describe here clearly highlights the problem of discriminating between unconsciousness and unresponsiveness and shows how a comprehensive hierarchical assessment with AIEs can help minimise diagnostic error. At the same time, the multimodal exploration performed here prompts an interesting

pathophysiological reflection on the relationships between DoC, AM and extreme parkinsonism.

3.1 | Consciousness beyond unresponsiveness

After admission at the IRU for a multifocal brain injury of vascular origin, the patient remained unresponsive for 5 weeks during which repeated CRS-R examinations resulted in a VS/UWS diagnosis. According to recent recommendations (Comanducci et al., 2020; Giacino et al., 2018; Kondziella et al., 2020), the patient underwent a series of eletrophysiological exams, including 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 (Schiff, 2015) or covert cortical processing (Edlow et al., 2021). However, this possibility was apparently inconsistent with the finding of a severely disorganised 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 an active fMRI paradigm. As described in a recent expert review (Comanducci et al., 2020), the rationale for such a hierarchical workflow 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, that is, complexity values that are only found in conscious subjects (Casali et al., 2013; Casarotto et al., 2016; Sarasso et al., 2015; Sinitsyn et al., 2020). In the absence of behavioural 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 anaesthesia 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 and 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.

3.2 | AM, 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, as in this case) 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; Shetty et al., 2009; Wijdicks & Cranford, 2005), there are only few studies specifically aimed at disentangling the impairment of responsiveness from 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 AIEs for DoC diagnosis has not been systematically conducted so far.

Due to the low incidence of AM, the majority of studies have been single-case reports (Nagaratnam et al., 2004; Shetty et al., 2009; Ure et al., 1998). AIEs, such as TMS-EEG for longitudinally tracking capacity for consciousness or fMRI for identifying residual volitional abilities, have not been employed prior to this case, partly due to the specialised expertise and settings required by these techniques.

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 (Comanducci et al., 2022; Formisano et al., 2011; Formisano & Zasler, 2014). 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) (Arnts et al., 2020; Mega & Cohenour, 1997).

In this case, despite the behavioural unresponsiveness, clinical extrapyramidal symptoms such as the diffuse rigidity, not-extinguishable glabellar reflex 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 disconnectivity 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 reactivation of fronto-thalamic and basal ganglia outflow (Formisano & Zasler, 2014; Kraus & Maki, 1997; Thibaut et al., 2019).

AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. Patients' selection and neurophysiological data collection were performed by A. C., C. D., S. C. and M. R. MRI data collection, analyses and interpretation: C. M., A. P., F. B. and V. B. The first draft of the manuscript was written by A. C. and M. M. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

Marcello Massimini is co-founder and shareholder, whereas Silvia Casarotto is advisor and shareholder of Intrinsic Powers, a spin-off of the University of Milan. The other authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

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

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