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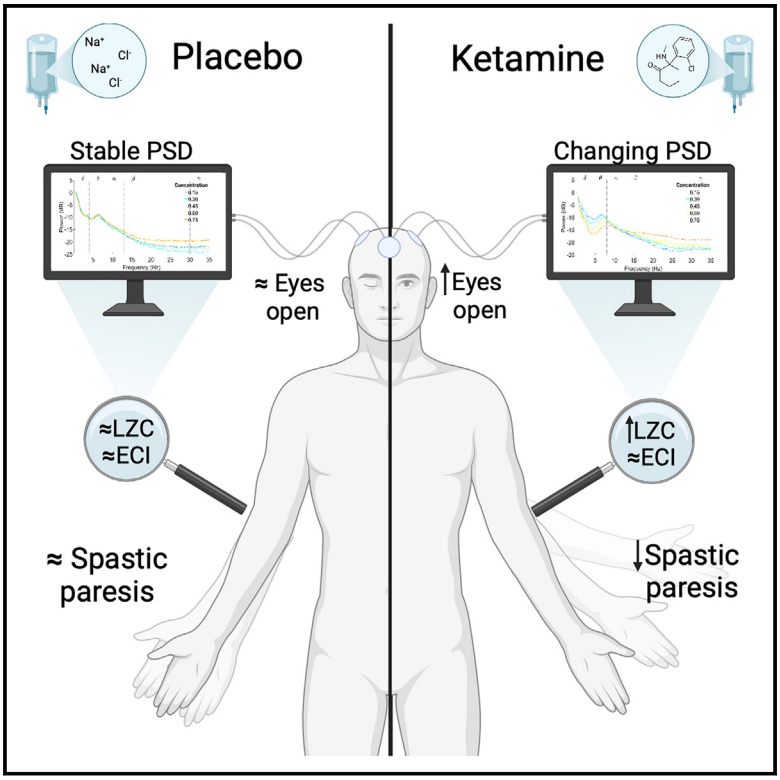
A pilot human study using ketamine to treat disorders of consciousness

Graphical abstract



Highlights

- Subanesthetic IV ketamine increases brain complexity in post-comatose patients
- Patients showed reduced spastic paresis and greater arousal with ketamine
- No new conscious behaviors were observed, with no change in overt consciousness
- No behavioral or physiological adverse effects were seen

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In brief

Drugs; Pharmacology; Biological sciences; Neuroscience.

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A pilot human study using ketamine to treat disorders of consciousness

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SUMMARY

Post-comatose disorders of consciousness (DoC) represent persistent neurological conditions with limited therapeutic options and a poor prognosis. Recent works advocate for exploring the effects of psychedelics to enhance brain complexity in DoC and ameliorate their consciousness. We investigated sub-anesthetic concentration of the atypical psychedelic ketamine for treating post-comatose prolonged DoC through a double-blind, placebo-controlled, cross-over trial involving three adult patients. Incremental concentrations of intravenous ketamine and saline were administered, alongside continuous electroencephalogram (EEG) recording and assessments of conscious behaviors and spastic paresis. Brain complexity, measured by Lempel-Ziv complexity (LZC) and explainable consciousness indicator (ECI), revealed increased LZC during ketamine infusion but no change in ECI. Patients exhibited reduced spastic paresis and increased arousal as time spent with eyes open but no positive change in diagnosis. No adverse effects were noted. This study contributes to understanding the relationship between consciousness and brain complexity and suggests a potential therapeutic role for ketamine in DoC.

INTRODUCTION

Post-comatose disorder of consciousness (DoC) is a devastating neurological condition that can affect people with severe brain injury. DoC includes the unresponsive wakefulness syndrome/vegetative state (UWS/VS)[1] (arousal but only reflexive movements and no consciousness), and the minimally conscious state (MCS),[2] with a distinction between MCS+ if linguistic abilities are (partially) preserved and MCS− if they are not.[3] DoC constitutes a significant public health and socio-economic issue, with far-reaching consequences for patients but also for their relatives. Besides consequences of having no or little awareness of themselves and their environment, prolonged DoC patients are frequently affected by severe comorbidities that decrease their quality of life, like spastic paresis,[4] which afflicts almost 90% of patients.[5] These patients often have unfavorable prognoses with limited treatment options.[6]

Brain complexity, the degree of integration and differentiation of brain activity,[7] is thought to be fundamentally linked to consciousness.[8] Brain complexity can be quantified via spontaneous or evoked neurophysiological activity (i.e., electroencephalogram [EEG]). These two greatly differ, and we refer to the relevant literature for understanding what they are and how to interpret them.[8,9] Spontaneous brain complexity can be measured with indexes such as the Lempel-Ziv complexity (LZC)[8] or the newly described explainable consciousness indicator (ECI).[10] Brain complexity is considered to be associated with brain oscillations like the alpha rhythm.[11] DoC patients share a lower-than-normal brain complexity, notwithstanding the heterogeneity of brain damages. Psychedelics, which are known to increase brain complexity in healthy participants,[11–13] could in theory increase it in DoC patients as well.[9,14] We present the first double-blind, placebo-controlled, cross-over feasibility study experiment using sub-anesthetic ketamine (EudraCT: 2021-002321-23), an atypical psychedelic, in patients with

prolonged DoC (more than 28 days since injury), aiming to promote recovery of consciousness and increased brain complexity. Firstly, we describe the challenges and the feasibility to implement the protocol and characterize the necessary infrastructural and intellectual means. Secondly, we report the behavioral and neurophysiological results of the experiment.

RESULTS

Feasibility

Running the experiment presented several challenges due to the nature of the population, the drug, and the protocol implemented. The first infrastructural necessity was a hospital or pharmacy authorized to store the substance. Ketamine, being a narcotic commonly used in clinical settings, requires a specialized storage unit with regulatory permits. Additionally, a room to conduct the experiment was necessary, with sufficient space for a bed for the patient, the target-controlled infusion (TCI) and EEG machines, and oxygen and monitoring systems. We used the patient's room in the rehabilitation center to ensure a familiar environment during the experience.

The personnel required for the experiment included someone to schedule the sessions, a pharmacist to prepare the syringe for substance administration, and an anesthesiologist familiar with DoC, who could ensure there were no contraindications for the patient's participation and monitor vital parameters during the infusion. A researcher knowledgeable of (high-density) EEG acquisition and analysis, who could possibly implement a pipeline that is (partially) present in the field for index of interest that has been used by different groups, was necessary. Finally, there is the need for a member who is trained in behavioral assessments for DoC. Optionally, other people involved in supplementary data collection or analysis that is foreseen must be included; these data might include electrocardiogram (ECG) or spastic paresis.

Working with psychedelics presents the unprecedented challenge of needing personnel accustomed to interacting with people experiencing modified states of consciousness, which is not typically part of standard healthcare training. This will likely change over time, given the increasing attention and discussion surrounding the regulation of psychedelic-assisted therapy.[15] In our study, we had the opportunity to consult with experts knowledgeable in this area, who provided guidance and assistance. Although the anesthesiologist may have had experience with ketamine-induced agitation, a psychedelic sitter can be beneficial for substances other than ketamine. In our experiment, there was not clear moment where such a figure had to intervene. It is possible that some patients may have benefited from some of the interactions (e.g., holding hands during experiment). Nevertheless, interaction between the sitter and the patient was minimized to avoid introducing noise into the EEG signal. Future experiments implementing other measures (e.g., ECG), which might be less susceptible to external perturbations, could allow for more varied interactions between the sitter and the patient. In conclusion, to increase the chances of having an optimal setting and reduce likelihood of bad trips, we still recommend having the psychedelic sitter present.

Patients were prescreened by the medical doctor on site, and the medical history and medication were checked by both the researcher directly involved in the project and the anesthesiologist. We did not exclude any patient after they were enrolled. Nevertheless, we moved experimental session three times due to technical reasons. Additionally, given the nature of the protocol (max 7 days between the two sessions), and the relative high number of people needed for each session, it has been proven practically complicated to combine everyone's agenda to perform experiments. Future studies might be more relaxed about timing between the two sessions to have more room for coordination of the team, especially if dealing with prolonged DoC. In the prescreening process, eight patients with DoC were admitted in the rehabilitation center we collaborated with. Of those, three did not meet the inclusion criteria (we initially had an age limit of 65 years, which then we lifted). Of the remaining five who met the inclusion criteria (around 63%), two stayed in the rehabilitation center for less than a month, making the procedure pragmatically not implementable due to time limits of the protocol. We included the remaining three patients (around 38%), and their families agreed to participate in the experiment. Note, however, that these figures about enrollment might not be representative given the fact that the rehabilitation center has a specialized unit for prolonged DoC patients with a long-lasting collaboration with our research center in experimenting new treatment options. In other words, other centers willing to launch similar (or larger) investigation with either acute patients, or centers with a shorter record of clinical trials, might have higher attrition rate. Insurance policies and healthcare regulations across different parts of the world may also affect the representativeness of patients' enrollment. While there are no costs for the family for participating in our study, other countries might have a heavier economic burden that might either make impossible or strongly bias which families (and thus patients) could participate in studies lasting several days. In fact, while the experimental protocol is relatively short, we preferred to have the patient accustomed to the setting where the experiment would happen.[16] This implies occupying a room and a bed before enrollment itself.

Patients

We included three patients with different diagnosis and etiologies. Case 1 was a 32-year-old male who had a car accident 13 years before the experiment. This patient was readmitted at the rehabilitation center for stabilization of a secondary epilepsy, with no active epilepsy at the time of experiment. He was diagnosed UWS but was considered MCS+ in two previous hospitalizations (10 and 8 years before enrollment). Case 2 was a 50-year-old male who had a subarachnoid hemorrhage secondary to the rupture of an aneurysm of the right middle cerebral artery. At enrollment 7 months post-injury, he was diagnosed MCS−, showing automatic motor responses (e.g., scratching his nose). Case 3 was a 62-year-old male who had a carbon monoxide intoxication. At the time of the examination 1 year post-injury, he was occasionally able to functionally communicate with oral "Yes"/"No" responses but never on two consecutive evaluations. The best diagnosis he was given during the behavioral assessments of this experiment was MCS+.

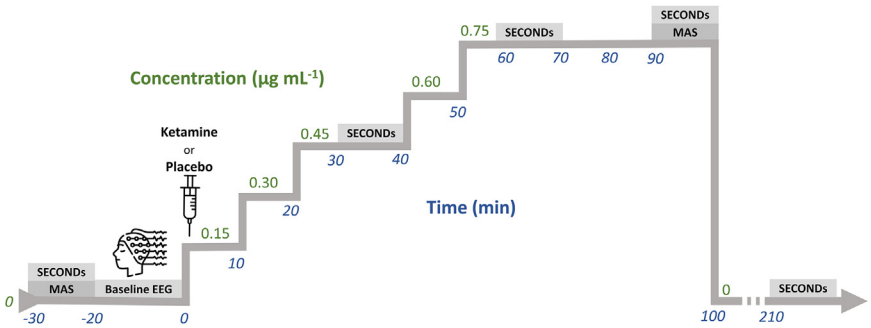

Figure 1. Illustration of the protocol: visual representation of one session of the trial.
We assessed behavior via the SECONDs and spastic paresis with the MAS. During the whole experiment, we recorded the brain activity using high-density electroencephalography. Heart rate, peripheral saturation of oxygen, and blood pressure were recorded every 5 min; video recording was performed throughout the experiment. The second session took place within a week

Each patient received two single sessions (racemic ketamine [Ketalar©, Pfizer] and saline solution [NaCl]) for 90 min with a target-controlled infusion in a random order (average 6 days apart, range: [5 7]). Each patient was evaluated twice behaviorally with the Simplified Evaluation of CONsciousness Disorders (SECONDs)[17] by the same experimenter before the experiment (pre-enrollment SECONDs). At the beginning of each session, we performed a baseline assessment of behavior (SECONDs) and a 20-min eyes-open baseline resting-state high-density EEG. We then increased the concentration by steps of 0.15 µg mL^{-1} every 10 min until a maximum of 0.75 µg mL^{-1} was reached. Simultaneously, high-density EEG was recorded continuously. Behavior was assessed with the SECONDs every 30 min. Another SECONDs was performed 2 h after the end of the infusion to control for prolonged effects. We evaluated spastic paresis with the Modified Ashworth Scale (MAS),[18] at the beginning and end of the session (done only for two patients, after an unexpected decrease in the first one). Heart rate, peripheral saturation in oxygen (SpO_2), and blood pressure were displayed continuously throughout the experiment and noted every 5 min. See Figure 1 for a representation of the experimental protocol and the STAR Methods section for more details.

No positive change in SECONDs, lower spastic paresis, and higher arousal with ketamine

The SECONDs provides a total score from 0 to 8 that gives a clinical diagnosis for the patient,[17] through evaluating the presence of the most representative MCS behaviors. Additionally, SECOND accounts for the level of arousal (i.e., time with eyes open) with four categorical levels (“0%–25%”; “25%–50%”; “50%–75%”; “75%–100%”). Pre-enrollment SECONDs was used to control if a given behavior observed during the experiment had been displayed before. Behavioral commands were kept the same throughout the two sessions (e.g., “Move your legs”).

At the group level, behavioral repertoire as assessed by the SECONDs did not change following ketamine administration. Qualitatively, ketamine decreased the behavioral scoring (see Figure 2A) in both conscious patients (MCS− and MCS+). Nevertheless, the UWS patient replied once to a command (“Move your leg”) at the $SECONDs_{60'}$ (ketamine at 0.75 µg mL^{-1}). Patients seemed to spend more time with eyes open as for our observation during the ketamine session. However, only the UWS patient showed a clear increase of time spent with eyes open with the SECONDs, whereas MCS+ demonstrated a ceiling effect (Figure 2B).

We report individual values for the MAS (bilateral assessment in elbow, wrist, knee, and ankle) pre- and post-sessions (Figure 2; Table S1 for the full report). In the MAS, lower score equals lower spastic paresis. The UWS patient presented an amelioration even during placebo, whereas there was a decrease in the MCS+ patient after ketamine (see Figure 2C). We observed a decrease of spastic paresis with the MCS− patient that was not measured via the MAS.

For a visual representation of the values of the physiological data for the three patients from the onset of the drug until 90 min after the experiment, see Figure S1. We did not report any adverse effect like vomiting, agitation, or skin rash.

Change in power spectra, higher LZC, but no change in ECI with ketamine

EEG recordings were performed with a 128-water-based channels cap (BrainVision GmbH, Germany). EEG was analyzed for the data before infusion (baseline) and for the 90 min during infusion (experiment). EEG power was computer per each epoch with Fourier transforms. Whole-brain LZC[19] has a value between 0 and 1 and was calculated for baseline and for each concentration. ECI provides a value between 0 and 1 for awareness and arousal, with a threshold of 0.5 (values higher than 0.5 are considered as “high,” otherwise they are considered as “low”).[10]

Power spectra change following ketamine infusion for the three patients, suggesting a change in the aperiodic component, that appeared to be flatter with increasing dose of ketamine. Additionally, periodic components seem to be changed, specifically with a change in the theta band that seems to either decrease or have a shift in the peak toward faster frequencies. For a display of the spectral density, see Figures 3 and consult the Supplementary Material to visualize the spectrogram (Figure S2).

At the group level, whole-brain LZC increased during the ketamine compared to the placebo session. At the individual level, we observed no clear dose-dependent effect on brain complexity for the UWS and MCS− patient, but a linear increase during ketamine in the MCS+ patient (Figure 4A). ECI arousal did not differ between the two sessions at the group level, and it was high for all concentrations in both sessions for all patients. There was no clear increase in the UWS patient, whereas it increased in

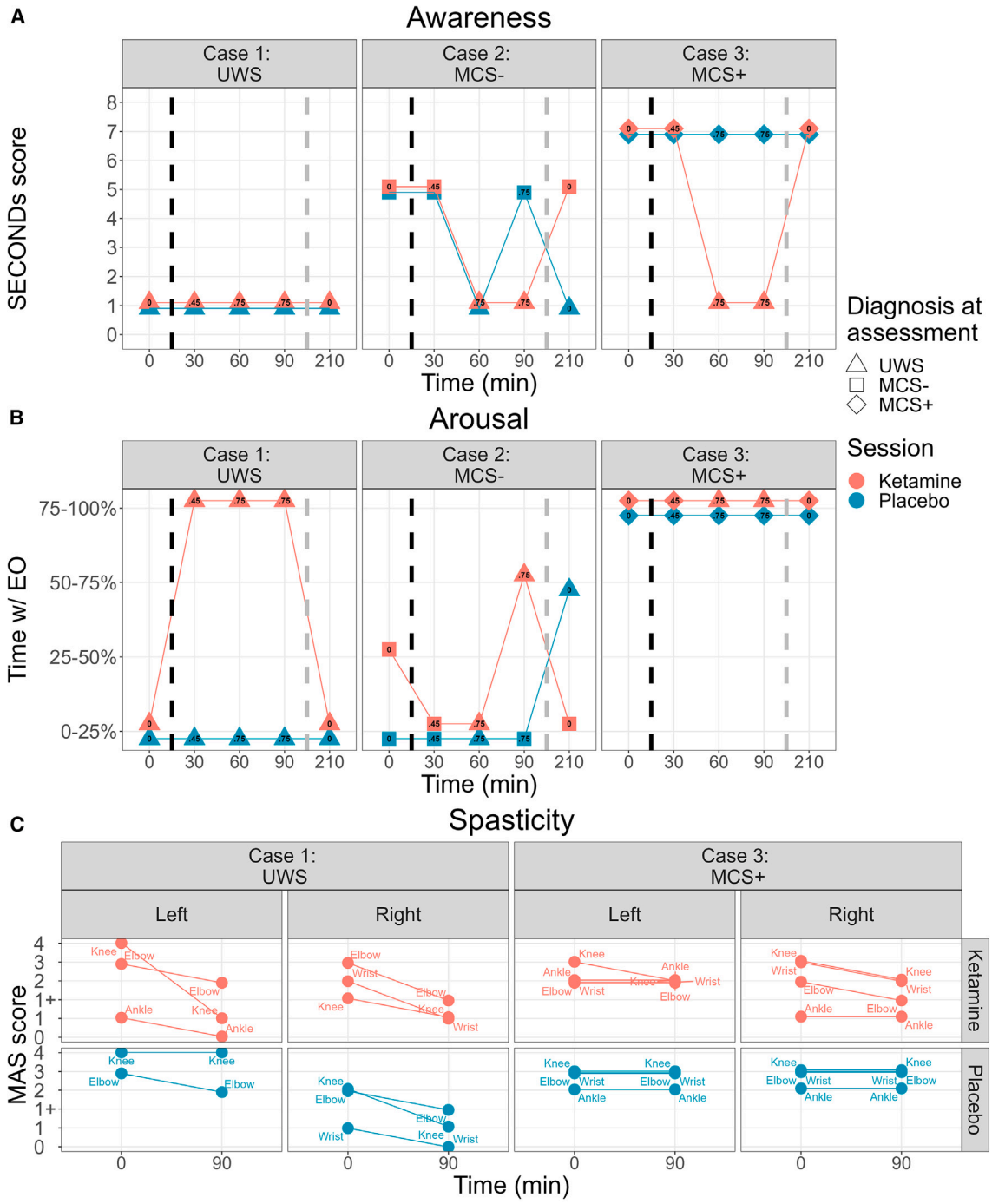

Figure 2. Behavioral results

(A) SECONDs scores following infusion of ketamine and placebo. UWS scoring is represented as triangles, MCS− as squares, and MCS+ as diamonds. For representational purposes, ketamine scores were increased by 0.1, and placebo ones were decreased by 0.1. The given concentration is displayed inside every point.

(B) Time spent with eyes open as considered in the SECONDs. The given concentration is displayed inside every point.

(C) MAS scores, divided by different joints, before and after infusion. For representational purposes only, a jitter was added to avoid overlaps. Note that the body parts that were considered not spastic (MAS = 0) at both baseline and at 90 min, within each assessment, are not shown. When the MAS was done at 90 min, the given concentration was 0.75 $\mu g\ mL^{-1}$. Baseline is here represented as "0". The vertical dashed black line represents the discontinuity between the recording before (Baseline) and after the infusion, whereas the gray one represents the discontinuity between the end of the infusion (90 min) and the follow-up assessment (+2 h from end of infusion).

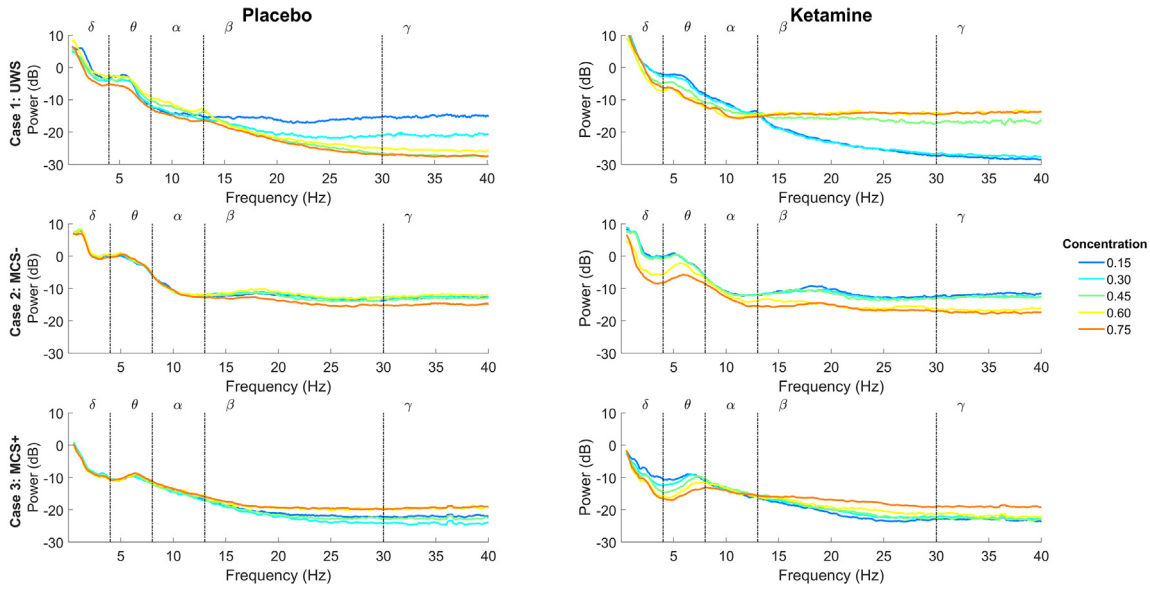

Figure 3. Power spectra: representation of the power spectral density from lowest (blue) to highest concentration (red) for the placebo and ketamine sessions for the three patients

the MCS− patient and ceiled for the MCS+ patient during ketamine compared to placebo (Figure 4B). At the group level, ECI awareness did not seem to differ between the two sessions. The UWS patient showed low awareness during the ketamine session but a high awareness at some concentrations during placebo (0.30, 0.45, and 0.75) (Figure 4C). It was high for all concentrations in both sessions for the MCS+ and the MCS− patients. Numeric values of the ECI and exploratory analysis of

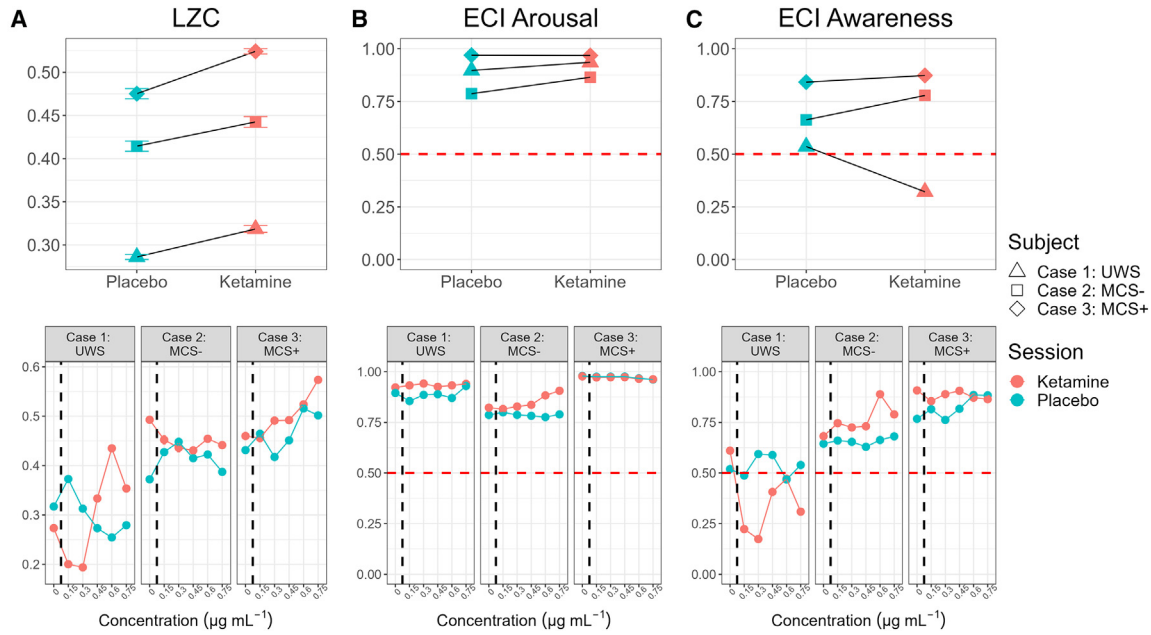

Figure 4. EEG complexity

(A) Top: distribution of brain complexity measured via whole-brain LZC shown for placebo and ketamine for each patient. Standard errors are calculated over electrodes. Bottom: distribution of the LZC as a function of the concentration.

(B) Top: representation of ECI arousal per patient across sessions. Bottom: ECI arousal as a function of concentration.

(C) Top: representation of ECI awareness for each patient. Bottom: ECI awareness as a function of concentration. The vertical dashed black line represents the discontinuity in the x axis between the recording before (baseline) and after the infusion. The horizontal dashed red line represents the threshold between high (>0.50) and low values (<0.50).

alpha centrality and correlation between LZC and ECI are in supplementary information (Methods S1, Table S2, Figures S3, and S4).

DISCUSSION

This feasibility study on the use of atypical psychedelics suggests that ketamine has a potential favorable effect on arousal (as indexed by time spent with eyes open), spastic paresis, and brain complexity in patients with prolonged DoC, with no adverse effects.

We observed sustained eye opening during the ketamine session as all three patients kept their eyes open more easily and for a longer time. We used as a measure of arousal, the estimated time with eyes opening per SECONDs assessment. First, this measurement is qualitative in nature, as it is based on the assessor-perceived time during assessment. Second, in a patient who keeps his eyes open more than three-fourths of the time, and in another all the time, both assessments would be considered in the same category "75%–100%." This implies that changes of time with eyes open, if not dramatic, might be overlooked. Third, the arousal score is only reported for the time during the assessment, thus missing the majority of the time of the experiment. Altogether, these points show limits of reporting a phenomenon with qualitative behavioral measures, which suggests the importance of having quantitative measures of arousal either behavioral (e.g., eye blinks) or neurophysiological (e.g., ECI arousal) for future experiments. Additionally, we did not observe any significant amelioration of overt consciousness during ketamine. The UWS patient responded to command once out of three trials, but this was not sufficient to be scored as "consistent command-following."[14] This behavior was observed in two previous hospitalizations but not in the pre-enrollment assessments. Both MCS patients were unresponsive during assessments at $SECONDs_{60'}$ and $SECONDs_{90'}$. Considering the known effects of ketamine,[20] we might have induced a state of disconnected consciousness[21,22] in which patients were conscious but unable to respond to external stimuli. We consider it crucial to extend future investigations with psychedelics in patients with DoC by including spontaneous behaviors (e.g., eyes blinking[23]) to, in principle, allow to infer the presence of consciousness even in cases of unresponsiveness. Even if the given concentration was sub-anesthetic for healthy participants, it might had been anesthetic-like for the patients. Given the behavioral change during the ketamine session (i.e., unresponsiveness), the MCS+ patient (occasionally able to communicate with oral "Yes"/"No") was asked if he experienced or remembered anything of what just happened. While he replied "no," we cannot be sure that even if he had, he would have been able to report it.

We observed a serendipitous objective reduction in spastic paresis in the two patients for whom MAS was tested and a subjective reduction in the MCS− patient. This is of great interest, as spasticity in DoC can conceal overt behaviors due to limited mobility and pain caused by movement.[24,25] Whether the effects are directly due to muscle relaxation or mediated by possible analgesic effects of ketamine during MAS manipulation, it is an important unanswered question that should be further investigated. The decrease of spasticity might be mediated at the level of the spinal cord or peripheral nerves and muscles. Differentiating between these possibilities here is impossible as our study design does not address this question, but it might be replied in a larger cohort where a stratification based on etiology and damage distribution at the brain, spinal cord, and muscle levels is possible. It is important to note that prolonged DoC may also be associated with tendon retraction and muscle shortening, which can obscure potential effects on muscle spasticity and complicate the scenario. These are worsened by longer time from injury and are dependent as well on the rehabilitation history of the patient. We observed a marked relaxation of the whole body in the three patients without any physical stimulation. Spontaneous range of motion increased, as exemplified by the MCS− patient who could reach the top of his head only at the end of the ketamine session (right after TCI was set to 0). Further behavioral and electrophysiological assessments (using the Nociception Coma Scale-Revised[26] and the Hmax/Mmax ratio,[27] respectively) should be conducted to better understand the underlying mechanisms of this interesting phenomenon.

Neurophysiologically, we observed a change in the power spectrum, which affected both periodic and aperiodic components. There is a recent interest in determining how the two contribute to characterize conscious states. If traditionally there has been a focus with specific bands (i.e., alpha),[28] now there are larger investigations looking at the aperiodic components.[29–31] The UWS patient (Case 1) presented a strong variability in the power spectrum during the placebo session, as observable in Figure 3. Although it is difficult to address the reason of such changes that particularly affect the lower concentrations of ketamine, future investigation should control for these variations. DoC patients fluctuate heavily,[32] and it is possible we captured it during our recording. Long recordings, even if challenging, still allow unique observations that are time- and concentration-dependent, as the marked change of the theta peaks with increasing concentration. Beside changes in power spectra, we observed as well an increase of whole-brain LZC. For the MCS+ patient, it resembled the effects observed in healthy participants.[11–13] Intriguingly, we did not observe a linear increase in the MCS− and the UWS patients. It is important to highlight that changes in (a)periodic components of the power spectrum have a direct effect on the values of LZC.[33] Variations of the power spectrum in spontaneous EEG signal are therefore not independent from the complexity of the brain.[30,34] Regarding ECI, we did not reproduce the low values of arousal already observed in healthy participants receiving ketamine.[10] This may be due to performing an arousal protocol when patients closed their eyes or the heterogeneity of given concentrations in the studies. Interestingly, the UWS patient presented high awareness in the placebo session but low in ketamine. Why ketamine might decrease the level of awareness measured by ECI is an interesting future research question in unresponsive patients, potentially extending the dichotomic differentiation (arousal vs. awareness) to a multidimensional paradigm.

Even if the literature suggests that consciousness and brain complexity are deeply intertwined,[8,35–37] we have observed heightened whole-brain complexity with depreciation of overconsciousness. Although this does not directly invalidate the assumption, a scenario with richer behavioral repertoire and no change in complexity would have done so.

In this work, we explored the use of intravenous ketamine sold under the form of Ketalar© (Pfizer). Nevertheless, future investigations should explore whether there are differences between ketamine, esketamine, and arketamine that have different pharmacological profiles.[38] Finally, those might have a preferential administration way that is optimal for behavior, spasticity, or neurophysiology.

Psychedelics are currently revolutionizing psychiatry. Our work explores one potential role for psychedelics in the vast realm of neurology and paves the way for future investigations. This feasibility study suggests that ketamine infusion is safe and induces promising therapeutic effects in patients with DoC. This is an initial effort to define the role of (a)typical psychedelics for DoC and contributes to the rich discussion based on the hypothesis that consciousness and brain complexity are fundamentally linked.

Limitations of the study

Although there are merits to this work, we want to highlight some limits as well. First, we asked the patients to keep their eyes open during the experiment, to avoid falling asleep in the placebo session. This is a difference with most of the current experiments in the psychedelic domain. One might ask how much our effect would change if we allowed eyes closed instead. Another difference is that our protocol is "1 week long," whereas other studies have longer period between sessions.[39] We consider having this short protocol more suited for carrying out this study given the rehabilitation setting. Second, we chose to use the SECONDs as behavioral tool, even if it is a rather new validated scale.[17] The rationale stems from the quickness of administration, as compared to the CRS-R, which made it more suitable to multiple assessments in a short period. In contrast with other tools, such as the CRS-R FAST,[40] the SECONDs has been validated in French, which is the language we spoke with the patients. Validation in other languages is ongoing (at the moment, only the mandarin version has been published).[41] Third, given the heterogeneous level of brain damage, it is possible that the optimal sub-anesthetic concentration that would have matched the previous one[42] in healthy participants was lower than 0.75 $\mu g\ mL^{-1}$. Anesthesia-like drug effect has already been linked to the amount of gray matter (e.g., slow-wave saturation with propofol).[43] Something similar could happen with ketamine. Nevertheless, even if we assumed that the optimal concentration was lower than the maximum given, we should have reached it twice: one time while increasing the concentration and another after stopping the infusion, when blood drug concentration would go to zero. We are not able to rule out however the opposite scenario, which is the concentration might have been too low: we might have given enough ketamine to observe an increased complexity and arousal but not sufficient to translate in a behaviorally detectable change. Linked to the previous point is that we might have induced disconnected consciousness and limits of the behavioral measures used. Previous investigations in different settings have supported the idea of region-specific markers that differentiate disconnectedness from unconsciousness.[22] We have here looked for the whole-brain LZC, as we did not have *a priori* region-specific hypothesis. A forth limitation is that the UWS patient was reintroduced to the rehabilitation facility due to a seizure episode. As said, there was no active epileptic activity at the time of the experiment, in which case other treatments (e.g., zolpidem) might have been more efficacious (see Gervais et al.[44] for a discussion of hypercritical states in DoC and hypothetical treatments). Fifth, we have here included only three male participants. While this happened by chance in the recruitment process, it limits the generality of the results, given the renowned sex difference of drug effects. The previous study we based our parameters on had a majority of males, so we are optimistic that the concentrations given are in line with the effects described in the previous paper.[42] Nevertheless, future investigation should try to have a gender balance. Finally, ECI training dataset is characterized by wakefulness, anesthesia, and DoC. Although it has an appropriate variety of different global conscious states, future ones might include pharmacological intervention (e.g., psychedelics) to better characterize this specific dataset.

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Olivia Gosseries (ogosseries@uliege.be).

Materials availability

This study did not generate new unique reagents or new genetic lines. All the information regarding the data and the code are available in section below.

Data and code availability

- Data: data are available upon request.
- Code: code is available on GitHub on https://github.com/pcardone95/ComplEXIT_DoC.
- Additional information: any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

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AUTHOR CONTRIBUTIONS

Conception and design of the study, P.C., C.M., and O.G.. Data collection, P.C., A.B., V.B., N.L., C.S., A.D., P.E., S.V.G., J.M., A.T., C.M., and O.G.

Data analysis, P.C., M.L., and A.P. Drafting paper, P.C., C.M., and O.G. Critical revision, all the authors.

DECLARATION OF INTERESTS

V.B. has had financial relationships with Orion Pharma, Metronic, Elsevier, Edwards Medical.

DECLARATION OF GENERATIVE AI AND AI-ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

During the preparation of this work, the authors used ChatGPT in order to ensure accuracy in English. After using this tool/service, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Curated EEG data	This paper	N/A
Software and algorithms		
MATLAB version 2018a	MathWorks, Inc.	https://www.mathworks.com/
R version 4.2.2	R Development Core Team	www.r-project.org
R Studio version 2024.04.2	R Development Core Team	https://posit.co/download/rstudio-desktop/
Other		
Analysis Scripts	This paper	https://github.com/pcardone95/ComplEXIT_DoC
EEG machine	BrainVision GmbH	N/A

EXPERIMENTAL MODEL AND STUDY PARTICIPANT DETAILS

In this feasibility study, we enrolled three patients from the William Lennox Neurological Rehabilitation Center located in Ottignies, Belgium. Each patient received intravenous infusions of either the drug (ketamine) or a placebo (saline solution) in a randomized sequence: the two MCS patients had placebo first, while the UWS had ketamine first. Chronologically, the order of experiment was first the MCS- patient, then UWS, and then MCS+. Both the experimenters and the patients' families were blinded to the treatment nature. For safety reasons, the medical doctor in charge of the patients and the pharmacist knew the order and nature of treatment, but they did not actively participate in the experimental sessions. Written informed consent was obtained from the patient's family prior to the study. An experienced anesthesiologist confirmed the medical fitness of the patient to ensure that they could safely participate in the experiment. The experiments were performed in the patient's room in the rehabilitation center to ensure familiarity with the environment and the presence of meaningful personal objects. Utmost consideration was given to their comfort (music, environmental perfume, and dim light) throughout the experiment (from baseline EEG, up to the end of the infusion). The music used aimed to create a smoothing and pleasant environment and was extracted from the playlist of a previous experiment.[45] A video-recording was shot during the whole duration of the two sessions to allow *a posteriori* behavioral observations and documentation. Ketamine was chosen instead of other (a)typical psychedelics because it is used in clinical settings and has already been extensively studied compared to other substances that have more recently attracted scientific scrutiny.

The administration of ketamine or placebo was delivered intravenously using a TCI system (computer running the StanPump software [SL Shafer, Stanford, California], connected to an infusion pump [Graseby 3400, Smith Medical International Ltd, United Kingdom], and using the pharmacokinetic model of Domino[46]). The catheter was placed in the arm or hand closest to the TCI, allowing ketamine infusion and the eventual administration of rescue medications. On the day of each session, the patient fasted for 6 h before infusion to avoid potential nausea and inhalation of gastric contents. We performed the two sessions at the same time of the day to account for circadian rhythms and sleep-pressure for two patients. Due to technical reasons, for the MCS- patient we had to perform a morning session and an early afternoon session. We initiated the infusion at 0.15 $\mu g\ mL^{-1}$, incrementing by 0.15 $\mu g\ mL^{-1}$ steps up to 0.75 $\mu g\ mL^{-1}$ (maximal concentration). The maximal concentration was estimated from the median of a previous study performed on healthy participants in a similar setting, where it led to drowsiness with responsiveness (sub-anesthetic concentration).[42] The patient was asked to maintain eyes open, and when not possible, an arousal protocol[17] was performed. EEGs were carried out 20 min prior the infusion and continued for up to 90 min post-infusion. ECG was recorded continuously along with the EEG for medical purposes. After observing an unexpected but subjectively major decrease of spasticity with the MCS- patient, we decided to include an evaluation of spasticity before and after infusion with the Modified Ashworth Scale[18] for the two following patients.

After the SECONDs and the MAS at 90′ minutes, we stopped the infusion and set blood concentration of the substance to zero. A subsequent SECONDs was done 2 h after the end of the experiment to assess potential prolonged effects. The presence of adverse effects was noted at the end of each session using an adverse events questionnaire. After termination of infusion, the patient was monitored closely for 2 h by one of the experimenters.

Physiological measurements (heart rate [HR], peripheral saturation of oxygen [SpO_2], blood pressure) were controlled via a patient monitor and transcribed every 5 min. Additionally, a psychedelic sitter was present throughout the experiment in case of need of psychological support. A video was recorded during the entire session (GoPro, GoPro Inc., USA).

We established the following inclusion and exclusion criteria:

Inclusion criteria.

(1) 18 years old or more
(2) Clinically stable, not dependent on mechanical ventilators for respiration
(3) Diagnosed as in an UWS, MCS or EMCS according to the international criteria and based on at least 2 SECONDs
(4) More than 28 days post-insult
(5) Informed consent from legal representative of the patient

Exclusion criteria.

(1) Known allergy or hypersensitivity to ketamine
(2) Active epilepsy (contrary advice by a neurologist upon standard EEG)
(3) A history of previous neurological functional impairment other than related to their acquired brain injury
(4) A history of psychotic disorders (schizophrenia or bipolar disorder)
(5) Use of drugs known to interact with ketamine. Among them: thyroid hormones, diazepam and barbiturates, drugs that interact with CYP3A4, tramadol or halogenated vapors
(6) Patient with coronary insufficiency
(7) Other sympathomimetic drugs
(8) Pregnancy

METHOD DETAILS

Behavioral scales and acquisition

The SECONDs is a fast and reliable tool that stems from the Coma Recovery Scale-Revised,[47] which allows the assessment of the level of consciousness through the most representative MCS behaviors.[47] It provides a total score from 0 to 8 that gives a clinical diagnosis (i.e., 0 is coma, 1 is UWS, 2–5 is MCS-, 6–7 is MCS+, 8 is EMCS).

The Modified Ashworth Scale (MAS)[18] is a 6-level ordinal scale with documented reliability.[48] MAS of the flexors of the wrist and elbow, the extensors of the knee and the plantar flexors were assessed bilaterally (8 assessments) at the beginning and the end of each session (one for ketamine, and the other for placebo). In the case of the UWS patient, the assessor was not blind to the nature of the drug, while for the MCS+ the assessor was blind. The two assessors were different.

EEG acquisition and analysis

Electrode impedances were set below 50 Ω at the beginning of the session, and right before the infusion started. EEG preprocessing was done with MATLAB (MathWorks, Inc., USA) using a modified pipeline from a previous publication.[28] EEG was analyzed for the data before infusion (baseline), and for the 90 min during infusion (experiment). Data were downsampled from 500 Hz to 250 Hz, band-filtered between 0.1 and 45 Hz, and epoched into 10 s segments. Epochs during the SECONDs were rejected, and channel and epoch rejection were performed with a semi-automatic procedure based on variance and visual inspection. Muscle artifact, eye-movements, and other sources of noise were rejected by an independent components analysis. Finally, bad channels were interpolated using a spherical spline interpolation, and data were re-referenced to the common average.

Power analysis between 0.5 and 45 Hz was performed on the preprocessed data with a multitaper frequency transformation (mtmfft) with discrete prolate spheroidal sequences (dpss), with a smoothing of 0.3Hz, using the ‘‘nextpow2’’ option for padding. The parameters are the same as previous investigation using the same pipeline.[28] Power was normalized per epoch, by dividing it for the total power of each epoch.

LZC was calculated over time per each electrode and epoch, based on the binarization of instantaneous amplitude of the Hilbert transform through the average instantaneous amplitude of the epoch, following an exhaustive production process. Each raw value of LZC was normalized by dividing it by the ratio of the length of the sequence and the $\log_2$ of the length of the sequence. Finally, individual values were average per electrode, so that there was 1 value per epoch per recording. The whole-brain value was considered as the average of the values per electrode. ECI was calculated on the same epochs of LZC. ECI capitalizes on machine learning approach to measure both arousal and awareness. ECI has been trained on several datasets, including normal wakefulness, anesthesia, and DoC (coma, UWS, MCS), to dissociate awareness and wakefulness. The model was thus the same as the original publication that yielded comparable results with the perturbational complexity index (PCI). For more details on the preprocessing and training of the ECI, consult the original publication.[10]

QUANTIFICATION AND STATISTICAL ANALYSIS

Given the pilot nature of our experiment, we have not reported any statistical modeling of the effects.

ADDITIONAL RESOURCES

Local ethical committee ref. 2021-211. EudraCT number: 2021-002321-23 (link: https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-002321-23/BE).