Neurophysiological Markers of (Dis)Connectedness: Insights from Ketamine

Naji Alnagger[1,2*], Paolo Cardone[1,2*], Javier Montupil[3,4], Jitka Annen[1,2,5], Charlotte Martial[1,2], Vincent Bonhomme[3,4], Olivia Gosseries[1,2#]

[1]Coma Science Group, GIGA-Consciousness, University of Liège, Belgium. [2]Centre du Cerveau, University Hospital of Liège, Belgium, [3]Anesthesia and Perioperative Neuroscience, GIGA-Consciousness, University of Liège, Belgium, [4]Department of Anesthesia and Intensive Care Medicine, University Hospital of Liège, Belgium, [5]Department of Data Analysis, University of Ghent, Ghent, Belgium

*Contributed equally

Author mail addresses

Naji Alnagger: n.alnagger@uliege.be

Paolo Cardone: p.cardone@uliege.be

Javier Montupil: javier.montupil@chuliege.be

Jitka Annen: jitka.annen@uliege.be

Charlotte Martial: cmartial@uliege.be

Vincent Bonhomme: vincent.bonhomme@uliege.be

Olivia Gosseries: ogosseries@uliege.be

#Corresponding author
Olivia Gosseries: ogosseries@uliege.be

Running head: Ketamine, neurophysiology, and disconnectedness

Potential Conflicts of Interest

VB has had financial relationships with Orion Pharma, Metronic, Elsevier, Edwards Medical. The other authors declare no conflict of interest.

Abstract

Ketamine is a versatile N-methyl-D-aspartate (NMDA)-antagonist used in various clinical settings, such as for acute, perioperative, and chronic pain management, as analgesic and sedative in minor surgeries, as antidepressant, for premedication of children, as component of general anaesthesia, or in sedation and analgesia regimen in intensive care. Ketamine dose-dependently induces psychoactive effects: at low, anti-hyperalgesic dose, these are only very minor or not detectable, but at sub-anaesthetic dose, they may include dissociative, psychotomimetic, and psychedelic events. At an anaesthetic dose, ketamine leads to a state of "(full) dissociation" or disconnection rather than unconsciousness, setting it apart from other anaesthetics. This unique set of characteristics makes ketamine a particularly interesting substance for studying awareness and consciousness in clinical settings. From this perspective, our chapter reviews ketamine's neurophysiological effects and neuroimaging data, its potential in consciousness research, and its relevance in studying brain disorders involving altered states of consciousness. We trace recent advancements in understanding ketamine's unique brain effects and report new investigations that have developed neurophysiological indexes for consciousness without behavioural output (e.g., disconnected consciousness) using ketamine-induced dissociative states along with other conditions as benchmarks. Specifically, we discuss the most recent tool, the Explainable Consciousness Indicator (ECI), which uses machine learning to assess the presence of awareness and wakefulness. Finally, we look at future investigations that may utilise ketamine as therapeutic approach to serious neurological conditions, such as disorders of consciousness.

Key words

Ketamine, Neurophysiological markers, Disconnected consciousness, behavioural responsiveness, complexity, machine learning, Novel approaches to disorders of consciousness

1 Introduction

Among the clinically established anaesthetics, ketamine has a special position because it offers analgesic and anaesthetic effects without cardiorespiratory depression. Ketamine maintains laryngopharyngeal protective reflexes. At present, indications for ketamine are permanently expanding, especially in the fields of psychiatry and drug-assisted psychotherapy. Ketamine has recently been established as rapid antidepressant. However, ketamine is also well known for its psychoactive and medical unwanted actions (1–6). All ketamine effects are strictly dose and context-dependent: At very small dose < 0.15 mg/kg, single ketamine use induces anti-hyperalgesic effects without (obvious) psychoactive response. At subanaesthetic analgesic and antidepressant dose of about 0.3 - 0.5 mg/kg racemic ketamine, it reduces vigilance, memory, and logical thinking. With increasing dose, it may cause altered perceptions, disorientation, dizziness, drowsiness, and various psychedelic, dissociative, and psychomimetic events with negative and positive quality. Some of these effects show hallucinogenic similarities to classic psychedelic drugs such as psilocybin and lysergic acid diethylamide (LSD) (7–9). With increasing dose, ketamine's anaesthetic effects manifest in a dichotomous manner: It induces unresponsiveness at a typical threshold of approximately 1.0 to 2.0 mg/kg intravenous (IV) racemic ketamine (10). Plasma concentrations to maintain surgical anaesthesia range between 2 and 3 µg/mL (11). Because (S)-ketamine is about twice as potent as the world-wide used racemate, comparable effects are achieved with half-dose (S)-ketamine (1). Nonetheless, above this threshold, further increasing dosage does not appear to deepen sedation (12). At higher doses, ketamine imparts a trance-like cataleptic state of "sensory isolation" with profound analgesia and often amnesia. This unique property allows for a clear

delineation between a sub-anaesthetic and anaesthetic ketamine response at a behavioural level. Far beyond, ketamine's most intriguing action is the maintenance of consciousness despite behavioural unresponsiveness (13,14). This preservation of awareness, coupled with dissociative and psychedelic effects, places ketamine in a unique drug category. Ketamine reaches across domains of anaesthesia and analgesia while inducing profound phenomenological experiences. This highlights its inherent incompatibility within only one typical group of drugs (9,15). Ketamine's pharmacology is still not fully understood, but the substance interacts with a multiplicity of sites, not only related to its first mechanism as N-methyl-D-aspartate (NMDA) receptor antagonist (16,17) (*please see details in pharmacology chapters of this book*).

This chapter explores neurophysiological and neuroimaging studies focussing on ketamine's uniqueness in inducing loss of responsiveness while maintaining conscious experiences. Clinicians need to be familiar with the concepts of "responsiveness" and "disconnected consciousness". These are possible for brain-injured patients and comatose patients after cardiac arrest who have conscious experiences yet are disconnected from the outside. Ketamine is also important for investigating mechanisms underlying conscious experiences and the science of consciousness (18). We will therefore highlight how "model ketamine" can be used to create indices which are clinically meaningful to individuate conscious patients with serious brain disorders. They may also serve as biomarkers in the longitudinal course of therapy.

2 Early Electrophysiological Work

At the time when the neural correlates of ketamine anaesthesia were first explored, there was still a lack of a precise clinical definition of consciousness. Attempting to reconcile

ketamine-induced reductions in behavioural responsiveness with the unexpected electrophysiological findings was challenging. When ketamine is administered as mono-anaesthetic, additional ketamine doses do not seem to enhance or deepen sedation once unresponsiveness has been achieved. This is different from opioids, sedative-hypnotics, or inhalational anaesthetic agents (12). Early work used electrophysiological signifiers as indicators of sedation depth, such as auditory evoked potentials. They represent electrical potential difference changes which are recorded with electrodes measuring brain activity in response to auditory stimuli. One of the most investigated modalities was the 40-Hz auditory steady-state response (40-Hz ASSR), which revealed intriguing differences between ketamine and other anaesthetics (19): with most anaesthetics, such as thiopental (20), sufentanil (21), propofol (22), and N_2O with or without enflurane (20,23,24), a decrease in the 40-Hz ASSR amplitude was observed, and an increase in the latency of the amplitude occurred. In contrast, ketamine increased the response to the 40-Hz tone (25). A different electrophysiological assessment of the sedation depth nowadays commonly used, is the bispectral index (BIS) (26). The BIS is derived from a combination of analyses of power spectra and time-domain analyses of electroencephalographic (EEG) signals. These are integrated with black-box algorithms for artifact reduction and adaptive filtering. The BIS provides a single numerical value that reflects the patient's depth of anaesthesia from 0 (absence of brain activity) to 100 (awake state). This allows for a straightforward interpretation of the index with lower values corresponding to lower levels of consciousness. Values between 40-60 represent deep hypnotic state general anaesthesia. Interestingly, when a 0.5 mg/kg ketamine bolus is administered as an adjunct to propofol or sevoflurane anaesthesia, the BIS increases (27,28). This result may be considered counterintuitive, because ketamine is expected to

increase the level of hypnosis. However, this BIS response may have been caused simply by disconnected consciousness. In other words, even without behavioural responsiveness, it is possible that a phenomenological experience is preserved with ketamine use in humans, irrespective of whether it is captured in an index or not.

3 Consciousness versus Responsiveness

Consciousness is an intrinsic phenomenon of everyday life, present from the moment we wake up until we fall asleep. There are different nuances to its definition, and the clinical perspective for anaesthesiologists may often centre around behavioural responsiveness at the bedside. Nonetheless, consensus in cognitive neuroscience equates consciousness with having an experience (29,30). This can exist in the presence or absence of behavioural responsiveness (18,31–33). The state of absence of responsiveness with the presence of subjective experience has been coined as "disconnected consciousness". Disconnected consciousness is naturally occurring in physiological states such as dreaming but can be induced pharmacologically. Besides sheer epistemological curiosity, defining consciousness in multidimensional materialistic terms has a direct impact on the lives and health of people.

One example is "intraoperative awareness", which is the unwanted presence of consciousness in patients under general anaesthesia during surgery. Intraoperative awareness has been reported to occur during more than 10% of the time in the operating theatre (34), with a likely even higher incidence not being reported due to patient amnesia. Additionally, "dreaming" during periods of unresponsiveness under dexmedetomidine and propofol anaesthesia is not uncommon (35). Identifying the

correlates of disconnected consciousness would allow clinicians to better manage these phenomena. Another example are patients suffering from post-comatose disorders of consciousness (DoC). DoC are characterised by impaired consciousness, with no functional communication or “appropriate use of objects” (36–38). An accurate diagnosis differentiating conscious from unconscious DoC patients may have critical ethical implications (39). Previously, it was believed that patients who are unresponsive at the bedside were not conscious. However, it is now clear that a significant percentage of these individuals are conscious, i.e., they have experiences despite being obviously unable to demonstrate them (40–43). Nowadays, such a state can be elucidated according to evidence gathered in electrophysiological and neuroimaging methods (38,44). The separation between behavioural responsiveness and consciousness can be similarly demonstrated by dreaming during sleep (45,46). Therefore, refining unbiased methods to identify consciousness and distinguish it from behavioural responsiveness is decisively important. Such progress does not only enhance our understanding of consciousness, but will improve diagnostic accuracy and ethical issues with respect to decision-making in several, serious clinical brain conditions and circumstances (44).

A measure proposed to identify the presence of consciousness during unresponsive states is the spectral exponent of the power spectral density (PSD) of the resting-state EEG (47,48). The spectral exponent is estimated from the slope of the PSD in log-log coordinates indicating the steepness of the decay of the PSD “background”. The PSD background decays from slower to faster frequencies according to an inverse power-law. The spectral exponent is linked to the balance between excitation and inhibition in neuronal signalling. With propofol and xenon anaesthesia, the spectral exponent was reduced when no experience were reported after awakening in healthy study subjects

(**Fig. 1a)** (47). In contrast, with ketamine anaesthesia, the spectral exponent remained unchanged in the low frequency range, but increased in the higher frequencies (**Fig. 1b and c**). After regaining consciousness from ketamine anaesthesia, healthy study participants reported vivid dream-like psychedelic experiences while being disconnected from the external environment. This is in line with previous subjective reports of conscious events during ketamine mono-anaesthesia in surgery.

place Figure 1 near here

While the resting-state EEG has been regarded as a feasible tool to determine consciousness, it may have limitations with respect to the accuracy of assessments. New investigations suggest that a "perturbation of the brain" is necessary to define whether consciousness is present or not (50,51). Transcranial magnetic stimulation (TMS) offers a way to perturb the brain in a non-invasive, reversible manner (52,53). When combining TMS with EEG, underlying features of conscious state can be revealed. For example, evoked alpha power decreases during disconnected consciousness, as shown by TMS-EEG recordings under ketamine anaesthesia or with rapid eye movement (REM) sleep (54). This is not seen in states of unconsciousness, such as in non-REM (NREM) sleep "without dreams" or under propofol anaesthesia, and may suggest that alpha activity is involved in the perception of sensory stimuli. It could therefore be a marker of disconnected consciousness (54). Another way to benefit from TMS-EEG recordings is the averaging of the EEG response to the pulse to register TMS-evoked potentials (TEPs). The TEP varies greatly as a function of conscious state (55). In normal wakefulness, TEPs are region-specific (56), but homologous in the way they vary over time and space (14,55). During dreaming, TEPs similarly preserve a variegated, long-lasting pattern involving

regions outside the one under the coil. In contrast, during NREM sleep, TEPs are much simpler with a higher local, short-lived amplitude (57). Interestingly, in pharmacological anaesthesia such as with GABAergic midazolam (58), TEPs look qualitatively like those of NREM sleep. In contrast, ketamine anaesthesia preserves the wakefulness-like shape of the TEPs, as if indicating "only disconnectedness" rather than unconsciousness in healthy volunteers (**Fig. 2**). While there are few reports on dose-dependent effects of anaesthetics in TMS-EEG (59), the TEP of sub-anaesthetic dose ketamine has similar features to the one of wakefulness (60). One way to quantify how much TEPs vary, is by means of the "brain complexity value". The brain complexity value is a comprehensive and easy-to-read measure that describes underlying physiological features indirectly. It has been strongly linked to consciousness.

place Figure 2 near here

An optimal balance between functional brain integration and differentiation is necessary to maintain consciousness (61–63). This balance underpins complex brain activity and seems to be inextricably linked to consciousness. It has recently been observed that the brain exhibits highly complex activity during normal awake consciousness. However, the complexity is low during states without consciousness, such as in dreamless sleep or coma (63,64). Complexity can be measured by various methods, one of the simplest being the Lempel-Ziv Complexity (LZC). It gauges the repetitiveness of brain activity after binarisation of recorded values (65) and can be used to assess the complexity of the TMS-evoked response in the EEG. This procedure results in the perturbational complexity index (PCI) (66). The PCI provides a single number that quantifies the complexity of the brain response to the perturbation, which can then be

used to determine whether an individual is conscious or not (66,67). Originally, the PCI was applied to demonstrate that in reduced consciousness states such as in DoC or propofol anaesthesia, PCI values were low. They indicated a stereotypical brain response to perturbation with a simple TEP of low complexity. The PCI was also used to discriminate consciousness levels in single subjects and individual patients across different states, including dreaming, dreamless sleep, DoC, locked-in syndrome, and various other levels of sedation related to agents like xenon and propofol (14,64,66). With reduced consciousness, the PCI is low, whereas with maintained consciousness such as normal awake states or in locked-in syndrome patients, PCI is high. It thus exemplifies the relative irreducibility of complex EEG signals during phenomenological experiences. Fascinatingly, during ketamine-induced loss of responsiveness, PCI values also remain high and comparable to those during normal awake consciousness (14,64). This finding aligns with ketamine's ability to produce profound unresponsiveness whilst preserving experience (**Fig. 3**). In fact, while healthy study subjects accounted for "ketamine dreams" upon emergence from anaesthesia, they reported no or little experience after emergence from propofol and xenon anaesthesia (14). Nevertheless, there is still the possibility that some patients "may experience something" under anaesthesia with non-ketamine agents (68). It is therefore indispensable to find a method to monitor consciousness that is easily implementable.

place Figure 3 near here

4 The Contribution of Artificial Intelligence to Elucidate Consciousness States

A shortcoming of single number measurements such as the PCI lies in the fact that they oversimplify consciousness, and might not capture its multifaced nature. This is evident by the fact that PCI cannot distinguish states of disconnected consciousness, such as ketamine-induced unresponsiveness, versus normal awake consciousness. New promising indices including the explainable consciousness indicator (ECI), provide one index for wakefulness and one for awareness. This allows for a differentiation between similar states of high awareness yet low arousal (69). While validated with TMS-EEG data, the ECI can also be employed in EEG-only recordings. Even though other measures used to detect the presence of consciousness (such as PSD and spectral exponents) can make such distinctions, they are typically calculated at the group level and rely on many epochs to improve the reliability of statistical estimates. This reliance on extensive data limits their applicability for real-time, single subject or individual patient assessments in clinical care. In contrast, the ECI applies convolutional neural networks (CNNs), a specific deep learning technique, to identify and discriminate between "salient" brain states from unrelated signals in real-time at the single-subject / individual patient level.

These models rely on training data to learn to distinguish the salient patterns associated with different states of consciousness as opposed to unrelated brain signals. Firstly, the CNN was trained using EEG data collected from various conditions with different levels of arousal and awareness, including sleep (57,70), anaesthesia (14), and DoC (71,72). The CNN captures spatial, spectral, and temporal information, learning relevant features that distinguish between high and low states of arousal and awareness. The training process involves techniques like transfer learning, where the model learns from one domain/dataset (e.g., sleep) and applies this knowledge to another (e.g., anaesthesia). Traditionally, these models are used in many domains, such as image and

speech recognition, but they are generally not explainable beyond the ability to interpret the value given in classification. These are referred to as “black-box” methods; they do not provide access to the reasons behind their classifications. However, the ECI model overcomes this limitation by using Layer-wise Relevance Propagation (LRP), which ensures that the CNN's decisions are both interpretable and explainable. LRP assigns relevance scores to each input feature, highlighting their contribution to the classification decision. This allowed to identify that EEG activity over parietal brain regions was more relevant for classifying states of consciousness rather than over frontal regions. In the landscape of the debate about whether the most relevant brain areas supporting consciousness reside in frontal or parietal brain parts (73–75), this may be a very important finding because the ECI demonstrated a good concordance with the PCI. Taken together the ECI may therefore be very useful in clinical settings where it is crucial to understand if a patient has preserved consciousness or not. However, although this method does not capture disconnectedness yet, it can detect consciousness even if a person is unresponsive such as under ketamine anaesthesia (**Fig. 4**).

Place Figure 4 near here

5 What Does Functional Magnetic Resonance Imaging Show – A View Towards Neurobiological Mechanisms

Brain complexity emerges through intricate interactions within the thalamocortical networks. Another way to study ketamine’s unique effects on the brain are neuroimaging methods such as functional magnetic resonance imaging (fMRI) to examine the brain’s resting state (RS) networks. The identification of ketamine’s impact on RS networks may

help to untangle its complex phenomenological responses. Ketamine produces alterations in many RS networks, showing dose-dependent effects (76). In particular, the default mode network (DMN) is suppressed between medial frontal regions and its posterior nodes. This suppression is suggested to be a hallmark of anaesthesia-related unresponsiveness. Reductions in frontal DMN connectivity and disconnection of frontoparietal connectivity have been reported with anaesthetics like sevoflurane and propofol (77). With ketamine anaesthesia in contrast, the executive control network connectivity, visual and auditory connectivity, and even the cross-modal connectivity between these sensory networks is maintained (76,78). These differences in network connectivity likely highlight the divergent sedation patterns and anaesthetic phenomenology caused by propofol as compared to ketamine. Additionally, during ketamine-induced unresponsiveness, there is a reorganisation of the DMN with other brain regions involved in external and internal stimuli processing. Brain regions get integrated into the DMN network connectivity (79). This reorganisation of the DMN and other networks such as the salience network may - in part explain - how ketamine can exert dissociative and psychedelic effects (80,81).

6 Future Directions: Ketamine's Psychedelic Potential for Therapy

Ketamine has been established as rapid-acting antidepressant in major depressive disorder with suicidal ideation, treatment-resistant depression, and other severe neuropsychiatric disorders (3,6,16,82). Similar to the uniqueness among anaesthetics, ketamine is also regarded as atypical psychedelic in contrast to the "classical serotonergic psychedelics" (9). While there is ongoing discussion whether the response

to ketamine is related to its phenomenology, pharmacology, or a combination of both (83–85), there are endeavours to characterise the phenomenology of ketamine via reported experiences (86). As already outlined, ketamine induces transient psychoactive events, including unusual “disorienting” experiences of dissociation and psychedelic-like changes in perception, but also positive events and mystical experiences, including awe and oneness with the environment. Sub-anaesthetic dose ketamine leads to different brain dynamics compared to higher doses, which has been shown in humans (7,15) and animal models (87–89). Sub-anaesthetic dose ketamine increases the LZC in resting-state EEG in healthy volunteers, while the PCI remained unchanged ((60,90), but also see (81) for possible interpretation). This introduces the appealing idea for therapeutic approaches with a drug that transiently increases brain complexity in patients who suffer from pathologically deficient levels of consciousness. Low brain complexity is a typical feature of the challenging patients with DoC (81,91). Enhancing brain complexity would theoretically allow for a richer experience in these difficult-to-treat patients. Current investigations are active using ketamine for this purpose as a novel clinical indication. So far, our first data have demonstrated that ketamine can indeed increase brain complexity in DoC patients without inducing new signs of consciousness (Cardone et al, under review).

7 Conclusions

Beyond all current knowledge, ketamine still holds more promises for the elucidation of our understanding of consciousness, specifically for differentiation between unconsciousness and disconnectedness. Encouraging researchers and clinicians to

consider responsiveness and consciousness as separate entities is crucial for understanding mechanisms of consciousness and especially for improving treatment approaches to desperately brain-injured patients. All of this is associated with tremendous significance for real-word implementation, as it may lead to a better care of patients undergoing surgery who are unresponsive but still have experiences, and much more in patients with DoC who are unable to display a motor output due to physical impairments but have a “mental life”. Nevertheless, it has to be clearly stated that ketamine mono-anesthesia is rarely performed outside of preclinical emergencies, anaesthesia for electroconvulsive therapy, or resource-poor settings. For decades, anaesthesiologists combine ketamine with GABA-ergic agents to prevent and treat unwanted psychoactive and medical effects.

In summary, we have presented recent ketamine study data trying to differentiate between correlates of responsiveness and consciousness based on various, currently applied neurophysiological and neuroimaging methods. Endeavours to enhance the clinical translatability of indices such as the ECI will hopefully change the future clinical practice for the benefit of DoC patients. In a historical context, this may become very important in view of the renewed discussion about medical treatment using classical psychedelics despite the unclarity about their long-term, lasting effects of mind-altering changes.

8 Take Home Messages

1) Ketamine is unique among anaesthetics for its ability to induce unresponsiveness without loss of consciousness. This highlights the differentiation between these two

aspects and makes ketamine a valuable tool in studying states of disconnected consciousness in both clinical and research settings.

2) Emerging tools like the Explainable Consciousness Indicator (ECI) might provide real-time assessments of consciousness by quantifying both awareness and arousal. This allows for the detection of disconnected consciousness in states like ketamine anaesthesia.

3) Ketamine uniquely preserves high brain complexity during states of unresponsiveness and disconnected consciousness. This distinct neurophysiological effect opens new lines of investigations into the therapeutic possibilities for disorders of consciousness.

Acknowledgement

This work was supported by the University and University Hospital of Liège (Liège, Belgium), the Belgian National Fund for Scientific Research (FRS-FNRS), the GIGA Doctoral School for Health Sciences, the Mind Science Foundation, the Fondation Léon Fredericq, the FNRS MIS project (F.4521.23), the fund Generet, the King Baudouin Foundation, the FNRS PDR project (T.0134.21), the BIAL Foundation, the ERA-Net FLAG-ERA JTC2021 project ModelDXConsciousness (Human Brain Project Partnering Project), and the DoC-Box project (HORIZON-MSCA-2022-SE-01-01-101131344). J.A. is postdoctoral fellow funded by the Fund for Scientific Research-Flanders (1265522N) (FWO). PC and NA are research fellows, and OG is research associate at the F.R.S.-FNRS.

References

1. Sinner B, Graf BM. Ketamine. Handbook of experimental pharmacology. 2008;182(182):313–33.

2. Newport DJ, Carpenter LL, McDonald WM, Potash JB, Tohen M, Nemeroff CB. Ketamine and Other NMDA Antagonists: Early Clinical Trials and Possible Mechanisms in Depression. Am J Psychiatry. 2015 Oct 1;172(10):950–66.

3. Krystal JH, Abdallah CG, Sanacora G, Charney DS, Duman RS. Ketamine: A Paradigm Shift for Depression Research and Treatment. Neuron. 2019 Mar 6;101(5):774–8.

4. Barrett W, Buxhoeveden M, Dhillon S. Ketamine: a versatile tool for anesthesia and analgesia. Curr Op Anaesthesiol. 2020 Oct 1;33(5):633–8.

5. McIntyre RS, Rosenblat JD, Nemeroff CB, Sanacora G, Murrough JW, Berk M, et al. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. Am J Psychiatry. 2021 May 1;178(5):383-399. doi.org/101176/appi.ajp202020081251.

6. Baek JJ, Hasassri E. Ketamine for Adolescent Depression: An Overview and Considerations for Future Directions. Am. J. Psychiatry Resid. J. 2022;17:2–4. doi: 10.1176/appi.ajp-rj.2022.170401.

7. Muthukumaraswamy SD, Shaw AD, Jackson LE, Hall J, Moran R, Saxena N. Evidence that Subanesthetic Doses of Ketamine Cause Sustained Disruptions of NMDA and AMPA-Mediated Frontoparietal Connectivity in Humans. J Neurosci. 2015 Aug 19;35(33):11694–706.

8. Vlisides PE, Bel-Bahar T, Nelson A, Chilton K, Smith E, Janke E, et al. Subanaesthetic ketamine and altered states of consciousness in humans. Br J Anaesth. 2018 Jul;121(1):249-259.

9. Aleksandrova LR, Phillips AG. Neuroplasticity as a convergent mechanism of ketamine and classical psychedelics. Trends Pharmacol Sci. 2021 Nov 1;42(11):929–42.

10. Rosenbaum SB, Gupta V, Patel P, Palacios JL. Ketamine. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 [cited 2024 Sep 6]. Ketamine - PubMed (nih.gov) Accessed 06 September 2024

11. Domino EF. Taming the ketamine tiger. Anesthesiology. 2010;113(3):678–84.

12. Green SM, Roback MG, Kennedy RM, Krauss B. Clinical practice guideline for emergency department ketamine dissociative sedation: 2011 update. Ann Emerg Med. 2011 May;57(5):449–61.

13. Blagrove M, Morgan CJA, Curran HV, Bromley L, Brandner B. The incidence of unpleasant dreams after sub-anaesthetic ketamine. Psychopharmacology. 2009 Mar 24;203(1):109–20.

14. Sarasso S, Boly M, Napolitani M, Gosseries O, Charland-Verville V, Casarotto S, et al. Consciousness and complexity during unresponsiveness induced by propofol, xenon, and ketamine. Curr Biol. 2015;25(23):3099–105.

15. Li D, Mashour GA. Cortical dynamics during psychedelic and anesthetized states induced by ketamine. NeuroImage. 2019 Aug 1;196:32–40.

16. Wohleb ES, Gerhard D, Thomas A, Duman RS. Molecular and Cellular Mechanisms of Rapid-Acting Antidepressants Ketamine and Scopolamine. Curr Neuropharmacol. 2017 Jan;15(1):11–20.

17. Zanos P, Moaddel R, Morris PJ, Riggs LM, Highland JN, Georgiou P, et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. Pharmacol Rev. 2018 Jul 1;70(3):621.

18. Bonhomme V, Staquet C, Montupil J, Defresne A, Kirsch M, Martial C, et al. General Anesthesia: A Probe to Explore Consciousness. Front Syst Neurosci. 2019;13:36.

19. Plourde G. Auditory evoked potentials. Best Pract Res Clin Anaesthesiol. 2006 Mar 1;20(1):129–39.

20. Plourde G, Picton TW. Human Auditory Steady-State Response During General Anesthesia. Anesth Analg. 1990 Nov;71(5):460.

21. Plourde G, Boylan JF. The auditory steady state response during sufentanil anaesthesia. Br J Anaesth. 1991 Jun 1;66(6):683–91.

22. Plourde G. The Effects of Propofol on the 40-Hz Auditory Steady-State Response and on the Electroencephalogram in Humans. Anesth Analg. 1996 May;82(5):1015.

23. Yli-hankala A, Edmonds HL, Heine MF, Strickland T, Tsueda K. Auditory steady-state response, upper facial EMG, EEG and heart rate as predictors of movement during isoflurane-nitrous oxide anaesthesia. Br J Anaesth. 1994 Aug 1;73(2):174–9.

24. Plourde G, Villemure C. Comparison of the effects of enflurane/N2O on the 40-Hz auditory steady-state response versus the auditory middle-latency response. Anesth Analg. 1996 Jan;82(1):75–83.

25. Plourde G, Baribeau J, Bonhomme V. Ketamine increases the amplitude of the 40-Hz auditory steady-state response in humans. Br J Anaesth. 1997 May;78(5):524–9.

26. Sigl JC, Chamoun NG. An introduction to bispectral analysis for the electroencephalogram. J Clin Monitor Comput. 1994 Nov 1;10(6):392–404.

27. Hans P, Dewandre PY, Brichant JF, Bonhomme V. Comparative effects of ketamine on Bispectral Index and spectral entropy of the electroencephalogram under sevoflurane anaesthesia. Br J Anaesth. 2005 Mar;94(3):336–40.

28. Sengupta S, Ghosh S, Rudra A, Kumar P, Maitra G, Das T. Effect of ketamine on bispectral index during propofol--fentanyl anesthesia: a randomized controlled study. Middle East J Anaesthesiol. 2011 Oct;21(3):391–5.

29. Seth AK, Bayne T. Theories of consciousness. Nat Rev Neurosci. 2022 Jul;23(7):439–52.

30. Montupil J, Cardone P, Staquet C, Bonhomme A, Defresne A, Martial C, et al. The nature of consciousness in anaesthesia. BJA Open. 2023 Dec;8:100224.

31. Sanders RD, Tononi G, Laureys S, Sleigh JW. Unresponsiveness ≠ unconsciousness. Anesthesiology. 2012 Apr;116(4):946–59.

32. Boly M, Sanders RD, Mashour GA, Laureys S. Consciousness and responsiveness: Lessons from anaesthesia and the vegetative state. Curr Op Anaesthesiol. 2013 Aug;26(4):444–9.

33. Martial C, Cassol H, Laureys S, Gosseries O. Near-Death Experience as a Probe to Explore (Disconnected) Consciousness. Trends Cogn Sci. 2020;24(3):173–83.

34. Lennertz R, Pryor KO, Raz A, Parker M, Bonhomme V, Schuller P, et al. Connected consciousness after tracheal intubation in young adults: an international multicentre cohort study. Br J Anaesth. 2023 Feb 1;130(2):e217–24.

35. Valli K, Radek L, Kallionpää RE, Scheinin A, Långsjö J, Kaisti K, et al. Subjective experiences during dexmedetomidine- or propofol-induced unresponsiveness and non-rapid eye movement sleep in healthy male subjects. Br J Anaesth. 2023 Aug;131(2):348–59.

36. Giacino JT, Ashwal S, Childs N, Cranford R, Jennett B, Katz DI, et al. The Minimally Conscious State. Neurol Rev 2002;64(10):350–1.

37. Fins JJ. Disorders of Consciousness, Past, Present, and Future. Camb Q Healthc Ethics. 2019 Oct;28(4):603–15.

38. Alnagger N, Cardone P, Martial C, Laureys S, Annen J, Gosseries O. The current and future contribution of neuroimaging to the understanding of disorders of consciousness. La Presse Médicale. 2023 Jun 1;52(2):104163.

39. Demertzi A, Ledoux D, Bruno MA, Vanhaudenhuyse A, Gosseries O, Soddu A, et al. Attitudes towards end-of-life issues in disorders of consciousness: a European survey. J Neurol. 2011 Jun;258(6):1058–65.

40. Schiff ND. Cognitive motor dissociation following severe brain injuries. JAMA Neurology. 2015;72(12):1413–5.

41. Jöhr J, Halimi F, Pasquier J, Pincherle A, Schiff N, Diserens K. Recovery in cognitive motor dissociation after severe brain injury: A cohort study. PLoS ONE. 2020 Feb 1;15(2):e0228474.

42. Bodien YG, Allanson J, Cardone P, Bonhomme A, Carmona J, Chatelle C, et al. Cognitive Motor Dissociation in Disorders of Consciousness. N E J Med. 2024 Aug 14;391(7):598–608.

43. Lejeune N, Fritz P, Cardone P, Szymkowicz E, Vitello MM, Martial C, et al. Exploring the Significance of Cognitive Motor Dissociation on Patient Outcome in Acute Disorders of Consciousness. Semin Neurol. 2024 Jun;44(03):271–80.

44. Thibaut A, Panda R, Annen J, Sanz LRD, Naccache L, Martial C, et al. Preservation of brain activity in unresponsive patients identifies MCS star. Ann Neurol. 2021 Jul;90(1):89-100.

45. Nir Y, Tononi G. Dreaming and the brain: from phenomenology to neurophysiology. Trends Cog Sci. 2010 Feb;14(2):88–100.

46. Tononi G, Boly M, Cirelli C. Consciousness and sleep. Neuron. 2024 May 15;112(10):1568–94.

47. Colombo MA, Comanducci A, Casarotto S, Derchi CC, Annen J, Viganò A, et al. Beyond alpha power: EEG spatial and spectral gradients robustly stratify disorders of consciousness. Cereb Cortex. 2023 May 24;33(11):7193-7210.

48. Maschke C, Duclos C, Owen AM, Jerbi K, Blain-Moraes S. Aperiodic brain activity and response to anesthesia vary in disorders of consciousness. NeuroImage. 2023 Jul 15;275:120154.

49. Colombo MA, Napolitani M, Boly M, Gosseries O, Casarotto S, Rosanova M, et al. The spectral exponent of the resting EEG indexes the presence of consciousness during unresponsiveness induced by propofol, xenon, and ketamine. NeuroImage. 2019 Apr 1;189:631–44.

50. Cattani A, Galluzzi A, Fecchio M, Pigorini A, Mattia M, Massimini M. Adaptation Shapes Local Cortical Reactivity: From Bifurcation Diagram and Simulations to Human Physiological and Pathological Responses. eNeuro. 2023 Jul;10(7):ENEURO.0435-22.2023.

51. Casarotto S, Hassan G, Rosanova M, Sarasso S, Derchi CC, Trimarchi PD, et al. Dissociations between spontaneous electroencephalographic features and the perturbational complexity index in the minimally conscious state. Eur J Neurosci. 2024;59(5):934–47.

52. Rosanova M, Casarotto S, Pigorini A, Canali P, Casali AG, Massimini M. Combining transcranial magnetic stimulation with electroencephalography to study human cortical excitability and effective connectivity. Neuromethods. 2012;67:435–57.

53. Klomjai W, Katz R, Lackmy-Vallée A. Basic principles of transcranial magnetic stimulation (TMS) and repetitive TMS (rTMS). Ann Phys Rehabil Med. 2015 Sep 1;58(4):208–13.

54. Darracq M, Funk CM, Polyakov D, Riedner B, Gosseries O, Nieminen JO, et al. Evoked Alpha Power is Reduced in Disconnected Consciousness During Sleep and Anesthesia. Sci Rep. 2018;8(1):16664.

55. Sarasso S, Rosanova M, Casali AG, Casarotto S, Fecchio M, Boly M, et al. Quantifying cortical EEG responses to TMS in (Un)consciousness. Clin EEG Neurosci. 2014;45(1):40–9.

56. Fecchio M, Pigorini A, Comanducci A, Sarasso S, Casarotto S, Premoli I, et al. The spectral features of EEG responses to transcranial magnetic stimulation of the primary motor cortex depend on the amplitude of the motor evoked potentials. PLoS ONE. 2017;12(9):1–15.

57. Nieminen JO, Gosseries O, Massimini M, Saad E, Sheldon AD, Boly M, et al. Consciousness and cortical responsiveness: a within-state study during non-rapid eye movement sleep. Sci Rep. 2016 Aug 5;6(1):30932.

58. Ferrarelli F, Massimini M, Sarasso S, Casali A, Riedner BA, Angelini G, et al. Breakdown in cortical effective connectivity during midazolam-induced loss of consciousness. Proc Natl Acad Sci U S A. 2010 Feb 9;107(6):2681–6.

59. Cardone P, Bodart O, Kirsch M, Sanfilippo J, Virgillito A, Martial C, et al. Depth of sedation with dexmedetomidine increases transcranial magnetic stimulation-evoked potential amplitude non-linearly. Br J Anaesth. 2023 Oct;131(4):715–25.

60. Farnes N, Juel BE, Nilsen AS, Romundstad LG, Storm JF. Increased signal diversity/complexity of spontaneous EEG, but not evoked EEG responses, in ketamine-induced psychedelic state in humans. PLoS ONE. 2020 Nov 1;15(11 November):e0242056.

61. Tononi G, Edelman GM. Consciousness and complexity. Science. 1998 Dec 4;282(5395):1846–51.

62. Demertzi A, Tagliazucchi E, Dehaene S, Deco G, Barttfeld P, Raimondo F, et al. Human consciousness is supported by dynamic complex patterns of brain signal coordination. Sci Adv. 2019 Feb 6;5(2):eaat7603.

63. Sarasso S, Casali AG, Casarotto S, Rosanova M, Sinigaglia C, Massimini M. Consciousness and complexity: a consilience of evidence. Neurosci Conscious. 2021 Aug 30;2021(2):1–24.

64. Casarotto S, Comanducci A, Rosanova M, Sarasso S, Fecchio M, Napolitani M, et al. Stratification of unresponsive patients by an independently validated index of brain complexity. Ann Neurol 2016;80(5):1–28.

65. Lempel A, Ziv J. On the Complexity of Finite Sequences. IEEE Transactions on Information Theory. 1976 Jan;22(1):75–81.

66. Casali AG, Gosseries O, Rosanova M, Boly M, Sarasso S, Casali KR, et al. A theoretically based index of consciousness independent of sensory processing and behavior. Sci Transl Med. 2013;5(198).

67. Comolatti R, Pigorini A, Casarotto S, Fecchio M, Faria G, Sarasso S, et al. A fast and general method to empirically estimate the complexity of brain responses to transcranial and intracranial stimulations. Brain Stimulation. 2019 Sep;12(5):1280–9.

68. Radek L, Kallionpää RE, Karvonen M, Scheinin A, Maksimow A, Långsjö J, et al. Dreaming and awareness during dexmedetomidine- and propofol-induced unresponsiveness. Br J Anaesth. 2018 Jul;121(1):260–9.

69. Lee M, Sanz LRD, Barra A, Wolff A, Nieminen JO, Boly M, et al. Quantifying arousal and awareness in altered states of consciousness using interpretable deep learning. Nat Comm. 2022 Feb 25;13(1):1–14.

70. Lee M, Baird B, Gosseries O, Nieminen JO, Boly M, Tononi G, et al. Graph Theoretical Analysis of Cortical Networks based on Conscious Experience. In: 2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC) [Internet]. Berlin, Germany: IEEE; 2019 [cited 2024 Aug 1]. p. 3373–6. Available from: https://ieeexplore.ieee.org/document/8857648/ Accessed 06 September 2024

71. Bodart O, Gosseries O, Wannez S, Thibaut A, Annen J, Boly M, et al. Clinical Measures of metabolism and complexity in the brain of patients with disorders of consciousness. NeuroImage Clin. 2017;14:354–62.

72. Rosanova M, Fecchio M, Casarotto S, Sarasso S, Casali AG, Pigorini A, et al. Sleep-like cortical OFF-periods disrupt causality and complexity in the brain of unresponsive wakefulness syndrome patients. Nat Comm. 2018 Dec 24;9(1):4427.

73. Del Cul A, Dehaene S, Reyes P, Bravo E, Slachevsky A. Causal role of prefrontal cortex in the threshold for access to consciousness. Brain. 2009 Sep;132(Pt 9):2531–40.

74. Boly M, Massimini M, Tsuchiya N, Postle BR, Koch C, Tononi G. Are the Neural Correlates of Consciousness in the Front or in the Back of the Cerebral Cortex? Clinical and Neuroimaging Evidence. J Neurosci. 2017 Oct 4;37(40):9603–13.

75. Sanders RD, Mostert N, Lindroth H, Tononi G, Sleigh J. Is consciousness frontal? Two perioperative case reports that challenge that concept. Br J Anaesth. 2018 Jul;121(1):330-332.

76. Bonhomme V, Vanhaudenhuyse A, Demertzi A, Bruno MA, Jaquet O, Bahri MA, et al. Resting-state Network-specific Breakdown of Functional Connectivity during

Ketamine Alteration of Consciousness in Volunteers. Anesthesiology. 2016 Nov 1;125(5):873–88.

77. Lee U, Ku S, Noh G, Baek S, Choi B, Mashour GA. Disruption of frontal-parietal communication by ketamine, propofol, and sevoflurane. Anesthesiology. 2013 Jun;118(6):1264–75.

78. Boveroux P, Vanhaudenhuyse A, Bruno MA, Noirhomme Q, Lauwick S, Luxen A, et al. Breakdown of within- and between-network resting state functional magnetic resonance imaging connectivity during propofol-induced loss of consciousness. Anesthesiology. 2010 Nov;113(5):1038–53.

79. Vanhaudenhuyse A, Demertzi A, Schabus M, Noirhomme Q, Bredart S, Boly M, et al. Two distinct neuronal networks mediate the awareness of environment and of self. J Cogn Neurosci. 2011;23(3):570–8.

80. Marguilho M, Figueiredo I, Castro-Rodrigues P. A unified model of ketamine's dissociative and psychedelic properties. J Psychopharmacol. 2023 Jan;37(1):14–32.

81. Cardone P, Alnagger N, Annen J, Bicego A, Gosseries O, Martial C. Psychedelics and disorders of consciousness: the current landscape and the path forward. Neurosci Conscious. 2024 Jan 1;2024(1):niae025.

82. Lapidus KAB, Levitch CF, Perez AM, Brallier JW, Parides MK, Soleimani L, et al. A randomized controlled trial of intranasal ketamine in major depressive disorder. Biol Psychiatry. 2014 Dec 15;76(12):970–6.

83. Yaden DB, Griffiths RR. The Subjective Effects of Psychedelics Are Necessary for Their Enduring Therapeutic Effects. ACS Pharmacol Transl Sci. 2020 Dec 10;4(2):568-572.

84. Olson DE. The Subjective Effects of Psychedelics May Not Be Necessary for Their Enduring Therapeutic Effects. ACS Pharmacology and Translational Science. 2021 Apr 9;4(2):563–7.

85. Johnston JN, Kadriu B, Allen J, Gilbert JR, Henter ID, Zarate CA. Ketamine and serotonergic psychedelics: An update on the mechanisms and biosignatures underlying rapid-acting antidepressant treatment. Neuropharmacology. 2023 Mar 15;226:109422.

86. Martial C, Cassol H, Charland-Verville V, Pallavicini C, Sanz C, Zamberlan F, et al. Neurochemical models of near-death experiences: A large-scale study based on the semantic similarity of written reports. Conscious Cogn. 2019;69:52–69.

87. Nicol AU, Morton AJ. Characteristic patterns of EEG oscillations in sheep (Ovis aries) induced by ketamine may explain the psychotropic effects seen in humans. Sci Rep. 2020 Dec 1;10(1):1–10.

88. Arena A, Comolatti R, Thon S, Casali AG, Storm JF. General anesthesia disrupts complex cortical dynamics in response to intracranial electrical stimulation in rats. eNeuro. 2021 Aug 5;8(4):ENEURO.0343-20.2021.

89. Arena A, Juel BE, Comolatti R, Thon S, Storm JF. Capacity for consciousness under ketamine anaesthesia is selectively associated with activity in posteromedial cortex in rats. Neurosci Conscious. 2022 Mar 4;2022(1):1–15.

90. Schartner MM, Carhart-Harris RL, Barrett AB, Seth AK, Muthukumaraswamy SD. Increased spontaneous MEG signal diversity for psychoactive doses of ketamine, LSD and psilocybin. Sci Rep. 2017 Apr 19;7.

91. Scott G, Carhart-Harris RL. Psychedelics as a treatment for disorders of consciousness. Neurosci Conscious. 2019;2019(1):1–8.

Figure Legends

Fig. 1: (**a**) EEG power spectral density (PSD) in resting state during wakefulness (green) and unresponsiveness with xenon (black), propofol (blue) or ketamine (red) in healthy study subjects. The authors investigated how the broadband PSD changes with these drugs, demonstrating (**b**) that the aperiodic component of ketamine remains partially unvaried in lower frequencies compared to wakefulness, (**c**) while it flattens in higher frequencies (from Colombo et al (2019) The spectral exponent of the resting EEG indexes the presence of consciousness during unresponsiveness induced by propofol, xenon, and ketamine. NeuroImage189: 631–644 with permission from Elsevier via Copyright Clearance Center Incorp.).

Fig. 2: Transcranial evoked potential (TEP) recordings during wakefulness (grey trace line left, middle, right), with propofol (blue trace line left), xenon (black trace line middle), or ketamine (red trace line right) with stimulation in Broadman area 6 and 7 (BA6 and BA7) in healthy volunteers. *TMS* transcranial magnetic stimulation (from Sarasso et al (2015) Consciousness and complexity during unresponsiveness induced by propofol, xenon, and ketamine, Curr Biol 25:3099–3105 with permission from Elsevier via Copyright Clearance Center Incorp.).

Fig. 3: The change of the perturbational complexity index (PCI) in Broadman area 6 and 7 (triangles indicate BA6 and squares BA7) in healthy volunteers during wakefulness (W) before anaesthesia (grey), and with propofol (blue), xenon (black), or ketamine (red) anesthesia. The PCI decreases with propofol and xenon as compared to wakefulness, whereas it does not with ketamine (from Sarasso et al (2015) Consciousness and complexity during unresponsiveness induced by propofol, xenon, and ketamine, Curr Biol 25:3099–3105 with permission from Elsevier via Copyright Clearance Center Incorp).

Fig. 4: Values of the Explainable Consciousness Indicator in awareness (ECI^{awa}) and arousal (ECI^{aro}) at different consciousness states in six healthy study subjects: (**a)** Disconnectedness with REM sleep shows high ECI^{awa}, but low ECI^{aro}, unconsciousness with NREM sleep shows low ECI^{awa} and low ECI^{aro}, whereas normal wakefulness shows high ECI^{awa} and high ECI^{aro}; (**b**) unconsciousness with propofol or xenon show low ECI^{awa} and low ECI^{aro}, whereas disconnectedness with ketamine shows high ECI^{awa} and low ECI^{aro}. *Sub01-06* study subjects number 1 - 6, *W–K* healthy wakefulness before ketamine, *W–P* healthy wakefulness before propofol, *W–X* healthy wakefulness before xenon (from Lee M et al (2022) Quantifying arousal and awareness in altered states of consciousness using interpretable deep learning. Nat Comm 13: 1–14 under a CC BY-4.0 commercial international license http://creativecommons.org/licenses/by/4.0/.)