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ORIGINAL ARTICLE

Complexity of Brain Dynamics as a Correlate of Consciousness in Anaesthetized Monkeys

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Abstract

The use of anaesthesia is a fundamental tool in the investigation of consciousness. Anesthesia procedures allow to investigate different states of consciousness from sedation to deep anesthesia within controlled scenarios. In this study we use information quantifiers to measure the complexity of electrocorticogram recordings in monkeys. We apply these metrics to compare different stages of general anesthesia for evaluating consciousness in several anesthesia protocols. We find that the complexity of brain activity can be used as a correlate of consciousness. For two of the anaesthetics used, propofol and medetomidine, we find that the anaesthetised state is accompanied by a reduction in the complexity of brain activity. On the other hand we observe that use of ketamine produces an increase in complexity measurements. We relate this observation with increase activity within certain brain regions associated with the ketamine used doses. Our measurements indicate that complexity of brain activity is a good indicator for a general evaluation of different levels of consciousness awareness, both in anesthetized and non anesthetizes states.

Keywords Entropy · Complexity · Anaesthetics · Consciousness · Brain dynamics

Introduction

The last few decades have witnessed significant advances in our understanding of the neural basis of consciousness, as new technological developments in brain imaging and electrophysiological methods allow for a precise spatio-temporal sampling of neural activity. Senior et al. (2006). Fundamental for this field is the idea that some features of brain activity correlate with different states of consciousness. The search for such features is crucial as it endows the field of consciousness with an empirical, falsifiable tool to quantify the elusive nature of subjective experience. Tononi and Edelman in their seminar paper suggest that one of these features may be complexity Tononi and Edelman (1998). Therefore, it is a common practice in consciousness research to investigate altered states of consciousness (e. g., coma, deep sleep stages, vegetative states or epileptic seizures), as the corresponding activity during such states largely differs from normal brain activity.

Anaesthesia is one of the most important brain states investigated in the framework of conscious studies, as it allows for a partial or total suppression of consciousness in a safe, controlled way. Indeed, unconsciousness is one of the features of general anaesthesia. It can be indirectly assessed by integrating different information such as clinical unresponsiveness (absence of movement or autonomic activation) or patient EEG. Different administration protocols lead to different depths in anaesthesia that could in principle correspondo differences in brain dynamics. However there is no single measurement (except for the lack of brain electrical activity) by which anaesthesiologist can objectively

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asses that a patient under general anaesthesia is unconscious. Among these method we have Perturbational complexity index (PCI), Spectral exponent Colombo et al. (2019), Biespectral Index Todd (1998).

Quantifiers based on information theory have proven to be effective in distinguishing between different brain states, such as sleep stages Nicolaou and Georgiou (2011), Bandt (2017), Kuo and Liang (2011) and in the detection of epileptic seizures Mateos et al. (2014), Mammone and Morabito (2011). These quantifiers do not require a large amount of signal pre-processing (in some cases they can be even directly applied to the raw signal) making them faster to implement in real time Zanin et al. (2012). These types of indices had also been used to characterise brain states in the domain of psychiatric and neurodegenerative diseases research Mateos et al. (2014), Mammone and Morabito (2011), Shumbayawonda et al. (2018). Within the particular field of anaesthetics research, measures such as Permutation Entropy Keller et al. (2017) have been used to quantify the effect of sevoflurane on EEG signals, obtaining better results than classical measures such as the Bispectral Index (BIS) Todd (1998), Li et al. (2008, 2010). Lempel-Ziv complexity has been used to study EEG signals in patients under the effects of propofol Zhang et al. (2001). Another study compares different entropic measures in patients under anaesthesia induced by GABAergic agents Liang et al. (2015).

In this work we used Electrocortical (ECoG) signals datasets provided by the Artificial Intelligence Laboratory of the University of Riken. The database consists of recordings from four macaques under the effects of four different anaesthetics schemes: propofol, ketamine, medetomidine and medetomidine-ketamine. The recorded brain activity was acquired within a controlled anaesthetic environment, providing accurate data sets which allows us for a precise analysis of the different possible states of consciousness.

As it is known, not all anaesthetics act similarly on the physiology of the central nervous system (CNS), so it is to be expected that EoCG signals have different dynamics depending on the drug used. Therefore, claiming that a single quantifier is optimal for studying states of consciousness for all anaesthetics could be wrong. To address this problem, we propose to analyse EoCG signals with three different information measures, which focus on studying unique characteristics of the signals. The first measure was the Shannon Entropy, which is a global quantifier of the system's uncertainty. The second quantifier is Lempel-Ziv Complexity, which measures the information redundancy within the signal. The third was Fisher's Information, which evaluates the local information contained in the signal. Each of these quantifiers focus on specific characteristics of the signal stream. The values of each quantifier were compared in each state of consciousness, and results were analysed through Complexity-Entropy planes in order to obtain supplementary information from the system. Also, we studied the distribution of information values over the cerebral cortex, and brain local variations according to different dynamical states. Results showed that two of the three quantifiers allow for the distinction of different states of consciousness. Significant differences were found between measurements for different anaesthetics schemes. Finally, it was observed that brain dynamics measurements from recovery states were significantly different from the baseline states.

Methods

Data

The data used in this study were taken from the open access database Neurotycho anesthesia and sleep task from the Artificial Intelligence Laboratory at Riken University Neu. The database consists of electrocorticographic (EoCG) signals recorded from the left hemisphere of four monkeys. The experiments consisted of measuring the electrophysiological activity of the monkeys in five different states of consciousness i) awake open eyes (AOE), ii) awake close eyes (ACE) iii) anaesthetised (AN) iv) recovery close eyes (RCE) v) recovery open eyes (ROE). For the anaesthetised states four different anaesthetics were used, ketamine (KT), medetomidine (MD), propofol (PF) and a combination of ketamine and medetomidine (KTMD), all information about the anaesthetics applied to each monkey and the number of trials performed can be found in Table 1. The protocol of the experiments, the doses of the drugs used and information on data acquisition is extensively detailed on the web page http://neurotycho.org/anesthesia-and-sleep-task. and in Yanagawa et al. (2013a). Data was acquired using 128-channel EoCG equipment with 1 KHz sampling frequency. Electrodes were placed on the left hemisphere of the monkeys, with 5 mm inter-electrode distance continuously covering the frontal, parietal, temporal and occipital lobes (Fig. 1A). Two of the four monkeys have electrodes on the medial side. The original signals had a duration of 5 to 20 minutes for each state. The data were downsampled from 1 KHz to 250

Table 1 Type of anaesthesia and number of trials applied to each monkey. Each trial was conducted on different days

Monkey	Anesthesia administered (number of trials)			
	Ketamin	Propofol	Medetomidine	Medetomidine + Ketamine
M1	2	2	2	2
M2	2	2	2	3
M3	-	-	-	3
M4	-	-	-	3

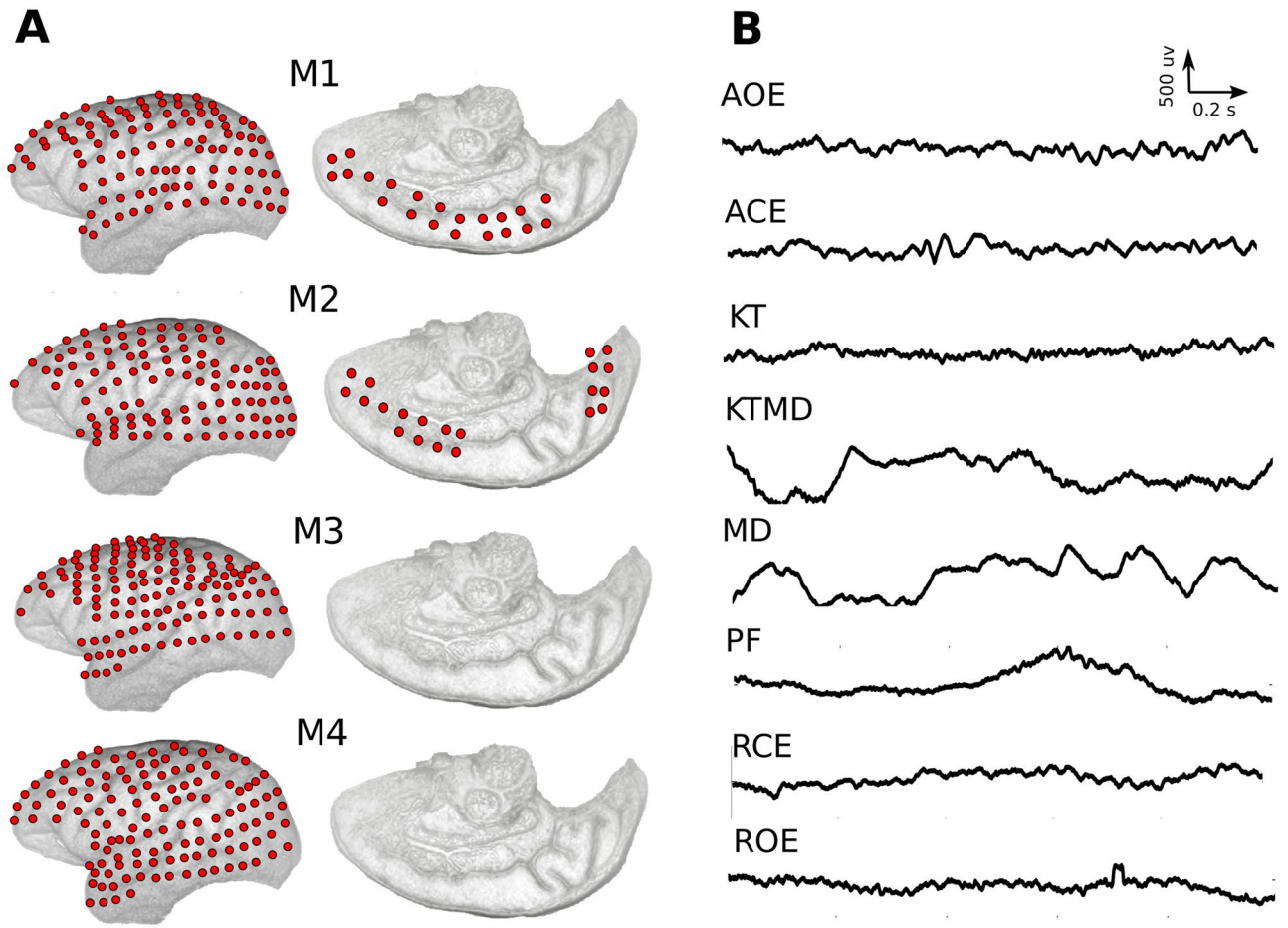

Fig. 1 **A**) Electrodes distribution over the brain for the four monkeys (M1 - M4) analysed in this work. **B**) Example of 2 sec recording of EoCG signals, belonging to a frontal channel of monkey 1 (M1). The signals correspond to the states: awake open eyes (AOE), awake close eyes (ACE), anaesthetised under kethamine (KT), kethamine + medetomidine (KTMD), medetomidine (MD), propofol (PF), recovery close eyes (RCE) and recovery open eyes (ROE)

Hz and preprocessed by applying a passband filter between 0.5 and 100 Hz and a notch filter at 50 Hz. The signal was cut in epochs 5s length, cleaned of artefacts visually and the whole signal was reconstructed again. From this signal, 5 minutes were taken. The first and last minutes of each state were discarded to be sure that the monkey was in the state and not in a transition. Finally, the signals to be analysed remained the same length of 3 min. In addition, with a view to a possible real-time analysis and robustness of the measurements, the signals were analysed with a non-overlapping running windows of 5 sec. Figure 1B shows an example of the signals obtained after preprocessing.

If we think about real time applications of these measurements, it is necessary to analyse the signals for short time, that is why we analysed the above signals using a non-overlapin running window of 5 sec (see Fig. 1 of the supplementary material). The results were similar to those obtained in the full signal analysis showing the robustness of the measurements.

Time Series Discretization using Ordinal Pattern Approach

As a pre-processing step, a discretization of the time series is performed. The study and characterisation of time series $\mathcal{X}(t)$ by recourse to information theory tools assume that the underlying probability distribution function (PDF) is given a priory. In the literature there are many methods to quantify continuous time series, such as binarization, histograms or wavelet, among others. However, an effective method that emerges naturally is the one introduced by Bandt and Pompe in 2002 called permutation vectors Bandt and Pompe (2002). This method is based on the relative values of the neighbours belonging to the series, so it takes into account the time structure or causality of the process that generated the sequence. To understand this idea, let us consider a real-valued discrete-time series $\mathcal{X}(t) = \{x_t \in \mathbb{R}\}$, and let $D \geq 2$ and $\tau \geq 1$ be two integers. They will be called the embedding dimension and the time delay, respectively.

From the original time series, we introduce a D-dimensional vector $\mathbf{Y}_t^{(D,\tau)}$:

$$\mathbf{Y}_t^{(D,\tau)} \rightarrow (x_{t-(D-1)\tau}, \dots, x_{t-\tau}, x_t) \qquad \text{with} \qquad t \geq (D-1)\tau \,. \tag{1}$$

The vector $\mathbf{Y}_t^{(D,\tau)}$ preserves the dynamical properties of the full dynamical system depending on the order conditions specified by D and τ. The components of the phase space trajectory $\mathbf{Y}_t^{(D,\tau)}$ are sorted in ascending order. Then, we can define a *permutation vector*, $\mathbf{\Pi}_t^{(D,\tau)}$, with components given by the original position of the sorted values in ascending order. Each one of these vectors represents a pattern (or motif) with $D!$ possible patterns. To clarify, let us show how all this works with an example. Suppose we have a continuous series such as $\mathcal{X}(t) = \{0.42,\ 1.6,\ 6.3,\ 0.15,\ 2.2\}$ and take the parameters $D = 3$ and $\tau = 1$. The embedding vectors $\mathbf{Y}_t^{(D,\tau)}$ are in this case defined as $\mathbf{Y}_1^{(3,1)} = (0.42,\ 1.6,\ 6.3)$; $\mathbf{Y}_2^{(3,1)} = (1.6,\ 6.3,\ 0.15)$; $\mathbf{Y}_3^{(3,1)} = (6.3,\ 0.15,\ 2.2)$, and the respective permutation vectors are $\mathbf{\Pi}_1^{(3,1)} = (0,\ 1,\ 2)$, $\mathbf{\Pi}_2^{(3,1)} = (1,\ 2,\ 0)$ and $\mathbf{\Pi}_3^{(3,1)} = (2,\ 0,\ 1)$.

Regarding the selection of the parameters, Bandt and Pompe Bandt and Pompe (2002) suggested working with $3 \leq D \leq 6$ and specifically considering an embedding delay $\tau = 1$. Nevertheless, other values of τ could provide additional information. It has been recently shown that this parameter is strongly related to the intrinsic time scales of the system under analysis Zunino et al. (2010), Soriano et al. (2011), Zunino et al. (2012).

Information Quantifiers

In this work we used three information quantifiers to characterise brain dynamics on the basis of ECoG recordings: Permutation Shannon Entropy (PE) Bandt and Pompe (2002), Permutation Lempel-Ziv complexity (PLZC) Zozor et al. (2014) and Fisher Information (FI) Fisher (1922). Beyond the myriad of information measures in the literature, we particularly chose these three quantifiers due to the fact that in principle each one can extract different features of the ECoG signals. In the following sections we give a brief description of each of them.

Permutation Shannon Entropy

Permutation Shannon entropy (PE) measures the uncertainty degree of a system. When the probability distribution of the system states is uniform (random signals) entropy tends to be maximal, while for purely deterministic signals such as periodic systems entropy is very small. Its a global measure of information, in the sense that it quantifies the information about the whole time series under consideration.

Given a time series $\mathcal{X}(t) \equiv \{x_t; t = 1, \dots, N\}$, with N the number of observations, the Shannon's logarithmic information measure (Shannon entropy) Shannon and Weaver (1998) of the associated probability distribution function (PDF), $P \equiv \{p_i; i = 1, \dots, M\}$ with $\sum_{i=1}^{M} p_i = 1$, and M the number of possible states is defined as:

$$\mathcal{S}[P] \ = \ -\sum_{i=1}^{M} p_i \log(p_i) \,. \tag{2}$$

When there is total certainty that the system is in the state i the probability $p_i = 1$ and this functional is equal to zero. In contrast, when the probability distribution is uniform, $P_u \equiv \{p_i = 1/M; \forall i = 1, \cdots, M\}$, knowledge about the system is minimum (all the states have the same probability) and the entropy reach its maximum.

Bandt and Pompe defined Permutation Entropy as Shannon entropy applied to the distribution of ordinal patterns Bandt and Pompe (2002). Given the series of ordinal patterns $\mathcal{W} = \{\Pi_1, \dots, \Pi_t\}$, obtained from the time series $\mathcal{X}$ and $p_j^{\Pi} = P(\Pi^j)$, with $j = 1, \dots, D!$ the probability of occurrence of the pattern Π_j, the normalised permutation entropy is defined as:

$$\mathcal{H}[P] = \frac{-\sum_{j=1}^{D!} p_j^{\Pi} \log(p_j^{\Pi})}{log(D!)} \tag{3}$$

Lempel–Ziv Complexity

To estimate the complexity of a time series $\mathcal{X}(t)$ we use Lempel–Ziv complexity (LZC) Lempel and Ziv (1976), which is based on Kolmogorov complexity. The Kolmogorov complexity of a sequence of symbols is the minimal size of the computer program that can produce it as an output Cover and Thomas (2006). Lempel-Ziv complexity is obtained as follows. A sequence of symbols $\mathcal{X}(t)$ is parsed into a number $\mathcal{W}$ of words by considering any subsequence that has not yet been encountered as a new word. The Lempel–Ziv complexity c_{LZ} is the minimum number of words $\mathcal{W}$ required to reconstruct the information contained in the original time series. For example, the sequence 10011011100101000 1011 can be parsed in 7 words: $1 \cdot 0 \cdot 01 \cdot 101 \cdot 1100 \cdot 1010 \cdot 001011$, giving a complexity $c_{LZ} = 7$. An easy way to apply the Lempel–Ziv algorithm can be found in Kaspar and Schuster (1987). The LZC can be normalized based in the length N of the discrete sequence and the alphabet length (α) as:

$$\mathcal{C}_{LZ} = \frac{c_{LZ}[log_{\alpha}N]}{N}$$

.

Although Lempel and Ziv developed the complexity for binary sequences, it can be used for any finite alphabet. Based on this, Zozor et al. (2014) applied LZC on signals

quantified by ordinal patterns, this method has the name of *Permutation Lempel–Ziv complexity*(PLZC).

Fisher Information

Shannon entropy $\mathcal{S}$ is a global information measure. To take into account local changes, it is customary use the Fisher information $\mathcal{F}$ Fisher (1922), Frieden (2004) define as:

$$\mathcal{F}[f] = \int \frac{\mid \nabla f(x) \mid^2}{f(x)} dx \tag{4}$$

Because of the presence of a gradient operator in this equation, Fisher information is sensitive to local (differential) changes. It constitutes a measure of the curvature of the distribution $f(x)$, so is sensitive to small, localised perturbations.

In order to compute the Fisher information of discrete time series, we adhere here to the proposal of Dehesa and coworkers Sánchez-Moreno et al. (2009) and define it for the discrete probability distribution $P \equiv \{p_i; i = 1, \dots, M\}$ as:

$$\mathcal{F} = 4 \sum_{i=1}^{M-1} (\sqrt{p_{i+1}} - \sqrt{p_i})^2 \,. \tag{5}$$

A system that has a very few possible outcomes has a very narrow PDF. The Shannon entropy of this probability distribution is close to zero (minimal uncertainty) whereas its Fisher information is maximal (very large curvature of the PDF). On the other hand, when the possible outcomes of the system have equal probability the PDF is a very flat curve. In this case, the Shannon entropy of the PDF is large whereas its Fisher information is close to zero. In other words, Fisher information and the Shannon entropy are inversely related Pennini and Plastino (2005).

Comparison of Different States of Consciousness

We compared the information/complexity values obtained for each state of consciousness. The complexity/entropy measures were applied over the permutation sequences of EoCG signals obtained by the method explained in section 2.2 We did this for each of the anaesthetic schemes applied (Fig. 2). The bar groups represent the anaesthesia applied –ketamine (KT), medetomidine (MD), propofol (PF), ketamine-medetomidine (KTMD)– and each individual bar is the state value –awake open eyes (AOE), awake close eyes (ACE), anaesthetised (AN), recovery close eyes (RCE), recovery open eyes (ROE). Mean values and errors were calculated over all channels of all monkeys. A statistical study was performed using a linear mixed model (ANOVA). The same letters in the figures represent states with no significant differences.

Figure 2 A1/A2 corresponds with the permutation entropy (PE) and permutation Lempel Ziv complexity (PLZC) analysis. These measures can differentiate between AOE, ACE and anaesthetised states AN however, cannot discriminate between recovery states RCE and ROE. In all cases awake monkeys have higher entropy/complexity in open eyes than close eyes. For the anaesthesia states we see that ketamine shows markedly higher values of PE and PLZC relative to the baseline state. Ketamine + medetomidine have similar values to AOE but higher than ACE. Medetomidine has the lowest entropy/complexity values of all anaesthetics and is markedly different from the baseline. Propofol has a similar behaviour to medetomidine with decreasing values relative to the baseline. The recovery states for both open eyes (RCE) and closed eyes (ROE) have values that exceed both the baseline and anaesthetised states in all cases. No significant differences in entropy or complexity are found between the RCE and ROE states. Seeing Fig. 2A3 we can conclude that Fisher information does not distinguish differences between any states.

As mentioned, the signal was analysed using non-overlapping running windows of 5 sec on the 3 min pre-processed signals, with a view to a possible real-time application. The results were similar to those obtained with the full signal (see Fig. 1 Supplemental Material), showing the robustness of the measurements used.

Generally, permutation entropy and Lempel–Ziv complexity are the only measures that can distinguish between awake open and closed eyes awake states. For all types of anaesthesia the recovery values overcomes the baseline values. None of the quantifiers can differentiate between closedand open eyes recovery states. An important point is that the permutation entropy and Lempel–Ziv complexity values are significantly different for the four types of anaesthesia. Fisher's information values cannot differentiate between any of the states, except for MD between awake and recovering when using medetomidine.

A different way to analyse these results is through the use of complexity-entropy planes. They allow access to relevant information that is not possible to reach through the separate study of these quantifiers. These planes can be used to obtain information that is not possible by analysing the signals separately. It also allows a better visualisation of the results. In the literature there are different types of complexity-entropy planes Martin et al. (2006), Rosso et al. (2007), Mateos et al. (2017), in this work we focus on the Permutation Lempel-Ziv complexity vs. permutation entropy plane ($LZ \times PE$) Mateos et al. (2020). This plane has been used to distinguish between chaotic and random signals Mateos et al. (2020), to analyse electrophysiological signals in altered states of consciousness Mateos et al. (2018) and to characterise sleep states Mateos et al. (2021).

Figure 2B shows the values of the EoCG belonging to the awake (open eyes) and anaesthetised (KT, KTMD, MD and PF) states in the Lempel–Ziv complexity–permutation entropy plane. The results show that ketamine has higher complexity and entropy values than in the awake condition. On the other hand, there is a marked decrease in entropy and complexity values for the case of propofol and medetomidine. Ketamine-medetomidine does not show significant changes with respect to the awake state. The entropy and complexity values correspond to anaesthetised states moving in areas that are above or below the awake state depending on the anaesthesia. This finding shows that each anaesthesia produces different changes in brain dynamics.

Differences between Brain Dynamics before and after Anaesthetic

In Figure 3 we see that for two of the three quantifiers the recovery and baseline values are different. Because of this, a more in-depth study was carried out. We calculated the difference between the recovery and awake values. This was done for both eyes closed and eyes open (ROE-AOE and RCE-ACE). In all cases, a statistical study was performed using a paired *t*-test. Figure 3A shows the difference between the complexity/entropy values belonging to recovery and awake open eyes over all the anaesthetics applied. All anaesthetics show significant differences for permutation entropy

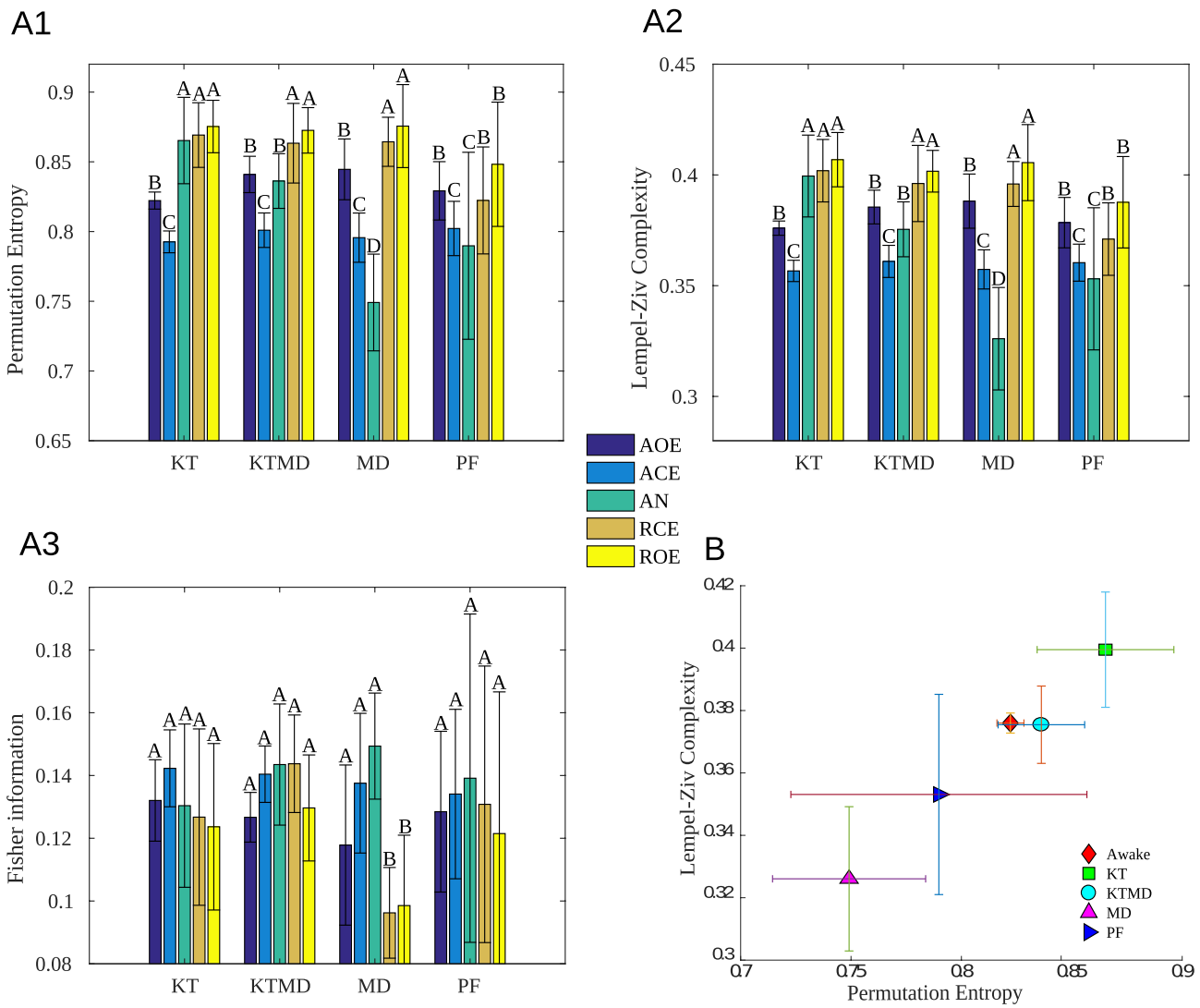

Fig. 2 Complexity/information measures for the different states of consciousness: awake open and close eyes (AOE, ACE), anaesthetised (AN), recovery open and close eyes (RCE, ROE). The anaesthetics used were: ketanime (KT), ketanime - medetomidine (KTMD), medetomidine (MD) and propofol (PF). **A1**) represent Permutation entropy analysis, **A2**), Lempel-Ziv complexity and **A3**) Fisher information. The bars and errors represent the mean value and standard deviation over all channels and all monkeys. The same letters correspond to states with no significant differences. **B**) Analysis of ECoG signals using Complexity-Entropy plane

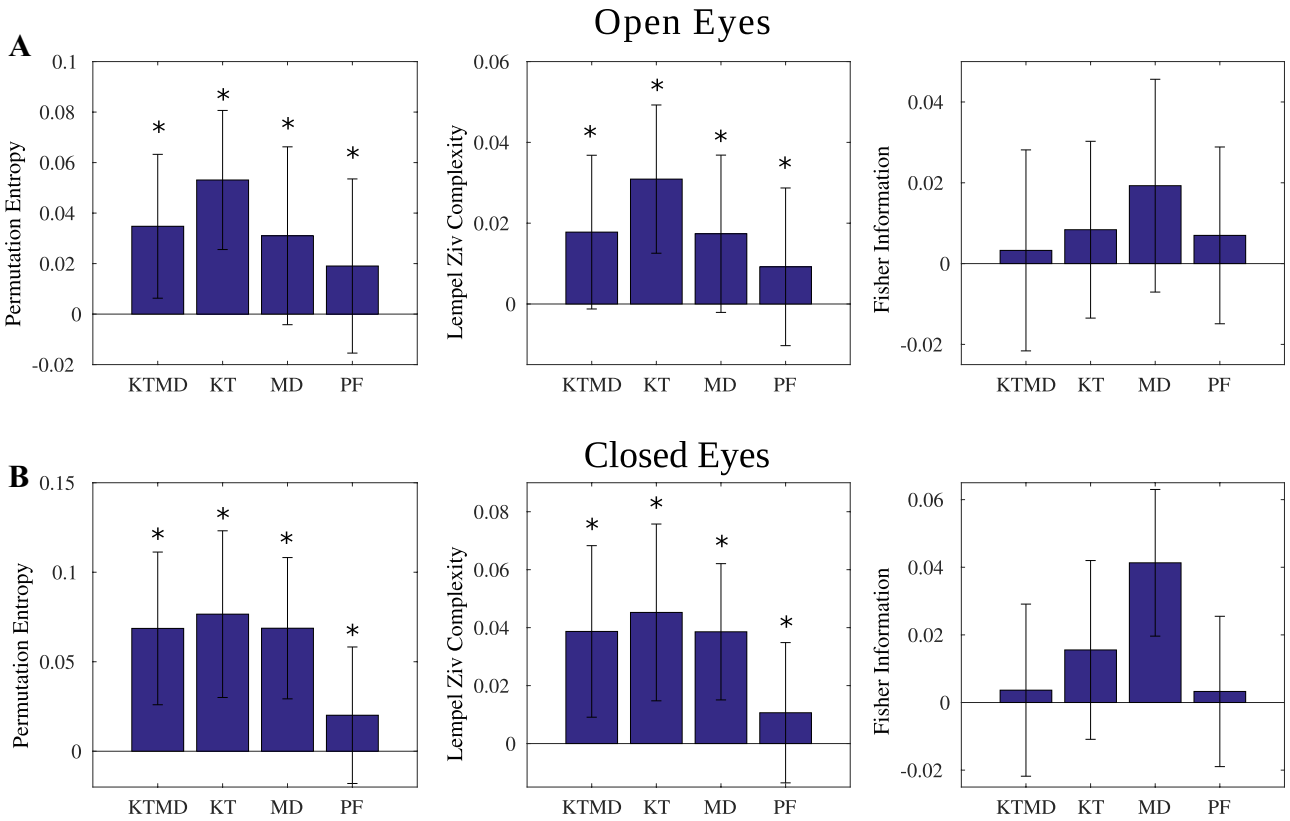

Fig. 3 **A**) Difference between the complexity brain dynamics during recovery open eyes and awake open eyes **B**) Similar study for the recovery closed eyes and awake closed eyes

and Lempel–Ziv complexity, but not for Fisher information. Permutation entropy and Lempel–Ziv complexity values are higher for the recovery case compared to the baseline. Ketamine presents the highest and propofol the smallest differences between states. Figure 3B shows the difference in complexity/entropy values between the awake and recovery colsed eyes states for each anaesthetic. As in the case of open eyes, permutation entropy and Lempel–Ziv complexity differences between states are significant. Ketamine–Medetomidine, have similar values than ketamine and medetomidine alone, while propofol has a lower value. These results show that although the monkeys state is reported as 'recovered' from the effects of anaesthesia, in fact the monkey has not reached its initial basal state. This fact shows the importance of information quantifiers for assessing states of consciousness as they can measure relevant information which cannot be acquired by visual analysis.

Analysis Per Channel

An important aspect to study is the distribution of complexity/information values over the brain in each state of consciousness. To this end, an analysis was carried out for each channel separately. We study monkey No. 1 because it is the only one in which the four anaesthetics were applied. For this analysis the ordinal pattern parameters used were $D = 5$ and $\tau = 1$.

Figure 4 shows the distribution of permutation entropy values for awake and anaesthetised states. In the awake state there is a distribution of high entropy values over the frontal-central and temporal areas, and medium values in parietal and occipital areas. Permutation entropy values decrease globally in ketamine–medetomidine, particularly in the frontal and medial areas where entropy decreased significantly. For ketamine the entropy values increased above the awake values, especially in the fronto-temporal, central and medial areas. Medetomidine low decreas values in the frontal and central area and and higer decreas values in the occipital area. Propofol presents a global decreased in entropy compared to awake states, especially in the temporal, prefrontal and central areas (anterior electrodes). Similar results were obtained by PLZC (see supplemental material). Fisher's data showed no significant changes between carcasses or anaesthetics (see supplemental material).

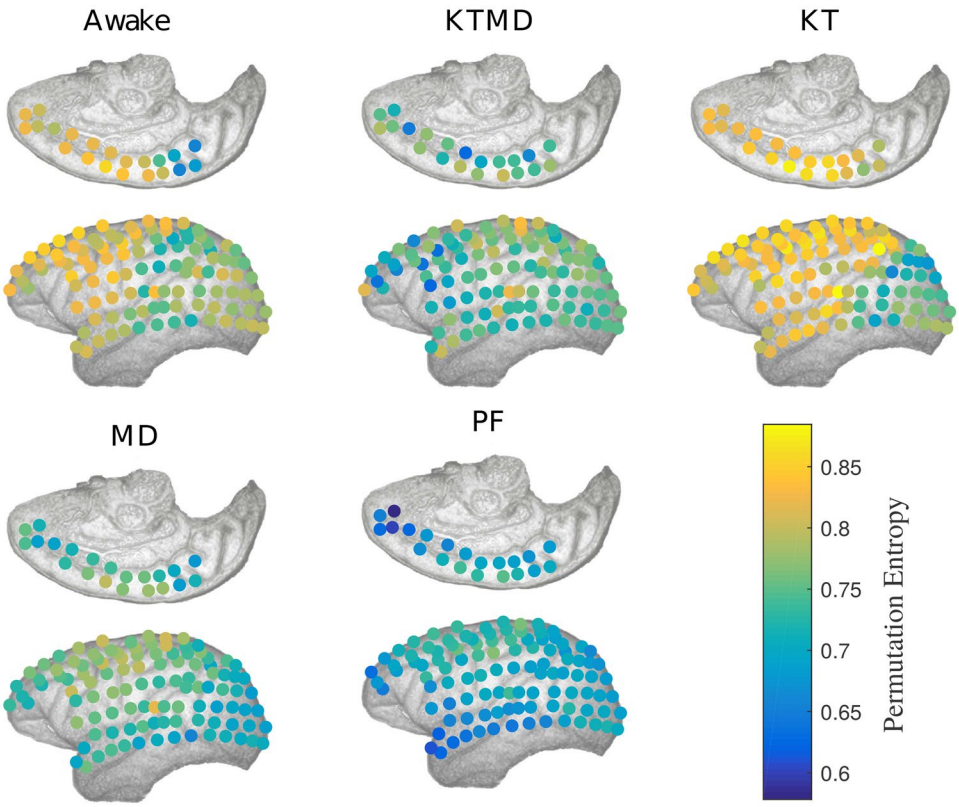

Fig. 4 Permutation entropy analysis for each of the 125 channels belonging to Monkey 1 for the states awake (AOE) and anaesthetised (KTMD, KT, MD,PF). The ordinal pattern parameters used for the analysis were $D = 5$ and $\tau = 1$

Discussion

In this study we investigate conscious awareness in anaesthetised monkeys. We find that brain dynamics, as recorded by electrocorticography, depends on the stage of consciousness and on the type of anaesthetics used. Four types of anaesthetics schemes were used (ketamine, medetomidine, propofol and a mixture of ketamine and medetomidine) and three main stages of consciousness awareness investigated (the animal can either be awake, anaesthetised or recovering from anaesthetics; we further investigated the effect of having the eyes closed or opened).

To understand how brain dynamics correlates with the level of conscious awareness we used three measures of signal complexity: permutation entropy, Lempel–Ziv complexity and Fisher information. Taken together, these measures cover a large spectrum of signal's features, allowing for a thorough characterisation of brain dynamics. However, even if such measures are very different, they are not independent. Indeed, we found that permutation entropy and Lempel–Ziv complexity are directly proportional so they can be used equivalently as quantifiers of the brain dynamics investigated (see Fig. 2B). This is in accordance with previous work, that shows that for the type of electrophysiological signals investigated in the current work, that is, very noisy signals, entropy and complexity tent to be equivalent Zozor et al. (2014). This means that patterns of temporal dynamics do not add more information about the signal than what is already present in the histogram of the signal. Furthermore, it can be also inferred from our results that Fisher information measures are inversely related to both permutation entropy and Lempel–Ziv complexity (see Fig. 2A3). This is because Fisher information is a local quantifier of the signal whereas permutation entropy and Lempel–Ziv complexity are global quantifiers. As we discuss in more detail in the methods section, global and local (differential) measures are inversely related. In other words, our results suggest there are strong correlations between measures of brain activity for the three information theory metrics used. We can conclude that in the dynamic range used, electrophysiological signals can be completely characterised by any of them. So, in the following, we discuss our results in terms of permutation entropy alone, and we refer to it as "complexity".

We found significant differences in the complexity of brain activity between different anaesthetics schemes. The general result is the following: medetomidine and propofol decrease the complexity of brain activity but ketamine doesn't. More specifically (see Fig. 2A1): 1) Under the effect of anaesthesia, the complexity of brain activity is the lowest in the anaesthetised state than in any other state investigated, both for medetomidine and propofol. 2) This is not true when ketamine is used (alone or accompanied by medetomidine). If ketamine is used alone, the anaesthetised state has more

complexity than the initial, awake state. By mixing ketamine with medetomidine, this effect is diminished.

Physiological, this can be explained in terms of the specific action of these anaesthetics. In the case of propofol, it works by binding to $GABA_A$ receptors, triggering widespread inhibition of neuronal activity. At low doses, propofol induces states of amnesia, sedation, atonia, whereas at higher doses it induces anaesthesia Khan et al. (2014), Hemmings et al. (2019). Experimental evidence suggests propofol inhibits the ability of the brain to maintain high levels of dynamical complexity, resulting in a low-entropy state insufficient for supporting conscious awareness Schartner et al. (2015), Sarasso et al. (2015). This finding supports previous research which shows a decrease in Lempel-Ziv complexity and permutation entropy values under the effects of this anaesthetic in scalp EEG studies Hudetz et al. (2016), Ferenets et al. (2007), Xu et al. (2004). Many study shows slow rhythms (< 4 Hz) are a ubiquitous feature of general anesthesia, being readily induced in humans by propofol Gugino et al. (2001), Murphy et al. (2011), Lewis et al. (2012), Purdon et al. (2013). As humans are induced into a state of general anesthesia via propofol, the normal alpha rhythm (8 - 13 Hz) in the occipital cortex disappears and a frontal alpha rhythm emerges. This spatial shift in alpha activity is called anteriorization Mukamel et al. (2014), Feshchenko et al. (2004). However, recent studies show that similar behaviour occurs for the delta bands Brake et al. (2021). In addition to the above, it has been shown that the appearance of spatially coherent frontal alpha oscillations. In addition studies discovered a coupling between the phase of low-frequency activity (0.1-2 Hz) and the amplitude of alpha rhythms (8 -14 Hz) in scalp EEG recordings during propofol general anesthesia Mukamel et al. (2011), Purdon et al. (2013). Similarly Purdon et. al showed the low-frequencies phases are modulated by alpha amplitude under the effect of propofol Purdon et al. (2013). The slow waves increment and the coupled with the modulation of alpha waves over low frequency waves, can result in electrophysiological signals becoming more periodic and therefore less complex or entropic. This can be clearly seen in Fig. 4 where the entropy values corresponding to Propofol decrease markedly especially in the frontal area.

The action of medetomidine is similar to that of propofol. This drug is a racemic mixture of two optical stereoisomers: dexmedetomidine (the active enantiomer) and levomedetomidine. It produces sympatholysis, sedation, and antinociceptive effects. It acts nonselectively on various subtypes of membrane-bound G protein-coupled α 2-adrenoceptors. Intracellular pathways include inhibition of adenylate cyclase and modulation of calcium and potassium ion channels. This drug produces a decrease in activity of the projections of the locus coeruleus to the ventrolateral preoptic nucleus. This is an essential component of the onset of the stage of sleep non-rapid eye movement (NREM). This could be an explanation why the medetomidine values are located in the same zone of the complexity-entropy plane as those observed for subjects in the NREM state Mateos et al. (2021). Our finding seems to be consistent with an fMRI study from subjects under different anaesthetics which showed that medetomidine had significantly lower entropy values than other anaesthetics Grandjean et al. (2014). Studies suggest that under resting state, EEG power shows a depression of inter-hemispheric EEG coherence in the gamma band at higher medetomidine dosage. These studies show that medetomidine does not suppress neural activity but dissociates connectivity in the somatosensory cortex Nasrallah et al. (2012, 2014). However, electrophysiological studies with metodomidine are fewer in number compared to those with propofol or ketamine. However, being an anaesthetic similar in nature to propofol, we can hypothesise that the effects on neuronal dynamics could be similar (but not the same). Therefore, entropy and complexity values decrease in the anaesthetised state with medetomidine, similar to what occurs with propofol. However, we have to take into account that when studying topological information, brain areas do not respond in the same way to the two anaesthetics. Contrary to propofol and medetomidine, brain activity under ketamine administration shows higher values of complexity in comparison with awake states. This result may be explained by the fact that ketamine acts primarily as an antagonist of glutamaterigic N-methyl-D-aspartate receptor (NMDA) Khan et al. (2014), Zanos et al. (2018), causing widespread, light central nervous system stimulation and a state typically referred to as ”dissociative anesthesia” Domino et al. (1965), Krystal et al. (1994).

Unlike propofol, which reduces consciousness even at low doses, ketamine often produces complex conscious experiences, including hallucinations, out-of-body experiences, and dream-like, immersive experiences Zanos et al. (2018). Ketanime’s blockade of NMDA is thought to dis-inhibit cortical neurons, causing widespread, uncoordinated excitatory activity Zanos et al. (2018), Schartner et al. (2017). This may result in an increase in the entropy of brain activity without abolishing consciousness, artificially expanding (or at least altering) the state-space repertoire. This decorrelated signal activity, made ketamine values move towards an area where the signals with higher randomness reside in the entropy-complexity planes Rosso et al. (2007), Mateos et al. (2020). The hypothesis in which the dynamic state of higher-than-normal entropy might correspond to a psychedelic or hallucinatory state of consciousness has become known as the Entropic Brain Hypothesis Carhart-Harris and Friston (2019), Carhart-Harris et al. (2014). Moreover, these results are consistent with other studies showing that Lempel-Ziv complexity and entropy increase under effect of ketamine Schartner et al. (2017), Liu et al. (2018), Zhang

et al. (2001). In other electrophysiological studies, ketamine affects sensory gating and alters the oscillatory characteristics of neuronal signals in a complex manner Lazarewicz et al. (2010). Study in human Magnetoencephalography (MEG) determined that ketamine increased beta amplitudes, decreased peak gamma frequency in visual cortex and significantly amplified gamma-band amplitudes in motor and visual cortices Shaw et al. (2015). Gamma-band oscillations alterations also appear in the acute state after administration of NMDAR antagonists to healthy humans Kocsis et al. (2013), Hong et al. (2010), Rivolta et al. (2012). An intracranial study in Rats shows spontaneous high-frequency oscillations (140 - 180 Hz) present in local field potentials recorded from the Nucleus Acumbens Hunt et al. (2006). Similarly, in ships with chronically-implanted subdural electrodes, Ketamine induces alternating bursts of theta-gamma oscillations that correlate with the dissociative state Nicol and Morton (2020). This increase in high frequency band oscillations could be one of the causes of the increased entropy/signal complexity in the Ketamine anaesthetised state. Adding to this connectivity studies in ketamine shows the disruption of cortical network connectivity Muthukumaraswamy et al. (2015), Bonhomme et al. (2016), Krzemiński et al. (2017), Scheidegger et al. (2012). However, there is another effect that can be added to the previous one due to the use of this drug, the disruption of cortical network connectivity Muthukumaraswamy et al. (2015), Bonhomme et al. (2016), Krzemiński et al. (2017), Scheidegger et al. (2012). This disconnection between brain areas would result in electrophysiological signals with more random characteristics givins as a result a greater entropy and complexity.

Although sedation, analgesia and sympatholysis are produced during the administration of medetomidine, this drug must be used as a coadjuvant as it does not reach satisfactory anaesthetic conditions by itself. Association with opioids or ketamine is recommended in veterinary practice. Drug combination as adjuvants is used to reach pharmacologic effects by increasing efficacy and potency of individual drugs. There is also, as a consequence, a reduction in total doses and side effects. The use of a lower dose of both anaesthetics may be the reason why when a mixture of ketamine and medetomidine is used, the values of complexity are least variable in relation with the awake state (Fig. 2A1).

It is important to highlight that although different anaesthetic drugs have similar observable clinical effects, the exact mechanisms of action and neurodynamic effects of these are still unknown Franks (2006). Indeed, some medications tend to act on specific receptors while others do so on various types of receptors whereas receptors have different affinity for different drugs, even in the case of receptors from the same structure family. Furthermore, the action of anaesthetics is further complicated by their dependence on drug concentration. Indeed, drugs that act on different receptors usually do so in an overlapping way. At low concentrations they bind and activate only high affinity receptors. As drug concentrations are increased, a mass effect generates the binding and activation of receptors with less affinity. It has been proposed that many anaesthetic drugs can also act in a nonspecific and generalised way in the nervous system. They may do this by modifying the solubility of plasma membranes and its components and even by modifying the dynamics of Brownian movements of molecules that intervene in the exocytosis of synaptic vesicles. These effects may alter the precision of global electrochemical signaling Bademosi et al. (2018), Hantal et al. (2019). Increasing concentrations of a drug which generates networks activation at low doses may generate a global depressant effect at high concentrations Brown et al. (2011).

Our study indicates that the only information quantifier that allows distinguishing between eyes opened or closed in awake states is permutation entropy. This is in agreement with recent work Quintero-Quiroz et al. (2018), in which it was possible to detect changes of states between eyes open and eyes closed in human scalp electroencephalography using permutation entropy or in similar studies using Lempel Ziv complexity Ibáñez-Molina et al. (2015). This difference in complexity is to be expected due to the appearance of alpha waves in AEC Berger (1929). These waves cause the signal to become more periodic (less number of different patterns are required) resulting in a decrease in complexity. This result is interesting because other measures of complexity based on information integration are not able to differentiate between these two states Casali et al. (2013). However, this measure present some limitation, none of the quantifiers used were able to differentiate between the brain activity of monkeys with eyes opened or closed during the recovery state. Furthermore, the open eyes recovery state had larger complexity than any other state for all the anaesthetics used. We consider that this result is important for the evaluation of anaesthetics effects in the medical setting, since it shows that visual inspection of raw signals is not always an accurate tool. This observation leads us to propose that an analysis of states of consciousness based on more reliable quantifiers would be useful in clinical practice. Our hypothesis is that recovery values return to baseline values after a sufficiently long time. Unfortunately we do not have extensive recording time to be able to corroborate this fact. Moreover, if such records were available, it would be interesting to study the average time it takes for each anaesthetic scheme to finish its neural dynamic effect completely. However, it must be taken into account that once drug administration has been interrupted, their uncoupling from receptors and sites of action is usually variable according to their physicochemical characteristics that determine their distribution and elimination mechanisms. This implies that the effects in different places can disappear in a differential way Kim et al. (2018),

Kushikata and Hirota (2014), Cascella et al. (2018). Furthermore, the activation or inhibition of specific receptors at different sites can generate both a reduction or an increase in the activity of underlying networks. For example, a drug that inhibits an inhibitory network can result in increased activity in a specific region of the nervous system.

The analysis per channel showed that the variation of complexity/entropy values under the effects of anaesthetics occurs over the entire brain surface. However, there are areas which are more sensitive to changes depending on the drugs used. The general trend is that ketamine induces an increase in complexity in frontal and fronto-parietal areas whereas propofol and medetomidine produce a whole-brain decrease in complexity. This is consistent with the idea that different drugs exert their effects on diverse sites of action distributed in a heterogeneous way among the nervous system's structures Varnäs et al. (2021), Saba et al. (2015). However, other studies on propofol show a decrease in the integration of information over occipital areas Luppi et al. (2019), Hahn et al. (2021). This difference in results may be due to the fact that the metrics used to measure differences between states of consciousness measure different characteristics of the system Sarasso et al. (2021).

Fisher information was not an efficient quantifier for distinguishing states of consciousness. This may be because changes in the ECoG dynamics are global –changes occur throughout the signal and not in localised segments, because Fisher information is a local quantifier, it is not able to detect the variations at a general level. However, these changes are detectable using global quantifiers such as permutation entropy or Lempel–Ziv complexity.

Among the limitations of this work we can mention the lack of knowledge about the subjective experiences of monkeys under the effects of ketamine. As explained above, the perception of reality seems to be altered and depends on the doses applied. We extrapolate results from reports described in humans Krystal et al. (1994), Zanos et al. (2018), but we recognise that there are limitations when comparing them with these types of animals. Another limitation is the limited number of monkeys (four) and the fact that they all received different anaesthetic regimens. Given the unavailability of such data sets, a small sample size was unavoidable. However, we hope to generalise these results in future work, in order to provide more powerful statistics.

In a recent study Sarasso et al. (2021) reviews more than 200 papers on complexity measures applied to the study of states of consciousness, classifying these measures into four groups: i) topological differentiation, ii) temporal differentiation, iii) metastability and ii) criticality and perturbation. The measures applied in this work would fall into the second group which capture brain differentiation but not brain integration. Particularly, with this database, different studies have been carried out focused on the analysis of the integration of brain information such as, for example, with networks generated by spectral Granger causality Yanagawa et al. (2013b), applying integrate information theory (IIT) Oizumi et al. (2016), Kitazono et al. (2018), using long-range correlation in different frequency bands Krzemiński et al. (2017), applying Topological data analysis Varley et al. (2020) or study of criticality Toker et al. (2021). However, beyond the valuable information that these studies provide for the understanding of brain dynamics, they are difficult to apply in real time, since they require having the information of the complete signals or the computation time is high. That is why we decided to apply information measures that are robust to noise, fast to compute and do not require a large amount of data.

Finally, a few words on the importance of the techniques used in this work for medical applications. The search for simple and direct quantifiers of brain activity characterising different depths of anaesthesia is fundamental for consciousness research but also crucial and in the medical setting. In particular, they serve as a guide to surgeons to evaluate the effectiveness of anaesthetics during surgical interventions. Currently, there are different indexes of anaesthesia depth commercially available (such as Fourier Transform Loomis et al. (1937), Bicoherence Todd (1998), Evoke potentials Hansson et al. (1998), Burst Suppression Ratio Jensen et al. (2004) or Approximate Entropy Bruhn et al. (2000)) that can be computed from electroencephalografic (EEG) recordings. The main drawback of these measures is that they often require great computational power and expensive equipment (consider, for example, the EEG anaesthesia monitor M-entropy, the BIS VISTA™ Monitoring System or Narcotrend EEG monitor, among others). For this reason, the search for new types of brain quantifiers of conscious awareness, such as those proposed by us, based on faster algorithms driven by open source development, is crucial in the field of anaesthesiology. Furthermore, we showed that electroencephalography data allow for a discrimination in brain dynamics under different anaesthetics drugs regimes, so it can be useful for assessing depth of anaesthesia and for decision making scenarios in the medical setting. Measuring the complexity of brain activity have potential applications in anaesthesiology such as patient safety, quality improvement and performance analysis. Benefits could arise from a pharmacoeconomic perspective as these quantifiers may help professionals for efficient drug delivery strategies. This could result in cost reductions. Furthermore, we believe that these techniques could feed machine learning algorithms in order to develop and improve closed loop systems for automatic anaesthetic drug delivery.

Conclusion

We have found that the complexity of brain activity correlates with conscious awareness. This is in agreement with other accounts that associate consciousness with brain dynamics, and in particular to the information content or complexity of neural activity and networks. Our results show that low complexity in brain dynamics is associated with the action of anaesthetics such as propofol and medetomidine, that inhibit neural activity. We also find that this is not the case for ketamine, for which the anaesthetic increase the complexity of brain activity. This results supports the idea that the anaesthetic action of ketamine is different than other drugs, as this drug increases, rather than decrease, neural activation, and is associated to hallucination and other altered states of consciousness.

Information Sharing Statement

The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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