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The Temporal Dimension of Consciousness: exploring Intrinsic Neural Timescales (INTs) and their role as a facilitator of consciousness

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Glossary

Term	Definition
INT	Intrinsic Neural Timescale. Temporal duration of spontaneous neural activity.
IIT	Integrated Information Theory of consciousness.
TTC	Temporospatial Theory of Consciousness.
GNWT	Global Neuronal Workspace Theory of consciousness.
ACW	Autocorrelation Window. Based on the computation of the signal's Autocorrelation Function (ACF), it's originally formalized as the time lag at which the ACF reaches its full width at half maximum (FWHM), but other variants exist.
DoCs	Disorders of consciousness. Clinical states characterized by partial or full loss of consciousness acquired after severe brain injuries.
CRS-R	Coma Recovery Scale – Revised. The gold-standard neurobehavioral scale for the clinical assessment of DoCs, consisting of the evaluation of six subscales.
GCS	Glasgow Coma Scale. The first behavioral scale for the clinical assessment of DoCs, consisting of the evaluation of three subscales.
PE	Permutation Entropy. Entropy measure based on a symbolization procedure.
PE-TD	Permutation Entropy Time Delay estimation. Based on PE, it is defined as the absolute minimum of the PE vs tau function. Detailed in Chapter 3.

Abstract

The long-standing quest for consciousness is gathering more and more interest in the scientific community. As the investigation of the nature of subjective experiences reaches unparalleled levels of refinement, the stakes become higher and higher, such that novel perspectives on the neuroscientific basis of consciousness are needed. Recently, it has been proposed that the temporal structure of the brain's spontaneous activity might be key for consciousness, despite having been overlooked by most current theoretical frameworks. We refer to this inquiry as the investigation of the "temporal dimension of consciousness". On the neuronal side, this temporal dimension can be approached by probing Intrinsic Neural Timescales (INTs) – defined as the intrinsic temporal durations of neural activity – and their properties, such as their spatial organization across the scalp. In this work, we aimed to deepen the current understanding of the role of INTs in the emergence of consciousness. Our work was carried out especially within the context of the clinical challenges posed by the differential diagnosis of disorders of consciousness (DoCs), which currently suffers from very high rates of error. We here present three studies that we have led as part of our research program. In the first study, we investigated the spatial relation between INTs and the average oscillatory speed in the alpha frequency range (7-13 Hz). Both, in fact, are measures that have been related to the temporal resolution of sensory processing, but their exact relation is far from clear. We hypothesized a clear correlative pattern between the two measures in the fully conscious state; further, we hypothesized that this relation would be disrupted together with loss of consciousness. We showed a significantly negative correlation, at the channel level, between INT lengths probed with the Autocorrelation Window – 0 (ACW – 0) and Alpha Peak Frequencies (APF) in the resting state hd-EEG recordings of our conscious population; additionally, we observed a total disruption of this correlation across different unconscious states – e.g. anesthetic induction (with two different agents) and in individuals with DoCs. These first findings indicate that the relation at different time scales between different measures of temporal processing are key for consciousness. In the second study, we advanced our current methodological arsenal to infer the duration of INTs, by validating a new tool based on Permutation Entropy (PE), which is specifically developed to avoid the confounding effects of the nonstationary and nonlinear nature of the neural signal. We first show, in simulated data, that this measure (which we named Permutation Entropy Time Delay estimation – PE-TD) is indeed less sensitive to nonstationarities and nonlinearities in a neural signal. Second, we observe a high topographic similarity between PE-TD and ACW-0, validating this approach in healthy awake volunteers; surprisingly, this spatial similarity was less evident in DoC data, which might hint at the differential effects of nonstationarity and nonlinearity in these two different states of consciousness. In the third and last study, the objective was to test for the presence of non-random dynamic transitions between different topographies of INTs, supporting claims of a dynamic repertoire of INTs. Leveraging two different datasets (MEG and hd-EEG), we employ a data-driven approach to identify "dynamic INT states." In MEG, we found 10 dynamic INT topographic states, with four maps displaying a significant correlation with myelination maps, indicating a cortical hierarchy. The dynamic transition time series showed intermediate randomness. In EEG, with 7 recurrent topographic states, we show higher randomness in unconscious individuals. Further, when consciousness is lost, dynamic INT transitions display less memory, indicating a less complex and thus a poorer dynamic INT repertoire. These findings extend our understanding of the temporal organization of the resting brain, linking it to consciousness as proposed by the Temporospatial Theory of Consciousness (TTC). Taken together, our results clearly indicate that INTs are involved in the emergence of consciousness, suggesting a clear potential in investigating the temporal dimension of consciousness, especially for the development of an objective index of consciousness, with clear implications for its clinical application.

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Chapter 1. Introduction

1.1.1 Theories of consciousness: brief overview and the introduction of the temporal dimension of consciousness

The last 30 years have seen increasing interest in the study of consciousness, encompassing all fields of neuroscience. Even if the mystery of the nature of consciousness is now considered one of the biggest questions faced by science (Kennedy and Norman, 2005), it was not well-received and even not encouraged by the academic world (Sutherland, 1989) - especially in the psychological and neuroscientific scholarly circles - arguably due to its elusive nature and to the limitations imposed by the lack of advanced methods of investigation (Seth, 2018). In retrospective, neuroscientists seem to agree (Seth, 2018; Storm et al., 2017) that the turning point from the almost complete lost interest in consciousness, which was prevalent especially among the behaviorist academic circles, to a dignified and respected research coincides with the pioneering work of Crick and Koch (Crick, 1998; Crick and Koch, 1990). In fact, it is in the last decade of the 20th century (with a few notable exceptions that date before this "symbolic" date (Baars, 1988)) that we can observe an increased amount of efforts directed at the investigation of the "neural correlates of consciousness" (NCCs) - a concept introduced in the aforementioned seminal works of Crick and Koch - which were then defined as "the minimal neuronal mechanisms jointly sufficient for any one conscious percept" (Crick, 1998). Initially, the race to finding a putative neural substrate of consciousness has been fueled by the search for NCCs: this, in turn, caused the accumulation of empirical evidence that needed to fit coherently in a solid theoretical framework in order to be fairly interpretable.

Eventually, an unprecedented and almost "Cambrian" explosion of theories of consciousness has characterized the last two decades, which stands antithetical to the initial skepticism surrounding the "major unsolved problem in biology" (Crick, 2004). Considering the methodological and theoretical challenges posed by consciousness to date, the fact that current theories of consciousness diverge greatly in their proposed explananda (e.g. the neural mechanisms targeted by each theory) comes with no surprise. Because of this remarkable divergence, several review articles and textbooks have proposed different strategies and taxonomies to navigate the vast array of theories and their proposed neural measures of consciousness (Boly et al., 2017; Cavanna and Nani, 2014; Gazzaniga and Mangun, 2014; Northoff and Lamme, 2020; Revonsuo, 2010; Storm et al., 2017).

Unfortunately, there is no definitive taxonomy that can easily explain the diversity of the landscape composed by all current theories of consciousness; however, the reader might find useful to know where the most popular approaches are located on different theoretical spectrums. To this aim, several axes of variation have been proposed in the last years, which will be now introduced in no particular order.

A major distinction, established at the beginning of this century, regards the difference between "access consciousness" and "phenomenal consciousness" (Block, 2005). Access consciousness is related to the contents of consciousness that are readily available to higher order cognition (hence the term "access"). The most striking feature of access consciousness is that, since this information is broadcasted to virtually all cognitive systems, individuals are able to self-report their subjective experience, which is then communicable to the experimenter. The most known theory on this end of the A-P (access-phenomenal) spectrum is the Global Neuronal Workspace Theory (GNWT) of consciousness (Mashour et al., 2020). Proponents of this theory claim that consciousness arises when information that is initially only represented locally becomes available to a higher-order network, that in turn allows it to be broadcasted globally to every other "specialized processors" (Mashour et al., 2020). A similar cognitive approach is followed by Higher-Order Theories (HOT) of consciousness (Brown et al., 2019). On the other hand, phenomenal consciousness is more about the features of subjective experience related to the state of "what if feels like" (Nagel, 1974) to be conscious. In its latest formulation, the Integrated Information Theory (IIT) of consciousness (Albantakis et al., 2023) proceeds from a set of phenomenal features of the subjective experience (axioms) to infer the necessary and sufficient associated properties (postulates) of the physical substrate able to give rise to consciousness. IIT proposes that consciousness is understood as the cause-effect power of the conscious system is unfolded: the higher the intrinsic cause-effect power of a system, reducible to a balance between "information" (the degree to which uncertainty can be reduced intrinsically by the system) and "integration" (quantifying the irreducibility of the system as a whole), the higher its quality of consciousness. The A-P distinction already uncovers the divergence of mechanisms between different theories. For example, the GNWT theorists claim that the hallmark of consciousness is a "global ignition" of a large-scale network supported by re-entrant activity, with frontal networks as a major hub sustaining this ignition mechanism; IIT, instead, proposes that integrated information converges towards a "hot zone" network, located roughly in posterior areas, that is irreducible to its smaller components. This localization controversy forms the argument of a second distinction between "back" and "front" of the brain theorists (Boly et al., 2017). Other diverging points between theories of consciousness concern methodologies and the focus on either stimulus-related activity and spontaneous activity (resting-state) (Northoff and Lamme, 2020). The latter, we argue, indicates that despite it might appear that there are irreconcilable differences between these theories, there is actually a great potential for convergence, as theories might be targeting different aspects of the same phenomenon – consciousness. Using the aforementioned : it is not logically impossible to reconcile the interplay between resting state activity, which molds the way the brain reacts to incoming inputs (Carhart-Harris, 2018), unlocking richer and less stereotyped activity in response to its surroundings. The richness/flexibility argument is arguably one evolutionary trait enabled by the appearance of consciousness, thus indicating great potential for convergence.

Consciousness is not easily accessible with current methodologies

Consciousness, however, is elusive to most current methodologies available to neuroscientists, irrespectively of the theoretical framework. A major problem contributing to this evasiveness is how challenging it is to disentangle neural activity strictly related to consciousness from its mere consequences – related events, but not directly necessary for consciousness. Cognitive confounds are a major example related to this conundrum. One does not need to factor in consciousness to explain attention, memory, and other cognitive functions (Mnih et al., 2015), even if they supposedly work with the information provided by conscious contents: therefore, there is no guarantee to observe the real neural underpinnings of consciousness, if the right experimental precautions are not taken. To this end, no-report paradigms (Tsuchiya et al., 2015) overcome the main confounds related to reporting one's own experience, which are connected to post-perceptual decision-making processes and language; however, it doesn't assure that only "raw" consciousness is isolated from these confounding factors, which has led to recent proposals of "no-cognition" paradigms (Block, 2019). Nevertheless, controversy still surrounds the debate on consciousness paradigms (Phillips and Morales, 2020), and no-cognition proposals do not represent a conclusive solution to this problem. For this reason, perhaps a tentative solution should be searched elsewhere: rather than working on methodological issues, can we obtain even better results by rethinking consciousness theories in terms of a unifying framework?

Therefore, to improve current efforts towards a unifying framework, we argue that a fundamental and cohesive set of coordinates needs to be developed. To this aim, the temporal dimension of consciousness has been proposed as a possible candidate (Kent et al., 2019; Kent and Wittmann, 2021). The rationale behind this research program, which justifies the working hypotheses elaborated in this work, is described in the next section.

1.1.2 The temporal dimension of consciousness: towards a unifying framework

A renowned statement by Nobel laureate Ilya Prigogine, one of the pioneers of chaos theory, asserts: "Time precedes existence." (Prigogine et al., 1997; Stengers, 1997). Before the growth of chaos theory and dynamical systems theory (DST), the prevailing knowledge of time was that of nothing more than an illusion, which only we humans, imperfect beings, had to deal with. With this popular phrase, Prigogine reasserted the importance of the temporal dimension in physics, which holds especially for self-organized systems: adaptive systems that maintain their internal organization without external control (Hesse and Gross, 2014). The brain is also thought to adhere to these principles of self-organization (Krohn et al., 2023), and general consensus bestows extended temporal properties to consciousness (Kent and Wittmann, 2021).

From phenomenology to quantification: the importance of considering multiple time scales

Surprisingly, most theories of consciousness often overlook time as one of its main explanatory elements. Often, theories of consciousness restrict their interest in time at the timescales that correspond to their explananda. Take the example of IIT: as there is evidence that the timescale at which the maximal irreducibility of a neural-like system falls into a short timescale of 100-300 ms (Hoel et al., 2016), which corresponds to a maximal variability in the temporal fluctuations of phenomenal contents (Tononi et al., 2016), IIT predictions are usually confined in this temporal range.

But the phenomenology of subjective experiences tells us differently. Consciousness is a unitary experience that rarely feels as a succession of discrete states – phenomenal contents. William James's "flow of consciousness" (James, 1890) and Husserl's "extended present" (Husserl, 2019), phenomenological accounts of that particular feeling of seamless continuity in which subjective experiences progress one after the other, which is inherent to consciousness, are nevertheless supported by modern neuroscientific studies (Petitot, 1999; Pöppel, 1989; Zahavi, 2005). In this sense, caution is prescribed and is very important to distinguish conscious contents (units) from consciousness itself (the continuous phenomenon). While it's true that evidence hints at the partitioning of experience into discrete units (Kornmeier et al., 2019; Nakajima et al., 1980; Poeppel and Logothetis, 1986; VanRullen and Koch, 2003), experience is also temporally integrated into a cohesive unit (Hasson et al., 2008; Lerner et al., 2011), at different timescales (slower and faster ones). Here, with timescales we define both the temporal duration of the physical stimuli which become conscious and the temporal duration of neural activity itself.

An important caveat: one has to be particularly cautious when inferring a 1:1 correspondence between the phenomenological features of the conscious experience *in* time – the *extended present* and the *temporal continuity* of subjective experiences - with neural mechanisms related to integrative processes. While we might be tempted by inducing this simplistic identity, temporal integration processes are also involved in other cognitive processes, such as working memory (Kent et al., 2019), and therefore the right experimental precautions need to be taken to disentangle the differential contribution of computational strategies employed by the brain to cognition and consciousness.

If the gap between slower and faster timescales of consciousness is not closed, there is a high risk of leaving out of the frame a critical phenomenal feature of subjective experience: the feeling of temporal unity.

Therefore, a rigorous theoretical framework for the scientific study of the subjective experience we colloquially refer to as consciousness can't be complete as long as its temporal dimension is not taken into account.

The temporo-spatial theory of consciousness (TTC)

The gap between the operational timescales of consciousness, which might appear an irresolvable problem at first, forms instead the first stepping-stone towards a unifying theory of consciousness for the Temporospatial Theory of Consciousness (Northoff and Zilio, 2022a). TTC's perspective on consciousness is that of a constructionist theory: its foremost assumption is that the brain actively shapes – constructs – its own inner temporal and spatial coordinates. More specifically to the scope of this work, in TTC's framework the brain's intrinsic time is not merely the neural correlate of the perception of time or the timing of neural events (Di Lernia et al., 2018; Paton and Buonomano, 2018), but rather the temporal dimension onto which its activity is embedded: its duration, related to the oscillatory and non-oscillatory components of neural activity (He et al., 2010), and its dynamics relative to the external environment's temporal fluctuations. The use of the term "intrinsic" also indicates that TTC shifts in the direction of a more significant role of the spontaneous brain's activity in the search for neural measures of consciousness, rather than the stimulus-related activity correlates proposed by most current approaches (Northoff and Lamme, 2020). Concerning its time coordinates, the brain's spontaneous activity is highly coordinated, showing a characteristic scale-free (He, 2014; Sorrentino et al., 2023) component which is strikingly discernable in electroencephalographic (EEG) signals. This fractal activity is associated with long-range temporal correlations (LRTC) (Palva and Palva, 2018): typical features of systems operating at the edge of chaos, they index its capacity for information processing. In practice, a system displaying LRTC possesses the capacity to retain memory over longer periods of time and therefore assists the integration of information over multiple timescales. This notion is popular in modern physics - especially in the field of DST – and, according to TTC, applies well to the scientific study of consciousness.

TTC starts with these assumptions briefly described here and elaborates on four putative mechanisms for consciousness (Northoff and Huang, 2017): a) expansion; b) globalization; c) alignment; d) nestedness. TTC overtly proposes a multidimensional framework for consciousness, avoiding the full identity of consciousness with a single neural marker as the "full NCC" (Koch et al., 2016), different states of consciousness can be characterized by how they vary along a multidimensional space. A detailed discussion of all four mechanisms goes beyond the scope of this piece of work; rather, we will enunciate the fundamentals of only one of such mechanisms - temporo-spatial alignment - before introducing the relevance of intrinsic temporal fluctuations in this theoretical framework.

Contents are not perceived *per se*, but are always part of a more extended scene. TTC starts from this phenomenological observation to posit that the brain "encodes the context by adapting (and thereby aligning) its own neural activity to the various inputs/stimuli that shape the context" (Northoff and Zilio, 2022a). Incoming inputs from the external environment are dynamically changing their statistical features; each of these features has its own characteristic timescale of variability – i.e. the rate of change of the luminance of a visual stimulus is more predictable at a shorter timescale than, for instance, the information about its trajectory in space. Therefore, we can speak of a multi-scale temporality of the world. The brain, according to TTC, is able to process and "put in context" conscious contents by aligning to the temporal structure of its own environment. Thus, temporo-spatial alignment is a key mechanism accounting for the "form" of consciousness. TTC predicts that, in the presence of a mismatch between the brain's own timescales and the environment, the individual can no longer distinguish between contents, not only because temporality (the sense of time) is lost, but also because contents are no longer embedded in the appropriate general background formed by healthy consciousness.

In conclusion, one key advantage of TTC is that, as a consequence of the assumption that multiple timescales are relevant for consciousness, it proposes a novel framework with great convergence potential. In this sense, current theories do not lose their scientific grounds, but instead their different predictions are understood as relative explananda of different mechanisms happening at different levels of investigation. Thus, we argue that taking into account the temporal dimension of consciousness is not only beneficial to TTC, but has the potential to improve the overall understanding of consciousness. In the next section, the state of the art on what is known about the brain's intrinsic timescales is presented.

1.2 Timescales and consciousness: temporal mechanisms of subjective experience

Gaining knowledge of a system’s temporal dimension means to unveil one of the characteristic dimensions at which it operates. Take, for instance, a simple example of a RLC (Resistor-Inductor-Capacitor) circuit, which are circuits that populate a lot of modern electronic devices. Without getting too much into the details, energy is constantly exchanged between the circuit’s subparts at a certain rate, parametrized as a time constant τ; when the circuit is working without interacting with other systems, knowing τ allows us to understand what is its dominant time scale. Gaining knowledge of the circuit’s temporal dimension is instrumental to knowing the rate at which it will respond to inputs, to predict its oscillatory behavior and other related phenomena. This simple example explicates that modelling a physical system often requires acquiring knowledge of the temporal scale at which it operates. Unfortunately, biological systems are often more intricate than electrical circuits, and operate on many different time scales: however, their knowledge becomes even more valuable in these cases, as it reveals important information about their temporal dynamics.

The brain, being simultaneously a physical object and a biological system, makes no exception to the laws of physics and is known to operate too at different time scales (for a review, see (Golesorkhi et al., 2021b; Wolff et al., 2022)).

The work of Hasson and colleagues (Chen et al., 2017, 2015; Hasson et al., 2008) is probably one of the first modern examples in introducing the notion of time scales into cognitive neuroscience. They define “temporal receptive windows” (TRW) (Hasson et al., 2008) as “the length of time before a response during which sensory information may affect that response”. The term references the better-known concept of spatial receptive fields (Sherrington, 1911), and mirrors it in the temporal domain. A single input, for instance, can influence a sensory system for a time that is longer than the input’s own duration: the longer the temporal extent of this influence on a neural system, the larger (or longer) the temporal receptive field of that particular system. In turn, the brain’s own durations should then reflect the ability to retain information about past events. These durations were originally quantified on the basis of task-evoked activity (Hasson et al., 2008). In this study, subjects were shown snippets of a silent movie which were alternatively temporally scrambled, progressively altering the temporal information of these visual stimuli. Brain areas reacted differently to the progressive amount of temporal scrambling of the visual stimuli: unimodal areas, which are more sensitive to the rapidly changing features of perceptual objects, were less sensitive to temporal scrambling, while higher order areas, devoted to the integration of information coming from multiple sensory modalities, were more sensitive to the temporal scrambling. Therefore, this simple yet elegant experiment demonstrates that the brain has two important input processing properties: not only it exhibits remarkable heterogeneity in the time scales of its own activity across the cortex, but this heterogeneity follows a hierarchical organization - with longer timescales in multimodal areas and shorter timescales in unimodal areas - which suggests functional significance. The hierarchical organization of the brain’s time scales was later confirmed by a considerable number of other studies (Baldassano et al., 2017; Chen et al., 2017; Honey et al., 2012; Lerner et al., 2011; Simony et al., 2016; Stephens et al., 2013; Watanabe et al., 2019; Yeshurun et al., 2021). Yet, while this description is backed by strong evidence at its support, it is as equally strongly reliant on task-evoked activity. These findings do indeed demonstrate that neural time scales exist and that they are related to the time scales of the external environment, but view is arguably limited and it neglects the temporospatial organization of the brain’s spontaneous activity. As a matter of fact, the brain displays highly structured dynamics, even when it is not explicitly meeting instantaneous environmental demands, as it happens while executing a task (Fox et al., 2005; Pezzulo et al., 2021; Raichle, 2015). Therefore, given the proposed significance of neural time scales for processing the statistical features of incoming inputs, and given the evidence showing that the intrinsic organization of resting activity “reverberates” in evoked activity (Arieli et al., 1996; Berkes et al., 2011; Kenet et al., 2003; Luczak et al., 2009), the possibility of hierarchically organized “intrinsic” neural time scales could not be ignored.

Inner time coordinates: Intrinsic Neural Timescales

The growing interest in this possibility led to the formulation of **Intrinsic Neural Timescales (INTs)**, which is a hypernym (i.e. a blanket term) encompassing every instance of temporal durations of neural activity recorded at rest. In this general overview, three core points regarding INTs will be presented: a) the existence of a hierarchy of timescales even at rest; b) its relation to other basic organizational principles of the brain; c) evidence of rest-task modulation of these properties. The three aforementioned core points amount to the assumption which will underlie the rest of this thesis: INTs, and their topographic and dynamic properties, are at the basis of the way the brain performs input processing.

The level of investigation on INTs, similarly to TRWs, spans across different degrees of granularity and modality (Wolff et al., 2022). At the cellular level, temporal windows of activity during pre-stimulus activity – a state with no explicit task instructions, comparably to resting-state - of single-cell primate recordings follow the same hierarchy: shorter in primary sensory regions and longer in integrative regions (Murray et al., 2014). Similar cellular studies explored the relevance of this hierarchy: the topographic distribution of timescales across the scalps overlaps with cytoarchitectonic gradients of ion channels directly related to excitation/inhibition and with gradients of gray matter myelination (T1w/T2w ratio) (Gao et al., 2020), and their absolute values generally increase following a posterior-to-anterior axis (Dotson et al., 2018; Murray et al., 2014; Runyan et al., 2017; Wasmuht et al., 2018)**.**

Does the human brain follow the same organizational principles? EEG and fMRI studies uphold the existence of a hierarchy of timescales at rest. In humans, the unimodal-multimodal gradient has been also anatomically codified along a so-called “**core-periphery**” architecture (Ji et al., 2019; Margulies et al., 2016; Schaefer et al., 2018). The principle of the core-periphery macroscale lies in the local-global gradients of connectivity that has been characterizing most recent brain parcellation schemes (Schaefer et al., 2018). These parcellation schemes can be further clustered into several networks that stand at the two polar opposites of a spatial gradient. At one end, core regions form hubs with high interregional functional connectivity, and include integrative regions such as the default-mode network, the fronto-parietal network (FPN), and the dorsal attention network (DAN), etc…; on the other extreme of this spectrum, periphery regions show more intraregional connectivity in spite of fewer connections between nodes outside of their networks, and is mainly constituted by sensory primary regions. INTs follow this gradient as well, with core regions showing higher INT values and periphery exhibiting shorter time scales overall (Golesorkhi et al., 2021a; Ito et al., 2020; Ryan V. Raut et al., 2020). It’s worth underlining the fact that a similar distribution can be observed at different frequency ranges (fMRI records activity that ranges between 0.01 and 0.1 Hz – the infraslow frequencies – while EEG conventionally consists of 1 to 60-70 Hz data), which further supports the idea that INTs play a basic role in the way the brain understands its surroundings. This intuition is also one of the basic assumptions of the studies presented in this thesis.

Further, thanks to the advantage of the very fine-grained spatial analysis allowed by single-unit and neuroimaging data, researchers have also discovered that the hierarchical spatial arrangement of timescales is not an exclusive property of the whole cortex, but it’s present in single regions as well (Badre and D’Esposito, 2009; Sarafyazd and Jazayeri, 2019; Voytek et al., 2015), hinting at a more basic dynamic principle of the brain. Considering this intriguing observation, emerging evidence seems to indicate that a gradient of temporal dynamics flows naturally from the landscape of structural organization of the brain, at the microscopic level (Duarte et al., 2017; Huang and Doiron, 2017; Huntenburg et al., 2018; Wang, 2020), and at the macroscopic level as well. However, the exact relation between, say, patterns of connectivity and INT hierarchy remains unknown and is still an active field of research.

Additionally, there is also growing evidence about INTs undergoing rest-task modulation. First, the overall core-periphery topography of INTs seems to be relatively stable across conditions, as demonstrated by the high spatial correlation between resting conditions and a heterogeneous pool of task states (Golesorkhi et al., 2021a). Nevertheless, task and region-specific changes, such as the shortening of INTs in core/multimodal regions during the execution of a story-math task (Golesorkhi et al., 2021a), are visible when subtracting task-specific activity from the resting state baseline. Furthermore, EEG data shows that INTs seem to intervene directly in the interaction between the spectral content of EEG and the temporal structure of an auditory task (Sancristóbal et al., 2022) and an overall modulation of cognitive resources employed during task execution (Gollo, 2019; Gollo et al., 2017; Klar et al., 2023; Sarracino et al., 2020). Although sparse, evidence accumulated so far points out that INTs shape cognition in multiple ways.

How are researchers able to probe timescales directly from neural activity? To test hypotheses as primary as the ones regarding the fundamental processing principles of the brain, the sharpest tools are required. In the next paragraph, different methodologies that are used to delve into the temporal dimension of neural systems are reviewed.

How can we measure INTs?

The standard method to infer the duration of timescales of a dynamic system from time series data requires, first and foremost, understanding the temporal relation between different time points at increasing lags. The rationale is the same guiding the already mentioned theoretical assumptions on timescales: patterns of neural activity that persist in time will result in a time series that is characterized by temporal correlations that show their maximal value at the same time as their dominant timescale. In other words: if there are timescales in a system, the time series will be more similar to a copy of itself when the observation is adjusted at a time lag matching the dominant timescale. Classically, this estimate is obtained through autocorrelation functions (ACF) (Park, 2018). Computing the ACF of a signal requires performing a linear correlation between the signal and a copy of itself, as a function of increasing time lags (i.e. sliding off the two identical time series on top of each other at equal steps). At time lag 0, the correlation of the signal with itself will be maximal, and will decrease as a function of time: the resulting function will display a characteristic shape that reveals the temporal structure of the signal under exam. Systems with dominant timescales possess a peculiar ACF, which decays at an exponential rate immediately after time lag 0 (Otto et al., 2019).

Neural signals follow the same logic (Honey et al., 2012; Palva and Palva, 2018); hence, the brain's INTs can be estimated by parametrizing its signal's ACF. Honey and colleagues first introduced the Autocorrelation Window (ACW) (Honey et al., 2012), which was then operationalized as the time lag at which the ACF reaches its full width at half maximum (FWHM). The choice of parametrization of the ACF, in this case, is justified since the FWHM is a robust metric for the width of a symmetric function, which is the case of the ACF. Since then, other ACW metrics have been developed with the same methodological considerations but with varying parametrization choices: the better characterized versions of ACW are the ACW-50, which is defined as the time lag at which the ACF falls at it 50% value, and the ACW-0 at its 0% value (Wolff et al., 2022). Very recently, the ACW has been also parametrized with decreasing percentages, from 40% to 10% of its ACF (Wolman et al., 2023). Different "flavors" of ACW are consistent with a framework that allows multiple timescales for spontaneous brain activity, in agreement with theories that link emergent properties of the brain with its criticality (Dürschmid et al., 2020; Fekete et al., 2018; Fuscà et al., 2023; Palva and Palva, 2018). It should be noted that, however popular the ACW approach, other methods have been developed for the same sake, based on autoregressive models of the neural signal (Ryan V. Raut et al., 2020; Spitmaan et al., 2020): these methods allow for the estimation of multiple timescales at once, and can be used interchangeably with the parametrized ACW.

ACW is a simple and efficient metric, which does not require particular computational power, but it has raised some concerns regarding its inherent limitations. A non-parametric alternative represented by the autoinformation function (AIF) – which substitutes linear correlation with mutual information - (Von Wegner et al., 2017) has not, to date, been used explicitly for the sake of estimating INTs. The assumption of a linear relation between successive timepoints is often violated in complex system's time-series data (Zunino et al., 2010), and therefore ACW estimates can, at least in principle, suffer from consistent measurement error. This methodological limitation is addressed in chapter 3, with the introduction of a novel methodology which does not assume collinearity between consecutive time points.

Temporal input processing: how does the brain use INTs?

So far, we have reviewed the main findings that link INTs to input processing and the current methodologies needed to test these hypotheses. However, without a mechanistic model of how INTs are able to support the way the brain processes information, these hypotheses would only remain circumstantial. Which are, then, the computational mechanisms supported by INTs and their hierarchical organization?

Picture the schematic example of an input, with its own temporal duration, of which its features are progressively sampled by different populations of neurons. The underlying assumption of this example is that increasingly complex features of the input will be processed in a hierarchical sequence by these populations – i.e. simplest features will be the first ones to be extracted, as in the case of computational models of visual object recognition (Yamins and DiCarlo, 2016). The input's features are processed in sequence until a coherent and stable representation of the visual input – an object – is obtained. INTs allegedly allow the same kind of operations, but instead on the temporal domain, by segmenting the input's features based on their different durations – temporal windows of input processing, as defined earlier in the works of Hasson and colleagues (Hasson et al., 2008), in the same way this thesis can be segmented into letters, words, sentences, paragraphs, etc…

The mechanisms that guide temporal segmentation of the incoming inputs are two: temporal integration and temporal segregation (Golesorkhi et al., 2021b; Himberger et al., 2018). Temporal integration is the process by which information at consecutive time points is pooled together by neural populations into one stable response; the temporal window that defines the borders of this mechanism is roughly equal to the system's dominant timescale. Treating the input's features as a point-like phenomenon, inputs that arrive at consecutive times but are still confined to the threshold imposed by the population's timescale will be "kept in memory", integrated and treated as if it were multiple manifestations of a single input. The opposite mechanism is what defines temporal segregation: shorter processing timescales allow for more temporal precision, but it also results in higher sensitivity to change. Within this temporal model, temporal features of the input are progressively processed by populations with increasingly longer dominant timescales, orchestrating the temporal dynamics of the brain as a response to the ever-changing input landscape of the environment, and the hierarchical organization of INTs fits perfectly with this description: in unimodal regions, where the ACW values are shorter, responses are faster in order to adapt to the constant fluctuations of the environment's statistics, while in multimodal regions longer timescales accommodate for the integration of multiple sensory evidence into one stable response. This view translates the role of INTs and their hierarchy from a simple organizational principle that arises from anatomical constraints to a basic mechanism which allows for maximal information gain. Modeling studies bring further support to these claims (Chaudhuri et al., 2015; Demirtaş et al., 2019). However, more needs to be done in order to unveil the exact correspondence between the input temporal structure and the computational advantages granted by INTs. More mechanistic explanations of this behavior are needed to understand better the environment-brain correspondence. Moreover, it can be argued (and rightfully so) that this particular ecological theory of input processing should be supported by more causal evidence of a direct link with the external environment. Implementing this view with a Bayesian framework – as in the case of "deep temporal models" (Friston et al., 2017) might be useful to understand why "sensing" the environment's temporal structure is key to producing efficient inferential behavior.

Relevance for consciousness: TTC

So far, INTs have been related to the basic principles that underlie the way the brain performs input processing. As already mentioned earlier in the previous chapter, the temporospatial structure of the brain's spontaneous activity is fundamental for consciousness, at least in the framework of TTC. Is there evidence in support of this claim, especially in the context of the temporal dynamics of the brain? Most importantly: do INTs play a role in allowing, sustaining and/or maintaining consciousness?

In a first attempt to draw the connection between INTs and consciousness, subjects undergoing fMRI recording sessions during sedation with propofol (Huang et al., 2018) displayed an average prolongation of their INTs. Additionally, Huang and colleagues observed that along with prolonged ACW values, the sedated subjects' BOLD signals shifted towards a slower regimen of overall activity, signaled by decreased global functional connectivity (Huang et al., 2021), which could arguably be the underlying cause of abnormally long INTs: weaker interactions may be the cause of slower temporal dynamics as well. However, more consistent evidence comes from an EEG study which investigated the change in ACW values in three different populations (anesthetized voluntary subjects, subjects undergoing sleep recordings and disorders of consciousness patients) during resting state (Zilio et al., 2021). These three states, while being very different from one another, are all characterized by a reduction in consciousness levels – i.e. they are all assumed to represent unconscious states. Comparing the trend of a single measure across different states of unconsciousness is indeed a good practice in consciousness studies, as it reveals consciousness-specific mechanisms rather than general dysfunctions in brain activity (Lau, 2022). An abnormal prolongation of INTs was consistent across all states of unconsciousness, in agreement with the group's hypothesis. As an additional control, another sample consisting of locked-in syndrome (LIS) and amyotrophic lateral sclerosis (ALS) patients was not statistically discernable from healthy controls; both ALS and LIS are purely motor syndromes, which don't affect consciousness levels and are not expected to show changes in their temporal dynamics if the assumption of INTs playing a role for consciousness is correct. Therefore, this study draws very important conclusions: INTs are, at least to some degree, involved in consciousness-specific mechanisms, which is coherent with the theoretical framework of TTC. Even further, ACW values were shown to be differently sensitive to auditory stimulation during different levels of sleep, which shows a non-trivial interaction between consciousness levels and the brain's intrinsic timescales. However, it still remains unclear whether the consistent observed slowing down of the intrinsic temporal dimension of the brain is an after-effect of the loss of consciousness or if they are truly necessary for its existence – i.e. the cause-effect relation between INTs and consciousness is still not known. While TTC, as already mentioned, is the only theory of consciousness that formulates the necessity of INTs - which follows directly from its core constructivist assumptions – it's still not known which of the temporal features of spontaneous brain activity is truly fundamental. The maximal efficiency of information gain from the perceptual environment earned through temporospatial alignment is a tempting solution to this problem, but it fails to provide a clear and rigorous correspondence to the phenomenon of consciousness. For this reason, it is suggested to postpone the details of this particular problem until more evidence is collected.

In conclusion, while empirical support for the significance of Intrinsic Neural Timescales (INTs) in consciousness remains limited, its potential is very promising. This prospect holds particular value as it addresses a notable gap in consciousness studies—the lack of a comprehensive account of the temporal variable.

The main objective of this thesis is to dig deeper into this overarching question. We harnessed this conceptual framework to address a very urgent concern, particularly pressing in clinical settings:

the differential diagnosis of disorders of consciousness (DoCs). The following subchapter will provide a general introduction to the challenges associated with assigning diagnostic labels to these patients.

1.3 Disorders of consciousness: a categorization challenge

When questioned about the matter, we are all very aware of the fundamental reality of consciousness: the intimate, subjective feeling that goes with our experience. Even more intuitively, we know exactly what our conscious experience is *not*: this happens to us every night, falling into the nothingness of NREM sleep, and transitioning into the ability to experience things once awake. This account is inevitably true when we refer to the first-person perspective of consciousness, but the same can't be said for the 2nd (or even 3rd) person perspective: that is, to judge with certainty whether another person is conscious is ultimately mind-boggling. In fact, there is even a popular philosophical argument often used in favor of the "hard problem of consciousness" (Chalmers, 2010) which argues for the existence of "philosophical zombies" (Chalmers, 1997): living beings that are physically indistinguishable from us, behaving in the exact same way as a conscious person would, but with the exception of the total absence of any degree conscious experience. Even if solipsist accounts of consciousness will not be the focus of this thesis, the investment in this philosophical argument reveals one very important challenge: how is it possible to judge with absolute certainty the presence/absence of consciousness, based only on external and concurrent factors, such as the observation of purposeful behavior?

Does complex behavior equate with consciousness?

The most important assumption that stands behind this question is that, while consciousness might allow the brain to perform very complex behavior – e.g. a *necessary* condition – it does not strictly mean that complex behavior is necessarily "backed up" by consciousness – consciousness, consequently, is not a "sufficient" condition for it. A popular argument formulated in the early 2000s infers this dissociation by indicating how the neurophysiological correlates of conscious processing are qualitatively different from those observable in the presence of complex but unconscious perception (Lamme, 2003). A more intuitive example of a subjective state where this dissociation might be more palpable to the reader is represented by the presence of phenomenal consciousness without attention (Vandenbroucke et al., 2012): in this study, authors found that sensory memory representations received a boost from an illusory visual effect (the popular Kanizsa illusion) which could not be explained by the sole interaction with working memory, suggesting a qualitative difference between phenomenology and higher cognition.

On the other hand, a different example backing up this *apparently* contradictory reasoning which underlines the inadequacy of the identity between consciousness and overt behavior comes from a condition known as "complex partial seizures": abrupt and transient losses of consciousness, with an epileptiform activity originating from a single epileptic focus, resulting in staring and unresponsiveness for the usual period of two minutes (Salpekar, 2019). Even if the dissociation from the external environment is evident, and a crucial diagnostic factor of this condition, there is extensive evidence of “automatisms” (semi-automatic and repetitive movements) (Escueta et al., 1977; Hoffmann et al., 2008; Penfield, 1952), preservation of goal-oriented behavior (McPherson et al., 2012) and, even in the presence of selective cognitive deficits, a relative sparing of the level of responsivity (Ali et al., 2012; Heydrich et al., 2010; Picard and Craig, 2009). Even if the case of complex partial seizures does not correspond entirely to a complete dissociation of consciousness and behavior, these confounding factors hinder the use of consciousness as a clear indicator of partial seizures (Berg et al., 2010) and leaves unanswered questions on the presence of consciousness even during these neural events. Taken together, these observations indicate that the lack of externally oriented responses does not necessarily imply the absence of consciousness during seizures (Gloor, 1986) and furthermore, that there is a clear possibility of a dissociation between consciousness and behavioral responsiveness.

In summary, these examples lead to a different but very important observation: consciousness can not only dissociate from volitional behavior, but it can also exist with no inputs from the external environment.

Before going further, there is an important caveat to be made here for the reader: this view is not agreed upon by the entirety of the consciousness community. Popular accounts of consciousness, such as the global workspace theory (Dehaene, 2014), require at least a certain amount of involvement of cognitive processing for consciousness. Therefore, the reader has to be aware that, by starting from the assumption of a dissociation between consciousness and cognition, we are not representing fully the ongoing debate on consciousness.

The absence of a clear definition of consciousness (Zeman, 2001) also stems from this ambiguity: how is it possible to produce unequivocal evidence of a phenomenon which is a) extremely hard to link to its physical nature (Chalmers, 1997) and b) without a set of common methodological tools? This discussion is far from being restricted to philosophical and epistemological matters, and often has a very tangible impact on the lives of people with severe brain injury. This is the case, for instance, of **disorders of consciousness (DoCs)**, which is the focus of the following paragraph.

Disorders of consciousness. A clinical challenge

DoCs are a clinical condition, acquired after severe brain injury, which leads to total or partial loss of consciousness (Giacino et al., 2014). In clinical practice, consciousness has been traditionally gauged by deconstructing it into two constructs accessible to clinical assessment: wakefulness (sometimes cited as “arousal” in the scientific literature) and awareness (Plum and Posner ’ s diagnosis of stupor and coma 2007). Wakefulness levels are very practical to assess, and it is done based on eye opening: if the patient’s eyes are spontaneously opened for a reasonable period, one can infer wakefulness in the patient under examination. However, the same can’t be said for the assessment of awareness (even when not considering that “awareness” and “consciousness” are terminologies easily confused in our daily language). Since, in this context, awareness is related to the individual’s own ability to connect and react to its surroundings (its levels of “connection” to the environment), its assessment is mainly based on the patient’s ability to respond to either simple commands or to non-trivial behavior which is assumed to be possible only in the presence of consciousness.

These are practical considerations which originate from the fact that, in healthy people, wakefulness and awareness usually follow a linear relation: for instance, when we gradually fall into sleep, the level of awareness follows accordingly, while we become more and more disconnected from our environment. But matters are much more complicated than that and, in the clinical context, it is very difficult to assign a correct diagnosis because of many other confounding factors. A not thorough list of these confounding factors would include, in no particular order: consciousness is known to wax and wane on an unpredictable period (Candelieri et al., 2011; Giacino et al., 2002), the pathophysiology of DoC is currently not well understood (Kondziella et al., 2020; McClenathan et al., 2013), current clinical standards require that the patient, at the same time is awake, cooperative, and that motor function is at least minimally preserved (Kondziella et al., 2016). The list could even get longer when taking into account the ethical implications of the heterogeneity in weight that different clinicians give to each of these alleged signs of consciousness (Demertzi et al., 2013) (a brief overview of the impact of these biases on the quality of life of people with disorders of consciousness is presented later on – at page).

Clinical literature has historically benefited from taxonomies: they are helpful when the task at hand involves merging uncertain and fuzzy evidence into a simple and effective diagnostic label, which then guides the appropriate treatment choice – similarly to a divide-and-conquer algorithm. The challenge of DoCs fits perfectly into this category.

A patient admitted into the Intensive Care Unit (ICU) following severe damage to the brain, which may have been caused coarsely by stroke, anoxia or traumatic damage (Kondziella et al., 2020), might fall into the category of **coma**. Coma constitutes an "absolute zero" of both wakefulness and awareness (Plum and Posner, 1972), featured by no evidence of a sleep-wake cycle from the EEG signal, closed eyes and total absence of communication or command-following. Coma is generally thought to underlie a drastic malfunctioning of either the subcortical ascending reticular activating system (ARAS), which has been known as an enabling factor for consciousness for decades (Saladin et al., 2018) or more generally to any etiology that results in a downregulation of excitatory activity across the cortex – disfacilitation (Gold and Lauritzen, 2002). Coma is almost never a definitive state, with an established (but arbitrary) acute window of 28 days (Giacino et al., 2018).

Thereafter, one possible outcome is brain death, which is usually diagnosed following the guidelines outlined in (Wijdicks et al., 2010). In accordance with international guidelines, brain death is synonymous with an irreversible loss of brain functionality; however, there is a worldwide flexibility of the criteria to establish brain death which makes the diagnosis at least controversial, depending on the country's official guidelines/legislation (Aboubakr et al., 2023).

On the other hand, comatose patients can transition into states that fulfill the conditions for partial or total recovery of consciousness. A brief overview on the current state of the art is presented in the next paragraphs.

Diagnostic labeling

In **Unresponsive Wakefulness Syndrome (UWS)** (the European Task Force on Disorders of Consciousness et al., 2010)**,** wake-sleep cycles and spontaneous eye opening are restored, indicating a partial recovery of the functionality of the ARAS, but with no discernable signs of awareness: a first-order dissociation of wakefulness and awareness, as anticipated a few paragraphs earlier. UWS, depending on the etiology of the disorder, might be labeled as “persistent” when the condition is stable for a period ranging from 3 to 12 months (Giacino et al., 2014). **The Minimally Conscious State (MCS)** (Giacino et al., 2002), instead, is associated with minimal behavioral evidence of awareness of the self or of the environment. From the clinician’s point of view, observing the signs of behavior with purpose include: a) intelligible communication (verbal or gestural); b) response to nontrivial motor commands such as reaching and grasping and manipulating objects according to shape and size; c) affective behavior. Perhaps, the most significant characteristic of MCS patients is the constant fluctuation in responsiveness, which means that these signs of awareness are not always available to the clinician in charge of the examination. Therefore, it is crucial to perform several assessments to avoid failure to miss the evidence of volitional behavior (Giacino et al., 2014). MCS can be further subdivided into two different subgroups, depending on what authors have proposed to represent the “complexity of observed behavioral responses” (Bruno et al., 2011). Patients showing signs of minimal preservation of language functionality fall into the **MCS PLUS (MCS+)** subcategory, while its absence denotes, even in the presence of non-reflexive behavior, a “less” complex behavior, which characterizes the **MCS MINUS (MCS-)** subcategory. This subdivision is backed by recent neuroimaging evidence, which shows that these differences originate from differences in functional connectivity related to cortical networks controlling language execution (Aubinet et al., 2018). However, in the same work, differences in the ability to verbalize are not sufficiently explained by differences in functional connectivity in other cortical networks that support functions of crucial importance to the sustainment of consciousness (such as internal awareness, auditory processing, input processing, etc…) which suggests that the MCS+/MCS- subcategorization might only be helpful to predict future levels of disability (Thibaut et al., 2020) rather than related to “true” levels of consciousness.

Lastly, patients regaining even higher levels of communication on a more constant basis are classified in the **Emergence from MCS (EMCS)** diagnostic class.

A complete schematic diagram that accounts for the progression from coma-inducing brain insults to one of the clinical outcomes discussed so far should also include the **locked-in syndrome (LIS)**, a condition caused by a specific damage to the corticospinal and corticobulbar pathways which mainly results in quadriplegia, aphonia and absence of horizontal eye movements, but leaves cognitive functions and consciousness intact (Laureys et al., 2005). As consciousness is spared, LIS patients do not fall into the category of DoCs: however, in the acute stage, LIS patients could be misdiagnosed as UWS or MCS (Giacino et al., 2014), and is therefore very important to be aware of the difference between these conditions.

Now that the diagnostic picture of DoCs has been described in broad strokes, it’s time for the reader to gain knowledge of the current diagnostic tools available to date. First of all, we will focus on the existing behavioral scales, which all aim at inferring consciousness from the patient’s behavioral responsiveness. Following, neuroimaging and electrophysiological evidence of dissonance between behavior and consciousness in DoCs, which shatters the exact relation between the two is presented. Concluding this section, a series of reasons to support the role of EEG in the establishment of an objective index of consciousness are presented.

Neurobehavioral scales

Several neurobehavioral scales have been developed to address the clinical challenge of the bedside evaluation of DoCs – more than a dozen (Seel et al., 2010). Even if diagnostic criteria for UWS, MCS and other subcategories have been laid out on a consensus-based process, the actual assessment process is another matter of discussion: hence, the variability of these behavioral scales.

Historically, the first behavioral scale developed specifically to detect awareness in post-comatose patients has been the **Glasgow Coma Scale (GCS)** (Teasdale and Jennett, 1974). GCS has gained immense popularity since its publication and it is still used nowadays in ICUs all over the world, especially at the admission in the clinical facilities. It probes consciousness based on three subscales – each composed of different subitems – that capture different aspects of responsiveness: eye-opening, motor and verbal. For each item in the scale, a subtotal score is given which is eventually aggregated into a total GCS score. Although clearly indicative of a patient's outcome, as shown in (Gennarelli et al., 1994; Reith et al., 2017), it is internationally discouraged to use GCS scores as the only feature when predicting a patient's outcome (Steyerberg et al., 2008). In retrospect, it's easy to recognize the GSC as a precursor, because it encapsulates all of the most important features that are now featured in modern-day's scales: among others, the subdivision of the behavioral signs of consciousness into different items, a separate scoring system for each subitem and the repetition of assessment. However, GCS's power to correctly assess consciousness is actually very limited (Giacino et al., 1991), and "second generation" scales have since then populated the tools available to the clinical community (the reader can find a list of the now-available scales at (Seel et al., 2010)). Currently available scales vary in the time required for the assessment procedure, the clinical items included, and the interpretability of the scale itself, but the current gold standard is represented by the **Coma Recovery Scale – Revised (CRS-R)** (Giacino et al., 2004). The CRS-R consists of 23 subitems, grouped into 6 different subscales: auditory, visual, motor, oromotor, communication and arousal functions. In every subscale, items are assessed separately with their own methods and are arranged in a hierarchical fashion: in other words, clinicians start with the evaluation of the lowest ranking item and proceed upwards in the hierarchy, where the behavioral sign of evidence becomes more and more significant if the patient responds correctly to the procedure. Then, the highest score obtained is assigned to that particular subscale, and the examination proceeds accordingly for every remaining subscale. As with the GCS, an aggregate score is used as an indicative diagnostic factor as well. Two important directions are also given to whom performs the examination. First, it is mandatory to perform several assessments with the CRS-R, in order to avoid missing signs of consciousness as the result of the fluctuating behavior of especially the MCS population; second, before any administration, the examiner should ensure the highest possible levels of arousal in the patient, which is obtained with a standardized Arousal Facilitation Protocol (AFP).

The misdiagnosis problem: consciousness dissociates from overt behavior. The case of cognitive-motor dissociation

Despite growing evidence that confirms the CRS-R as the gold standard in clinical practice (Giacino et al., 2014; Seel et al., 2010), the dissociation between behavior and consciousness remains a true obstacle to using these scales as a single source of information for the differential diagnosis of DoCs. In fact, the diagnostic accuracy of these scales has been challenged empirically. Alarmingly, the UWS cohorts usually show a ~40% misdiagnosis rate (Schnakers et al., 2009), even considering that the introduction of CRS-R has had a positive impact and increased the chances of differentiating MCS patients that had been misdiagnosed as UWS based on clinical consensus, identifying an estimated 41% of such "false negative" cases (Schnakers, 2020; Schnakers et al., 2009). Additionally, recent studies confirm that the proportion of MCS misdiagnosis stands at a ~40% rate (Wang et al., 2020), further corroborating the thesis that the signs of consciousness are insufficiently summarized by overt behavior.

Supporting this thesis leads to a logical consequence: there is a substantial amount of patients that don't show any unequivocal sign of consciousness, but who in reality have retained their cognitive capacities associated with consciousness and can't (or won't) respond meaningfully when probed behaviorally. In this case, it's not trivial to remember that the greatest pitfall, when using neurobehavioral scales, is that they presuppose that motor functionality is preserved to a certain degree – which is a gamble at least when dealing with severely brain injured individuals. Hence, it's perfectly plausible to indicate the dissociation between motor and cognitive function as an important contributing factor to the high misidentification rate of DoCs. This condition is now recognized as "cognitive motor dissociation" (CMD) (Schiff, 2015).

It's unanimously recognized that Owen and colleagues (Owen et al., 2006) have laid a cornerstone of the identification of covert cognition in behaviorally unresponsive DoC patients. This group was the first to identify covert awareness of a 23 year old patient, which was then diagnosed as UWS, providing strong neuroimaging evidence of neural activity perfectly comparable to a healthy individual's through the administration of a mental imagery task during a fMRI recording session. In the task, the patient was instructed to visualize two different scenarios: one in which they were playing tennis and another in which they were navigating their own house – two scenarios that were very familiar to the patient. Picturing ourselves in these two situations causes changes in two separate brain areas: respectively, the supplementary motor area and the parahippocampal gyrus (Boly et al., 2007). Leveraging this notion, the ongoing activity can reveal which of the two alternative scenarios the patient is imagining and can be practically decoded solely based on neuroimaging evidence. In this seminal study, the activity decoded from the BOLD data was indistinguishable from that of healthy subjects performing the same task, suggesting the presence of reproducible awareness in a patient with no observable meaningful behavior – at least, based on their fMRI activity. A following study by Monti and colleagues (Monti et al., 2010) applied similar reasoning, aiming at guessing a yes/no answer, which was bound to either one of the two mental imagery scenarios previously described, based only on the decoding of the fMRI activity of a heterogeneous sample of UWS patients. This technique revealed evidence of covert awareness in 17% of the sample, suggesting again the inefficacy of behavioral assessment of consciousness.

Since then, a considerable number of neuroimaging (Bardin et al., 2011; Naci et al., 2013; Naci and Owen, 2013) and EEG studies (Cruse et al., 2012, 2011; Goldfine et al., 2011; Lulé et al., 2013) have provided further evidence of the dissociative phenomenon of CMD, with different variations on the same theme of "active paradigms": command following tasks used as a proxy to behavior, when behavior is inaccessible with other methods. However, please note that even active paradigms have attracted criticisms from the scientific community, mainly due to the bias induced by the statistical methods necessary to test these hypotheses (Peterson et al., 2015). Hence, international guidelines nowadays do not recommend the use of these neuroimaging tools as the only source of information and strongly indicate the use of multiple sources, integrating for instance clinical consensus and neurobehavioral assessments in the diagnostic process (Kondziella et al., 2020).

Recently, two meta-analyses have collected converging evidence of CMD (even if the nomenclature is still inconsistent in the literature (Schnakers et al., 2022)): very closely to the first estimates, around 14–17% of “behavioral” UWS may be included in this subpopulation (Kondziella et al., 2016; Schnakers, 2020), confirming its relevance in the landscape of DoCs.

Levels of consciousness: is a single dimension sufficient?

Now that we have a clearer picture of the ever-evolving taxonomy of DoCs, we have also gained an important insight: consciousness comes in different degrees, or “levels”. The clinical compromise of assigning a diagnostic label to DoCs necessarily implied that there is a graded, mono-dimensional spectrum which encompasses the total absence of consciousness and full consciousness, including every dysfunctional state that’s in between. However convenient for clinical work, this notion has spread to the field of consciousness as a whole, with examples not only in the description of reduced consciousness, such in anesthesia (Sanders et al., 2012), sleep (Brown et al., 2010), epilepsy (Cavanna et al., 2008), but also for other kinds of altered consciousness (Carhart-Harris and Friston, 2019), where its level is assumed to be even higher than during normal wakefulness. This theoretical leakage has urged scholars to rethink the assumption that global states of consciousness can be reduced to a single analytic dimension (Bayne et al., 2016). In fact, the notion of graded consciousness does not fit very well with the first-person perspective that is inherent of every scientific account of consciousness, which is very hard to imagine to not exist in an all-or-none fashion. But later in their review, the authors put forward one of the most convincing arguments against lining up consciousness on a single scale, which descends from evidence on conscious states themselves. The authors compare two very different states: light sedation and REM sleep. A mono-dimensional level of analysis would reveal that one condition has higher consciousness overall: however, both are associated with a dissociation from the external environment, retained awareness of the self, etc.. and there is (rightfully) no reason to claim superiority of, for instance, REM sleep over light sedation. The alternative is that multiple dimensions are to be accounted for when dealing with global states of consciousness: following their example, REM sleep might display higher consciousness in some dimensions, and the same for light sedation.

In harmony with the view proposed by Bayne and colleagues, the constructionist approach of TTC (Northoff and Zilio, 2022a) approaches the problem of the diagnosis of DoCs on similar grounds. As a result of the descriptive partition of consciousness of four temporo-spatial mechanisms relevant to consciousness, TTC distinguishes four related dimensions of consciousness. Even if in its most recent formulation, TTC poses a particular focus on one of these dimensions (temporo-spatial nestedness) (Northoff and Zilio, 2022a) to explain global states of consciousness, it imposes no strict boundaries on where a single state of consciousness can be represented in the multidimensional grid of its four dimensions/mechanisms. In this thesis, we will only deal with the temporal dimension of consciousness in DoCs as elaborated in TTC, because the novelty of this paradigm imposes a cautious approach to the question; however, we don’t argue that the temporal dimension of consciousness by itself will represent a sufficient parameter of global states of consciousness, as we align ourselves with a multidimensional view proposed earlier in this paragraph.

In conclusion, as already stressed in the first chapter of this introductory section, there are only a few basic assumptions upon which researchers agree when dealing with the intricate reality of approaching consciousness from a scientific point of view. One of these starting points is that consciousness is generated from within the brain, which clearly indicates why researchers are pursuing the goal of an “objective” index of the level of consciousness, independently of behavioral assessments: if complex behavior does not necessarily descend from consciousness - and the existence of CMD is a crystalline example of such dissociation – only an empirical, theory-driven index of consciousness independent of behavioral confounds can solve this major conundrum and improve the well-being of post-comatose patients. A multidimensional approach has been recently proposed as a solution to the high misdiagnosis rate of DoCs in clinics. TTC fits and expands this framework, offering a multidimensional view of the problem of identifying consciousness. Here, we deepen our understanding of one of the proposed mechanisms/dimensions, the temporal dimension of consciousness, operationalized as intrinsic neural timescales (INTs) derived from the EEG signal of these patients. Furthermore, we argue that an additional advantage of this approach is that measuring INTs only requires the recording of resting-state activity, which provides unparalleled cost-effectiveness if compared to neuroimaging techniques and also avoids the technical problems of inferring consciousness with the aid of active paradigms.

Experimental hypotheses

The general aim of this thesis is to explore the role of the temporal dynamics of the brain's spontaneous activity, and more specifically how Intrinsic Neural Timescales (INTs) are involved in forming adequate consciousness states. This aim is directed at improving the quality of the differential diagnosis of disorders of consciousness (DoC), which currently suffers from very high error rates.

In the first study, which we report in the next chapter, we hypothesized a negative correlation at the channel level between INTs and the speed of oscillations in the alpha frequency range (7-13 Hz), which is known to be involved in temporal mechanisms of sensory processing, similarly to INTs. Further, we hypothesized, as posited by TTC, a disruption of this relation in loss of consciousness. To test these predictions, we correlated these two measures in different states of consciousness, including DoCs and two anesthesia datasets.

In the next study, we improve current methodologies for the estimation of INTs by introducing Permutation Time Delay estimation (PE-TD), an approach inspired by information theory which we applied for the first time in neural time series data. PE-TD detects the time scale at which neural time series data displays more predictability, which corresponds to the characteristic time scale at which the signal is more similar to itself. We demonstrate, with simulated data, the differential effects of non-stationarity and non-linearity regimes when using PE-TD or ACW-0, and we test for the validity of this novel measure by probing the similarity in the topographies obtained with the two methods. Further, we hypothesized increased differences in the INTs detected with PE-TD in DoCs, due to differences in non-stationarity and non-linearity in loss of consciousness.

In the third and last study, we investigate on the presence of a dynamic repertoire of INT topographies, as posited by TTC. We inferred the dynamic topographic states composing the alleged dynamic repertoire of INTs explored by the brain at rest by employing a data-driven approach, applying a clustering algorithm to the dynamic ACW-0 time series in both MEG and hd-EEG datasets. First, we used source-reconstructed resting-state MEG data to ensure the validity of the method and to compare the obtained dynamic INT states with current knowledge of the spatial gradients of INTs across the cortex. In a second step, since TTC explicitly predicts that loss of consciousness is accompanied by a poorer dynamic repertoire of INTs, we tested for the randomness in the behavior of the time series describing the dynamic transition between different INT states and on its memory properties as a proxy to the richness of the dynamic INT repertoire; we proceeded to test these hypotheses on a hd-EEG sample consisting of individuals with DoCs.

Datasets

The three studies presented in the following chapters have been led thanks to a research collaboration with the Huashan Hospital of Shanghai, China. The institution has provided us with a hd-EEG dataset composed of resting-state recordings of individuals with DoC. We will overview the dataset briefly in the following paragraph; a more thorough description of the dataset can be found in the Methods sections of chapters 2, 3 and 4.

The DoC sample of the dataset consisted of eighty-one participants with DOC (39 UWS and 42 MCS; mean age = 46.65 ± 15.89 years; sex-ratio = 2.24) with varying etiology (stroke = 43; anoxia = 7; traumatic brain injury = 31). Subjects were record in resting-state conditions with a hd-EEG (256 channels) system for a minimum of 5 min, using a 256-channel system (GES 300, Electrical Geodesics, Inc., USA). The diagnostic labels were assigned by trained clinicians by the JFK Coma Recovery Scale–Revised (CRS-R) (Giacino et al., 2004).

The same experimental conditions were applied to two healthy awake control populations: a sample of twenty participants (age 37.15 ± 11.29 years) and another sample of forty-four participants (age 31.3 ± 16.1 years).

Chapter 2

The contents of this study have been already published in Neuroimage (Buccellato et al., 2023).

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(https://www.sciencedirect.com/science/article/pii/S1053811922009235)

2. Disrupted relationship between intrinsic neural timescales and alpha peak frequency during unconscious states –A high-density EEG study

Abstract

Our brain processes the different timescales of our environment's temporal input stochastics. Is such a temporal input processing mechanism key for consciousness? To address this research question, we calculated measures of input processing on shorter (alpha peak frequency, APF) and longer (autocorrelation window, ACW) timescales on resting-state high-density EEG (256 channels) recordings and compared them across different consciousness levels (awake/conscious, ketamine and sevoflurane anesthesia, unresponsive wakefulness, minimally conscious state). We replicate and extend previous findings of: (i) significantly longer ACW values, consistently over all states of unconsciousness, as measured with ACW-0 (an unprecedented longer version of the well-known ACW- 50); (ii) significantly slower APF values, as measured with frequency sliding, in all four unconscious states. Most importantly, we report a highly significant correlation of ACW-0 and APF in the conscious state, while their relationship is disrupted in the unconscious states. In sum, we demonstrate the relevance of the brain's capacity for input processing on shorter (APF) and longer (ACW) timescales - including their relationship - for consciousness. Albeit indirectly, e.g., through the analysis of electrophysiological activity at rest, this supports the mechanism of temporo-spatial alignment to the environment's temporal input stochastics, through relating different neural timescales, as one key predisposing factor of consciousness.

2.1 Introduction

Our conscious experience is naturally extended in time: a conscious experience progresses seamlessly through the direction defined by the “arrow of time ”and integrates (seemingly) without effort a vast array of temporal scales that range from millisecond to seconds (Kent and Wittmann, 2021). In fact, we are part of a complex environment which is not only spatially structured (e.g., point correlations between two or more points in the visual field), but produces also time-varying inputs: this results in an input space which is characterized by a variety of different timescales, ranging from shorter to longer ones (Golesorkhi et al., 2021b). Recently, it has been proposed that the exploration of the neural mechanisms behind the interaction between these different timescales are crucial to close the gap between current theories of consciousness (for a review, see (Northoff and Lamme, 2020)): however, the implications of these processes for the development of a reliable index of consciousness remain to be investigated. It is generally accepted that the brain has adapted to “align” to the stochastics of our spatial perceptual space (e.g., the statistics associated to spatial information in our input environment) to maximize computational efficiency (Simoncelli and Olshausen, 2001; Sterling and Laughlin, 2015; Tesileanu et al., 2020). Similarly, in order to properly encode and align to the different temporal regularities (timescales) of the external inputs, the brain itself shows different preferential timescales in its spontaneous activity: the so-called Intrinsic neural timescales (INTs) (Golesorkhi et al., 2021b; Hasson et al., 2015; Wolff et al., 2022). Recent studies show that INTs are key for processing and encoding inputs with a complex statistical structure like music, human language, and others (Hasson et al., 2015; Himberger et al., 2018; Yeshurun et al., 2021): INTs seem to exert their influence on input processing through temporal processing mechanisms such as temporal integration and segregation – that is, when brain regions either pool together or distinguish two consecutive inputs based on a preferential temporal window (Golesorkhi et al., 2021b; Wolff et al., 2022). Do INTs have a role in yielding and maintaining consciousness? Indeed, whether differences in the degree of temporal integration - including deficits affecting this specific mechanism – correspond to differences in the degree of the brain’s capacity for consciousness is still an open question. Recent studies using fMRI (Huang et al., 2018) and EEG (Zilio et al., 2021) show abnormal prolongation of INTs in various unconscious states such as anesthesia, sleep, and unresponsive wakefulness state (UWS). These studies, albeit indirectly, draw a suggestive link between the breakdown of temporal input processing and loss of consciousness. Another index of temporal input processing is alpha peak frequency (APF), commonly measured as the peak in power in the alpha frequency range (7–13 Hz) (Angelakis et al., 2004). APF is linked specifically to the mechanism of temporal precision and temporal resolution of sensory input processing (see (Mierau et al., 2017) for a review): in fact, APF has been demonstrated to be systematically accelerated as a function of task demands across several cognitive domains (Haegens et al., 2014; Hülsdünker et al., 2016), as a function of cortical engagement/disengagement at systems level (Mierau et al., 2017), or more generally to a self-regulated dependence on input stochastics (Lefebvre et al., 2015). Additionally, APF displays a fluctuating behavior at very short timescales, in the range of milliseconds (Cohen, 2014): being a state-dependent signature of sensory input processing at many different levels of abstraction, it is only logical that alpha rhythms will display a high temporal variability. This temporal property of APF can be measured by an analysis method first developed in (Cohen, 2014) called “frequency sliding ”, which involves the computation of the first temporal derivative of the range-restricted phase time series of the neural signal: as a result, one can obtain a time series of instantaneous frequencies in the selected range, which is useful to capture its variability at a fine-grained temporal resolution. Recent studies report a role for alpha frequency sliding in temporal processing of incoming inputs, similarly to what has been put forward for INTs: the speed of alpha frequency sliding predicts the temporal resolution of visual perception (Samaha and Postle, 2015), regulates event-related desynchronization during a visual perception task (Noguchi et al., 2019), tracks the insurgence of on- and off-thoughts (Hua et al., 2022) and predicts more general temporal integration mechanisms (Shen et al., 2019). These results support the hypothesis that the duration of alpha cycles organizes the gating of incoming inputs. If that is the case, one may hypothesize that the APF, based on alpha phase cycles, is related to the temporal windows measured by ACW: but this remains to be demonstrated on empirical grounds. This is further hinted by the fact that both ACW and APF are related to input processing albeit on different timescales, e.g., shorter/single inputs (Golesorkhi et al., 2021b; Wolff et al., 2022; Zilio et al., 2021) and longer/input stochastics (Hua et al., 2022; Mierau et al., 2017). Given the supposed relevance of the interaction at different temporal processing neural mechanisms as key mechanisms of consciousness (Northoff and Zilio, 2022a) and that both ACW and input processing are altered during the loss of consciousness (Zilio et al., 2021), one would expect that its relationship with APF is also altered, if not disrupted, in unconscious states (Hight et al., 2014; Lechinger et al., 2013). Based on the theoretical assumption that the interaction between different neural mechanisms at shorter and longer timescales are crucial for consciousness, we assumed that an APF-ACW relationship in the conscious brain would be evident: however, their relationship in the unconscious states remains unclear. The goal of the present high-density (256 channel) EEG study is to investigate the relationship between longer and shorter neural timescales that are related to temporal input processing, as operationalized by the autocorrelation window (ACW) (Fallon et al., 2020; Honey et al., 2012; Ryan V. Raut et al., 2020; Smith et al., 2022), and APF, respectively, in the spontaneous activity of both awake/conscious and unconscious. For this purpose, we used resting-state EEG data recorded during induction with two different anesthetic agents (sevoflurane and ketamine) and patients with disorders of consciousness (DoC) (Giacino, 1997), which include unresponsive wakefulness state (UWS) and minimally conscious state (MCS) (Giacino and Schiff, 2009). This allowed us to specify the relevance of the intrinsic brain activity’s capacity for temporal input processing on different timescales - including longer (ACW) and shorter (APF) ones – and how this relates to consciousness, e.g., as predicted by the temporo-spatial alignment mechanism postulated by the Temporo-Spatial Theory of Consciousness (TTC) (Northoff and Huang, 2017; Northoff and Zilio, 2022a). We hypothesized that ACW and APF to be negatively related with each other in the awake/conscious state, whereas we assume a disrupted relationship during loss of consciousness. Our approach can be sketched in three different points: i) to investigate INTs using ACW during awake and unconscious states. Applying a recently introduced longer version of the ACW, e.g., ACW-0 (Golesorkhi et al., 2021a; Smith et al., 2022), we hypothesized abnormal ACW-0 prolongation in all unconscious states (UWS, MCS (Giacino and Schiff, 2009), ketamine anesthesia, sevoflurane anesthesia) compared to the fully awake or conscious state. ii) probing APF (“frequency sliding ”) in awake and unconscious states. A shift towards slower resting-state EEG activity is well documented in unconscious states, with prevailing power in the delta (0–4 Hz) band at the expenses of the power in the alpha and theta (4–7 Hz) bands (Chennu et al., 2014; Engemann et al., 2018; Schiff et al., 2014; Wutzl et al., 2021; Zilio et al., 2021). For this reason, we hypothesized a group level shift towards the slower end of peak alpha oscillations in unconscious states, as measured with APF, which to our knowledge hasn't been used yet to investigate consciousness. iii to investigate the relationship of ACW and APF in both awake and unconscious states. In this study, we were interested specifically in the intrinsic relationship between these two variables. In other words, we are particularly interested in the covariation of the INTs with respect to the oscillatory alpha component that is intrinsic to the brain: for this reason, we used a channel-wise approach. A channel-wise correlation is more akin to the observation of a general mechanism on a group level (Golesorkhi et al., 2021a; He, 2013; Huang et al., 2015), distinguishing it from the more common approach of subject-wise correlations, for which its source of variance is to be found in the interindividual variability (which is not the aim of this study). We hypothesized a significant correlation in the awake state while, on the other hand, we hypothesized that ACW and APF would no longer relate (e.g., correlate) in the different unconscious states.

2.2 Methods

2.2.1 Participants

2.2.1.1 Anaesthesia datasets

Ketamine

Before the anaesthetic administration, 5 min resting-state EEG recordings of 10 right-handed subjects undergoing general surgery (age 32.90 ± 9.48 years, 4 women), were collected in awake condition (eyes-closed). A Geodesics system (Ges300, EGI, USA) and a 256-channels electrode cap (HydroCel 130) (following 10–20 international systems) were used to collect the data. Subsequently, the same 10 subjects received a 1 mg/kg ketamine infusion, diluted in 10 ml of 0.9% normal saline for a 2 min period, until they reached an OAA/S (Observer's Assessment of Alertness/Sedation) score of 1. An ultrashort-acting opioid remifentanil (1 μg/kg) and neuro-muscular relaxant rocuronium (0.6 mg/kg) were given for endotracheal intubation. After having confirmed the anesthetic induction, diluted ketamine was infused again for a 20 min period (1 mg/kg/h). Starting from 15 min after the loss of consciousness, the resting-state EEG signal was acquired again for another 5 min. Earplugs were provided to the subjects to avoid disturbance from environmental noise. For both conditions, the EEG was acquired at a sampling rate of 1000 Hz and the electrode impedance kept under 5 K Ω. All channels were referenced online to Cz.

Sevoflurane

For the sevoflurane dataset, a similar protocol to the one described in the previous ketamine subsection was followed for 10 different participants (age = 41.4 ± 13.10 years, 2 women), and their EEG signal was recorded with the same equipment already described in the previous section. 8% sevoflurane was initially administered in 6 L/min 100% oxygen until the subjects' OAA/S score reached 1; then, remifentanil (1 μg/kg) and rocuronium (0.6 mg/kg) were administered for the endotracheal intubation. After this induction step, the end-tidal concentration of sevoflurane was kept at 1.3 MAC (2.6%). For both anesthetic agents, the electrocardiogram, non-invasive blood pressure and pulse oximetry were monitored for the whole du- ration of the experiment period. More clinical information about the anaesthetized subjects can be found in (Zilio et al., 2021) (Zilio et al., 2021) (see Table 2).

2.2.1.2 Disorders of consciousness dataset

Eighty-one participants with DOC (39 UWS and 42 MCS; mean age = 46.65 ± 15.89 years; sex-ratio = 2.24; etiology: stroke = 43; anoxia = 7; traumatic brain injury = 31) underwent a recording session of resting-state hd-EEG for a minimum of 5 min, using a 256-channel system (GES 300, Electrical Geodesics, Inc., USA). EEG recording was performed at bedside: before the recording, examiners performed standard systematic procedures, such as the Arousal Facilitation Protocol (Giacino et al., 2004), to induce wakefulness. To avoid the artifactual effects of altered arousal levels on spontaneous brain activity, no sedative agent (mostly midazolam) was administered in the 24 h period that preceded the recording session. Any source of electronic noise was inspected and reduced at the source by the experimenter/physician who performed the EEG experiment; furthermore, to reduce environmental noise, participants wore an additional pair of sound-shielding ear- muffs (3 M Company). The severity of the disturbance of consciousness was assessed on admission with the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974), while the differential diagnosis was per- formed by trained clinicians by repeated behavioral assessments using the JFK Coma Recovery Scale–Revised (CRS-R) (Giacino et al., 2004). Through the CRS-R, the clinicians evaluate 6 hierarchical items (testing auditory, visual, motor, oro-motor, communication, and arousal functionality), which results in a score that ranges from 0 to 23: systematic evidence of behavioral responsiveness displayed in at least one of these items was sufficient to include a patient in the MCS category. A control sample of 20 healthy participants (age 37.15 ± 11.29 years) also underwent a 5 min resting-state hd-EEG recording session. The same aforementioned 256-channel system (GES 300, Electrical Geodesics, Inc., USA) was used to record the healthy participants' EEG signals. Participants were asked to lay on the bed and try to keep their eyes open, in order to mimic the experience of EEG recordings in DOC patients. EEG data was re-referenced online to Cz and acquired at a sampling rate of 1000 Hz, while impedance of all electrodes was kept below 20 K Ω. Additional information about both datasets is summarized in Table 1 and Table 2 .

Dataset	n (subjects)	recording length (minutes)	mean age (years) + SD	sex (m/f ratio)	n (channels)	sampling rate (Hz)
UWS	39	5	48,6 (15,7)	2,8	256	1000
MCS	42	5	44,7 (16,1)	1,8	256	1000
Ketamine	10	5	32,9 (9,4)	1,5	256	1000
Sevoflurane	10	5	41,4 (13.1)	4	256	1000

Table 1. Summary statistics of the unconscious state EEG datasets used in this study. Pre- and post-induction clinical information about both anaesthesia datasets are included in (Zilio et al., 2021).

Dataset	mean delay (days) + SD	anoxia (%)	TBI (%)	stroke (%)
UWS	345 (402)	10,3	30,8	58,9
MCS	428 (431)	7	45,3	47,7

Table 2. Additional information specific to the DoC dataset. Please note that "mean delay" refers to the average number of days that separates the day of the electroencephalographic recording from the acute event (in the DoC cohort).

2.2.2 Ethics statement

Informed written consent before participation was obtained from all participants (or from their caregivers). This research was approved by the Ethical Committee of the Huashan Hospital of Fudan University (approval number HIRB-2014–281) and conducted in accordance with the Declaration of Helsinki guidelines.

2.2.3 Pre-processing

Pre-processing and data analysis, including statistical analysis, were carried on using in-house MATLAB software (The MathWorks, 2019b) and the EEGLAB toolbox (Delorme and Makeig, 2004). For both anesthesia and UWS/MCS datasets, we proceeded with an identical pre-processing procedure. First, the data was resampled to 250 Hz to reduce the computational cost of data analysis. Then, a band-pass finite impulse response (FIR) filter between 0.5 and 40 Hz (Hamming window) was applied to the EEG channel data. Noisy channels were identified and excluded from further analysis through a semi-automatic procedure. The criteria for the rejection procedure were as follows: we removed flatline channels (channels which showed no activity for more than 5 s), correlated channels (with a correlation thresh- old at 0.8), low-frequency drifts, noisy channels and short-timed bursts not related to neural activity (threshold at sd = 5 for data portions relative to baseline). Next, bad channels were interpolated with a spherical method and channel activity was re-referenced to the common average reference. Stationary artifacts, such as those related to eye movements, muscular noise and interferences from heart activity were dealt with by re moving those components identified by independent component analysis (ICA).

2.2.4 Estimating intrinsic neural timescales –The Auto-Correlation Window - 0 (ACW-0)

The length (in ms) of the INTs can be probed by the Auto-Correlation Window. This metric has been defined in many different ways in the literature, and different methodological approaches can be pursued. For this study, we chose to probe INTs at the channel level by computing the ACW-0 on the broadband preprocessed signal. Here, the ACW-0 is defined as the first zero-crossing of the temporal auto-correlation function (ACF) of the EEG time series (Golesorkhi et al., 2021a): in simpler terms, it is the exact time lag after which the ACF crosses its 0% value. Likewise, the ACW-50 is defined as the full-width length of the time lag after which the ACF crosses its 50%. We computed the temporal autocorrelation with a lag of 0.5 s, with a sliding window approach (20 s windows with a 50% overlap, which equals to a 10 s step size), in concordance with (Golesorkhi et al., 2021a; Honey et al., 2012; Zilio et al., 2021). It is worth underlining that regardless of the methodological choices one can make when computing these measures, its core topographical properties remain unchanged (Golesorkhi et al., 2021a).

2.2.5 Instantaneous alpha peak frequency (APF)

As our hypothesis centered on the relationship between the INTs and the spectral content in the alpha frequency range (7–13 Hz), we measured the dynamics of the peak alpha frequency oscillations with the “frequency sliding ”method developed by MX Cohen (Cohen, 2014). Here, we will briefly describe the procedure we implemented; for a complete account of this procedure, we refer the reader to (Cohen, 2014; Gulbinaite et al., 2017; Samaha and Postle, 2015). For each channel, the previously preprocessed broadband EEG data was bandpass filtered with a FIR filter, with 15% filter transition width. Then, the analytic signal of the EEG data was obtained through the Hilbert transform, from which the phase angle time series were extracted for the phase angle at each timepoint is defined as the angle between the vector of the analytic representation of the time series with the real axis. The instantaneous frequency is thus computed as the first derivative of the phase angle time series obtained with the procedure described so far. A median filter (filter order 10) was applied to the instantaneous frequency time series in order to attenuate the noise effects due to brief “jumps ”in the phase angle time series, which are relevant especially when computing instantaneous frequencies in a range with relatively low power (as is often the case during unconscious states).

2.2.6 Statistical analysis

We tested whether significant differences in the medians of our metrics, when contrasting conscious vs unconscious populations, were present: since data did not meet parametric assumptions, we resorted to the non-parametric Wilcoxon rank-sum test. The threshold level for the rejection of the null hypothesis was set to 5%. Levene’s test was used to test for significant differences in the variance of the ACW-0 against the ACW-50 values. The Benjamini-Hochberg procedure was used throughout this study to correct for false discovery rate (Benjamini and Hochberg, 1995). Correlation coefficients between variables like ACW-0 and APF were computed using Spearman's rho test; this choice was driven by the fact that we did not have a priori hypothesis on whether the interaction be- tween variables is purely linear or nonlinear. P-values for Spearman's rho were computed using permutation distributions of the samples. To test for significant differences between Spearman's rho coefficients between populations, we developed a non-parametric permutation test. Particularly, to produce a null distribution of correlation coefficients for this permutation test, channel-level variables were randomly re-shuffled between subjects for 10,000 iterations. At each iteration, the Spearman's rho was computed for the reshuffled data for both variables and conditions, obtaining two coefficients; the difference between these two variables was computed and assigned to the ith permutation distribution position. Eventually, for each pairwise comparison, a p-value was computed as the number of times the permutation distribution showed values more extreme than the difference in the test correlation coefficient. The significance level threshold was set to 5%.

2.2.7 Data/code availability statement

Data used in this article are subjected to sharing restrictions due to privacy issues regarding sensitive clinical data. MATLAB (R2019a release) was used for this study. Most of the data analysis was conducted using the EEGLAB (http://sccn. ucsd.edu/eeglab/) toolbox, an open-source MATLAB package. Custom MATLAB scripts used in this study are available upon reasonable request. Relevant code to replicate our analysis is freely available at http:// www.georgnorthoff.com/code .

2.3 Results

2.3.1 Prolongation of ACW-0 during anaesthesia with ketamine and sevoflurane

Following previous studies, which highlight that ACW-0 contains higher information content than ACW-50 (Golesorkhi et al., 2021a; Smith et al., 2022), we tested if we could replicate similar results in our healthy sample. ACW-0 showed a significantly wider distribution than that of ACW-50 (Levene's $W = 20.0752$; $p < 0.001$), which implies a higher informative content of ACW-0 and supposedly a better inter-individual discrimination. For this reason, we chose ACW-0 over ACW-50 to test our hypotheses.

We next investigated ACW-0 in the subjects under anesthesia. A previous study showed longer ACW-50 in anesthesia (and other disorders of consciousness) (Zilio et al., 2021); this leaves open whether they also show changes in ACW-0. Group-wise, ACW-0 was significantly longer during the anaesthetized condition compared to awake states, in both sevoflurane (mean(Ans) = 0.2069s, mean(Aw) = 0.1477s; $p < 0.05$) and ketamine (mean(Ans) = 0.2804s, mean(Aw) = 0.2105s; $p < 0.05$) (Fig. 1, a-b). These findings suggest that the anesthetic state lengthens the average intrinsic neural timescales. It should also be noted that while ACW-0 showed large inter-subject variability in the awake state, this was no longer the case in ketamine, where subjects showed a more similar distribution in their ACW-0. Together, our findings show a general prolongation of INTs in both pharmacologically-induced unconscious states and less inter-individual differences of ACW-0 in ketamine.

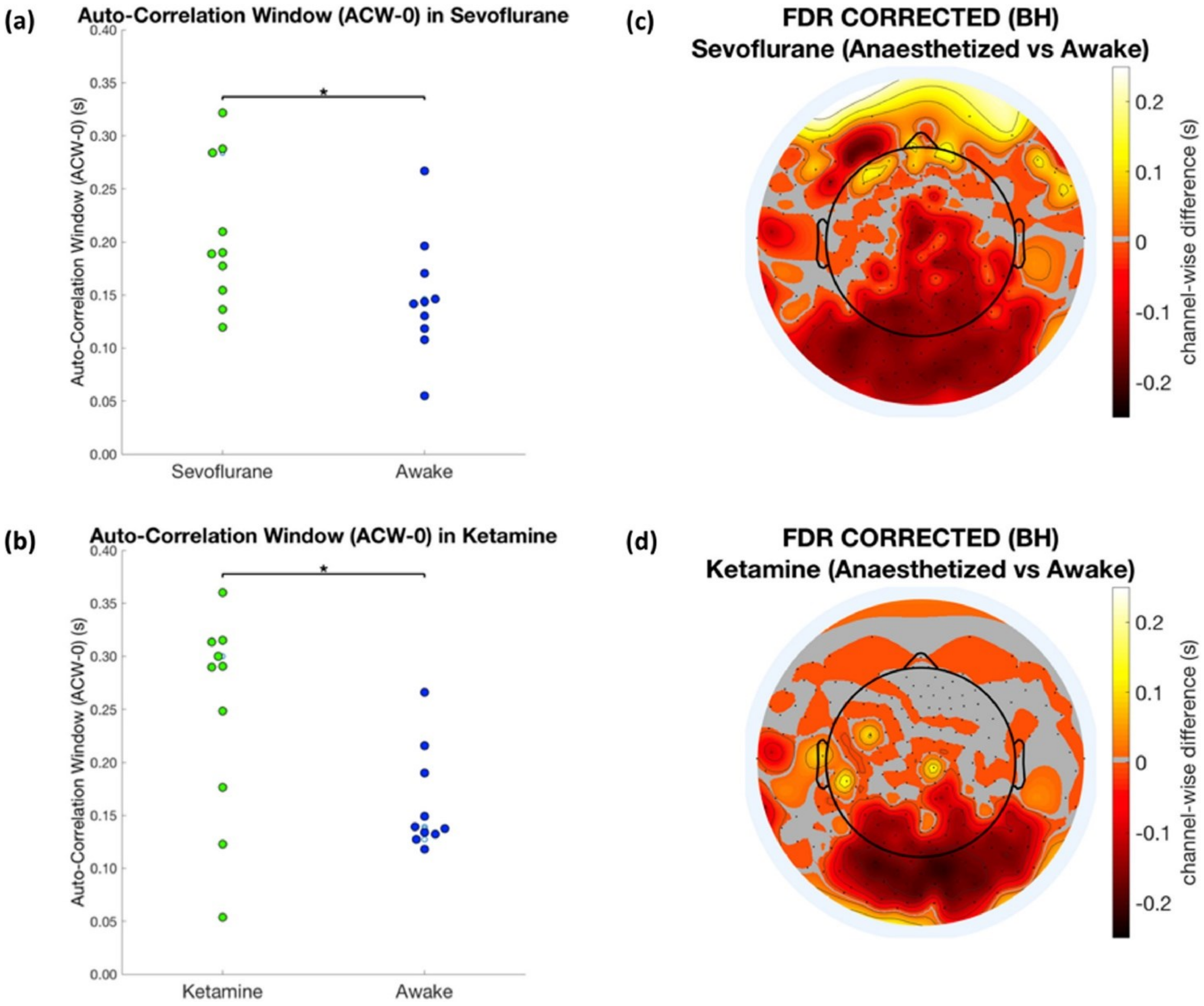


Fig. 2.1. ACW-0 values in ketamine and sevoflurane. (a-b) Swarm charts for the subject-wise average length of ACW-0 in sevoflurane and ketamine, compared to values of the same cohort during wakefulness. ACW-0 is measured in seconds. In all swarm charts presented in this study, * represent $p < 0.05$, ** represents $p < 0.01$ and *** represents $p < 0.001$. n.s., when shown, stands for “non-significant” ($p > 0.05$). (c-d). Topoplots for the channel-wise difference in ACW-0 values between anaesthetized and wakeful states. The colormap shows, at each channel, the difference in ACW-0 between the two groups (anaesthetized – awake). Non-significant channels ($p > 0.05$ after FDR correction) are greyed out from the topoplot.

2.3.2 Decreased alpha peak frequency in anesthetic states

We next investigated alpha peak frequency (APF), that is frequency sliding, in both awake and anesthetic state. We obtained alpha peak frequency values in the awake state and compared them to the values observed in the anaesthetized state. Here, the average APF showed significantly lower values than during awake states: this applied to both sevoflurane (mean (Ans) = 8.7151 Hz, mean (Aw) = 9.9429 Hz; $p < 0.01$) and ketamine (mean(Ans) = 8.2676 Hz, mean (Aw) = 9.641 Hz; $p < 0.001$) (Fig. 2a). Together, these findings clearly indicate generally slower APFs in both ketamine and sevoflurane.

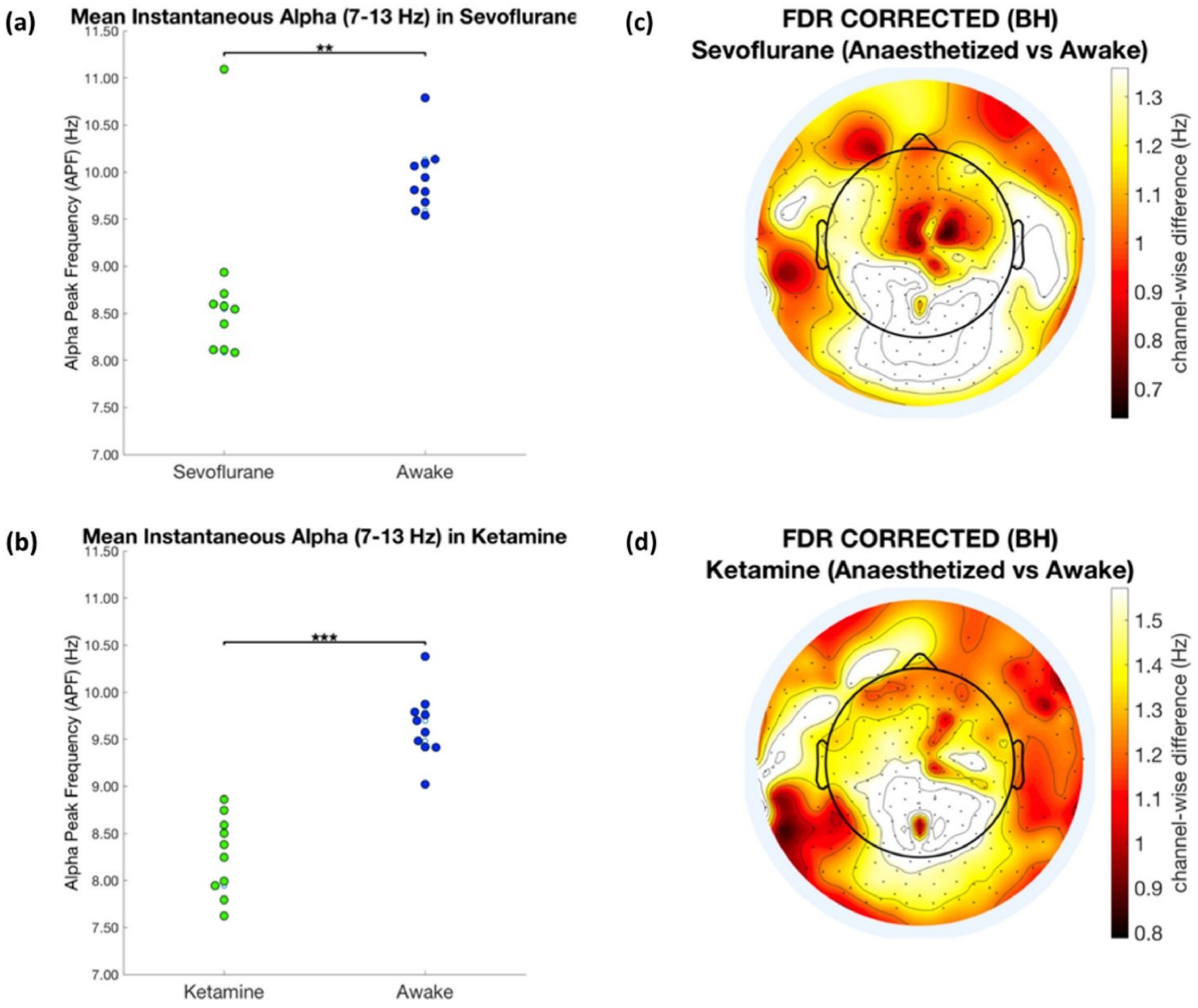


Fig. 2.2. Instantaneous frequency in the alpha frequency range (7–13 Hz) in ketamine and sevoflurane. (a-b) Swarm charts for the subject-wise average speed of APF in sevoflurane and ketamine, compared to values of the same sample during wakefulness. APF is measured in Hz. In all swarm charts presented in this study, * represent $p < 0.05$, ** represents $p < 0.01$ and *** represents $p < 0.001$. (c-d). Topoplots for the channel-wise difference in APF values between anaesthetized and wakeful states. The colormap shows, at each channel, the difference in APF between the two groups (anaesthetized – awake). Non-significant channels ($p > 0.05$ after FDR correction are greyed out from the topoplot.

2.3.3 Relationship of autocorrelation window and alpha peak frequency in awake and anesthetic states

How are the temporal windows, measured by ACW-0, related to the input processing indexed by APF? To explore their relationship, we carried out a channel-wise analysis (i.e., averaging values across subjects in order to obtain a single value for each electrode, instead of grand-averaging across electrodes to obtain a subject's statistical summary for that particular measure (Gutiérrez-Tobal et al., 2021)). We first computed ACW-0 and APF in a channel-based way (rather than subject-based way). These channel-based results (not shown here) generally agree with the above described subject-wise analyses for both sevoflurane (ACW-0: mean(Ans) = 0.2069s, mean (Aw) = 0.1477s; $p < 0.001$; instantaneous alpha frequency: mean(Ans) = 8.7151 Hz, mean (Aw) = 9.9429 Hz; $p < 0.01$) and ketamine (ACW-0: mean(Ans) = 0.2471s, mean (Aw) = 0.2105s; instantaneous alpha frequency: mean(Ans) = 8.2676, mean (Aw) = 9.6410; $p < 0.001$).

Second, we searched for topographic effects by comparing the topographic patterns of ACW-0 and APF (Fig. 1, c-d; Fig. 2, c-d). We observe that a main effect for ACW-0 for both anesthetic agents was over occipital channels, with more electrodes being significantly different in sevoflurane with respect to ketamine. On the other hand, all channels were significantly slower in the alpha frequency range for both ketamine and sevoflurane.

Third, to investigate the relationship between these two measures, i.e., ACW-0 and APF, in the awake state, we correlated their channel-wise results described in the first two steps. In the awake condition, as expected, the correlation was moderate and highly significant (Fig. 3, a-b), being negative in the awake states of both subject groups (Spearman's rho (sevoflurane) = - 0.44, $p < 0.001$; Spearman's rho (ketamine) = - 0.41, $p < 0.001$): a longer ACW-0 value, which signified a longer decay of the signal's autocorrelation function, is related to slower oscillatory activity in the alpha frequency range. Hence, longer temporal windows, i.e., longer ACW-0, decrease and thus slow down alpha frequency.

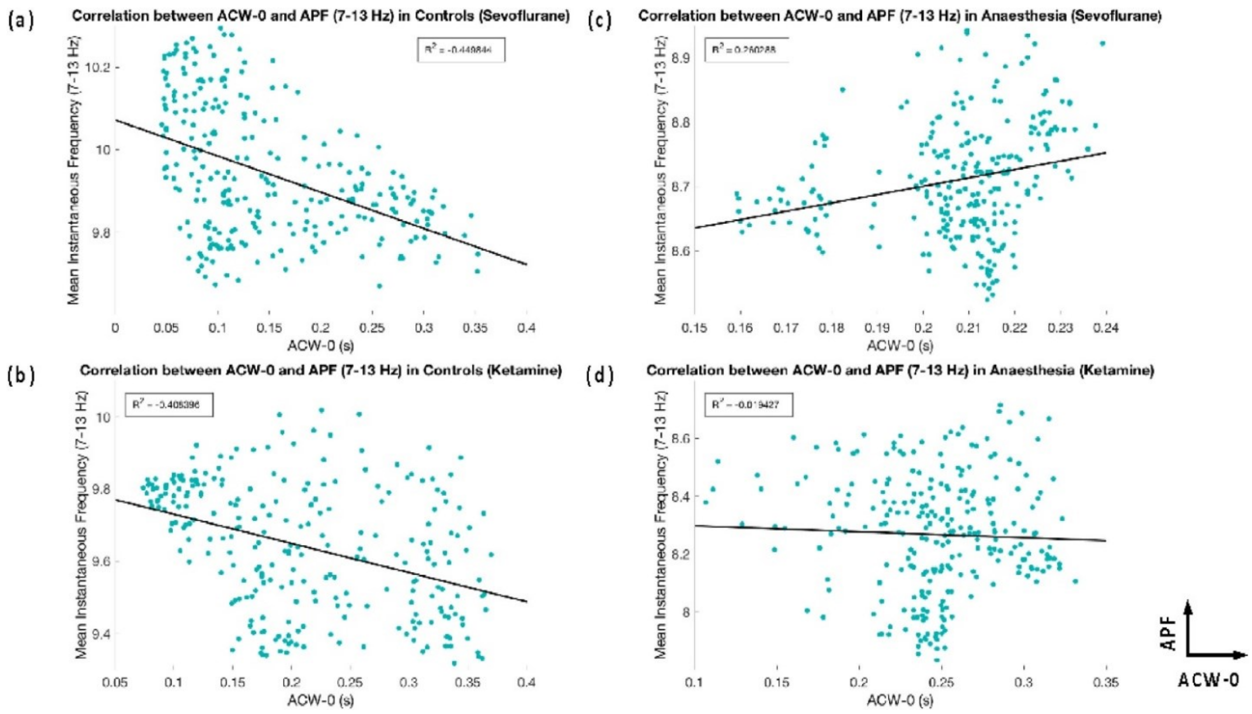


Fig. 2.3. Relationship of ACW-0 and mean instantaneous alpha frequency in awake and anesthetic state. State-dependency of the correlation between ACW-0 and APF: a negative channel-wise correlation in the awake subjects ($p < 0.001$) (a) and a slightly positive one in the same subjects after sevoflurane administration ($p < 0.001$) (c). Same within-subjects change of direction from a negative ($p < 0.001$) (b) to a non-significant correlation ($p > 0.05$) (d) in ketamine. Please note that here, the linear fit is only shown for visualization purposes and does not represent a linear relationship between the two variables (since Spearman's rank correlation does not assume linearity).

Fourth, when probing the same relationship during anaesthetized states, the correlation analysis between ACW-0 and instantaneous alpha frequency on the same subjects yielded a weak correlation (Fig. 3, c-d) in the sevoflurane condition (Spearman's rho = 0.26, $p < 0.001$) while in ketamine the correlation was not significant at all (Spearman's rho = - 0.02, $p > 0.05$). Finally, a permutation test was carried out to make sure the difference in the correlation coefficients between awake and anesthetic states was not spurious: with this method, the difference was significant for sevoflurane ($p < 0.05$) but not for ketamine ($p = 0.0559$).

Together, these findings show a negative relationship between the length of the ACW-0 and the alpha peak frequency in the awake state. Longer ACW-0 is related to lower alpha peak frequency. This was observed only in the awake state whereas this relationship was no longer present or disrupted during loss of consciousness caused by sevoflurane induction, as confirmed by our rather stringent statistical test. On the other hand, even if we observed the same effect for ketamine (at least qualitatively speaking), this effect did not meet our strict statistical requirements for significance: however, we do not exclude that this might well be due to our small sample size and to the present poor understanding of subjective experiences during ketamine induction (Vlisides et al., 2018), and we warrant that further studies are needed to clarify this distinction.

2.3.4 Relationship of autocorrelation window and alpha peak frequency in unresponsive wakefulness (UWS) and minimally conscious state (MCS)

Is the loss of the relationship of ACW-0 and instantaneous alpha frequency specific to anesthesia, or can its disruption also be observed in other altered states of consciousness (as in UWS and MCS)? To show that our results were consistently related to a general characteristic of loss of consciousness (rather than reflecting drug-related effects), we applied the same pipeline previously described to an EEG dataset of 81 DoC subjects including both UWS and MCS.

First, group-wise and channel-wise, both UWS and MCS groups showed significantly longer ACW-0 values when compared to healthy controls (Healthy Controls - HC mean = 0.18394s; UWS mean = 0.32004 s; MCS mean = 0.30513 s; HC vs UWS: $p < 0.001$; HC vs MCS: $p< 0.001$), validating and extending previous results (Zilio et al., 2021). No significant differences in ACW-0 were observed when comparing UWS and MCS subjects ($p > 0.05$) (Fig. 4a).

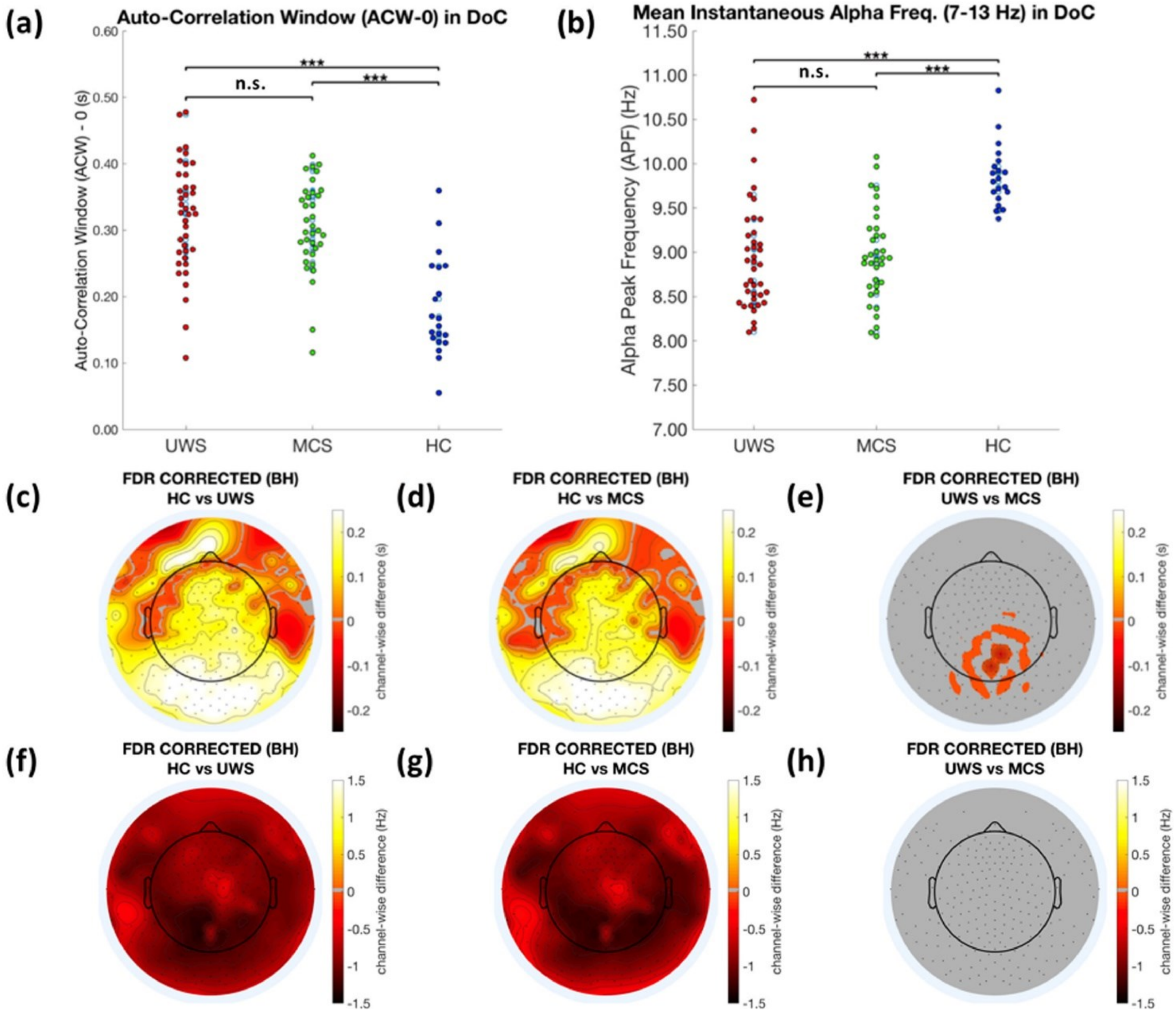


Fig. 2.4. ACW-0 and average speed of alpha oscillations in disorders of consciousness (DoC). (a) Swarm charts showing the subject-wise average length of ACW-0 across UWS, MCS subjects and healthy controls. (b) Same visualization but for the average instantaneous alpha frequency. (c-e) Topoplots for the channel-wise statistical comparison of the ACW-0 length between healthy and UWS subjects (c), healthy and MCS (d), UWS and MCS (e). (f-h) Topoplots for the channel-wise statistical comparison of the average instantaneous alpha frequency between healthy and UWS subjects (f), healthy and MCS (g), UWS and MCS (h). The colormap shows, at each channel and for each measure, the differences between the respective groups compared. Non-significant channels ($p > 0.05$ after FDR correction) are greyed out from the topoplot.

Second, the mean instantaneous alpha peak frequency was significantly lower in both UWS and MCS compared to healthy controls (HC mean = 9.8589 Hz; UWS mean = 8.9334 Hz; MCS mean = 8.9483 Hz; HC vs UWS: $p < 0.001$; HC vs MCS: $p < 0.001$). As in the case of ACW-0, no significant difference in instantaneous alpha frequency was observed between the two patients' groups, i.e., UWS and MCS ($p > 0.05$) (Fig. 4b).

Third, based on the finding that both ACW-0 and APF are altered in UWS and MCS, we investigated their relationship. We correlated these two variables at the channel level, as we did in the anesthesia dataset. Replicating our results in the awake subjects of the anesthesia datasets, we again show negative correlation of ACW-0 and APF in the healthy control group (Fig. 5a) (Spearman's rho = - 0.42, $p < 0.001$). As in the anesthetic states, we did not observe significant correlation of ACW-0 and APF in the UWS group (Fig. 5, c) (Spearman's rho = 0.11, $p < 0.05$), while the MCS group showed significant correlation but in a positive - rather than negative – direction (Fig. 5, c) (Spearman's rho = 0.40, $p < 0.001$) (Fig. 5). The permutation test confirmed that the difference between the correlation coefficients yielded by the healthy subjects and the DoC group was not spurious (UWS vs. HC: $p < 0.001$; MCS vs HC: $p < 0.001$) while the difference was not significant between UWS and MCS ($p > 0.05$).

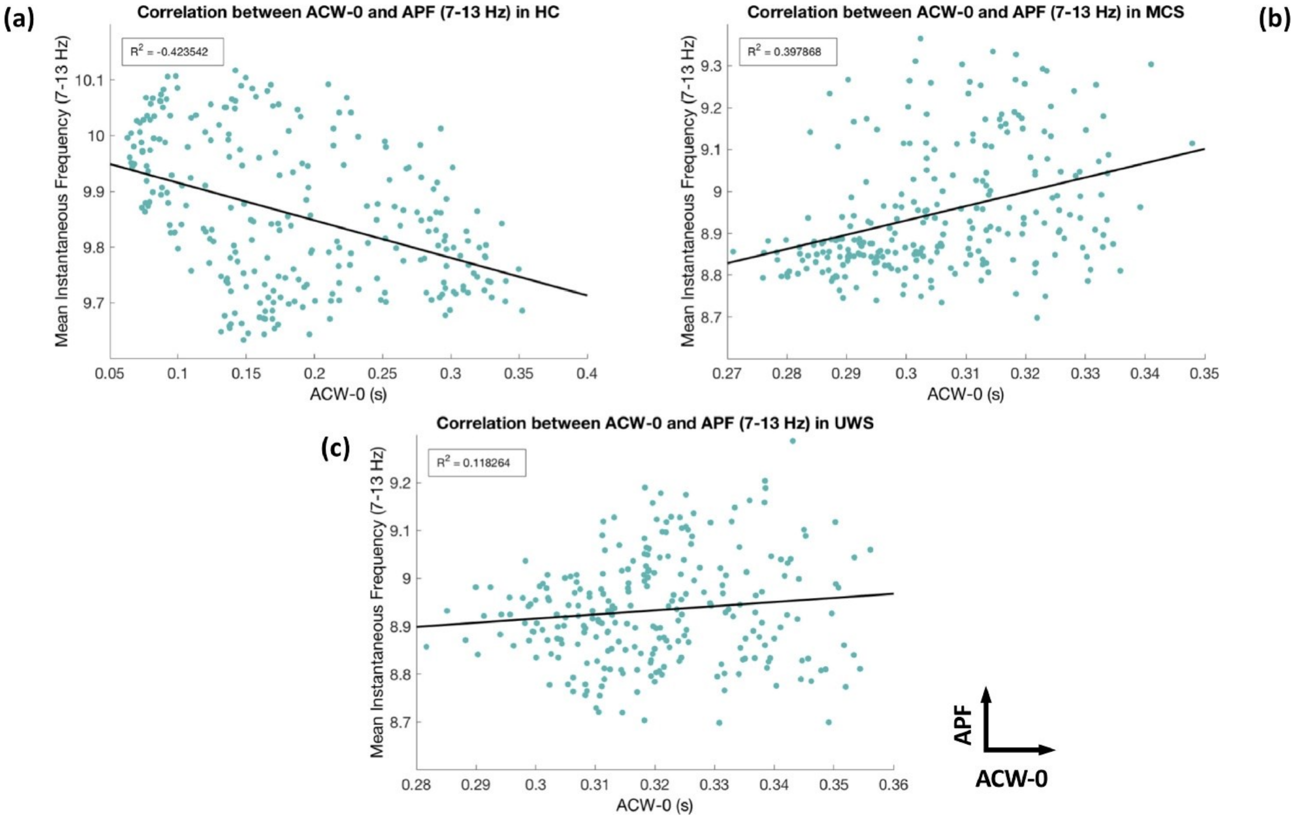


Fig. 2.5. Relationship of ACW-0 and mean instantaneous alpha frequency in the DoC cohort. Channel-wise correlations in the DoC cohort. A state-dependent correlation between the two variables is observed: from a negative correlation in healthy subjects, ($p < 0.001$) (a) and a moderately positive one in MCS patients ($p < 0.001$) (b) to a very weak correlation ($p < 0.05$) (c) in UWS. Please note that the linear fit is only shown for visualization purposes (as in Fig. 3).

Together, these findings show that ACW-0 and APF negatively correlate in the healthy subjects, which confirms the findings related to conscious subjects shown in Section 2.3.3. In contrast, their correlation is disrupted in both MCS and UWS, again consistent with the disruption of their relationship observed during loss of consciousness caused by anesthetic induction (Section 2.3.4).

2.3.5 Power does not drive the relationship between INTs and the speed of alpha oscillations

Through the Hilbert transform, it is possible to obtain two features from the resulting EEG analytic signal: its phase angle and power time series. This raises the question of whether the correlations of ACW and APF in our data are driven by the phase angle or the power contained in the signal of APF. Following a slight modification of the method by (Cohen, 2014), we therefore conducted additional analyses to isolate these two components in the APF.

To ensure that the negative APF-ACW correlation in the healthy sample was driven by the phase-based frequency content of the signal, and not by its power – as the power in the alpha frequency range differs consistently between different states of consciousness – we calculated the instantaneous power by itself (i.e., independent of the phase-related processes) in the same frequency range (7–13 Hz), in a similar fashion to the frequency sliding method implemented here: the only exception is that, after applying the Hilbert transform, the power was obtained (which is obtained by squaring the amplitude of the analytic signal) instead of the phase angle driving the instantaneous frequency, for which its computation - unlike that of pure power - relies on the phase signal component (Cohen, 2014).

Correlating the average instantaneous power in the alpha range with ACW-0 yields a very weak correlation (Spearman's rho = −0.18; $p < 0.001$, see Supplementary Mat.) in the healthy control group. The significant correlation was absent also in the other unconscious state samples (see Supplementary Mat.): this suggests that the contribution of the power itself to our previous APF-ACW correlation was minimal to absent – at least with our analysis method.

Together, these data strongly suggest that the observed difference between conscious and unconscious states - with regard to the ACW-0/APF relationship - is mainly driven by their differences in the phase-based instantaneous alpha frequency component, whose effect dissociates from that of the instantaneous power in the same frequency range. This hints at the possibility of a phase-related process in mediating the relationship of APF and ACW.

2.4 Discussion

We here investigated the relationship of intrinsic neural timescales (INTs) and the alpha peak frequency (APF) in conscious and unconscious states. We show that INTs, as measured by ACW-0, and the dynamic behavior of APF, are significantly related to each other in the awake state. In contrast, such correlation is no longer present in our four different unconscious state EEG datasets. Given that both ACW and APF are known to mediate input processing, our findings support the relevance - although indirectly - of the brain's intrinsic capacity for temporal processing across different timescales, e.g., longer and shorter, for consciousness; this lends further support to the importance of the brain's temporo-spatial alignment to external environmental inputs for consciousness as postulated by the TTC (Northoff and Huang, 2017; Northoff and Zilio, 2022a).

Since here we dealt with indices of temporal processing that span across different timescales (the shorter ones of APF and longer ones represented by ACW-0), our working hypothesis is also in line with the theoretical frameworks that put forward a key role for the interaction of different neural timescales in predisposing adequate states/levels of consciousness (Kent and Wittmann, 2021; Northoff and Zilio, 2022b). In fact, many theories of consciousness operationalize consciousness by the analysis of discrete snippets of “functional” times (Northoff and Lamme, 2020), but often the continuous temporal nature of consciousness is underrated – including the interaction of neural mechanisms at different timescales. Therefore, the exploration of this continuous nature of the conscious experience represents the rationale of this present study.

2.4.1 Prolongation of intrinsic neural timescales in unconscious states

Our results show that an abnormal prolongation of the INTs matches loss of consciousness in the EEG signal of subjects across different unconscious states (i.e., two different anesthetic agents and DoC); this is in line with previous studies in EEG (Zilio et al., 2021) and fMRI (Huang et al., 2018). We extend these prior findings by using a different proxy metric for the assessment of INTs, e.g., ACW-0 rather than ACW-50, which was not yet computed on these unconscious states. It is important to underline that, in (Zilio et al., 2021), ACW-50 was used instead of ACW-0: we argue that this is further confirmation for the fact that the ACW, regardless of which of the slightly different methodologies available in the literature (ACW-0 vs. ACW-50), consistently yields longer values when consciousness is lost, either partially or totally. In fact, the difference between the two ACW metrics lies only in the observed time-lag after the computation of the autocorrelation function (ACF) of the neural signal (the time at which the autocorrelation function (ACF) reaches its 0% value for the ACW-0, as opposed to its 50% value for the ACW-50): hence, they measure distinct degrees of autocorrelative patterns of the neural activity - that is, shorter and longer ones.

Our results further support and confirm the key role of ACW in highlighting fundamental mechanisms of consciousness, including its capacity for input processing (Zilio et al., 2021). Specifically, the abnormally long windows in the unconscious state suggest abnormally high temporal integration of inputs across different time points (Golesorkhi et al., 2021b; Wolff et al., 2022) while, unlike in healthy subjects, there is minimal temporal segregation of inputs – this may lead to rather blurry and undifferentiated perception and cognition of the inputs without their differentiation from each other (Northoff and Zilio, 2022a). Additionally, we report a suppression of the inter-subject variability of average ACW-0 values in ketamine with respect to the awake condition, while this was not the case for sevoflurane. Hence, at least qualitatively, it seems that ketamine abolishes inter-individual differences, contrary to what can be observed in the sevoflurane subjects, which hints at a possible differential response of INTs mechanism to different anesthetic agents.

2.4.2 Slowing down of alpha peak frequency in unconscious states

In addition to ACW, we also investigated dynamic phase angle-based APF, i.e., frequency sliding, for the first time in unconscious states. We show a significant slowing of the speed of oscillations in the alpha (7–13 Hz) range, in line with previous studies showing changes in static power-based APF (Klimesch, 2012; Labonte et al., 2023; Lechinger et al., 2013). Like ACW, APF has been linked to input processing, albeit on a much shorter timescale. Specifically, APF is involved in crucial perceptual mechanisms such as cognitive control (Hülsdünker et al., 2016), gating of information (Benwell et al., 2019; Cecere et al., 2015; Gulbinaite et al., 2017) and perceptual temporal resolution (Noguchi et al., 2019; Samaha and Postle, 2015; Shen et al., 2019): it has been proposed that the duration of an alpha cycle works as an internal “clock” that is aligned to the statistical temporalities and the demands coming from the perceptual environment, which is constantly updated - as is shown by its fluctuating behavior and its covariation with overt perceptual temporal resolution (Cecere et al., 2015; Samaha and Postle, 2015). Furthermore, in the context of DoC, matters are more complicated: models of recovery of consciousness based on corticothalamic integrity outline a series of intermediate spectral phenotypes between the prevalence of delta activity, that is normally associated to behavioral unresponsiveness, and the recovery of “healthy” alpha peaks (Forgacs et al., 2017). However, the nature of this dataset – which does not contain multiple recordings from the same subject - prevents us from following the trajectory of the participant's recovery of consciousness, which makes it harder to locate group level differences that arise from different levels of corticothalamic pathway integrity. However, a general slowing of activity restricted to the alpha frequency range can be expected: in fact, previous literature reports significantly slower alpha oscillations during loss of consciousness, which also covaries with behavioral responsiveness (Fingelkurts et al., 2012; Klimesch, 2012; Labonte et al., 2023; Lechinger et al., 2013). We extend these findings by applying the “frequency sliding” method to unconscious state EEG datasets which, to our knowledge, was not explored yet in the literature.

In this study, we did not observe any meaningful difference between the length of the INTs in the UWS and MCS groups: this might be interpreted as a limiting factor in our methodology. Recently, the assumption that the contrast of these two clinical conditions serves as a minimal contrast for consciousness has been challenged (see (Hermann et al., 2021) for a deeper analysis on these matters). Current clinical methods for the assessment of consciousness (through the detection of significant signs of behavioral responsiveness from the patient) may, in restricted occasions, limit the statistical power of measures that don't specifically target neural correlates of behavioral responsiveness, because of the impossibility of detecting covert consciousness with such diagnostic scales (Kondziella et al., 2020): for this reason, the relative lack of predictive power in the “raw” values of INTs in distinguishing UWS and MCS is to be expected. Instead, the consistency of our results across DoC and anesthesia indicate that the abnormal prolongation of ACW-0 values is ultimately related to loss of consciousness.

2.4.3 State-dependency of the correlation of longer (ACW-0) and shorter (APF) timescales in conscious and unconscious states

Our key finding is that, as we hypothesized, the regular relationship that exists at rest between INTs and the instantaneous speed of alpha oscillations during awake conscious states is disrupted during loss of consciousness: this is observed in at least three different unconscious states (UWS, MCS and sevoflurane anesthesia). The negative correlation shown in the healthy awake subjects suits expectations, since a general slowing down of intrinsic oscillations is logically compatible with longer timescales of neural activity: this, to our knowledge, was never assessed empirically until now. We argue that this points out the importance of the relationship between longer (ACW-0) and shorter (APF) timescales in the conscious brain, which seems to provide an intrinsic cross-scale temporal organization or structure of neural activity.

Furthermore, the disruption of this negative relationship is far from trivial, since the direction of change of ACW-0 and APF values is preserved in unconscious states (ACW-0 gets longer and APF gets slower even during these states). The intrinsic dynamic relationship between neural oscillations and the preferential timescales of neural activity is regarded as a crucial factor that can be observed in the search for the neural predisposing factors of consciousness (NPC) according to the TTC framework (Northoff and Huang, 2017; Northoff and Zilio, 2022a). Here, we observed a correspondence between the abolishment of consciousness and the loss of these intrinsic dynamic ACW-APF relationship, which may alter the dynamic background or context of our subjective experience, i.e., phenomenal consciousness (Northoff and Zilio, 2022a). Hence, our findings on ACW-0, APF and their relationship are consistent over the DoC and the anesthesia samples; this strongly suggests that they are related to the state of consciousness rather than the underlying cause, e.g., anesthetic agent or brain lesion.

Most importantly, a remark is needed to interpret the lack of statistical significance in our ketamine sample. Unlike most anesthetic agents, ketamine is known to induce a “dissociative” state (Domino and Warner, 2010) even at sub-anesthetic doses: patients are - at least behaviorally - not responsive to environmental inputs, but preserve a dose-dependent degree of awareness, which sometimes results in reports of conscious, dream-like experiences (Collier, 1972) after the anesthetic’s effects wear out. In fact, recent studies have produced evidence of spatio-temporal patterns of neural activity comparable to those observed in awake subjects (Sarasso et al., 2015) - or even more complex than in wakefulness (Li and Mashour, 2019) - which makes a case for the presence of covert, but rich, internal conscious experiences during ketamine, despite of the complete observed unresponsiveness. Our correlational results are not dissonant with such interpretations, since we do not observe a statistically significant change in the relationship between ACW and APF during ketamine-induced loss of consciousness. In light of this interpretation, the prolongation of INTs and the average slowing down in the alpha frequency range dynamics could be more related to the predisposition for adequate levels/states of consciousness; on the other hand, their relationship, similarly to neural complexity measures such as the perturbational complexity index (PCI), could be related to the actual realization of a conscious experience. Alternatively, one might also interpret the lack of significance in our ketamine sample as resulting from the combination of unfavorable factors, such as our stringent statistical testing and a current poor understanding of subjective experiences during ketamine-induced loss of consciousness.

In view of what has been discussed so far, it is also crucial to elaborate on the mathematical relationship between ACW-0 and APF, in order for a better understanding of our correlation results. In fact, it is stated in the Wiener-Khinchin theorem (Chatfield, 2003) that, under a few assumptions (such as that of wide-sense stationarity of the time series), the power spectral density of a signal is equal to the spectral decomposition (usually in the form of a Fourier transform) of its autocorrelation function. This observation would lead to a sort of “trivialization” of our correlation results in our healthy population.

However, the sole fact that the correlation is disrupted in different states of unconsciousness works as a preliminary hint, suggesting that the relationship between these two exact measures is far from stereotypical. Speculating on the variables that could mediate this atypical relationship, we argue that the clear contribution of the slope of the 1/f spectral aperiodic component of the EEG signal (He, 2014), to the resulting ACW values has shown in a recent study (Zilio et al., 2021), hints at the possibility that these scale-free dynamics may serve as a shared background for both the ACW and APF of a neural signal, thus contributing to a modulation of their relationship (Wainio-Theberge et al., 2022). We suggest that future studies, especially simulation analyses that take into account the oscillatory dynamics and the network structure of the brain – for instance, oscillator models such as the Kuramoto model (Bick et al., 2020; Cabral et al., 2014) or computational frameworks like The Virtual Brain software (Sanz-Leon et al., 2015) – will shed a light on the mathematical relationship between these two measures and eventually inform on which parameters can modulate this relationship.

2.4.4 Relation to theories of consciousness

Our study aligns well with theories of current consciousness, most notably the TTC. Temporo-spatial alignment is a key mechanism which targets the brain's input processing, namely, how it adapts and thereby aligns its own dynamic to the stochastics of the environmental (and bodily) inputs at different timescales. We show that two measures of input processing, ACW and APF operating at distinct timescales, are related in the awake state whereas they are prolonged, slowed down and disrupted in the unconscious state. Albeit indirectly, this suggests a key role of the dynamic of input processing at different timescales for consciousness, thus supporting the assumption of temporo-spatial alignment. However, our findings may also be related (and reconciled) to theories of consciousness that associate the sustained and integrative brain activity that is generated after an input is consciously processed (Dehaene and Changeux, 2011; Mashour et al., 2020): by integrating notions from these different theories of consciousness, conscious cognition may well be facilitated or even sustained by the right balance between the different intrinsic computational timescales at which the brain preferentially works during conscious states.

Moreover, our findings support the recent claim of the need to consider and integrate different timescales on both neural and phenomenal levels (Kent and Wittmann, 2021; Northoff and Zilio, 2022b). We therefore advocate for the importance, as stated in the first paragraph of this discussion, of a methodological approach that integrates the investigation of consciousness over different timescales, as we tentatively pursued in this study. This has been proposed as an important step to reconcile various theories of consciousness (Northoff and Zilio, 2022a), including the Integrated Information Theory (IIT) (Oizumi et al., 2014; Tononi et al., 2016): this is a promising approach since, for instance, IIT shares with TTC the assumption of integrative spatiotemporal mechanisms of neural activity as key for consciousness.

2.4.5 Limitations

Thus far, we have underlined the relevance of one's capacity for temporal input processing as a necessary (but not sufficient, coherent with the concept of NPC) condition for adequate levels of consciousness; however, we need to emphasize how resting-state studies, such as this one, although useful to assess levels of consciousness (Kondziella et al., 2020; Qin et al., 2015) can only link indirectly these two aspects of the human brain. Only with task data can this relationship be properly investigated, especially on how phase-related processes are involved and to eventually quantify how it actually impacts the phenomenology of subjective experience.

Another limitation is related to the pioneering stage at which this study has been developed. Consciousness research has only recently started to involve intrinsic brain activity in its theoretical frameworks and it has been argued that even so, its temporal dimension is often neglected in many popular theories - apart from some exceptions (Kent and Wittmann, 2021) - and thus there is still room for improvement for its practical diagnostic/prognostic use in clinical settings; future studies will need to synthesized these findings in a quantitative way, such that physicians could use it in their clinical practice.

Lastly, in this study we use all of the sensor space information that is contained in the hd-EEG data of our samples. It is well known how both of our measures have a particular topography, especially regarding the prominent occipital distribution of alpha oscillations (Mantini et al., 2007; Mierau et al., 2017) and the postero-anterior spatial gradient of alpha peak frequencies (Mahjoory et al., 2020) which are well known features of the EEG signal. For this reason, sensor data may not be enough to capture the spatial topography of the relationship between INTs and APF, which may be very important in understanding the underlying circuitry behind these temporal mechanisms: source-level analysis will be crucial in solving this issue and may yield more accurate information, which in turn could prove resourceful to improve on the diagnostic and prognostic issues that affect people with DoCs.

2.5 Conclusions

Our brain allows us to process environmental inputs, including their temporal stochastics, across different timescales. Taken together, our results show how two measures of input processing operating on shorter (APF) and longer (ACW) timescales are related to each other in the awake fully conscious state. In contrast, when we lose consciousness (as in anesthesia and UWS/MCS), their relationship deviates from the negative correlation shown in healthy awake states: we suggest that this might be due to the abnormal ACW prolongation and slowing-down of APF, which we have shown is characteristic of unconscious states, but future studies are needed to clarify the implications of this deviation. These findings further support the key role of the brain's capacity of input processing on different timescales for consciousness. This is well in line with the assumption of temporo-spatial alignment, i.e., our capacity to process and connect to external environmental inputs, being one of the four key mechanisms of consciousness as postulated in the Temporo-spatial Theory of Consciousness (TTC). Future studies combining ACW and APF with specific psychological tasks and phenomenological reports are warranted to substantiate the neuro-phenomenal implications of temporo-spatial alignment.

Supplementary Materials

Please find additional information at the following link: https://ars.els-cdn.com/content/image/1-s2.0-S1053811922009235-mmc1.docx

Chapter 3

The contents of this study have already been published in Entropy (Buccellato et al., 2023).

Buccellato A, Çatal Y, Bisiacchi P, Zang D, Zilio F, Wang Z, Qi Z, Zheng R, Xu Z, Wu X, et al. Probing Intrinsic Neural Timescales in EEG with an Information-Theory Inspired Approach: Permutation Entropy Time Delay Estimation (PE-TD). Entropy. 2023; 25(7):1086. https://doi.org/10.3390/e25071086

(https://www.mdpi.com/1099-4300/25/7/1086)

3. Probing Intrinsic Neural Timescales in EEG with an Information-Theory Inspired Approach: Permutation Entropy Time Delay Estimation (PE-TD)

Abstract

Time delays are a signature of many physical systems, including the brain, and considerably shape their dynamics; moreover, they play a key role in consciousness, as postulated by the temporo-spatial theory of consciousness (TTC). However, they are often not known a priori and need to be estimated from time series. In this study, we propose the use of permutation entropy (PE) to estimate time delays from neural time series as a more robust alternative to the widely used autocorrelation window (ACW). In the first part, we demonstrate the validity of this approach on synthetic neural data, and we show its resistance to regimes of nonstationarity in time series. Mirroring yet another example of comparable behavior between different nonlinear systems, permutation entropy–time delay estimation (PE-TD) is also able to measure intrinsic neural timescales (INTs) (temporal windows of neural activity at rest) from hd-EEG human data; additionally, this replication extends to the abnormal prolongation of INT values in disorders of consciousness (DoCs). Surprisingly, the correlation between ACW-0 and PE-TD decreases in a state-dependent manner when consciousness is lost, hinting at potential different regimes of nonstationarity and nonlinearity in conscious/unconscious states, consistent with many current theoretical frameworks on consciousness. In summary, we demonstrate the validity of PE-TD as a tool to extract relevant time scales from neural data; furthermore, given the divergence between ACW and PE-TD specific to DoC subjects, we hint at its potential use for the characterization of conscious states.

3.1 Introduction

Complex physical systems are characterized by their own intrinsic temporal and spatial dimensions. It follows that a deeper understanding of such dimensions is required to capture the complexity and predict the future behaviors of such systems.

In particular, this temporal dimension might be influenced by one or more sources of delay, which contribute significantly to the system's temporal structure by generating dominant time scales of activity (Otto et al., 2019). Therefore, capturing the essential features of a complex system also requires the inference of these time delays directly from time series data. This task is of utmost relevance, as intrinsic temporal dependence structures characterize many dynamical processes with a vast range of examples, ranging from optics to biology, astronomy, and many others (Erneux, 2009).

Immersed in an environment characterized by a diverse set of time scales, the brain is no exception. Growing evidence has shown that the brain displays different preferential temporal durations in both its spontaneous and its task-evoked activities (Golesorkhi et al., 2021b; Hasson et al., 2015; Northoff et al., 2023), likely adapting to the temporal durations of external environmental inputs (Simoncelli and Olshausen, 2001; Sterling and Laughlin, 2015). These concepts are summarized in the notion of intrinsic neural timescales (INTs), which are defined as "temporal windows of neural spontaneous activity during which neural activity is strongly correlated with itself" (Wolff et al., 2022). Time delays, such as (but not restricted to) INTs, are ubiquitous features of self-organizing dynamic systems such as the brain. However, INTs are not only a signature of self-organized complexity: an additional functional role for processes such as temporal integration and segregation has been recently proposed (Golesorkhi et al., 2021b; Honey et al., 2012; Wolff et al., 2022). Therefore, accurate estimation of the temporal dependences of neural spontaneous activity—specifically in the form of INTs—might also improve the understanding of behavior and cognition.

Starting with the introduction of the notion of INTs, the dominant timescales of neural activity have been probed by means of different methodologies. The majority of studies of these issues have leveraged the property of autocorrelation function (ACF) to estimate the timescale over a signal that shows periodic patterns (Park, 2018): thus the auto-correlation window (ACW) approach, which involves computing the ACF of the signal of interest and the later estimating its fall to its 50% or 0% value (Golesorkhi et al., 2021a; Honey et al., 2012; Smith et al., 2022; Wolff et al., 2022). With ACW, various groups have successfully found coherent results across different modalities, such as fMRI, M/EEG, and single-cell recordings (Hasson et al., 2015; Honey et al., 2012; Huang et al., 2018; Zilio et al., 2021), and that the relevance of INTs extends to perception and cognition (see (Wolff et al., 2022) for a review).

ACF is a valuable tool that is not exclusive to neuroscience: it is widely used to estimate time delays in complex systems across several academic disciplines (Otto et al., 2019). However, one alternative solution to this standard has been recently proposed, which relies on the popular information-theory quantifier developed in (Bandt and Pompe, 2002): permutation entropy (PE). PE belongs to a larger family of measures that quantify the informational content of an observable phenomenon, which are all rooted in the original formulation Shannon's entropy (Shannon, 1948). Given the probability distribution $P=\{pi;i=1,…,k\}$

$$S(P) = -\sum_{t=1}^{k} p_i \, lnp_i$$

S quantifies the degree of uncertainty associated with the probability distribution of the observed phenomenon. The members of this family of information–theoretical measures usually differ from one another with respect to how the process' probability distribution is inferred from empirical data. Importantly, estimation of the probability distribution of a time-series is problematic. Counting the relative frequency of events (Rosso et al., 2009) (for example, via coarse-graining values and placing them in bins) assumes ergodicity, which is rarely true for systems that have memory (e.g., biological systems (West et al., 2008)). In this way, the ordering of events in the direction of the arrow of time is lost. PE solves these issues with a “symbolization” procedure, which involves decomposing the continuous signal of interest into a series of “motifs”—signal partitions that are ranked into ordinal patterns; based on the relative occurrence of these motifs, a probability distribution is inferred, onto which the Shannon entropy formula can be applied. A brief description of the method is provided in the Methods section (Section 3.2.1); for a thorough description of PE, which is not the focus of this study, please refer to (Bandt and Pompe, 2002).

In this sense, PE is particularly suited to inferring temporal relations in a time series since its symbolization technique considers temporal patterns. How can PE support the estimation of time delays from time series? Symbolization requires two parameters: the embedding dimension D, which controls how many consecutive time points are needed to “build” a symbol/ordinal pattern; and the embedding delay tau, which controls the temporal distance between the consecutive time points of a single symbol. If PE is computed multiple times with an increasing tau—which is equal to increasing the temporal granularity of the investigation—a particular graph is obtained, which might display one or multiple local minima. Those minima should then correspond to the time delays of the time series: the intuition is that the entropy associated with the observed phenomenon should be minimal when the temporal granularity (tau) matches its dominant time scale. An alternative way of conceptualizing this method is that it is directed at capturing the complete duration of events. If tau is equal to the period, then each symbol encompasses the whole period, and every symbol is the same. This process results in a probability distribution with maximum precision and therefore minimum entropy.

A series of studies of model systems and real-world systems have confirmed that PE exhibits a minimum value at a tau corresponding to the system’s own time scale (Soriano et al., 2011; Wu et al., 2012; Zunino et al., 2010); however, despite evidence of the efficacy of PE in recovering time scales from time series, this method has yet to be used in a neuroscientific context, in which the estimation of time scales—and particularly the estimation of INTs—is a relevant matter.

The importance of INTs is not restricted to temporal input processing (Kolvoort et al., 2020; Northoff et al., 2023; Sancristóbal et al., 2022). In fact, recent evidence has shown that loss of consciousness is consistently followed by an anomalous alteration of INT values (Buccellato et al., 2023; Huang et al., 2018; Zilio et al., 2021), compared to the range of values typically displayed by healthy conscious populations; that this peculiar alteration is observed across different unconscious states (sleep, anesthesia, and disorders of consciousness—DoC (Giacino, 1997)) suggest a strong relation to consciousness (Hermann et al., 2021). In this sense, the temporospatial theory of consciousness (TTC) (Northoff and Huang, 2017; Northoff and Zilio, 2022a) postulates an important role for the temporal dynamics of the brain’s spontaneous activity in shaping the form/context of conscious states. Hence, in the framework of TTC, the estimation of INTs goes even beyond the experimental need to predict future behaviors of a complex system such as the brain and is therefore an important prerequisite to investigating different states of consciousness.

Testing for hypotheses that relate INTs to conscious states requires the cleanest experimental contrast possible. However, unconscious states are notoriously characterized by different regimes of nonstationarity (Galadí et al., 2021; Kaplan et al., 2005) and nonlinearity (Casali et al., 2013; Tononi, 1998): this fact might hinder the experimental methods used to uncover differences exclusively related to consciousness, which often rely on strong assumptions of the nonstationarity and/or nonlinearity of the analyzed signal.

Hence, given the important challenges that neural data—and especially EEG data—pose for the identification of time delays, permutation entropy–time delay estimation (PE-TD) is a promising approach that could aid the advance of many neuroscientific disciplines and is well suited to test for hypotheses relevant to consciousness research.

Our aim for this study is two-fold: (i) the validation and exploration of the use of PE-TD for the estimation of neural time scales, with the aid of synthetic data (when the ground truth is known) and real-world EEG data; and (ii) providing evidence for a parallel role of these measures in exploring the properties of EEG recordings from people with clinical loss of consciousness.

3.2 Methods

3.2.1 Estimation of EEG Time Scales through Permutation Entropy—PE-TD

Permutation entropy (PE) calculation requires a symbolization procedure: a series of steps that map ordinal patterns into permutation patterns directly from time series data. The symbolization procedure is briefly recapitulated here.

Given a time series *X* = {Xt:t = 1, ⋯, N}, symbolization involves the careful choice of two parameters: the embedding dimension D and the embedding delay tau (τ). The first step involves producing vectors of length D, consisting of consecutive time-ordered values: for instance, at D = 3, each vector will consist of three consecutive time points. The embedding delay tau controls the temporal distance that separates each consecutive value in the vector: at tau = 1, the original time granularity will be preserved; while at tau = 2, vectors will consist of every other time point from the original time points, and so on.

Thus, the symbol S is constructed as:

$$S_i = \{X_i, \quad X_{i+t}, \quad X_{i+2t}, \dots, X_{i+D-1}\}$$

for i = 1, 2, …, N

Next, the values in each of vector Si are ranked in ascending order, and their vector entries are substituted by their rank order, eventually resulting in the formation of an ordinal pattern. Every ordinal pattern will then correspond to a permutation pattern (a "symbol"). The last step involves computing the Shannon entropy of the probability distribution P, of which its pi units are the frequencies associated with all the possible permutation patterns extracted with the symbolization procedure:

$$PE = -\sum_{t=1}^{D!} p_i \, ln p_i$$

PE-TD

Fixing the parameter D and measuring PE values as functions of the embedding delay tau, one can easily visualize how tau influences the resulting PE values. The most important assumption is that the signal will be more “predictable” if tau matches the timing of the intrinsic time delays of the system: a system that has an intrinsic time delay will have a narrower probability distribution at that particular time scale/tau (and thus, more predictability) since events that happen periodically in a time series will result in the same permutation pattern at that particular temporal grain. This phenomenon, in turn, is associated with the observation of a clear minimum in the PE vs. time delay graph.

We extracted the absolute minimum of the PE vs. time-delay graph for each time series that we analyzed. Time series data, in the particular case of this study, were represented by either synthetic signals or EEG channel data. Hence, we defined the permutation entropy–time delay (PE-TD) estimation of the intrinsic time scale as the corresponding minimum of the PE vs. time delay graph, multiplied by the sampling rate, to convert this estimation into seconds.

One important step when applying this method is the choice of an appropriate upper limit for tau: setting a low upper limit would probably neglect the effects of higher intrinsic time scales, while an excessively high number would unnecessarily slow the computational time (as PE values are computed iteratively at each tau). After careful consideration, we decided to proceed with 100 as the maximum delay to apply on our resting-state hd-EEG data, based on two considerations: (i) the range of INT values shown in previous studies were comparable to those empirically observed at this threshold; and (ii) PE values do not considerably fluctuate well before our threshold. Embedding dimension D was set to 5 to balance the computational speed and the higher prediction accuracy, which is usually accomplished with higher D values (Soriano and Zunino, 2021).

In this study, we used the algorithmic implementation shown in (Unakafova and Keller, 2013) to calculate PE values, providing a fast computation time without sacrificing accuracy.

An example of the PE vs. tau graph and its associated minimum in an EEG channel is provided in Figure 1a.

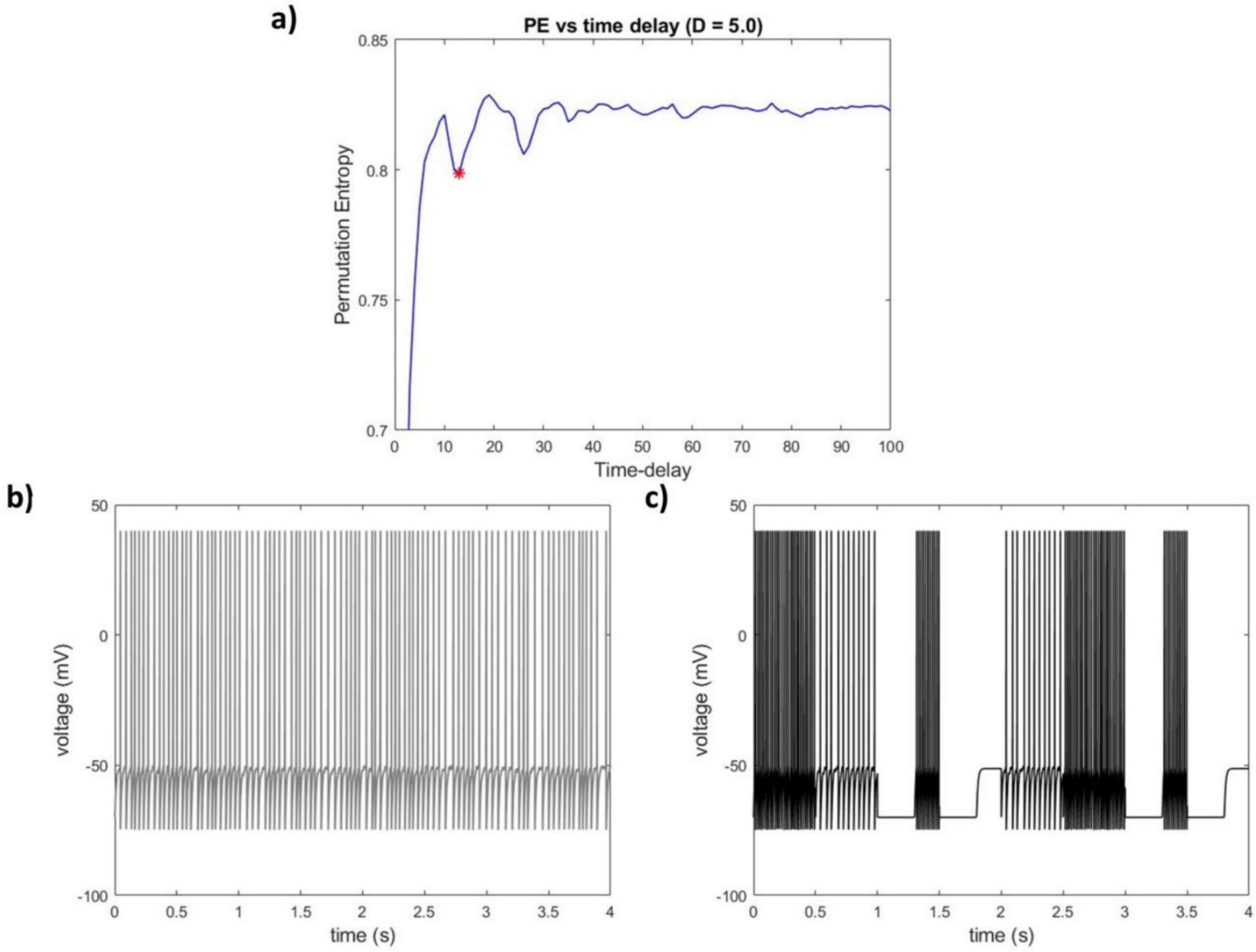


Figure 3.1. Time delay estimation through permutation entropy (PE) in a neural environment. (a) PE values as a function of increasing time embedding tau for a single channel hd-EEG recording. Estimating time delays in a physical system through PE relies on the notion that, when the tau parameter matches the time delay of the system, PE values are expected to dip significantly. The distribution of permutation patterns obtained with a tau matching the system's dominating temporal scale is narrower; therefore, the system becomes more "predictable": thus the dip in PE values. (Red star indicates the minimum of the PE vs time-delay graph.) (b) An example of a stationary integrate and fire (IAF) neuron signal. (c) Concatenating multiple (8) IAF stationary segments to obtain a simple case of a synthetic nonstationary signal allowed us to investigate the effects of nonstationarity on PE-TD.

3.2.2 ACW-0

The auto-correlation window (ACW) is an established method used to probe INTs (Golesorkhi et al., 2021b; Honey et al., 2012; Wolff et al., 2022). It is based on the autocorrelation function r, which is defined as a signal x's correlation with itself on different time lags:

$$r_l = \frac{c_l}{c_0}$$

$$c_l = \frac{1}{N}\sum_{t=1}^{T-l}(x_\tau - \bar{x})(x_{\tau-1} - \bar{x})$$

where l denotes lag, and $\underline{x}$ denotes the mean of x.

Here, we computed the ACW-0, which is defined as the first zero-crossing of the temporal autocorrelation function (ACF) of the EEG time series (Golesorkhi et al., 2021a); ACW-0 might also be understood as the time lag after which the ACF crosses its 0% value. To this end, we computed a temporal autocorrelation with a lag of 0.5 with sliding windows of 20 s and a 50% overlap (10 s step size). Further details about ACW can be found in (Golesorkhi et al., 2021b; Honey et al., 2012; Zilio et al., 2021).

3.2.3 Simulations

Nonstationarity refers to a general property of signals with statistical moments (usually the mean or variance) that are not constant in time but vary to a certain degree; it is a property that biological signals, especially those recorded from the brain, display consistently (Kaplan et al., 2005).

Nonstationarity potentially affects the accuracy of time delay estimation. In (Huang et al., 2022), a simple method to assess the impact of nonstationarity on time-delay estimation with the use of synthetic signals is provided, building on a process originally described in (Mikosch and Stărică, 2004) for financial time series. In this study, we have adapted the aforementioned method to test for the behavior of PE-TD in regimes of nonstationarity in a neuroscientific context: to this end, we integrate the process illustrated in (Mikosch and Stărică, 2004) with a biologically plausible neuronal model, such as integrate-and-fire (IAF) models, to generate a simple case of in silico nonstationarity in the firing pattern of a single neuron. Integrate-and-fire neuron models (Burkitt, 2006; Gerstner and Kistler, 2002) describe the behavior of a single neuron from the point of view of its membrane potential. An IAF neuron possesses its own resting membrane potential Vrest: after it receives a series of inputs (inhibitory or excitatory), which can be modeled separately, it produces a spike only after its membrane potential surpasses a threshold Vth. The potential is reset immediately after a spike is produced.

Parameters used for the IAF models used in this study are listed in Table 1.

Parameter	Value
V_{rest}	-70 mV
V_{reset}	-75 mV
V_{th}	-50 mV
Sampling rate	10 kHz
Resistance	10 MΩs
Decay time constant	10 ms

Table 3.1. Model parameters for the integrate-and-fire (IAF) neuron used in this study.

The procedure can be broken down into a few consecutive steps.

First, we generated a series of "stationary" IAF time series of equal length (40,000 time points);

Then, we obtained a nonstationary IAF signal by concatenating the previously synthetized stationary signals into a single signal;

Eventually, by comparing the time scales measured in the synthetic nonstationary signal and the average of the time scale estimated on the stationary segments, one can assess the resilience of the tested measure to nonstationarity.

The rationale is rather straightforward: since the temporal structure of the concatenated nonstationary signal depends on the contribution of the temporal structure of its composing segments, a small distance between the time scales extracted from these two indicates high resistance of the tested measure.

Eight IAF segments of 4 s (40,000 time points) were generated with the parameters illustrated in Table 1. The input structure fed into the model varied randomly between each iteration to avoid repeating a particular stationary regime: inputs were randomly—but equally—distributed into either a DC input component (mean = 4 A, std = 1) or white noise with fixed mean (mean = 0) and variance = 1, effectively creating a simple case of a plausible nonstationary neuron: the input structure is known to affect IAF firing rate (Salinas and Sejnowski, 2002) and therefore its statistical properties. To compare signals of comparable length, we truncated the original stationary segments before concatenating them into the new nonstationary signal; in this way, we obtained a nonstationary signal of equal length (4 s). The procedure was repeated 500 times to avoid spurious results caused by sampling.

To characterize PE-TD's behavior in a non-linear dynamic system model, we carried a parameter search over a very well-known model for non-linear feedback systems with intrinsic time delays: the Mackey–Glass oscillator (Mackey and Glass, 1977). In a Mackey–Glass system, a variable of interest x is under the control of a feedback system that, like in many biological systems (Bélair et al., 1995), acts within a certain time lag, creating the conditions for the emergence of intrinsic time scales on its time series. In this study, the models were implemented by the following differential equation described in (Zunino et al., 2010):

$$dx/dt = -x + \frac{ax(t-\tau_s)}{1 + x^c(t-\tau_s)}$$

with t as a time index, τs as the time delay feedback, a as the feedback strength, and c describing the degree of nonlinearity. The Mackey–Glass differential equation was integrated via Euler's method with time step Δt = 0.001; simulations lasted 5 s. A parameter search with a fixed c over a and tau was conducted by iterating one of the two parameters while fixing the other over the following range of values: a = 1 to 46 and tau = 50 to 300 with steps of 1.

3.2.4 Experimental Data (EEG)

Eighty-one participants with DoCs (39 UWS and 42 MCS; mean age = 46.65 ± 15.89 years old; sex-ratio = 2.24; etiology: stroke = 43; anoxia = 7; traumatic brain injury = 31) were recorded in resting state—at bedside—for 5 min using a Geodesics system (Ges300, EGI, Eugene, OR, USA) and a 256-channel electrode cap (HydroCel 130, EGI, Eugene, OR, USA) (following 10–20 international systems). Before the EEG recording session, the experimenters performed standard systematic procedures, such as the Arousal Facilitation Protocol (Giacino et al., 2004), to ensure high wakefulness and arousal levels in the participants. No sedative agents were administered in the 24-h period that preceded the recording session to avoid drug-induced interference in the spontaneous brain activity's signal. The severity of the disturbance of consciousness was assessed by administering, on admission, the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974), while the differential diagnosis was performed by trained clinicians by repeated behavioral assessments using the JFK Coma Recovery Scale–Revised (CRS-R) (Giacino et al., 2004). Additionally, a control sample of 44 healthy participants (age ± years) underwent a 5-min resting-state hd-EEG recording session; an additional sample of 20 healthy participants (age ± years) was used for further validation. The same aforementioned 256-channel system (GES 300, Electrical Geodesics, Inc., USA) was used to record both the datasets from the healthy participants. Healthy participants were asked to lie on the bed and keep their eyes open to mimic the experience of EEG recording in DoC patients. EEG data were re-referenced online to Cz and acquired at a sampling rate of 1000 Hz, while the impedance of all electrodes was kept to less than 20 KΩ. Further details about the datasets used in this study can be found in (Buccellato et al., 2023; Zilio et al., 2021).

3.2.5 Pre-Processing

Pre-processing and data analysis, including statistical analysis, were carried out using in-house MATLAB software (The MathWorks, 2019b) and the EEGLAB toolbox (Delorme and Makeig, 2004).

The same pre-processing pipeline was used on all of the EEG datasets used in this study. First, the data were resampled to 250 Hz; then, a band-pass finite impulse response (FIR) filter between 0.5 and 40 Hz (Hamming window) was applied to the EEG channel data. Noisy channels were identified and rejected through a semi-automatic procedure. The rejection criteria used in our procedure were: removal of flatline channels (channels inactive for more than 5 s); correlated channels (with a correlation threshold of 0.8); low-frequency drifts; noisy channels; and short-timed bursts not related to neural activity (threshold at sd = 5 for data portions, relative to baseline). Next, bad channels were interpolated with a spherical method, and channel activity was re-referenced to the common average reference.

Artifacts related to eye movements, muscular noise, and heart activity were identified by independent component analysis (ICA), and their related independent components were removed from the signal.

3.2.6 Statistics

Root mean square error (RMSE) was used to assess the performance of PE-TD under nonstationary regimes in a series of LIF simulations.

To test for significant differences in the PE-TD values of the HC and UWS samples, Wilcoxon's non-parametric rank-sum test was used, with the threshold level for the rejection of the null hypothesis set to 5%.

Spearman's rank correlation coefficient was assessed to characterize the channel-wise relation between ACW-0 and PE-TD in both the conscious and unconscious groups. Furthermore, a bootstrap distribution test, with 10,000 iterations, was performed to assess the significance in the difference between Spearman's correlation coefficients in conscious/unconscious states. The threshold for rejecting the null hypothesis was set to 5%. To further validate the state-dependent differences between correlation coefficients in different conditions, we assessed significance with Fisher's z transform (Kotz and Johnson, 1992) as well.

3.3 Results

3.3.1 Simulations

In this section, we use synthetic signals to show how the estimation of time delays from time series data through PE-TD might be affected by: (i) nonstationarity; and (ii) parameter choice of model non-linear systems.

The Effect of Nonstationarity on the Accuracy of PE-TD

An important a priori condition, when assessing the impact of nonstationarity on time delay estimation with the methodology described in Section 3.2.1, goes beyond the sheer comparison of stationary vs. nonstationary regimes. In fact, it is important to know that the model's true time scale—the ground truth—can be recovered through the tested measure in the first place; if this condition is not met, the risk of spurious positive observations is not negligible. For what concerns an IAF neuron model, PE-TD is surprisingly accurate at recovering the average time delay between one spike and another, which involves simple recovery of time intervals from the spike rate (RMSE = 0.00015 s); this fact suggests that employing an IAF model is an appropriate choice.

A series of IAF stationary segments (see Figure 1b for an example) were concatenated into a single nonstationary signal (see Figure 1c for an example of such a signal) for 500 iterations to produce the testing substrate. The average error between the average PE-TD values obtained on stationary segments and on the nonstationary concatenated signals was very low (RMSE = 0.0011 s), suggesting that the impact of nonstationarity for the estimation of IAF time scales was minimal to null—at least for the time scales related to spike production in simplified model neurons.

PE-TD Behavior as a Function of Parametrization Choice in a Non-Linear Delay System

As a first step, we evaluated the optimal parameter choice for c (the degree of non-linearity) in our Mackey–Glass oscillator for both auto-correlation window 0 (ACW-0) and PE-TD; we proceeded in this order since c was not a variable of interest in this study.

Figure 2a shows the error (computed as a simple algebraic subtraction) between the model's time scale—which was fixed at tau = 160—and the time scale estimated with ACW-0, plotted against the parameter c; Figure 2b shows the same plot for PE-TD. For both measures, qualitatively similar results indicate that, for low c values, the estimation is quite unstable; however, beyond c = 10, the error becomes negligible, with an optimum for both measures reached at c = 16. However, PE-TD shows a peculiar steady decrease in accuracy after the dip reached at c = 16. Therefore, c was fixed at this value for the next round of simulations.

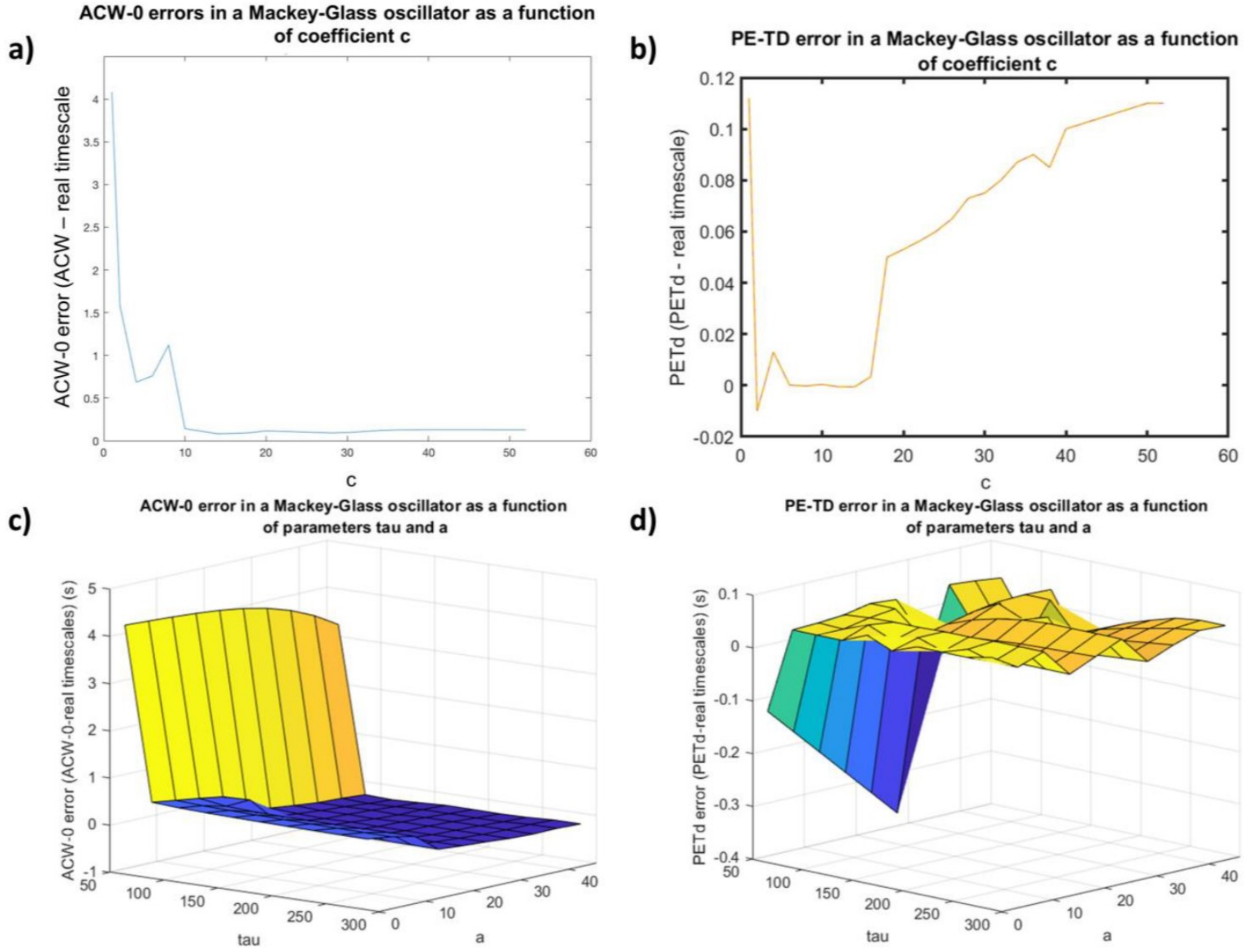


Figure 3.2. Differential behavior of autocorrelation window (ACW-0) and PE-TD in model parameters for a model nonlinear delay system to perform the interpretation of estimated time delays. (a) Estimation error (in seconds) as a function of parameter c (degree of nonlinearity) when using ACW-0 to estimate the time delay of a Mackey–Glass oscillator. Stable performance is reached at c = 16. (b) Same graph for PE-TD. PE-TD behaves similarly to ACW-0, as the performance reaches an optimal accuracy around c = 16. However, after this increase in accuracy, the performance of PE-TD decreases steadily as a function of c. (c) Third plot of the estimation error as a function of both a (feedback strength) and tau (time delay) when using ACW-0. (d) Same graph for PE-TD. PE-TD seems to perform stably at earlier timescales and with weaker feedback strength than ACW-0.

In the subsequent part of the study, we engaged in a parameter search—with a fixed c—over two parameters of interest, which are known to influence the state in which the Mackey–Glass oscillator is found (Zunino et al., 2010): the time scale tau and the feedback strength a.

Figure 2c shows the time scale estimation error plotted as a function of increasing tau (shown on the x axis) and a (shown as different colored lines) for ACW-0. With increasing values of tau, ACW-0 performance reaches stable accuracy only after the time delay feedback approaches tau = 160; this point is true for most feedback strength values beyond a = 6. We observed a similar pattern for feedback strength: at very low a values, it takes longer taus for the estimation to become more accurate compared with higher values.

PE-TD shows a similar behavior, as shown in Figure 2d. In fact, regardless of feedback strength, PE-TD seems to perform accurately when tau reaches a threshold of tau = 100. At shorter time scales, feedback strength seems to influence whether PE-TD overestimates the real underlying time scale.

3.3.2 PE-TD in EEG and DoC

PE-TD Values Converge with INTs Probed with ACW-0

To be able to confirm the appropriateness of PE-TD for testing hypotheses relevant to the brain, we need to assess the degree to which this measure convergences and/or diverges with ACW-0, which has reinforced its position as the benchmark measure of INTs.

One of the most recognizable features of INTs is their hierarchical spatial organization: unimodal regions show shorter timescales compared to the longer time scales of transmodal cortical areas, related to the different time requirements to integrate (and segregate) their perceptual space (Golesorkhi et al., 2021b). Do findings obtained through PE-TD converge with this important property of the brain? The topoplot in Figure 3a shows (although in electrode space) a fair hierarchical distribution of PE-TD values, coherent with findings obtained with ACW-0. We observed a significantly high spatial correlation between the two maps obtained with PE-TD and ACW-0 (Figure 4a, R = 0.90; $p < 0.001$), suggesting a preservation of the hierarchical spatial distribution of INTs captured by PE-TD. To validate these findings, we repeated the same analysis on another sample of healthy subjects (N = 20) with similar results (R = 0.93, $p < 0.001$).

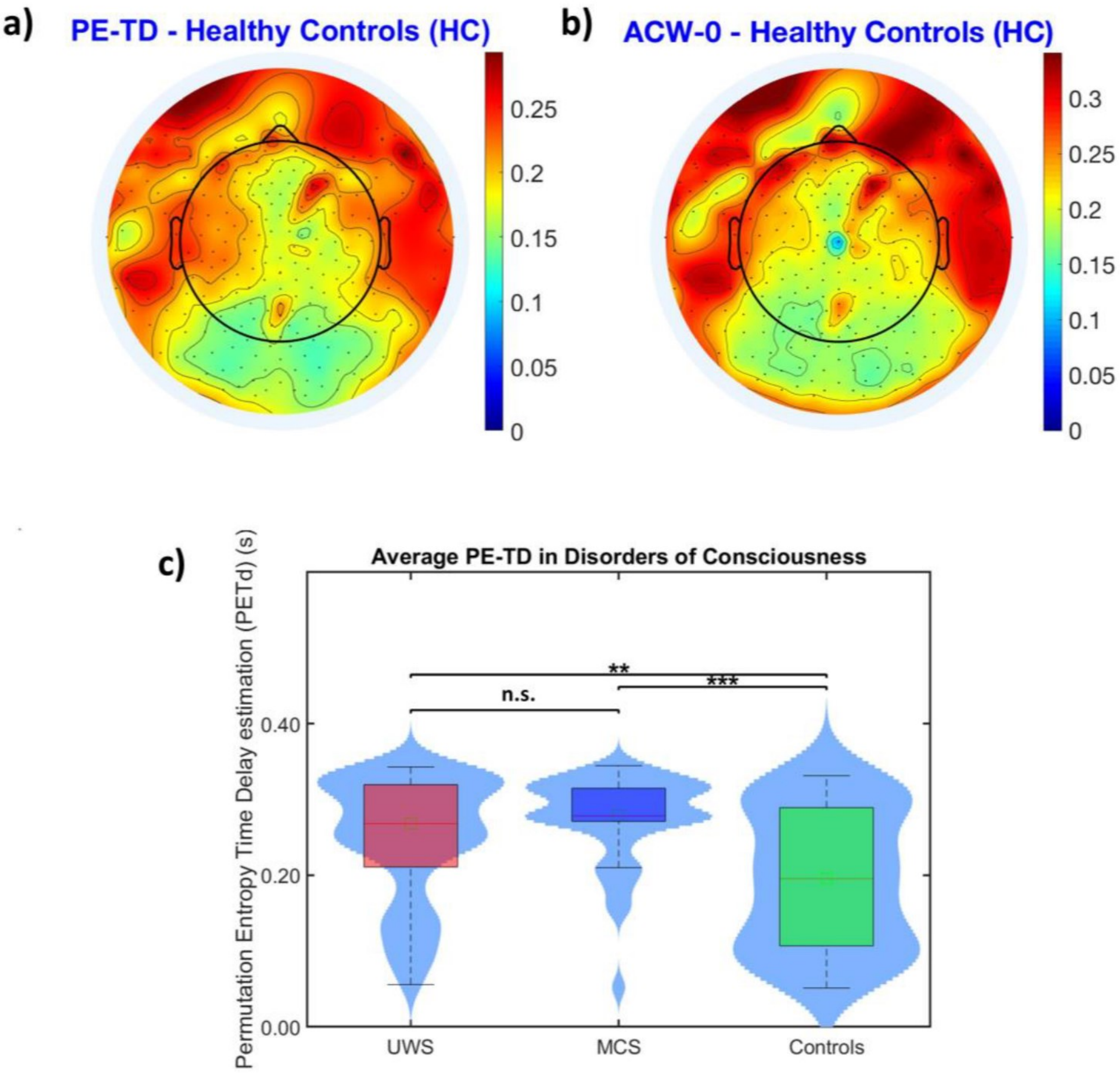


Figure 3.3. The distribution of INTs in healthy populations and their abnormal average prolongation in disorders of consciousness (DoCs), probed with PE-TD. (a) Topopolot depicting the average distribution of INT values (in seconds) probed with PE-TD in a healthy population (N = 44). (b) Topoplot depicting the same average distribution of INT values probed with ACW-0. The overall INT scalp distribution is clearly consistent between the two different measures, as confirmed by a very high channel-wise correlation between the two measures ($R = 0.90$, $p < 0.001$, presented in Figure 4). (c) Violin plots for the subject average length of PE-TD values in DoCs vs. healthy controls (HC). (HC mean = 0.19 s; UWS mean = 0.24 s; MCS mean = 0.27 s; HC vs. UWS: $p < 0.001$; HC vs. MCS: $p < 0.001$; UWS vs. MCS: $p > 0.05$). (** represents $p < 0.01$ and *** represents $p < 0.001$. n.s., when shown, stands for “non-significant” ($p > 0.05$)).

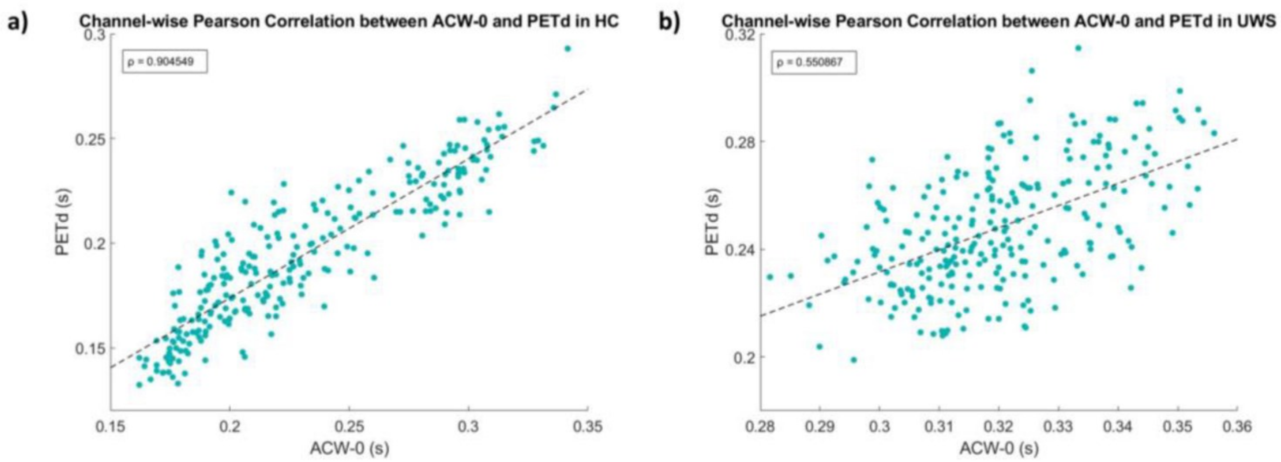


Figure 3.4. State-dependent decreased channel-wise correlation between PE-TD and ACW-0 in loss of consciousness (LOC). (a) Pearson's correlation coefficient in healthy subjects (R = 0.90, $p < 0.001$). (b) Pearson's correlation coefficient in UWS (R = 0.55, $p < 0.001$). The decrease in correlation observed in UWS is confirmed by a bootstrap distribution test ($p < 0.001$) and is validated with a Fisher's z transform test ($p < 0.001$) (see Section 3.2—Methods).

Previous studies (Buccellato et al., 2023; Northoff et al., 2023; Zilio et al., 2021) have shown that loss of consciousness is accompanied by an abnormal prolongation of INTs, as probed with ACW-0. Does this outcome apply to methods that estimate INTs through information theory? Replicating previous results, PE-TD values in both UWS and MCS showed a significantly higher subject-wise average compared to those from healthy controls, but there were no significant differences between UWS and MCS (Figure 3c. HC mean = 0.19 s; UWS mean = 0.24 s; MCS mean = 0.27 s; HC vs. UWS: $p < 0.001$; HC vs. MCS: $p < 0.001$; UWS vs. MCS: $p > 0.05$). To summarize, our findings showed that, through PE-TD, we were able to replicate: (i) the hierarchical distribution of INTs in two unrelated healthy populations; and (ii) the abnormal prolongation of INTs in resting-state EEG recordings in DoC patients previously shown in other studies, with fairly similar data distributions.

Increased Distance between INTs Obtained with PE-TD and ACW-0 during Loss of Consciousness

Loss of consciousness not only entails a different capacity for input processing (Northoff and Zilio, 2022a) but also a significant change in signal properties (Walter and Hinterberger, 2022). Is it possible to take advantage of these differences to qualify the differences between conscious and unconscious subjects? We introduce a characterization of loss of consciousness as an increase in the discrepancy between the spatial organization of INTs probed with PE-TD and that obtained with ACW-0.

To this end, we used the channel-wise linear correlation between average values of PE-TD and ACW-0 as a proxy measure of the spatial similarity between the two measures; then, we tested for statistical differences between the correlation coefficients obtained with HC and UWS. Figure 4 shows that the linear relation between PE-TD and ACW-0 changes drastically from HC (Figure 4a) to UWS (Figure 4b) (RHC = 0.90; $p < 0.001$; RUWS = 0.55; $p < 0.001$). We tested for significance through the bootstrap distribution test described in Section 2.4. The difference in the correlation coefficients was highly significant ($p < 0.001$): the statistical significance was confirmed and validated with Fisher’s z transformation test ($p < 0.001$).

3.4 Discussion

The purpose of this study was to show that the estimation of a system’s time delays through serial computation of permutation entropy (PE) values as a function of its embedding time delay parameter (which we refer to as PE-TD, permutation entropy–time delay estimation) is compatible with the estimation of neural activity’s time scales; additionally, we suggest a parallel utilization of PE-TD, which could offer some important insights into the mechanisms of consciousness as well, coherent with the theoretical framework of TTC.

With this point in mind, we followed two parallel strategies. In the first part of the study, through a series of simulations, we demonstrated that PE-TD works well in estimating the time scale of a simple IAF neuron model and that it is well resistant to nonstationary regimes; furthermore, we showed how the performance of PE-TD in a nonlinear time-delayed model, such as the Mackey–Glass oscillator, is affected by parametrization choice, which could hint at strategies aimed to improve the interpretation of PE-TD in real-world applications.

In the second part, we employed PE-TD on a dataset consisting of resting-state hd-EEG recordings of DoC patients and healthy controls, demonstrating that PE-TD is able to replicate the abnormal prolongation of INTs during clinical loss of consciousness, as previously shown in other studies; additionally, we observed a divergence in the results obtained through PE-TD and ACW-0 when consciousness is lost, which we suggest is due to different signal properties of EEG recordings of people with DoCs.

The estimation of INTs is a fundamental aspect of TTC, which posits an important role for the temporal structure of the brain’s spontaneous activity in shaping consciousness. A crucial assumption for this postulate is that the brain has adapted its features to the external environment’s statistical input structure, an evolutionary force driven by the limited computational resources of the brain and the consequential need to maximize the information extracted from the outside world (Rosenblith, 2013): the dynamics of its intrinsic temporal structure (e.g., INTs) make no exception because inputs/stimuli possess their own temporal scales (e.g., the temporal dimension at which the input structure changes its relevant features), and the brain “aligns” to these timescales for proper and efficient encoding.

Additionally, a peculiar characteristic of TTC is the notion of “common currencies” (Northoff et al., 2020): e.g., the dimensions of consciousness and neural activity share topographical and dynamical intrinsic properties. Hence, the utmost importance of estimating INTs in this theoretical framework encourages methodological advances to ensure the soundness of the scientific approach to the study of consciousness.

In this study, we observed that our first implementation of PE-TD in a neuroscientific context worked surprisingly well in extracting the average time between two consecutive spikes of an IAF neuron directly from its time series; therefore, we suggest that PE-TD is fit to study neural time scales even at a microscale level of investigation (e.g., single neurons).

Other studies have demonstrated that PE does not require a strict assumption of stationarity of the underlying process (Kreuzer et al., 2014): this fact is reflected in the overall better performance of PE as an estimator of financial time series, as recently shown in (Huang et al., 2022). In this study, we present similar evidence as in (Huang et al., 2022) but within the context of a single spiking neuron, which helps to contextualize this informational theoretic approach to a different field of knowledge. Furthermore, we linked the potential cause of nonstationarity in a neural time series (a varying external input structure) to its effects on the behavior of a single spiking neuron.

In cases such as delay systems, non-linear effects are non-negligible (Otto et al., 2019). For this reason, a measure capable of extracting the underlying temporal structure of the system of interest with sufficient accuracy is of utmost importance.

We were interested in unveiling the probable causes of the differences between ACW—which is the standard measure for estimating time delays in neural signals—and PE-TD. Computing the ACW of a signal requires the computation of its autocorrelation function (ACF). ACF (and therefore ACW) is known to behave similarly to ordinal-based time scale quantifiers in linear conditions (Huang et al., 2022) and is actually a better solution when it comes to quantify linear dynamics (Box et al., 2016). However, most real-world systems—including the brain—have non-linear dynamics: as such, it is important to know the basis of divergence between these two measures.

First, we established the minimum degree of non-linearity of a Mackey–Glass oscillator (c coefficient, see Section 3.2—Methods) that resulted in comparable performance between ACW-0 and PE-TD.

Second, we observed different behaviors of ACW-0 and PE-TD when both models' timescales and the feedback strength varied. For ACW-0, the estimation error seems to decrease monotonically as the model's intrinsic timescale becomes longer, achieving stable performance after a threshold (tau = 160). Accordingly, for the feedback strength parameter, we show an unsurprising trend toward higher accuracy with higher feedback values, which however can be appreciated only at shorter timescales. If similar results were to be shown for neural simulated data, it would suggest that neural populations with sufficiently strong reentrant connections and with sufficiently long intrinsic time signatures can be efficiently probed using ACW-0 with an acceptable estimation error.

On the other hand, PE-TD displayed a different but comparable performance. The lower error range suggests higher accuracy of PE-TD for the estimation of timescales in the Mackey–Glass model; furthermore, the accuracy reaches stability at shorter values of tau, suggesting that PE-TD is a better fit when we assume shorter intrinsic timescales in the neural population of interest. With respect to feedback, we did not observe any meaningful difference with the performance of ACW-0. Our results are useful to informing real-world application of these two different time delay quantifiers; however, we do not want to advance the claim that these observations can translate directly to neuroscience. Further simulation studies will need to quantify the minimum values of connection strength and the durations of intrinsic dynamics that are acceptable for a correct time delay estimation.

While our simulations provide a first set of evidence that advances the use of PE-TD in a neuroscientific context, this study also advances the use of PE-TD on real-world neural data by replicating a series of results obtained from hd-EEG datasets that have already been probed with ACW-0 in past studies (Buccellato et al., 2023; Zilio et al., 2021).

We confirm that PE-TD is able to satisfactorily reveal the established INT hierarchical distribution across the scalp (Golesorkhi et al., 2021a), with the high correlation observed at the channel level, between INTs measured by ACW-0 and PE-TD (Figure 4a). To further validate this claim, we confirmed the same results in a second independent dataset. A postero-anterior gradient of intrinsic timescales can be qualitatively appreciated by the two very similar topographical plot (topoplots) shown in Figure 3a,b.

Moreover, we also replicated the same abnormal prolongation of INTs that is typically appreciated in different unconscious states (Buccellato et al., 2023; Zilio et al., 2021), as in the case of disorders of consciousness (DoCs) (Figure 3c). As an additional confirmation of the validity of these results, replication was not restricted to the aforementioned abnormal prolongation of INTs: we also observed a similar range of INT values compared to those obtained through ACW-0. Together, our results encourage the use of PE-TD in the investigation of human INTs as well since it produces outputs comparable to ACW-0.

Altogether, these findings suggest a close, but not complete, overlap between the timescales estimated by PE-TD and ACW-0. This parallelism allows for an indirect link between PE-TD and the spectral characteristics of an EEG signal (e.g., its power spectrum density, PSD). In fact, despite a well-known mathematical relation between a signal’s ACF and its PSD, there is evidence of a clear dissociation between the timescale probed in a signal and its spectral features (Zilio et al., 2021), suggesting that the correspondence between the two is far from trivial: for instance, two signals can show a similar PSD but very different ACW values, and vice versa, two signals with the same timescales might have very different PSDs. In the case of PE-TD, even if there is no direct link between the spectral composition of the brain signals and their estimated timescales, it is plausible to infer a similar degree of dissociation: even if a slower spectrum (e.g., with higher power in the slow frequency range) is expected to produce slower INT values on average, the relation between the two is likely nonlinear due to the contribution of the aperiodic component present in neural signals. Future studies will need to shed light on this conundrum—especially in light of the availability of the novel methodology presented in this study. In the last section of this study, we advanced one step further and took advantage of the inherent differences between ACW and PE-TD as an instrument to gain further insight into the neurophysiological features of consciousness.

The channel-wise correlation between ACW-0 and PE-TD can be thought of as a “closeness” measure: the higher that the correlation is, the more similar that the results obtained and their spatial distribution across the scalp are, while lower correlation values would signal increased distance between the two. With this idea in mind, we asked whether the “closeness” between ACW-0 and PE-TD would show a state-dependent difference when consciousness is severely impaired, as in unresponsive wakefulness syndrome (UWS). We observed a significant drop in the correlation coefficient in UWS compared to the healthy controls (HC) sample, even if the correlation coefficient remained moderate (but nonetheless significant).

How can one interpret this increased distance between ACW-0 and PE-TD when consciousness is lost or impaired? We suggest that the cause must be searched for in the different signal properties related to loss of consciousness. For instance, unconscious states have recently been characterized by a qualitatively distinct nonstationary attractor landscape (Galadí et al., 2021), which constrains the past and future states of a system. Therefore, differences in the behavior of a dynamical system are expected to generate differences in the properties of its time series, for instance, its nonstationarity. PE, as we have demonstrated, is resilient to the signal's nonstationarities; this fact suggests that the increased distance between the time scales obtained with PE-TD and those obtained with another method, such as the ACW, might be due to increased differences in the signal's nonstationary characteristics. We suggest that this characterization of different states of consciousness relates to the nonlinear behavior of a system and its statistical features (e.g., the degree of nonstationarity in its time series). This theory is consistent with many current theories of consciousness: for instance, the degree to which brain activity is differentiated in time is a relevant indicator of consciousness in the latest iterations of IIT (Koch et al., 2016), while the dynamic properties of the broadcasting networks are coherent with increasing nonstationarity during conscious access (Mashour et al., 2020). In the framework of TTC, these findings are also coherent with an expected poorer "dynamic repertoire" (Hudetz et al., 2015) of the spontaneous activity's temporospatial structure characterizing unconscious states (Northoff and Huang, 2017; Northoff and Zilio, 2022a). Indeed, TTC advances the claim that consciousness does not only manifest in the time series data captured from the brain as neural correlates of consciousness (NCCs, (Koch et al., 2016)), but it is also dependent on the preservation of baseline conditions that are necessary—but not sufficient—for the actuation of consciousness, summarized in the notion of neural predisposing factors of consciousness (NPCs) (Northoff and Lamme, 2020; Northoff and Zilio, 2022a). For instance, in this theoretical framework, NPC candidates are represented by the "scale-freeness" of the brain's spontaneous activity (Zhang et al., 2018; Zilio et al., 2021) and the richness of its intrinsic dynamics (Carhart-Harris, 2018; Casali et al., 2013; Tononi, 1998), which are known properties of nonlinear physical systems: a shift (or disruption) in these properties is expected to drive unexpected consequences for their signals' statistical properties (Petelczyc and Czechowski, 2023). Therefore, this disruption of nonlinear properties in the brain's spontaneous activity and its effects on the statistical features of the time series that it generates are tied to potential differences in nonstationarity regimes between conscious and unconscious states, explaining the ACW-PE-TD distance that we observed in UWS. However, this theory requires strong experimental evidence; thus, future studies are warranted to investigate this particular interplay between these different TTC-based mechanisms/dimensions of consciousness.

Limitations

Thus far, we have provided evidence for the use of ordinal quantifiers (PE) to estimate neural time scales. However, a recent study (Soriano and Zunino, 2021) showed that the use of ordinal statistics still has room for improvement, e.g., using weighted permutation entropy (PE) to account for amplitude. In this study—which to our knowledge is the first neuroscientific example of the use of ordinal quantifiers for time-delay estimation—we proceeded with PE because of how better understood it is in comparison with its more recent variants.

PE-TD, in its first implementation, only takes the absolute minimum of the PE vs. time delay graph as its estimated INT. We followed these heuristics of the novelty of this approach in neuroscience and, furthermore, to allow for an approachable comparison with the ACW. However, we do not suggest that the absolute minimum is always the relevant time scale of an EEG signal, as multiple time scales are to be expected, even in the same brain population: this fact is already implied in the way that INTs are extracted through ACW, which has multiple versions (Wolff et al., 2022) that are believed to capture different neural time scales. Pragmatically, the high correlation between PE-TD and ACW-0 in our healthy subjects suggests that, at least for the preliminary use of PE-TD, it is an appropriate choice; however, future studies must include the investigation of other local minima for the relation of different minima to neural/behavioral events.

On the other hand, along with the replication of the abnormally prolonged average INT values in DoCs obtained through ACW (Buccellato et al., 2023; Zilio et al., 2021) we observe a similar lack of significance in the difference between the UWS and MCS diagnostic groups, as already shown in (Buccellato et al., 2023). Because of the current clinical challenge posed by the presence of covert consciousness (Bayne et al., 2016; Owen et al., 2006), we argue that the lack of predictive power of average INT values to distinguish between different states of consciousness, even with PE-TD, is not an intrinsic weakness of this approach but rather a symptom of the discrepancy between behavioral responsiveness and consciousness itself (Hermann et al., 2021). Therefore, we encourage further studies, which are needed to refine the study of INTs and to improve on its potential as a diagnostic/prognostic marker of conscious states.

3.5 Conclusions

Intrinsic neural timescales (INTs) are a remarkable feature of the human brain: they are related to temporal input processing and, in the theoretical framework of TTC, allow for adequate conscious states through their interaction with the environment—namely “temporospatial alignment”. However, INTs are not known a priori and need to be estimated from neurophysiological data. In this paper, we have advanced the use of permutation entropy (PE) to this end, a methodology that is already applied to estimate time delays in different fields of physics. First, we tested the suitability of this methodology for its use on neural data with synthetic time series, demonstrating its resistance to extreme regimes of nonstationarity and providing some heuristics for interpreting output values. Moreover, our empirical investigation motivates the use of PE-TD in hd-EEG data, replicating previous results and yielding high similarity with values obtained with previous standard methodologies (ACW-0). Further, we also observed an increased dissimilarity between INTs probed with PE-TD and with ACW-0 in clinical loss of consciousness: we suggest that this finding is a first step toward a deeper characterization of different states of consciousness. In conclusion, we demonstrated that PE-TD is a valid methodology for the measurement of INTs from resting-state EEG data and we further propose that, because of its characteristic resistance to nonstationarity, it could be even helpful to better discriminate between different state of consciousness.

Chapter 4

The following article is currently under submission for publication.

4. Dynamic repertoire of Intrinsic Neural Timescales becomes poorer as consciousness is lost – evidence from M/EEG resting state recordings

Abstract

The brain's spontaneous activity is highly organized and exhibits complex spatiotemporal dynamics; among these basic features, the brain displays intrinsic durations of its own activity – Intrinsic Neural Timescales (INTs). INTs are hierarchically organized, with shorter timescales in unimodal areas and longer in multimodal areas. While much is known about INTs and especially their topographic properties and their dynamics remain yet to be investigated. Specifically, it is not known whether the unimodal multimodal hierarchical organization undergoes by itself recurrent changes, consistent with the existence of a dynamic repertoire of INT topographic states, and whether the richness of this repertoire is related to consciousness. To this aim, we characterized recurrent dynamic INT states by clustering the dynamic ACW-0 (dACW-0) matrices of both source-reconstructed HCP resting-state MEG data and of a hd-EEG (256 channels) resting-state dataset composed of healthy individuals and people with disorders of consciousness (DoCs). We found that the dynamic transitions between different INT states, which exhibited changing degrees of both hierarchical and non-hierarchical topographies, displayed a nontrivial non-random behavior, with evidence of Markov-based memory effects. Unlike in healthy subjects, this memory property was disrupted in DoC patients. Together, our data show the richness of the dynamic repertoire of INT topographic states in the healthy awake state which, given our DoC data, is key in maintaining the level or state of consciousness. This lends empirical support to the Temporospatial theory of consciousness (TTC), and may also provide a biomarker for clinical differential diagnosis of DoCs.

4.1 Introduction

At a superficial glance, understanding consciousness does not seem to require enormous efforts, given how familiar we are with its subjective aspects. However, its true essence remains elusive: considered one of the biggest unsolved questions in science, it's remarkable that a universally accepted definition of consciousness is still not a reality (Seth, 2018).

The consequences of this scientific conundrum resonate outside of theoretical debates. For instance, one of the most significant challenges in the clinical world is the assessment of residual consciousness in what is known as disorders of consciousness (DoCs) (Giacino et al., 2014), which are clinical states characterized by reduced or total loss of consciousness and are due to acquired severe brain injuries. The taxonomy of DoC is still under debate (Bayne et al., 2016; Golden et al., 2024), but it can be roughly described with two main diagnostic categories: the unresponsive wakefulness syndrome (UWS) (the European Task Force on Disorders of Consciousness et al., 2010) and the minimally conscious state (MCS) (Giacino et al., 2002). Currently, clinicians rely on behavioral evaluations at the bedside to infer levels of consciousness in this population, primarily focusing on the observation of residual non-reflexive behavior as a proxy to consciousness (Schnakers, 2020). Nevertheless, consciousness levels often dissociate from behavioral responsiveness, which further complicates the clinical frame (Schiff, 2015), resulting in a high misdiagnosis rate which ranges around 30-40% (Schnakers et al., 2009; Wang et al., 2020). Henceforth, there is a burgeoning interest in developing a theory-driven objective index of consciousness (Gazzaniga and Mangun, 2014), based on neuroimaging or electrophysiological tools. Among recent proposal, the ones that identify a promising candidate for a diagnostic marker of consciousness in the dynamic features of the brain's activity at rest (Barttfeld et al., 2015) align well with theoretical frameworks that emphasize the role of the brain's spontaneous activity for consciousness (Carhart-Harris, 2018; Fingelkurts et al., 2010; Northoff and Lamme, 2020; Northoff and Zilio, 2022a).

In fact, neural activity is characterized by complex spatiotemporal patterns that are inherently dynamic – i.e. they are not static and vary with time (Hadriche et al., 2013; Li et al., 2022), thus reflecting what has been described as "dynamic repertoire" (Hadriche et al., 2013; Hudetz et al., 2015; McIntosh and Jirsa, 2019). It has been hypothesized that the underlying causes of this dynamic behavior are related to the fact that the brain operates in a critical regime – i.e. at the edge between order and chaos (Tognoli and Kelso, 2014). Within this framework, neural dynamics are modelled as a trajectory drawn while exploring a state space composed of a fixed set of pre-defined macrostates – spatially extended configurations – which are short-lived but preserve a degree of stability over time (Heiney et al., 2021). One can then propose a "dynamic repertoire" for the brain, which describes the set of macrostates available to the brain for exploration (Hadriche et al., 2013; Hudetz et al., 2015).

However, matters are complicated by two methodological constraints: i) we currently don't have access to the real dynamic repertoire of the brain; ii) the chances that the true number of possible brain configurations would make this an intractable problem are very high. Dealing with the high dimensionality of this problem has been addressed through strategies of dimensionality reduction. Notably, the application of dimensionality reduction algorithms, such as the k-means algorithm

(Hartigan and Wong, 1979), for partitioning dynamic functional connectivity (dFC) matrices into clusters, has revealed that resting-state networks (RSNs) (Raichle, 2015) undergo continuous reorganization even at brief timescales and in the absence of overt stimulation, task demands, or most intriguingly, across different states of consciousness (Britz et al., 2010; Cabral et al., 2017a; Cavanna et al., 2018; Di and Biswal, 2015; Park and Friston, 2013; Tagliazucchi et al., 2012). This dynamic view of the brain is not specific to RSNs and has been extended to several other spatiotemporal patterns of the brain's activity, leading to the current notion of "dynamic brain states" (Li et al., 2022): a series of "spatially distributed patterns", which are explored by the brain in a non-trivial manner reflecting its capacity to process information efficiently (Hoel et al., 2016).

Characterizing the dynamic repertoire of basic neural features has to potential to deepen our understanding of the brain's intrinsic dynamics and how they relate to consciousness. Even if k-means clustering is not the only algorithm that has been employed to this aim (we refer the reader to (Cavanna et al., 2018) for an overview on other strategies, such as symbolization procedures, used in dFC studies), this strategy has allowed to draw a link between shifts in how the brain spontaneously rearranges its functional networks and, among others, changes in cognitive performance (Cabral et al., 2017b; Gonzalez-Castillo et al., 2019), drug induced alteration of consciousness levels (Li et al., 2022; Lord et al., 2019) and, most fittingly to the aim of this study, differences in states of consciousness (Cavanna et al., 2018). The latter observation is consistent with theoretical proposals such as the "dynamic core hypothesis" of consciousness (Edelman et al., 2011; Tononi, 1998): the dynamic core is assumed to be a minimally sufficient network for consciousness which coordinates the bidirectional flux of information from other brain areas to itself, and its dynamic reshaping is also assumed to be a basic property of the conscious brain. In turn, a reduction in the richness of this dynamic process is posited to yield a diminished quality of consciousness - which is currently being supported by increasing experimental evidence (Barttfeld et al., 2015; Hudetz et al., 2015; Hutchison et al., 2014; Kafashan et al., 2016; Li et al., 2022; Mashour and Hudetz, 2018).

However, nothing is currently known about the dynamics of a different intrinsic property of the brain: the timescales (or durations) of its own activity – Intrinsic Neural Timescales (INTs) (Golesorkhi et al., 2021b; Wolff et al., 2022). Across cortical and subcortical networks, INTs are distributed in a hierarchical way (Demirtaş et al., 2019; Honey et al., 2012; Murray et al., 2014), often codified as a "core-periphery" organization (Golesorkhi et al., 2021a), with longer timescales in multimodal, higher-order brain areas and lower durations on unimodal, lower-order areas: this suggests a fundamental role of INTs for temporal processing mechanisms such as temporal integration and segregation (Wolff et al., 2022), forming a basic computational principle of the brain that shapes cognition in multiple ways. Furthermore, INTs serve as a crucial facilitator of consciousness in the Temporospatial Theory of Consciousness (TTC) (Northoff and Huang, 2017; Northoff and Zilio, 2022a). TTC posits that INTs enable consciousness by allowing the brain's dynamics to "align" or synchronize to the timescales of its environment; moreover, it also suggests that a rich "repertoire" of timescales allows for better alignment, forming the basis of healthier consciousness levels and a richer phenomenology. However, studies to date have never investigated INTs in a dynamic framework, which leaves open many questions around its dynamic behavior. Growing evidence shows that a disruption of the average INT durations is indeed related to diminished levels of consciousness (Buccellato et al., 2023; Huang et al., 2018; Zilio et al., 2021), but there is, to our knowledge, no literature which reports evidence of a dynamic repertoire of INTs and its association with consciousness.

Does the brain display a dynamic repertoire of INTs? And, if so, is a poorer dynamic INT repertoire related to lower level or state of consciousness, as postulated by TTC? Our investigation followed a dual strategy. Initially, we utilized MEG resting-state recordings from the open access Human Connectome Project dataset (Van Essen et al., 2013) to validate the approach proposed in this study; more specifically, we aimed at determining whether clustering algorithms could reveal spontaneous dynamic reorganization over time in the spatial organization of INTs across the cortex of healthy fully awake subjects. In fact, the use of source-reconstructed MEG data offers the opportunity of enhanced spatial resolution, enabling a comparison of the dynamic INT states' topographic properties with established maps from unrelated studies but indexed in the same coordinate space. This allowed us to explore the dynamic properties of the time series describing the transition between dynamic INT topographies. Secondly, we employed a high-density EEG (256 channels) dataset, which included both healthy conscious subjects and individuals with disorders of consciousness (DoC). In this second step, the objective was assess whether disruptions in these dynamic features – e.g. a diminished dynamic repertoire - were related to loss of consciousness.

4.2 Methods

4.2.1 Data

4.2.1.1 MEG Data Acquisition and Experimental Details

The open access resting-state (rs) magnetoencephalogram (MEG) data from the Human Connectome Project (HCP) repository was used in the first section of this study (Larson-Prior et al., 2013; Van Essen et al., 2013, 2012).
The dataset used in this study consisted of 89 age and sex matched subjects; during each 5 minutes resting-state scan, subjects were instructed to lie, with eyes open, while a fixation cross was presented on a screen. Each subject underwent three consecutive resting-state recordings of the same length. Further details, about the subject population demographics and the acquisition parameters, can be found in (Larson-Prior et al., 2013).

4.2.1.2 MEG Preprocessing

We used the standard preprocessing HCP pipeline data from HCP (specifically, at the rmegpreproc stage) (Larson-Prior et al., 2013). Briefly, channels correlating weakly in their proximities and with a high variance ratio were deemed as noisy and removed; non-neural and artifactual components (eye blinks, muscle or sensor artifacts) were removed, on the basis of a semi-automatic ICA procedure. Differently from the standard HCP pipeline, bad segments that were identified on z-scored amplitude. To avoid artifacts related to signal temporal discontinuity, flatline channels and muscle artifacts were linearly interpolated instead of removed.

4.2.1.3 Source reconstruction

Source reconstruction was obtained following the icamne step of the standard HCP processing pipeline; ICs were already obtained at the icaclass step. At this level, independent component decomposition is repeated iteratively with different initial conditions, selecting as the best decomposition the iteration with the lowest artifact residual and largest number of brain components for the following processing steps. The icamne procedure applies weighted minimum norm estimation (wMNE) to project sensor maps of the brain ICs into a source space, consisting of 8004 vertices individually registered on the surface cortical sheets.

Eventually, the data was spatially interpolated to match the HCP-MMP parcellation atlas (360 parcels) (Glasser et al., 2016), applying the ft_virtualchannel function from the MATLAB toolbox fieldtrip (Oostenveld et al., 2011) which uses singular value decomposition (SVD) to obtain a time series for each parcel.

The template parcels were further subdivided into 12 networks, following the network categorization proposed in (Ito et al., 2020) (Visual1, Visual2, Auditory, Somatomotor, Dorsal Attention, Posterior Multimodal, Ventral Multimodal, Orbito Affective, Language, Cingulo Opercular, FPC, and DMN). To obtain the core-periphery organization, as in the aforementioned study, Visual1, Visual2, Auditory, and Somatomotor regions were assigned as belonging to the periphery, and the rest to the core.

4.2.1.4 EEG data acquisition and experimental details

Eighty-one individuals with DoC (n_{UWS} = 39; n_{MCS} = 42; mean age = 46.65 ± 15.89 years old; sex-ratio = 2.24; etiology: stroke = 43; anoxia = 7; traumatic brain injury = 31) were recorded in resting state—at bedside—for 5 min using a Geodesics system (Ges300, EGI, Eugene, OR, USA) and a 256-channel electrode cap (HydroCel 130, EGI, Eugene, OR, USA) (following 10–20 international systems). Standard systematic procedures, such as the Arousal Facilitation Protocol (Giacino et al., 2004), were followed to ensure high wakefulness and arousal levels in the participants undergoing the recording session. To avoid interference related to medication, examiners did not administer any sedative agents in the 24-h period that preceded the recording session. The clinical assessment was performed on admission, through the Glasgow Coma Scale (GCS) (Teasdale and Jennett, 1974), while the differential diagnosis was carried by trained clinicians by repeatedly applying the JFK Coma Recovery Scale–Revised (CRS-R) (Giacino et al., 2004), selecting the best total score over all assessments. Additionally, a control sample of 44 healthy controls (HC) (age 31.3 ± 16.1 years) underwent a 5-min resting-state hd-EEG recording session, recorded with the same 256-channel system (GES 300, Electrical Geodesics, Inc., USA). Healthy participants were asked to lie on the bed and keep their eyes open to mirror the EEG recording of the DoC sample. EEG data were re-referenced online to Cz and acquired at a sampling rate of 1000 Hz, while the impedance of all electrodes was kept to less than 20 KΩ. Further details about the datasets used in this study can be found in (Zilio et al., 2021).

4.2.1.5 EEG pre-processing

Pre-processing and data analysis (including statistical analysis) were carried out with custom MATLAB software (The MathWorks, 2019b) and the EEGLAB toolbox (Delorme and Makeig, 2004).

An identical pre-processing pipeline was used for all EEG datasets used in this study. First, data were resampled at 250 Hz; then, a band-pass FIR filter (Hamming window) between 0.5 (order = 1650) and 40 Hz (order = 750) was applied to the EEG data at the channel level. Noisy channels were rejected using a standard semi-automatic procedure. Criteria for rejection were: removal of flatline channels (channels inactive for more than 5 s); weak channel correlation (with a threshold at $r = 0.8$); low-frequency drifts; noisy channel activity; and shortly-lived bursts unrelated to neural activity (threshold at $sd = 5$ relative to baseline). This procedure resulted in the removal of 9 channels on average per subject. Next, bad channels were interpolated with a spherical method, and channel activity was re-referenced to the common average reference (CAR).

Artifactual activity, such as that related to muscular noise, eye movements or heart activity were identified by independent component analysis (ICA), using the infomax ICA algorithm; subsequently, the identified ICs were removed from the signal. Data rank was reduced by dropping the rereference channel before the ICA procedure.

4.2.2 Dynamic ACW-0

The auto-correlation window (ACW) is the standard method used to probe INTs (Golesorkhi et al., 2021b; Honey et al., 2012; Wolff et al., 2022); the method is based on the computation of the signal's autocorrelation function (ACF), which is obtained correlating the signal with itself at increasing time lags.

Here, we computed the ACW-0, which is parametrized as the first time lag at which the temporal auto-correlation function (ACF) of the EEG time series reaches its zero value (Golesorkhi et al., 2021a).

As we were interested in the dynamics of INTs, the ACW-0 was computed using a sliding-window approach (Lechner and Northoff, 2023) on all M/EEG datasets (window size = 8 s; step size = 10%), resulting in a time series of 366 time points for each recording.

These sliding window parameters, especially the window size, were chosen according to evidence that shows that dynamic connectivity measures, which are tightly related to INTs (Chaudhuri et al., 2015), show increased reliability when probed with sliding windows of a comparable duration (Fraschini et al., 2016; Sorrentino et al., 2023).

4.2.3 k-means clustering

The k-means algorithm is an established unsupervised learning algorithm which seeks to cluster data in order to partition the input data into a pre-established k number of groups (clusters). After the clustering process a low dimensional representation of the data is obtained, and each n observation will belong to one and only one cluster.

As we were interested in obtaining a discrete set of states dynamic INT states, we used MATLAB's kmeans function to partition dynamic ACW-0 (dACW-0) matrices into the most recurrent topographic INT distributions across the subjects' scalp. First, the subjects' dynamic ACW-0 matrices were concatenated horizontally, to obtain a *channelsXwindows* matrix, which was consequently normalized (min-max feature scaling) before the clustering procedure. Consequently, the k-means++ algorithm (Association for Computing Machinery and Society for Industrial and Applied Mathematics, 2007, pp. 1027–1035) was iteratively run 25 times, with k ranging from 2 to 30. The k-means procedure can vary across iterations, since it starts by randomly assigning k centroids at each iterations; therefore, we ran the clustering procedure multiple times to avoid the interference of random seeds. We applied both squared Euclidian distance and cityblock (L1 distance) as distance metrics. The optimization criterion applied to select the best number of k across all iterations consisted in choosing the knee point of the k vs within-cluster variance graph, which ensured choosing the highest variance explained with the lowest number of k clusters. From this step on, the resulting clusters were treated as a surrogate of topographic INT states.

Once the best number of clusters was selected, each INT sliding window was assigned as belonging to a state based on a competitive back-fitting procedure, similarly to (Murray et al., 2008): first, each window was spatially correlated to all k map states, and then the state was assigned based on the highest spatial correlation value obtained. This yielded, for each subject, a time series of the same temporal resolution of its original dACW-0 time series, representing the temporal succession of states as a function of time.

4.2.4 Core-periphery organization

To probe for the presence of a degree of hierarchical organization in the MEG INT topographic states, parcel-level INT values were spatially correlated with a myelination index map obtained from (Rosen and Halgren, 2021). This map is obtained from HCP diffusion MRI (dMRI) data from over a thousand healthy individuals, and indexes the average density of T1w/T2w at each parcel. To ensure spatial correlation, the myelination map followed the same parcellation scheme (360 parcels) as the source-reconstructed MEG data.

To obtain a summary index of the core-periphery organization, parcels were further subdivided into the 12-networks categorization suggested in (Ito et al., 2020), and INT values averaged over all parcels belonging to the same network.

4.2.5 Permutation Entropy

Randomness (unpredictability) in the INT states time series was probed by means of Permutation Entropy (PE) (Bandt and Pompe, 2002). PE estimates the amount of temporal information in a time series by computing a probability distribution function on the basis of a symbolization procedure described in (Bandt and Pompe, 2002). PE values were computed varying the embedding dimension parameter D (from D = 2 to D = 7) and the embedding delay tau (from tau = 1 to tau = 4). Resulting PE values were normalized to ensure comparability across subjects.

In this study, we used the PE function from the EntropyHub open-source MATLAB toolbox (Flood and Grimm, 2021).

4.2.6 Markov properties

Statistical properties of the INT states time series were investigated by modeling them as Markov Chains (Gagniuc, 2017) and subsequently testing these models for 0-th and 1-st order Markovianity. Testing these hypotheses yields knowledge about the temporal dependences in the states' time series: if the system under exam only holds memory of the previous state when transitioning into the current one, then its time series holds a property known as "Markovianity", and it can be modeled as a 1st order Markov Chain. If this property does not hold – current states do not depend on previous states – then we are observing a 0th order Markov Chain.

First, the empirical transition matrix T was obtained. To statistically test for the 0-th and 1st Markov property, we used a log-likelihood ratio test, which compared the log-likelihood LL_m of the model order being tested and the log-likelihood LL_n at one order higher: for instance, to test for 0th order Markovianity, 0th and 1st order log-likelihoods were compared, 1st and 2nd order to test for 1st order Markovianity.

We assumed that the likelihood ratio test statistics followed a chi squared distribution with degrees of freedom *df*

$$df = (ns^{m} - ns^{m}) \times (ns - 1)$$

where ns is the number of states and m is the Markov order being tested. Consequently, p-values were defined as

$$p = 1 - (-2 \times (LL_{m} - LL_{n})$$

with threshold for significance at $a = 0.05$.

4.2.7 Exponential decay fitting

The memory property of the dynamic INT state transition time series was probed in a series of steps. First, we computing a version of the autocorrelation function which suited better ordinal data: we pursued this aim by computing Cramer's V (Bergsma, 2013) on a copy of the signal at different time lags. The choice of Cramer's V, instead of the more classic ACF, was guided by the fact that the time series is made of ordinal variable, and Pearson's correlation is defined on continuous data.

The decay rate was obtained by fitting an exponential decay of the form

$$D = A \times e^{-dr \times x} + C$$

to the Cramer's V categorical autocorrelation time series (where *A* and *C* define the lower and upper bound of the fitted function, *dr* is the decay rate and *x* is the time lag). Since this function displayed an exponential decay only in its first portion, we performed the fitting only on a truncated version of it (until lag = 30). The fit was performed through the curve_fit function from the scipy Python library.

4.2.8 Statistics

Summary statistics of the repertoire of INT topographic states were indexed at subject level and consisted of the average state coverage (in percentages), which describes the relative amount of time spent in one particular state with respect to the total duration of the recording.

A spatial permutation “spin test” was applied to address the correspondence problem faced when correlating two cortical maps (Alexander-Bloch et al., 2018). To correct family-wise error rate when performing multiple statistical tests, the Holm-Bonferroni method was applied.

To compare PE values at group level, we applied the non-parametric Wilcoxon rank-sum test with significance threshold at 5%. Spatial correlation, in this study, corresponds to computing a linear Pearson’s r.

The null hypothesis of equal means in the decay rate in the DoC sample was tested with the non-parametric Alexander-Govern approximation test. Post-hoc pairwise comparisons were performed with the Wilcoxon rank-sum test.

To check for significance on the group states’ properties, the INT state time series were temporally scrambled iteratively (1000 repetitions each) to produce a test distribution: significance was set at $\mathrm{a} = 0.05$.

4.3.Results

4.3.1 MEG

4.3.1.1 Basic topographic features of dynamic INT state properties

The time series representing the dynamics of the intrinsic timescales displayed by the MEG resting state recordings were subject to the clustering procedure described in the previous section. The number of INT topographic maps that described best the data, according to the criterion described in the methods section, was ten (ns = 10), which was then selected for further analysis. The ten dynamic INT maps are shown in Figure 1.

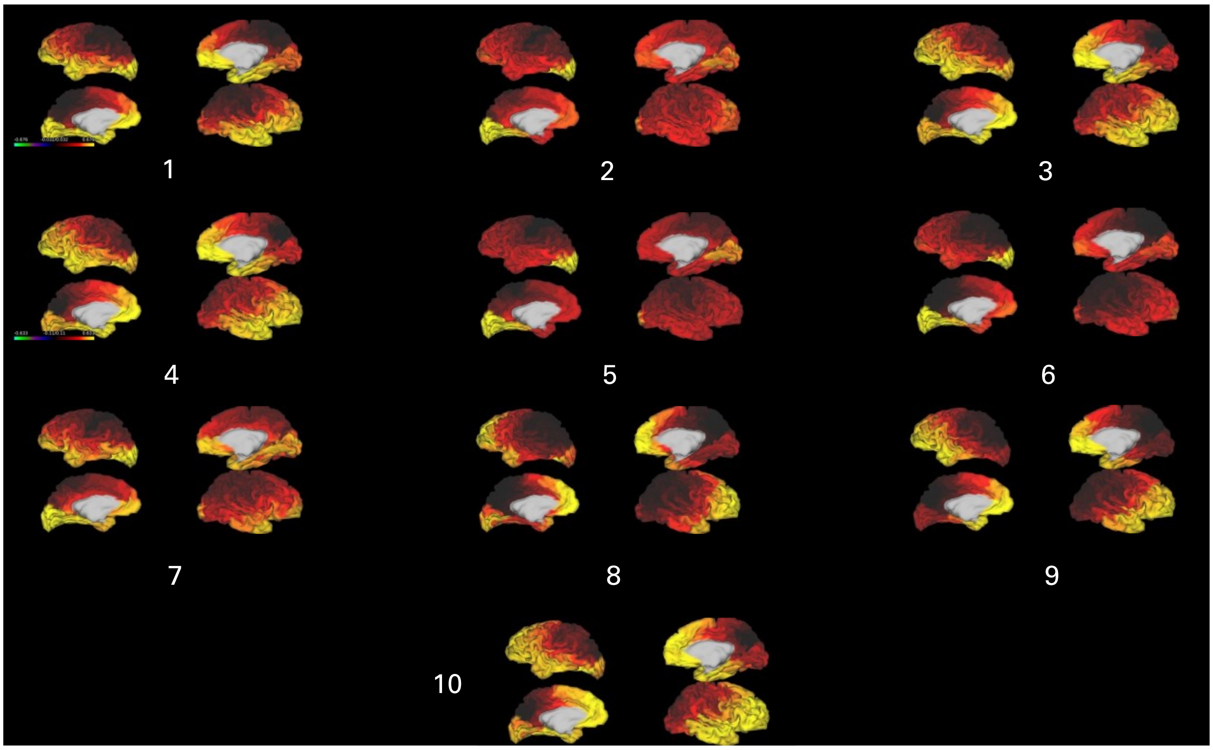


Figure 4.1. MEG topographic plots of the ten states describing the INT dynamic repertoire, obtained with k-means clustering. Dynamic INT states, which we define as the recurrent topographic patterns of INTs found after clustering the dynamic ACW-0 matrices, are here pictured and numbered from one to ten. These states are not ranked according to any arbitrary principle, and therefore the number assigned to each state does not identify them with any particular property: however, we will refer to particular states using the numerology assigned here. Colormap is organized as following: in red, lower values of INT; in yellow, lower values of INTs; black indicates very low INT values. INT values range from 0 to 1, as data is normalized before clustering.

A few qualitative properties of the dynamic INT states found here are already evident from eye inspection. First, while in MEG there seems to be an overall modest level of heterogeneity in the spatial distribution of INTs, we can infer the presence of two main categories: states with a hierarchical distribution of timescales – i.e. following a spatial gradient from shorter to longer durations – and, on the other hand, states with a more homogeneous scalp distribution of INT durations.

Together, we observe a hierarchical organization of INTs, which is in line with recent findings (Chen et al., 2015; Golesorkhi et al., 2021a; Hasson et al., 2008; Honey et al., 2012). However, we extend these findings showing changes in this topography which have, to the best of our knowledge, not been observed before in the literature. Importantly, we stress the fact that in none of the previous studies there has been any dynamic analysis of INT topographic states. Furthermore, we observe that motor areas usually display the lowest INT values in almost all of the 10 states displayed here; this has already been observed in INT topography of humans, primates (Golesorkhi et al., 2021a; Murray et al., 2014) and most recently in mice too (Çatal et al., “Brain-wide intrinsic neural timescales reflect behavioral patterns”, *under review*).

Do these observations carry any topographic significance? To test the claim that only some of the dynamic INT states follow a significant hierarchy, we spatially correlated these states with a myelination index map (T1w/T2w ratio). The degree of myelination displays a gradient that follows a cortical hierarchy (low myelination in higher order areas and viceversa), and is thus used as a proxy to map the hierarchical properties of the cortical features overall. Results can be found in Table 1.

k	**p-value (spin test)**	**Pearson's R**
1	0.21178821178821178	-0.39351949732122415
2	0.2057942057942058	-0.3361540855510716
3	0.5294705294705294	-0.19759643207123512
4	0.030969030969030968	-**0.5394107979228234**
5	0.46253746253746253	-0.224267676962528
6	0.0999000999000999	-0.4341370946792285
7	0.3786213786213786	-0.2819697682852491
8	0.014985014985014986	-**0.5842701975581087**
9	0.002997002997002997	-**0.6440353192025658**
10	0.014985014985014986	-**0.5898422570133**

Table 4.1. **Spatial correlations between the kth INT topographic states and the myelination index in MEG.** In bold, the correlations that resulted significant after testing for significance. p-values are obtained after a permutation "spin-test" and corrected for multiple comparisons.

All maps correlated negatively with the myelination index, which substantiates the use of the k-means algorithm: in fact, the myelination index is expected to be lower, on average, in higher order areas, and INT durations usually get longer in those same areas. This strongly supports the validity of our method. Only four out of the ten maps (maps 4, 8, 9 and 10) survived the spatial permutation test ("spin-test"), which is coherent with a dynamic perspective on INTs undergoing spontaneous reorganization and rearrangements of their topographical distribution as a function of time.

Further, we tested for a core-periphery organization (Golesorkhi et al., 2021a) in all states by dividing the parcels into the 12-networks organization described in the Methods section (Chapter 2.4). A core-periphery ratio (C/P ratio) index was obtained by dividing the average INT duration of the kth map's core regions by the duration of the periphery regions: the higher the C/P ratio, the more pronounced the core-periphery organization is assumed to be. Results are displayed in Table 2.

A linear relation between the degree of cortical hierarchy and the C/P ratio arises when comparing Table 1 and Table 2: the higher the degree of hierarchy in the state under examination, the longer (on average) the intrinsic timescales of that state in the core regions, which further supports the validity of our methodology.

k	**C/P ratio**
1	1.11
2	1.13
3	1.0
4	1.67
5	1.2
6	1.2
7	1.13
8	1.98
9	2.2
10	1.87

Table 4.2. Core-periphery (C/P) ratio index of the kth INT topographic state.

Each state's average coverage (%), describing the "syntax" (Von Wegner et al., 2017) properties of the dynamic INT repertoire, is shown in Supplementary Figure 2.

Concluding this section, we showed that the pairwise within-subject correlation between the average time spent in a state (e.g. 30 windows in state 2, 15 in state 1, etc…) across all three resting-state recordings is, on average, fairly high ($r_{12} = 0.82$; $r_{13} = 0.76$; $r_{23} = 0.78$), suggesting that the relative percentage of time exploring these states – the individual's dynamic repertoire – is relatively stable across recordings.

4.3.1.2 Markov properties and Permutation Entropy

A time series describing transitions from state to state can be modelled as a Markov Chain. To test whether our time series followed Markovian properties to some degree, and hence generated by a non-random process (Ross, 1981), we tested for 0th and 1st order Markovianity. The null hypothesis for 0th order Markovianity was rejected for all subject ($p < 0.001$). The null hypothesis, instead, was accepted when testing for 1st order Markovianity; within the context of the statistical test used here, this result indicates that the data is more likely to be explained by a 1st order Markov chain rather than by a 2nd order Markov chain.

Having assessed the statistical properties of the transitions between INT topographies, we also investigated the amount of temporal information contained in these time series. To this end, we computed Permutation Entropy (PE) on our MEG sample ($D = 3$; $tau = 1$). Average sample values (mean = 0.38 ; std = 0.12) are consistent with a non-random system. Backing up the latter claim, the average PE values of the temporally shuffled INT state time series (mean = 0.91) confirm that, in this sample, lower PE values do not arise as a result of chance.

4.3.2 EEG

4.3.2.1 Basic topographic features of dynamic INT states

Having checked for the validity of using k-means clustering to obtain a set of maps describing the dynamics of INTs in MEG data, we proceeded to testing the hypothesis, as posited by TTC, that the brain’s dynamic INT repertoire is fundamental for consciousness – i.e. it gets poorer when consciousness is lost (Northoff and Huang, 2017; Northoff and Zilio, 2022a; Wolff et al., 2022). To test this hypothesis, we applied the same procedure to a hd-EEG dataset consisting of DoC patients.

Differently to what we have seen in MEG, our EEG sample resulted in $k = 7$ states which described best the variability of the data. Therefore, we proceeded with this number for further analysis; the maps are shown in Figure 2.

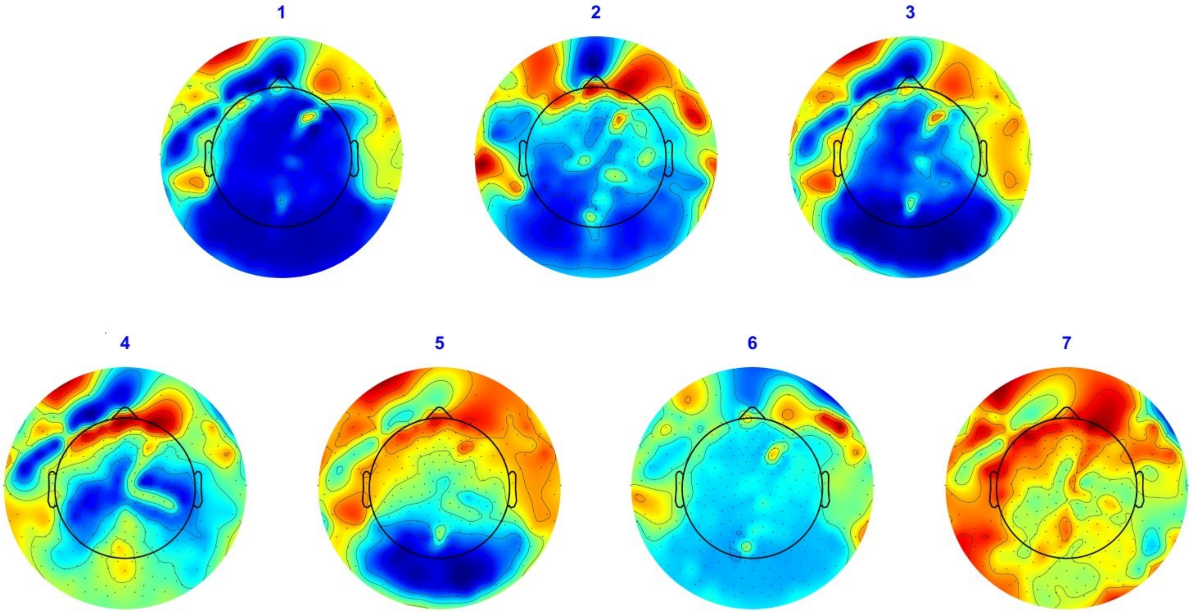


Figure 4.2. EEG topographic plots of the ten states describing the INT dynamic repertoire, obtained with k-means clustering. As with the dynamic INT states found in MEG (see Fig. 1), we do not present these states with any form of ranking. Colormap is organized as following: in red, higher values of INT; in blue, lower values of INTs; yellow tints indicate intermediate values. INT values range from 0 to 1, as data is normalized before clustering.

Regarding the most frequent state explored on average in the different subgroups (Supplementary Figure 4), we can appreciate significant differences especially between the healthy sample (HC) and the most severe diagnoses of loss of consciousness (UWS). Healthy subjects explored on average state 1 and 7 more frequently: both states correspond qualitatively with the same spatial gradient which is appreciable in “static” ACW topographies (Zilio et al., 2021) and in our MEG data too. On the other hand, while the MCS group spent more time on state 2, which resembles a more nuanced version of a hierarchical topography, the UWS group is instead characterized by the overrepresentation of state 6, which doesn’t apparently show any spatial structure whatsoever. The very low INT values on the right hemisphere might be a direct result of brain lesions overrepresented in our UWS sample.

4.3.2.2 Markov properties and Permutation Entropy

Is a poorer INT dynamic repertoire associated with loss of consciousness? To address this question, we first assessed Markov properties of the INT states time series separately for our three EEG groups, similarly to what we have shown in section 3.2.

In all groups, both conscious and unconscious, no subject fulfilled 0^{th} order Markovianity ($p < 0.001$), while all groups could be better described by a 1^{st} order Markov chain ($p < 0.001$). Therefore, even in the most severe cases of loss of consciousness, the brain seems to retain a structure to the transition between states in its INT dynamic repertoire.

In a successive step, we probed the amount of temporal information by computing PE ($D = 3$, $tau = 1$) in all groups and compared them (Figure 4a). A non-parametric statistical test indicated that populations differed significantly ($p < 0.05$): post-hoc comparisons revealed a significant difference between the HC and the UWS group (mean HC = 0.35, std HC = 0.13; mean UWS = 0.46, std UWS = 0.0985; $p < 0.01$) and the HC and the MCS group (mean MCS = 0.44, std MCS = 0.10; $p < 0.01$), but not between the UWS and MCS group ($p > 0.05$). The two DoC groups showed significantly higher PE values when compared to healthy conscious subjects, which is consistent with a more random behavior of the transitions between INT topographies over time.

Temporally shuffling the transition time series resulted in very highly disordered behavior (mean = 0.92), as in the MEG dataset.

4.3.2.3 Memory effects of the dynamic INT transition time series

Lastly, we probed the memory properties of the transitions between INT states.

A system which displays memory may display an autocorrelation function (ACF) that decays exponentially as a function of time lags. If that applies, one can estimate the degree of memory by fitting an exponential curve to the ACF, extracting the decay rate parameter of the resulting fit: a lower decay rate corresponds to a longer temporal reach on the influence of a perturbation on the examined system – i.e. more memory – and viceversa.

First, we computed Cramer’s V as a function of increasing time lags as a surrogate of the ACF; in this particular case, our time series are not composed of continuous variables, and therefore Pearson correlation could not apply. An example of a single subject’s Auto-Cramer’s V graph can be found in Figure 3a. In the next step, we estimated the decay rate after fitting an exponential decay function to the subjects’ Auto-Cramer’s V functions. Figure 3b shows an example of a function fit, overlapped with the Auto-Cramer’s V of the same individual, to show a sample of the quality of the fit.

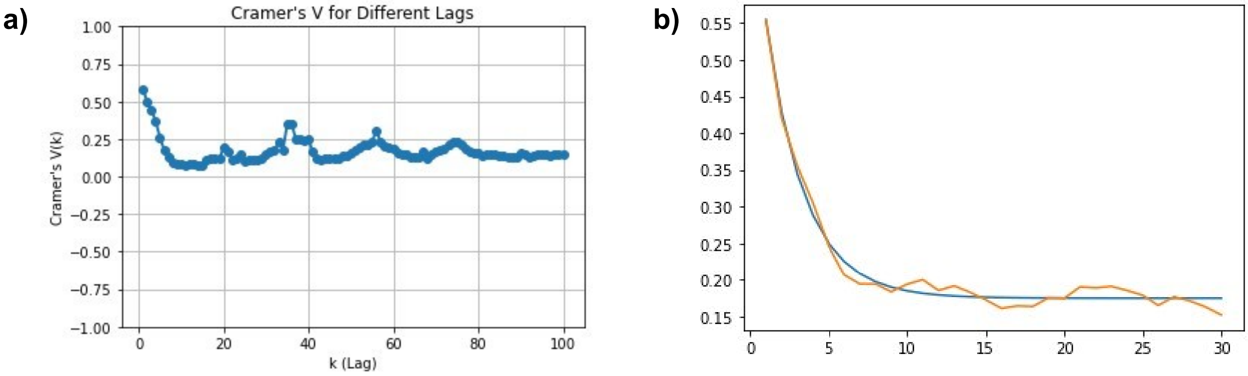


Figure 4.3. The procedure to infer memory effects of the spontaneous dynamic exploration of INT states in EEG. 3a. The Auto-Cramer's V function is obtained, similarly to an autocorrelation function, by computing Cramer's V values between the dynamic INT transition time series and a time-lagged copy of itself as a function of increasing time lags. Here, an invidual's Auto-Cramer's V function is visualized as an example. **3b.** A graph showing the quality of the fit of an individual subject's Auto-Cramer's V function with an exponential decay. In orange, the subject's function is depicted, while in blue the fitted decay is displayed.

We found significant differences in the three groups' decay rates (Figure 4b) (mean HC = 0.38; mean UWS = 0.46; mean MCS = 0.41; $p < 0.05$). The HC sample displayed a lower decay rate estimate on average. Post-hoc comparisons showed significant differences only between the HC and the UWS population ($p < 0.05$), but not between HC and MCS ($p > 0.05$) and UWS vs MCS ($p > 0.05$). However, when grouping UWS and MCS as a single DoC group (without taking into account the clinical diagnostic labels), the difference remained significant (Figure 4c, $p < 0.01$).

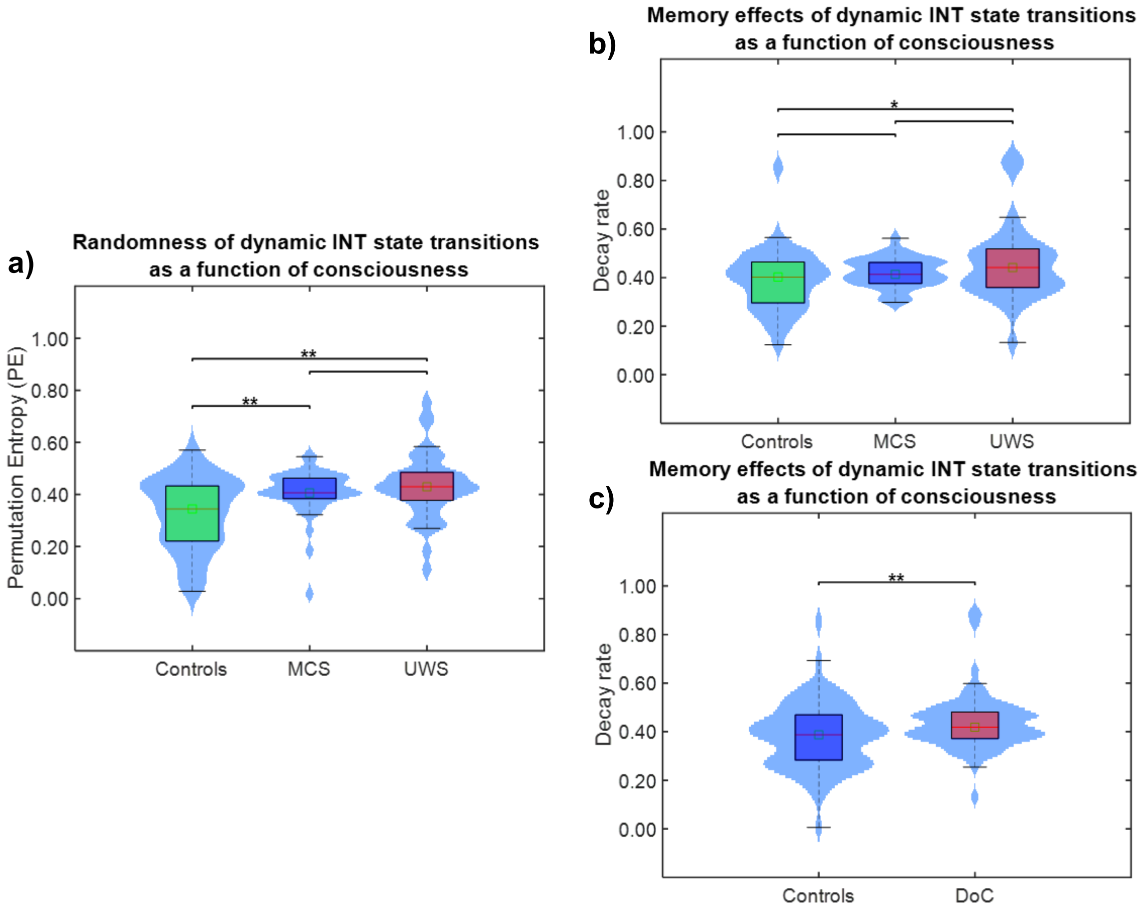


Figure 4.4. Randomness and memory effects of the dynamic INT transition time series as a function of different states of consciousness. 4a. Violin plots depicting the subject-wise average PE value of the dynamic INT transition time series in healthy wakeful consciousness (HC), compared to UWS and MCS. PE value are normalized, ranging from 0 (extreme predictability) to 1 (absolute randomness). In all violin plots, * indicates $p < 0.05$, ** indicates $p < 0.01$ and *** indicates $p < 0.001$. The absence of any sign stands for non-significance ($p > 0.05$). **4b** Violin plots depicting the subject-wise average decay rate of the exponential fit to the dynamic INT transition time series in healthy wakeful consciousness (HC), compared to UWS and MCS. **4c** Violin plot depicting the same data as 4b, but UWS and MCS are grouped together as a single DoC category.

4.4 Discussion

Here, we investigated the brain's spontaneous topography of Intrinsic Neural Timescales (INTs) and its dynamic behavior, modeled as a series of dynamic transitions from one INT state to another, therefore characterizing its dynamic repertoire. To our knowledge, this is the first study that directly tests the hypothesis that the INT's dynamic repertoire plays a significant role for consciousness, as predicted by the Temporospatial Theory of Consciousness (TTC) (Northoff and Zilio, 2022a).

In order to pursue this aim, we first needed to provided support for the existence of dynamic repertoires of intrinsic timescales. Our methodological strategy involved the estimation of INTs, by using the well-known Autocorrelation Window – 0 (ACW-0), with a windowed approach, and the consequent use of clustering algorithms to obtain a set of dynamic INT states. This process unveiled the existence of a non-trivial dynamic behavior in the topographic organization of INTs, with significant memory effects; additionally, we also showed that the detriment of this dynamic behavior is related to loss of consciousness, at least in a clinical population of post-comatose patients.

Further, we observed a striking similarity between the optimal number of INT states we detected in our analysis and the optimal number of microstates found in an unrelated MEG resting-state dataset (Tait and Zhang, 2022), which is in both cases 10. Microstate analysis is a very well established methodology in EEG, which aims at identifying the "global patterns of scalp potential topographies" (Michel and Koenig, 2018) and their dynamics. Computing microstates involves a very similar methodological strategy to the one presented in this study, with the difference that microstates are not computed from the topographic distribution of features computed from the neural signals such as dFC or dACW, but directly from neural signals.

Moreover, we point out that even if the literature about EEG microstates is pretty consistent, with 4 usually being the optimal number of clusters, a hd-EEG study has found an optimal number of 7 microstates (Custo et al., 2017), which is again the same number of dynamic INT maps we have found in our study, increasing the similarities of this method with microstate analysis.

The seemingly contradictory differences we found between MEG and EEG regarding the optimal number of INT states can be traced to a series of factors. A first source of divergence might be due to differences in spatial resolution, as in our source reconstructed MEG data is significantly higher (360 parcels) than our hd-EEG data (256 channels). In fact, it's reasonable that, with a higher number of data points, the number of possible spatial configurations increases accordingly, as argued also in (Tait and Zhang, 2022). Another alternative explanation is our choice for the criterion used to select the optimal number of INT states; in fact, microstates (Custo et al., 2017; Tait and Zhang, 2022) and dFC studies (Allen et al., 2014) which have used a similar criterion have found a similar optimal number of dynamic states, supporting our findings.

Microstates are thought to reflect the instantaneous mode of interaction between different networks (Koenig et al., 2002), and have been found to be able to predict the patterns of connectivity across the cortex (Abreu et al., 2021). As there is a direct relation between connectivity and INTs (Chaudhuri et al., 2015; Ito et al., 2020; Ryan V Raut et al., 2020), it would not be surprising if INTs and microstates also shared a common ground. But the chain of logic delineated here (microstates - connectivity patterns – INT topography) is only speculative, and we warrant for future studies that directly probe the link between these basic features of the brain.

INT's most remarkable feature is its hierarchical organization across the cortex (Golesorkhi et al., 2021a; Honey et al., 2012; Ito et al., 2020), which can be expressed as a core-periphery topography (Golesorkhi et al., 2021a). We show that three of the ten INT dynamic states follow a significant hierarchical organization by spatially correlating each INT state to a myelination index map (Rosen and Halgren, 2021), which was used as a proxy to cortical hierarchy, as in other studies (Burt et al., 2018; Fotiadis et al., 2023; Wu et al., 2020). While not directly predicted before, it is plausible that the scalp distribution of INTs undergoes several different topographies: if the process that produces these maps is truly dynamic and carries functional meaning, then a repetition of different "flavors" of the same hierarchical principle would be of little use. Nevertheless, this leaves the functional significance of the non-hierarchical INT states open to question. We suggest that, in some occurrences, departing from the computational constraints given by a hierarchical organization towards a more homogeneous distribution of INTs could be useful to improve inter-regional synchrony, which we assume would serve a currently unknown adaptive role for the processing of the temporal features of the incoming stimuli.

However, the functional significance of the maps we found in M/EEG can only be a matter of speculation at this point, since we have only restricted our interest to resting-state data. For instance, we suggest that only by observing if and how the relative distribution of state occupancy is affected by different experimental conditions can reveal the functional meaning of occupying a dynamic INT state that does not express a marked hierarchical organization.

Our main finding is that the dynamic transition between the different INT topographies is not generated by a random process, as we provide evidence that its time series carry a significant degree of information. First and foremost, 0^{th} order Markovianity is never appliable to our data, which indicates that the transition matrices obtained through our analysis are not the consequence of a spurious effect of window size. Further, as our dynamic transition time series can be modeled at least by a 1^{st} order Markov process, we show that there is an underlying process which generates the observed transitions between states (Ross, 1981). Substantiating further this observation, we found moderate (PE = 0.38) average Permutation Entropy (PE) values in the dynamic transition time series extracted from the MEG dataset. The choice of using PE was motivated by the fact that this measure takes temporal dependences into account more than other entropy measures (Bandt and Pompe, 2002), which makes it more sensitive to changes related to the temporal structure of a time series. Therefore, in this study PE can be interpreted as a measure of how predictable the dynamic transition time series are: high PE values imply that the transitions between states are more random and thus "chaotic", as if they were generated at random, while lower values indicate higher predictability and therefore a stereotypical underlying process. Instead, moderate entropy values generally imply "meaningfully complex" data (Murphy et al., 2020). The effects of randomness on PE values can be observed by temporally shuffling the state transition time series, with PE approaching its upper limit, as we observe accordingly in our findings. These results suggest that the spontaneous exploration of different INT topographies is underpinned by a nonrandom dynamic process. Moreover, in our EEG dataset, we observed similar

PE values in the healthy sample, which indicates the existence of a typical range of predictability in healthy individuals populations that is not dependent on the modality of the data.

Loss of consciousness is accompanied by increased state transition randomness. Assuming that these time series truly reflect INT dynamics, we posit that this reflects an impaired ability in individuals with reduced consciousness to adapt to changes in the temporal structure of input environments. INTs are thought to index the brain’s capacity to process temporal information of incoming inputs (Golesorkhi et al., 2021b; Himberger et al., 2018). Moreover, as we have already argued, the topography of INTs shapes its computational capacities, thus representing a specific computational mode. Our ancillary analysis further confirms this assumption, since memory effects tend to be less pronounced in the state transitions of the DoC sample: less memory indicates lower temporal dependence between consecutive states, which is indicative of a less complex underlying process. Therefore, it can be argued that, when the ability to switch meaningfully to the proper computational mode (hierarchical vs non-hierarchical), neural representations of the environment are degraded accordingly. However, we stress the fact that the scope of this study is restricted to resting-state data, and that we can only infer about actual input processing mechanisms. Future research, particularly on task-evoked activity data, is warranted for a more precise interpretation of these results in terms of the capacity for input processing, where a more random exploration of INT states entails a lower “predisposition” to proper temporal input processing.

These findings are particularly significant for TTC, as they provide first-hand evidence of one of its predicted mechanism of consciousness: richer dynamic INT repertoires in conscious individuals, with respect to reduced or absent consciousness states. As we have already argued, a diverse array of timescales can substantially enhance the subject’s capacity to capture the intricate temporal nature of its environment (Golesorkhi et al., 2021b), which helps in aligning with the distinct timescales present in the environment (temporospatial alignment (Northoff and Huang, 2017)). Phenomenologically, this would translate in a higher quality of the subjective experience, at least from the temporal perspective: with more fine-grained “sampling” (understood as temporal integration/segregation mechanisms (Himberger et al., 2018; Wolff et al., 2022)) of the incoming inputs, we are not only able to better distinguish the contents of consciousness from one another, but also to embed these single contents into a slower-paced flow of consciousness, integrating them into the coherent and unitary experience that is one of the most immediate phenomenological features of consciousness.

Here, we found no significant difference between the UWS and MCS groups, which could be considered a limitation. Recent discussions challenge the assumption that the UWS-MCS contrast is a minimal contrast for consciousness (Hermann et al., 2021), mainly because common standard clinical methods are reliant on overt behavioral responsiveness may limit statistical power in assessing consciousness, especially when covert consciousness is involved (Kondziella et al., 2020). Therefore, we identify the causes of lack of discriminative power of our analyses in the fact that we have proceeded with the clinical diagnosis obtained through these behavioral assessments and haven’t probed for the presence of covert consciousness with other established neurophysiological indices.

Arguably, a methodological limitation of this study is related to the use of sliding window analysis to track the temporal changes of ACW-0 values (dACW-0), as several concerns have been raised against the use of this technique in functional connectivity studies (Laumann et al., 2016; Lurie et al., 2020). In the case of dFC studies, while there are many factor that might be confounded for genuine FC changes from window to window, the main concern seems to be related to sampling errors. In the case of our dACW-0 analysis, we chose this simple but limited approach because of the novelty of this hypothesis, as a windowed analysis does not require any modeling of the underlying dynamics which remain unknown to this day. Further, we mitigated the sampling error effect by using relatively large sized windows (8 s), as detailed in the Methods section. However, limitations inherent to this method can only be addressed by either applying different methods, such as statistical autoregressive models (Liégeois et al., 2019), or by future studies that take advantage of the temporal structure of an experimental task to test whether the changes in dACW-0 time series match behavioral state changes.

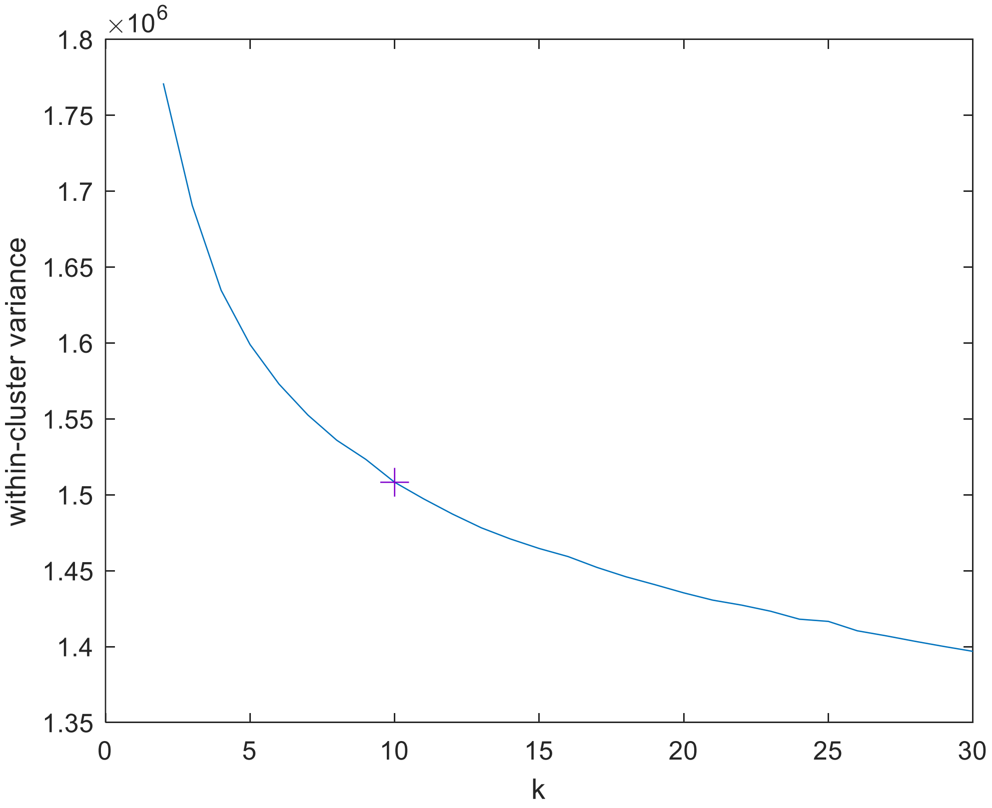
Likewise, we employed a k-means clustering algorithm guided by the same parsimony principle that led to the use of sliding windows. There are two main problems with this unsupervised learning algorithm, which stem from the same constraint: the number of clusters is decided a priori by the experimenter. Because of that, a first issue is that the algorithm will always find clusters for which there is no guarantee of their actual significance, while the second issue is related to the choice of k (the number of clusters), which can be either be guided by visual inspection or by using more strict criteria. For instance, in microstates analysis, it is indicated to use a meta-criterion (a “democratic” voting based on the collective scoring of other criteria) (Michel and Koenig, 2018) to select the optimal number of clusters, but in our study we decided to use a single criterion to improve the interpretability of our results – including the pitfalls of our methodology. We suggest two alternatives that can potentially improve the validity of the present study in future studies. On one hand, one can test whether similar dynamic INT states arise when employing different dimensionality reduction strategies, such as principal component analysis, independent component analysis, or other related algorithms; alternatively, through the use of simulated data, where the ground truth is known, one can test for the sensitivity of the k-means algorithm to truly detect the spatiotemporal configurations that are theoretically explorable by the brain.

Additionally, the clustering procedure was applied to concatenated group data, treating groups as a whole, and not on single subjects; this was done because we were interested in comparing different conditions (conscious vs unconscious), and not in the individual differences in the subjects’ dynamic INT topographies. Nevertheless, as we have also shown that dynamic INT repertoire might represent an individual’s brain fingerprint, we suggest that training a clustering algorithm with single subject data might be of interest, especially to probe the role of these repertoires for efficient input processing.

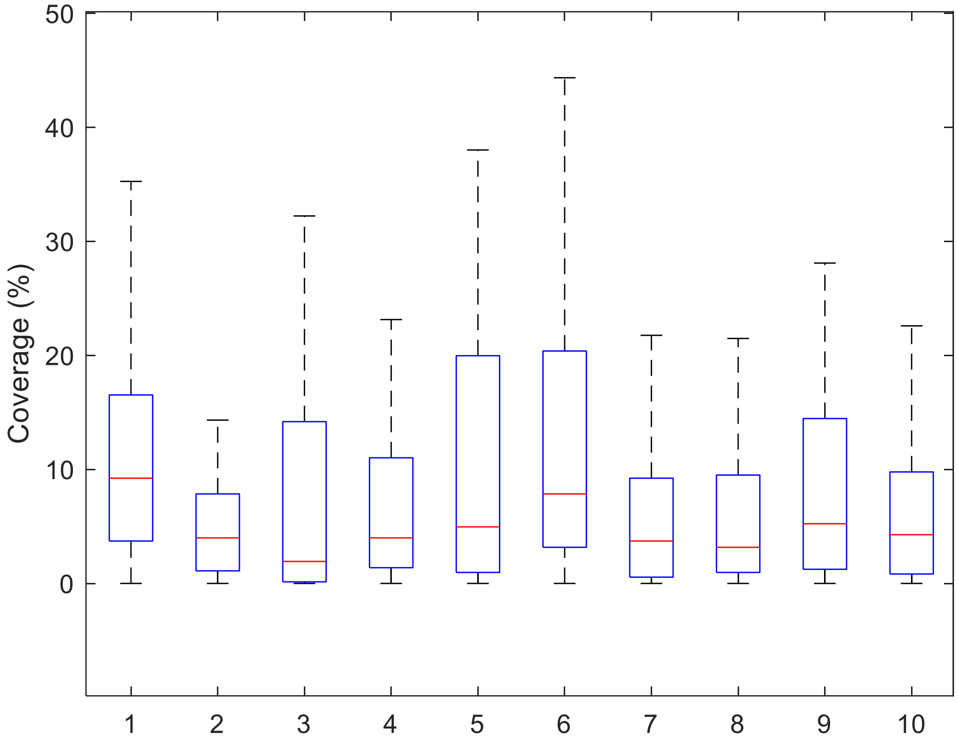
4.5 Conclusions

This study, investigating the brain's dynamic topography of Intrinsic Neural Timescales (INTs) in two different modalities (MEG and EEG), provides evidence of a non-random dynamic behavior of the transition between different dynamic INT states, derived from applying a k-means clustering procedure on a sliding windows ACW-0 analysis. Source reconstructed MEG data confirmed that at least a good percentage of the dynamic INT states are consistent with a core-periphery organization, which is consistent with previous literature, but reveals a new set of non-hierarchical INT topographies. However, the functional significance of non-hierarchical states remains speculative. Applying the same analysis in a hd-EEG dataset consisting of disorders of consciousness (DoC) patients, we found that the dynamic transitions between INT states are nonrandom, with loss of consciousness associated with increased unpredictability, implying a poorer INT dynamic repertoire. These results provide direct evidence for the Temporospatial Theory of Consciousness (TTC), which postulated richer dynamic INT repertoires in conscious states, assuming that these would enhance temporal processing and contribute to a higher quality of subjective experience. We suggest that a future finer-grained characterization of dynamic INT repertoires possesses a very high potential for the diagnostic labeling of DoC patients, because of how cost-effective resting-state recordings are in the clinical setting.

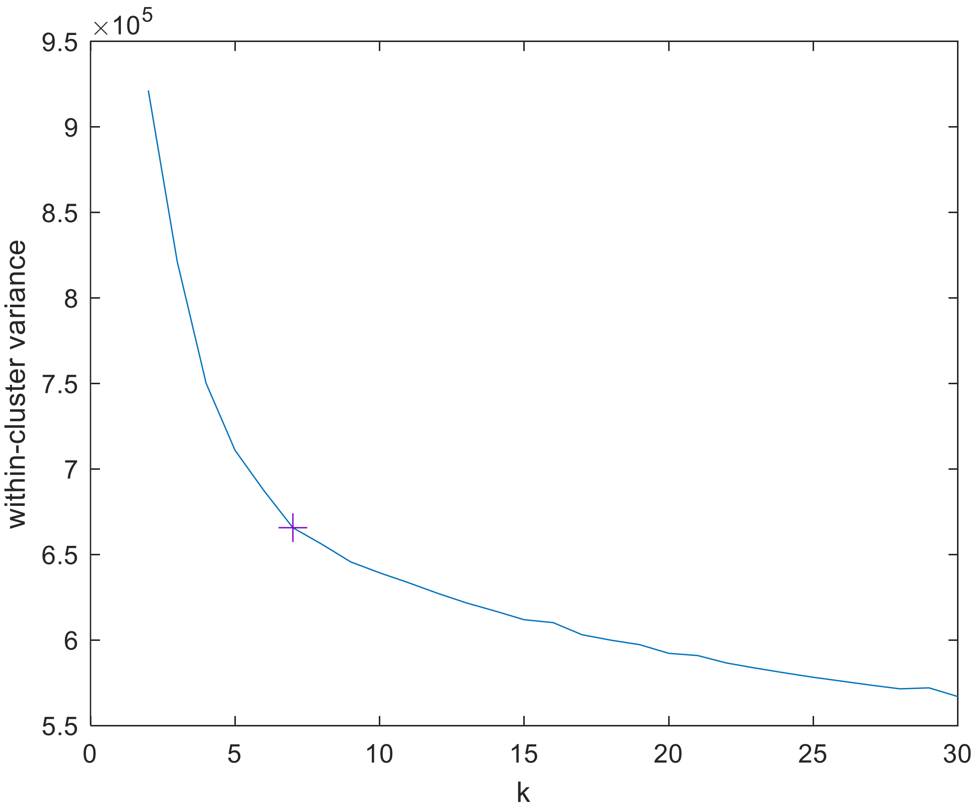
Supplementary Figures



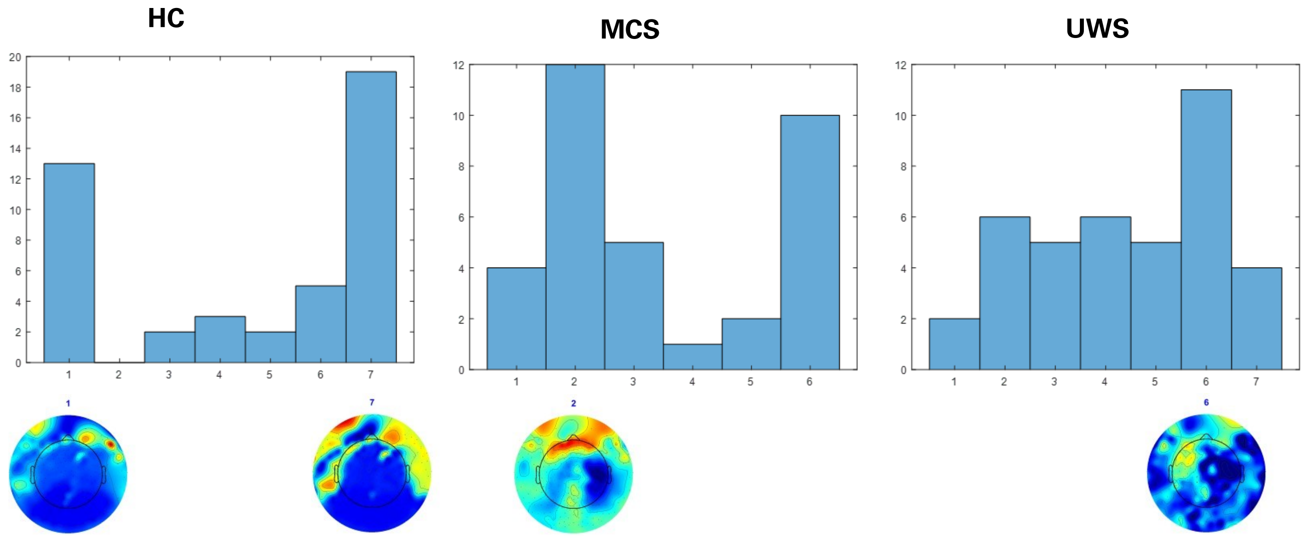
Supplementary Fig. 1 Knee-point criterion to select the optimal number of clusters (MEG data).



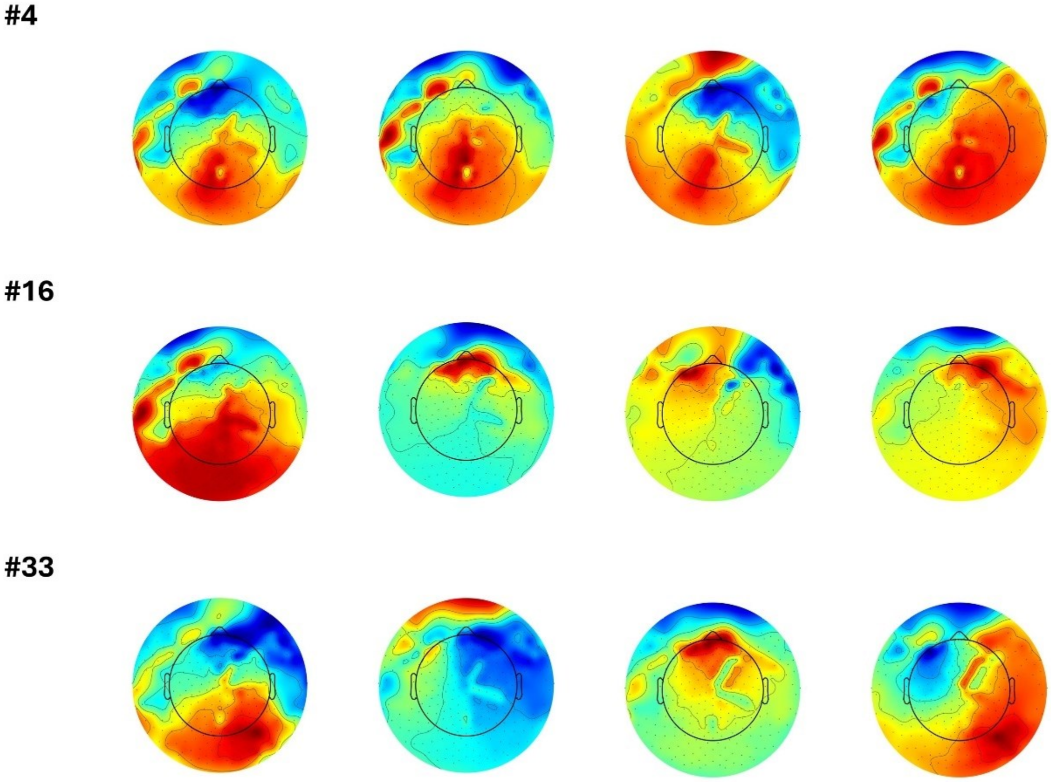
Supplementary Fig. 2. Average state coverage, in percentage, for each of the 10 MEG dynamic INT states, computed across all subjects and recording sessions.



Supplementary Fig. 3. Knee-point criterion to select the optimal number of clusters (EEG data).



Supplementary Figure 4. Average coverage of EEG dynamic INT states in different states of consciousness.



Supplementary Figure 5. Single subject microstate analysis in the healthy sample.

As an additional control to the quality of the topographies obtained in this results, a canonical microstate analysis was performed on a single-subject basis on the EEG dataset. 3 random subjects from our healthy population are shown here for visualization. We used the +microstate MATLAB toolbox (Tait and Zhang, 2022b) on the sensor level, with k = 4 to compare the resulting topographies to the four canonical EEG microstates (A, B, C, D) which are consistently reported in the literature (Michel et al., 2018). The procedure was repeated 20 times to avoid the effects of randomness on the initial choice of the centroids. Details on the standard microstate pipeline can be found in the toolbox’s documentation. The similarities between these individual microstates and the canonical microstates can be compared with those in (Michel et al., 2018). Even if these individual topographies are not as smooth as those obtained in group analysis, the reader can observe a significant overlap between the two, especially with those usually known as microstate A and B (see Fig. 2B of (Michel et al,, 2018). From this overlap, we additionally validate the use of clustering algorithms on INT topographies, as there seems not to be any concern regarding the topography of the “original” EEG time series.

Chapter 5

5. General discussion

The present line of work intends to enhance our understanding of the implications of deteriorated consciousness, especially following severe brain injuries, for the temporal properties of the brain’s spontaneous activity – i.e. Intrinsic Neural Timescales (INTs). To this aim, we probed the general disruption of INTs during instances of loss of consciousness, including their relation to well-characterized neural oscillatory mechanisms and the dynamic exploration of different INT topographies at rest.

We start with concise summaries of each study detailed thus far, before discussing in more detail the broader implications of our work. Additionally, we deduce (where feasible) the putative mechanisms underpinning our observations and suggest future ramifications facilitated by our work.

Summary of Study 1:

Temporal input processing – the ability to track the temporal information of the incoming stimuli – has been related to individual variability in the frequency of synchronous fluctuations in the alpha (7-13 Hz) frequency range – the Alpha Peak Frequency (APF) – and to intrinsic temporal fluctuations of the brain’s spontaneous activity – Intrinsic Neural Timescales (INTs). We used a hd-EEG resting-state dataset, composed of recordings from healthy individuals, anesthetized volunteers and disorder of consciousness (DoC) patients to investigate the relation between these two measures of temporal input processing and its relevance for consciousness. Our investigation revealed that, during the awake fully conscious state, these two different EEG measures of temporal processing are interconnected, while operating on shorter (APF) and longer (ACW) time scales, showing an expected negative correlation at the channel level. This relationship undergoes deviation from this negative correlation in states of unconsciousness, such as anesthesia and UWS/MCS, reflecting abnormal ACW prolongation and a slowing-down of APF at the group level. The consistency of the results across qualitatively different unconsciousness states strongly suggests that the disruption is relevant for consciousness and does not reflect a general malfunctioning of brain functionality. These findings underscore the vital role of the brain's capacity for input processing across various timescales in consciousness, aligning with the principles of temporo-spatial alignment in the Temporo-spatial Theory of Consciousness (TTC).

Summary of Study 2

This study focuses on advancing the current methodologies in the estimation of time delays for neural time series data, introducing an information-theory derived measure, Permutation Entropy – Time Delay estimation (PE-TD), as a robust alternative to autocorrelation window (ACW) for estimating time delays. First, we demonstrated its validity on synthetic neural data, showing that the time delay estimation of simple simulated neural data can be hindered by non-stationary regimes, and that PE-TD shows a more stable performance even at high non-stationarity, therefore resulting more resistant compared to ACW-0. Next, we used a hd-EEG dataset of resting-state recordings of both healthy conscious individuals and a DoC population. Intriguingly, PE-TD successfully measures intrinsic neural timescales (INTs) from hd-EEG human data, showing very high topographic similarity with the topographic maps obtained with ACW-0 . Notably, the spatial correlation between ACW-0 and PE-TD maps decreases in a state-dependent manner during loss of consciousness, suggesting potentially different regimes of non-stationarity and non-linearity in conscious and unconscious states. This study provides evidence for the effectiveness of PE-TD in extracting relevant timescales from neural data and hints at its potential for characterizing conscious states, especially in disorders of consciousness. The proposed PE-TD methodology shows promise for discriminating between different states of consciousness in the clinical setting, to perform diagnostic labeling of DoC patients thanks to the high cost-effectiveness of resting-state EEG recordings.

Summary of Study 3

INTs are known to display a cortical hierarchy, with shorter timescales in the unimodal sensory areas at the bottom of the hierarchical organization and longer durations in the multimodal, higher-order integrative areas, which has been functionally related to efficient temporal processing of the temporal structure of the feature space of the environment and to adequate levels of consciousness. It is currently unknown whether this topographic organization displays a dynamic behavior, consistent with predictions of a dynamic repertoire of INTs This study addresses this gap by analyzing two resting-state datasets: an open-access MEG dataset, source-reconstructed before analysis, and a hd-EEG dataset comprising healthy individuals and patients with disorders of consciousness (DoC). Utilizing a data-driven approach, we delineate the dynamic repertoire of INTs of both datasets, identifying "dynamic INT states" through the employment of a clustering algorithm on the dynamic ACW-0 time series, which identified the recurrent INT topographies observed in the data. In MEG, 10 dynamic INT states optimally described the tested population: three of these states correlated significantly with a myelination map outsourced from a different study, therefore strongly suggesting that these states displayed a cortical hierarchy. The dynamic transition time series, which describes the succession of states of each individual recording, displayed intermediate levels of randomness. On the other hand, the EEG data was best described with 7 topographic states. We found significant differences in the randomness of the dynamic transition time series, with unconscious people exhibiting significantly higher levels of randomness, confirming a more “chaotic” dynamic exploration of these states at rest. Further, we corroborate these findings by showing that, when consciousness is lost, the dynamic INT transitions display less memory, hinting at a less complex dynamic behavior and therefore a poorer dynamic INT repertoire. In summary, we expand previous findings on the spatial organization of time scales in the resting brain by providing evidence for a dynamic repertoire of INTs, and that the richness of this repertoire is related to consciousness quality, as posited by the Temporospatial Theory of Consciousness (TTC).

Novelty of the methods

Facing a relatively new scientific challenge, as that of the neural basis of the temporal properties of consciousness, often requires to rethink and introduce novelties in the methodologies at disposal, guided by the twin principles of efficiency and soundness. This is the case of the methods introduced here. First, PE-TD is designed to overcome the issues of estimating an autocorrelation function of a signal in the presence of nonstationarity and nonlinearity, which greatly affects EEG signals and especially those of DoC individuals. Second, the methods introduced in the last study are not completely novel: as already well detailed in the text, clustering algorithms have been used for decades to summarize topographic data in neuroscience, with the most popular example of microstate analysis. However, to our knowledge, this is the first example of the application of such methods to INT topographies. INTs and its distinct uni-transmodal spatial organization is a consistent finding: nevertheless, its dynamics could not be investigated until the introduction of the methods detailed here, opening for exciting venues in the field – especially to the analysis of the change of the spatial asset of INTs as a function of different task paradigms.

5.1 A deeper insight into the temporal dimension of consciousness: are INTs a promising marker of consciousness?

The overarching theme of the work presented here is the scientific investigation of the temporal dynamics of the brain at rest and how they are able to shape our conscious experience. Specifically, in the three studies collected here, we have tested hypotheses regarding the role of Intrinsic Neural Timescale (INTs) as a necessary condition for consciousness, which has been argued to also capture valuable information useful to develop an objective index of consciousness (Northoff and Zilio, 2022a; Wolff et al., 2022). We have referred to this inquiry as one regarding the “temporal dimension of consciousness”.

To this aim, we have worked under the theoretical constraints of the Temporo-Spatial Theory of Consciousness (TTC) (Northoff and Huang, 2017; Northoff and Zilio, 2022a). This theory of consciousness, similar to other current theories (Carhart-Harris, 2018; Fingelkurts et al., 2010), puts great focus on spontaneous brain activity, thus producing a great array of theoretical predictions which are related to the spatiotemporal patterns of neural activity at rest. To understand the foundations of this theory, it is important to underline that TTC is also firmly rooted in phenomenological principles: similarly, for instance, to IIT - which starts by formulating five essential properties of the subjective experience to infer an equal number of postulates which must be satisfied by a physical substrate of consciousness (Albantakis et al., 2023) – TTC also starts by a fundamental assumption: the spatiotemporal structure of the activity intrinsically generated by the brain and the spatiotemporal structure of conscious experience share a common ground. Therefore, TTC links the brain and the phenomenological features of the subjective experience by proposing that topographic and dynamic properties of the brain serve as an a-priori "common currency", explicitly linking brain and mind. Therefore, the four mechanisms of consciousness proposed by TTC are also explicitly formulated as neuro-phenomenal hypotheses – i.e. they forward specific experimental predictions related to the phenomenology of the individuals being tested – which is in fact granted by the assumption of a "common currency", a phenomenological feature that resurfaces in neural activity and that is directly observable by the experimenter. During the process of testing hypotheses in the framework of TTC, this means that a phenomenological property will always have a neuronal counterpart which is measurable and that can be experimentally manipulated.

Where does our work fit into this theoretical framework, and in which sense does it confirm its predictions, or even contribute to a refinement of its principles?

Related to our investigation on INTs, TTC advances the mechanism of "temporo-spatial alignment". Conscious contents are usually the focus of theoretical predictions, but it is a given fact that contents are perceived in a context. A useful analogy is that we don't have access to, say, the smile of the Mona Lisa *per se*: we are aware of the smile of the Mona Lisa, that is in the homonymous painting of Leonardo Da Vinci, which is currently being preserved in a single room of the Louvre museum in Paris, France, and so forth.

TTC proposes that this context-dependent processing of conscious contents occurs thanks to the "alignment" of the brain's own temporal dynamics to the multi-scaled temporal structure of the environment. Take the example of a visual object, such as a face stimulus: it will display features that change at a faster pace - as its average luminance, among others - and other features that change at slower pace, like the position of the nose relative to the rest of the face. On the neuronal side, INTs represent the feature of the brain's temporal dynamics that is actively "aligned" with the environment to ensure that the content is perceived in its corresponding contextual frame, or "put into context". This position is justified by evidence that shows that INTs play a fundamental role for computational mechanisms related to temporal input processing, such as temporal integration and temporal segregation mechanisms (Golesorkhi et al., 2021a; Himberger et al., 2018). At the phenomenological level, a disruption in temporo-spatial alignment is predicted to have dramatic consequences for the temporal granularity of the subjective experience. This neuro-phenomenal prediction is detailed in (Northoff and Zilio, 2022a), making use of an analogy with a spectator's point of view on a tracking field, where a running race is taking place. In one case, when the subjects' INTs are well aligned with its environment, the experience is well-detailed thanks to correct amounts of temporal input processing, which allows the viewer to distinguish the details of the runners' actions (the start, the incessant leg movements, etc…) thanks to temporal segmentation, while still maintaining track of the general course of the race, thanks to temporal integration mechanisms. On the other hand, if INTs are detached from its environment, the experience will be gradually less detailed and it will be harder to distinguish between consecutive events: stimuli will be less and less temporally precise, and the race will appear as blurry and undifferentiated at once.

These predictions, while being very precise with respect to the changes relative to the phenomenology of the conscious experience, still lack a substantial understanding of the neuronal side. In fact, we argue that our current methodological tools still don’t allow to access fully and objectively the subjective experience of consciousness, and therefore the neuro-phenomenal hypotheses that can be currently tested still require an asymmetric understanding of the two aspects (neuronal and phenomenological), tipping the needle more towards the neuronal side. Nevertheless, knowledge about the underlying generative mechanisms of INTs is still scarce. Improving this body of knowledge has been the rationale guiding the experimental studies produced during these three years of research, and the key to understanding this present work.

5.1.1 The disruption of the relation between APF and INTs during loss of consciousness might reveal novel perspectives on the pathophysiology of disorders of consciousness

In the first study, we have presented evidence of a dynamic relation between INTs an EEG feature with a very high historical significance for neuroscience, which is arguably one of the most well-studied properties of the brain (Mierau et al., 2017): the peak frequency in the alpha frequency range (7-13 Hz) (Haegens et al., 2014). The circuit mechanisms that underlie the modulation of the synchronous firing in the alpha range are not understood fully, but there is a significantly bigger body of evidence compared to INTs. This knowledge and our observation of a disruption between two different EEG features can be exploited to gain a deeper understanding of the link between the pathophysiological mechanism at the basis of DoC and the abnormal prolongation of the duration of INTs, which we have also observed in this study.

Because of the role of INTs in input processing, we will only focus on the mechanisms that drive shifts in the alpha range during the processing of sensory inputs. A very common pathophysiological effect of severe brain damage is a general deafferentation and the weakening of input strength to neurons in the cortex (Fridman et al., 2014; Giacino et al., 2014). Many modeling studies (Cohen, 2014; Herrmann et al., 2016; Lefebvre et al., 2015) indicate that input strength has a high modulatory power on the oscillatory speed in the alpha range: a higher input intensity corresponds to an acceleration of the oscillations in this range. On the other hand, INTs are known to react differently to inputs as a function of consciousness (Klar et al., 2023; Wolman et al., 2023), suggesting a corresponding mechanism; however, to our knowledge, there is no study that explicitly tests the sensitivity of INTs to input strength. This, we argue, might be one of the first causes of the dissonance between INTs and APF as a function of loss of consciousness, which would link this phenomenon to a very simple and common observation about the breaking down of brain functionality in DoCs.

Is it possible to track any physiological mechanisms that explains the spatial divergence between APF and INTs when consciousness is lost? There is evidence that alpha rhythms propagate slowly and locally across the cortex (Hindriks et al., 2014), and are therefore better explained in terms of local propagation rather than in terms of connectivity patterns. In light of this study, it might be unsurprising to detect a dissociative effect between the local speed of alpha rhythms, which might be more related to a local propagation mechanism that is hindered by the severe brain injuries sustained by DoC patients (McClenathan et al., 2013), and the local duration of INTs, which are more related to long-range cortico-cortical connections (Chaudhuri et al., 2015; Ryan V Raut et al., 2020): often, but not always, severe brain injuries result in the severing of cortico-cortical connections (Achard et al., 2012; Snider et al., 2020), and this dissociation might be reflected in the disruption we observed. This interpretation provides a first attempt at a mechanistic account of the relation between two similar mechanisms related to temporal sensory processing mechanisms at different time scales. We warrant for studies that explicitly model the relation between propagation velocity and the interaction between intrinsic time scales and alpha oscillations, which can also be helpful in disentangling between the effects of different etiologies on the temporal dynamics of the spontaneous activity of DoC patients.

5.1.2 Overcoming methodological limitations in time scale estimation with Permutation Entropy (PE): the non-stationary character of EEG time series data

In physics, a nonlinear delay system is a dynamical system in which its subcomponents interact nonlinearly to generate outputs that don't depend solely on its present state, but also the history of past states, culminating in a delayed effect of the system on itself (Otto et al., 2019). To avoid any type of misunderstanding, we advise to not confuse the concepts of time delayed systems and systems with a diverse distribution of time scales, since the presence of time-delayed mechanisms does not necessarily imply the presence of such distributed time scales, as we will explicate in more detail in the next section.

Time-delayed systems are ubiquitous in physics and biology, and the estimation of time delays from time series data is often the subject of methodological debates; recently, the classical use of ACF has been challenged (Siefert, 2007) due to how sensitive its computation is to non-stationary regimes. We define non-stationary regimes as the overt behavior of a system yielding stochastic processes whose statistical features do change consistently with time: e.g. in the context of EEG time series data, the presence of trends in average amplitude values over time. To address and overcome the methodological limitations which affect the estimation of time delays in neurophysiological data, we were inspired by approaches that utilize Permutation Entropy (PE) to yield successful time delay estimation, with increased performance even in chaotic systems such as chaotic oscillators (Zunino et al., 2010), numerical simulations of chaotic processes (Matilla-García and Ruiz Marín, 2009), weather time series data (Soriano and Zunino, 2021) and semiconductor lasers (Soriano et al., 2011). By itself, PE is a popular tool which was already widely used in neuroscience a long time ago before the introduction of PE-TD, usually as a proxy measure of complexity (Zanin et al., 2012) and fruitfully even to detect differences in consciousness states

(Arsiwalla and Verschure, 2018); however, its use for the estimation of time delays in neural data is an absolute first not only for consciousness studies, but for neuroscientific literature in general. Even if we show, with simulated neural activity data, how ACF might suffer from the effects of non-linear and non-stationarity regimes, literature investigating explicitly changes in stationarity in loss of consciousness is not very rich.

The few studies that specifically investigate the non-stationary nature of the EEG signal and how it changes in DoCs generally indicate that stationarity increases along with the loss of consciousness (G-Guzmán et al., 2023; Kreuzer et al., 2014; Panda et al., 2022; Untergehrer et al., 2014). While investigating the stationarity of neural time series during loss of consciousness might appear trivial, as it is often assumed that brain dynamics lose variability as a function of degrading quality of conscious states, the phenomenology of different states of consciousness suggests a different story: while the comparison with healthy wake conscious states might always reveal a decrease in the richness of brain dynamics, it does not necessarily imply a homogeneous degree of change in all unconscious states. Hence, characterizing different regimes of non-stationarity in altered states of consciousness might represent a worthwhile opportunity window into the neuronal mechanisms of consciousness. Further, we argue that a more stationary brain during unconsciousness is consistent with the view of a brain that loses the richness of its dynamics and that tends to have more stability in its energy landscape, which is also confirmed by the results of our third study, which is presented in the next paragraph.

5.1.3 Dynamic repertoires of INTs: insights into a new perspective on temporal input processing

Up to this point, we have analyzed the properties of the brain's temporal dynamics, represented by INTs, in relation to temporal processing, pathophysiology, and reduced states of consciousness. Nevertheless, a comprehensive understanding of INTs and how they contribute to overall brain functioning, as well as their impact on the quality of the subjective experience, requires that we explore the origins of these temporal dynamics.

First of all, time delays in neural populations may originate as a consequence of many factors, some of which are pinpointed in (Campbell, 2007). We will briefly identify a few of these factors, which we think are very important to characterize how they relate to INTs. First, Campbell identifies a first source of time-delayed activity in the propagation velocity of the action potential along the axon: conduction velocity can differ greatly, especially depending on the degree of myelination of the axons that carry the electric signal. We can already draw a first parallel with INTs and their spatial organization: across the cortex, there is a very high spatial correspondence between the spatial gradient of myelination, indexed by the T1w/T2w ratio map obtained from (Gao et al., 2020) and the temporal hierarchy of INTs (Golesorkhi et al., 2021a; Ito et al., 2020; Murray et al., 2014), which we also confirm in our third study. A second source of time-delayed interactions is to be found in the kinetic properties of the synapses composing neural populations. We warrant modeling studies investigating in detail whether synaptic properties can influence INTs and their properties, as evidence is still too scarce to draw any conclusions related to this matter. Time delays also allow for different functions, which are surprisingly close to properties related to INTs. For instance, in systems with sufficient inhibitory feedback, time delays allow for the creation of spontaneous oscillations (Plant, 1981), which might contribute to the length of INT duration in different areas, and synchrony patterns between different populations (Wang and Buzsáki, 1996; Wang and Rinzel, 1992), which might contribute to the modularity of INT durations in the cortical hierarchy.

Given these parallels, we propose that the duration of INTs across the cortex is related to-time delayed interactions between neural populations, since both display similar properties and similar methodologies are used in order to measure them. However, time delays can only influence partially the durations of INTs: time delays, in fact, are indeed related to inhibitory feedback mechanisms, but the oscillatory component of the brain signal, which is not directly controlled by time delayed interactions, is also greatly influenced by neural circuitry. Therefore we recommend extreme caution, avoiding a 1:1 correspondence between time delays and INTs, as these are concepts which do not overlap completely; similarly, we also recommend the use of “time delays” only when explicitly referring to delayed activity in neural activity signals.

As we have just seen, neural architecture (i.e. the structural arrangement of neural populations and their patterns of connection) inevitably shapes brain dynamics: for instance, a dominant role for the connectivity motifs observed within and between neural populations has been established in the last decades of neuroscientific investigation (Braitenberg and Schüz, 1998). Are there fundamental organizational aspects of the brain that result in the hierarchy of time scales we observe in vivo? Unsurprisingly, these questions have been initially tackled through modeling studies (Chaudhuri et al., 2015), as there are many advantages to developing a model when the aim is to uncover a correspondence between the brain’s organizational principles and its functionality. First of all, it allows for a parsimonious description of the data: the experimenter chooses the model which suits best the hypothesis being tested and incorporates only the minimally sufficient information necessary to build that particular model, therefore eliminating all the irrelevant information contained in a typical empirical dataset. Most importantly, it gives the experimenter direct control over the parameters of the model, allowing specific interference with the properties of the brain which are being tested: this is usually not possible in real-world scenarios, even in the strictest experimental conditions, as the complexity of the brain and its countless interactions does not guarantee a clear-cut modulation of the independent variable.

In this study, an empirical directed connectivity matrix obtained from macaque data was used to develop a macroscale dynamic model of the cortex composed of abstract neural populations (threshold-linear recurrent network models) of both excitatory and inhibitory nature. A crucial step in the modelling is the insertion of a gradient of excitatory input strengths which was different for each area, therefore integrating a realistic anatomical gradient in the local circuitry of their brain model. Doing so, the authors were able to demonstrate that a temporal hierarchy naturally emerges only when factoring both the diversity in the areas’ local excitatory connection strengths and the distinct profile of long-range connectivity across areas, and thus it’s the interaction between local and global properties that lies at the core of the topography of neural timescales we observe *in vivo*.

The work of Chaudhuri and colleagues is the first successful description of a putative circuit mechanism for the origin of a hierarchy of time scales in the brain. We argue that our results contribute to updating the current understanding of neural time scales, since here we have provided evidence that hints at the possibility that time scales can spontaneously commit to multiple spatial arrangements cortex; not a single, anatomically constrained hierarchy, but an array of alternative arrangements that are continuously explored even in the absence of explicit environmental needs. However, if one hand the functional significance of a temporal hierarchy has been well-characterized, the purpose of one or more alternative INT topographies remains unknown.

Unfortunately, the downside of a novel finding presents itself as a total lack of similar observations in the literature, which makes it harder to draw any inference that does not appear at best incomplete or anecdotal. However, a recent study on the development of temporal hierarchies in children (Moraczewski et al., 2020) might be of interest to the future directions we might undertake by venturing deeper into the temporal dynamics of the brain. In this study, children were presented with stimuli, at different time durations, which were then temporally scrambled to destroy their temporal structure, in order to assess the different areas' sensitivity to temporal information (similar to the seminal work of Hasson and colleagues (Hasson et al., 2008; Lerner et al., 2011; Stephens et al., 2013)). In parallel, the experimenters probed the children's performance in reading other people's intentions, often labeled as "theory of mind" (Schurz et al., 2014), since the coexistence of multiple processing time scales is thought to be necessary for the integration of information which, in turn, is fundamental to predicting other individuals' future behavior (Koster-Hale and Saxe, 2013). They found that longer time scales are important for the children's socio-cognitive performance, as children displayed less specialization to longer input durations in higher-order areas, and that the degree of this sensitivity to longer input duration was positively correlated with their performance in socio-cognitive skills. Importantly, memory performance was unaffected, suggesting a dissociation of the effects of the absence of the longer timescales in the developing years of life. The authors thus suggest that the presence of longer time scales at the farthest end of the temporal hierarchy are needed to put information in "context", which they deem as necessary for higher-order cognitive abilities such as the ones related to theory of mind. Relating these results with our proposal of a dynamic INT repertoire, the absence of the slower component of the temporal hierarchy may be interpreted as a shallower hierarchy, since the remaining modules of the hierarchy are not affected. A shallower hierarchy, in turn, is more similar to the topographies we find in our study that don't show a significant correlation with the myelination index map obtained from dMRI, that we have informally defined as "homogeneous" states. A shallower hierarchy does not seem to impair consciousness or normal cognition, as developing young people are perfectly capable of navigating in complex environments and are assumed to have consciousness levels comparable to adults, but it appears to selectively target at least social skills. Therefore, this study suggests that exploring a state that does not display a full gradient as the one displayed without resorting to dynamic analysis does not prevent any of those higher-order cognitive skills or consciousness, but it does seem to selectively affect some domains of cognition. The question which will need to be answered in the future is whether these shallower hierarchical INT states grant any sort of computational advantage to the brain and, if so, to identify them.

Why do we assume functional relevance for the topographic states spontaneously explored by the brain? We start our reasoning by reintroducing a pivotal assumption in the study of the brain's spontaneous activity: the brain at rest does not simply sit in an idle state until the next input or "command", but it actively and incessantly reshapes its own activity in a manner that allows it to process proficiently any incoming stimuli (Fox and Raichle, 2007) – in other words, its intrinsic dynamics are not an epiphenomenon but a functional "tool" which might have even granted advantages in our evolutionary history. Following this line of reasoning, if a brain feature shows dynamic behavior at rest, its change in time must subserve one or more functions which give it immediate advantage compared to not changing in time: e.g. transitioning from one metastable functional network to another to allow for goal-dependent adaptation to the environment. Likewise, we assume that, if further confirmed by experimental evidence, these dynamic INT states subserve different functions and are not only a collateral observation of which its origins can be only traced to neural noise. What would these functions be? We advance two tentative proposals, which are neither mutually exclusive nor necessarily coherent with one another, since we only advance them in the spirit of explorative hypotheses and we don't mean to further any dogmatic theoretical principles.

Both alternatives start from the assumption that, in a temporary state with a shallower temporal hierarchy, the processing hierarchy would not completely disappear. Instead, since a hierarchical organization of information processing implies a directional flow of information, we propose that such information flow would temporarily lose its directionality, in favor of other regimes of information transfer from one cortical area to another.

The two alternative proposals differ in the putative functions fulfilled by these metastable non-hierarchical INT topographies. In the first alternative, a non-hierarchical INT topography represents a diminished degree of inter-areal communication in favor of an increase in intra-areal information transfer; information about the temporal features of the inputs would "stagnate" more. We propose that such state could be useful to disconnect temporarily from the environment, in a sort of "anti-temporospatial alignment" mechanism. In turn, such a "dealignment" from the temporal structure of the environment could be used to consolidate an internal simulation of the outside world. In frameworks such as Predictive Coding (PC) (Pezzulo et al., 2021), where prior belief are constantly updated in light of a posteriori evidence of the outside world, this disconnection would allow a slower update of its a priori, without the interference of the constant (and noisy) flow of environmental information. In terms of the phenomenology of consciousness, these states would correspond to a higher likelihood of mind wandering, which can be easily tracked with a recently developed dedicated experimental setting (Hua et al., 2022). On the other hand, information might not "stagnate" but instead homogeneously proceed in the same direction. This proposal draws inspiration from the broadcasting mechanism put forward by the Global Neuronal Workspace Theory of consciousness (Mashour et al., 2020) (GNWT). GNWT proposed that, when information is broadcasted from a dedicated network to virtually all higher-order areas and therefore available for further processing, the information becomes a content which is consciously perceived. However, in a temporary state with shallower temporal hierarchy, we don't assume a central hub which routes information in all directions, but instead we presume that, as information proceeds at a similar pace in all areas, it would be almost automatically available to all the cortex at once. This proposal, however intriguing, is less parsimonious, as it requires the existence of an auxiliary synchronization mechanism which we are currently unable to identify without a deeper understanding of INTs.

Corollary: temporal complexity of state transitions

In this last study, we used permutation entropy (PE) as a measure of the unpredictability of the dynamic INT state transitions. The use of tools borrowed directly from information theory to estimate the temporal properties of the mechanisms guiding the change in time across different topographies is not new in neuroscience. For instance, in microstates studies (Michel et al., 2018) there is a recent and sudden surge in interest for the characterization of their dynamic features. The novelty of quantifying these temporal features with entropy-based measures stands in contrast to classical approaches such as modeling the microstate series as a Markovian Chain. In this statistical model, the probability of transitioning between states depends only on the previous state of the system. This approach fails in considering the non-stationary nature of the transitioning process and its memory effects (Van De Vill et al., 2010), and is therefore not suited for a fine-grained analysis of microstate dynamics. On the other hand, complexity measures have been suggested to overcome these issues. In general, “complexity” encompasses every attempt at characterizing the behavior of a complex system: a physical system with interactions that are not too repetitive nor too random. Laying at the “edge of chaos”, complex systems become unpredictable on short time scales: complexity measures aim at characterizing the magnitude of this unpredictability. However, in this context, complexity has a specific meaning: capturing the unpredictability of the transitioning patterns between maps. For instance, when in front of a low heterogeneity of the transitioning patterns, the analysis will yield low complexity values, from which we can then infer a “rigidity” of the underlying process. That is, for instance, the case of Alzheimer’s disease patients, which have been found to have a lower Lempel-Ziv Complexity (LZC (Ziv and Lempel, 1977)) values in their state transitions (Tait et al., 2020). The LZ algorithm, which is at the basis of the well-known *zip* compression of digital files, aims at reconstructing the “dictionary” from which the observed time series has been “written”: a very complex system will yield a vast number of different patterns, and therefore a more numerous dictionary. Estimating this dictionary means preserving the most informative components of the data, thus allowing for efficient compression. A score is obtained at the completion of the LZ algorithm: i.e. LZC, which quantifies the richness of patterns in the data, without the need for assumptions of stationarity or Markovianity. Other well-known measures have been used to estimate the complexity of microstate transitioning, such as the Lempel-Ziv-Markov chain algorithm (LZMA2) (Artoni et al., 2022), Hurst exponent analysis (VanDe Ville et al., 2010) and entropy rate estimation (von Wegner et al., 2017; von Wegner et al., 2018). This brief overview on these methods are important to understand why we chose to approach the same problem – the characterization of the behavior of state transitions- in this INT study through PE. Permutation Entropy, while still maintaining the same advantages described just now over classical methods, allows to control in a more intuitive way the temporal grain at disposal. This is because the two PE parameters illustrated in the methods section of the study, which control the time step and the number of successive time points considered as part of an individual symbol (a “permutation”; that is, a unique pattern), also allow to calibrate the analysis at the desired time scale. In fact, when investigating INTs, ensuring absolute rigor in the right choice of the time scale of investigation is even more crucial, in order to avoid generating an uncontrollable amount of confounding factors in the analysis. Therefore, PE represents a choice which conforms to both principles of adherence to the aim and parsimony, which we have pursued in the course of this study.

5.1.4 Limitations

The spatiotemporal organization of the brain at rest is fundamentally important to capture the intimate nature of consciousness, and we have most certainly substantiated this claim by providing novel evidence on the role of INTs for consciousness.

There is nevertheless a general limitation that affects all of the studies collected here. We have so far often underlined the role of INTs in temporal processing mechanisms. Consequently, we always assumed that a change in INTs leads to changes in these computational mechanisms, which we considered a fair assumption, given the evidence that supports these claims (Golesorkhi et al., 2021b). However, since we have only tested our hypotheses on resting-state data, these studies only support partially claims of a direct relation between consciousness and input processing. We did not neglect this very important aspect in our choice to proceed in this way but rather, the choice was dictated by a compromise between cost-effectiveness and resources availability. In the first place, the focus of our research is the development of objective indices of consciousness with explicit implications for its uses in clinical settings. To undergo an EEG resting-state recording session at the bedside is cheaper and more feasible for clinicians in the ICU, compared to the very rigid constraints imposed by an experimental setting. Individuals with DoCs are not easily accessible to examination given their comorbidities with often have the priority for a clinician which has to ensure their survival, and it would require extreme efforts to even perform a single experimental examination with neurophysiological methodologies, not even considering the fleeting nature of awareness typical of these conditions (Giacino et al., 2002). Therefore, it’s not surprising that the vast majority of available DoC datasets consist of resting-state recordings. Additionally, TTC is a relatively new theory of consciousness, and therefore it still requires refinement of its most basic theoretical basis, which we have pursued by following its most important assumption: the brain spontaneously constructs its own time and space. Here, we have focused on the temporal dimension of consciousness, but we don’t suggest a supremacy of this dimension over the spatial mechanisms; rather, we argue that these two aspects are very complementary, and one can’t be truly captured without recurring to the other to understand consciousness: this is why, in the third study, we have put forward a new role for the spatial organization of INTs for consciousness. Hence, we can only encourage studies which explicitly investigate these aspects both in relation to task-evoked activity and with its most spatial properties.

5.1.5 Vision: future perspectives

Consciousness research is undergoing rapid evolution, marked by the continual emergence of new theoretical frameworks and perspectives. Consequently, numerous novel neurophysiological indicators of consciousness have been evaluated in clinical contexts over the past decade, as detailed in the introductory chapter of this thesis. The scientific endeavors outlined herein align with this evolving landscape. However, there remain significant unanswered questions that must be addressed before the methods proposed in this work can be effectively integrated into clinical practice. In the following paragraph, we will briefly confront these challenges and offer suggestions aimed at fostering a comprehensive, forward-thinking vision for neuroscientific approaches to INTs research and, in particular, for fully introducing the temporal dimension of consciousness.

INTs have provided useful insights into the brain's perceptual mechanisms; however, it's only in TTC that they are assumed to be a necessary condition for consciousness. Since it's introduction, TTC has then accumulated evidence of a consistent cofluctuation between conscious states and INTs (as detailed in this thesis). As this is not a trivial task, much about the ways in which INTs vary as a function of other quantitative measures of consciousness has been overlooked. Therefore, one of the first objectives to be pursued in the next 5 years should be to unveil this relation between INTs and the currently available proposed indices of consciousness. Pursuing this does not only entail the advancement of the theoretical corpus of TTC, but has very practical implications. In fact, however promising, INTs alone can't provide an easy solution for the diagnosis/prognosis of DoC; however, as recently shown, introducing multiple sources of information into the diagnostic task benefits greatly the performance of machine learning classifiers trained to perform such classification tasks (Engeman et al., 2018). Further, multimodal strategies such as the ones described in (Gallucci et al., 2023) can greatly improve the predictive power of INTs and of neighboring measures of the temporal dimension of consciousness. Clearly, overcoming the issue of the circularity of diagnostic labeling is necessary to "unlock" the possibility of true prediction for quantitative indices of consciousness.

A second challenge that needs to be faced is the computational speed of the current methods and its implications for online use. The family of ACW metrics, for instance, does not suffer particularly from this problem: however, as shown in the second study, it suffers greatly from the non-stationarities and from the non-linear nature of the EEG signal. This is an issue, especially if one wants to bring in these methods into a brain-computer interface (BCI) paradigm for DoC patients. Setting up an EEG in the ICU is especially challenging, as these bedridden patients are often connected to extensive medical equipment, which limits access to the scalp and hinders the EEG electrodes placement, increasing the chance of noise in the recorded signals. This is exactly the reason why developing a metric such as PE-TD is fundamentally important for the introduction of INTs into these experimental settings. However, the current challenge of PE-TD is that it does not easily translate into this practice, as the iterative computation of permutation entropy requires long periods of time, not compatible with BCI online use. I suggest how to overcome this issue in two ways: either PE-TD is computed on a few channels of interest, or to improve the computational efficiency at the basis of PE calculation.

5.2 Conclusions

Consciousness flows in the same direction of the arrow of time, from conscious content to conscious content, with seamless continuity. Despite the fundamental reality of this statement, the temporal properties of consciousness are often overlooked. We followed a line of work which, throughout the entirety of this work is referred to as the investigation of the "temporal dimension of consciousness". Specifically, we tested whether Intrinsic Neural Timescales (INTs) – the temporal duration of neural activity at rest – play a significant role in the emergence of consciousness, indicating them as a promising candidate for the development of an objective index of consciousness with the underlying aim of improving the differential diagnosis of disorders of consciousness (DoCs). Previous findings have illustrated the relevance of the temporal hierarchy of consciousness for efficient temporal input processing and for consciousness. We have extended these findings by showing that: i) the dissociation between INTs and the oscillatory speed in the alpha frequency range (7-13 Hz) is relevant for consciousness and might underlie an important pathophysiological mechanism; ii) current methodologies used to infer the duration of INTs can be improved, in spite of the nonstationary character of neural signals, with a novel information-theoretical measure which we named "Permutation Entropy Time Delay estimation (PE-TD); iii) INTs display a dynamic repertoire of topographies across the scalp, which is explored in a more random manner as consciousness is lost. The studies collected so far give ground to predictions posited by the Temporospatial Theory of Consciousness (TTC), and have the potential to refine its theoretical principles. Taken together, we provide evidence for the relation between the temporal dynamics of spontaneous brain activity, represented by INTs, and consciousness, demonstrating the current potential of the investigation of the temporal dimension of consciousness.

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