



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



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### 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 anaesthesia, 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-know 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.

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## Glossary

INTs: Intrinsic Neural Timescales. At rest, the brain shows a spatial pattern of different temporal durations during which activity remains correlated with itself. This has been linked to temporal input processing (temporal integration/segregation) and with self-organizing properties of complex dynamical systems such as the brain.

ACW: Auto-Correlation Window. One of available methods to measure the length (in seconds) of INTs. It is computed as the time-lag at which the autocorrelation function of the EEG signal decays to its 0% value.

APF: Alpha Peak Frequency. One of the most known features of the EEG signal, it describes the peak frequency in the alpha (7–13 Hz) frequency band. Distinguished from IAF (Individual Alpha Frequency), which is usually computed on the power spectrum from the whole duration of an EEG recording, APF takes into account the fluctuating behaviour of alpha frequency oscillations at the milliseconds scale.

## 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, 2021a; 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 anaesthesia, 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; Hülzdünker 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 behaviour at very short timescales, in the range of milliseconds (Cohen, 2014): being a state-dependant 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; 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 anaesthetic 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 anaesthesia, sevoflurane anaesthesia) 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. Materials and methods

### 2.1. Participants

#### 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  $32.90 \pm 9.48$  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 remifentanyl (1  $\mu$ g/kg) and neuromuscular relaxant rocuronium (0.6 mg/kg) were given for endotracheal intubation. After having confirmed the anaesthetic 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 $\Omega$ . 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 =  $41.4 \pm 13.10$  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, remifentanyl (1  $\mu$ g/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 anaesthetic agents, the electrocardiogram, non-invasive blood pressure and pulse oximetry were monitored for the whole duration of the experiment period.

More clinical information about the anaesthetized subjects can be found in (Zilio et al., 2021) (see Table 2).

#### 2.1.2. Disorders of consciousness dataset

Eighty-one participants with DOC (39 UWS and 42 MCS; mean age =  $46.65 \pm 15.89$  years; sex-ratio = 2.24; aetiology: 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 earmuffs (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 performed by trained clinicians by repeated behavioural 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 behavioural 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  $37.15 \pm 11.29$  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 $\Omega$ .

Additional information about both datasets is summarized in Table 1 and Table 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.

### 2.3. 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 anaesthesia 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 threshold 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-

**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	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 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).

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

moving those components identified by independent component analysis (ICA).

#### 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., 2021b; 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).

#### 2.5. Instantaneous alpha peak frequency (APF)

As our hypothesis centred 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).

#### 2.6. 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 between 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 reshuffled 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 *i*th 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%.

#### 2.7. 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>.

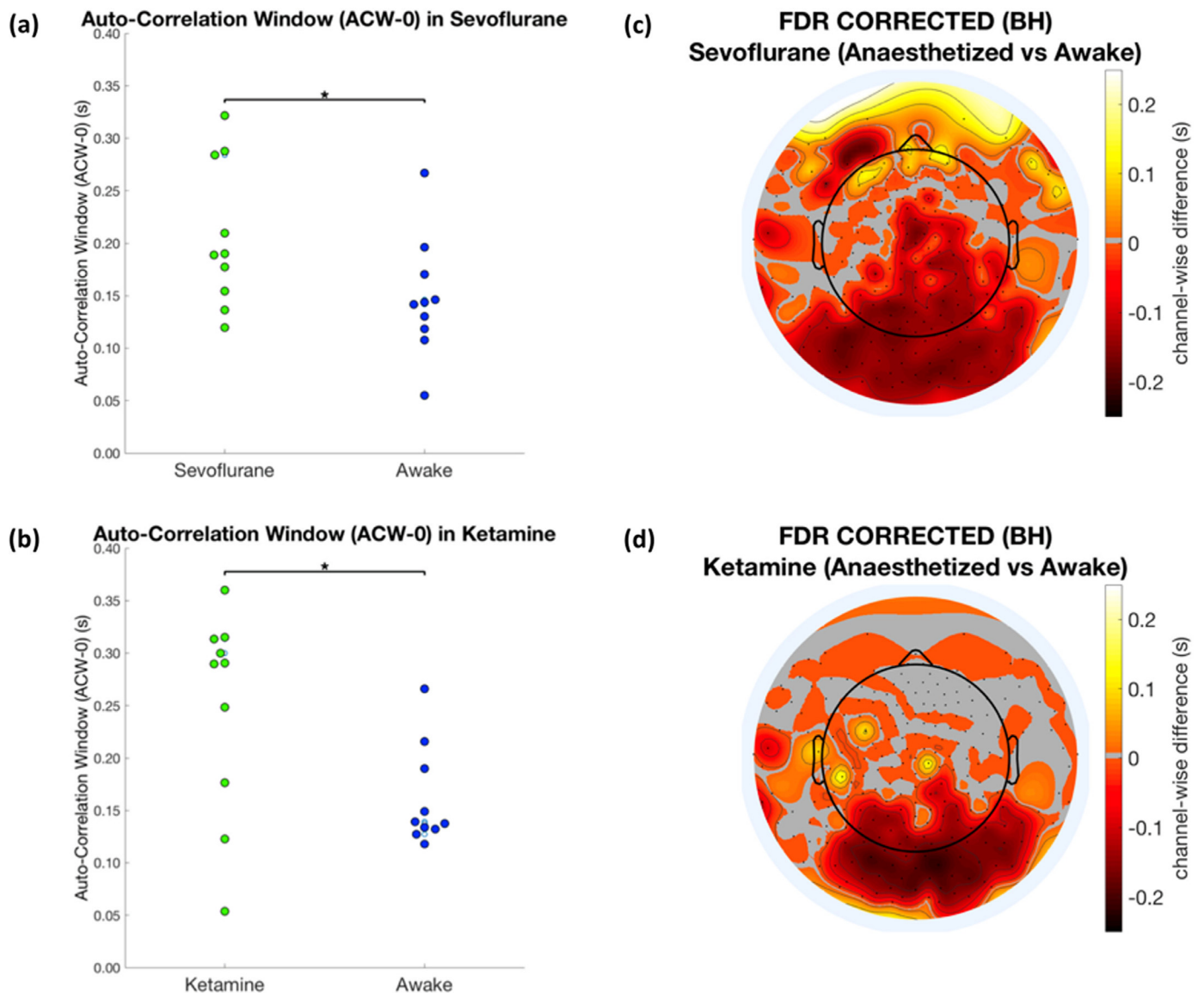
### 3. Results

#### 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 anaesthesia. A previous study showed longer ACW-50 in anaesthesia (and other dis-





**Fig. 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 topoplots.

orders 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 anaesthetic 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.

### 3.3. Decreased alpha peak frequency in anaesthetic states

We next investigated alpha peak frequency (APF), that is frequency sliding, in both awake and anaesthetic 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.

### 3.4. Relationship of autocorrelation window and alpha peak frequency in awake and anaesthetic 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

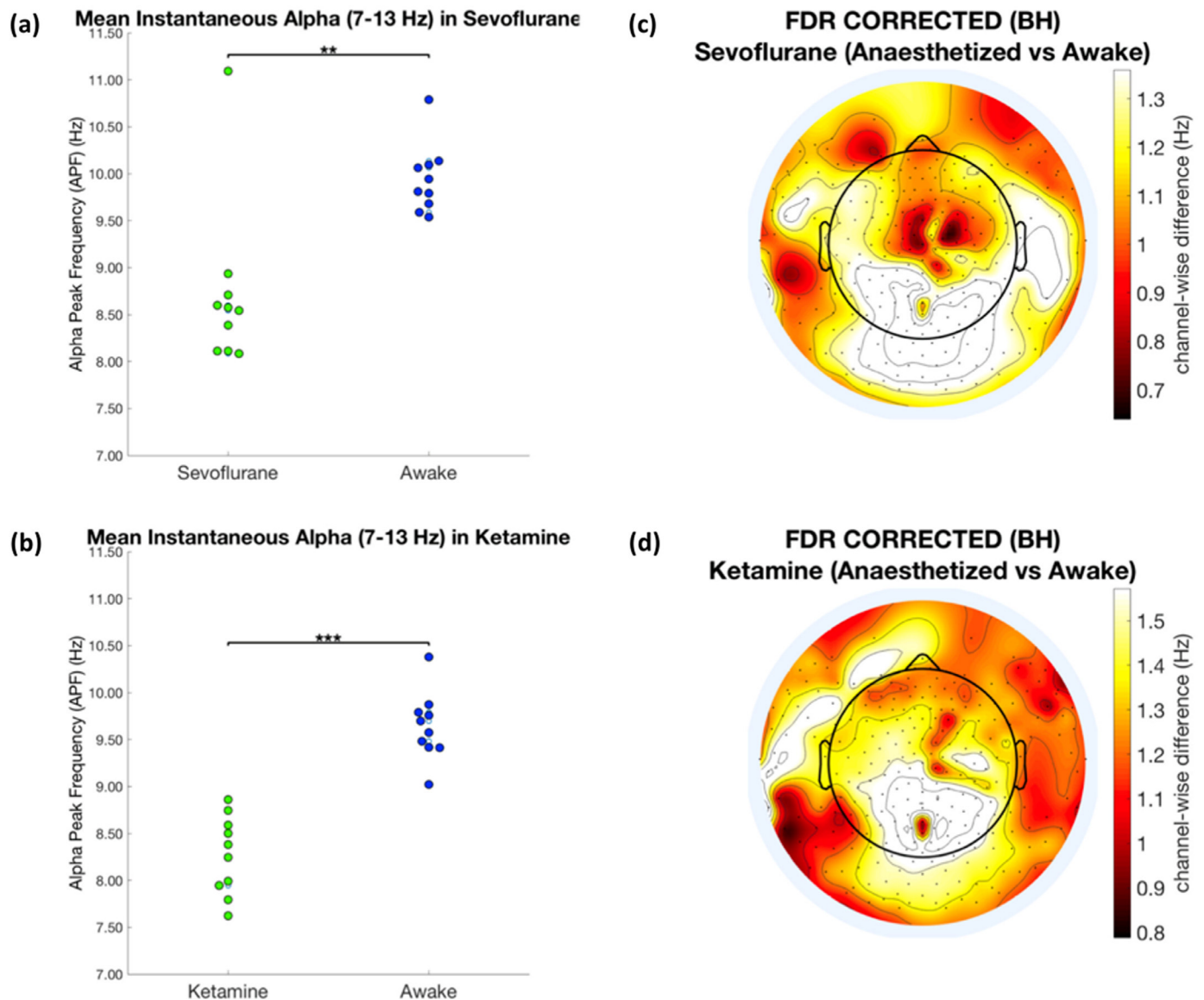


Fig. 2. Instantaneous frequency in the alpha frequency range (7–13 Hz) in ketamine and sevoflurane.

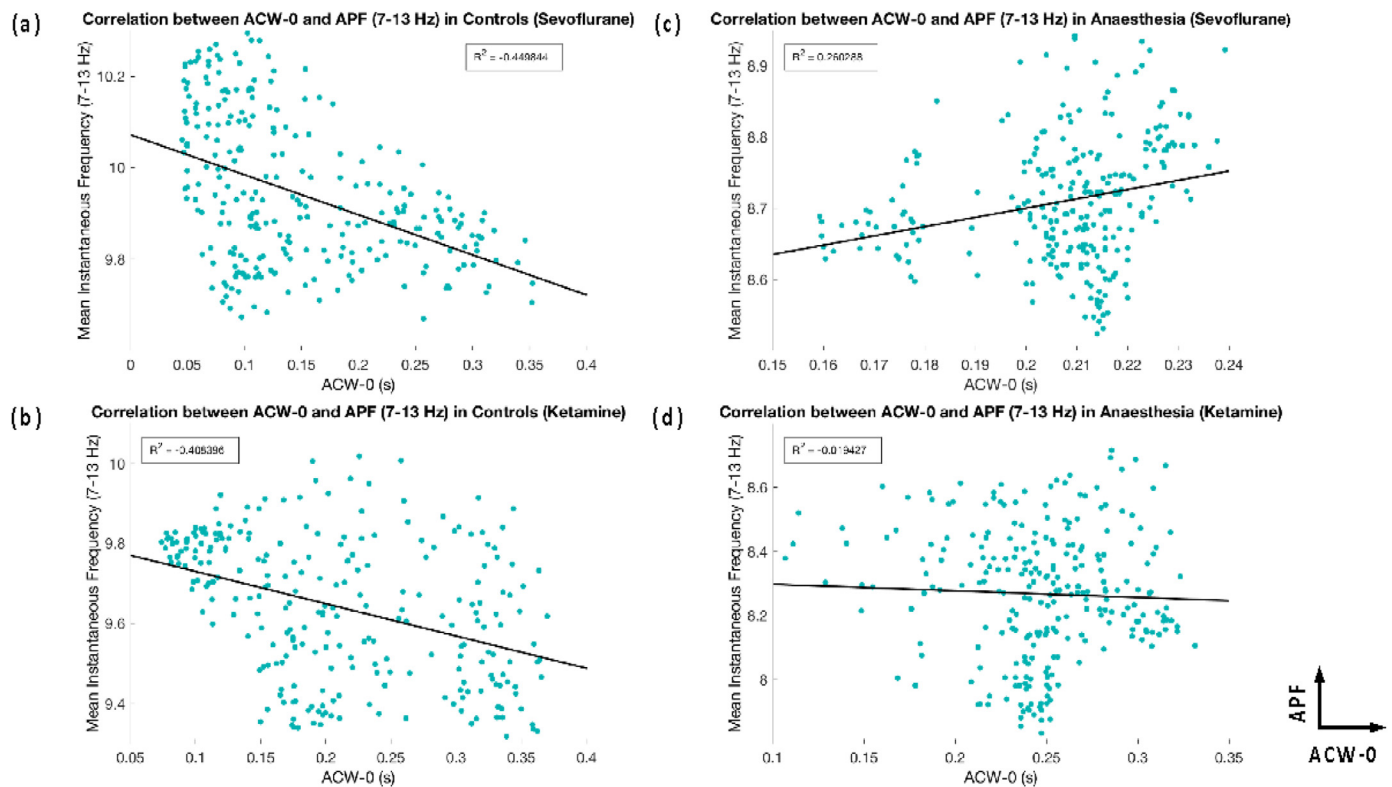
(a-b) Swarm charts for the subject-wise average speed of APF in sevoflurane and ketamine, compared to values of the same sample during wakefulness. APF is measured in Hz. In all swarm charts presented in this study, \* represent  $p < 0.05$ , \*\* represents  $p < 0.01$  and \*\*\* represents  $p < 0.001$ . (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.

(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 Hz, 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 anaesthetic 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.

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 = -



**Fig. 3.** Relationship of ACW-0 and mean instantaneous alpha frequency in awake and anaesthetic 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).

0.02,  $p > 0.05$ ). Finally, a permutation test was carried out to make sure the difference in the correlation coefficients between awake and anaesthetic 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.

### 3.5. 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 anaesthesia, 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

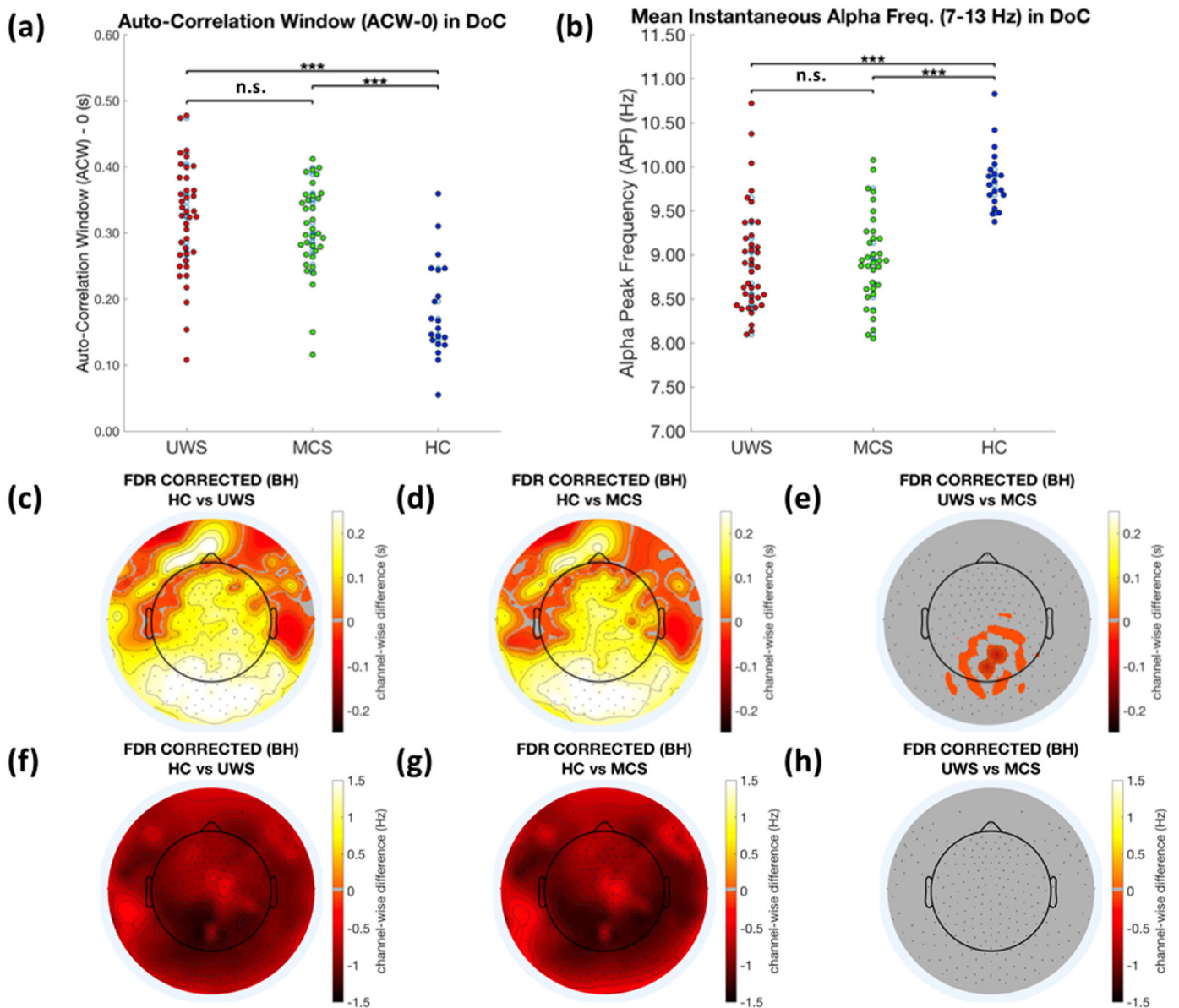
healthy controls (Healthy Controls - HC mean = 0.18394s; UWS mean = 0.32004 s; MCS mean = 0.30513 s; HC vs UWS:  $p < 0.001$ ; HC vs MCS:  $p < 0.001$ ), validating and extending previous results (Zilio et al., 2021). No significant differences in ACW-0 were observed when comparing UWS and MCS subjects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

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 anaesthesia dataset. Replicating our results in the awake subjects of the anaesthesia 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 anaesthetic 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 ( $p > 0.05$ ).

Together, these findings show that ACW-0 and APF negatively correlate in the healthy subjects, which confirms the findings related to





**Fig. 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.

conscious subjects shown in Section 3.4. 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 anaesthetic induction (Section 3.4).

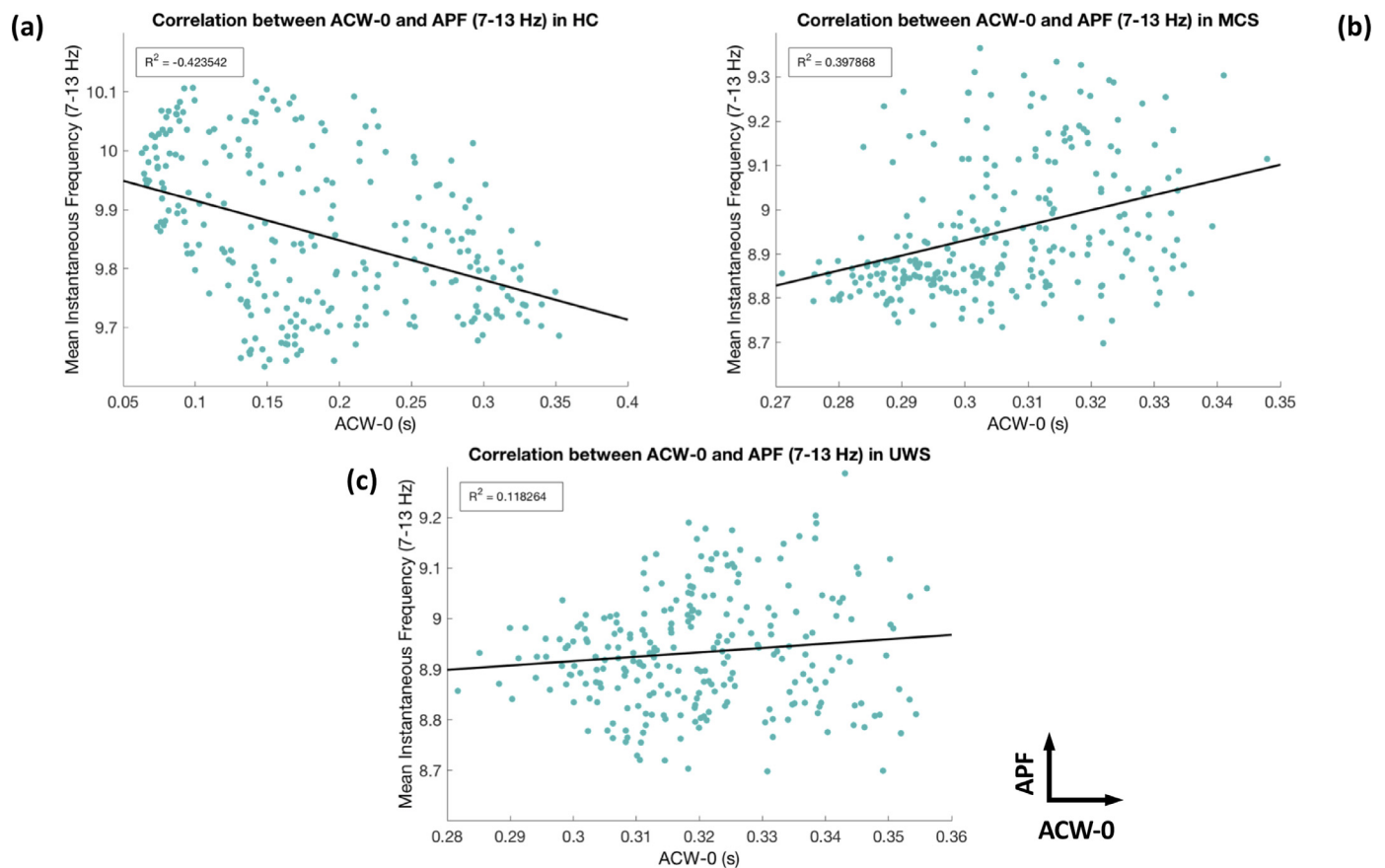
### 3.6. Power does not drive the relationship between INTs and the speed of alpha oscillations

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).





**Fig. 5.** Relationship of ACW-0 and mean instantaneous alpha frequency in the DoC cohort.

Channel-wise correlations in the DoC cohort. A state-dependant 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).

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.

#### 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 behaviour 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, 2022b).

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, 2022a). 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.

##### 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 anaesthetic 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, 2022b). 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 anaesthetic agents.

#### 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., 2022; 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 behaviour 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 behavioural 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 behavioural responsiveness (Fingelkurts et al., 2012; Klimesch, 2012; Labonte et al., 2022; 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 inter-

preted 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 behavioural responsiveness from the patient) may, in restricted occasions, limit the statistical power of measures that don’t specifically target neural correlates of behavioural 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 anaesthesia indicate that the abnormal prolongation of ACW-0 values is ultimately related to loss of consciousness.

#### 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 anaesthesia). 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, 2022b). 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, 2022b). Hence, our findings on ACW-0, APF and their relationship are consistent over the DoC and the anaesthesia samples; this strongly suggests that they are related to the state of consciousness rather than the underlying cause, e.g., anaesthetic agent or brain lesion.

Most importantly, a remark is needed to interpret the lack of statistical significance in our ketamine sample. Unlike most anaesthetic agents, ketamine is known to induce a “dissociative” state (Domino and Warner, 2010) even at sub-anaesthetic doses: patients are - at least behaviourally - not responsive to environmental inputs, but preserve a dose-dependant degree of awareness, which sometimes results in reports of conscious, dream-like experiences (Collier, 1972) after the anaesthetic’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 mea-

sures 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 unfavourable 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.

#### 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 (Northoff and Zilio, 2022a; Kent and Wittmann, 2021). 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.

#### 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.

## 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 anaesthesia 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.

#### 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.



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## Declaration of Competing Interest

None.

## Credit authorship contribution statement

**Andrea Buccellato:** Conceptualization, Formal analysis, Data curation, Visualization, Writing – original draft, Writing – review & editing. **Di Zang:** Conceptualization, Investigation, Resources, Writing – original draft, Writing – review & editing. **Federico Zilio:** Software, Data curation, Writing – review & editing. **Javier Gomez-Pilar:** Software, Writing – review & editing. **Zhe Wang:** Investigation. **Zengxin Qi:** Investigation. **Ruizhe Zheng:** Investigation. **Zeyu Xu:** Investigation. **Xuehai Wu:** Investigation. **Patrizia Bisiacchi:** Writing – review & editing, Supervision. **Alessandra Del Felice:** Writing – review & editing, Supervision. **Ying Mao:** Resources, Writing – original draft, Writing – review & editing, Supervision. **Georg Northoff:** Conceptualization, Writing – original draft, Writing – review & editing, Supervision.

## Data Availability

The data that has been used is confidential.

## Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.neuroimage.2022.119802](https://doi.org/10.1016/j.neuroimage.2022.119802).

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