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Complementary roles of neural synchrony and complexity for indexing consciousness and chances of surviving in acute coma

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ABSTRACT

An open challenge in consciousness research is understanding how neural functions are altered by pathological loss of consciousness. To maintain consciousness, the brain needs synchronized communication of information across brain regions, and sufficient complexity in neural activity. Coordination of brain activity, typically indexed through measures of neural synchrony, has been shown to decrease when consciousness is lost and to reflect the clinical state of patients with disorders of consciousness. Moreover, when consciousness is lost, neural activity loses complexity, while the levels of neural noise, indexed by the slope of the electroencephalography (EEG) spectral exponent decrease. Although these properties have been well investigated in resting state activity, it remains unknown whether the sensory processing network, which has been shown to be preserved in coma, suffers from a loss of synchronization or information content. Here, we focused on acute coma and hypothesized that neural synchrony in response to auditory stimuli would reflect coma severity, while complexity, or neural noise, would reflect the presence or loss of consciousness. Results showed that neural synchrony of EEG signals was stronger for survivors than non-survivors and predictive of patients' outcome, but indistinguishable between survivors and healthy controls. Measures of neural complexity and neural noise were not informative of patients' outcome and had high or low values for patients compared to controls. Our results suggest different roles for neural synchrony and complexity in acute coma. Synchrony represents a precondition for consciousness, while complexity needs an equilibrium between high or low values to support conscious cognition.

1. Introduction

The integrity and organization of neural responses to external stimuli are indicative of conscious processing and cognition (Braiman et al., 2018; Casali, 2013; Massimini et al., 2005; Tononi et al., 2016). Converging evidence suggests that to maintain consciousness, the brain needs synchronized communication of information across brain regions, and sufficient complexity in neural activity to perform the neural operations supporting consciousness (Casali, 2013; Deco et al., 2015; Tagliazucchi et al., 2016; Tononi et al., 2016). When consciousness is pathologically lost, for example, when a patient falls into a coma, information processing in the brain is drastically altered.

Coordination of neural activity during rest (Carrasco-Gómez, 2021; Pugin et al., 2020) and also of neural responses to environmental stimuli such as sounds (Binder et al., 2017; Lechinger et al., 2016) is diminished or even completely abolished in patients with disorders of consciousness. The degree of phase-locking to external stimuli (Lechinger et al., 2016) and of resting-state functional connectivity, measured via functional magnetic resonance imaging (fMRI) (Pugin et al., 2020) or electroencephalography (EEG) (Carrasco-Gómez, 2021; Zubler et al., 2017), correlate with patients' clinical state or chances to regain consciousness.

Likewise, in the absence of consciousness, neural activity loses information content, resulting in a reduction of entropy or complexity (Luppi et al., 2019; Medel et al., 2020; Miskovic et al., 2018; Schartner et al., 2015), experimentally observed in anesthesia (Liu et al., 2018; Sarasso et al., 2015), sleep (Miskovic et al., 2018), and during epileptic seizures (Mateos et al., 2017). The information content or complexity of neural responses can be associated with levels of neural noise, in other words, how orderly or random neural activity is. Electrophysiologically, the

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levels of neural noise in the brain have been associated with the level of non-oscillatory background EEG activity, which is quantified through the steepness of the 1/f power decay (Colombo et al., 2019; Medel et al., 2020; Miskovic et al., 2018). White noise, a temporally uncorrelated signal, has a flat spectral slope, while a highly correlated neural population that fires in synchrony will have a steeper 1/f (Voytek et al., 2015). When consciousness is reduced, such as in sleep (Miskovic et al., 2018) or anesthesia (Lendner et al., 2020; Medel et al., 2020), the 1/f slope becomes steeper, likely due to a reduction in neural complexity or 'noise' in these states of low information content. Importantly, the steepness of the 1/f slope has been shown to strongly correlate with the complexity of resting-state EEG activity (Colombo et al., 2019), suggesting that these two measures may capture similar neural processes of structure or noise in neural activity.

Although some studies have examined either neural synchorny or complexity separately, these have predominantly focused on naturally or artificially induced loss of consciousness in healthy conditions, and/or neural activity during rest (Mai et al., 2019; Miskovic et al., 2018; Sarasso et al., 2015). It remains under-investigated whether similar mechanisms of reduced neural noise are also observed in pathological loss of consciousness and in response to environmental stimuli.

In patients with disorders of consciousness, the integrity of neural responses to external stimuli has been shown to track depth and severity of coma (Boly et al., 2011; Daltrozzo et al., 2009; Fischer et al., 2004; Pfeiffer et al., 2017; Tzovara, 2016; Tzovara et al., 2013). Auditory evoked potentials (AEPs) are particularly important in the acute coma phase, during the first days after coma onset, as they are informative of chances of regaining consciousness (Comanducci et al., 2020; Tzovara, 2016; Tzovara et al., 2013), and of long-term cognitive outcome (Juan et al., 2016). However, the electrophysiological properties of neural responses to external stimuli during acute coma are not well characterized. In particular, it remains unknown whether the sensory processing network, which has been shown to be preserved in acute coma (Cossy et al., 2014; Pfeiffer et al., 2017; Tzovara, 2016; Tzovara et al., 2013), suffers from a loss in synchronization and information content as resting-state neural activity does in non-pathological loss of consciousness (Miskovic et al., 2018; Sarasso et al., 2015).

Here, we focused on a group of post-anoxic coma patients who were treated with therapeutic hypothermia (Beccaria et al., 2010). This population is particularly important for studying loss of consciousness in pathological conditions, as patients suffer from global ischemia, and do not have focal lesions. We focused our investigations in the first 24 h of coma onset, where patients were under hypothermia and sedation, a condition in which conscious access to the environment can be excluded. We hypothesized that neural synchrony in response to auditory stimuli would reflect coma severity, similar to what has been shown using resting-state fMRI (Pugin et al., 2020) or resting-state EEG (Carrasco-Gómez, 2021; Zubler et al., 2017). Moreover, we hypothesized that complexity, or neural noise in AEPs, would reflect the presence or loss of consciousness, rather than the patients' clinical state, similar to previous reports investigating neural complexity in sleep (Miskovic et al., 2018) or anesthesia (Liu et al., 2018; Sarasso et al., 2015). We quantified neural synchrony through metrics of EEG connectivity (Phase-locking value; PLV (Lachaux et al., 1999) and information transfer (Schreiber, 2000; Vicente et al., 2010)), and complexity or noise through metrics of entropy (Lempel-Ziv (LZ) complexity (Lempel and Ziv, 1976) and singular value decomposition (SVD) entropy), as well as through the steepness of the 1/f slope (Pritchard, 1992).

2. Results

2.1. Phase-locking of EEG responses in coma and wakefulness

EEG data were recorded in a cohort of 67 post-cardiac arrest comatose patients, in the first day of coma, under sedation and hypothermia, and in 13 age-matched healthy controls. Patients and controls were presented with series of pure tones as previously described (Rossetti et al., 2014; Tzovara, 2016; Tzovara et al., 2013). Our first goal was to quantify the neural synchrony of EEG responses to sounds and its links to patients' outcome and consciousness. To this aim, we computed the PLV between all electrode pairs in the alpha range (8–12 Hz) (see 4. Materials and Methods on the rationale behind using the PLV, and Supplemental Information (SI): S1.2 for additional controls), as motivated by analysing the power spectra of these patients (SI: S1.1) and previous work on similar patient cohorts (Kim et al., 2020; Kustermann et al., 2019; Wiley et al., 2017).

Table 1
Prediction characteristics in pilot and validation groups. A threshold of PLV = 0.69 resulted in the highest PPV of PLV calculated in the alpha band for patients in the pilot group. With this threshold, the PPV in the validation group was also 0.87.

Group	PPV	NPV	Sensitivity	Specificity	Accuracy
Pilot	0.87	0.7	0.91	0.81	0.87
Validation	0.87	0.7	0.81	0.78	0.8
Overall	0.87	0.7	0.81	0.78	0.8

PPV: Positive predictive value, NPV: Negative predictive value *All ps<0.05 in both pilot and validation group*

In a pilot group of $N = 39$ patients, the PLV significantly differed between survivors and non-survivors in 71 electrode pairs ($p < 0.01$, FDR-corrected, Fig. 1). Importantly, the PLV was significantly higher for survivors compared to non-survivors in the vast majority of electrode pairs (69 out of 71; Fig. 1). We then focused on the identified pairs, and calculated the average PLV per participant, in order to increase sensitivity in linking PLV to patients' outcome.

As expected, the average PLV of the retained electrode pairs was significantly different between survivors and non-survivors in the pilot group (survivors: $N = 22$, $M = 0.77$, SD = 0.06; non-survivors: $N = 17$, $M = 0.55$, $SD = 0.14$), $t(37) = 6.39$, $p < 0.001$). This finding is not surprising, as these electrode pairs were selected based on their difference in phase-locking between survivors and non-survivors. The generalization of this finding was tested in an objective way in the validation group of $N = 28$ patients, which had not been used to select electrode pairs. In the validation group, the average PLV over the selected electrode pairs was also significantly different between survivors ($N = 17$, $M = 0.75$, $SD = 0.07$) and non-survivors ($N = 11$, $M = 0.62$, $SD = 0.09$) ($t(26) = 3.85$, $p < 0.001$), suggesting that our findings generalize to new patients. When compared with healthy controls ($N = 13$, $M = 0.76$, $SD = 0.04$), non-survivors had significantly lower PLVs ($t(22) = 4.78$, $p < 0.001$), whereas there was no significant difference between healthy controls and survivors ($t(28) = 0.54$, $p = 0.59$).

2.1.1. Prediction of awakening from coma based on phase-locking

The analysis of PLV showed that the EEG responses of survivors had on average higher phase-locking compared to non-survivors. Next, we evaluated whether this difference could be linked to patients' outcome at the single-patient level. Based on the observation that survivors of the pilot group had generally higher PLV than non-survivors (Fig. 2, unfilled circles), we calculated the threshold in PLVs resulting in the most accurate discrimination of survivors vs. non-survivors in the pilot group. The optimal threshold was identified as PLV = 0.69. The vast majority of survivors in the pilot group ($N = 20$ out of 22) had a higher PLV than the threshold, and the vast majority of non-survivors ($N = 13$ out of 17) had a lower PLV (Fig. 2). This resulted in a positive predictive value (PPV) for awakening of 87% and an accuracy for predicting overall outcome of 87% in the pilot group (Table 1; Fig. 2).

This pattern of results largely generalized in the validation group. Out of the 17 survivors of the validation group, 13 had a PLV higher than the threshold identified from the pilot group; three patients had a PLV lower than the threshold; while one survivor was unclassified because their PLV was equal to the identified threshold (Fig. 2). Among the

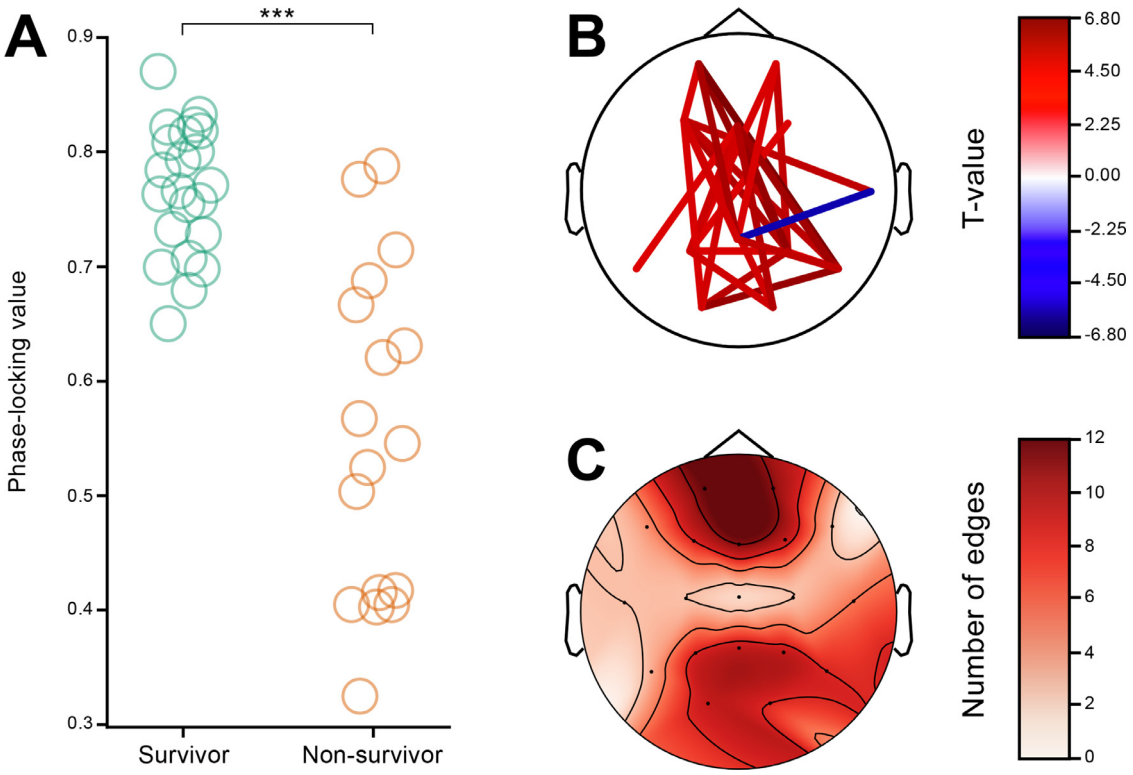

Fig. 1. *PLV of patients in the pilot group.* **(A)** Average PLV across all electrode pairs was higher for survivors (N = 22, green circles) than non-survivors (N = 17, orange circles), $t(37) = 5.02$, $p < 0.001$. **(B)** Illustration of electrode pairs that significantly differed between survivors and non-survivors of the pilot group, with the respective connections color-coded according to their t-values. For illustration purposes we only display electrode pairs with $p < 0.0005$. **(C)** Topographic heat map indicating number of connections per electrode that significantly differed between survivors and non-survivors in the pilot group. The topography is color-coded by the number of edges for each electrode. $^{***}p<0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

11 non-survivors in the validation group, two patients had a PLV higher than the threshold while two patients were at the threshold level. The PPV for awakening in the validation group was 87% and the overall accuracy for predicting coma outcome 80% (Fig. 2, filled circles; Table 1). The PPV for awakening was significantly different from chance, evaluated by randomly permuting the patients' outcome and re-estimating a threshold 100 times ($p < 0.001$). Notably, a PPV of 0.87 is at comparable levels with the outcome prediction approaches that are currently used in the clinical routine (See SI: S1.3; Rossetti et al., 2017).

Interestingly, the PLV in all control participants was higher than the identified threshold (Fig. 2, purple circles). We next grouped together pilot and validation patients and contrasted survivors ($N = 39$, $M = 0.76$, $SD = 0.07$), non-survivors ($N = 28$, $M = 0.58$, $SD = 0.13$), and controls ($N = 13$, $M = 0.76$, $SD = 0.04$). We found a significant group effect on PLV, ($F(2, 77) = 35.3$, $p < 0.001$). Post-hoc comparisons showed that PLV for awake controls was indistinguishable from that of survivors (Fig. 2, green circles), also when grouping together pilot and validation participants ($t(50) = 0.09$, $p = 0.93$). Likewise, the PLV of non-survivors remained significantly lower than that of both survivors ($t(65) = 7.39$, $p < 0.001$) and healthy controls ($t(39) = 4.89$, $p < 0.001$). To further validate these results, we also computed the corrected imaginary PLV (ciPLV), which is less prone to volume conduction (Bruña et al., 2018), the Pairwise Phase Consistency (PPC) which is resilient to differences in statistical power (Vinck et al., 2010), and the Transfer Entropy (TE), which is informative of the directionality of information transfer across electrodes (Huang et al., 2015; Vicente et al., 2010) (SI: S1.2 for these control analyses). These control analyses provided similar main effects of group as the PLV, suggesting that differences in neural synchrony persist across metrics.

2.1.2. Phase-locking in the first day of coma and outcome at 3 months

We additionally evaluated whether the PLV during the first day of coma was informative of patients' cognitive state at three months. This was evaluated based on the Cerebral Performance Category (CPC) rating (Jennett and Bond, 1975), which is more informative of the patients' cognitive state than a dichotomy between survival and non-survival (Booth et al., 2004). A CPC rating of five indicates that the patient is not alive, and four, not present in the current sample, in a persistent vegetative state. A CPC rating of three is used to describe patients with a severe disability, unable to function independently, while a CPC rating of one and two describe patients who are able to function independently, however only a rating of one indicates ability to resume normal life (Booth et al., 2004; Jennett and Bond, 1975). We found a group difference in the PLV among survivors split on outcome classified according to the CPC, $F(2, 37) = 5.24$, $p = 0.01$. However, this difference did not persist when testing it with a robust correlation method (Regression coefficient 95% CI [-0.05, 0.005]). In pair-wise comparisons of different CPC score levels, patients with CPC of 1 had a significantly higher PLV in the first day of coma than patients with CPC 3 ($N = 6$, $M = 0.69$, $SD = 0.07$), $t(27) = 2.81$, $p < 0.01$, as had patients with CPC 2 compared to patients with CPC 3, $t(14) = 2.99$, $p < 0.01$ (Fig. 3). PLV was not different between patients with CPC 1 ($N = 23$, $M = 0.77$, $SD = 0.06$) and 2 ($N = 10$, $M = 0.78$, $SD = 0.04$).

2.2. Lempel–Ziv complexity of EEG responses

After establishing that the phase-locking of auditory EEG responses is informative of patients' outcome rather than the presence or absence of consciousness, we aimed at characterising their temporal structure

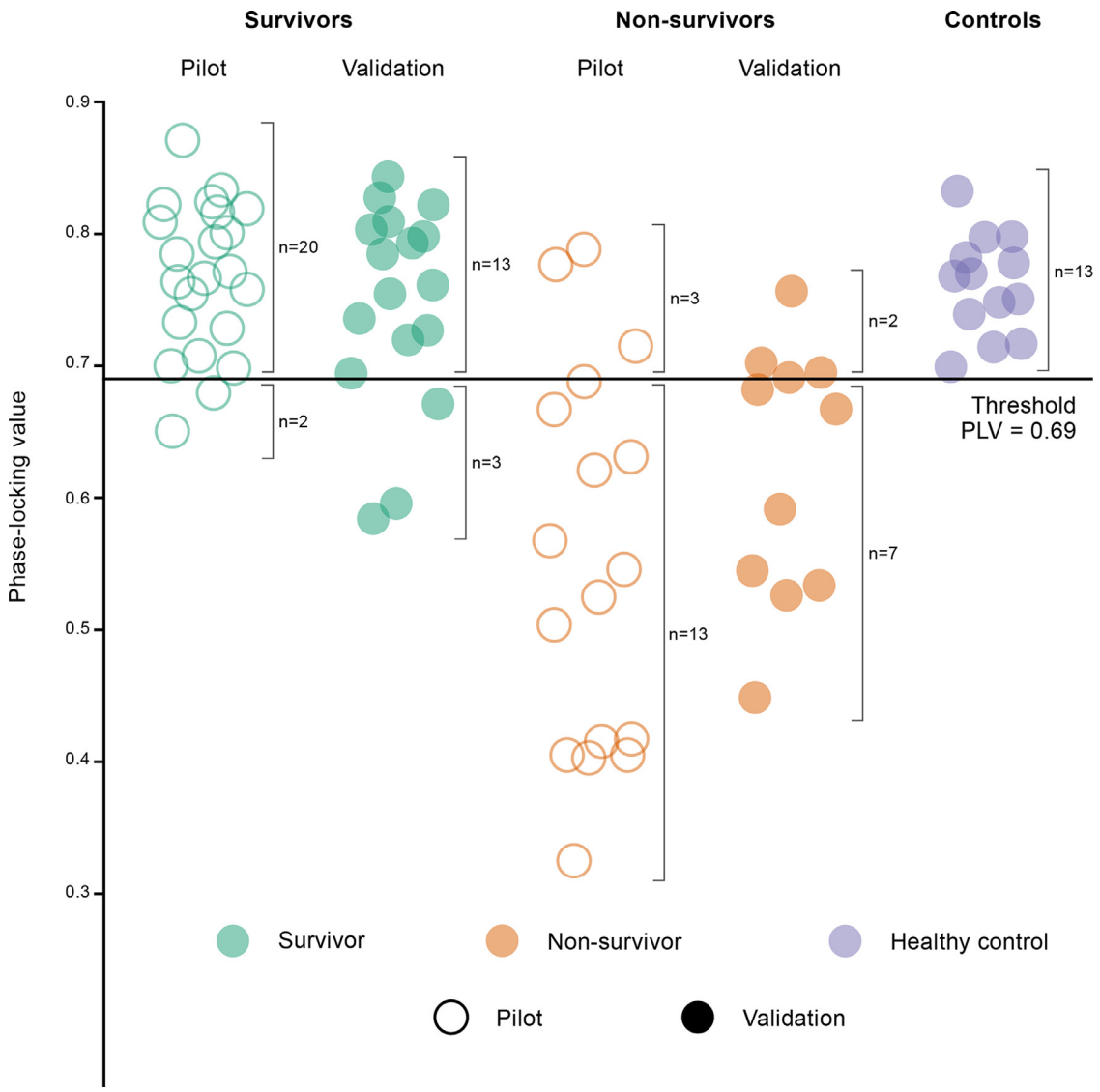

Fig. 2. *Outcome prediction based on PLV.* Outcome prediction is based on the average PLV per participant, across the 71 electrode pairs found to be significantly different between outcomes in the pilot group (unfilled circles). A similar tendency was observed in the PLV of patients in the validation group (filled circles), with the vast majority of survivors (green) having higher PLV than non-survivors (orange). The horizontal line indicates the PLV threshold identified by the pilot group, corresponding to a PLV of 0.69. All healthy controls had a PLV higher than this threshold (purple circles). The numbers displayed on the figure correspond to the number of patients that fell above or below the threshold. Patients whose PLV was equal to the threshold are included in the display but not in the reported numbers. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

and complexity. To this end, we computed the LZ complexity across all electrodes, which quantifies the temporal richness of EEG responses. Similar to previous investigations (Brito et al., 2020), we computed different versions of LZ complexity. The first was LZc, consisting of LZ complexity normalized by the complexity of temporally randomized surrogate signals (Fig. 4A). The second was LZc_n, where the LZ complexity was normalized with phase-randomized surrogate signals to account for possible effects of power spectra (LZc_n; Fig. 4C). Last, we additionally computed the LZ complexity normalized by the maximal number of possible subsequences for a signal of a certain length (SI: S1.5).

2.2.1. *Neural complexity does not reflect patients' outcome*

Similar as in the PLV analyses, we started from the pilot group of N = 39 patients, to explore possible links between complexity in the first day of coma and patients' outcome. In the pilot group, there was no significant difference in LZc between survivors ($N = 22$, $M = 0.18$, $SD = 0.03$) and non-survivors ($N = 17$, $M = 0.23$, $SD = 0.08$; $U(22, 17) = 139$, $p = 0.18$, with a Mann–Whitney U test as the distributions of LZc values did not fulfill the assumption of normality). Likewise, LZc_n was also not significantly different between outcomes in the pilot group (survivors: $M = 0.71$, $SD = 0.06$; non-survivors: $M = 0.74$, $SD = 0.16$; $U(22, 17) = 131$, $p = 0.12$). Neither LZc nor LZc_n values at the single electrode level were informative of the patients' outcome (SI: S1.4).

2.2.2. *Link between neural complexity and loss of consciousness*

We next evaluated whether neural complexity was informative of the presence or absence of consciousness. We grouped together survivors and non-survivors from both pilot and validation groups and tested whether there was a difference in complexity between all patients and healthy controls. Patients had significantly lower complexity than controls with LZc (patients: $M = 0.21$, $SD = 0.06$; controls: $M = 0.24$, S0.; $U(67, 13) = 271$, $p < 0.05$) and LZc_n (patients: $M = 0.74$, $SD = 0.12$; controls: $M = 0.82$, $SD = 0.03$; $U(67, 13) = 209$, $p < 0.01$). This led us to post-hoc contrasts. Compared to survivors, healthy controls had significantly higher LZc ($U(39, 13) = 116$, $p < 0.01$; Fig. 4A, green vs purple circles), and LZc_n ($U(39, 13) = 97$, $p < 0.001$). However, there was no

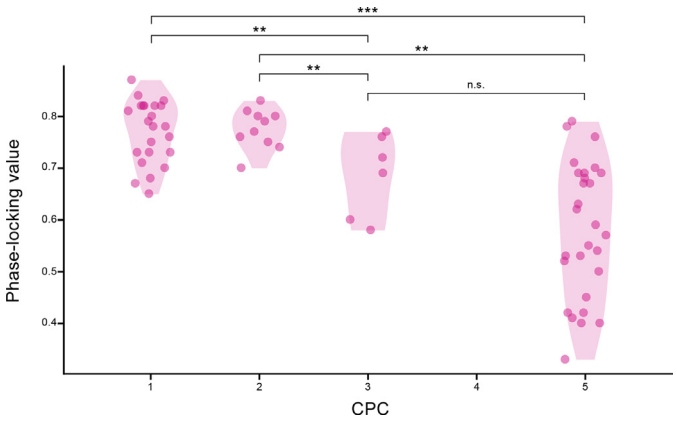

Fig. 3. *Link between PLV in first day of coma and CPC at three months.* Patients with CPC 1 (N = 23) had a greater average PLV than patients with CPC 3 (N = 6), $t(27) = 2.81$, $p < 0.01$ and CPC 5 (N = 28), $t(49) = 6.45$, $p < 0.001$. Likewise, patients with CPC 2 (N = 10) had greater PLV than patients with CPC 3 ($t(14) = 2.99$, $p < 0.01$) and CPC 5 ($t(36) = 4.63$, $p < 0.001$). There was no difference between patients with CPC 1 and 2 ($t(31) = 0.24$, $p = 0.81$), nor between patients with CPC 3 and 5 ($t(32) = 1.92$, $p = 0.064$). $^{**}p<0.01$, $^{***}p<0.001$.

difference between healthy controls and non-survivors neither in LZc, nor in LZc_n (U(28, 13) = 155, $p = 0.46$); $U(28, 13) = 112$, $p = 0.052$).

2.3. 1/f spectral dynamics in coma and wakefulness

To characterise the complexity of EEG dynamics in coma, in addition to LZ complexity, we also computed the background power decay, expressed as the 1/f slope of the EEG power spectrum. Similar as in previous reports (Colombo et al., 2019), the slope of the 1/f exponent was computed across EEG electrodes in the 2–20 and 20–40 Hz range, as well as in the 2–40 Hz range (Fig. 5).

2.3.1. 1/f slope is not informative of patients' outcome

We first examined whether the 1/f slope was informative of patients' outcome in the pilot group of patients. The 1/f slope was steeper for survivors (N = 22, M = -2.11, SD = 0.48) than non-survivors (N = 17, M = -1.22, SD = 0.94) in the 2–40 Hz range ($U(22, 17) = 85$, $p < 0.01$). However, it was not significantly different between survivors and non-survivors neither in the 2–20 (survivors: M = -1.68, SD = 0.43; non-survivors: M = -1.08, SD = 0.81; $U(22, 17) = 112$, $p = 0.04$), nor in the 20–40 Hz range (survivors: M = -2.83, SD = 1.26; non-survivors: N = 17, M = -2.09, SD = 1.09; $U(22, 17) = 121$, $p = 0.06$) after correcting for multiple comparisons across the three frequency bands ($\alpha = 0.05 / 3 = 0.017$). We then tested whether the difference in 1/f slope in the 2–40 Hz range could be replicated in the validation group of patients. However, in the validation group the 1/f slope between survivors and non-survivors did not differ (survivors: N = 17, M = -1.67, SD = 0.69; non-survivors: N = 11, M = -1.38, SD = 1.07; $U(17, 11) = 83$, $p = 0.64$). Thus, similar to the LZ complexity, the 1/f slope was not informative of patients' outcome.

2.3.2. 1/f slope is altered by the loss of consciousness

We next grouped pilot and validation patients together, and contrasted them to healthy controls to test whether coma, characterized by the absence of consciousness, may modulate the background power decay compared to awake conditions. To this aim, we first tested whether there was a group difference on the 1/f slope in any of the frequency bands. We found a significant main effect of group in the 2–20 Hz range ($H(2) = 18.07$, $p < 0.001$), 20–40 Hz range ($H(2) = 23.32$, $p < 0.001$), and also in the 2–40 Hz range ($H(2) = 8.73$, $p < 0.05$). In post-hoc contrasts, we investigated which groups were driving these effects. In the 2–20 Hz range, survivors (M = -1.62, SD = 0.49) had a significantly steeper 1/f slope than healthy controls (M = -0.71, SD = 0.26; $U(39, 13) = 26$, $p < 0.001$). There was no difference between non-survivors (M = -1.11, SD = 0.89) and survivors ($U(39, 28) = 400$, $p = 0.064$), nor between non-survivors and healthy controls ($U(28, 13) = 134$, $p = 0.183$). In the 20–40 Hz range, healthy controls (M = -4.25, SD = 0.6) had a

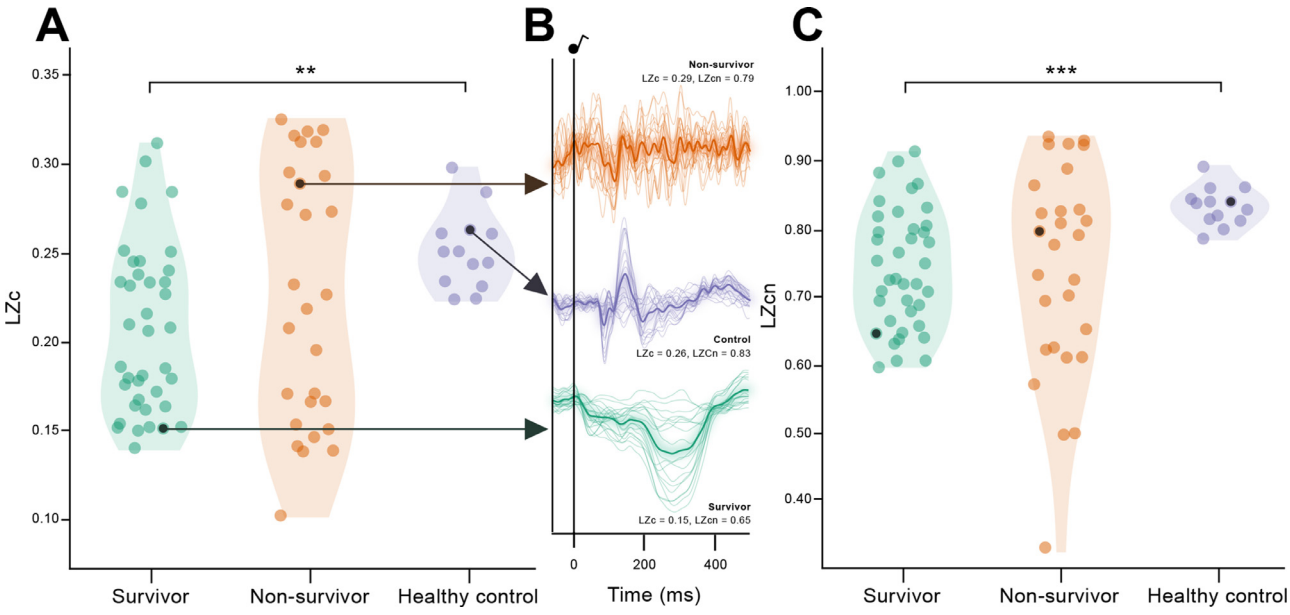

Fig. 4. *LZ complexity for patients and controls.* **(A)** LZc was higher for healthy controls (purple; M = 0.24, SD = 0.02) than survivors (green; M = 0.20, SD = 0.05; $U(39, 13) = 116$, $p < 0.01$), and not different between healthy controls and non-survivors (orange; M = 0.22, SD = 0.07; $U(28, 13) = 155$, $p = 0.46$). **(B)** Example auditory evoked responses for patients having particularly low (survivor, green lines), or high (non-survivor, orange lines) LZc, as well as for a healthy control (purple). The patient associated with each example evoked response is indicated by a black circle on plot **A** and **C.** **(C)** For LZc_n, healthy controls (M = 0.824, SD = 0.026) had significantly higher LZc than survivors (M = 0.74, SD = 0.08; $U(39, 13) = 97$, $p < 0.001$), however there was no difference between healthy controls and non-survivors (M = 0.73, SD = 0.15; $U(28, 13) = 112$, $p = 0.052$). $^{**}p<0.01$, $^{***}p<0.001$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

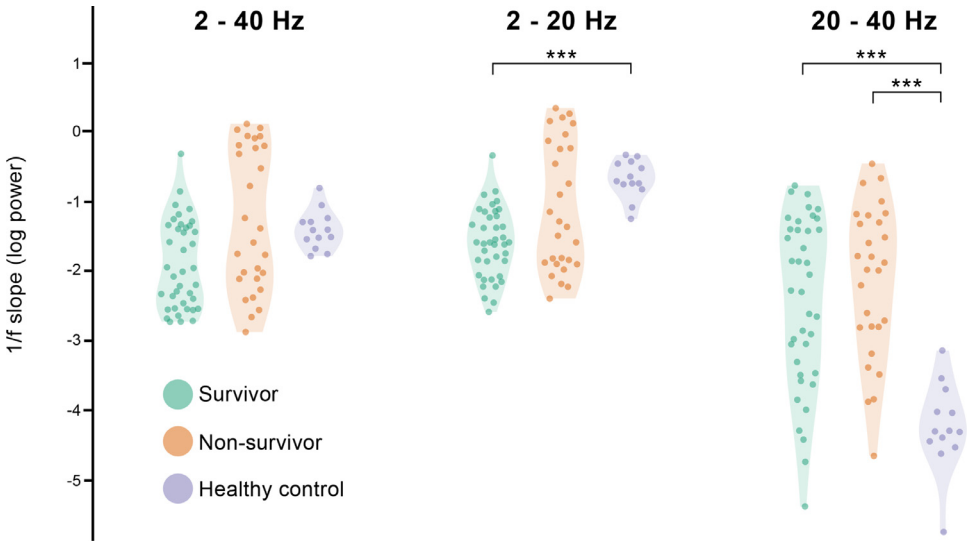

Fig. 5. *1/f slope for patients and controls.* In the 2–40 Hz range (left) there were no significant differences in any of the groups. In the 2–20 Hz range (middle), survivors had a significantly steeper 1/f slope than healthy controls ($U(39, 13) = 26$, $p < 0.001$). In the 20–40 Hz range (right), healthy controls had a steeper 1/f slope than both survivors ($U(39, 13) = 456$, $p < 0.001$), and non-survivors ($U(28, 13) = 343$, $p < 0.001$). The reported differences refer to post-hoc contrasts, after correcting for the multiple comparisons. ***$p<0.001$.

steeper 1/f slope than both survivors (M = -2.45, SD = 1.21; $U(39, 13)$ = 456, $p < 0.001$), and non-survivors (M = -2.15, SD = 1.07; $U(28, 13)$ = 343, $p < 0.001$), while there was no difference between survivors and non-survivors ($U(39, 28)$ = 469, p = 0.33). Last, in the 2–40 Hz range, there were no significant difference for any of the post-hoc contrasts: survivors (M = -1.92, SD = 0.62) vs. non-survivors (M = -1.28, SD = 0.99): $U(39, 28)$ = 355, p = 0.015; survivors vs. healthy controls (M = -1.42, SD = 0.26): $U(39, 13)$ = 139, p = 0.016; non-survivors vs. healthy controls: $U(28, 13)$ = 180, p = 0.966).

2.4. Linking complexity and 1/f spectral dynamics

Although not informative of single patients' outcome, both the LZ complexity and the 1/f slope shared similar characteristics at the group level: survivors had relatively low complexity and 1/f slope, non-survivors showed either low or high values, and healthy controls were in between (Figs. 4, 5). This observation prompted us to examine whether a possible link between LZ complexity and the 1/f slope could be observed at the single participant level.

We observed a strong correlation between LZ complexity and the 1/f slope both for coma patients and healthy controls (Fig. 6). LZc was significantly correlated with the 1/f slope in the 2–20 Hz range for patients (r = 0.85, $p < 0.001$; Fig. 6A). LZc and 1/f slope were positively correlated for healthy controls as well, although not significantly (r = 0.54, p = 0.06; Fig. 6A). LZc_n was significantly correlated with the 1/f slope in the 2 - 20 Hz range for both patients (r = 0.69, $p < 0.001$ and controls (r = 0.70, $p < 0.01$; Fig. 6B).

3. Discussion

We investigated electrophysiological properties of neural responses to sounds in acute coma, and their link to consciousness and patients' outcome. First, we assessed neural synchrony, quantified as the phase-locking of EEG responses. Phase-locking was significantly lower in non-survivors compared to both conscious controls and survivors (Fig. 2). Second, we quantified neural noise as the complexity (Fig. 4) and the 1/f slope (Fig. 5) of EEG responses. Both of these measures had high or low values in patients compared to controls, and did not reflect outcome from coma. Importantly, the phase-locking of auditory responses on the first day of coma was predictive of the patients' chances of awakening in two different cohorts of patients.

3.1. Neural synchrony as a prerequisite for the return of consciousness

We showed that coma patients who later survive show higher phase-locking in neural responses to auditory stimuli in the first day of coma than patients who do not. Alterations in phase-locking in response to external stimuli associated with absence of consciousness has been previously reported in sleep (Lee et al., 2019) and in patients with disorders of consciousness (Lechinger et al., 2016). Previous studies found greater synchrony in response to auditory stimuli in healthy controls than in patients with disorders of consciousness and showed that the degree of phase-locking was positively correlated with auditory function (Binder et al., 2017) measured through the Coma Recovery Scale - Revised (Giacino and Kalmar, 2006). Interestingly, investigations of neural synchrony of EEG activity on the first day of coma have reported similar findings in resting-state activity as our findings on auditory EEG responses, and notably, higher synchrony for survivors compared to non-survivors (Carrasco-Gómez, 2021; Zubler et al., 2017).

The neural origin of a stronger phase-locking in AEPs for survivors compared to non-survivors still remains unknown. One possible interpretation is that there are stronger preserved thalamo-cortical connections for survivors compared to non-survivors, and therefore different parts of the cortex receive similar thalamic inputs, without necessarily being inter-connected at a cortical level. Nevertheless, because both survivors and non-survivors are unconscious, thalamo-cortical connections are likely to be weaker in both patient groups (Forgacs et al., 2017) compared to awake controls. Another interpretation is that there is a global disruption of cortico-cortical connectivity for non-survivors, which may have resulted from greater brain injury. With our current experimental setup of sparse EEG electrode coverage it is not possible to localize the neural origin of differences in phase-locking between survivors and non-survivors. However, previous studies using functional magnetic resonance imaging in post-anoxic coma have reported diminished cortico-cortical resting-state connectivity for non-survivors compared to survivors, and no evident thalamo-cortical connections or differences therein, likely because these were weakened for all coma patients (Pugin et al., 2020). Although links between EEG spectra during acute coma and eventual thalamic atrophy may exist, these are known to manifest six months after coma onset (Schnakers et al., 2018). Taken together, past studies suggest that alterations in cortico-thalamic circuits may be linked to power spectra during acute coma, but likely manifest several days or months after coma onset. Future studies can use high-density EEG to shed light on the neural origins of phase-locking of auditory responses in acute coma, and test its precise neural underpinnings.

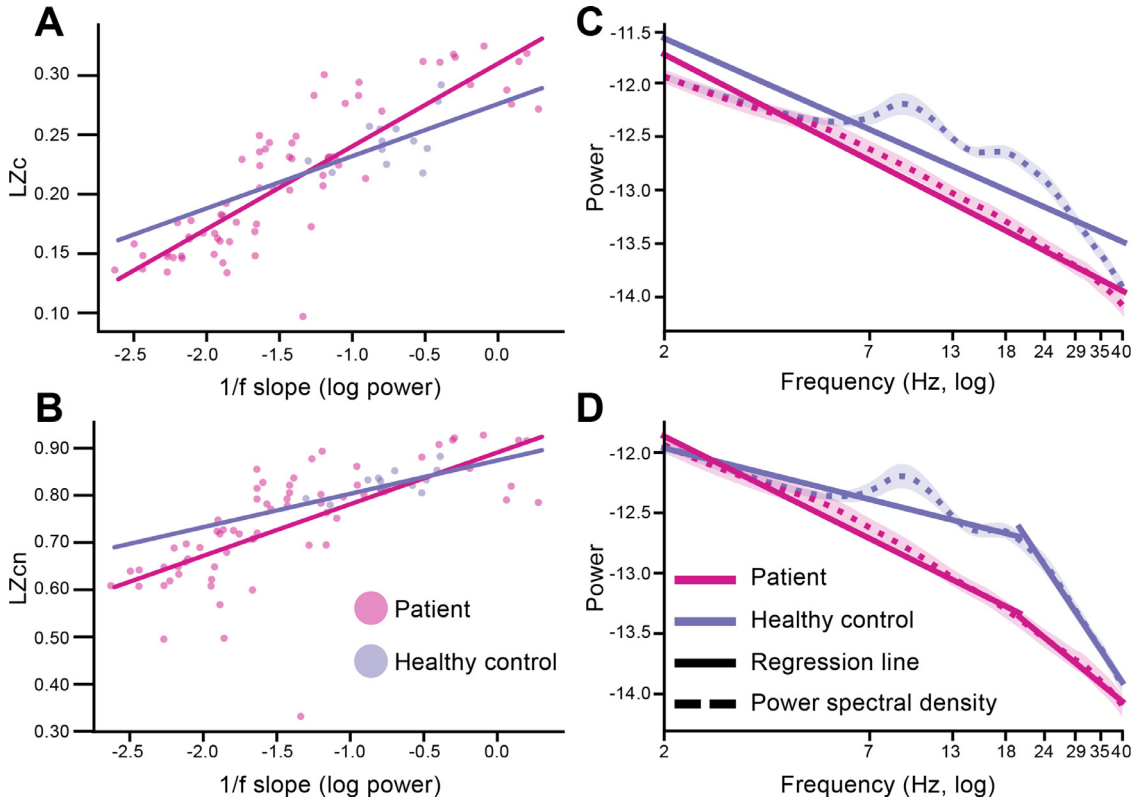

Fig. 6. *Link between* complexity *and 1/f slope for patients and controls.* **(A)** LZc and 1/f slope in the 2–20 Hz range were strongly correlated for patients (pink, $r = 0.85$, $p < 0.001$), however not significantly correlated for controls (purple, $r = 0.54$, $p = 0.06$). **(B)** LZc_n and 1/f slope in the 2–20 Hz range were significantly correlated for patients ($r = 0.69$, $p < 0.001$) and controls ($r = 0.70$, $p < 0.01$). **(C)** Regression fit of the 1/f slope in the 2–40 Hz range. **(D)** Regression fit independently for the 2–20 and 20–40 Hz range. **(C, D)** The shaded areas indicate the standard error across patients/controls; Power values are represented in the log space. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Our results extend previous findings which are mainly based on resting-state activity and are performed a few days (Pugin et al., 2020), or several months (Binder et al., 2017) after coma onset. Other past approaches used transcranial magnetic stimulation (TMS) evoked potentials, to study phase-locking at different levels of consciousness (Lee et al., 2019). These studies circumvent sensory pathways, while our approach, based on responses to auditory stimuli would rely on at least partially intact sensory pathways. The sensory processing network has been shown to be preserved in acute coma (Cossy et al., 2014; Pfeiffer et al., 2017; Tzovara, 2016; Tzovara et al., 2013), suggesting that auditory stimulation can reach cortical areas in this patient group.

One limitation of previous studies is that they have mainly compared phase-locking between states of consciousness and not within an unconscious state, such as coma. In the present study, EEG recordings in coma were performed during therapeutic hypothermia (33°C and under standardized sedation, conditions in which conscious access to external stimuli can be excluded both for survivors and non-survivors. Unlike previous reports that show a modulation of phase-locking by consciousness (Lechinger et al., 2016; Lee et al., 2019), here we found that the levels of phase-locking in post-cardiac arrest comatose patients who later survive are indistinguishable from those of healthy controls. By contrast, non-survivors have a significantly lower PLV than both survivors and controls. These findings suggest that high levels of phase-locking are not a sufficient condition for consciousness, but rather a strong prerequisite for its presence or return.

3.2. Phase-locking of auditory EEG responses predicts outcome from coma

Importantly, our results showed that the PLV was predictive of coma outcome, and in particular of the patients' chances of awakening. This follows other measures that are predictive of awakening, such as the EEG reactivity (Rossetti et al., 2017), the resting-state EEG power spectrum (Kustermann et al., 2019) and functional connectivity (Kustermann et al., 2020), and the progression of auditory discrimination (Juan et al., 2016; Pfeiffer et al., 2017; Tzovara, 2016; Tzovara et al., 2013). Our results suggest that the PLV in response to auditory stimuli could be an additional predictor of awakening. Although the PLV may be prone to volume conduction, we confirmed the reported differences in neural synchrony between survivors, non-survivors and controls by computing two other measures: the ciPLV (Bruña et al., 2018) and TE (Huang et al., 2015; Vicente et al., 2010). Both of these measures quantify neural synchrony and are less prone to volume conduction, which generally occurs with zero time-lag (Bruña et al., 2018; Vicente et al., 2010). The ciPLV controls for volume conduction by being insensitive to zero-lag synchrony (Bruña et al., 2018), while TE expresses how much uncertainty about a signal can be reduced by knowing the past of another signal, and is less sensitive to contributions of instantaneous synchronization such as volume conduction (Vicente et al., 2010).

More generally, the advantages of using measures of neural synchrony to predict outcome from coma are three-fold: (a) the PLV provides comparable positive predictive power to established outcome predictors currently used in clinical practice (Cronberg et al., 2020; Rossetti et al., 2016); (b) it is a continuous measure that can be informative of both negative and positive outcome, depending on the specified threshold; (c) it is fully automatic and can provide information about cerebral performance at 3 months already within the first 24 h of coma onset. Future research can evaluate the predictive value of measures of neural synchrony in additional, larger patient cohorts, and other coma etiologies.

3.3. Neural complexity in coma

Several studies have investigated links between neural complexity and consciousness and have reported that complexity diminishes in the absence of consciousness (Luppi et al., 2019; Medel et al., 2020; Miskovic et al., 2018; Schartner et al., 2015). Neural complexity has been investigated in sleep (Casali, 2013; Casarotto et al., 2016; Miskovic et al., 2018), anesthesia (Casali, 2013; Casarotto et al., 2016; Liu et al., 2018; Sarasso et al., 2015), and in patients who have emerged from coma (in a vegetative and minimally conscious state) (Casali, 2013; Sitt et al., 2014). All these previous studies, mainly performed in resting-state neural activity, report that in the absence of consciousness complexity of neural responses decreases.

Our findings in acute coma and auditory EEG responses partially confirm these previous findings. For the majority of patients, and in particular for patients with good outcome, neural complexity is significantly lower than the neural complexity of awake controls. In addition, in our cohort there is a subgroup of patients that have higher complexity values than awake controls, challenging the view that neural complexity diminishes in the absence of consciousness. Although this may seem surprising at first, it is not totally unexpected. Our cohort of patients consists of patients in acute post-anoxic coma. EEG recordings were performed in the first day of coma, shortly after patients suffered a global ischemia, and while their electrophysiology and metabolism are undergoing drastic changes (Carrasco-Gómez, 2021; Tzovara, 2016; Tzovara et al., 2013). Moreover, it has also been shown that complexity of resting-state EEG assumes a wide range of values in patients with disorders of consciousness, and also differs between acute and chronic states (Gosseries et al., 2011).

In our study, the cohort of non-survivors is particularly unique, as most of these patients die only a few days after the EEG recordings. They are therefore not commonly included in other studies with patients with disorders of consciousness, which predominantly focus several weeks or months after coma onset, as according to a recent review, no previous study has investigated LZ complexity in acute coma (Nilsen et al., 2020). Further studies need to evaluate neural complexity in acute coma, both in AEPs and also in resting state activity.

One possible explanation for the high or low complexity values observed in non-survivors compared to controls, is that an unfavorable outcome from coma may be associated with malignant EEG patterns, such as suppressed background EEG activity (Westhall et al., 2016). Thus, an unfavorable outcome may be associated with more stochastic fluctuations in neural activity and loss of temporal structure in response to external stimuli, which could result in the bistable pattern of complexity values for non-survivors. Further studies can investigate links between neural complexity and pathological patterns in the comatose EEG.

3.4. 1/f slope as a proxy for neural noise in coma

Similar to neural complexity, the slope of the non-oscillatory EEG background power decay is modulated by the loss of consciousness. Compared to wakefulness, the 1/f EEG slope is steeper in sleep (Lendner et al., 2020; Miskovic et al., 2018) and following administration of anesthetics associated with diminished consciousness (Colombo et al., 2019).

Previous studies propose that there may be a link between the steepness of the 1/f slope and the excitation to inhibition (E/I) balance, based on both simulations (Gao et al., 2017; Lombardi et al., 2017) and empirical work, linking the steepness of the 1/f slope to the ratio of E/I synapses in the rat hippocampus (Gao et al., 2017). The steepness of the 1/f EEG slope has also been found to be modulated by selective attention (Waschke et al., 2021), which has in turn been linked to the firing rate of inhibitory neurons (Snyder et al., 2016). Moreover, rapid eye movement sleep, which is a state of increased inhibitory interneuron activity, representing a shift towards inhibition (Niethard et al., 2016), has been shown to have a particularly steep 1/f slope (Lendner et al., 2020).

Another interpretation for the 1/f slope, at a more macroscopic level, is that its steepness is related to neural noise or randomness in electrophysiological activity. In this view, a less steep 1/f slope, similar as observed in some non-survivors of our cohort, may indicate less synchronized firing of neurons and therefore higher levels of stochasticity or neural noise (Dave et al., 2018; Usher et al., 1995; Voytek et al., 2015). More experimental work is needed in order to identify the neural mechanisms that are driving changes in the steepness of the 1/f slope.

Here, our cohort of survivors confirms the view that the steepness of the 1/f slope relates to consciousness (Colombo et al., 2019; Lendner et al., 2020), as they have a steeper 1/f compared to controls, which can be interpreted as higher inhibition, or lower neural noise. By contrast, the cohort of non-survivors contains some patients with a steeper 1/f than controls, and some other with a less steep slope. One possible interpretation for these findings is that they may be due to differences in neural noise or E/I ratio across coma patients. Coma is often linked to states of cortical hyperexitability (Kroeger and Amzica, 2007) and suppression of cortical inhibition (Amzica and Kroeger, 2011). A shift in the E/I ratio may be observed in particular in coma patients with abnormal EEG patterns, such as burst suppression which represents a state of reduced inhibition (Amzica and Kroeger, 2011). This could explain the less steep slope that was observed in the 20–40 Hz range for coma patients compared to controls, as a less steep 1/f slope may be associated with a shift towards excitation (Gao et al., 2017), or with higher levels of neural noise which may bepresent with more stochastic EEG activity in pathological conditions.

Previous studies have mainly assessed the 1/f EEG slope using resting-state data (Colombo et al., 2019; Miskovic et al., 2018), while our investigations focus on auditory stimulation. A recent study showed, however, that the spectral slope is also modulated by modality-specific attention to external stimuli in an event-related design (Waschke et al., 2021), illustrating the viability of measuring and testing for differences in the 1/f slope to evoked responses.

Our decision to investigate the spectral slope in the 2–20 Hz and 20–40 Hz independently was driven by previous reports of difference between the 1/f power decay above and below 20 Hz (Colombo et al., 2019; Robinson et al., 2001). The biological mechanism behind these observations is not known. Computational work has attempted to model broadband power spectra through recurrent neural networks, and suggesting that fast frequency activity may reflect local dynamics while slow activity may be indicative of more distributed connections (Chaudhuri et al., 2017), an interpretation corroborated by Robinson et al., 2001, who suggest thalamic low-pass filtering may contribute to differences in power decay across the 1/f spectrum. Although the precise mechanism remains unknown, our findings on the 1/f slope suggest that faster and slower neural activity are differentially altered by the comatose state and patients' outcome.

Interestingly, previous studies have related the 1/f slope to complexity of EEG responses, with neural complexity and the 1/f slope showing remarkably strong correlations in anesthesia (Colombo et al., 2019; Medel et al., 2020), paralleling our present findings in coma (Fig. 6). In our case, this strong correlation persisted even when normalizing the LZ complexity through phase randomized surrogate EEG signals, controlling for potential effects of power (Brito et al., 2020). This finding replicates previous observations in resting-state EEG during anesthesia (Colombo et al., 2019), and strengthens the view that the steepness of the 1/f slope tracks the structure or noise of EEG responses.

3.5. Limitations and perspectives

One possible limitation of the present study is that outcome prediction was made in patients where prognosis might have been affected by clinical decisions to withdraw life support. Nevertheless, the decision to withdraw life support was driven by a standardized multidisciplinary well-established approach (Rossetti et al., 2017), independently of the present analyses, which were not available to clinicians at the time of

decision. Another limitation is that coma patients were sedated and under therapeutic hypothermia. It is not possible to evaluate to which extent our results were affected by sedation, or the hypothermic treatment. However, similar levels of sedation and hypothermic treatment were administered to both survivors and non-survivors. Therefore, if these were the main factors driving any of our findings, we would not observe any differences in phase-locking of survivors and non-survivors, and likewise LZ complexity or 1/f would not show different patterns for the two patient cohorts.

Because our control group consisted of age-matched healthy and awake volunteers, it is impossible to isolate the effect of coma from the effect of sedation and hypothermia with this control population. Future studies could investigate the same paradigm in healthy individuals undergoing similar levels of sedation as coma patients, to isolate fine-grained effects of sedation from effects of acute coma. It is however important to note that the same level of sedation in healthy controls would not result in an unconscious state, and for instance would not be sufficient to perform surgical procedures.

Moreover, it is worth mentioning that although here we analyzed AEPs, the majority of previous studies have focused either on resting-state activity (Carrasco-Gómez, 2021; Zubler et al., 2017), or TMS evoked potentials. In particular, studies using TMS evoked potentials have jointly quantified properties of synchrony and complexity of EEG responses, commonly using the perturbational complexity index (PCI) (Casali, 2013; Sarasso et al., 2015). The PCI indexes levels of consciousness by stimulating the brain via TMS and measuring the complexity of the resultant neural response. Both loss of neural synchrony and complexity can result in lower scores on measures of complexity: less distributed interactions in response to the external stimulation result in less neural synchrony, spatially restricting the response leading to a lower complexity score. By contrast, more stereotypical responses in the interacting areas result in more redundant information in the signal, and therefore less complexity. Thus, the PCI is not sensitive to whether synchrony or complexity is lost, as loss of either will result in a lower PCI score. This provides the advantage of clinical applications, but it lacks in interpretability. Here, with our approach we disentangled the two properties of neural synchrony and complexity in AEPs. This allowed to highlight a crucial role for synchrony in tracking outcome from coma, while for complexity or neural noise in tracking consciousness. Future studies can perform direct comparisons in synchrony and complexity among EEG responses to auditory stimuli, to TMS and resting-state activity.

Last, it still remains unknown the extent to which our present results are driven by the specific clinical settings of our study. All of the included patients were in the acute phase of coma, under sedation and hypothermia. These conditions were chosen as they represent a state where any conscious access to the environment is very unlikely. However, they leave open the question of whether part of our findings might be driven by sedation, or the acute coma state. Future studies could examine similar processes in later states of coma, and/or without sedation.

3.6. Summary

In summary, we investigated synchrony and complexity, or neural noise of electrophysiological responses to auditory stimuli in two groups of coma patients and a group of healthy controls. Neural synchrony, quantified by phase-locking, was significantly higher for survivors compared to non-survivors, but at indistinguishable levels between survivors and controls. Phase-locking was predictive of patients' outcome at three months, with 0.87 positive predictive value for awakening. By contrast, neural complexity and the 1/f slope were not informative of patient outcomes, and had high or low values for coma patients compared to healthy controls. Our results challenge the view that neural synchrony is a marker of conscious processing. Instead, they propose a dual role for synchrony and complexity of neural information in pathological loss of consciousness. On the one hand, preserved neural synchrony may be a necessary condition for the presence or return of consciousness. On the other hand, to support conscious perception, neural complexity needs to find an equilibrium state between extreme high or low values which represent pathological loss of consciousness.

4. Methods and materials

4.1. Experimental design

We included 67 post-cardiac arrest comatose patients (17 women; $M_{age} \pm SEM_{age}$, 61.8 ± 1.8 years) from a patient cohort admitted to the Lausanne University Hospital, from September 2009 to May 2014, as previously described (Rossetti et al., 2014; Tzovara, 2016; Tzovara et al., 2013). The study was approved by the ethics committees of the Lausanne University Hospital, Switzerland. Patients were split in two groups: a pilot group of 39 patients, where we performed exploratory analyses, and a validation group of 28 patients, where we assessed whether findings of the pilot group could generalize to new patients. We additionally included 13 healthy control participants (10 women; $M_{age} \pm SEM_{age}$, 53.7 ± 1.3 years), all of whom reported normal hearing, without a history of neurological or psychiatric disorders.

Patients and controls were presented with pure sinusoidal tones (16-bit stereo, sampled at 44.1kHz) binaurally through earphones. A 10 ms linear amplitude envelope at stimulus onset and offset was applied to avoid clicks. Sounds were presented with a constant interstimulus interval of 700 ms, and consisted of standard and deviant tones (Tzovara et al., 2013). Standard tones had a 1000 Hz pitch and a 100 ms duration. Deviant tones differed from standards in terms of duration (150 ms), pitch (1200 Hz), or interneural time difference (700 μs, left ear leading). Participants were presented with 1500 tones split into three blocks of equal length, each lasting ~7min. For the purpose of the present study, we only considered responses to standard sounds that occurred after another standard sound and before a deviant in duration, and responses to duration deviant sounds, as they have been previously shown to be highly informative of outcome from coma (Tzovara, 2016).

4.2. Patient description

All patients were in an acute coma defined as a Glasgow Coma Scale < 6 (Teasdale and Jennett, 1974) at admission (Oddo and Rossetti, 2014). Following resuscitation from cardiac arrest, patients were treated with mild therapeutic hypothermia (33°C) for 24 h. During this time, they were administered midazolam (0.1mg/kg/h) and fentanyl (1.5μg/kg/h) for sedation and vecuronium (0.1mg/kg boluses) to control shivering.

The decision to withdraw intensive care support included at least 2 of the following criteria: incomplete recovery of brainstem reflexes, early myoclonus, unreactive EEG in normothermia, and bilaterally absent cortical somatosensory evoked potentials (Rossetti et al., 2010). Patients' outcome was evaluated according to the CPC (Jennett and Bond, 1975) using semi-structured phone interviews at three months following cardiac arrest. All patients with a CPC score other than five was classified as survivors ($N_{survivors}$=39; $N_{non-survivors}$=28). No patients were in a coma or vegetative state, indicated by CPC score of four at three months.

4.3. EEG acquisition and preprocessing

EEG (Viasys Neurocare) was recorded from 19 electrodes arranged following the international 10–20 system, sampled at 1024 Hz with an online reference to the Fpz electrode. Impedances were kept below 10 kΩ. For patients, EEG recordings took place in the intensive care unit, at the patients' bedside, during therapeutic hypothermia, less than 36 h after resuscitation from cardiac arrest. Recordings of healthy controls were performed with the same equipment in a hospital room to ensure consistency. Control participants were instructed to close their eyes and listen to the sounds while lying on a reclined chair.

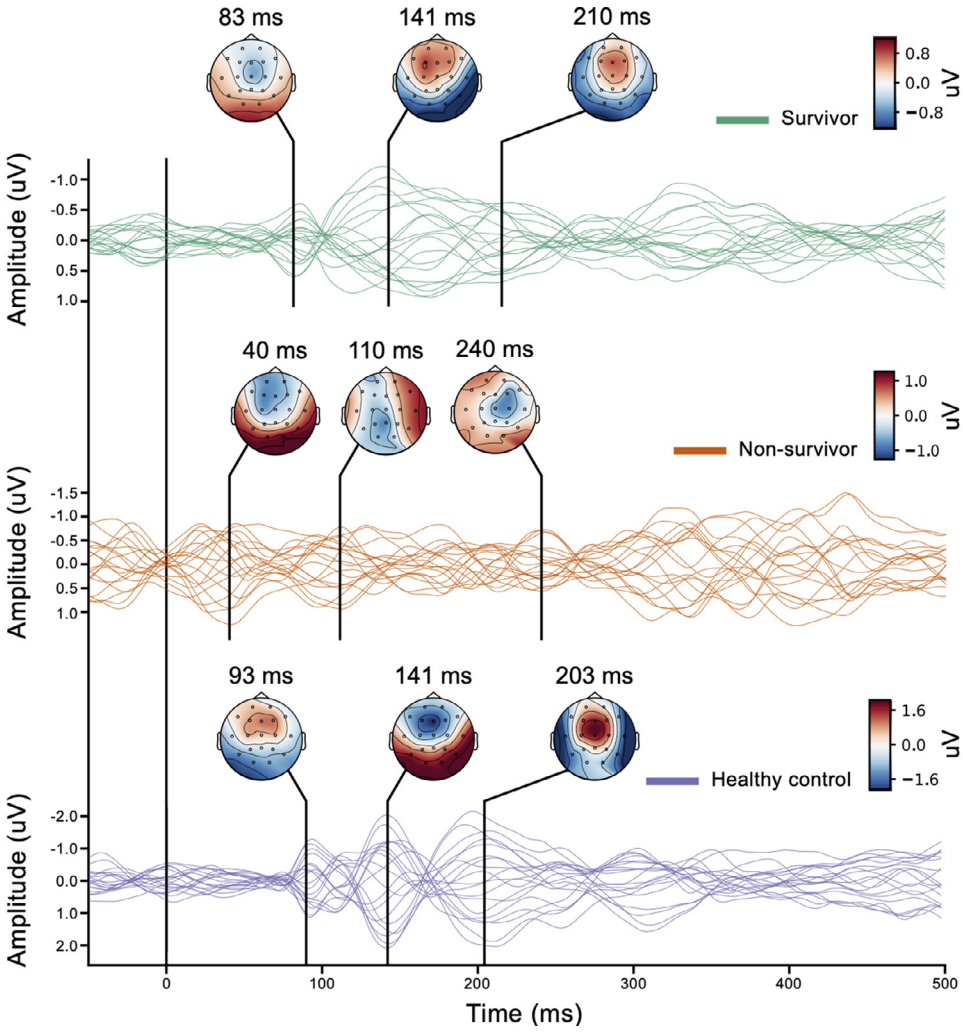

Fig. 7. *Exemplar average ERPs and topographies.* Example responses for one survivor (green), one non-survivor (orange) and one control subject (purple). The time points for plotting topographic maps were selected based on local maxima in global field power, within a 0–250 ms temporal window. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

We extracted epochs from 50 ms before stimulus onset to 500 ms post-stimulus onset (Fig. 7 for exemplar ERPs). An artifact rejection criterion of ±100 μV was applied offline to all electrodes, and noisy electrodes were interpolated using 3D splines (Perrin et al., 1987) (Survivors: M = 0.44; SEM = 0.14; Non-survivors: M = 0.75, SEM = 0.23). Data were also visually inspected for removing any remaining noisy epochs. Data were re-referenced to the common average reference, and band-pass filtered from 0.1 to 40 Hz.

4.4. EEG data analysis

4.4.1. Phase-locking value

The consistency of EEG responses on the scalp was measured through the PLV between electrode pairs. Our choice to focus on the PLV was motivated by previous studies investigating alterations in phase-locking by consciousness (Lee et al., 2019). The reason for choosing PLV over other measures of neural synchrony is that the PLV quantifies phase consistency without being confounded by differences in power (Bastos and Schoffelen, 2016), which may be present between patient groups and patients and controls. The PLV assesses latencies with limited variation between trials (Lachaux et al., 1999), and it is thus suited to investigate synchronization across EEG channels following auditory stimulation. To ensure that our findings are not caused by volume conduction (Bastos and Schoffelen, 2016), we repeated our main contrasts with the ciPLV (Bruña et al., 2018) and TE (Huang et al., 2015; Vicente et al., 2010).

We also calculated the PPC, which is resilient to differences in statistical power between experimental conditions (Vinck et al., 2010) (SI S1.2).

PLV was calculated by band-pass filtering the EEG signal and extracting the phase of the signal. The PLV at a time-point t across trials was then defined as

$$PLV_{i,j}(t) = \frac{1}{N}\left|\sum_{n=1}^{N} e^{i(\varphi_i(t,n)-\varphi_j(t,n))}\right| \quad (1)$$

where t denotes a time-point, n the trial number, N the total number of trials, and $\varphi_i(t,n) - \varphi_j(t,n)$ is the difference in instantaneous phase between signal i and j in trial n at time t. The PLV varies between 0, no phase-locking, and 1, constant phase lag between the two signals.

We calculated the PLV for each time-point across trials for all 171 electrode pairs in the alpha (8–12 Hz) frequency range with the spectral connectivity function of MNE Python (v0.20.7) (Gramfort et al., 2013), using multitapers to band-pass filter EEG signals. The PLV of each time-point in the epoch length was averaged to obtain one PLV for each pair of electrodes. The decision to focus on the alpha band was driven by characteristics of the power spectrum in the current sample (SI: S1.1) and previous studies linking alpha power during therapeutic hypothermia to outcome of post-cardiac arrest comatose patients (Kim et al., 2020; Kustermann et al., 2019; Wiley et al., 2017).

Patient-average **PLV** was calculated as

$$\mathbf{PLV} = \frac{1}{N(N-1)/2}\sum_{i=1}^{N}\sum_{j=i+1}^{N} PLV_{i,j} \quad (2)$$

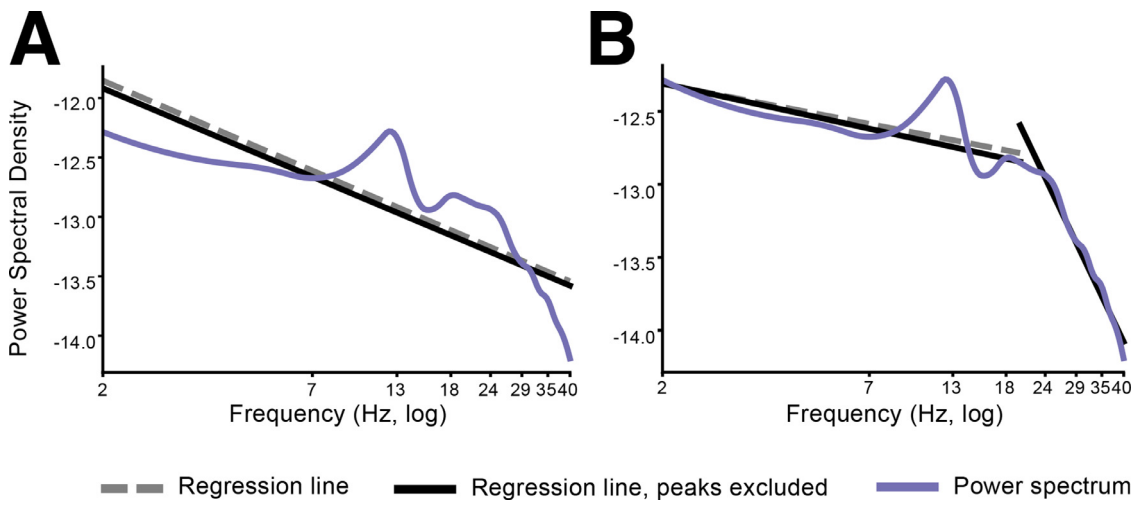

Fig. 8. *Example of least-square fits to the PSD.* Example of least-square fits for one electrode across trials for one healthy control participant, fitted to the original PSD (gray dotted line) and to the PSD after removing oscillatory peaks (black solid line), in double-logarithmic space. **(A)** The regression estimates were fitted to the entire frequency range (2–40 Hz). **(B)** Fit of regression estimates separately for the 2–20 Hz and 20–40 Hz range. The y axis displays normalized power in the log scale.

where N is the total number of electrodes, and i and j are pairs of electrodes.

4.4.2. Lempel–Ziv complexity

LZ complexity (Lempel and Ziv, 1976) reflects the rate of new patterns within a sequence and is commonly used to quantify the complexity of EEG signals (Casali, 2013; Sarasso et al., 2015). Following previous approaches that have applied measures of LZ complexity to EEG signals (Brito et al., 2020; Casali, 2013; Schartner et al., 2015), we calculated the LZ complexity for each electrode using a binary sequence conversion. We first transformed the EEG signal into a binary sequence by estimating the signal's median value per electrode after concatenating the epoched data, and assigning to each time-point the value 0 or 1 depending on whether it was below or above the median. Complexity was then quantified as the number of subsequences found in this binary sequence. Similar to previous studies (Brito et al., 2020; Schartner et al., 2015), we calculated the normalized LZc by dividing the LZ complexity of the original signal by the average LZ complexity of 50 randomly shuffled versions of the original signal to obtain a measure of observed complexity relative to the maximum empirical complexity of the signal (denoted LZc). Additionally, we computed LZc_n, normalizing the LZ complexity trough phase-randomization, by dividing the original LZ complexity with the average LZ complexity of 50 phase-permuted versions of the original EEG signal (denoted LZc_n) (Brito et al. (2020)).

The LZ complexity scores were averaged across electrodes, resulting in one single measure of complexity in the auditory-evoked EEG per participant. This is a standard approach for the field of EEG research, that has been previously used to assess consciousness levels in anesthesia (Casali, 2013; Sarasso et al., 2015; Schartner et al., 2015), sleep (Andrillon et al., 2016; Casali, 2013; Mateos et al., 2017), and patients with disorders of consciousness (Casali, 2013). For comparison, we additionally computed the SVD entropy (SI: S1.6).). Results were similar with both metrics, as SVD was strongly correlated with both LZc (Survivors: $r = 0.82$, $p < 0.001$; Non-survivors: $r = 0.86$, $p < 0.001$) and LZc_n (Survivors: $r = 0.65$, $p < 0.001$; Non-survivors: $r = 0.68$, $p < 0.001$), similar as previous studies have suggested (Mateos et al., 2017). As LZ complexity and SVD entropy captured similar patterns in the EEG data, and have similar reliability (Gudmundsson et al., 2007), we focused on the LZ complexity, as this metric is commonly used in the field of consciousness research (Casali, 2013; Sarasso et al., 2015; Schartner et al., 2015).

4.4.3. 1/f Slope

The non-oscillatory background decay of the power spectrum has an inverse linear relationship between $log(power)$ and $log(frequency)$, with a $1/f$-like shape (He et al., 2010; Motokawa, 1949; Pritchard, 1992). Because the PSD background decay follows an inverse power law, where $PSD(f) = 1/f^n$ (Pritchard, 1992), the non-oscillatory PSD background decay can be defined as the slope of a linear regression of the PSD on a logarithmic scale (Colombo et al., 2019). The 1/f slope is then defined as the exponent of this linear regression, whose steepness reflects the background EEG power decay.

To compute the background decay, we estimated the PSD per electrode and patient as described in the Supplementary Materials (See SI: S1.1), and computed the logarithm of both the power and the frequency. We excluded oscillatory peaks and thus obtained the background decay by implementing a similar procedure to that of previous studies (Colombo et al., 2019; Lendner et al., 2020). This consisted of fitting a least-square line to power spectrum in logarithmic space. Then, to obtain the 1/f slope of the PSD background, we identified and excluded points in the power spectrum where power was high and not decaying, if their residual was larger than one median absolute deviation of the residual distribution for that electrode. Subsequently, we fitted a new least-square line to the remaining frequency bins, expected to give a slope corresponding to the spectral exponent of the PSD background (Fig. 8). To obtain a single measure per participant, we averaged each electrode's 1/f slope.

We used this method to obtain the 1/f slope in the 2–40 Hz range as well as in the 2–20 and 20–40 Hz range, following other reports showing a change in the PSD decay around 20 Hz (Colombo et al., 2019).

4.5. Prediction of outcome from coma

To link the metrics of electrophysiological dynamics with patients' outcome, we split the patients in two groups: 39 patients formed a pilot group ($N_{survivors}$=22; $N_{non-survivors}$=17), and the remaining patients a validation group ($N_{survivors}$=17; $N_{non-survivors}$=11). We used the pilot group to perform exploratory analyses linking patients' outcome to the metrics of this study (PLV, complexity, 1/f slope). The validation group was then used to assess whether findings on the pilot group can generalize to new patients.

For the PLV, the phase-locking between some electrode pairs may be more informative of patients' outcome than between others. We therefore identified which electrode pairs had a significantly different phase-

locking between survivors vs. non-survivors in the pilot group of patients. We then calculated the average PLV over these electrode pairs for each patient or control. The average of this subset of electrodes was used to predict patient outcomes.

For all metrics, we identified the optimal threshold splitting survivors and non-survivors in the pilot group by identifying the threshold that led to the least miss-classified patients, and that provided the highest PPV for awakening. To assess the predictive power of the identified threshold in outcome prediction, we used it to predict patient outcomes in the validation group, which had not been included in any of the previous steps.

4.5.1. Outcome prediction validation

To assess the significance of the outcome prediction results, we permuted the patient labels in the pilot group 100 times (SI: S1.7) For each permutation, a new threshold was identified by maximizing prediction of survival in the pilot group of patients. This threshold was then used to estimate outcome prediction in the validation group, keeping the original outcome of the patients. The true outcome prediction was compared with the distribution of outcomes derived from permuted data based on a Wilcoxon signed-rank test ($p < 0.05$), in a similar approach as previous studies (Kustermann et al., 2020).

4.6. Statistical analysis

As the first step in identifying markers of patients' outcome, we tested for differences in spectral power, PLV, LZ complexity, and 1/f slope between survivors and non-survivors of the pilot group. To this aim, we used two-sided independent samples t-tests when assumptions for normality were fulfilled (spectral power and PLV), and Mann-Whitney U tests when they were not (LZc, LZc_n, 1/f slope). Normality was tested based on skew and kurtosis, using the test for normality implemented in SciPy (Virtanen et al., 2020). We employed False Discovery Rate (FDR) correction using the Benjamini Hochberg procedure to control for multiple comparisons across frequencies (in the power spectra), or across electrode pairs (in the PLV).

As a follow up analysis, we tested for effects of group (survivor, non-survivor, and control). For the PLV, we performed a one-way anova, with main factor of group. For LZ complexity measures and 1/f slope we used Kruskal-Wallis H-tests, as a non-parametric version of one-way ANOVAs, as the distribution of values on these two metrics did not meet the assumption of normality. In a post-hoc analysis of these measures, we compared individual pairs of groups with unpaired t-tests (PLV), or the Mann-Whitney *U* test (LZc, LZc_n, 1/f slope). For the 1/f slope we corrected for multiple comparisons across the three different frequency bands.

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Data and materials availability

Because of the sensitive nature of the clinical data, data and materials can be made available from the corresponding authors upon reasonable request.

Code availability

https://github.com/slerknes/synchrony-and-complexity-in-coma.

Declaration of Competing Interest

The authors declare that they have no competing interests.

Supplementary material

Supplementary material associated with this article can be found, in the online version, at 10.1016/j.neuroimage.2021.118638

Credit authorship contribution statement

Sigurd L. Alnes: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft, Writing – review & editing. **Marzia De Lucia:** Data curation, Funding acquisition, Investigation, Resources, Writing – review & editing. **Andrea O. Rossetti:** Data curation, Funding acquisition, Investigation, Resources, Writing – review & editing. **Athina Tzovara:** Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Resources, Supervision, Writing – original draft, Writing – review & editing.

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