Conscious processing of narrative stimuli synchronizes heart rate between individuals

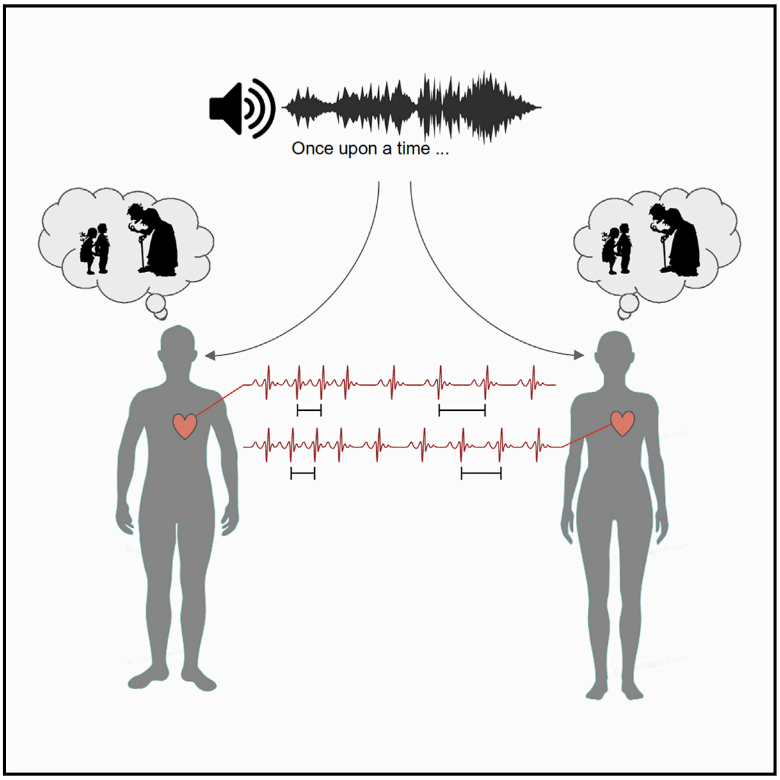
Pauline Pérez, Jens Madsen, Leah Banellis, Başak Türker, Federico Raimondo, Vincent Perlbarg, Melanie Valente, Marie-Cécile Niérat, Louis Puybasset, Lionel Naccache, et al.

Cell Reports

Article

Conscious processing of narrative stimuli synchronizes heart rate between individuals

Graphical abstract



Highlights

- Narrative stimuli can synchronize fluctuations of heart rate between individuals
- This interpersonal synchronization is modulated by attention and predicts memory
- These effects on heart rate cannot be explained by modulation of respiratory patterns
- Synchrony is lower in patients with disorders of consciousness

Authors

Pauline Pérez, Jens Madsen, Leah Banellis, ..., Damian Cruse, Lucas C. Parra, Jacobo D. Sitt

Correspondence

parra@ccny.cuny.edu (L.C.P.), jacobo.sitt@inserm.fr (J.D.S.)

In brief

Stories affect our hearts and bind us together. Pérez et al. show that attention to narratives can synchronize fluctuations of heart rate between individuals. Heart synchronization predicts memory and cannot be explained by respiration. Finally, synchrony is lower in patients with disorders of consciousness and might inform prognosis.

Pérez et al., 2021, Cell Reports *36*, 109692
September 14, 2021
https://doi.org/10.1016/j.celrep.2021.109692

CellPress

Cell Reports

CellPress OPEN ACCESS

Article

Conscious processing of narrative stimuli synchronizes heart rate between individuals

Pauline Pérez,[1,2,3,14] Jens Madsen,[4,14] Leah Banellis,[5,6] Başak Türker,[1,2,3] Federico Raimondo,[1] Vincent Perlbarg,[7] Melanie Valente,[1] Marie-Cécile Niérat,[12] Louis Puybasset,[8,9] Lionel Naccache,[1,2,3,10,11] Thomas Similowski,[12,13] Damian Cruse,[5,6] Lucas C. Parra,[4,15,16,*] and Jacobo D. Sitt[1,2,3,15,16,17,*]

[1]Paris Brain Institute, ICM, 75013 Paris, France
[2]Inserm U 1127, 75013 Paris, France
[3]CNRS UMR 7225, 75013 Paris, France
[4]Department of Biomedical Engineering, City College of New York, New York, NY, USA
[5]School of Psychology, University of Birmingham, Birmingham B15 2TT, England
[6]Centre for Human Brain Health, University of Birmingham, Birmingham B15 2TT, England
[7]Bioinformatics and Biostatistics Core Facility, iCONICS, IHU-A-ICM, Institut du Cerveau et de la Moelle épinière, Paris, France
[8]Department of Anesthesia and Intensive Care, Pitié-Salpetrière Hospital, Paris, France
[9]Sorbonne Université, CNRS, INSERM, Laboratoire d'Imagerie Biomédicale, LIB, Paris, France
[10]Department of Neurophysiology, Hôpital de la Pitie-Salpetriere, AP-HP, 75013 Paris, France
[11]Faculté de Médecine Pitié-Salpêtrière, Sorbonne Université, 75013 Paris, France
[12]Sorbonne Université, INSERM, UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique, 75005 Paris, France
[13]AP-HP, Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Service de Pneumologie, Médecine Intensive et Réanimation (Département R3S), 75013 Paris, France
[14]These authors contributed equally
[15]These authors contributed equally
[16]Senior author
[17]Lead contact
*Correspondence: parra@ccny.cuny.edu (L.C.P.), jacobo.sitt@inserm.fr (J.D.S.)
https://doi.org/10.1016/j.celrep.2021.109692

SUMMARY

Heart rate has natural fluctuations that are typically ascribed to autonomic function. Recent evidence suggests that conscious processing can affect the timing of the heartbeat. We hypothesized that heart rate is modulated by conscious processing and therefore dependent on attentional focus. To test this, we leverage the observation that neural processes synchronize between subjects by presenting an identical narrative stimulus. As predicted, we find significant inter-subject correlation of heart rate (ISC-HR) when subjects are presented with an auditory or audiovisual narrative. Consistent with our hypothesis, we find that ISC-HR is reduced when subjects are distracted from the narrative, and higher ISC-HR predicts better recall of the narrative. Finally, patients with disorders of consciousness have lower ISC-HR, as compared to healthy individuals. We conclude that heart rate fluctuations are partially driven by conscious processing, depend on attentional state, and may represent a simple metric to assess conscious state in unresponsive patients.

INTRODUCTION

In healthy individuals, heart rate fluctuates with breathing and changes in parasympathetic and sympathetic tone (Levy and Martin, 1989; Cooke et al., 1998; Palma and Benarroch, 2014). Physical activity naturally increases heart rate, but just thinking about physical activity may also increase heart rate (Bernardi et al., 1996). Similarly, mental exercises such as meditation can reduce heart rate (Kyeong et al., 2017). The effect of cognition on heart rate is perhaps even more direct than these traditional accounts (Park and Tallon-Baudry, 2014; Park et al., 2014). We also know that suspense and surprise can transiently increase heart rate (Ekman et al., 1983). Most likely these immediate effects of the mind on the heart subserve the purpose of preparing the body for imminent action (McCorry, 2007). Despite this evidence, the role of (un)conscious perception (Dehaene and Changeux, 2011) on heart rate is less clear. It is well established that the brain can unconsciously detect novelty in the stimulus, as demonstrated with event-related potential studies (e.g., MMN [Bekinschtein et al., 2009; Morlet and Fischer, 2014; Schlossmacher et al., 2020] and N400 [Cruse et al., 2014; Rohaut et al., 2015]). Recent evidence shows that the timing of an individual heartbeat may be affected by the perception of an unexpected sound, but only when consciously perceived (Raimondo et al., 2017). We hypothesized that conscious processing of perceptual information will affect heart rate. Therefore, we expected that fluctuations in heart rate will depend on attention to the stimulus and will be

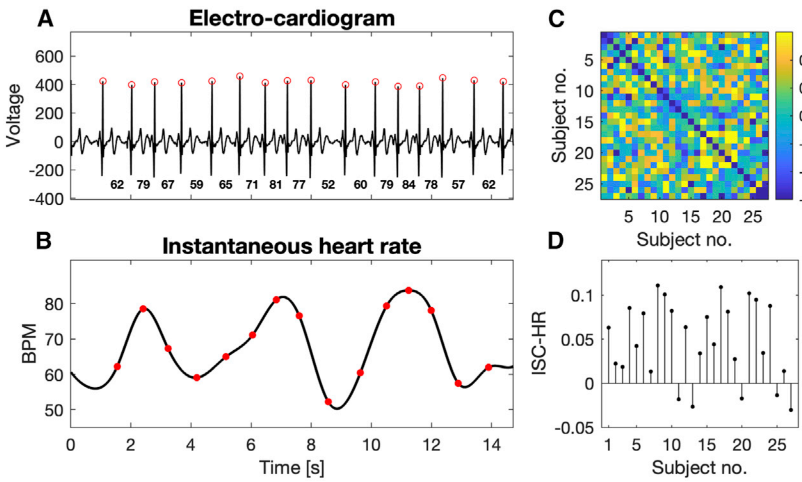


Figure 1. Inter-subject correlation of heart rate

(A) Electro-cardiogram with peak of the R-wave detected (red o).

(B) The inverse of the interval between two R-waves defines the instantaneous heart rate (red o). This is interpolated (black) to convert heart rate into a signal with a uniform sampling rate across subjects.

(C) Pearson's correlation coefficient of this instantaneous heart rate between pairs of subjects.

(D) Inter-subject correlation of heart rate (ISC-HR) is computed for each individual as the mean across a row of this correlation matrix. Example in this figure is taken from the first audiobook segment of dataset 1.

predictive of memory performance, a known factor (Mack and Rock, 1998) and a correlate of conscious perception (Trübutschek et al., 2019).

To test these predictions, we leveraged the fact that natural narrative stimuli guide cognitive processes resulting in reliable neural responses. This was first observed by measuring hemodynamic brain activity during movies: when humans watch the same movie, they have similar fluctuations in brain blood oxygenation (Hasson et al., 2004). Specifically, the temporal fluctuations of the signal measured with functional magnetic resonance (fMRI) are correlated between subjects. Significant inter-subject correlation of brain activity has now been observed with other neuroimaging modalities, including electroencephalogram (EEG), magnetoencephalography (MEG), and functional near-infrared spectroscopy (fNIRS) (Dmochowski et al., 2014; Liu et al., 2017; Lankinen et al., 2014). Thus, neurophysiological fluctuations appear to synchronize on a wide range of timescales, from milliseconds to several minutes. This phenomenon is also not constrained to movies but has been observed for speech, music, or during driving (Bernardi et al., 2014; Pérez et al., 2017; Madsen et al., 2019). There are even significant correlations in the spatial patterns of fMRI activity between speakers and listeners (Chen et al., 2017) or the time courses of EEG signals of two individuals engaged in a conversation (Zhang et al., 2014). This similarity of neural activity in response to narrative stimuli suggests that these stimuli elicit similar perceptual and cognitive processes in different subjects.

Consistent with this, inter-subject correlation crucially depends on the cognitive state of the participant. Subjects that are not attentive or do not follow the narrative show significantly reduced inter-subject correlation, both in EEG and fMRI (Ki et al., 2016; Cohen et al., 2018; Regev et al., 2019). A drop in inter-subject correlation is also observed in patients with disorders of consciousness relative to healthy controls (Naci et al., 2014, 2016; Iotzov et al., 2017). Indeed, a cohesive narrative is crucially important to elicit synchronized brain activity in fMRI, in particular at long timescales (Honey et al., 2012). It comes as no surprise then that inter-subject correlation has been found to be predictive of a variety of behavioral outcomes, such as audience retention, memory of content, efficacy of advertising, efficacy of communication and political speeches, and more (Schmälzle et al., 2013, 2015; Dmochowski et al., 2014; Hasson et al., 2015; Chen et al., 2017; Cohen et al., 2018).

There are many studies reporting a correlation also forphysiological signals across subjects (Palumbo et al., 2017). Generally, this has been linked to physical or social interaction (Konvalinka et al., 2011; Ardizzi et al., 2020; Gordon et al., 2020), or at the very least, a co-presence at the same place and time (Golland et al., 2015). However, consistent with our hypothesis, the simultaneous experience is not crucial for synchronization. A few recent studies report a correlation of heart rate fluctuations across subjects watching the same movie at different times and ascribe this to shared emotions elicited by the film (Golland et al., 2014; Steiger et al., 2019).

We note that our analysis and prediction focuses on time-precise variation of heart rate (HR), which we capture in a synchronization of HR fluctuations across subjects. This differs significantly from the extensive reports of cognitive effects on the magnitude of HR variability (Thayer et al., 2009) and their relationship to neural activity during narrative stimuli (Lane et al., 2009; Wallentin et al., 2011; Chang et al., 2013).

Our hypothesis predicted that this synchronization phenomenon will occur not just for the film, but more generally for narrative stimuli, that inter-subject correlation of heart rate will be modulated by attention, that it will correlate with cognitive performance, and more dramatically, that it will be reduced in patients with disorders of consciousness. We confirm these predictions in a series of four experiments and conclude that heart rate synchronization has the potential to become a marker of cognitive state in a clinical setting.

RESULTS

In all four experiments, we presented narrative stimuli to each subject while recording their electrocardiogram (EKG) (Figure 1A), and in experiments 3 and 4, we also recorded respiratory activity. Recordings were aligned in time between subjects, and instantaneous HR was estimated as the inverse of the RR intervals (i.e., the time elapsed between two succesive R-waves) (Figure 1B). Mean and standard deviation (SD) of these instantaneous

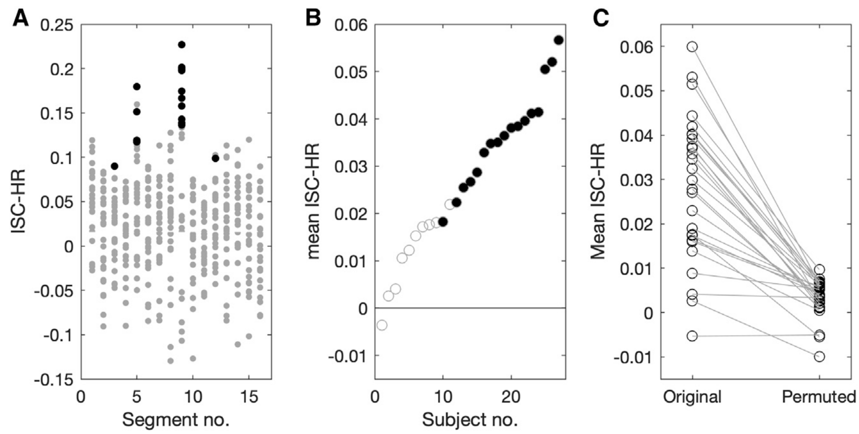


Figure 2. ISC-HR resolved in time and by subject

In experiment 1, subjects listened to segments of audio narratives of 60-s each (n = 16).

(A) ISC-HR is computed for each subject (n = 27) and each segment.

(B) For each of the 27 subjects ISC is averaged over the 16 segments. Subjects are ordered by their ISC values. Black points (A and B) indicate statistically significant ISC values. Gray points are not statistically significant. Statistical significance is determined using circular shuffle statistics (10,000 shuffles and corrected for multiple comparisons with FDR of 0.01). Specifically, the heart rate signal of each subject is randomly shifted in time.

(C) As additional control here ISC is compared to the ISC obtained when story segments are swapped between subjects at random.

measures provide HR and HR variability (HRV) for each subject. The instantaneous HR signals are upsampled to a common sampling rate and correlated between all pairs of subjects (Figure 1C). Inter-subject correlation of HR (ISC-HR) is then defined for each subject as the average Pearson's correlation with all other subjects (Figure 1D).

Auditory narratives synchronize listeners' heart rate fluctuations

The objective of the first experiment was to determine whether a common auditory narrative elicits similar heart rate fluctuations in healthy volunteers (experiment 1). Subjects were presented with 1-min segments of an audiobook of Jules Verne's "20,000 Leagues Under the Sea." First, we tested whether there was significant inter-subject correlation of the instantaneous HR. To this end, we compared the ISC-HR values to values computed on signals randomly shifted in time within-subjects (see STAR Methods). When this analysis is performed on individual 1-min segments, only a few subjects show significant non-zero ISC-HR (Figure 2A, black dots; false discovery rate [FDR] at 0.05). When averaging ISC-HR values over the 16 min, 17 of the 27 subjects show statistically significant HR correlation (Figure 2B; FDR at 0.05). No significant negative correlations were found. As an additional control, we randomly shuffled the 1-min story segments between subjects breaking the narrative synchrony across subjects. As expected, we observed a significant drop in ISC values between the original and permuted conditions (Figure 2C; paired t test [26] = 9.11, $p = 2 \times 10^{-9}$). We conclude that the narrative stimulus induces similar HR fluctuations across subjects. ISC-HR therefore captures how strongly the stimulus drives the fluctuations of HR in each subject.

Results on average HR and HRV and their potential relation to ISC-HR are generally unremarkable for these data and are discussed in the STAR Methods (Figure S1).

Attention modulates synchronization of HR fluctuations during audiovisual narratives

We demonstrated above that an auditory narrative can synchronize HR fluctuations across subjects. In the second experiment, we aimed to determine if this synchronization was modulated by attention to the stimulus (experiment 2). We used short and engaging instructional videos of 3- to 5-min duration, similar to our previous work (Cohen et al., 2018). Each subject viewed 5 videos in sequence normally. Then they viewed the same videos a second time, but with the instruction to count backward silently in their mind in steps of 7. This secondary task aims to distract subjects from viewing the video (Ki et al., 2016; Cohen et al., 2018).

We find that ISC-HR drops in the distracted condition relative to the normal attentive state (Figure 3A). An ANOVA shows a strong fixed effect of attention ($F[1,104] = 70.64$, $p = 6.93e{-}09$) and a fixed effect of the video ($F[4,104] = 10.48$, $p = 3.59e{-}07$) as well as a random subject effect ($F[26,104] = 1.54$, $p = 8.62e{-}02$). The effect of attention is significant for each video individually (follow-up pairwise t test, all $p < 0.05$), and when averaging over all 5 videos with a total duration of 22:33 min, we see a numerical drop in ISC-HR with distraction in all but one of the 27 subjects (Figure 3B).

Attention modulates HRV but this is not the driving factor in modulation of ISC

For experiment 2, in addition to ISC, we also analyzed heart rate variability (HRV), defined here as the SD of instantaneous HR (Figure S2B). We see an increase in HRV when subjects are distracted. An ANOVA shows a fixed effect of attention ($F[1,92] = 31.48$, $p = 1.04e{-}05$), random effect of subject ($F[23,92] = 12.50$, $p = 1.39e{-}09$), but we see no significant video effect ($F[4,92] = 0.71$, $p = 5.89e{-}01$). Perhaps the increase in HRV in the distracted condition could explain the drop in ISC-HR. If this was the case, we would expect that HRV correlates negatively with ISC-HR because, by definition, the two are inversely related. However, the opposite seems to be the case: subjects with higher HRV also have higher ISC-HR (Figure S2D). Therefore, it appears that the modulation of HRV and ISC-HR are independent phenomena. The effects on mean HR were generally unremarkable (Figures S2A and S2C).

Synchronization of HR fluctuations is modulated on a the timescale of 5–10 s

It is well established that during waking rest, HR fluctuates at various timescales (Baharav et al., 1995). This is reproduced in the present context of video presentation (experiment 2) by

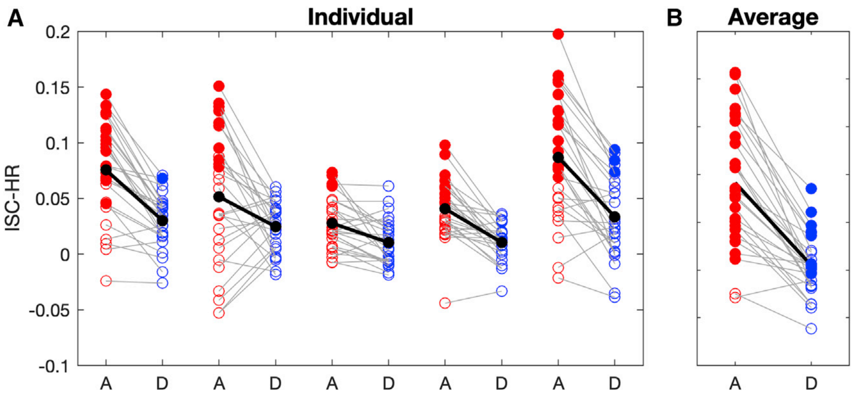


Figure 3. Inter-subject correlation of the instantaneous heart rate is modulated by attention

In experiment 2, 27 subjects watched 5 educational videos of 3- to 5-min duration each. Here, ISC is measured against the attentive condition (i.e., both attentive and distracted subjects are correlated against the HR collected during the attentive condition). Filled points indicate individually statistically significant ISC-HR (FDR <0.01).

(A) Subjects watched the same videos twice, either in an attentive (A, red) or distracted (D, blue) condition. ISC was systematically higher in the attentive condition for the five videos. Gray lines indicate individual subjects and the black lines the group average.

(B) Same results when average across the five videos.

computing HRV after band-pass filtering the instantaneous HR in different frequency bands (Figure 4A). To determine which timescale dominates ISC and its modulation with attention, we computed ISC similarly resolved by frequency band (Figure 4B). We find that ISC and its modulation with attention are dominant in the low-frequency range from 0.10 Hz to 0.15 Hz ($p < 0.0029$ as a single cluster). It is worth noting that ISC was not modulated by attention in the high-frequency peak (around 0.3 Hz), which corresponds to the dominant frequency of breathing (Figure S5A).

Attention modulates synchronization of HR fluctuations during audio-only narratives but does not synchronize breathing

Given the dependence of HR fluctuations on attention, we expected that HR would be predictive of cognitive processing of the narrative. In experiment 3, we recorded HR during the presentation of auditory narratives. Afterward, we asked subjects to recall factual information presented in the story (e.g., "What were the names of the two main characters?"). Subjects listened to four auditory narratives, in either an attentive or distracted condition. This time the narratives were children's stories of 8- to 11-min duration, and the secondary task consisted of counting target tones that were inserted in the audio asynchronously across subjects. To rule out order effects, we now divided the participants in two groups. In group 1 ($n = 9$), subjects listened to stories 1 and 2 in the attentive condition and stories 3 and 4 in the distracted condition. In group 2 ($n = 12$), subjects listened to the same stories with the attention condition reversed.

We find again that ISC-HR drops significantly when subjects are distracted (Figure 5A, paired t test $t[20] = 7.4$, $p = 5e{-7}$). Similar to experiment 2 with video, 13 of the 21 subjects show a statistically significant correlation of HR in the attentive condition and none in the distracted condition. As expected, subjects performed significantly better in recalling elements of the story in the attentive condition as compared to the distracted condition (Figure S3; Wilcoxon signed-rank test, $z = 4.03$, $p = 5.7e{-5}$).

Our hypothesis postulates that ISC-HR is the result of similar conscious processing of the narrative stimulus, thus, we predicted that subjects with higher ISC-HR will be better at remembering elements of the stories. Indeed, we find that ISC correlates with memory recall performance across conditions (Figure 5B; $r[40] = 0.729$, $p = 3.1e{-9}$; Spearman's correlation is used here due to the bounded nature of the percent measure). More importantly, even within the normally attentive condition with a normal fluctuation of HR, we find that ISC-HR is predictive of memory performance ($r[19] = 0.56$, $p = 8.6\ e{-3}$). In the distracted conditions, there was no correlation with memory performance ($r[19] = -0.23$, $p = 0.30$, Bayes factor BF01 = 3.57) possibly because ISC-HR was not statistically significant for any of the subjects. Overall, we conclude that ISC-HR is indicative of conscious processing of the narrative.

Inter-subject correlation of heart rate is not driven by synchronous breathing

It is well established that HR fluctuations are driven, in part, by breathing (Angelone and Coulter, 1964). This phenomenon is known as respiratory sinus arrhythmia and can affect a range of frequencies (Hirsch and Bishop, 1981; Stanley et al., 1996). It is possible that the attentional modulation in this frequency band is caused by synchronization of breathing between subjects. In experiment 3, we collected respiratory movement concurrently with the EKG and measured inter-subject correlation of breathing. First, we tested if the power spectrum of the raw respiratory signal changes with attention and found small increases in power at "high" frequencies (above 0.3 Hz) (Figure S5A). Second, we validated the relationship between respiratory and cardiac activity by computing the correlation between respiratory signal and instantaneous HR. In the attentive condition, 12 of 21 subjects showed a significant cardio-respiratory coupling, and in the distracted condition, 15 of 21 subjects showed a significant cardio-respiratory coupling (Figure S5B). In addition, we found a non-significant reduction in breathing-HR correlation in the distracted versus the attentive condition (Figure S5B; $t[20] = 2.0$, $p = 0.18$ [FDR corrected], BF10 = 1.2). Third, we tested for significant ISC in the raw breathing signal and several of its features, specifically, the instantaneous respiratory frequency and amplitude computed separately for inspiration and expiration (using the breathmetrics toolbox) (Noto et al., 2018). We did not find a significant ISC of the raw breathing signal in any of the subjects, nor was there any effect of attention when comparing across all subjects (Figure S5C; (paired t test, $t(20) = -0.8$, $p = 0.75$ [FDR corrected], BF01 = 3.21). Similarly,

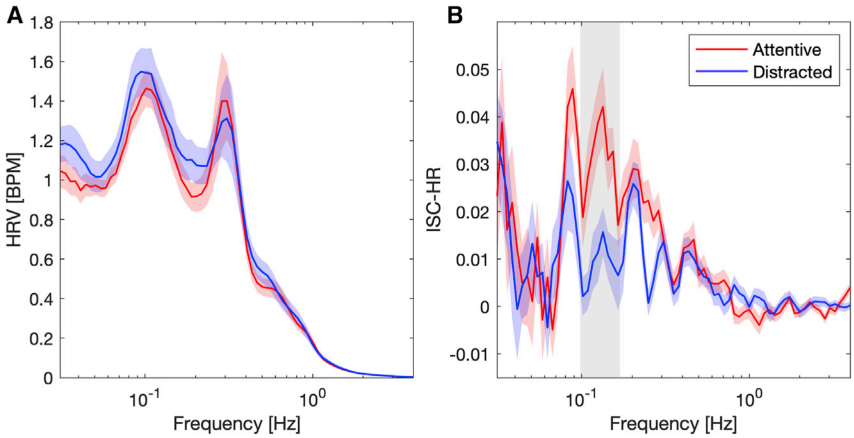


Figure 4. Spectrum of instantaneous HR and ISC-HR and its modulation with attention

For experiment 2, instantaneous HR was band-pass filtered with center frequency on a logarithmic scale and a bandwidth of 0.2 of the center frequency.

(A) HRV is computed here as the root-mean-square of the band-passed instantaneous HR averaged over the 5 videos (~15 min total).

(B) ISC-HR is computed as before, but now on the band-passed instantaneous HR and averaged over the 5 videos. In both panels, significant differences between attending and distracted conditions are established in each band with a paired t test over the 27 subjects (gray-shaded area; multiple comparisons corrected with one-dimensional cluster statistics, $p < 0.05$). Colored-shaded areas indicate SEM.

none of the respiration features showed significant ISC, or a drop in ISC, for the distracted conditions (Figures S5C–S5G). In other words, the auditory narratives did not reliably entrain the subjects breathing nor was this modulated by attention. On the flipside, although BF analysis provides some evidence for a lack of synchronized breathing, the evidence is only moderate (in all instances 1 < BF < 4 in favor of this null hypothesis) (Figures S5B–S5G).

Finally, to determine if delayed influences of respiration could explain the results obtained from HR, for each subject and condition, we subtracted from the HR signals any instantaneous or time-delayed linear correlation of the respiratory signal and recomputed the ISC-HR. We obtained similar modulation of ISC with attention (Figure S5H; t test: $t[20] = 5.57$, $p = 1.9e{-}05$, BF = 1,222).

In conclusion, although we do not have strong evidence against a synchronization of breathing, these results do suggest that the effect of cognition on synchronizing HR cannot be explained in this study by the synchronization of breathing.

Synchronization of heart rate fluctuations is disrupted in patients with disorder of consciousness

Given the dependence on attention and conscious processing of these synchronized HR fluctuations, we predicted that patients with disorders of consciousness (DOC) will have diminished HR synchronization when presented with an auditory narrative. We recorded EKG in 19 DOC patients, in addition to 24 healthy controls (experiment 4). The patients were hospitalized to determine their state of consciousness and neurological prognosis. Patients were behaviorally assessed using the standard Coma Recovery Scale-revised (Giacino et al., 2004). State of consciousness was determined using the currently accepted categorization (Bruno et al., 2011), patients were classified either in (1) coma, (2) vegetative state/unresponsive wakefulness syndrome (UWS), (3) minimally conscious state minus (MCS−), (4) minimally conscious state plus (MCS+), or (5) exit minimally conscious state (EMCS) (see Table S3 for a detailed description of the patients). Patients and healthy subjects listened through headphones to a children's story of 10-min duration. Using the data from healthy subjects, we first replicated the results of experiment 3 showing that ISC computed for HR is systematically larger than the ISC of any of the respiratory features tested (Figure S6). We then computed ISC-HR by correlating HR with that of healthy controls. As expected, ISC-HR values were lower in patients (Figure 6A; t test: $t[41] = 3.14$, $p = 0.003$, BF10 = 12.3). Within patients, no significant correlation was found between ISC-HR and state-of-consciousness (Figure 6A; Spearman's correlation, $R[17] = -0.28$, $p = 0.24$, BF01 = 4.10) or between ISC-HR and the Coma Recovery Scale-Revised (CRS-R) (Giacino et al., 2004) (Figure 6B; Spearman's correlation, $R[17] = -0.3$, $p = 0.22$, BF01 = 3.39). Reduced HRV is sometimes found in traumatic brain injury patients (Riganello et al., 2012). We therefore analyzed HRV to verify that the drop in ISC-HR is not a noise-floor effect (i.e., if HRV drops in patients, it may be difficult to measure inter-subject correlation above random fluctuations) (Figure S7B). Contrary to what was expected, we found higher HRV in the DOC patients compared to healthy controls ($t[41] = 2.34$, $p = 0.02$, BF10 = 2.53), ruling out a noise-floor effect. We also found higher mean HR in DOC patients compared to healthy controls (Figure S7A; $t[41] = 4.7$, $p = 2.9e{-}05$, BF = 639). However, given the previous lack of correlation between ISC and mean HR, we do not believe this contributed to the decrease of ISC-HR in patients.

When measured individually, only 2 of 19 patients showed statistically significant ISC-HR (FDR corrected $p < 0.05$) (Figure 6, purple filled circles). For these two patients, outcomes at the 6-month follow-up were mixed; one patient fully regained consciousness whereas for the other, life-sustaining therapies were withdrawn before the follow-up assessment. Among the remaining 17 patients, only one additional patient recovered consciousness, although in a completely aphasic condition. These results suggest that the patients' ISC-HR might carry prognostic information with a specific emphasis on conscious verbal processing. To test this hypothesis, we first correlated the patients' ISC-HR to the CRS-R improvement after 6 months of the initial assessment. We found a positive correlation between ISC-HR and CRS-R improvement, although not statistically significant (Figure 6C; Spearman's correlation, $R[14] = 0.43$, $p = 0.097$, BF10 = 0.57, second assessment was available only for 16 patients). A limitation of behavioral assessment of patients is that

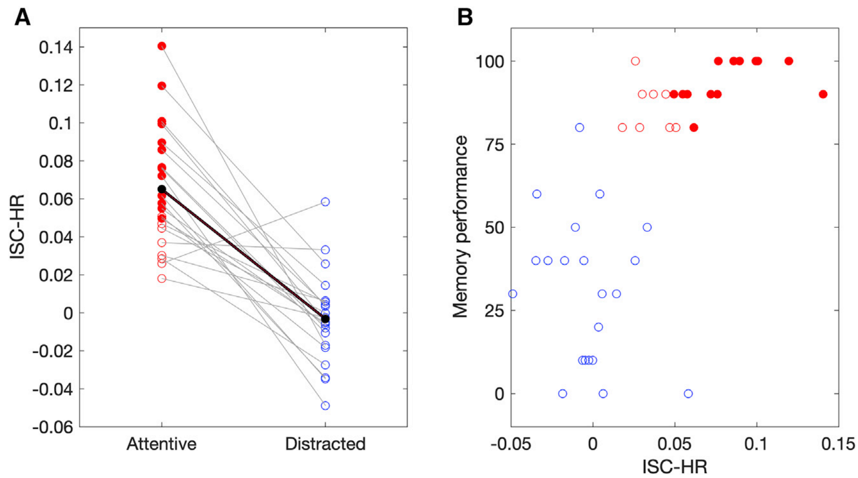


Figure 5. Inter-subject correlation is higher when subjects were attentive to the auditory narrative and this correlation indexes the subjects' memory performance

In experiment 3, subjects listened to four recordings of children's stories 8–10 min in duration. Subjects were instructed to either attend to a story normally (attentive, red), or to count backward when they heard a target sound inserted in the audio (distracted, blue). Again, ISC is measured against the attentive condition (i.e., both attentive and distracted subjects are correlated against the HR collected during the attentive condition). Filled points indicate individually statistically significant ISC-HR (FDR <0.01).

(A) ISC-HR for each subject (n = 21) averaged over four stories.

(B) Memory performance measured as percent of correct answers to free recall questions about the content of the stories. Filled and empty circles indicate significant and non-significant ISC-HR, respectively ($p < 0.05$ shuffle statistics).

it does not detect covert awareness (Owen et al., 2006; Schiff, 2015), a condition that can occur in up to 15% of the UWS patients (Kondziella et al., 2016). Therefore, we also correlated the patients' ISC-HR to an anatomical measure of brain integrity-whole-brain white matter fractional anisotropy. This fractional anisotropy (FA) index has been linked to neurological recovery in DOC patients (Velly et al., 2018). We found a significant correlation between ISC-HR and the FA index (Figure 6D; Spearman's correlation, R[9] = 0.73, p = 0.01, BF10 = 5.52; FA index was available only for 11 patients).

DISCUSSION

The hypothesis that motivated this set of experiments was that conscious processing of information modulates instantaneous heart rate. This fluctuating heart rate will synchronize across subjects when presented with narrative stimuli that are processed similarly. We tested the predictions resulting from this hypothesis in a series of four experiments. In the first experiment with healthy volunteers, we confirmed that heart rate fluctuations correlate between subjects for auditory narratives. In the second and third experiments, we confirm that distracting the participants with a secondary task reduced this correlation for video and audio narratives alike. Importantly, we confirm the prediction that synchronization of HR fluctuations is predictive of memory performance. We also determined that HR synchronization is likely not driven by synchronous breathing across subjects for the present audio narratives or educational videos. Finally, in the fourth experiment, we presented an auditory narrative to patients with disorders of consciousness and found that their heart rate fluctuations do not correlate with that of healthy subjects. In total, we found that natural stimuli induce small but highly reliable correlations of HR, which are detectable in individual subjects and readily reproduced across four different experiments. We found a robust link between this HR synchronization and conscious processing of the audiovisual stimuli. To establish the causal direction of this link, future work will require simultaneous neural recordings and prospective interventions.

There is extensive literature demonstrating that physiological signals such as heart rate, respiration, and skin conductivity can synchronize between individuals (Palumbo et al., 2017). This literature emphasizes physical interaction and social relationships as the factors driving this synchronization. Even in the context of music, theater, or film, the emphasis is on the concurrent and shared experience of an audience that synchronizes heart rate to one another (Konvalinka et al., 2011; Bernardi et al., 2017; Kaltwasser et al., 2019; Ardizzi et al., 2020). Here, we have emphasized that it is the stimulus that synchronizes HR, or more precisely, a similar processing of a common stimulus. There is no need for individuals to directly interact, be related to one another, or perceive the stimulus together at the same time. Consistent with our hypothesis, previous reports already show that emotional movies can synchronize the HR of viewers, even when watching the movie individually (Golland et al., 2014; Steiger et al., 2019). Those studies argue that this is a common effect of "emotions" across subjects, yet emotions are increasingly considered to have an idiosyncratic physiological manifestation in each individual (Siegel et al., 2018). It is quite possible that other factors were at play in these earlier studies with firms. Therefore, our finding that HR synchronizes for audio recordings of children's stories was not already evident from the prior literature, nor was it expected for animated educational videos that were not designed to elicit emotions. More importantly, it was not immediately obvious that these similar HR fluctuations should be modulated by attention and predictive of memory performance. Our hypothesis is based on the more basic observation that heart rate is affected by a variety of cognitive factors (Thayer and Lane, 2009; Thayer et al., 2009) with the additional assumption that different subjects will be affected similarly.

There is also an extensive literature on the inter-subject correlation of brain signals evoked by dynamic natural stimuli, starting with experiments in fMRI while subjects watched movies (Hasson et al., 2004). This work demonstrated that subjects process natural stimuli similarly, and similarity of brain activity is predictive of memory performance (Hasson et al., 2008). Subsequent experiments replicated these findings with EEG

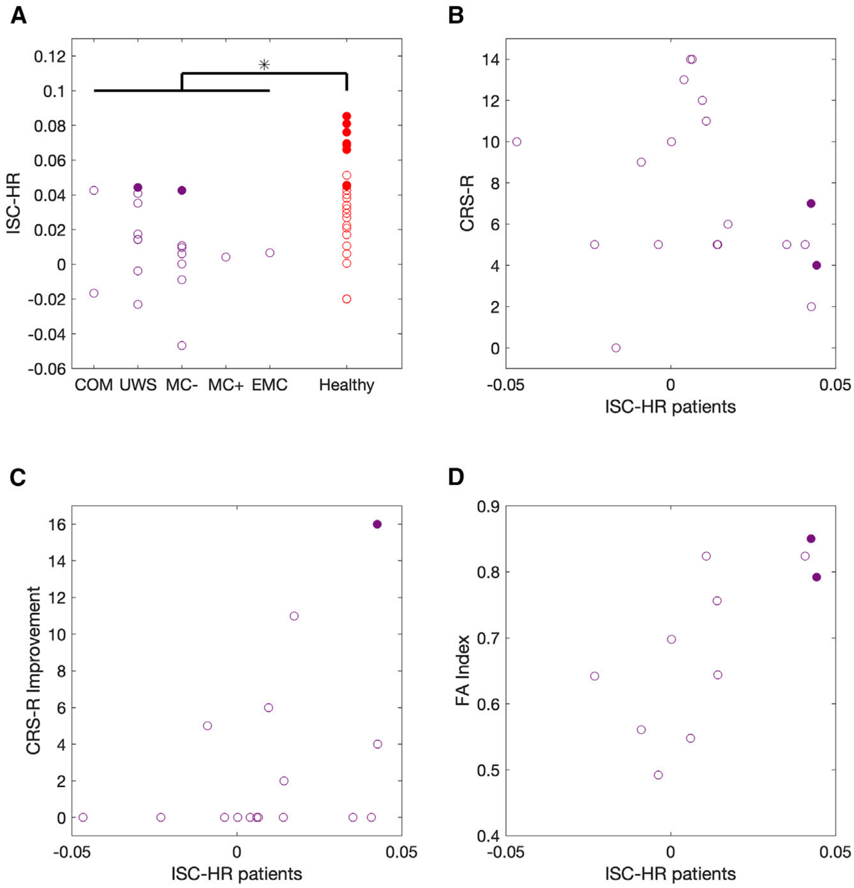


Figure 6. Audio narratives synchronize HR fluctuations in healthy controls but not in patients with disorder of consciousness

In experiment 4, subjects listened to a children's story (La part des ancêtres from Leonora Miano; 10 min).

(A) ISC-HR is measured by correlating instantaneous HR with that of healthy subjects. Filled cycles indicated statistically significant ISC.

(B) Comparison of the ISC-HR with Coma Recovery Scale-Revised in patients (n = 19).

(C) Comparison of the ISC-HR with improvement of Coma Recovery Scale-Revised 6 months after the first assessment (n = 17).

(D) Comparison of ISC-HR and whole-brain white matter fractional anisotropy in patients were available (n = 11).

(Dmochowski et al., 2014; Cohen and Parra, 2016). Additionally, the ISC of EEG is reduced when subjects are distracted (Ki et al., 2016) and is reduced in patients with disorder of consciousness (Iotzov et al., 2017), similar to what we find here with the instantaneous heart rate. Given these parallels, we expect that HR fluctuations will also synchronize across subjects listening to engaging music (Madsen et al., 2019), and HR synchronization will be a good indication of how engaging a narrative is (Dmochowski et al., 2014; Cohen et al., 2017; Stuldreher et al., 2020).

We suggest that some previous work on physiological synchronization of autonomic signals can be reinterpreted in the context of the present conscious-processing hypothesis. For example, the same performance is judged differently depending on the social relationship of performer and audience member, suggesting that it is a different way of processing information in the audience member (Konvalinka et al., 2011). In our view, it is the processing of the common stimulus, and not the co-presence in the same physical space, that causes the synchronization of the heart rate fluctuations. We predict that many results obtained with live performances (Konvalinka et al., 2011; Palumbo et al., 2017; Kaltwasser et al., 2019) or in-person interactions (Cohen et al., 2018) could be recovered with asynchronous playback of the same experience recorded with video. Evidently the experience may be less powerful than live in-person experiences (Golland et al., 2015), but the modulating factors of relationships, emotions, or empathy may still prevail in this virtual context.

We postulate that factors intrinsic to the story, such as semantics and emotions, drive a synchronized heart rate. This may include semantics of single-word to syntactic and multi-sentence levels of representation as well as prosody, valence of single words, and more complex semantically mediated emotions. Capturing semantics and emotions require attention to the stimulus and some level of language comprehension. In this view, it is the narrative content that drives attention, engagement, interest, and emotions. It is possible, indeed likely, that the variations in ISC are due to this differing narrative content. Indeed, we find a strong difference in ISC between stimuli, even within the same type of animated educational videos. Dependence of ISC on the stimulus has been found in previous EEG studies (Dmochowski et al., 2014; Cohen et al., 2018; Madsen et al., 2019) and for heart rate in studies involving live performance for different pieces of classical music (Bernardi et al., 2017). In contrast to EEG, we may expect that ISC-HR is less sensitive to low-level features of a stimulus. Neural-evoked responses can be driven by low-level features such as luminance or sound fluctuations, which can elicit strong responses that would be trivially synchronized across subjects (Hasson et al., 2004; Poulsen et al., 2017). It is less clear to us how such low-level stimulus fluctuations could drive HR fluctuations.

We have shown here that the effect on HR synchronization is dominant in the low frequency band around 0.1 Hz, which falls in the frequency range of respiratory sinus arrhythmia (Angelone and Coulter, 1964). However, we show here that breathing does not synchronize between subjects during passive listening or watching, nor was respiratory sinus arrhythmia dependent on attention. Although there are a variety of studies demonstrating a synchronization of breathing, most are contingent on synchronization of movement (e.g., speaking, singing, and dancing) (Müller and Lindenberger, 2011; Codrons et al., 2014;

Rochet-Capellan and Fuchs, 2014). Studies with individual playback of video or speech have shown only very limited synchronization effects (Garssen, 1979; Rochet-Capellan and Fuchs, 2013), and to our knowledge, there is no study that demonstrates that this synchronization depends on attention, consistent with our present result. Furthermore, it is worth noting that ISC was modulated by attention in the low-frequency peak of HRV but not the high-frequency peak around 0.3 Hz that is the predominant breathing frequency. This parallels the observation in sleep, where the LF peak but not the HF peak is attenuated during slow-wave sleep (Baharav et al., 1995), a period of deep sleep characterized by sensory decoupling (Andrillon and Kouider, 2020) and a breakdown of cortical connectivity (Massimini et al., 2005). Given the link between respiratory sinus arrhythmia and parasympathetic cardiac control (Katona and Jih, 1975), we therefore conclude that attention does not affect parasympathetic activity. One caveat to this conclusion is that respiration fluctuates on a slower timescale. It is possible that with longer recording or narrative stimuli different from those used in this study, one may find a synchronization of breathing. Indeed, a framework of embodied cognition would predict a range of brain-body interactions to underlie consciousness and cognition.

Here, we used linear instantaneous correlation to measure synchrony. Physiological synchrony is sometimes measured with more complex analysis methods in order to capture time-delayed or non-linear relationships (Konvalinka et al., 2011; Liu et al., 2016). Such relationships may be expected in asymmetric scenarios such as an audience synchronizing with performers (Konvalinka et al., 2011) or mother and child (Palumbo et al., 2017). However, in the present study, we have a group of participants who experience the stimulus in an identical setting, and we found reliable synchronization of HR without the need to employ more complex analysis methods. For respiration, it is possible that individual subjects may have systematically delayed or differing responses compared to others. Although we accounted for delayed influence of respiration on HR, we avoided more complex analysis of interaction between individual pairs of subjects because the duration of the recordings may not support the increase in number of modeling parameters.

Finally, in a proof-of-concept we show that ISC-HR might be useful as a simple marker of cognitive state in unresponsive patients. Note that this is in line with previous work on ISC of EEG (Iotzov et al., 2017), fMRI (Naci et al., 2014), and similar findings with galvanic skin response (Sinai, 2015). Although we were able to distinguish patients from healthy controls, we were not able to resolve conscious states among patients. When contrasted to other methods (e.g., using EEG [Engemann et al., 2018], positron emission tomography [PET] [Stender et al., 2014], or fMRI [Demertzi et al., 2019]) this limitation—for the moment—curbs the potential use of this method to detect consciousness in patients. However, the results do suggest that the ISC-HR might carry information related to the patients' recovery. What we show here is that a positive result provides evidence of cognitive processing. The absence of a positive result cannot be taken as a failure to follow the narrative, rather, it can indicate a differing response in a particular patient, a weaker HR fluctuation, or simply more noise in the recordings. A combination with other techniques such as EEG (Rohaut et al., 2017), fMRI (Demertzi et al., 2019), or PET (Hermann et al., 2021) should be included to provide a more complete picture. Clinical practice already routinely uses such a multi-faceted approach (Comanducci et al., 2020; Kondziella et al., 2020). Further validation with a larger sample of patients is needed to assess the clinical impact of the proposed method and to determine the optimal combination with other paraclinical tests. One of the limitations of this method is that it requires that the patients not only be conscious, but also to be able to process language. This double requirement may explain the positive test in one patient who recovered with preserved language processing, and a negative test in a patient who recovered in an aphasic condition. In addition, we believe that the 10-min story we used may have been too short for a reliable measure of ISC-HR. In the present experiments, we required at least 15 min of instantaneous heart rate to detect significant ISC and a link to memory. We suggest that future studies—designed to enhance and validate the clinical utility of this method—should use one or several narratives totaling at least 30 min of concurrent heart rate recordings. In addition, our results also indicate that the actual content of the story, and how engaging it is for the subject, plays a role in the individual ISC. Given the limited cognitive status of the patients, it is critical to maximize this factor. We also suggest that the narratives should be adapted for every single patient, for instance by changing the name of the leading character using the patients' own name. By doing so, we will amplify the patients' attention while keeping the overall structure of the story comparable across subjects.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.celrep.2021.109692.

ACKNOWLEDGMENTS

This work was supported by the Paris Brain Institute (France) and the program "Investissements d'avenir" (ANR-10- IAIHU-06); Sorbonne PhD grant ("recherches interdisciplinaires émergentes" France to P.P.); CARNOT maturation grant (Con&Heart to J.D.S.); Sorbonne Universités EMERGENCE (Brain-body interactions, a new window for conscious evaluation in brain-injured patients to J.D.S.); EU-PerMed (Project PerBrain to J.D.S.); French Embassy UK (Seeding Grant 2018 to J.D.S. and D.C.); Medical Research Council New Investigator Research Grant (UK) (to D.C.); and the National Science Foundation (DRL-1660548 to J.M. and L.P.).

AUTHOR CONTRIBUTIONS

P.P., J.M., L.N., T.S., D.C., L.C.P., and J.D.S. contributed to the conception and design of the study. P.P., J.M., L.B., B.T., V.P., M.V., M.-C.N., L.P., D.C., L.C.P., and J.D.S. contributed to the acquisition of data. P.P., J.M., F.R., L.C.P., and J.D.S. contributed to the analysis of data. P.P., J.M., L.N., D.C., L.C.P., and J.D.S. contributed to the drafting of the manuscript and/or the figures.

DECLARATION OF INTERESTS

The authors declare no competing interests.

Received: December 11, 2020
Revised: June 15, 2021
Accepted: August 19, 2021
Published: September 14, 2021

REFERENCES

Andrillon, T., and Kouider, S. (2020). The vigilant sleeper: neural mechanisms of sensory (de)coupling during sleep. Curr. Opin. Physiol. *15*, 47–59.

Angelone, A., and Coulter, N.A., Jr. (1964). Respiratory sinus arrhythemia: a frequency dependent phenomenon. J. Appl. Physiol. *19*, 479–482.

Ardizzi, M., Calbi, M., Tavaglione, S., Umiltà, M.A., and Gallese, V. (2020). Audience spontaneous entrainment during the collective enjoyment of live performances: physiological and behavioral measurements. Sci. Rep. *10*, 3813.

Baharav, A., Kotagal, S., Gibbons, V., Rubin, B.K., Pratt, G., Karin, J., and Akselrod, S. (1995). Fluctuations in autonomic nervous activity during sleep displayed by power spectrum analysis of heart rate variability. Neurology *45*, 1183–1187.

Bekinschtein, T.A., Dehaene, S., Rohaut, B., Tadel, F., Cohen, L., and Naccache, L. (2009). Neural signature of the conscious processing of auditory regularities. Proc. Natl. Acad. Sci. USA *106*, 1672–1677.

Bernardi, L., Valle, F., Coco, M., Calciati, A., and Sleight, P. (1996). Physical activity influences heart rate variability and very-low-frequency components in Holter electrocardiograms. Cardiovasc. Res. *32*, 234–237.

Bernardi, G., Cecchetti, L., Handjaras, G., Sani, L., Gaglianese, A., Ceccarelli, R., Franzoni, F., Galetta, F., Santoro, G., Goebel, R., et al. (2014). It's not all in your car: functional and structural correlates of exceptional driving skills in professional racers. Front. Hum. Neurosci. *8*, 888.

Bernardi, N.F., Codrons, E., di Leo, R., Vandoni, M., Cavallaro, F., Vita, G., and Bernardi, L. (2017). Increase in Synchronization of Autonomic Rhythms between Individuals When Listening to Music. Front. Physiol. *8*, 785.

Bruno, M.-A., Vanhaudenhuyse, A., Thibaut, A., Moonen, G., and Laureys, S. (2011). From unresponsive wakefulness to minimally conscious PLUS and functional locked-in syndromes: recent advances in our understanding of disorders of consciousness. J. Neurol. *258*, 1373–1384.

Chang, C., Metzger, C.D., Glover, G.H., Duyn, J.H., Heinze, H.J., and Walter, M. (2013). Association between heart rate variability and fluctuations in resting-state functional connectivity. Neuroimage *68*, 93–104.

Chen, J., Leong, Y.C., Honey, C.J., Yong, C.H., Norman, K.A., and Hasson, U. (2017). Shared memories reveal shared structure in neural activity across individuals. Nat. Neurosci. *20*, 115–125.

Codrons, E., Bernardi, N.F., Vandoni, M., and Bernardi, L. (2014). Spontaneous group synchronization of movements and respiratory rhythms. PLoS ONE *9*, e107538.

Cohen, M.X. (2014). Analyzing Neural Time Series Data: Theory and Practice (MIT Press).

Cohen, S.S., and Parra, L.C. (2016). Memorable audiovisual narratives synchronize sensory and supramodal neural responses. eNeuro *3*, ENEURO.0203-16.2016.

Cohen, S.S., Henin, S., and Parra, L.C. (2017). Engaging narratives evoke similar neural activity and lead to similar time perception. Sci. Rep. *7*, 4578.

Cohen, S.S., Madsen, J., Touchan, G., Robles, D., Lima, S.F.A., Henin, S., and Parra, L.C. (2018). Neural engagement with online educational videos predicts learning performance for individual students. Neurobiol. Learn. Mem. *155*, 60–64.

Comanducci, A., Boly, M., Claassen, J., De Lucia, M., Gibson, R.M., Juan, E., Laureys, S., Naccache, L., Owen, A.M., Rosanova, M., et al. (2020). Clinical and advanced neurophysiology in the prognostic and diagnostic evaluation of disorders of consciousness: review of an IFCN-endorsed expert group. Clin. Neurophysiol. *131*, 2736–2765.

Cooke, W.H., Cox, J.F., Diedrich, A.M., Taylor, J.A., Beightol, L.A., Ames, J.E., 4th, Hoag, J.B., Seidel, H., and Eckberg, D.L. (1998). Controlled breathing protocols probe human autonomic cardiovascular rhythms. Am. J. Physiol. *274*, H709–H718.

Cruse, D., Beukema, S., Chennu, S., Malins, J.G., Owen, A.M., and McRae, K. (2014). The reliability of the N400 in single subjects: implications for patients with disorders of consciousness. Neuroimage Clin. *4*, 788–799.

Dehaene, S., and Changeux, J.-P.J.P. (2011). Experimental and theoretical approaches to conscious processing. Neuron *70*, 200–227.

Demertzi, A., Tagliazucchi, E., Dehaene, S., Deco, G., Barttfeld, P., Raimondo, F., Martial, C., Fernández-Espejo, D., Rohaut, B., Voss, H.U., et al. (2019). Human consciousness is supported by dynamic complex patterns of brain signal coordination. Sci. Adv. *5*, eaat7603.

Dmochowski, J.P., Bezdek, M.A., Abelson, B.P., Johnson, J.S., Schumacher, E.H., and Parra, L.C. (2014). Audience preferences are predicted by temporal reliability of neural processing. Nat. Commun. *5*, 4567.

Ekman, P., Levenson, R.W., and Friesen, W.V. (1983). Autonomic nervous system activity distinguishes among emotions. Science *221*, 1208–1210.

Engemann, D.A., Raimondo, F., King, J.R., Rohaut, B., Louppe, G., Faugeras, F., Annen, J., Cassol, H., Gosseries, O., Fernandez-Slezak, D., et al. (2018). Robust EEG-based cross-site and cross-protocol classification of states of consciousness. Brain *141*, 3179–3192.

Garssen, B. (1979). Synchronization of respiration. Biol. Psychol. *8*, 311–315.

Giacino, J.T., Kalmar, K., and Whyte, J. (2004). The JFK Coma Recovery Scale-Revised: measurement characteristics and diagnostic utility. Arch. Phys. Med. Rehabil. *85*, 2020–2029.

Golland, Y., Keissar, K., and Levit-Binnun, N. (2014). Studying the dynamics of autonomic activity during emotional experience. Psychophysiology *51*, 1101–1111.

Golland, Y., Arzouan, Y., and Levit-Binnun, N. (2015). The Mere Co-Presence: Synchronization of Autonomic Signals and Emotional Responses across Co-Present Individuals Not Engaged in Direct Interaction. PLoS ONE *10*, e0125804.

Gordon, I., Gilboa, A., Cohen, S., Milstein, N., Haimovich, N., Pinhasi, S., and Siegman, S. (2020). Physiological and Behavioral Synchrony Predict Group Cohesion and Performance. Sci. Rep. *10*, 8484.

Hasson, U., Nir, Y., Levy, I., Fuhrmann, G., and Malach, R. (2004). Intersubject synchronization of cortical activity during natural vision. Science *303*, 1634–1640.

Hasson, U., Furman, O., Clark, D., Dudai, Y., and Davachi, L. (2008). Enhanced intersubject correlations during movie viewing correlate with successful episodic encoding. Neuron *57*, 452–462.

Hasson, U., Chen, J., and Honey, C.J. (2015). Hierarchical process memory: memory as an integral component of information processing. Trends Cogn. Sci. *19*, 304–313.

Hermann, B., Stender, J., Habert, M.O., Kas, A., Denis-Valente, M., Raimondo, F., Pérez, P., Rohaut, B., Sitt, J.D., and Naccache, L. (2021). Multimodal FDG-PET and EEG assessment improves diagnosis and prognostication of disorders of consciousness. Neuroimage Clin. *30*, 102601.

Hirsch, J.A., and Bishop, B. (1981). Respiratory sinus arrhythmia in humans: how breathing pattern modulates heart rate. Am. J. Physiol. *241*, H620–H629.

Honey, C.J., Thesen, T., Donner, T.H., Silbert, L.J., Carlson, C.E., Devinsky, O., Doyle, W.K., Rubin, N., Heeger, D.J., and Hasson, U. (2012). Slow cortical dynamics and the accumulation of information over long timescales. Neuron *76*, 423–434.

Iotzov, I., Fidali, B.C., Petroni, A., Conte, M.M., Schiff, N.D., and Parra, L.C. (2017). Divergent neural responses to narrative speech in disorders of consciousness. Ann. Clin. Transl. Neurol. *4*, 784–792.

Jenkinson, M., Beckmann, C.F., Behrens, T.E., Woolrich, M.W., and Smith, S.M. (2012). FSL. Neuroimage *62*, 782–790.

Kaltwasser, L., Rost, N., Ardizzi, M., Calbi, M., Settembrino, L., Fingerhut, J., Pauen, M., and Gallese, V. (2019). Sharing the filmic experience - The physiology of socio-emotional processes in the cinema. PLoS ONE *14*, e0223259.

Kass, R., and Raftery, A. (1995). Bayes Factors. J. Am. Stat. Assoc. *90*, 773–795.

Katona, P.G., and Jih, F. (1975). Respiratory sinus arrhythmia: noninvasive measure of parasympathetic cardiac control. J. Appl. Physiol. *39*, 801–805.

Ki, J.J., Kelly, S.P., and Parra, L.C. (2016). Attention Strongly Modulates Reliability of Neural Responses to Naturalistic Narrative Stimuli. J. Neurosci. *36*, 3092–3101.

Kondziella, D., Friberg, C.K., Frokjaer, V.G., Fabricius, M., and Møller, K. (2016). Preserved consciousness in vegetative and minimal conscious states: systematic review and meta-analysis. J. Neurol. Neurosurg. Psychiatry *87*, 485–492.

Kondziella, D., Bender, A., Diserens, K., van Erp, W., Estraneo, A., Formisano, R., Laureys, S., Naccache, L., Ozturk, S., Rohaut, B., et al.; EAN Panel on Coma, Disorders of Consciousness (2020). European Academy of Neurology guideline on the diagnosis of coma and other disorders of consciousness. Eur. J. Neurol. *27*, 741–756.

Konvalinka, I., Xygalatas, D., Bulbulia, J., Schjødt, U., Jegindø, E.M., Wallot, S., Van Orden, G., and Roepstorff, A. (2011). Synchronized arousal between performers and related spectators in a fire-walking ritual. Proc. Natl. Acad. Sci. USA *108*, 8514–8519.

Kyeong, S., Kim, J., Kim, D.J., Kim, H.E., and Kim, J.J. (2017). Effects of gratitude meditation on neural network functional connectivity and brain-heart coupling. Sci. Rep. *7*, 5058.

Lane, R.D., McRae, K., Reiman, E.M., Chen, K., Ahern, G.L., and Thayer, J.F. (2009). Neural correlates of heart rate variability during emotion. Neuroimage *44*, 213–222.

Lankinen, K., Saari, J., Hari, R., and Koskinen, M. (2014 May 15). Intersubject consistency of cortical MEG signals during movie viewing. NeuroImage *92*, 217–224.

Levy, M.N., and Martin, P.J. (1989). Autonomic neural control of cardiac function. In Physiology and Pathophysiology of the Heart. Developments in Cardiovascular Medicine, Vol. 90, N. Sperelakis, ed. (Springer), pp. 361–379.

Liang, F., Paulo, R., Molina, G., Clyde, M., and Berger, J. (2008). Mixtures of g Priors for Bayesian Variable Selection. J. Am. Stat. Assoc. *103*, 410–423.

Liu, Y., Piazza, E.A., Simony, E., Shewokis, P.A., Onaral, B., Hasson, U., and Ayaz, H. (2017). Measuring speaker–listener neural coupling with functional near infrared spectroscopy. Scientific reports *7* (*1*), 1–3.

Liu, S., Zhou, Y., Palumbo, R., and Wang, J.L. (2016). Dynamical correlation: A new method for quantifying synchrony with multivariate intensive longitudinal data. Psychol. Methods *21*, 291–308.

Mack, A., and Rock, I. (1998). Inattentional Blindness (MIT Press).

Madsen, J., Margulis, E.H., Simchy-Gross, R., and Parra, L.C. (2019). Music synchronizes brainwaves across listeners with strong effects of repetition, familiarity and training. Sci. Rep. *9*, 3576.

Massimini, M., Ferrarelli, F., Huber, R., Esser, S.K., Singh, H., and Tononi, G. (2005). Breakdown of cortical effective connectivity during sleep. Science *309*, 2228–2232.

McCorry, L.K. (2007). Physiology of the autonomic nervous system. Am. J. Pharm. Educ. *71*, 78.

Mori, S., Oishi, K., Jiang, H., Jiang, L., Li, X., Akhter, K., Hua, K., Faria, A.V., Mahmood, A., Woods, R., et al. (2008). Stereotaxic white matter atlas based on diffusion tensor imaging in an ICBM template. Neuroimage *40*, 570–582.

Morlet, D., and Fischer, C. (2014). MMN and novelty P3 in coma and other altered states of consciousness: a review. Brain Topogr. *27*, 467–479.

Müller, V., and Lindenberger, U. (2011). Cardiac and respiratory patterns synchronize between persons during choir singing. PLoS ONE *6*, e24893.

Naci, L., Cusack, R., Anello, M., and Owen, A.M. (2014). A common neural code for similar conscious experiences in different individuals. Proc. Natl. Acad. Sci. USA *111*, 14277–14282.

Naci, L., Graham, M., Owen, A.M., and Weijer, C. (2016). Covert narrative capacity: Mental life in patients thought to lack consciousness. Ann. Clin. Transl. Neurol. *4*, 61–70.

Noto, T., Zhou, G., Schuele, S., Templer, J., and Zelano, C. (2018). Automated analysis of breathing waveforms using BreathMetrics: a respiratory signal processing toolbox. Chem. Senses *43*, 583–597.

Owen, A.M., Coleman, M.R., Boly, M., Davis, M.H., Laureys, S., and Pickard, J.D. (2006). Detecting awareness in the vegetative state. Science *313*, 1402.

Palma, J.-A., and Benarroch, E.E. (2014). Neural control of the heart: recent concepts and clinical correlations. Neurology *83*, 261–271.

Palumbo, R.V., Marraccini, M.E., Weyandt, L.L., Wilder-Smith, O., McGee, H.A., Liu, S., and Goodwin, M.S. (2017). Interpersonal Autonomic Physiology: A Systematic Review of the Literature. Pers. Soc. Psychol. Rev. *21*, 99–141.

Park, H.-D., and Tallon-Baudry, C. (2014). The neural subjective frame: from bodily signals to perceptual consciousness. Philos. Trans. R. Soc. Lond. B Biol. Sci. *369*, 20130208.

Park, H.-D., Correia, S., Ducorps, A., and Tallon-Baudry, C. (2014). Spontaneous fluctuations in neural responses to heartbeats predict visual detection. Nat. Neurosci. *17*, 612–618.

Pérez, A., Carreiras, M., and Duñabeitia, J.A. (2017). Brain-to-brain entrainment: EEG interbrain synchronization while speaking and listening. Sci. Rep. *7*, 4190.

Poulsen, A.T., Kamronn, S., Dmochowski, J., Parra, L.C., and Hansen, L.K. (2017). EEG in the classroom: Synchronised neural recordings during video presentation. Sci. Rep. *7*, 43916.

Raimondo, F., Rohaut, B., Demertzi, A., Valente, M., Engemann, D.A., Salti, M., Fernandez Slezak, D., Naccache, L., and Sitt, J.D. (2017). Brain-heart interactions reveal consciousness in noncommunicating patients. Ann. Neurol. *82*, 578–591.

Regev, M., Simony, E., Lee, K., Tan, K.M., Chen, J., and Hasson, U. (2019). Propagation of information along the cortical hierarchy as a function of attention while reading and listening to stories. Cereb. Cortex *29*, 4017–4034.

Riganello, F., Dolce, G., and Sannita, W.G. (2012). Heart rate variability and the central autonomic network in the severe disorder of consciousness. J. Rehabil. Med. *44*, 495–501.

CellPress
OPEN ACCESS

Rochet-Capellan, A., and Fuchs, S. (2013). Changes in breathing while listening to read speech: the effect of reader and speech mode. Front. Psychol. *4*, 906.

Rochet-Capellan, A., and Fuchs, S. (2014). Take a breath and take the turn: how breathing meets turns in spontaneous dialogue. Philos. Trans. R. Soc. Lond. B Biol. Sci. *369*, 20130399.

Rohaut, B., Faugeras, F., Chausson, N., King, J.R., Karoui, I.E., Cohen, L., and Naccache, L. (2015). Probing ERP correlates of verbal semantic processing in patients with impaired consciousness. Neuropsychologia *66*, 279–292.

Rohaut, B., Raimondo, F., Galanaud, D., Valente, M., Sitt, J.D., and Naccache, L. (2017). Probing consciousness in a sensory-disconnected paralyzed patient. Brain Inj. *31*, 1398–1403.

Rouder, J.N., Morey, R.D., Speckman, P.L., and Province, J.M. (2012). Default Bayes factors for ANOVA designs. J. Math. Psychol. *56*, 356–374.

Schiff, N.D. (2015). Cognitive Motor Dissociation Following Severe Brain Injuries. JAMA Neurol. *72*, 1413–1415.

Schlossmacher, I., Dellert, T., Pitts, M., Bruchmann, M., and Straube, T. (2020). Differential Effects of Awareness and Task Relevance on Early and Late ERPs in a No-Report Visual Oddball Paradigm. J. Neurosci. *40*, 2906–2913.

Schmälzle, R., Häcker, F., Renner, B., Honey, C.J., and Schupp, H.T. (2013). Neural correlates of risk perception during real-life risk communication. J. Neurosci. *33*, 10340–10347.

Schmälzle, R., Häcker, F.E., Honey, C.J., and Hasson, U. (2015). Engaged listeners: shared neural processing of powerful political speeches. Soc. Cogn. Affect. Neurosci. *10*, 1137–1143.

Siegel, E.H., Sands, M.K., Van den Noortgate, W., Condon, P., Chang, Y., Dy, J., Quigley, K.S., and Barrett, L.F. (2018). Emotion fingerprints or emotion populations? A meta-analytic investigation of autonomic features of emotion categories. Psychol. Bull. *144*, 343–393.

Sinai, L. (2015). Naturalistic paradigms for neuroimaging and bedside measures of conscious awareness. Electronic Thesis and Dissertation Repository. https://ir.lib.uwo.ca/etd/2988.

Stanley, G., Verotta, D., Craft, N., Siegel, R.A., and Schwartz, J.B. (1996). Age and autonomic effects on interrelationships between lung volume and heart rate. Am. J. Physiol. *270*, H1833–H1840.

Steiger, B.K., Kegel, L.C., Spirig, E., and Jokeit, H. (2019). Dynamics and diversity of heart rate responses to a disaster motion picture. Int. J. Psychophysiol. *143*, 64–79.

Stender, J., Gosseries, O., Bruno, M.A., Charland-Verville, V., Vanhaudenhuyse, A., Demertzi, A., Chatelle, C., Thonnard, M., Thibaut, A., Heine, L., et al. (2014). Diagnostic precision of PET imaging and functional MRI in disorders of consciousness: a clinical validation study. Lancet *384*, 514–522.

Studlreher, I.V., Thammasan, N., van Erp, J.B.F., and Brouwer, A.M. (2020). Physiological synchrony in EEG, electrodermal activity and heart rate reflects shared selective auditory attention. J. Neural Eng. *17*, 046028.

Thayer, J.F., and Lane, R.D. (2009). Claude Bernard and the heart-brain connection: further elaboration of a model of neurovisceral integration. Neurosci. Biobehav. Rev. *33*, 81–88.

Thayer, J.F., Hansen, A.L., Saus-Rose, E., and Johnsen, B.H. (2009). Heart rate variability, prefrontal neural function, and cognitive performance: the neurovisceral integration perspective on self-regulation, adaptation, and health. Ann. Behav. Med. *37*, 141–153.

Trübutschek, D., Marti, S., Ueberschär, H., and Dehaene, S. (2019). Probing the limits of activity-silent non-conscious working memory. Proc. Natl. Acad. Sci. USA *116*, 14358–14367.

Velly, L., Perlbarg, V., Boulier, T., Adam, N., Delphine, S., Luyt, C.E., Battisti, V., Torkomian, G., Arbelot, C., Chabanne, R., et al.; MRI-COMA Investigators (2018). Use of brain diffusion tensor imaging for the prediction of long-term neurological outcomes in patients after cardiac arrest: a multicentre, international, prospective, observational, cohort study. Lancet Neurol. *17*, 317–326.

Wallentin, M., Nielsen, A.H., Vuust, P., Dohn, A., Roepstorff, A., and Lund, T.E. (2011). Amygdala and heart rate variability responses from listening to emotionally intense parts of a story. Neuroimage *58*, 963–973.

Zhang, J.R., Sherwin, J., Dmochowski, J., Sajda, P., and Kender, J.R. (2014). Correlating Speaker Gestures in Political Debates with Audience Engagement Measured via EEG. In Proceedings of the 22nd ACM International Conference on Multimedia (MM '14) (Association for Computing Machinery)), pp. 387–396.

STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Deposited data		
Raw and analyzed data	This paper	https://doi.org/10.17605/OSF.IO/MHVY7
Software and algorithms		
Processing and analysis scripts	This paper	https://doi.org/10.17605/OSF.IO/MHVY7

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Jacobo SITT (Jacobo.sitt@inserm.fr).

Materials availability

This study did not generate unique reagents.

Data and code availability

All healthy participants' data have been deposited at OSF and are publicly-available. The DOI is listed in the Key resources table. In the case of patients' data, raw physiological data cannot be open due to consent limitations.

All original code has been deposited at OSF and is publicly-accessible. The DOI is listed in the Key resources table.

Any additional information required to reanalyse the data reported in this paper is available from the lead contact upon request.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

Experiment 1: auditory narratives

Twenty-seven native English speakers and healthy participants (22 females, age range 18-26, median 21 years old) contributed data to this analysis. The study was approved by the STEM ethics committee of the University of Birmingham, England. All subjects provided written informed consent.

Experiment 2: instructional videos

Thirty-one students at the City College of New York participated in this study (19 females, age range 18-46, median 28 years old), of whom 4 were removed from analysis due to bad signal quality resulting in usable data for N = 27 participants. The experimental protocol was approved by the Institutional Review Boards of the City University of New York. All subjects provided written informed consent.

Experiment 3: auditory narratives with respiration

25 French native healthy participants participated in this study (15 females; age range 22-28, median age 25 years old), of whom four were removed because of missing respiratory and/or cardiac data. The study was promoted by the Inserm (CPP C13-41) and approved by the Comité de Protection des Personnes Ile-de-France 6. All subjects provided written informed consent.

Experiment 4: Disorders of consciousness

Nineteen patients (8 females, age range 18 to 77, median age 50 years old) with disorders of consciousness (mostly resulting from brain lesions) and 24 healthy control subjects (14 females; age range 23-27, median 25 years old) participated in this study. Among the 19 patients, we diagnosed 2 patients in coma, 8 VS patients, 8 MCS patients (7 MCS- and 1 MCS+) and 1 EMCS (see supplemental data for more details). The Ethical Committee of the Pitie-Salpetriere approved this research under the French label of 'routine care research'.

METHOD DETAILS

Experiment 1: auditory narratives

All participants listened to a 16-minute extract of an audiobook read by a male British English voice (20,000 leagues under the sea. Author: Jules Verne. Read by: David Linski. Public Domain (P) 2017 Blackstone Audio, Inc.) while their EKG was recorded. The audiobook extract was taken from the first chapter and half of the second chapter. The text is relatively suspenseful as it describes reports of an unknown monster that destroys ships. We divided the story into essays of approximately 1 minute each so that participants could take breaks between segments if they wished.

The instructions given to the subject were 'to listen to the story and look at a fixation cross'. The stimuli were delivered by headphones - ER·1 Insert Earphones (Etymotic Research), using Psychopy v3.1.2. The EKG was recorded with two electrodes on the chest using SenseBox of ANT Neuro, sampled at 500Hz.

EKG data was cut into the 16 epochs of approximately 1-minute corresponding to each audio-segment.

Experiment 2: instructional videos

All participants watched 5 instructional videos while their EKG were recorded (19 females, age range 18-46, median 28 years old) in an attentive condition (A), where they were instructed to simply watch videos as they would regularly watch a video. Each educational video was 3-5 minutes long, chosen from popular YouTube channels covering biology, physics, and computer science. These are new recordings on videos we had tested previously (Cohen et al., 2018). After the students had watched all 5 videos, they were asked to answer 10-12 questions about factual information about material conveyed in each video. Lastly, students were instructed to watch the video again in a distracted condition (D). In this condition participants were asked to silently count in their mind backward from a random prime number above 800 and below 1000, in steps of 7.

The experiment was carried out in a sound-attenuated booth. Subject wore headphones and watched the videos on a 19'' monitor. The EKG was recorded with a BioSemi Active Two system at a sampling frequency of 2048Hz. 2 EKG electrodes were placed below the left collar bone and one on the left lumbar region. For segmentation of the EKG signal onset and offset triggers were used, in addition a flash and beep sound was embedded right before and after each video which were recorded using a StimTracker (Cedrus) to ensure precise alignment across all subjects.

Experiment 3: auditory narratives with respiration

All participants listened to four stories while their EKG and respiration was recorded using a Polygraph Input Box (PIB of EGI-Geodesic's physiological measurement system). This includes a chest belt to measure respiratory movement (Respiration Belt MR - Brain Products) and 2 EKG electrodes placed on the left subclavicular area and below the left axillary area. The four audio stimuli come from https://www.franceinter.fr/emissions/une-histoire-et-oli: (1) Nadine et Robert les poissons rouges- Delphine de Vigan (8 min) (2) les villages du versant – Alice Zeniter (8 min) (3) Opaque et Opaline - Alex Vizorek (11 min) (4) le renard et le poulailler – Guillaume Meurice (10 min).

To test whether the ISC-HR is modulated by attention we divided the subjects into 2 groups: Group 1 (9 subjects) was recorded with stories (1) and (2) in a distracted condition, and (3) and (4) in an attentional condition. In group 2 (12 subjects) the stories were counterbalanced, stories (1) and (2) in the attentional condition, and (3) and (4) in the distracted condition. In the attentional condition (A), the subject's task was to pay attention to the story while disregarding tones (320/360/400/440/482 Hz, 400ms long) that were played in random intervals (between 800ms and 1100ms) in the background of the story. After each story the subjects received a control debriefing questionnaire including 5 questions testing the memory performance of the story content. In the distracted condition (D), the subject's task was to count backward starting from 100 indexing the occurrence of 'counting' tones (same tones as in the attentional condition) in-between 2 'reset' tones (Audacity- the type of tones is a linear decay between 1300 and 400 Hz during 400ms). The reset tones were added uniformly and randomly every 14 s on average. After each 'reset' tone, subjects had to reset the counting back to 100. At the end of the block the subjects had to report the smallest number obtained between 2 'reset' tones. Subjects were instructed not to pay attention to the story and also receive the same debriefing questionnaire.

Experiment 4: Disorders of consciousness

All patients and healthy participants listened to an auditory narrative (La part des ancêtres - Leonora Miano - 10 minutes, from: https://www.franceinter.fr/emissions/une-histoire-et-oli) through headphones while their EKG was recorded with a Polygraph Input Box (PIB of EGI-Geodesic's physiological measurement system). The only instruction given to all subjects (healthy controls and patients) was to listen to the story. These patients were hospitalized in neurointensive care at Pitié Salpetrière (medical center with expertise in disorder of consciousness) to determine their state of consciousness, to adapt treatment, and to evaluate their neurological prognosis. During this evaluation, we performed several exams: clinical assessment, MRI, EEG, evoked response potential, and positron emission tomography. The state of consciousness is determined with behavioral assessments, using the Coma Recovery Scale-revised (Giacino et al., 2004) - a score which allows differentiating between consciousness states: Coma (the patient does not open their eyes), Vegetative State (VS - Eye-opening, and alternance between wakefulness and sleep), Minimally Conscious State (MCS - the patient is able to follow their own face in the mirror or to follow a simple instruction) and Exit Minimally Conscious State (EMCS - patient can communicate with code).

QUANTIFICATION AND STATISTICAL ANALYSIS

Computation of intersubject correlation of heart rate (ISC-HR)

Previous studies have relied on the quantification of synchrony of neuroimaging based time series (i.e., BOLD in fMRI (Hasson et al., 2015) or signals from EEG electrodes (Cohen et al., 2018)). We follow a similar logic for the electrocardiographic (EKG) signal. We focus on the modulation of heart rate, by doing so we can determine if subjects increase or decrease their heart rate simultaneously, independently of their absolute level of heart rate. Step 1: We measure the EKG signal and detrend it using a high-pass filter (0.5 Hz cutoff) and subsequently notch filtered at either 50Hz (Experiment 1, 3 and 4) or 60 Hz (Experiment 2). We compute the instantaneous HR by detecting RR intervals from the EKG (Figure 1A). Peaks of the R-wave were found using *findpeaks* (built-in MATLAB function). Step 2: The instantaneous HR signal is then interpolated to keep the same sampling frequency for all subjects (Figure 1B). Step 3: This interpolated instantaneous HR signal is used to compute an inter-subject correlation matrix by calculating the Pearson's correlation between each subjects' instantaneous HR signal (Figure 1C). Step 4: the intersubject subject correlation of heart rate (ISC-HR) for each subject is obtained by computing the mean of the fisher-Z transformed correlations of that given subject to the rest of the group. Step 5: the inverse of the fisher-Z transformation is applied to the ISC-HR value (Figure 1D).

For Experiment 2 (Figures 3 and 4) in step 3 we computed the inter-subject correlation matrix between the instantaneous HR signals in the attentive and distracted conditions with the instantaneous HR in the attentive conditions rather than within condition. In Experiment 3 (Figure 5) we again used the instantaneous HR signals obtained when the groups were attentively listening to the stories as reference when computing the inter-subject correlation matrix for step 3 (Figure 6.). For Experiment 4 we used the healthy participants as reference in the computation of the inter-subject correlation matrix in step 3. All other steps were as explained above.

Statistical significance of ISC-HR

The instantaneous HR signals for a given epoch are first aligned across subjects. Then ISC-HR was calculated for all subjects in all epochs and the ISC across epochs. To test whether the ISC-HR value for each epoch was statistically significant (for Figure 2A), circular shuffle statistic was used: Each subject's instantaneous HR is circularly shifted by a random amount within the 60 s segments and the ISC-HR is re-computed. This procedure is repeated 10.000 times and the ISC-HR of the epoch is compared to this distribution of ISC-HR values for the circular shifted instantaneous HR signals. The p value is obtained by counting how many circular shifted ISC-HR values were below the actual ISC-HR value. For Figure 2B we repeat the circular shift to compute ISC-HR values and then average across epochs; p values are then computed on these averaged ISC-HR values. For Figure 2C, instead of circular shifts within 60 s story segments, we instead randomly swapped segments between participants.

Cluster statistics

One dimensional cluster statistics was computed by adapting the procedure described in Cohen (2014) as follows. First, for each subject, we subtracted the spectrum in the attentive condition versus the distracted condition. Second, for each frequency we computed a t test comparing the contrast to zero. Third, we identified clusters of consecutive frequencies with p values < 0.05 and stored the sum of t-values within the cluster. Fourth, we run 10000 permutations in which we randomly reversed the sign of the subjects attentive versus distracted contrast and repeated steps 2-3 while keeping the sum of t-values of the largest cluster. Finally, we compared the clusters' t-values obtained in step 3 with the distribution of permuted cluster t-values obtained in step 4. Clusters with larger than 95% (corresponding to p value < 0.05) of the permuted distribution were considered significant after multiple comparison cluster correction.

Bayes Factors

Bayes Factors are an established approach (Kass and Raftery, 1995) to compare the likelihood of a Null hypothesis to the likelihood of an alternative hypothesis expressing a measurable effect size. In our case, we were not able to measure a significant effect of synchronized breathing, and the question becomes whether there is sufficient evidence for a lack of synchronization, i.e., is there sufficient evidence in favor of the Null hypothesis. A Bayes Factor (BF) is the likelihood ratio between the Null and alternative hypothesis. When a BF lies between 3 and 10 it is considered moderate evidence in favor of the Null hypothesis. A crucial assumption when computing a BF is the effect size of the alternative hypothesis. If no specific effect size can be assumed a-priori, it is common to assume a distribution over a range of effect sizes. Rouder et al. (2012) formalizes this approach for the t test. The conventional Null hypothesis for the t test states that there is no difference between mean values of two groups and that mean values are normally distributed. For the alternative hypothesis Rouder assumes the Jeffreys-Zellner-Siow prior, which states that the effect size follows a Cauchy distribution, where effect size is the difference of means over the standard deviation. A similar default prior can be used for ANOVA (Rouder et al., 2012) and regression problems (Liang et al., 2008). These default prior methods have the advantage that one can compute the BF directly from sample sizes and the t-statistics, F-statistics, or R-square, respectively. To compute a BF we use the MATLAB code of Bart Krekelberg, which implements these default priors (https://github.com/klabhub/bayesFactor).

Frequency analysis of heart rate fluctuations

To investigate which timescale the inter-subject correlation and HRV is modulated by attention we do a frequency analysis of the instantaneous HR signal (Figure 4). The instantaneous HR signal was band-pass filtered using 5th order butterworth filters with logarithmic spaced center frequencies with a bandwidth of 0.2 of the center frequency. The ISC was computed in each frequency band referenced to the attentive group (Figure 4A). The HRV was computed as the standard deviation of the instantaneous HR normalized with the average HR (Figure 4B).

CellPress
OPEN ACCESS

Computation of Fractional Anisotropy index (FA index)

Diffusion Tensor Images (DTI) were acquired on a 3T Siemens Skyra scanner (64 diffusion gradient directions, b value = 1000 s/mm^2, TR/TE = 3000/80 ms, voxel size = 2x2x2 mm^3). DTI data were pre-processed using the FDT package from the Functional MRI of the Brain (FMRIB) software library (FSL) package 5.01 (Jenkinson et al., 2012). This consisted of: 1) correcting for motion and distortions caused by eddy currents; 2) brain segmentation using the brain extraction tool algorithm; 3) computing the fractional anisotropy (FA) maps using the diffusion-tensor model; 4) registration of the FA and MD maps on the FA template in the standard Montreal Neurological Institute (MNI) space using linear as well as nonlinear spatial transformations. FA values were averaged within a deep white-matter mask defined in the MNI space as the outline of the ICBM-DTI-81 white-matter labels atlas (Mori et al., 2008). For each subject, this FA value was normalized with the mean of FA values measured from 10 healthy volunteers acquired with the same imaging protocol, such that an average FA index of 1.0 can be considered normal.