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EEG signature of near-death-like experiences during syncope-induced periods of unresponsiveness

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ABSTRACT

During fainting, disconnected consciousness may emerge in the form of dream-like experiences. Characterized by extra-ordinary and mystical features, these subjective experiences have been associated to near-death-like experiences (NDEs-like). We here aim to assess brain activity during syncope-induced disconnected consciousness by means of high-density EEG monitoring. Transient loss of consciousness and unresponsiveness were induced in 27 healthy volunteers through hyperventilation, orthostasis, and Valsalva maneuvers. Upon awakening, subjects were asked to report memories, if any. The Greyson NDE scale was used to evaluate the potential phenomenological content experienced during the syncope-induced periods of unresponsiveness. EEG source reconstruction assessed cortical activations during fainting, which were regressed out with subjective reports collected upon recovery of normal consciousness. We also conducted functional connectivity, graph-theoretic and complexity analyses. High quality high-density EEG data were obtained in 22 volunteers during syncope and unresponsiveness (lasting 22±8 s). NDE-like features (Greyson NDE scale total score ≥7/32) were apparent for eight volunteers and characterized by higher activity in delta, theta and beta2 bands in temporal and frontal regions. The richness of the NDE-like content was associated with delta, theta and beta2 bands cortical current densities, in temporal, parietal and frontal lobes, including insula, right temporoparietal junction, and cingulate cortex. Our analyses also revealed a higher complexity and that networks related to delta, theta, and beta2 bands were characterized by a higher overall connectivity paralleled by a higher segregation (i.e., local efficiency) and a higher integration (i.e., global efficiency) for the NDE-like group compared to the non-NDE-like group. Fainting-induced NDE-like episodes seem to be sustained by surges of neural activity representing promising markers of disconnected consciousness.

1. Introduction

Syncope refers to an episode of transient disconnection from the environment characterized by a relatively rapid onset, typically leading to falling, and a subsequent spontaneous, complete, and prompt (after 1 min at most) recovery. Syncope is caused by a transient global cerebral hypoperfusion and is typically characterized by large amplitude slow waves (Brignole et al., 2001). Although syncope is a common disorder affecting people of all ages (Mathias et al., 2001) and even sometimes intentionally induced by teenagers using the so-called "fainting lark" maneuver for amusement purposes (Johnson et al., 1984), the associated subjective experience remains under-explored. Dreams and dissociative symptoms sometimes amounting to out-of-body experiences, are common manifestations of syncope (Brandt et al., 2009). However, they are only occasionally mentioned in scientific literature as they are usually disregarded due to their mystical nature and the lack of systematic investigations by clinicians.

Typically, an episode of vasovagal syncope causes unresponsiveness and outwardly loss of consciousness. These neurocardiogenic or reflex syncopes are quite common and are known to be harmless unlike other

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causes of fainting (Brignole et al., 2001). The lack of spontaneous responsiveness during a vasovagal syncope does not, however, necessarily indicate a transition to a state of unconsciousness (Sanders et al., 2012). Indeed, unresponsiveness also characterizes episodes of disconnected consciousness, corresponding to subjective experience without awareness of the external world (Martial et al., 2020). Consciousness and behavioral responsiveness may decouple, as repeatedly shown by brain imaging studies in specific pharmacologically-induced states (Sarasso et al., 2015) as well as in severe pathological conditions such as in patients diagnosed at the bedside with unresponsive wakefulness syndrome but who may willfully modulate their brain activity using active task paradigms (Monti et al., 2010). Although not as frequently reported, this distinction between (un)responsiveness and (un)consciousness has also been testified by the detailed subjective reports upon awakening from less severe and transient pathological conditions such as syncope-episodes (Lempert et al., 1994a).

In 1994, while investigating motor phenomena of syncope in a cohort of healthy young adults, Lempert et al. (1994b) were among the first to report syncopal hallucinations. Hyperventilation followed by Valsalva maneuver was used to document the sequence of events during abrupt-onset syncope. Out of 42 young adult volunteers, 25 subsequently reported visual and auditory hallucinations, such as out-of-body experiences, encountering relatives or more blurred entities, and hearing voices (Lempert et al., 1994a; 1994b). Some of the participants admitted being reluctant to "return to reality" (Lempert, 1996). The authors qualified those memories as similar to near-death experience (NDE, defined as an episode of disconnected consciousness containing prototypical [mystical] features) (Martial et al., 2020) in line with the description given by Pr. Moody in his bestseller "*Life after Life*" (Moody, 1975), because of their close resemblance to subjective experiences reported after pathological and severe prolonged periods of cerebral hypoxia (i.e., cardiac arrest) (van Lommel et al., 2001). Interestingly, vivid pleasant hallucinations have also been observed in other severe brief cerebral hypoxia episodes such as in rapid acceleration during training by Airforce pilots (Whinnery and Whinnery, 1990) or in apnea (Annen et al., 2021). So far, although some mechanisms such as rapid eye movement (REM) sleep intrusions (Nelson et al., 2006) have been suggested to form the basis of subjective experience reported after fainting and strikingly resembling NDE, very little is known about the neural and subjective effects of syncope-episodes.

The aim of this study is to explore brain activity during syncope-induced disconnected consciousness with the use of source reconstruction methods applied on high-density electroencephalography (EEG) recordings. We further investigate the relationship between the cortex's electrical signals with the reported behavioral data and subjective experience. Finally, we explore differences between volunteers who reported an episode of disconnected consciousness that encompasses prototypical features of NDEs and those who did not, both in brain complexity measure and in the organization and dynamics of cortical networks.

2. Materials and methods

2.1. Participants

Prior to the experiment, potential adult volunteers were enquired about their medical history and went through a physical examination by a certified anesthesiologist, an intensivist, and a neurologist to exclude any history of psychiatric, neurological, cardiac, or respiratory disorders as well as of the use of medications acting on the central nervous system, and regular drug and alcohol intake. Informed written consent was obtained from all eligible participants. The experimental protocol (Supplementary Appendix 1, SA1) was approved by the ethical committee of the Faculty of Medicine of the University of Liège in accordance with the tenets of the Declaration of Helsinki and its later amendments.

2.2. Experimental procedure

The experimental session took place in a room of the anesthesiology department. Upon arrival, each volunteer was instructed on the methods to self-induce syncope using the Valsalva maneuver (SA1). After 10 min of resting state sitting down monitored by high-density EEG recording (5 min eyes-open and 5 min eyes-closed in a randomized order, SA1), volunteers attempted to self-induce a syncope (SA1). To ensure volunteers safety during episodes of loss of consciousness, a tilt table was strategically positioned behind them to catch and support their fall. Brain activity was recorded throughout the session using a Net-Amp 300 system (Electrical Geodesic Inc., Eugene, OR, USA) with a 256 electrodes HydroCel Geodesic Sensor Net. Electrode impedances were kept lower than 50 kΩ throughout the recording in line with Geodesic's recommendations (impedances were checked both at the beginning and at the end of the recording). Video documentation was provided by three video cameras (SA1). Syncope-episodes were jointly reviewed by two authors (VCV and AP) on video recordings (SA1). All episodes were evaluated with respect to behavioral features: number of Valsalva maneuvers to induce a syncope, loss of consciousness (i.e., loss of muscle tone and mydriases) (Lempert, 1996; Wieling et al., 2009), falls, myoclonus, non-myoclonic movements, eye movements, and vocalizations. The episode's duration was estimated based on the observation of the behavioral response from the fainting induction to the return of responsiveness (eyes opening, talking). Upon return to responsiveness, subjects were asked to report memories (if any), related to the syncope-episode. After the free recall report (audiotaped), the Greyson NDE scale (Greyson, 1983) (see SA2) was administered to assess potential NDE phenomenological content experienced during the syncope.

2.3. Demographics and syncope-episodes behavioral features

For each subject, demographic, syncope-episodes behavioral features and duration (before and after removal of EEG artifacted epochs) were collected along with NDE scores (Table 1 and SA3).

2.4. EEG analysis

EEG pre-processing and analyses were implemented in MATLAB (MathWorks, Natick, MA, USA). For each subject, eyes-open and eyes-closed baseline periods as well as the syncope-episode were extracted. EEG traces were downsampled to 250 Hz and band-bass filtered between 0.5 and 40Hz: higher frequencies were not considered to avoid as much as possible the influence of muscular artifacts.

EEG signals were then inspected and cleaned from artifacts (for a detailed description of the procedure, see SA4.1; see SA12 for additional analyses), retaining 185 electrodes out of 256 for all the following analyses (Chennu et al., 2014). The noise-free EEG signals were re-referenced to the channels' average and divided in two seconds non-overlapping and consecutive epochs. The mean power spectral densities (PSDs) as a function of frequency were estimated for all the electrodes using a Hanning-windowed Fast Fourier Transform (FFT) and presented for 14 representative electrodes (see SA5.1) in three conditions: eyes-closed rest, eyes-open rest and syncope (for syncope episodes both the PSDs averaged over the whole group and the average PSDs of subjects with NDE scores ≥ 7 versus the average of subject with NDE scores <7 were taken into account, see SA5 for an in-depth description).

2.4.1. Source reconstruction of band-limited signals

EEG signals were band-pass filtered in six bands of interest: delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta1 (13–18 Hz), beta2 (18–30 Hz) and gamma (30–40 Hz). Cortical standardized current densities (sLORETA (Pascual-Marqui et al., 2002), cortical activations hereafter), were estimated based on 185 electrodes for each band and condition (eyes-closed rest, eyes-open rest, and syncope), using Brainstorm functions (Tadel et al., 2011) and OpenMEEG software (Gramfort et al., 2010) (see

Table 1
Phenomenology reported after syncope according to the Greyson NDE scale. The presence of the item corresponds to a rating of 1 or 2 of the response scoring.

Greyson NDE scale items	NDE-like group ($n = 8$)	Non-NDE-like group ($n = 14$)	Fisher's exact test *p*-value
"*Did time seem to speed up or slow down?*"	8	12	.515
No. of participants (%)	(100 %)	(86 %)	
"*Were your thoughts speeded up?*"	7	3	**.006**
No. of participants (%)	(88 %)	(21 %)	
"*Did scenes from your past come back to you?*"	4	0	**.010**
No. of participants (%)	(50 %)	(0 %)	
"*Did you suddenly seem to understand everything?*"	0	0	–
No. of participants (%)	(0 %)	(0 %)	
"*Did you have a feeling of peace or pleasantness?*"	7	8	.193
No. of participants (%)	(88 %)	(57 %)	
"*Did you have a feeling of joy?*"	4	2	.137
No. of participants (%)	(50 %)	(14 %)	
"*Did you feel a sense of harmony or unity with the universe?*"	5	3	.081
No. of participants (%)	(63 %)	(21 %)	
"*Did you see, or feel surrounded by, a brilliant light?*"	2	0	.121
No. of participants (%)	(25 %)	(0 %)	
"*Were your senses more vivid than usual?*"	6	5	.183
No. of participants (%)	(75 %)	(36 %)	
"*Did you seem to be aware of things going on elsewhere, as if by extra sensory perception?*"	0	0	–
No. of participants (%)	(0 %)	(0 %)	
"*Did scenes from the future come to you?*"	0	0	–
No. of participants (%)	(0 %)	(0 %)	
"*Did you feel separated from your body?*"	8	8	.051
No. of participants (%)	(100 %)	(57 %)	
"*Did you seem to enter some other, unearthly world?*"	4	0	**.010**
No. of participants (%)	(50 %)	(0 %)	
"*Did you seem to encounter a mystical being or presence, or hear an unidentifiable voice?*"	2	0	.121
No. of participants (%)	(25 %)	(0 %)	
"*Did you see deceased or religious spirits?*"	0	0	–
No. of participants (%)	(0 %)	(0 %)	
"*Did you come to a border or point of no return?*"	0	0	–
No. of participants (%)	(0 %)	(0 %)	
Total score	10±2	4 ± 1	**<0.001**
Mean±SD (range)	(7–14)	(0–5)	**(*t*-test)**

NDE-like=near-death-like experience; SD=standard deviation.

SA6). For each subject, condition, and band, the mean cortical activations map was obtained averaging over time-samples (SA7).

2.4.2. Between-group comparisons

Subjects were divided into two groups: "NDE-like" (Greyson NDE score ≥7/32) and "non-NDE-like" (Greyson NDE score <7/32, Greyson, 1983). Between-group differences in gender composition and behavioral manifestations of the syncope were assessed using Fisher exact test, while for the other features, permutation tests on unpaired t-statistics were performed (10,000 permutations (Ludbrook and Dudley, 1988), see SA3).

For each band, between-group differences in cortical activations during syncope episodes were assessed using a single threshold permutation test for the maximum t-statistics (Statistical NonParametric Mapping, SnPM, 10,000 permutations (Nichols and Holmes, 2001), SA4.2). As a control, the same analyses were performed also for eyes-closed and eyes-open rest conditions (SA7, whole cohort of volunteers).

With the aim of checking for the putative influence of residual artifactual activity on the processed signals (possibly due to a non-perfect artifact cleaning procedure), we performed the same between-group cortical analyses on:

i) subjects with syncope episodes showing myoclonic activity (SA10, NDE-like group=8 subjects, non-NDE like group=8 subjects; cortical activations estimated from cleaned signals).
ii) subjects with syncope episodes characterized by the presence of vocalizations (SA11, NDE-like group=7 subjects, non-NDE like group=4 subjects; cortical activations estimated from cleaned signals).
iii) Full-band cortical activations of subjects' raw signals (before the artifact cleaning procedure), and artifact-free signals (SA12).
iv) Band-wise cortical activations of subjects' raw signals (before the artifact cleaning procedure, SA12).

2.4.3. Regression analyses

Linear regressions between demographic data and syncope-episodes behavioral features on the one side and NDE total scores on the other were estimated (SA8).

For each band and condition (eyes-closed and eyes-open rest and syncope-episode), voxel-wise cortical activations were then submitted to linear regressions with NDE total scores: putative associations between cortical activations and NDE scores were thus tested on multiple voxels (15,000), obtaining a series of statistical cortical images. For each band and condition, significant relationships were assessed using a single threshold permutation test for the maximum t-statistics (10,000 permutations (Nichols and Holmes, 2001), SA4.2). Significance threshold was set at $p < 0.05$ (the same threshold holds for all the analyses herein presented); descriptive statistics is presented, unless otherwise stated, as mean ± standard deviation.

2.4.4. Complexity

We next estimated the complexity of the cortical full band signals (1–40 Hz). For each subject (i.e., syncope episode), and voxel, the cortical activation time-course was divided in 2 s consecutive epochs (50 % overlap between contiguous epochs). For each epoch the signal was binarized using the approach described in Schartner et al. (2015) and the complexity was then estimated using Lempel-Ziv algorithm (Lempel and Ziv, 1976). Complexity at each voxel was finally obtained as the average over the epochs pertaining to the voxel time-course. At the end

of the procedure, we obtained a map quantifying the complexity of each single cortical voxel (one map for each subject). For each group (NDE-like and non-NDE-like), the mean signal diversity cortical distribution was estimated by averaging across subjects (see SA13). Between-group differences in complexity during syncope episodes were then assessed using a single threshold permutation test for the maximum t-statistics (10,000 permutations).

2.4.5. Cortical segmentation

The cortex was segmented using a slightly modified version of the Desikan-Killiany atlas (Desikan et al., 2006), resulting in 60 cortical regions (see SA14). For each subject/syncope episode, and band of interest (delta, theta, alpha, beta1, beta2 and gamma), the time course of each region was obtained by averaging over the time courses of its constituent voxels.

2.4.6. Functional connectivity between cortical areas

For each subject/syncope episode, the connectivity between each couple of cortical areas was estimated using the debiased weighted Phase Lag Index (Vinck et al., 2011) (connectivity hereafter). For the purpose, each syncope episode was segmented into 2 s epochs with a 50 % overlap between contiguous ones. For each epoch and couple of cortical areas, the connectivity in each band of interest was obtained by averaging over its frequency bins. The average connectivity for each subject/syncope episode and band was finally estimated for each couple of areas by averaging over the epochs pertaining to the syncope episode itself. At the end of the procedure, for each subject and frequency band a cortical connectivity map was obtained. For each band, between-group (NDE-like versus non-NDE-like) differences were estimated by means of couple-wise unpaired *t*-tests (i.e., between all possible couples of cortical areas). T-values significance for each between-group series of tests (one series for each band), were assessed using a single threshold permutation test for the maximum t-statistics (10,000 randomizations). Connectivity maps were generated using BrainNet Viewer Toolbox (Xia et al., 2013).

2.4.7. Graph-theoretic analysis

For each subject, connectivity values across all cortical regions pairs were organized in symmetric 60×60 matrices for each band of interest. Connectivity matrices were thresholded, varying the connection density to retain between 50 % and 10 % of the higher connectivity values in steps of 2.5 % (Chennu et al., 2016). Connectivity matrices were presented as graphs, with cortical areas as nodes and non-zero connectivity as between-nodes links. Each weighted graph was then characterized by a set of metrics estimated using Brain Connectivity Toolbox functions (Rubinov and Sporns, 2010):

i) graph strength: the network graph strength is estimated as the average over nodal strengths (note that the strength of a node is defined as the sum of its connectivities).
ii) local efficiency: the local efficiency of a node is the global efficiency of the subgraph composed by the neighbors of the node itself. The graph local efficiency is estimated as the average over the local efficiencies of the graph nodes: this measure reflects the degree of segregation within a network.
iii) global efficiency: The global efficiency is the average inverse shortest path length in the network and gives an estimate of the degree of large-scale network integration.
iv) modular structure and modularity: The modular structure of a graph is obtained by subdividing the network in groups of nodes (maximizing the number of within-group links and minimizing the number of between-group links). Modularity represents the degree of reliability of a given modular structure (Newman, 2006).
v) participation coefficient: it quantifies the extent to which a node within a module is connected with other modules.

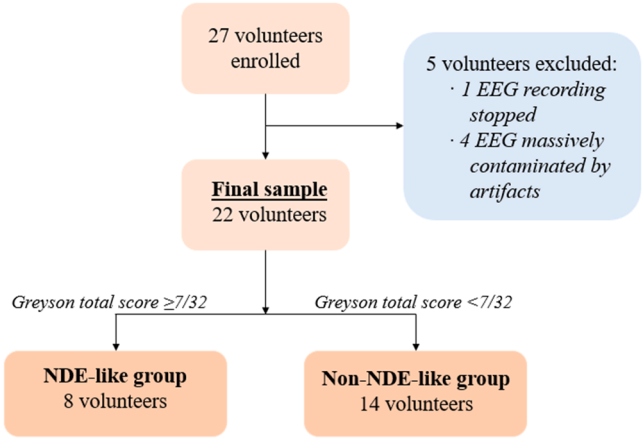

Fig. 1. Flow chart of sample.

For each subject and band, each metric was averaged over the considered connection densities (50–10 %, in steps of 2.5 %). The collected graph parameters of each band (graph strength, local coefficient, global efficiency, modularity and participation coefficient) were singularly submitted to an unpaired *t*-test (NDE-like versus non-NDE-like group). For each band, p-values (one for each graph metric) were adjusted for multiple testing using the False Discovery Rate procedure (Benjamini and Hochberg, 1995).

3. Results

3.1. Participants

Twenty-seven volunteers were enrolled in the study. The final sample consisted of 22 volunteers (10 females; age 24±4 years). Five subjects were excluded (see Fig. 1 and SA9). Groups did not differ regarding demographics (age: NDE-like group=25±6, non-NDE-like group=24±3, $p = 0.41$; gender: NDE-like group=4[50 %], non-NDE-like group=6[43 %], $p = 1$; see SA3-A and SA3-B for details). Eight subjects (36 %) out of 22 had NDE scores higher than 7 (scores ≥7 identify a NDE for research purposes (Greyson, 1983). The NDE-like group reported more often the experience of speeding thoughts, seeing scenes from the past and entering some unearthly world, as compared to the non-NDE-like group (Table 1). The only syncope-episodes behavioral feature showing significant between-groups differences was vocalizations, which were more frequent in the NDE-like group (see SA3-A and SA3-B for syncope-episodes behavioral features).

3.2. Syncope-episodes are characterized by higher delta and theta activity with respect to eyes-closed and eyes-open rest

Syncope-episodes were characterized by higher PSD at low frequencies (theta and delta bands) on the whole scalp but especially when considering pre-frontal and frontal areas. Higher frequency activity (beta bands) was also observed during syncope-episodes in frontal areas as compared to both resting state conditions (SA5-A, SA5-B).

3.3. Between-group comparisons

Scalp level analyses revealed that NDE-like volunteers as compared to non-NDE-like ones, were characterized by 1) a higher PSD in delta/theta bands both in frontal and posterior regions, and 2) a higher PSD in beta1/beta2 bands especially when considering midline areas. At variance with non-NDE-like volunteers, the NDE-like group was characterized by the presence of two different peaks within delta band, the former at 1 Hz (in line with non-NDE-like subjects), and the latter at 3–4 Hz (see SA5-C and D).

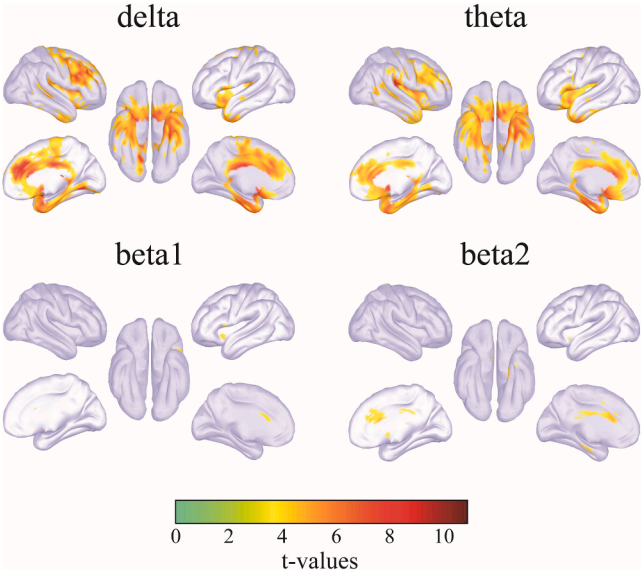

Fig. 2. Cortical level differences between NDE-like and non-NDE-like groups for significant frequency bands. T-values cortical maps of the NDE-like versus non-NDE-like comparisons are presented for those bands showing significant between-group differences after SnPM correction. Thresholds for significance at $p = 0.05$ are $|t| = 4.46$ for delta, $|t| = 4.43$ for theta, $|t| = 4.41$ for beta1 and $|t| = 4.45$ for beta2 bands. Thresholds for significance at $p = 0.001$ are $|t| = 7.02$ for delta, and $|t| = 7.16$ for theta. Voxels with $p > 0.05$ are left uncolored. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

At the cortical level, the NDE-like group showed higher activations (after SnPM correction), in all bands except for alpha (Fig. 2, SA7-G and SA7-H). Delta and theta strongly differentiated the NDE-like from the non-NDE-like group, as higher cortical activations were found in several cortical areas including cingulate cortex, mesio-temporal lobe, insular cortex, orbitofrontal cortex, right dorsolateral prefrontal cortex, right temporoparietal junction, and the anterior portion of the temporal lobes (see also SA7-I, J and K). Higher activations in beta1 band were apparent when considering the left anterior cingulate cortex and the left insula. Beta2 showed higher activations within the cingulate cortex and the anterior sections of the mesio-temporal lobe. Although not significant, higher activations (or power densities, when considering scalp analysis), where observed for all frequency bands and most cortical (scalp) regions. Of note, the same analyses performed on cortical activations derived from raw (i.e., non-cleaned) signals did not show any significant between-group difference (SA12-C).

No significant result was observed also for band-wise comparisons between NDE-like and non-NDE-like groups in both eyes-closed and eyes-open rest conditions (SA7-A, B and C, and SA7-D, E and F respectively). When considering either the myoclonus or the vocalizations subgroups, we observed that band-wise between group (NDE-like versus non-NDE-like) significant differences were largely superimposable to those observed for the whole cohort of subjects (SA10–11). Finally, when considering full band (1–40 Hz) cortical activations, we observed significant between group differences for the cleaned signals (i.e., artifact-free), and largely non-significant ones for the raw signals (SA12-A, B). These results taken together provide convincing evidence of the non-artifactual nature of our signals and thus of the reliability of findings herein presented.

3.4. Band-wise regression between cortical activations and NDE scores

Significant positive relationships were found between syncope episodes' delta, theta and beta2 bands activity and NDE scores (Fig. 3, SA8-C, D, E and F). Delta showed cortically widespread significant associations with NDE scores, albeit characterized by a slight right-hemispheric prevalence. Involved cortical structures included insula, cingulate cortex, mesiotemporal lobe and specifically the parahippocampal gyrus, temporal poles, orbitofrontal cortex, right dorsolateral prefrontal cortex, and right temporoparietal junction. Theta was characterized by significant positive regressions involving right temporoparietal junction, anterior cingulate cortex, lateral orbitofrontal cortex, mesiotemporal lobe (including the parahippocampal gyrus), temporal poles, and right insula (SA8). Beta2 showed positive relationships with bilateral clusters of voxels within the insula, the medial and lateral orbitofrontal cortices. Regressions performed either on eyes-closed rest or eyes-open rest did not yield any significant result for any band (SA8-A and SA8-B).

3.5. Higher complexity in NDE-like subjects during syncope episodes

We observed a significantly higher cortical diversity for the NDE-like group as compared to the non-NDE-like group in a variety of cortical areas including large portions of the parietal cortex, the right temporoparietal junction (bilaterally but with a right hemispheric prevalence), sections of the right temporal cortex and of the posterior frontal lobe, the precuneus and the posterior cingulate cortices. Of note, except for the above-mentioned area, the whole frontal lobe did not show any significant between-group difference (see Fig. 4).

3.6. Heightened functional connectivity in delta-theta and high-beta bands for the NDE-like group

We observed a significantly higher connectivity in NDE-like subjects compared to non-NDE-like subjects in delta, theta, and beta2 bands during syncope. For all the three bands, but especially for delta and theta, the enhancement involved widespread cortical areas (Fig. 5). At variance, no significant difference was found either for alpha, beta1 or gamma bands (see SA15).

More specifically, delta band was characterized by a higher connectivity involving areas pertaining to the parietal, occipital and temporal lobes of the right hemisphere, while frontal areas were relatively spared. When considering the left hemisphere, there was an involvement of areas encompassing all lobes including many limbic areas, with a lower involvement of parietal areas. Theta band showed a higher connectivity in areas pertaining to bilateral parietal, occipital and temporal lobes. Lastly, beta2 was characterized by a lower number of significant connectivity compared to the former bands. Right hemisphere areas of the parietal and especially of the occipital lobe showed significant connectivity with frontal and temporal areas.

3.7. Graph theoretical metrics

Delta, theta and beta2 bands had a significantly higher graph strength, local efficiency and global efficiency in the NDE-like group as compared to the non-NDE-like group (see Fig. 6). No differences were found when considering either modularity or participation coefficient (see SA16). At variance, no significant difference in connectivity network parameters was apparent either for alpha, beta1 or gamma bands (see SA16).

4. Discussion

This study demonstrates the capability of syncope to induce episodes of disconnected consciousness, intriguingly resembling NDE episodes. Indeed, eight volunteers out of 22 (36 %) reported a subjective experience that met criteria for an NDE-like (i.e., scoring ≥7 on the Greyson NDE scale (Greyson, 1983)). This finding is consistent with previous work suggesting the possibility to experience visual and auditory hallucinations (Brandt et al., 2009; Sanders et al., 2012; Martial et al., 2020; Sarasso et al., 2015; Monti et al., 2010;Lempert et al., 1994a, 1994b;

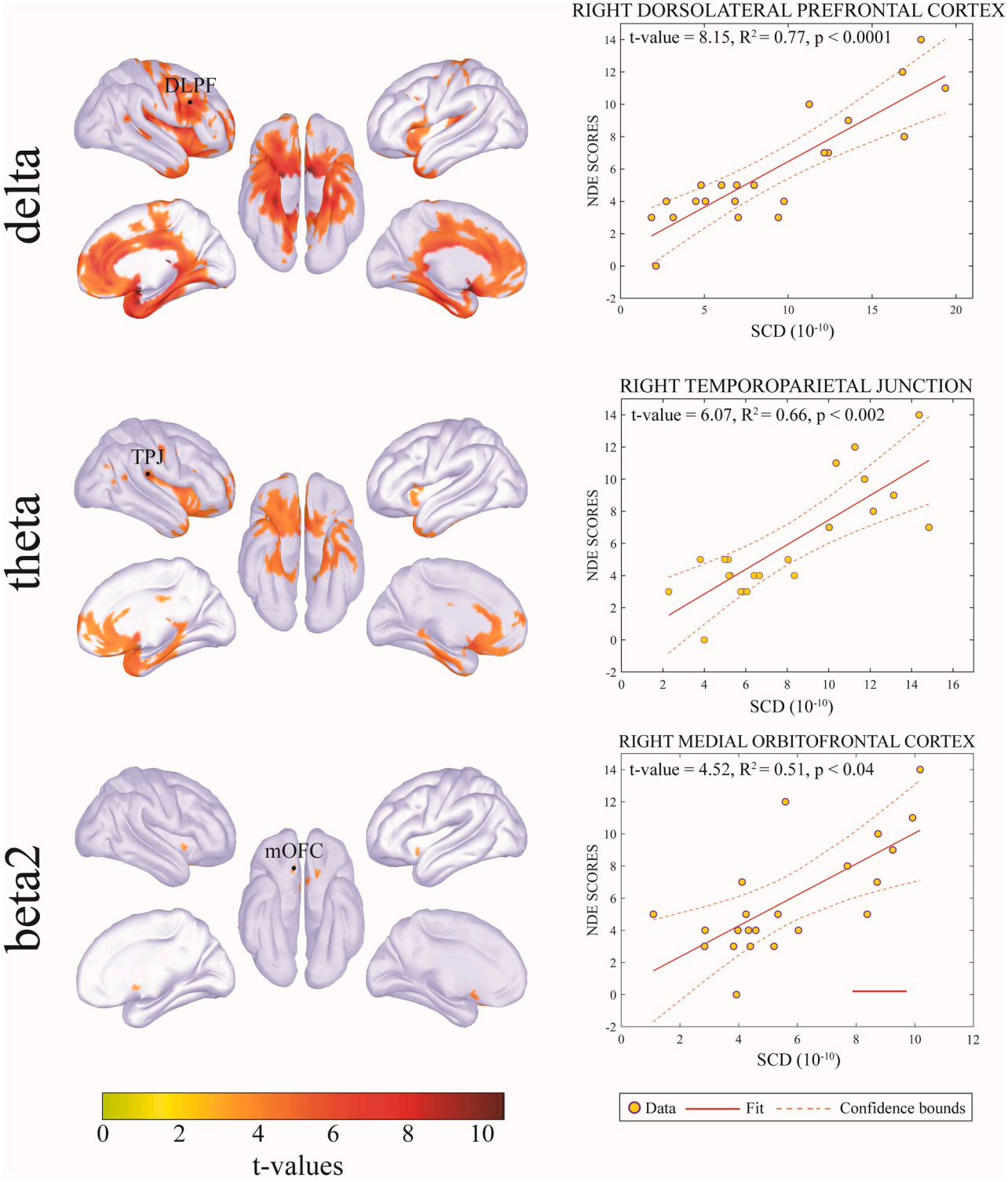

Fig. 3. Band-wise regressions between cortical activations and total NDE scores. T-values maps of the regressions between band-wise cortical activity (for all cortical voxels), and Greyson NDE total scores are presented for those bands showing significant relationships with NDE scores after SnPM correction: in the first column t-values statistical maps are presented. Thresholds for significance at $p = 0.05$ are $|t| = 4.25$ for delta, $|t| = 4.13$ for theta, and $|t| = 4.17$ for beta2 band. Thresholds for significance at $p = 0.001$ are $|t| = 6.38$ for delta, and $|t| = 6.44$ for theta. Voxels with $p > 0.05$ are left uncolored. In the second column, for each band, the scatterplot (yellow dots) with the related regression line (red line) along with its confidence bounds at 95 % (red-dotted lines) are presented for one of the voxels yielding the maximum significance. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Nelson et al., 2006), a feeling of euphoria or an impression to have a clearer mind (Cudaback, 1984) during cerebral hypoxia. Volunteers from the NDE-like group reported more often the experience of speeding thoughts, seeing scenes from the past and entering some unearthly world as compared to the other group. While the latter is one of the most frequently reported prototypical features in classical NDEs, the two formers are among the less frequently reported ones (Martial et al., 2019).

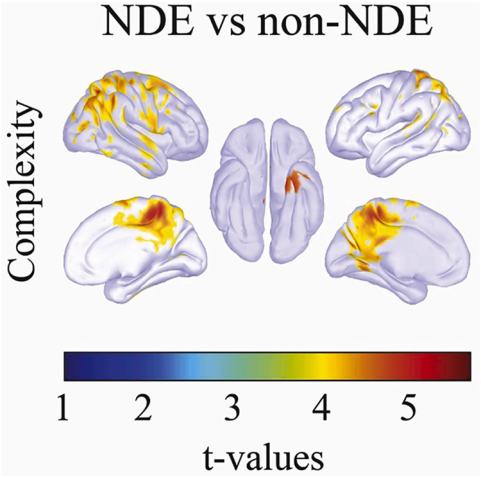

Fig. 4. Full-band Complexity: Between group (NDE-like vs non-NDE-like) cortical differences. T-values cortical maps of the NDE-like versus non-NDE-like comparisons related to complexity measures are presented. The threshold for significance at $p = 0.05$ is $|t| = 4.01$. Voxels with $p > 0.05$ are left uncolored. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

EEG results showed a slowing of background rhythms paralleled by the emergence of high amplitude delta activity that classically reflect cerebral hypoperfusion in syncope (Brenner, 1997). The increases in delta and theta oscillations were most clearly evident in frontal and pre-frontal regions. This is consistent with Ammirati and colleagues' (Ammirati et al., 1998) study demonstrating a diffuse high-amplitude (4 to 5 Hz) brainwave slowing, followed by a brain-wave amplitude increase with the reduction of frequency at 1.5 to 3 Hz in tilt-induced vasovagal syncope. Importantly, we also identified that the NDE-like group was further characterized by higher frequency activity (mostly in beta2 band), during syncope-episodes. Delta and theta strongly differentiated the NDE-like from the non-NDE-like group, with higher cortical activations in several regions including those at the junction of temporal, parietal, and frontal cortices. Interestingly, high amplitude delta and theta oscillations are neurophysiological signatures strongly associated with memory consolidation during slow wave sleep (Diekelmann and Born, 2010; Hutchison and Rathore, 2015; Marshall and Born, 2007; Stickgold and Walker, 2007; Tononi and Cirelli, 2006), while dreaming is most prominent when oscillatory activity is lower (Picard-Deland et al., 2023). Indeed, EEG oscillations in theta bands have been associated with the activation of memory-related structures including the parahippocampal gyrus (Carr et al., 2011; Karlsson and Frank, 2009; Brokaw et al., 2016), and have been found both in the hippocampus and in cortical structures serving as an arousal mechanism for the transition from sleep to wake in humans (Cantero et al., 2003). As such, we might hypothesize that the storage of newly encoded information into long-term memory during transient syncope-episodes may be modulated by theta and delta oscillations. Although the role of theta waves in memory consolidation is less clearly understood in some literature (see Headley and Paré, 2017) for a recent review), particularly in REM sleep, cortical delta oscillations have been suggested to play a crucial role in memory consolidation during slow wave sleep (Marshall et al., 2006; Mölle et al., 2004) and in other states (Headley and Paré, 2017), reflecting the exchange of information between the cortex, striatum, and hippocampus (Headley and Paré, 2017).

Our analyses revealed tight positive associations between theta and delta cortical activity and the richness of the subjective experience in specific regions of interest such as insula, temporoparietal junction, cingulate cortex and parahippocampal gyrus. Of note, these regions have been identified as key regions for self-awareness and the (sometimes disturbed) perception of our body, such as the association between right temporoparietal junction activity and out-of-body experiences (De Ridder et al., 2007), and that of the insula with interoception (Picard and Friston, 2014). The former region is regarded, according to a leading theory of consciousness (Koch et al., 2016), as an important part of the so-called posterior 'hot zone', purportedly crucial for consciousness. We did not however detect other marked correlations between the subjective experience and other parts of this suggested 'hot zone'. It is noteworthy that this key temporoparietal junction was also evidenced in a recent human study revealing a transient surge of gamma activities in some dying patients (Xu et al., 2023). Although speculatively, the authors, as well as previous works by Vicente et al. (2022) and Chawla et al. (2017) also demonstrating marked electrical surges after cessation of blood circulation, hypothesize that this marked activation could be suggestive of conscious processing in dying patients. Although these pioneer works are the first empirical studies that might potentially account for the subjective experiences reported by NDE experiencers in near-death conditions, we must remain cautious and future studies are needed to empirically demonstrate it.

Complexity analyses revealed a significantly higher cortical diversity for the NDE-like group as compared to the non-NDE-like group in several regions suggested to be part of the 'hot zone' including the temporoparietal junction, precuneus and posterior cingulate cortices, known for their involvement in episodes of disconnected consciousness (Herbet et al., 2014; Siclari et al., 2017) or impression of being "in a parallel world" (Balestrini et al., 2016). Moreover, functional connectivity analysis showed that delta band was characterized by a higher connectivity involving a number of areas pertaining to the parietal, occipital and temporal right lobes, theta band by a higher connectivity in areas pertaining to bilateral parietal, occipital and temporal right lobes for the NDE-like group as compared to the non-NDE-like group and beta2 band by a higher connectivity in the occipital lobe, but involving also sections of the parietal and temporal lobes. Taken together with the findings obtained by the graph theoretic analyses, this strongly suggests that networks related to delta, theta, and beta2 bands, are characterized by a higher overall connectivity paralleled by a higher segregation (i.e., local efficiency) and a higher integration (i.e., global efficiency) for the NDE-like as compared to the non-NDE-like group. The combination of high differentiation, integration and segregation, could be supportive of the emergence of episodes of disconnected consciousness in the NDE-like group. In line with leading theories of consciousness, which propose that high integration, segregated processing and differentiation of neural activity are essential for the emergence of conscious experiences (Tononi and Edelman, 1998; Tononi, 2004), our results suggest that the brain activity of NDE-like group's subjects may have reached a successful balance between these three processes that could have enabled the emergence of these NDEs-like.

A plausible hypothesis which would account for some (if not all) NDE (-like) features is that of REM intrusions, with the inactivation of the locus coeruleus and the REM-inhibiting serotonergic dorsal raphe nuclei as being central to an arousal system predisposed to REM intrusion and NDE(-like) (Nelson et al., 2006; Nelson, 2014). Indeed, two empirical studies have shown that people reporting NDEs have arousal systems predisposed to blending REM intrusions with waking consciousness (Nelson et al., 2006; Kondziella et al., 2019). The REM intrusion hypothesis gains further credibility from a neurophysiological standpoint as, in line with our findings, recent studies have shown that delta slow waves do occur also during REM sleep (Bernardi et al., 2019), and that REMs are characterized by the presence of frontal beta-theta networks involving the dorsolateral prefrontal and the anterior cingulate cortex (Vijayan et al., 2017). Interestingly, Bernardi et al. (2019) have recently described in humans delta bursts that bear striking resemblance to the ponto-geniculo-occipital waves observed in nonhuman species and proposed as substrate of dream imagery (Stuart and Conduit, 2009). Further empirical studies are needed to explore if these delta bursts could be linked to human dreams.

As accurately elucidated by Frohlich et al. (2021), a historically

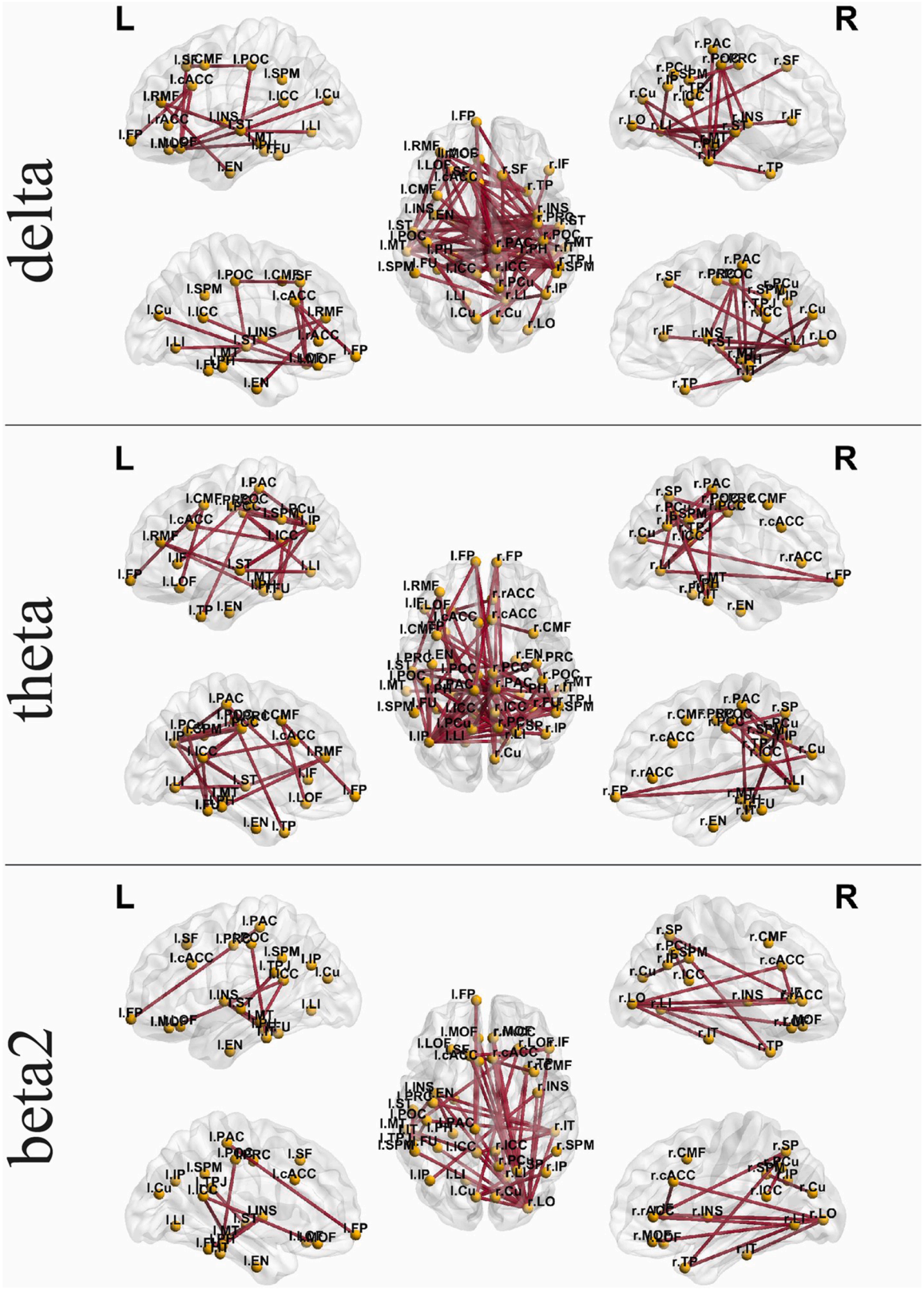

Fig. 5. Heightened connectivity between cortical areas in the NDE-like group. T-values cortical maps of significant connectivity differences between the NDE-like and the non-NDE-like group are presented for delta, theta and high-beta bands (first, second and third panel respectively). Connectivity between couple of areas (dark yellow spheres) showing significant between-group differences are illustrated using red lines whenever the connectivity is higher for the NDE-like group. For each band the left and right hemispheres lateral and medial views along with the dorsal view are shown. Note that for lateral and medial views, only intra-hemispheric connectivity is depicted. For each band only nodes (i.e., cortical areas) showing at least one significant connectivity with another node are presented. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

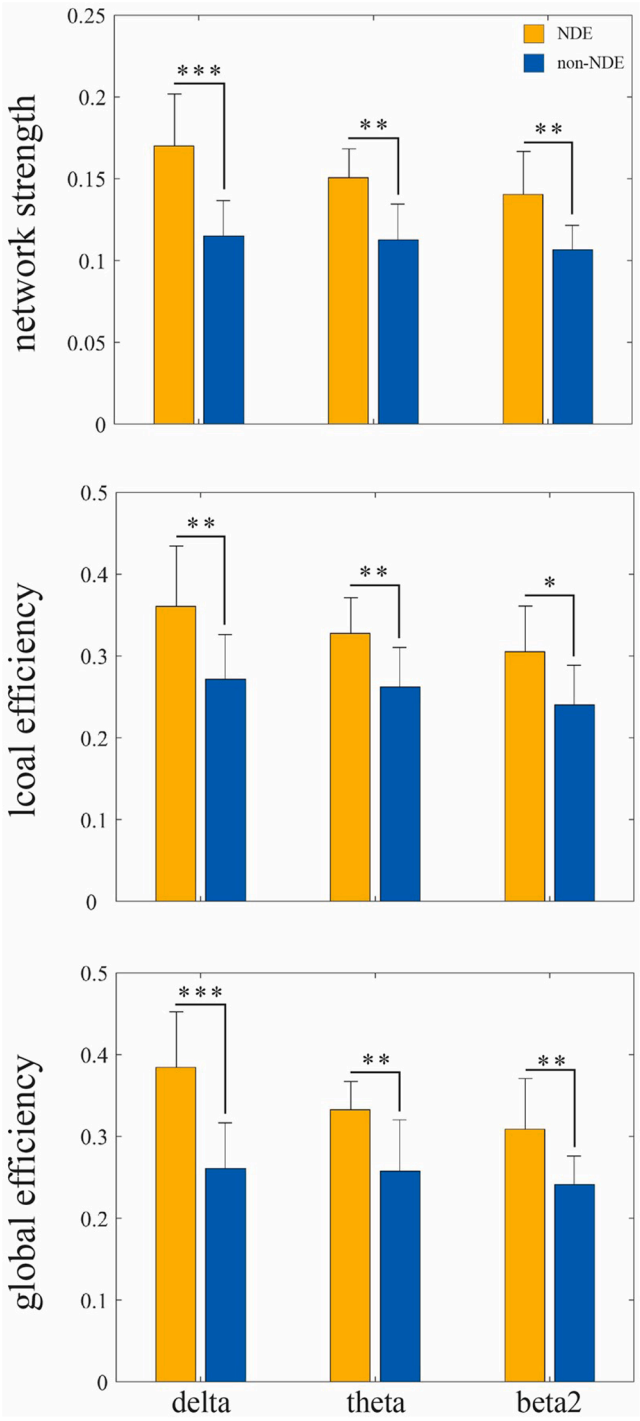

Fig. 6. Graph theoretic metrics for delta, theta and high-beta networks. For each metric of interest (network strength, local efficiency and global efficiency), descriptive statistics of the NDE-like (yellow bar) and the non-NDE-like group (blue bar) are presented as mean + standard deviation for delta, theta and high-beta band. For each metric and band, significant between group comparisons are highlighted by horizontal lines connecting the NDE-like to the non-NDE-like group bar. Significance at $p < 0.001$, $p < 0.01$ and $p < 0.05$ are respectively identified by three, two and one asterisk. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

rooted consensus in research is that the delta rhythm is an indicator of unconsciousness (or highly diminished consciousness), such as in anesthesia, slow wave sleep, and coma. However, a constantly growing body of evidence from recent research has revealed a prominent role of delta activity also during conscious mental states (Frohlich et al., 2021). Notably, a similar emergent theta and delta rhythmicity in psychedelic experiences induced by N,N-Dimethyltryptamine (DMT) which are characterized by vivid visual imagery and somatic effects, has been recently observed (Timmermann et al., 2019; Timmermann et al., 2023). In the same line, our results are also consistent with previous studies that have shown an increase of theta and delta power in ketamine-anesthetized subjects (Lee et al., 2013; Sarasso et al., 2015; Vlisides et al., 2018; Vlisides et al., 2017). Analogously to what happens during fainting, people under ketamine-induced anesthesia are behaviorally unresponsive but may provide delayed subjective reports of rich perceptions upon awakening (Sarasso et al., 2015). Interestingly, both DMT- and ketamine-induced experiences are known to closely resemble NDE phenomenology (Martial et al., 2019; Timmermann et al., 2018), just like we here demonstrate the resemblance of syncope-induced dream-like states with NDEs. Future research should be aimed at elucidating the association between delta rhythmicity and states of disconnected consciousness. In addition, it is worth mentioning that dream-like experiences may occur more often than expected, considering that some individuals may experience it, but it may not be necessarily stored in long-term memory.

Limitations of our study include the fact that physiological monitoring modalities such as electrocardiography used during the experimental session for the safety of the volunteers were not recorded. Other limitations are the lack of high-gamma characterization and the fact that all syncope-episodes were characterized by the presence of large artifacts both spontaneous (i.e., collapsing from an upright position at the beginning of the fainting), and exogenous (related to the experimental procedures: i.e., moving the participants on the verticalization table). Epochs contaminated by these non-stationary artifacts could not always be cleaned using the independent component analysis and were thus rejected, with the aim of ensuring a strict and reliable EEG cleaning procedure (dubious epochs were always removed). It is however worth mentioning we still retained on average more than the 70 % of time for each syncope episode (see Table SA3-A). Moreover, the removed sections depended on the single recording (i.e., they were not all at the beginning or at the end of the syncope episode): we did not observe any prevalence of a period over the others.

Indeed, the robust and highly significant association patterns between the content of dream-like experiences and cortical activity during the syncope-episodes, provides convincing evidence that the transient organized cortical electrical activity during the period of unresponsiveness may be linked to this specific dream-like experience.

However, caution is warranted in interpreting these results, as for other studies' aiming at reproducing NDEs-like in controlled laboratory settings using different approaches (Timmermann et al., 2018; Fritz et al., 2024). The hypothesis that the subjective experiences, as well as the associated pattern of electrical activity observed in this study, occur also in people who report a classical NDE in severe cerebral hypoxia is appealing but remains an open issue. A limitation of using syncope as a model for NDE-like is the absence of a life-threatening situation or a perceived imminent danger, which is a key aspect of classical NDEs. However, syncope offers the advantage of being a safe and reversible experimental model to study the NDE phenomenology in controlled laboratory settings. Future research is needed to further explore the subjective experiences associated with syncope, including those that may not meet the validated cut-off score on the Greyson NDE scale.

We believe that one final remark on the broadband activations observed in NDE-like subjects both at the scalp and the cortical level (SA12-A, B) is due. Analogous global power increases were described, among others, by Llinás et al. (1999) in patients with neurological (i.e., epilepsy), or neuropsychiatric disorders as compared to healthy

controls. Interestingly, even if the power enhancement encompasses almost all frequencies, two specific frequency ranges appear significantly higher in patients: delta-theta on the one side and beta-gamma on the other (Llinás et al., 1999). These findings are of particular interest for the present study as they are roughly superimposable to the results herein presented. As such, the thalamocortical dysrhythmia hypothesis elucidated by the authors —although completely reversible in our case, could inferentially be a plausible explanation of the broadband power increase we reported (note that significant enhancements were found in delta and theta band on the one side and in beta band on the other). Llinas and colleagues hypothesize that a deep hyperpolarization of the thalamus would cause the appearance of low-frequency oscillations. These oscillations, would in turn activate thalamocortical pathways, resulting in i) the emergence of large-scale and coherent, low-frequency oscillatory activity also at the cortical level, and ii) a reduction of lateral inhibition promoting high frequency oscillations. In our cohort of subjects, the NDE-like group showed a significantly higher low frequency activity as compared to the non-NDE group: we hypothesize that the higher hyperpolarization observed in the former group could have triggered the promotion of broad-band activity following the mechanisms described by Llinás et al. (1999). Indeed, the average syncope duration in the NDE-like group was higher than that observed in the non-NDE group (24 ± 9 s against 21 ± 7 s), although the difference was not significant (SA3, Tables SA3-A, B): a longer syncope-related hypoperfusion period in the NDE-like subjects would have resulted in higher delta activity as compared to the non NDE-like subjects. We must underline though, that the adherence to Llinas and colleagues' hypothesis is merely inferential, since with EEG data is not possible to ascertain whether and how "deep" brain structures like the upper brainstem, thalamus, or basal forebrain are affected by syncope, as stated by Van Dijk et al. (2014) in their EEG study on vasovagal syncope.

5. Conclusions

In conclusion, we showed that the volunteers reporting NDE-like features during fainting were characterized by higher cortical activity in delta, theta, and beta bands in temporal, parietal, and frontal areas. The richness of the NDE-like content was associated with delta, theta and beta2 bands cortical activations in temporal, parietal and frontal lobes. In addition, we found that cortical activity shows a higher complexity, and that networks related to delta, theta, and beta2 bands are characterized by a higher overall connectivity paralleled by a higher segregation (i.e., local efficiency) and a higher integration (i.e., global efficiency) for the NDE group as compared to the non-NDE one. Taken together, our findings convincingly support existing evidence of prominent delta and theta activity paralleled by activity at high frequency (i.e., beta2) as indicators of conscious mental states and strongly suggest that the slow oscillatory activity may provide a temporal frame favorable for the emergence of episodes of disconnected consciousness and of their subsequent memory encoding. Further studies on the syncope model and a thorough characterization of its neurobiological and phenomenological features could yield important insights on the relationship between delta oscillations and consciousness.

Data and code availability

Data and code may be provided to interested researchers upon reasonable request to the corresponding author, after clearance from the local Ethics Committee.

CRediT authorship contribution statement

Charlotte Martial: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation. **Andrea Piarulli:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation. **Olivia Gosseries:** Writing – review & editing, Methodology, Investigation, Data curation. **Héléna Cassol:** Data curation, Investigation, Writing – review & editing. **Didier Ledoux:** Writing – review & editing, Resources, Investigation, Data curation, Conceptualization. **Vanessa Charland-Verville:** Writing – review & editing, Project administration, Investigation, Data curation, Conceptualization. **Steven Laureys:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare there is no conflict of interests.

Data availability

Data will be made available on request.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.neuroimage.2024.120759.

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