

Impaired consciousness during temporal lobe seizures is related to increased long-distance cortical–subcortical synchronization

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Loss of consciousness (LOC) is a dramatic clinical manifestation of temporal lobe seizures. Its underlying mechanism could involve altered coordinated neuronal activity between the brain regions that support conscious information processing. The consciousness access hypothesis assumes the existence of a global workspace in which information becomes available via synchronized activity within neuronal modules, often widely distributed throughout the brain. Re-entry loops and, in particular, thalamo-cortical communication would be crucial to functionally bind different modules together. In the present investigation, we used intracranial recordings of cortical and subcortical structures in 12 patients, with intractable temporal lobe epilepsy (TLE), as part of their presurgical evaluation to investigate the relationship between states of consciousness and neuronal activity within the brain. The synchronization of electroencephalography signals between distant regions was estimated as a function of time by using non-linear regression analysis. We report that LOC occurring during temporal lobe seizures is characterized by increased long-distance synchronization between structures that are critical in processing awareness, including thalamus (Th) and parietal cortices. The degree of LOC was found to correlate with the amount of synchronization in thalamo-cortical systems. We suggest that excessive synchronization overloads the structures involved in consciousness processing, preventing them from treating incoming information, thus resulting in LOC.

Keywords: Temporal lobe epilepsy; consciousness; synchrony; EEG; global workspace

Abbreviations: BKG = background period; CG = posterior cingulate gyrus; EC = entorhinal cortex; ETSI = extra-temporal lobe synchronization index; h^2 = non-linear correlation coefficient; LOC = loss of consciousness; MS = middle part of the seizure period; MTG = middle temporal gyrus; P = lateral parietal cortex; SO = seizure onset period; TETSI = temporal–extra-temporal synchronization index; Th = thalamus; TSI = temporal lobe synchronization index

Introduction

Epilepsy is a prevalent disorder, affecting 1% of the population and negatively impacting quality of life (Hauser and Beghi, 2008). One of the most dramatic clinical manifestations during focal onset seizures is loss of consciousness (LOC). Whereas the structural and functional changes observed in partial seizure have been largely studied, the mechanisms leading to LOC are poorly known (Blumenfeld and Taylor, 2003). These mechanisms could share common brain alterations with those observed in other neurological or physiological conditions including deep sleep, comas and vegetative states (Baars, 2005). The study of clinical situations with LOC may add important insights to our knowledge of the brain circuitry engaged in the normal conscious state. In particular, all these conditions could be explained by an alteration of the 'global workspace' functioning (Dehaene and Naccache, 2001; Dehaene *et al.*, 2003a; Baars, 2005). The consciousness access hypothesis indeed assumes the existence of a global workspace (Dehaene and Naccache, 2001; Baars, 2005) in which information becomes available via synchronized activity within neuronal modules, often widely distributed throughout the brain (Tononi and Edelman, 1998; Dehaene and Naccache, 2001; Baars, 2002). Re-entry loops and, in particular, thalamo-cortical communication would be crucial to functionally bind different modules together (Tononi and Edelman, 1998; Llinas and Ribary, 2001). Conversely, the deactivation of thalamic structures, frontal and parietal cortices, which often correlates to the appearance of slow oscillations, would prevent information processed by sensory regions from accessing the workspace (Steriade *et al.*, 1993; Fiset *et al.*, 1999; Blumenfeld and Taylor, 2003; Maquet *et al.*, 2005; Velly *et al.*, 2007).

In the past decade, research using methods developed in non-linear dynamics has also investigated the relationship between consciousness and EEG characteristics. It has been shown that the complexity of the EEG is related to sleep–wake and conscious states (Coenen, 1998; Breakspear *et al.*, 2003). Complexity may be expressed by correlation dimension, a quantitative estimation of the degrees of freedom contributing to the generation of the EEG signal. The EEG complexity varies with the states of sleeping and waking (Gallez and Babloyantz, 1991). High complexity was found to characterize the beta EEG while this number decreases during the relaxed state, accompanied by alpha activity in the EEG and further decreases during slow wave sleep (Lopes da Silva, 1991). In addition, highly synchronized activity was found during slow wave sleep (Ferri *et al.*, 2005), linking low state of consciousness with highly synchronized EEG activity.

Excessive synchronization between subcortical and cortical modules would thus constitute a core mechanism of LOC. The demonstration of such a mechanism requires direct recordings from these brain regions on a fast timescale, while assessing the state of consciousness (Crick and Koch, 2003).

Seizures constitute an ideal model system to test this hypothesis. Loss of consciousness, when it occurs, is a dynamic and reversible process (Blumenfeld and Taylor, 2003). In the present article, we have studied mechanisms leading to LOC in temporal lobe epilepsy (TLE) seizures. These seizures are characterized by epileptic discharges originating from one or several regions of

the temporal lobe and propagating through an interconnected network within both cortical and subcortical structures (Guye *et al.*, 2006). Loss of consciousness occurs in a large proportion of TLE patients and has been the subject of several studies historically based on intracerebral recordings (Gloor *et al.*, 1980; Munari *et al.*, 1980). Nevertheless, one of the major limits of such studies is the lack of accepted tools to measure LOC during an epileptic seizure. The clinical appreciation of LOC is a rather elusive concept in epileptology, related to its subjective nature (Gloor, 1986; Luders *et al.*, 1998). An exterior description cannot directly account for the subjective experience of the patient during a seizure. In general, clinical studies rely on indirect criteria for the measure of consciousness. Recent studies have proposed 2–4 criteria to estimate consciousness during seizures (Lee *et al.*, 2002; Lux *et al.*, 2002; Blumenfeld *et al.*, 2004a, c). Different hypotheses have been proposed to explain how those seizures could impair consciousness. Intracerebral recordings (Guye *et al.*, 2006) and single photon emission computed tomography (SPECT) studies have suggested that secondary involvement of thalamus (Th) and/or subcortical structures during seizures plays a role in the impairment of consciousness (Lee *et al.*, 2002; Blumenfeld *et al.*, 2004a). Blumenfeld *et al.* (2004a, c) also suggest (according to SPECT and EEG studies) that LOC occurs when the associative cortices are secondarily impaired. In addition, some studies have suggested that alteration of consciousness is related to the spread of epileptic discharge to cortical structures contralateral to the origin of the seizures (Lux *et al.*, 2002) but LOC may occur during apparently unilateral seizures (Gloor *et al.*, 1980; Munari *et al.*, 1980).

None of these studies have thoroughly investigated the relationship between LOC and the dynamics of EEG changes during seizure. In the present investigation, we used intracranial recordings of cortical and subcortical structures in patients with intractable TLE, as part of their presurgical evaluation to investigate the relationship between states of consciousness and neuronal activity within the brain. The synchronization of broadband non-filtered EEG signals between distant regions was estimated as a function of time by using non-linear regression analysis. Since LOC during seizures may result from a secondary involvement of Th and/or subcortical structures (Lee *et al.*, 2002; Blumenfeld *et al.*, 2004a), or impairment of associative cortices (Blumenfeld *et al.*, 2004a, c), we focused on three regions of the temporal lobe [two mesial regions: the hippocampus (Hip) and the entorhinal cortex (EC), and one lateral region: the middle temporal gyrus (MTG)] as well as three regions outside the temporal lobe [the Th, the lateral parietal cortex (P), and the posterior cingulate gyrus (CG)].

Finally, we used the 'global workspace' model of consciousness to propose a framework of understanding the mechanisms of LOC during partial seizures.

Material and Methods

Selection of patients and SEEG recordings

Twelve patients (Table 1) undergoing pre-surgical evaluation of intractable TLE were selected among a series of 125 patients who had been

Table 1 Main patient characteristics

| Patients | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
|---------------------------------|-------|---|-------------------------|----------------|---------|--------|-------|---------|------------------------------------|----------|----------|-------|
| Age (years) | 43 | 32 | 39 | 24 | 22 | 17 | 36 | 36 | 35 | 23 | 43 | 43 |
| Gender | F | M | F | M | M | M | F | M | F | M | F | M |
| Epilepsy duration (years) | 25 | 15 | 19 | 21 | 10 | 12 | 20 | 18 | 32 | 10 | 11 | 35 |
| Aetiology | Cry | FCD | PVHT | BT | BT | HS | HS | Cry | FCD | FCD | PE | Cry |
| Aura | Fear | Anxiety cold olfactive hallucination | Epigastric sensation | Cold shiver | Deja vu | No | No | Anxiety | Epigastric sensation anxiety | Auditory | Auditory | No |
| LOC | No | Yes/no | Yes/no | Yes | Yes | Yes/No | No | Yes | No | No | No | Yes |
| Epilepsy sub-type | MTLE | MTLE | MTLE | MTLE | MTLE | MTLE | MTLE | MTLE | MTLE | LTLE | LTLE | LTLE |
| Side | Right | Left | Left | Left | Right | Left | Right | Left | Right | Right | Right | Right |
| Mean seizure duration (mn:s) | 01:16 | 02:28 | 03:55 | 01:28 | 00:58 | 01:21 | 00:41 | 01:03 | 01:02 | 06:18 | 02:40 | 00:44 |
| Surgery | ATL | ATL | NOp | ATL | ATL | ATL | ATL | NOp | ATL | NCR | NCR | NCR |
| Engel class | I | III | – | II | I | II | I | – | II | I | I | I |
| Follow-up (years) | 5 | 3 | – | 3 | 3 | 4 | 2 | – | 2 | 2 | 1 | 3 |
| Number of analysed seizures/LOC | 3/0 | 3/1 | 4/1 | 3/3 | 2/2 | 6/2 | 2/0 | 4/4 | 2/0 | 3/0 | 2/0 | 2/2 |

Cry = cryptogenic (normal MRI); FCD = focal cortical dysplasia; PVHT = periventricular nodular heterotopia; BT = brain tumour, HS = hippocampal sclerosis; PE = post-encephalitis; MTLE = mesial temporal lobe epilepsy; LTLE = lateral temporal lobe epilepsy; ATL = anterior temporal lobectomy; NOp = not operated; NCR = neocortical temporal resection; LOC = proportion of analysed seizures with loss of consciousness.

explored with intracerebral electrodes between 2000 and 2006. All patients had a comprehensive evaluation including detailed history and neurological examination, neuropsychological testing, routine MRI, surface EEG and stereoelectroencephalography (SEEG, depth electrodes) (Fig. 1A). SEEG was carried out as part of the patients' normal clinical care, and informed consent was given in the usual way. Patients were informed that their data might be used for research purposes. Patients were retrospectively selected if they satisfied the following criteria: (i) seizure involved the temporal lobe at seizure onset; (ii) at least one orthogonal intracerebral electrode reached the Th; or (iii) an electrode explored the lateral parietal lobe (lateral contacts) and the CG (internal contacts).

SEEG recordings were performed using intracerebral multiple contacts electrodes (10–15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart) placed intracranially according to Talairach's stereotactic method (Talairach *et al.*, 1992). A pre-planning of the implantation was performed on 3D T1-MRI images using a custom software (Regis *et al.*, 2005) for surface-rendering calculation, cortical anatomy analysis and sulci labelling (for more details see <http://brainvisa.info>). Video EEG recording was prolonged as long as necessary (up to a maximum of 10 days) for the recording of several of the patient's habitual seizures.

Intracerebral electrodes were then removed and an MRI performed, permitting visualization of the trajectory of each electrode (3D T₁-weighted images and T₂-weighted coronal images, Siemens, 1.5 T). Finally, computed tomography (CT)-scan/MRI data fusion was performed to anatomically check the location of each contact along the electrode. For the precise location of the contact in the Th, both Talairach's (Talairach and Tournoux, 1988) and Shaltenbrand's (Schaltenbrand and Wahren, 1977) atlases were used according to our previous study (Guye *et al.*, 2006). The exploration of the Th was not a primary objective except in two cases with a lesion affecting both Th and mesial temporal structures. For the remaining patients, thalamic recording (mainly the medial pulvinar group or the posterior part of the dorsomedian nucleus) was derived from the most internal leads of the single multi-contact electrode clinically required to explore the superior temporal gyrus and the posterior temporo-operculo-insular regions, thought to be potentially involved in the epileptogenic zone. Therefore, in these patients, no electrode was

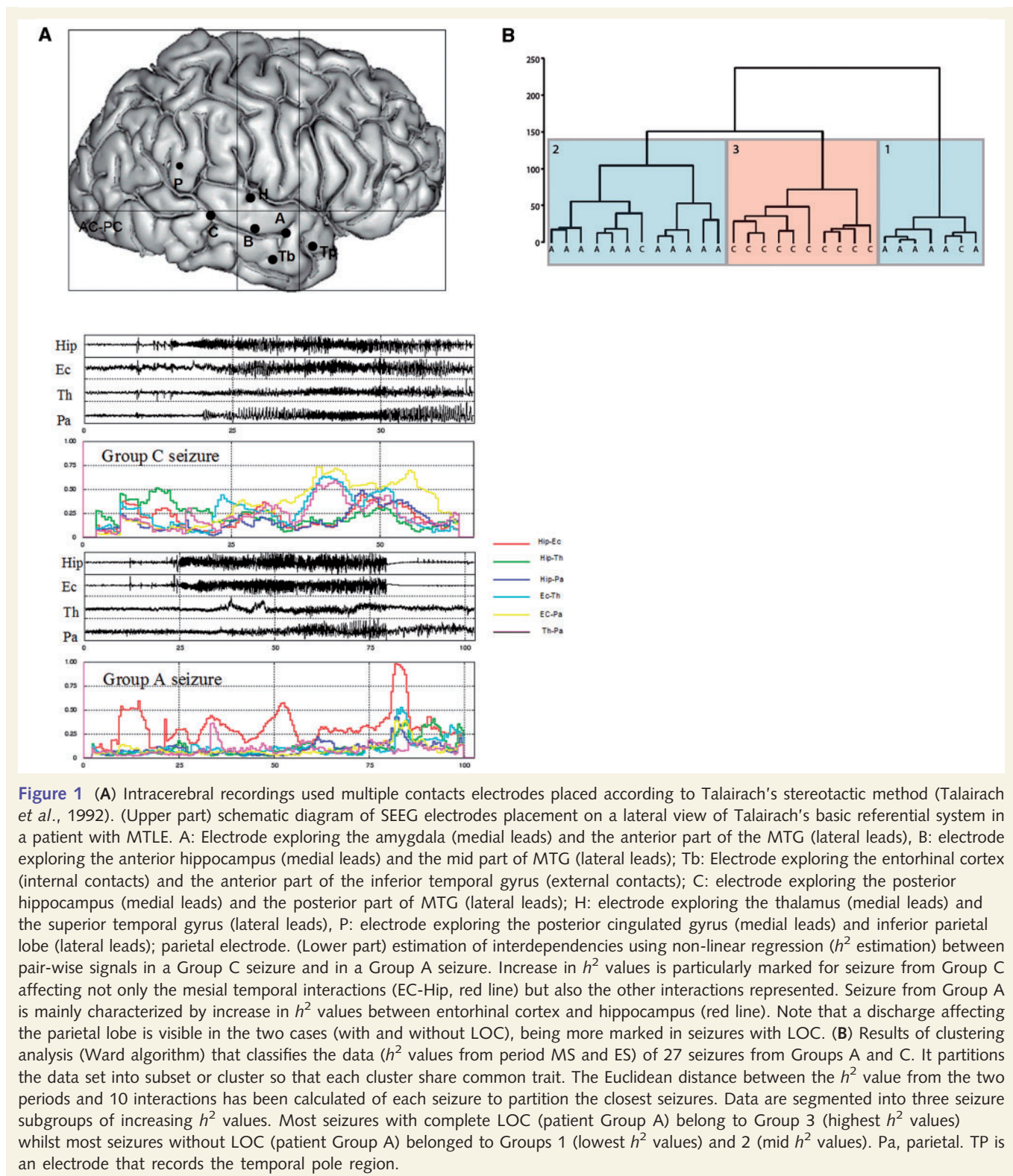
specifically implanted to record the Th in addition to those required by the diagnostic SEEG procedure.

Both spontaneous seizures and seizures induced by direct electrical stimulation were studied. Signals were recorded on a 128 channel Deltamed™ system. They were sampled either at 256 Hz or at 512 Hz and recorded on a hard disk (16 bits/sample) using no digital filter. Two hardware filters are present in the acquisition procedure. The first is a high-pass filter (cut-off frequency equal to 0.16 Hz at –3 dB) used to remove very slow variations that sometimes contaminate the baseline. The second is a first-order low-pass filter (cut-off frequency equal to 97 Hz at –3 dB) to avoid aliasing.

Determination of LOC during seizures: the consciousness seizure scale

Ninety-nine video recorded seizures from those 12 patients were analysed. To assess the degree of alteration of CS we created an eight criteria scale (Table 2) to avoid, as far as possible, the potential bias of external analysis of consciousness from video taped data.

This scale takes into account different aspects of consciousness in humans: (i) unresponsiveness (Criteria 1 and 2); (ii) visual attention (Criteria 3); (iii) consciousness of the seizure (Criteria 4); (iv) adapted behaviour (Criteria 5); and (v) amnesia (Criteria 6 and 7). We balanced those criteria with a 'global appreciation criteria' scored between 0 and 2 representing the global appreciation of LOC made by the epileptologist about the conscious state of his patient. Each seizure was scored twice (1 week apart), independently by two epileptologists (LV and FB), from 0 to 9. The mean of the two scores has been retained for the study. The intra-rater and inter-rater interclass correlation coefficients (ICC's) were computed for the consciousness seizure scale (CSS) quotations in order to test the validity of the scale (Snijders and Bosker, 1999). Seizures were not kept for analysis if: (i) the video was of poor quality; (ii) the patient was not tested or tested too late, or presented secondary generalization, or (iii) if more than two criteria could not be scored. Finally, 35 seizures were retained for the rest of the study (Table 3).



SEEG signal analysis

Definition of regions of interest

In this study, we specifically analysed the relationship between bipolar intracerebral EEG signals (derived from two contiguous leads of the same electrode) recorded from regions of interest. The same regions were studied in each patient and included three regions of the

temporal lobe (two mesial regions: Hip and CE and one lateral region: MTG) and three regions outside the temporal lobe: Th, P and CG.

Periods of interest

In order to compare the 35 seizures previously selected, four periods of interest were defined. Each period has been defined according to the

Table 2 The eight criteria scale estimating loss of consciousness during seizure

| Criteria | Assessment of the criteria |
|--|--|
| 1. Unresponsiveness (0 or 1). | The patient does not execute simple verbal commands (e.g. 'clap your hands', 'open the mouth', 'close your eyes'). |
| 2. No visual attention (0 or 1). | The patient presents no adequate visual response to external stimuli (e.g. the patient does not look at the examiner during examination). |
| 3. No interaction with the examiner (0 or 1). | The patient does not present any signs (other than visual attention) of response to the examiner. |
| 4. No consciousness of the seizure (0 or 1). | The patient does not report to be in seizure state at any time of the seizure course (e.g. he/she does not call the examiner at the beginning of the seizure). |
| 5. Inappropriate behaviour (0 or 1). | The patient presents with an automatic, uninhibited behaviour or an unreactive state. |
| 6. Postictal amnesia (0 or 1). | The patient does not remember his/her seizure. |
| 7. Amnesia of the seizure events (0 or 1). | The patient does not remember the events that have occurred during the seizure. |
| 8. Global appreciation of consciousness by an experienced physician (0, 1 or 2). | 0. No alteration 1. Middle alteration 2. Complete alteration. |

Table 3 Three groups of seizures were established according to the CSS scale

| Groups | Score (-/9) | Level of consciousness | Number of seizures | Number of patients | Averaged duration of seizures (mn:s) | Number of stimulated seizures |
|--------|-------------|--------------------------------------|--------------------|--------------------|--------------------------------------|-------------------------------|
| A | 0–1 | Preserved consciousness | 17 | 8 | 2:36 | 11/17 |
| B | 2–5 | Moderate alteration of consciousness | 6 | 2 | 1:45 | 1/6 |
| C | ≥6 | Profound alteration of consciousness | 12 | 5 | 1:28 | 5/12 |

Group A includes seizures without LOC characterized by a low score at CSS (0–1), Group B includes seizures with a intermediary state of consciousness (CSS scores ranging from 2 to 5) and Group C includes seizures with complete LOC (CSS score ≥ 6).

dynamical properties of intracerebral signals during a seizure. These periods have, therefore, been defined independently of the clinical analysis of the seizures. They reflect the neural activity during the seizure (three periods) as compared to a background one.

Background

This period of 30 s was selected at least 1 min before the onset of the ictal discharge, during a period of awake quiet rest. When a seizure was elicited by electrical stimulation, the BKG period was selected one minute before the onset of the first stimulation.

Seizure onset

We have arbitrarily chosen a duration of 10 s including 5 s before and 5 s after the appearance of a rapid discharge in mesial and/or lateral temporal structures. This rapid discharge was delimited by visual inspection. A time-frequency representation of signals was also used to accurately determine the beginning of the rapid activity (Guye *et al.*, 2006).

Middle part of the seizure

Fifteen seconds after the end of the rapid discharge has been selected as part of the clonic discharge.

End of the seizure

This period included the last 10 s of the seizure, defined as the end of the discharge in the temporal lobe structures.

Estimation of long-distance synchronization during seizures

The synchronization of EEG signals between two distant regions may be estimated using various methods (Stam, 2005; Ansari-Asl *et al.*,

2006). Although these methods are based on different concepts, the common approach in the bivariate case is to estimate a statistical relationship between two EEG signals recorded from two distant regions.

In the present article, relationships between signals recorded from six structures (Hip, EC, MTG, Th, CG and P) were estimated using non-linear regression analysis (Pijn and Lopes Da Silva, 1993) according to a pair-wise procedure. Details of the method can be found in our previous studies (Wendling *et al.*, 2001; Bartolomei *et al.*, 2004). In brief, non-linear regression analysis provides a parameter, referred to as the non-linear correlation coefficient h^2 , which takes values in the range [0, 1]. Low values of h^2 denote that signals X and Y are independent. In contrast, high values of h^2 indicate a dependence of signal Y with respect to signal X , i.e. signal Y may be explained by a transformation (possibly non-linear) of signal X . In practice, this transformation is approximated from (X, Y) data points by a piecewise linear regression curve. It is also noteworthy that the method involves time-lags: the h^2 coefficient is equal to the maximum value of the non-linear correlation when the delay τ between $X(t)$ and $Y(t+\tau)$ is progressively varied from $-\tau_{\max}$ to $+\tau_{\max}$.

The non-linear regression analysis was performed as a function of time by using a sliding window (duration: 2 s, sliding steps: 0.25 s). The h^2 values were averaged over each period of interest defined above, for each of the 10 considered pairs of signals (see below) and for each of the 35 seizure recordings. In the present study, h^2 values were computed on broadband signals (0.5–90 Hz), providing a global estimation of non-linear interdependencies.

Statistical analysis

For each seizure, the correlation values computed from each ictal period (seizure onset, middle part of the seizure period, end of the

seizure) were normalized with respect to the value obtained in the background period using a Z-score transformation:

$$Z_{h^2}^{\text{Pol}} = \frac{h_{\text{Pol}}^{-2}}{\sigma_{h_{\text{BKG}}^2}}$$

where Pol denotes the considered period of interest (SO, MS or ES), h_{Pol}^{-2} denotes the average h^2 value computed over the considered Pol and where $\sigma_{h_{\text{BKG}}^2}$ denotes the standard deviation of h^2 values computed over the BKG period. For simplicity, $Z_{h^2}^{\text{Pol}}$ will be simply denoted by Z_{h^2} . Intuitively, this value indicates, for each interaction, the change in signal synchronization relative to the background period. As the data were not normally distributed, a non-parametric Mann–Whitney test has been used to estimate whether Z_{h^2} values were different between two different groups of seizures defined with the CSS: one with no alteration of consciousness (Group A) and one with profound alteration of consciousness (Group C). This test has been repeated for 10 interactions and a Bonferroni correction was therefore applied to the P -values obtained from those tests ($P < 0.005$ was considered as significant).

Three synchronization indices have then been calculated. The temporal lobe synchronization index (TSI) represents the average Z_{h^2} value calculated from signals recorded from the three temporal lobe structures (Hip, EC, MTG). An 'extra-temporal lobe synchronization index', (ETSI) was defined as the average Z_{h^2} value obtained from signals generated by the three extra-temporal lobe regions (Th, CG and P). Finally, a 'temporal–extra-temporal synchronization index' was defined as the average Z_{h^2} value computed for of interactions between the three temporal lobe regions and the three extra-temporal lobe brain regions. Those indices were calculated to give a better spatial repartition of the correlations measured during the seizures. The non-parametric Mann–Whitney test has been applied to compare the different indices between the two groups described above (A and C). A Wilcoxon test has been used to compare the values of indices obtained in the same patients in Group C (see details in Results section).

Finally, we performed a non-parametric correlation test (Spearman test) to find a correlation between the scores of alteration of consciousness and the synchronization indices (temporal lobe, extra-temporal lobe and temporal–extra-temporal).

Results

Determination of loss of consciousness

Loss of consciousness was quantified using an eight level score (CSS, Table 2). Seizures were divided into three groups: (i) Group A (no LOC) with a score ≤ 1 ; (ii) Group B (intermediate or partial LOC) with a score ranging from 2 to 5; and (iii) Group C (LOC) with a score ≥ 6 . Characteristics of the groups can be found in the Table 3. The intra-rater and inter-rater ICC's computed for the CSS quotations were found to be high, 0.93 and 0.99, respectively, providing a good validation of the reproducibility of the CSS. We first analysed Groups A and C, since Group B represented a transition state, which would be characterized afterwards.

Comparison of the level of synchronization between the Groups A and C

To assess whether synchronization across different structures correlates with the level of consciousness, we used non-linear regression analysis in order to estimate, as a function of time, the level of broadband signal (0.5–90 Hz) synchronization between any two structures from the six temporal and extra-temporal structures (h^2 estimation) during seizures with and without LOC. Three seizure periods were considered: onset (SO), middle (MS) and end of seizure (ES). For each period, Z scores of h^2 values (Z_{h^2}) were computed relative to a reference, background activity period, distant from seizure onset and we restricted our analysis to 10 interactions. The 10 interactions have been arbitrarily chosen in order to avoid having too great a number of pair-wise correlations (and thus to keep a reasonable statistical threshold for significance in the multiple comparison context) and to reflect the synchronization process within the temporal lobe (Hip-MTG), between temporal lobe and thalamus (Th-MTG; Th-Hip), between Th and parietal cortex (Th-CG, Th-Par), between parietal lobe and cingulate gyrus (Par-CG) or temporal lobe (Par-Hip, CG-Hip; CG-MTG; MTG-Par).

Synchronization levels were increased during the seizure onset period without significant differences between Groups A and C. This result suggests that the first period mainly reflected synchronized activity within the epileptogenic zone (Bartolomei *et al.*, 2004) and suggests that the structures involved in LOC are different from those responsible for seizure genesis (Fig. 2).

In contrast, and as depicted in Fig. 3, seven out of ten interactions were significantly increased in Group C as compared to Group A for the middle and end of seizure periods, in particular for the parietal cortex, the CG and the Th.

A clear separation thus appeared between Groups A and C, as only Group C displayed marked enhanced h^2 values, particularly pronounced for interactions outside the temporal lobe (see example in Fig. 1A), suggesting the specific involvement of extra-temporal structures in LOC.

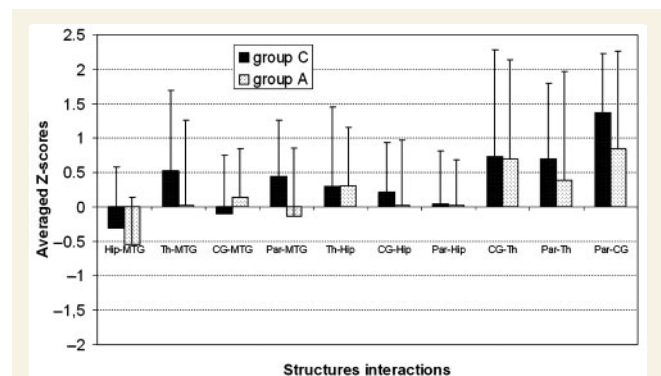


Figure 2 Estimation of changes in synchronization relative to background (Z_{h^2} values) in 10 interactions at seizure onset. No significant differences were found between Group A and Group C seizures.

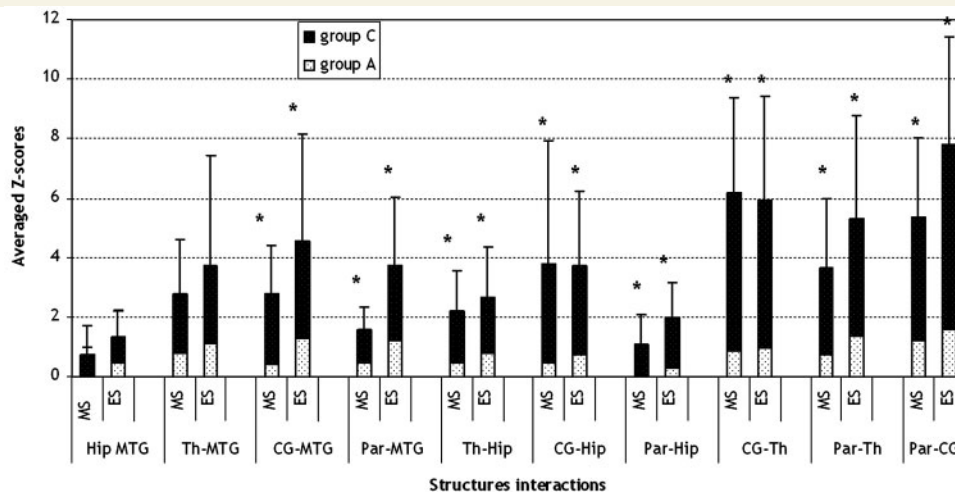


Figure 3 Estimation of changes in synchronization relative to background (Z_{h^2} values) in 10 interactions observed during the 'middle part of seizure' period (MS) and the 'end of seizure period' (ES). Significant differences were found between Groups A and C seizures for several interactions (asterisk).

Evaluating the level of consciousness from a clinical viewpoint is a subjective process. To test the robustness of the consciousness score we used, we also performed a clustering analysis of h^2 values from period MS and ES. Such hierarchical classification led to a segmentation of data into three groups with increasing h^2 values (Fig. 1B). Most seizures with LOC (83%) belonged to Group 3, with the highest h^2 values, whilst most seizures without LOC (90%) belonged to Groups 1 (lowest h^2 values) and 2 (mid h^2 values). The separation of Group A into two distinct groups according to h^2 values may reflect different types of seizures involving distinct cortical structures. Seizure classification according to h^2 values thus replicates the clinical one. Together, these results show that LOC is associated with a specific spatial pattern of abnormal synchronization among intra- and extra-temporal structures.

Comparison of the synchronization indices between the two groups: regional variations of increased synchronization

If extra-temporal synchronization constitutes a signature of LOC, separate from abnormal patterns within temporal structures which are responsible for the actual seizure event, then a specific topological distribution of abnormal synchronization should be associated with LOC. We calculated three regional synchronization indices. The TSI represents the average of the Z_{h^2} values between signals from the three studied temporal lobe structures; the ETSI between the three extra-temporal lobe regions, and the temporal/extra-temporal synchronization index (TETSI) between the three temporal and the three extra-temporal lobe regions. Figure 4A represents the evolution of the three indices during the three periods of the seizures SO, MS and ES between Groups C and A. There was no difference between Groups A and C during the seizure onset period. TSI values were also similar whether

seizures were associated or not with LOC during the three seizure periods, further supporting the non-involvement of temporal lobe—epileptogenic—structures in LOC. In contrast, there was a large and significant difference in TETSI and ETSI values between groups during the middle ($P < 0.0000$ and $P = 0.0002$, respectively), and end ($P < 0.0002$ and $P = 0.002$, respectively) of seizure periods (Fig. 4A). The non-LOC and LOC groups are, thus, best differentiated by the amount of synchronization in extra-temporal regions (Fig. 4B). The ETSI (reflecting interactions between Th, CG and parietal cortex) appears to be the most different between the two groups. Moreover ETSI values are significantly higher than the TETSI one within the C group during the MS ($P < 0.005$) and ES ($P = 0.002$) periods. This highlights that, when patients lose consciousness, these structures (P, CG and Th) interact much more with each other than with the other structures.

Correlation between level of synchronization and the level of alteration of consciousness

Having established the spatio-temporal profile of LOC, we assessed the transition between consciousness and LOC. To this aim, we have looked for a statistical correlation between the level of interaction between structures outside the temporal lobe (ETSI values) and the level of alteration of consciousness as scored using the SCS scale. We included for this comparison the seizures from Groups A, B and C.

There was a strong statistical correlation between the level of interaction between structures outside the temporal lobe (ETSI values) and the level of alteration of consciousness during the middle and end of seizure periods (Fig. 5; $r = 0.69$; $P = 0.0001$). The transition between consciousness and synchronization is shown in Fig. 5. Group B (intermediate LOC) values were spread in the narrow transition phase of the curve between the low and high ETSI values. Seizures without and with LOC

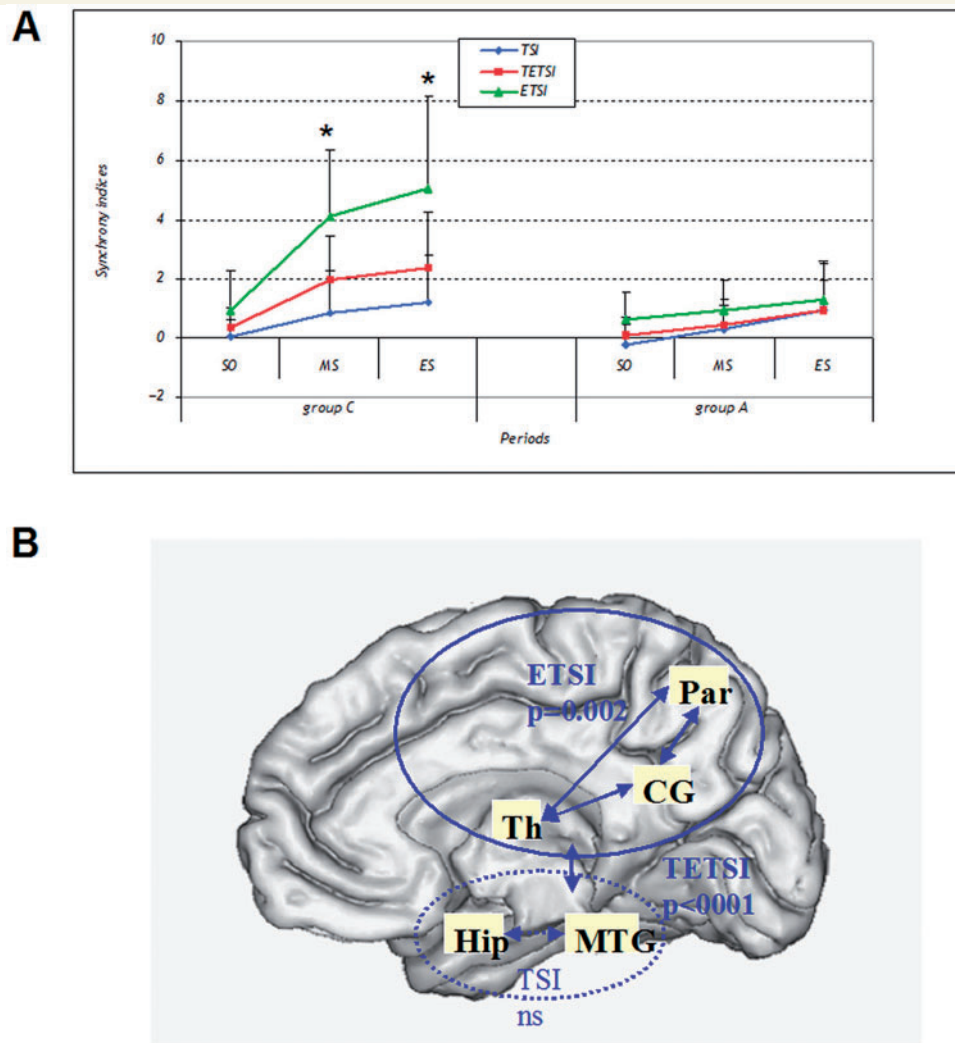


Figure 4 (A) Variations of the synchronization indices (TSI, TETSI and ETSI) in the two patient groups during SO, MS and ES periods. Synchronization indices exploring the extra-temporal interactions are largely and significantly increased in seizures with loss of consciousness (Group C) compared to seizures without loss of consciousness (Group A). (B) Schematic spatial representation of the three synchronization indices and their statistical variations by comparing Groups C and A values during the MS period.

recorded in the same patients tended to be distributed in the low and high ETSI values, respectively, further suggesting that increased cooperation outside temporal lobe regions underlies LOC, not seizures *per se*.

Discussion

In the present study, we reveal a previously undescribed result: that LOC occurring during TLE seizures is directly related to excessive synchronization of neuronal activity in extra-temporal lobe structures, in particular Th and associative cortices (affecting the posterior cortices). Consciousness is preserved at seizure onset as long as synchronization remains confined to temporal lobe structures.

The international classification of epileptic seizures makes impaired consciousness the cornerstone by which the main

categories of partial seizures, simple and complex, are distinguished (Commission, 1981). It emphasizes an essential characteristic that in many cases has significant repercussions on the quality of life of the epileptic patient. Nevertheless, there are some confounding features in studying consciousness during a seizure. Indeed, several cognitive functions may be impaired during a seizure that may masquerade as LOC. Examples include aphasia (Lux *et al.*, 2002) or amnesia (Gloor, 1986). Moreover, there is no scientifically accepted definition of consciousness. To find the target of our scientific investigation, we used a 'common sense' definition of consciousness (Searle, 1998). In clinical practice, consciousness is generally equated with the waking state, and the ability to perceive, interact and communicate with the environment and with others in the integrated manner that wakefulness normally implies (Monaco *et al.*, 2005). Based on that definition, we made a precise clinical appreciation of consciousness from the video taped seizures based on the CSS.

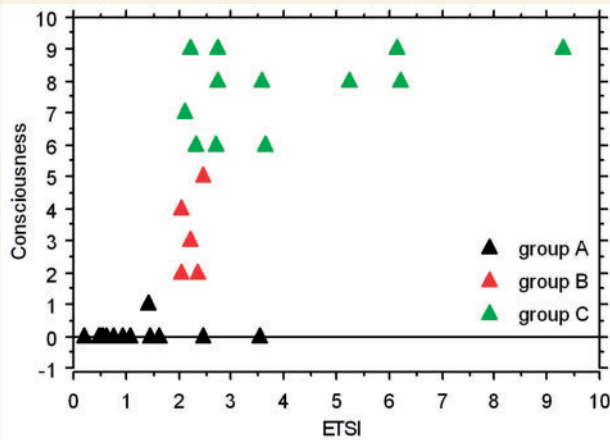


Figure 5 Relationship between ETSI values (MS period) and the loss of consciousness estimated by the 'seizure consciousness scale' (CSS).

Three groups of seizures have thus been defined according to the CSS. Two groups corresponding to well-defined differentiated conscious states were particularly compared: one with profound alteration of consciousness (Group C) and one with no alteration of consciousness (Group A). Comparing the electrophysiological properties of signals from these two groups reveals clear differences between them: seizures of Group C involve a more synchronized and wider neural network than seizures of Group A. Moreover, we have found a significant correlation between the level of synchronization in altered brain networks and the level of alteration of consciousness, pointing out a strong relation between the exterior, subjective appreciation of consciousness and an objective measure of signal synchronization during seizures.

We found that, in the two groups, temporal lobe seizures are characterized by an increase of interstructural synchronization, suggesting strong synchrony of involved neural networks. This increase was maximal in the mid-seizure and end seizure periods, developing after seizure onset. This is in agreement with previous studies (Bartolomei *et al.*, 2001, 2004; Guye *et al.*, 2006; Ponten *et al.*, 2007; Schindler *et al.*, 2007) and matches the clinical observation that LOC is delayed as compared to the seizure onset.

Increase in neural synchronization is thus partly inherent to the seizure dynamic. During seizures with LOC, this phenomenon is largely exacerbated since we have found that the correlation values are globally higher during seizure with LOC. The most specific feature of seizures with LOC appears to be the higher synchronization in 'extra-temporal' structures than in the temporal regions. Moreover, a significant correlation has been found between the degree of synchronization in extra-temporal lobe structures and the alteration of level of consciousness. As mentioned in the introduction, these structures were selected as playing a role in the normal state of consciousness. Our study points out the role of parietal cortices in LOC and particularly the CG. This region is highly interconnected to other associative cortices including anterior cingulate, mid-dorsal prefrontal and lateral parietal cortices (Parvizi *et al.*, 2006). Excessive synchronization in a network including Th and parietal cortex is reminiscent of what has been found in fMRI studies of generalized epileptic

discharges. A large body of evidence indeed suggests that a deactivation of precuneus/posterior cingulate cortex is a crucial phenomenon determining LOC in these epilepsies (Gotman *et al.*, 2005).

Excessive synchronization in associative cortices appears thus to be strongly linked with LOC. This may appear paradoxical, because synchronization between brain distant areas is thought to be an essential mechanism allowing conscious perception (Melloni *et al.*, 2007). The Th probably regulates cortico-cortical synchronization between distant brain areas and it has been proposed that the thalamo-cortical system would be essential for conscious activity in the brain (Tononi and Edelman, 2000; Llinas and Ribary, 2001; Crick and Koch, 2003; Edelman, 2003) by forming re-entrant loops between Th and cortical areas. This neural synchronization between distant brain areas occurring during conscious perception is thought to be transient, lasting about 100 ms (Edelman, 2003; Melloni *et al.*, 2007). Temporal patterning of neural activity and a precisely regulated trade-off between correlated and decorrelated activation patterns are thought to be crucial for normal brain functions (Uhlhaas and Singer, 2006). In patients with LOC, the synchronization mechanisms are increased in a different way in comparison with the physiological states. This 'ictal' synchronization is indeed abnormally prolonged and stable (several seconds) occurring between a large amount of neuronal structures and thus breaks down the normal and regulated synchronization.

We propose that this abnormal synchronization occurs in a distinct neural space indispensable for conscious process. The global workspace (GW) theory is indeed one of the most developed theories of consciousness (Dehaene and Naccache, 2001; Dehaene *et al.*, 2003b; Sergent and Dehaene, 2004; Dehaene *et al.*, 2006). As previously mentioned, this theory postulates that conscious processing is associated with a distinct neural space, constituted by a distributed neural system with long distance connectivity. The global workspace model proposes that, at any given time, many modular cerebral networks are active in parallel, processing information in an unconscious manner. Information becomes conscious, however, if the corresponding neural population is mobilized by top-down attentional amplification into a self-sustained brain-scale state of coherent activity that involves many neurons distributed throughout the brain. Neurophysiological, anatomical and brain-imaging data strongly argue for a major role of prefrontal cortex, anterior cingulate and the areas that connect to them including parietal cortex, in creating the postulated brain-scale workspace (Dehaene and Naccache, 2001). Some structures explored in this study (inferior parietal, posterior cingulate and Th) are supposed to take part in this interconnected network as it is defined in this model (Dehaene and Naccache, 2001).

In this perspective, we propose that during seizures with LOC, information cannot be processed within the global workspace because structures that are the most important for its activity are over-synchronized (in time and space). In contrast, seizures without LOC disturb the global workspace to a lesser degree, permitting at least partial functioning of long distance cortico-cortical connections between modules and the access to consciousness.

One possible limit of our work is inherent to the number of studied structures. Notably, selected patients have no systematic exploration of the frontal lobe, which is one of the major structures of the global workspace (Dehaene and Naccache, 2001). The recording of frontal and contralateral structures was not clinically justified in the patients explored here. It is, however, probable that changes observed in posterior networks also affect anterior brain networks as suggested by SPECT studies, showing a strong correlation between frontal and parietal blood flow decrease in TLE seizures associated with LOC (Blumenfeld *et al.*, 2004b). The synchronization mechanism we describe may thus, also extend to frontal regions and whether bilateral propagation is necessary for LOC remains to be determined.

Another limit is that we cannot firmly prove that the hypersynchrony observed within the global workspace is the specific phenomenon underlying the LOC or just revelatory of a wider process within the brain. We argue that the first hypothesis is the most relevant for several reasons. First, during the seizure, the patient still exhibits some brain function as reflex visual attention (66% of the seizures from Group C). Second, the level of alteration of consciousness may vary within a seizure (Johanson *et al.*, 2003) indicating that LOC is a rapidly reversible phenomenon and might thus not be related to a massive alteration of brain functions. Finally, other studies of LOC have never revealed very significant changes concerning the primary cortices, but significant differences in Th (Lee *et al.*, 2002; Blumenfeld *et al.*, 2004a) or associative cortices (Blumenfeld *et al.*, 2004a) activities.

During generalized epileptic activities, fMRI images reveal impairment of Th, parietal and frontal regions (Gotman *et al.*, 2005; Hamandi *et al.*, 2006) but no differences in primary cortices.

Studies on vegetative state also reveal impairment of connectivity within associative cortices with a preservation of the activity of primary cortex as proved by the recording of evoked potential (Laureys *et al.*, 1999a, b).

In summary, the results of the current study demonstrate that LOC during temporal lobe seizure is due to excessive synchronization between Th and associative cortices. In the future, new strategies aimed at preventing excessive synchronization in sub-cortical structures, and hence avoiding LOC, would dramatically improve patient life and safety, even if seizures themselves are not suppressed.

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