Coherent neural activity and brain synchronization during seizure-induced loss of consciousness

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A B S T R A C T

Epileptic seizures are often characterized by profound alteration of consciousness. This is particularly frequent in temporal lobe seizures, a subgroup of seizures originating in the temporal (and usually mesial temporal) brain areas. The mechanisms of alteration of consciousness in temporal lobe seizures have long been discussed and several theories have been proposed. Recent investigations have provided new hypotheses linking abnormal synchrony provoked by epileptic discharges and the dysfunction of brain regions involved in consciousness processing. In particular, the global workspace theory proposes that conscious processing results from coherent neuronal activity between widely distributed brain regions, with fronto-parietal associative cortices as key elements. Recently, we have shown that AOC was contemporary to non-linear increases of neural synchrony within distant cortico-cortical and cortico-thalamic networks. We have interpreted these results in the light of global workspace theory, and suggest that excessive synchrony could prevent this distributed network from reaching the minimal level of differentiation and complexity necessary to the coding of conscious representations.

Key words
Consciousness • Temporal Lobe Epilepsy • Global Workspace • Synchrony

Introduction

Epilepsy is a frequently occurring ensemble of diseases affecting nearly 1% of the general population. Alteration of consciousness (AOC) is usual in generalized seizures (in which the epileptic process affects the cerebral cortex bilaterally and widely) and frequently occurs in partial epilepsies (in which seizures start from a limited part of the cerebral cortex and secondarily spread to other cortical and subcortical regions). In particular, AOC is the most dramatic clinical manifestation of temporal lobe seizures (TLS), occurring in approximately 70% of patients (Maillard et al., 2004) causing important handicap and potential injury (Wirrell, 2006). Whereas the structural and functional changes observed in temporal lobe epilepsies have been largely studied, the mechanisms leading to AOC are poorly known (Blumenfeld and Taylor, 2003; Cavanna and Monaco, 2009). In this review we will comment on the results of recent investigations obtained in our group, relating AOC in TLS to an excess of neural synchrony in brain sites participating to consciousness processing (Arthuis et al., 2009; Bartolomei and Naccache, 2011).

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Alteration of Consciousness in Temporal lobe Epilepsy: a summary of putative mechanisms

AOC is classically defined by the presence during seizures of at least two clinical features: incapacity of the patient to interact with the examiner and amnesia of events occurring during the seizure (Commission, 1981; Gloor, 1986). The limitations of such a definition have been stressed (Gloor, 1986; Cavanna et al., 2008). It is acknowledged that AOC is a complex phenomenon, requiring the assessment of multiple aspects of cognitive functions during seizures. It is thus particularly important to disentangle the problems inherent to the interference with ictal memory and language disorders (Gloor, 1986; Monaco et al., 2005). We recently proposed an eight points scale to describe the different clinical facets of AOC during seizures (Arthuis et al., 2009) (Table I). This scale allows for a more precise definition of loss of consciousness during seizures. Its use in analysing seizures has revealed that TLS may exhibit several degrees of altered consciousness.

As previously mentioned, several theories have been proposed to account for the AOC during TLS seizures. A first theory was proposed by Penfield and Jasper (see also Gastaut and Broughton, 1972) suggesting that AOC stems from an alteration of the reticular ascending system due to the propagation of the ictal discharge ("centrencephalic theory"). This theory is close to the recent "network inhibition hypothesis" proposed by Blumenfeld and colleagues (Englot and Blumenfeld, 2009). According to SPECT and EEG approaches, they proposed that AOC occurs when the associative cortices are secondarily impaired and disclose slow (non-epileptic) activity (Blumenfeld et al., 2004a; 2004b). This abnormal activity over the associative cortices disrupts the normal functioning of cortices involved in normal attentional/conscious networks and creates a situation close to the slowing of cortical activity in sleep. The "deactivation" of cortical structures could depend on subcortical driving under the influence of epileptic discharge.

In the past, few studies have used direct intracerebral recordings to specifically address the question of AOC. In opposition to the "centrencephalic" hypothesis, Gloor et al. and Munari et al. proposed that AOC is linked to the extension of the epileptic discharge to a certain amount of cortical areas, interfering with cognitive processing of consciousness. In addition, AOC may occur during apparently unilateral TLS (Gloor et al., 1980; Munari et al., 1980).

Alteration of Global Workspace (GWS) Functioning during TLS seizures

The hypothesis of GWS alteration during temporal lobe seizures with AOC has been recently proposed and may finally reconcile the cortical and subcortical theories of AOC during TL seizures (Arthuis et al., 2009; Bartolomei and Naccache, 2011). The GWS model of consciousness (Baars, 1989) proposes that at any given time many modular cerebral networks are active in parallel, and process information in an unconscious manner, while consciousness would correspond to the broadcasting of information to a global workspace (Dehaene et al., 1998; Dehaene and Naccache, 2001; Dehaene et al., 2006). In particular, conscious access would be related to a mechanism of top-down attentional amplification into a self-sustained brain-scale state of coherent activity that involves many neural regions distributed throughout the brain. The long-distance connectivity of these "workspace neurons" can, when they are active for a minimal duration, make the information available to a variety of processes including perceptual categorization, long-term memorization, evaluation and intentional action. According to this model, global availability of information throughout the workspace is what we subjectively experience as a conscious state. Neurophysiological, anatomical, and brain imaging data strongly argue for a major role of prefrontal cortex, anterior cingulate, and the areas that connect to them, in creating the postulated brain-scale workspace (Dehaene and Naccache, 2001). The transient links between regions engaged in the GW could be related to long distance phase synchrony in the beta range (Gaillard et al., 2009). In this context, the exploration of AOC contemporary to seizures can provide precious specification of the range of neural coherence associated with conscious processing.

In line with this hypothesis, we postulated that abnormal synchronization between subcortical and cortical modules constituting the GW could constitute a core mechanism of AOC in TLS.

Table I. - The Consciousness Seizure Scale (CSS).	
Criteria	Assessment of the criteria
1. Unresponsiveness (0 or 1).	The patient does not execute simple verbal commands (ex: "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" (ex: 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 (ex: he/she does not call the examiner at the beginning of the seizure).
5. Inappropriate behavior (0 or 1).	The patient presents with an automatic, uninhibited behavior or an unreactive state.
6. Post ictal 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.

It has been known for a long time that epileptic phenomena are associated with important changes in brain synchrony mechanisms (Gotman, 1996; Bartolomei et al., 1999; Bartolomei et al., 2005; Guye et al., 2006). This abnormal synchronization can be quantified by measuring the interdependencies between signals recorded in different brain regions involved in the epileptic seizures when invasive (depth electrode) recordings are required (Fig. 1). Numerous methods have been proposed over the past decades, often categorized according to their ability to assess linear (coherence or linear regression analysis) or nonlinear (mutual information, nonlinear regression analysis or similarity between state-space trajectories reconstructed from observed signals) properties of the relationship (Wendling et al., 2009).

Using these methods, it is therefore possible to study functional couplings between several brain regions involved or not during seizures. Among these, the so-called nonlinear regression analysis provides a parameter, referred to as the nonlinear correlation coefficient h^2, which takes values in (0, 1) and has been particularly used to study epileptic seizures. Low values of h^2 denote that two signals X and Y under analysis are independent. On the other hand, high values of h^2 mean that the second signal Y may be explained by a transformation (possibly nonlinear) of the first signal X (i.e. both signals are dependent).

Several studies have shown that TLS are characterized by specific increase in neural synchrony that may largely involve regions distant from the sites of origin of the seizures (Guye et al., 2006). Until recently however, the relationship between increased synchrony and AOC was unknown, even if it was predicted that increased synchrony could be associated with AOC (Tononi and Edelman, 1998). This prompted us to investigate the relationship between altered synchrony in TLS and AOC in patients undergoing intracerebral recordings of cortical and subcortical structures as part of their presurgical evaluation (Arthuis et al., 2009).

In twelve patients, we first quantified the AOC from video-SEEG recordings using the 8 criteria scale (CSS). Seizures were classified into three groups according to the degree of AOC: group A: no AOC, Group B: intermediate AOC; group C: complete AOC. We particularly studied group C in comparison with group A (Fig. 1C). The interdependencies between bipolar intracerebral EEG signals (derived from two contiguous leads of the same electrode) were estimated using the nonlinear regression method and included three regions of the temporal lobe (two mesial regions: hippocampus (Hip) and entorhinal cortex (CE) and one lateral region: middle temporal gyrus (MTG)) and three regions outside the temporal lobe: thalamus (Th), lateral parietal cortex (P) and posterior cingulate gyrus (CG) (Fig. 1A-B). In comparison with the preictal ("background") peri-
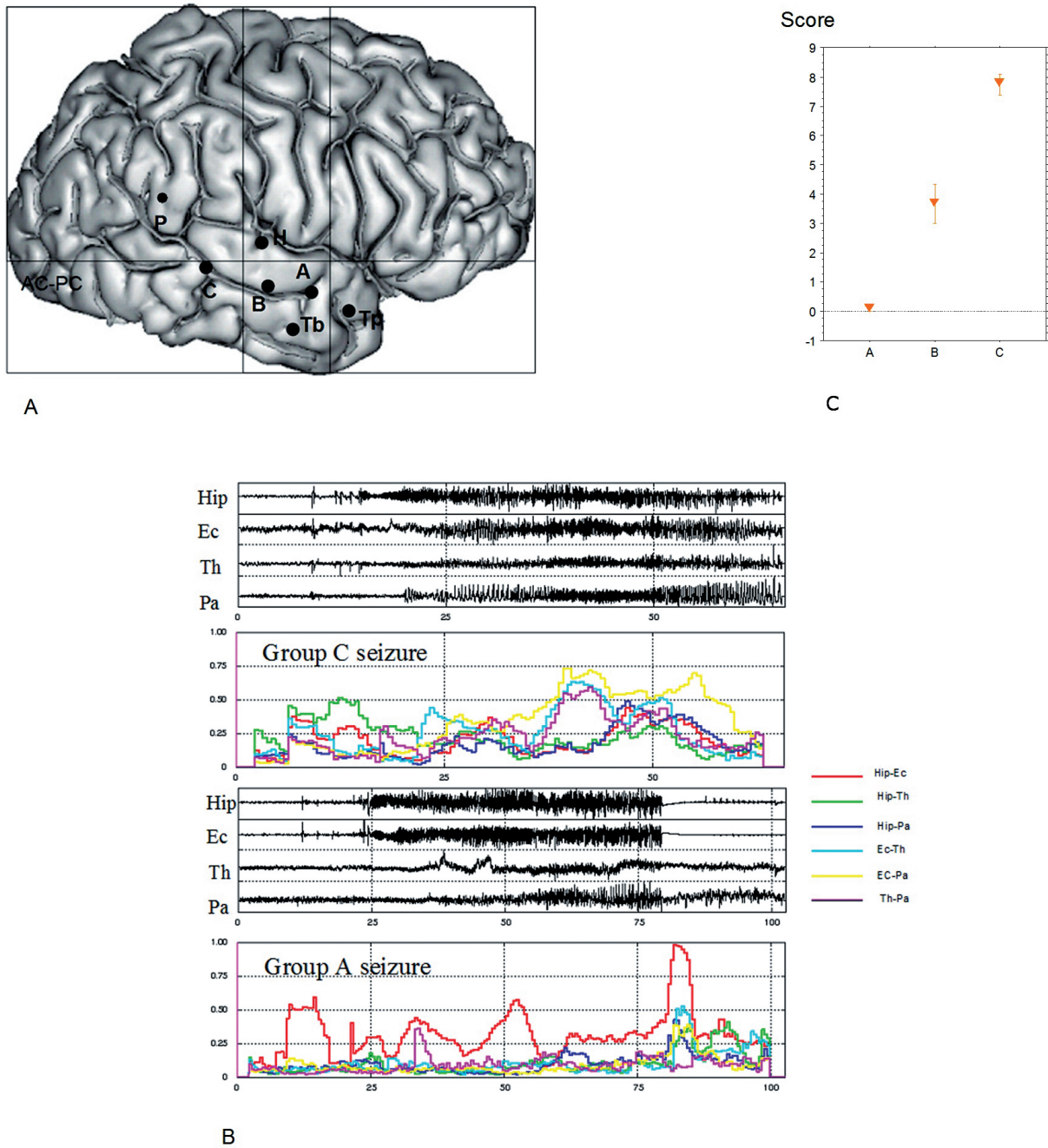
Fig. 1. - A. Sketch of stereotactic electrodes placement. Electrodes Tp, Tb, A, B, C, and H explore the temporal lobe. H ends into the pulvinar group of the thalamus. P is located in the parietal region B Two exemples of seizure with AOC (group C) and without AOC (group A). Intracerebral recordings are obtained from multiple contacts electrodes placed according to Talairach's stereotactic method. Four regions are shown: Hip: Anterior Hippocampus, EC: entorhinal cortex; Th: Thalamus (pulvinar) and Pa: posterior parietal cortex. Seizures started in the medial temporal lobe before affecting thalamus and parietal cortex. In each case, the estimation of interdependencies used non linear regression (h^2) between pair wise signals. Increase in h^2 values is particularly marked for seizure from group C affecting not only the mesial temporal interactions (EC-Hip, red line) but also the other interactions represented. Seizure from group A is mainly characterized by increase in h^2 values between entorhinal cortex and hippocampus (red line) (adapted from Arthuis et al., 2009, with permission). C. The three groups of seizures are shown and differentiated according to the consciousness score (A: no AOC, B: intermediate AOC, C: complete AOC).
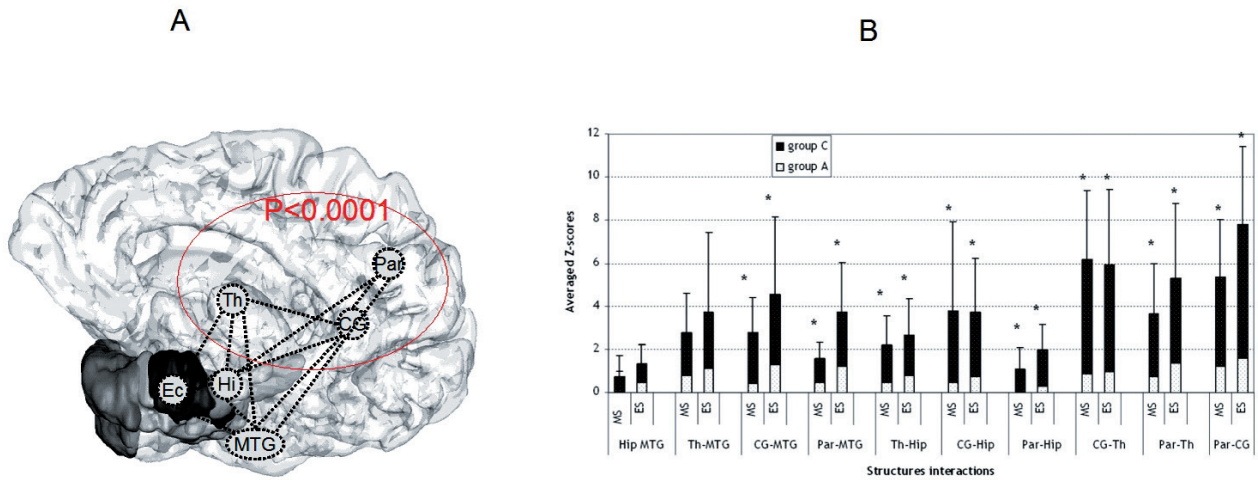
A

B

Fig. 2. - A. Interactions between several regions of the temporal lobe (Ec: entorhinal cortex, Hi: hippocampus, MTG: middle temporal gyrus), the thalamus (Th) and the parietal cortex (posterior cingulated, CG and lateral parietal cortex Par) are represented. Interactions between Th-CG and Par are the most significant comparing groups A (no AOC) and C (complete AOC). B. Estimation of changes in synchrony relative to background (Zh^2 values) in 10 interactions oberserved during the "middle part of seizure" period (MS) and the "end of seizure period "(ES). Significant differences were found between group A and group C seizures for several interactions (asterisk). Hip: hippocampus, MTG: middle temporal gyrus, CG: cingulate gyrus (posterior), Th: Thalamus, Par: lateral parietal region (adapted from Arthuis et al., 2009 with permission).

od, the groups did not differ in terms of neural synchrony within the temporal lobe at seizure onset. In contrast, a clear separation appeared between groups A and C, as only group C (with complete AOC) displayed marked enhanced h^2 values, particularly pronounced for interactions outside the temporal lobe (Fig. 2) suggesting the specific involvement of increased synchrony in extra-temporal structures in AOC. A crucial result was to demonstrate that the degree of AOC as measured by the CSS scale significantly correlated with the degree of thalamo-cortical and cortico-cortical synchrony of structures
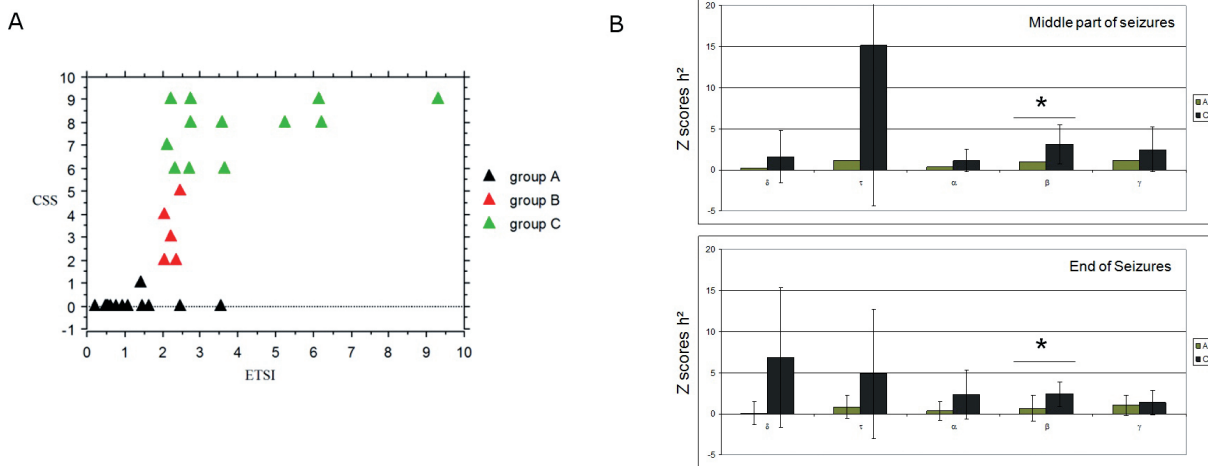
A

B

Fig. 3. - A. Relationship between synchronization level (ETSI: extra temporal synchrony index) values and the loss of consciousness estimated by the "seizure consciousness scale" (SCS). (adapted from (Arthuis et al., 2009) with permission). B. Estimation of changes in synchrony in EEG sub-bands relative to background (Zh^2 values) in interactions Th-Par-CG observed during the "middle part of seizure" period and the "end of seizure" period "(ES). Significant differences (Wilcoxon Rank test corrected for multiple comparison) were found between group A and group C seizures for beta band (asterisk).
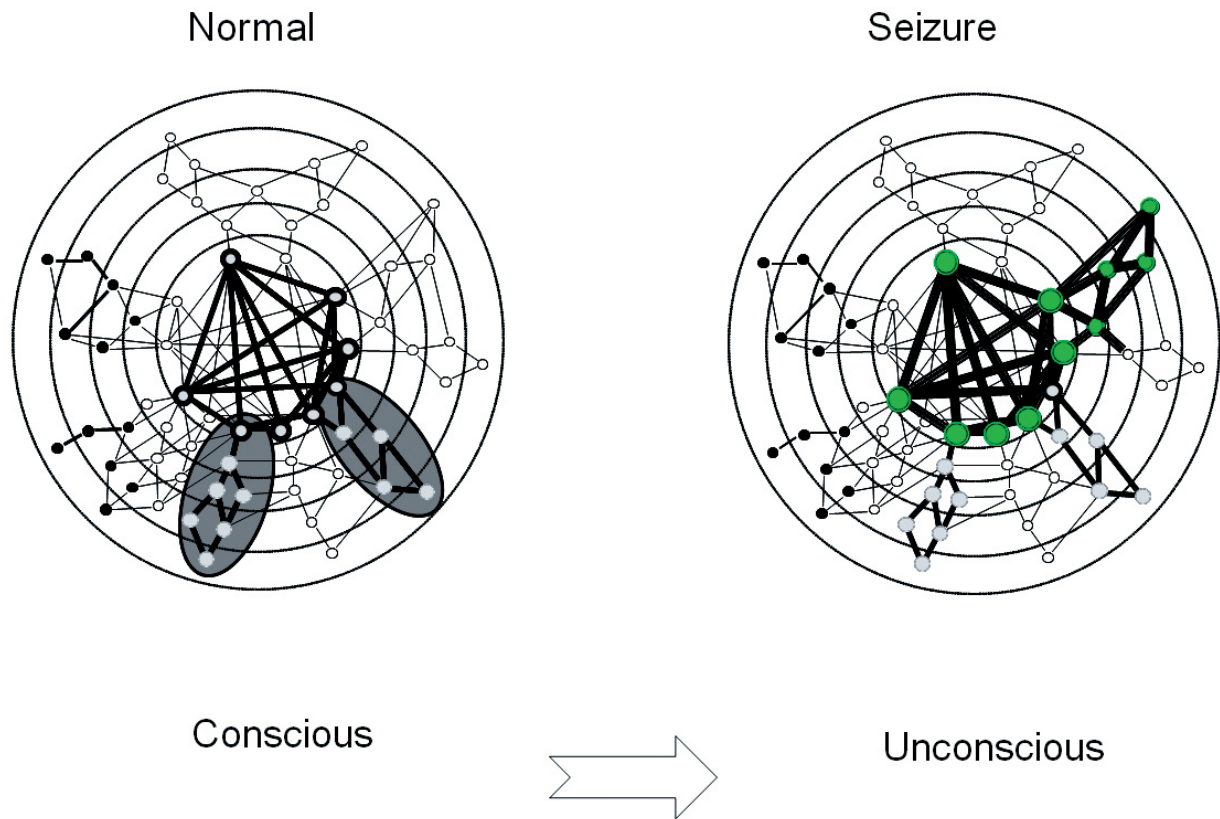
Normal

Seizure

Conscious ⟹ Unconscious

Fig. 4. - This figure schematizes the alteration of Global Workspace (GWS) during seizures with consciousness altera-tions. Left: Normal functioning in an awake subject. Some peripheral modules are engaged in cognitive processes (black circles). Two of them (large grey circles) are transiently engaged in the GWS by transient long distance synchrony (thick black bars) linking associative cortices and subcortical structures. Right: seizure with AOC. An excessive and sustained synchrony between GWS core structures (in green) and the affected neural processor prevents the minimal level of GWS information differentiation to be reached and consciousness disappears.

outside the temporal lobe (Fig. 3A). The transition between consciousness and loss of consciousness as a function of synchronization followed a sharp sigmoid curve, suggesting a bi-stable system. Group B (intermediate AOC) values were spread in the nar-row transition phase of the curve between the low and high h^2 values. Seizures without and with AOC recorded in the same patients were distributed in the low and high h^2 values, respectively, further sug-gesting that increased cooperation outside temporal lobe regions underlies AOC.

Maximal synchronization was found to occur between the pulvinar (an associative thalamic nucleus) and the parietal cortex, in particular the precuneus/posterior cingulate region. This find-ing is in line with the role of these regions in the process of normal consciousness, in particular self consciousness (Cavanna, 2007). The excess of syn-chronization in these networks is prominent in theta (4-8 hz) (p = 0.06) and more significantly in beta sub-bands (12-25 Hz) (p = 0.01) as shown in Figure 3B. It is striking to note that the beta synchrony was found to be involved in the normal processing of consciousness (Gaillard et al., 2009). This result advocates for an active synchrony in a subcortical-cortical network and not simply a deactivation of the cortical function. We finally propose that during seizures with loss of consciousness, information cannot be processed within the GWS because struc-tures that are the most important for its activity are over-synchronized (in time and space) (Fig. 4). In contrast, seizures without loss of consciousness dis-turb the GWS to a lesser degree, permitting at least partial functioning of long distance cortico-cortical connections between modules and the access to consciousness.

Conclusion

The impairment of consciousness in partial seizures is a frequent and dramatic manifestation. In this context, a better understanding of its mechanisms is crucial. As it is not associated with alterations of vigilance, the mechanisms leading to consciousness alteration in partial seizures is probably linked to an interference between ictal activity and cognitive systems processing consciousness. In light of the GWS model, we propose that an excessive synchrony between thalamus and associative cortices occurring in seizures with AOC is responsible of an interruption of the GWS normal functioning. We postulate that the level of impairment of consciousness is dependent on the level of synchronization in the GWS. This relationship is nonlinear, suggesting the existence of a threshold effect.

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