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Rhinal–hippocampal interactions during *déjà vu*

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HIGHLIGHTS

- The phenomenon of *déjà vu* is caused by acute disturbance of mnemonic systems of the medial temporal lobe (MTL).
- In epileptic patients investigated with intracerebral electrodes, *déjà vu* can be more readily induced by stimulation of the rhinal cortices than the hippocampus.
- This study is the first to report the signal correlations of intracerebral EEG signals between MTL structures during *déjà vu*, demonstrating large collaboration between these brain structures.

ABSTRACT

Objective: The phenomenon of '*déjà vu*' is caused by acute disturbance of mnemonic systems of the medial temporal lobe (MTL). In epileptic patients investigated with intracerebral electrodes, *déjà vu* can be more readily induced by stimulation of the rhinal cortices (RCs) than the hippocampus (H). Whether *déjà vu* results from acute dysfunction of the familiarity system alone (sustained by RC) or from more extensive involvement of the MTL region (including H) is debatable.
Methods: We analysed the synchronisation of intracerebral electroencephalography (EEG) signals recorded from RC, H and amygdala (A) in epileptic patients in whom *déjà vu* was induced by electrical stimulation.
EEG signal correlations (between signals from RC, A and H) were evaluated using a nonlinear regression.
Results: In comparison with RC stimulations that did not lead to *déjà vu* (DV−), stimulations triggering *déjà vu* (DV+) were associated with increased broadband EEG correlation ($p = 0.01$). Changes in correlations were significantly different in the theta band for RC–A ($p = 0.007$) and RC–H ($p = 0.01$) and in the beta band for RC–H ($p = 0.001$) interactions.
Conclusion: Déjà vu is associated with increased EEG signal correlation between MTL structures.
Significance: Results are in favour of a mechanism involving transient co-operation between various MTL structures, not limited to RC alone.

1. Introduction

A large majority of normal subjects experience the sensation of *déjà vu*, in which the current situation is experienced as having already been seen or more generally already lived through (see review in Brown (2003)). Various theories have been proposed to account for this phenomenon, which, being unpredictable, is clearly not easily studied in an experimental context. Neurological models involving *déjà vu* as a pathological symptom represent a unique opportunity to better understand the underlying mechanism. In particular, studies in epileptic patients with intracerebral electrodes (implanted to localise the epileptogenic process during pre-surgical assessment) have largely contributed to identifying the brain regions involved in *déjà vu*, and it is now established that alteration in electrical activity (whether provoked by epileptic

Abbreviations: H, hippocampus; RC, rhinal cortex; EC, entorhinal cortex; A, amygdala; h^2, coefficient of nonlinear correlation; MTL, medial temporal lobe; DV, *déjà vu*.

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seizures or by intracerebral electrical stimulation) within the medial temporal lobes (MTLs) may produce *déjà vu*. It has therefore been proposed that *déjà vu* results from an acute perturbation of MTL memory systems (Bancaud et al., 1994; Bartolomei et al., 2004; Gloor et al., 1982; Halgren et al., 1978).

Recently, it has been more specifically suggested that acute disturbance of brain networks underlying recognition memory occurs in *déjà vu* (Barbeau et al., 2005; Bartolomei et al., 2004; Guedj et al., 2010; Spatt, 2002). Animal and human studies have revealed functional specialisation in MTL, with different structures playing different roles in recognition memory (Brown and Aggleton, 2001; Eichenbaum et al., 2007). Recognition memory relies on two processes: familiarity, being simply the knowledge that an item has already been encountered; and recollection, which involves remembering contextual episodic detail (Squire et al., 2007). Although debate is ongoing, it has been proposed that anterior subhippocampal structures (including the perirhinal and lateral entorhinal cortices) are more specifically involved in familiarity ('knowing'), whereas recollection ('remembering', retrieval) requires the involvement of the whole MTL system and critically the hippocampus (H) (Brown and Aggleton, 2001; Eichenbaum et al., 2007). Interestingly, patients with temporal lobe epilepsy may report two types of seizure phenomena: one characterised principally by an impression of familiarity, that is, a feeling of *déjà vu*; and the other more suggestive of recollection, that is, more complete experiential phenomena consisting of detailed episodes (Bancaud et al., 1994; Vignal et al., 2007).

In line with this framework, Spatt proposed that *déjà vu* could be related to isolated dysfunction of anterior subhippocampal structures, leading to the illusion of *déjà vu* (Spatt, 2002). This hypothesis was reinforced a few years later when our group reported that *déjà vu* was elicited more often by anterior subhippocampal than by hippocampal electrical stimulations in the context of pre-surgical procedures for intractable epilepsy (Bartolomei et al., 2004). More recently, we reported that in comparison to healthy subjects and to epileptic subject without *déjà vu*, epileptic patients having *déjà vu* had metabolic alteration affecting the entorhinal cortex and relatively sparing H (Guedj et al., 2010). Overall, a first hypothesis concerning the origin of *déjà vu* could thus be that of isolated dysfunction of a 'familiarity system' dependent on anterior subhippocampal structures.

Although this is a hypothesis worth investigating, it has to be viewed with some caution. First, such a familiarity system has been described for single-item recognition (Aggleton and Brown, 1999), but it remains speculative whether this type of stimulus-related familiarity bears any relation to the type of familiarity experienced for complex daily activities. Second, recent investigations have shown that memory processes are sustained by the synchronisation of neural activities between MTL structures in the gamma/theta range (Fell et al., 2001, 2003, 2008; Guderian and Duzel, 2005; Mormann et al., 2008). In this context, it seems dubious whether a familiarity system can be dysfunctional in isolation without affecting other MTL structures, particularly considering the widespread interconnections within this region. A second hypothesis could be that *déjà vu* is related to abnormal activation of MTL regions (including both subhippocampal and hippocampal regions) (Moulin et al., 2005; O'Connor and Moulin, 2008, 2010). In this case, the pathophysiological mechanisms underlying *déjà vu* would have to be more complex to account both for the fact that subhippocampal stimulation is more prone to elicit this phenomenon and that the whole MTL is consequently engaged.

To explore these questions, we studied the neural coupling by estimating signal correlations occurring between MTL structures during direct electrical stimulation of rhinal cortices producing *déjà vu* in human epileptic patients.

2. Materials and methods

2.1. Selection of patients and SEEG recordings

Among 130 consecutive stereoelectroencephalography (SEEG) procedures performed in our centre between 2000 and 2007, we have selected patients fulfilling the following criteria:

- patients had depth electrodes reaching the rhinal region (anterior parahippocampal gyrus), the amygdala (A) and the anterior hippocampus;
- patients reported to have univocal *déjà vu* experience after stimulation of the rhinal cortex (Bartolomei et al., 2004); and
- comparisons could be made between stimulations inducing *déjà vu* and stimulations not inducing *déjà vu*.

The main clinical characteristics of the patients are indicated in Table 1.

All had intracerebral recordings for partial epilepsy in the context of pre-surgical evaluation of drug-resistant epilepsy. Depth-electroencephalography (EEG) recordings were performed according to the SEEG approach in which intracerebral multiple contact electrodes (10–15 contacts, length: 2 mm, diameter: 0.8 mm, 1.5 mm apart) are placed intracranially, according to Talairach's stereotactic method (Talairach et al., 1974). The electrodes were positioned in each patient based upon hypotheses about the localisation of the epileptogenic zone formulated from available noninvasive information. Implantation accuracy was controlled by telemetric X-ray imaging. A postoperative computed tomography (CT) scan without contrast medium was then used to verify both the absence of bleeding and the location of each contact. After the removal of intracerebral electrodes, a magnetic resonance imaging (MRI) scan was performed that allowed visualisation of the trajectory of each electrode. Finally, CT-scan/MRI data fusion was achieved to anatomically locate each contact along the electrode trajectory. An example of the SEEG implantation scheme is illustrated in Fig. 1A. Signals were recorded on a 128-channel Deltamed™ system. They were sampled at 256 Hz and recorded on a hard disk (16 bits per sample) using no digital filter. The acquisition system includes two hardware filters. The first is a high-pass filter with cut-off frequency equal to 0.16 Hz at −3 dB. It removes very slow variations that may contaminate the baseline. The second is a first order low-pass anti-aliasing filter (cut-off frequency equal to 97 Hz at −3 dB). SEEG was carried out as part of the patients' normal clinical care, and patients were informed that their data might be used for research purposes.

2.2. Direct intracerebral stimulation of MTL structures

As previously reported by our group (Bartolomei et al., 2004), stimulation of the anterior subhippocampal ('rhinal') regions most efficiently elicits *déjà vu* in epilepsy patients. The term 'rhinal cortex (RC)' will be subsequently used, designating the ensemble of the entorhinal and perirhinal cortices, and localised in the anterior parahippocampal region in humans. In accordance with previous findings (Halgren, 1982), the induction of *déjà vu* is an inconstant phenomenon, variable from one stimulation to the other in the same patient. Stimulations in which *déjà vu* was induced (DV+) were compared with stimulation of the same regions in the same patients that did not induce *déjà vu* (DV−). Electrical stimulation was carried out as part of the standard pre-surgical assessment to provide additional electroclinical data about the epileptogenic zone (by determining the sites in which seizures can be triggered) (Bartolomei et al., 2004). After each stimulation, each subject was invited to report any subjective sensation in the range of emotional

Table 1
Main characteristics of the studied patients.

	Age/ Gender	Epilepsy Type	MRI	Stimulated regions/ Side	DV+ Stim Number	DV+ Stim Intensity	DV−Stim Number	DV−Stim Intensity
P1	34/M	TLE-	Neocortical cavernoma	EC/R	3	1.5 1.5 2.5	–	
P2	43/M	TLE	Periventricular Heterotopia	EC/R	1	0.5	3	0.2 1.5 1.5
P3	31/M	TLE	Hippocampal sclerosis	PC/L	1	1.5	4	1 1.5 1.5 2.5
P4	23/M	TLE	Normal	EC/R	3	1 0.5 1	2	 0.5 1
P5	46/F	TLE	Normal	EC/L	1	0.5	1	0.8
P6	30/F	OLE	Dysembryoplasic tumour(DNET)	EC/L	1	1.5	2	1.5
P7	23/F	OLE	Focal cortical dysplasia	EC/R	1	1.5	–	

Notes: TLE, temporal lobe epilepsy; OLE, occipital Lobe epilepsy; DV+, number of studied stimulations that had induced *déjà vu*; DV−, number of studied stimulations that had not induced *déjà vu*; EC, entorhinal cortex; PC, perirhinal cortex; R, right; L, left, M, male; F, female.

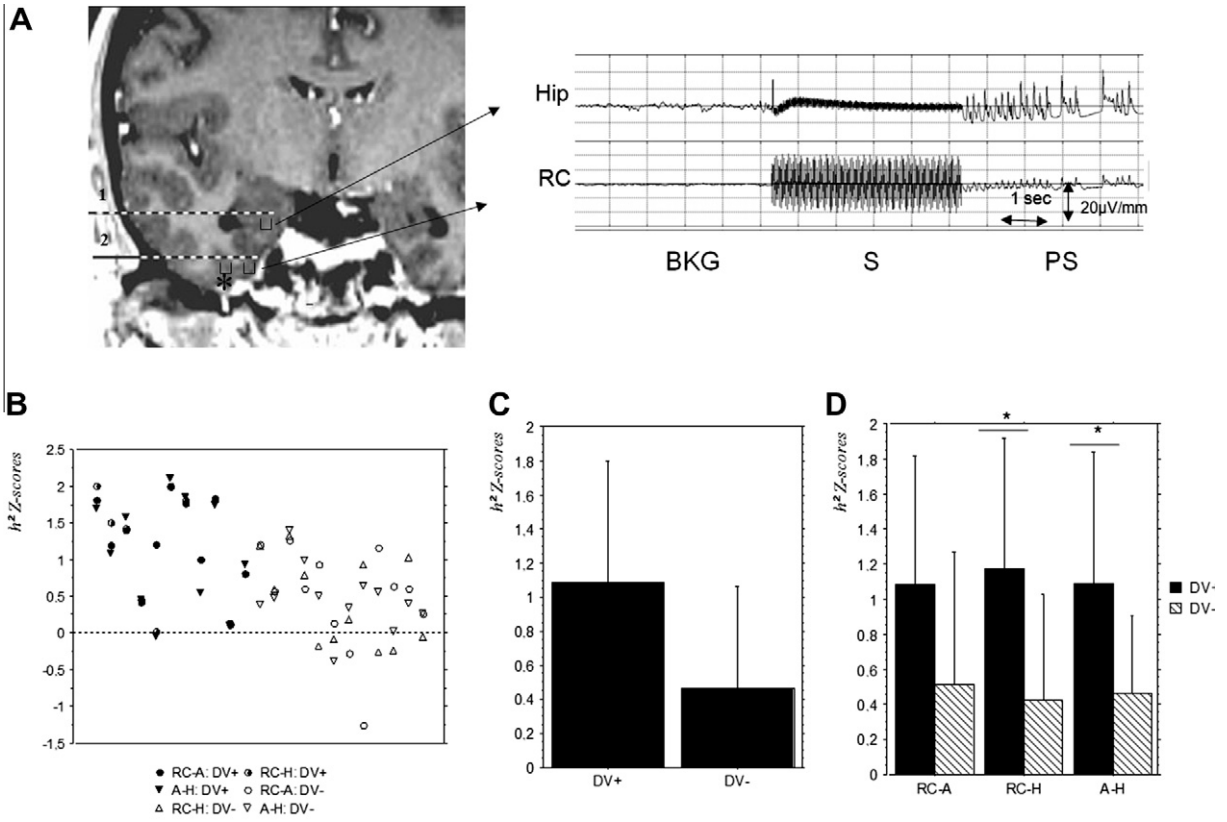

Fig. 1. (A) Two depth electrodes are represented reaching (1) the hippocampal head and the entorhinal cortex (electrode 2, EC). Stimulation (∗) is applied via the two leads close to the EC region that is recorded. □: sites of recordings (bipolar derivation between two adjacent contacts). Right part: SEEG signals recorded from the hippocampus (Hip) and Entorhinal cortex (EC). The stimulation artefact (S) is visible followed by after-discharge. The background pre-stimulation period (BKG) and the post-stimulation period (PS) are indicated. (B) Variation of correlations between mesial temporal lobe regions (amygdala A, hippocampus H, rhinal cortex RC) is indicated in terms of the *z*-score values of h^2 obtained in the period PS relative to the period BKG in stimulations inducing «*déjà vu*» (DV+) and stimulations not inducing «*déjà vu*» (DV−). DV+ discloses greater changes than DV− values. (C) Differences between *z*-score values are significant between stimulations inducing «*déjà vu*» (DV+) and stimulations not inducing «*déjà vu*» (DV−). (D) Interactions between the rhinal cortex (RC), amygdala (A) and hippocampus (H) in broad band signals between DV+ stimulations and DV− stimulations.

or "psychical" feelings, including *déjà vu* sensation. Note that investigators were not blind to this study and that we cannot entirely rule out a suggestibility effect.

Electric stimulation was produced by a regulated neurostimulator designed for safe diagnostic stimulation of the human brain (Inomed®). High-frequency stimulation at 50 Hz (pulse duration 1 ms) was applied in a bipolar fashion to two adjacent contacts located in the brain structure of interest during a 5-s period. The location of the contacts was checked by co-registration of the CT scan (performed during SEEG) and MRI. After removal of depth

electrodes, an MRI (post-MRI) was performed that permitted visualisation of the trajectory of each electrode. To realign the CT-scan image onto a post-MRI image, we used manual landmarks. Landmarks were (1) anatomical, that is, salient and accurately locatable points of the morphology of the visible anatomy, and (2) based on CT scan depth electrode implantation onto the skull, still visible on the post-MRI data after removal of depth electrodes. Finally, a rigid transformation was applied to the CT scan image to realign it exactly onto the post-MRI image, using MEDINRIA software (http://www-sop.inria.fr/asclepios/software/MedINRIA/).

Fig. 1A shows the reconstruction of two electrodes ending within the entorhinal cortex (2) or H (1).

The current intensity was gradually increased, ranging from 0.5 to 2 milliamperes (mA), until a clinical effect or the appearance of an EEG after-discharge was obtained (Fig. 1A). During stimulation, patients were sitting in bed and were asked to read or to count. They were not aware of when, or whether or not, stimulation was applied.

2.3. Signal analysis

Signal analysis is aimed at determining if changes in correlations between EEG signals of recorded mesial temporal structures (A, RC and H) were observed during DV+ stimulation. Two models of prediction could be envisaged. If *déjà vu* results from a localised effect, then no changes in functional coupling between MTL structures should be observed; on the other hand, if *déjà vu* is the result of a more widespread involvement of MTL structures, we should expect to observe a change in neural functional coupling between structures. In this study, statistical coupling between SEEG signals recorded from distinct mesial structures was estimated using nonlinear regression analysis. This method has been largely used to interpret the degree and the direction of functional couplings in networks of neuronal populations from which depth-EEG signals are recorded (Arthuis et al., 2009; Guye et al., 2006). The method is aimed at quantifying the association degree between two depth-EEG signals $X(t)$ and $Y(t)$ recorded from two neuronal populations P_x and P_y. An interesting feature of this method is that it can deal with either linear or nonlinear relationships between signals, conversely to linear regression or coherence methods that are only sensitive to the linear component of the relationship.

The nonlinear regression analysis method provides two quantities, namely the nonlinear correlation coefficient (h^{2*}_{xy}) and the time delay (τ_{xy}) calculated on a pair of signals $X(t)$ and $Y(t)$:

$$h^{2^*}_{XY} = \max[h^2_{XY}(\tau)] = h^2_{XY}(\tau_{XY})$$
$$\tau_{\min} \leqslant \tau \leqslant \tau_{\max} \quad (1)$$

Where

$$h^2_{XY}(\tau) = 1 - \frac{VAR\,[Y(t+\tau)/X(t)]}{VAR\,[Y(t+\tau)]}$$

and where

$$VAR\,[Y(t+\tau)/X(t)] \hat{=} \arg\min(E[Y(t+\tau) - f(X(t))]^2)$$

As depicted in Eq. (1), the nonlinear correlation coefficient h^{2*}_{xy} is computed from the conditional variance of $Y(t+\tau)$ given $X(t)$, that is, the reduction of variance of $Y(t+\tau)$ is obtained by predicting y amplitude values from x amplitude values. In practice, the f function is obtained by building a piecewise linear regression curve from signal samples. This function is used to estimate $VAR[Y(t+\tau)/X(t)]$. Eq. (1) also shows that the time delay (τ_{xy}) corresponds to the time shift τ between the two signals $X(t)$ and $Y(t+\tau)$ that maximises the nonlinear correlation coefficient value (h^{2*}_{xy}) on the considered time window.

Depth-EEG signals are highly non-stationary during stimulation procedures. Changes induced by electrical stimulation are transient and often abrupt. To cope with this feature, we performed the analysis of pre- and post-stimulus periods using a sliding window. Here, two parameters are crucial: (1) the window duration, and (2) the sliding step. Regarding the window duration, the trade-off is to keep it "as short as possible" to capture transient abrupt changes while still allowing for statistically robust computation of the nonlinear correlation coefficient h^2, and hence the z-scores. Our preliminary tests showed that at least 20 independent couples of XY values are necessary for computing the h^2 coefficient. As the autocorrelation function of the depth-EEG activity dramatically drops after 50 ms, a 1-s duration window (1000 ms) is a good compromise. A good estimation of the h^2 coefficient requires to increase the sliding window duration but, this window duration should be kept as small as possible to not smoothen (i.e., mask) synchrony changes. As we chose a minimum number of 20 independent couples of X and Y samples to estimate the h^2, the duration of the analysis window was chosen to be equal to $20 \times 50 = 1000$ ms. Regarding the sliding step, we chose to use an overlapping of 50% between two adjacent windows, 0.5 s in our case. This 'optimal' value (Bendat and Piersol, 1971) allowed us to double the number of h^2 coefficient values that are used to compute the mean h^2 values (average over the pre-stimulus and the post-stimulus periods), which are themselves used in the calculation of the z-score.

Finally, our intent was to focus on the transition between the period that just precedes the stimulation and the period that follows. We arbitrarily defined the duration of the pre-stimulation to be equal to 20 s (i.e., 40 values of the h^2 coefficient are used to compute the mean). For the post-stimulus period, we chose 3 s (i.e., six values of the h^2 are used to compute the mean), as this value corresponds to the minimum duration of the post-discharge observed in patients.

For the sake of simplicity, the nonlinear correlation coefficient h^{2*}_{xy} will be simply denoted by h^2 in the following. The h^2 values were computed on both broadband signals (providing a global estimation of nonlinear interdependencies) and on signals filtered in the classical EEG sub-bands, namely delta (0.5–3.4 Hz), theta (3.4–7.4 Hz), alpha (7.4–12.4 Hz), beta (12.4–24 Hz) and gamma (24–97 Hz). For filtered signals, Hamming finite impulse response (FIR) filters were chosen for their linear phase that is more appropriate for the time delays in selected sub-bands. Filter order was equal to 256 (corresponding to 1-s duration at a sampling rate of 256 Hz). In addition, a notch filter (cut-off frequency band equal to 49.5–50.5) to eliminate the power line artefacts and the instrumentation noise was also applied. This allowed for determination of h^2 and τ values between pair-wise signals from RC, H and A. The analysis was performed on bipolar signals recorded from two adjacent contacts located in each of the mesial structures. The localisation of electrode contacts was done using post-implantation MRI.

Two periods were considered for analysis (Fig. 1A): a 20-s background period chosen just before the start of the stimulation (BKG) and a 3-s period following the end of the stimulation (post-stimulation, PS), the period during which patients may report the occurrence of *deja vu*. The h^2 values were averaged over the BKG and PS periods. Changes in h^2 values obtained during the PS period relative to the BKG period were evaluated by calculating the variation of h^2 values in term of z-scores (Zh^2 = (mean h^2 (PS) – mean h^2 (BKG))/SD (BKG)). These values were then averaged over time to get an estimate (mean ± SD) of the degree of coupling between mesial structures, either broadband or in each EEG sub-band.

To analyse the frequency dependence of the signal correlation processes obtained in individual subjects after stimulation, we also characterised the correlation among depth-EEG signals using a

time–frequency approach. The method we developed included two steps: the filtering of depth-EEG signals into narrow frequency bands Δf_i (typically 2 Hz, overlapping by 1 Hz) and the computation of the non-linear correlation coefficient value $h^{2*}_{xy}(t, \Delta f_i)$ on sub-band signals. The result was represented in the form of time–frequency colour-coded maps where 'hot' colours (yellow to red) denote high values of $h^{2*}_{xy}(t, \Delta f_i)$ (close to 1) and 'cold' colours (blue to green) denote low values of $h^{2*}_{xy}(t, \Delta f_i)$ (close to 0).

3. Results

3.1. Stimulations eliciting déjà vu

A sensation of *déjà vu* occurring in isolation or in association with emotional symptoms was evoked in seven patients (Table 1) by direct electrical stimulation of the RC region. A total of 11 stimulations were followed by *déjà vu*. Mean stimulation intensity was 1.23 ± 0.6 mA. Fig. 1A shows the stimulation artefact and the regional after-discharge evoked by the stimulation of the RC in a single patient.

3.2. Correlation of EEG signals during déjà vu

Functional couplings between regions of interest were studied using nonlinear regression analysis. Specifically, interdependencies between signals from the A, H and rhinal regions after 23 stimulations in the seven patients (11 DV+ stimulations, 12 DV− stimulations in the same regions in the same patients (five among seven studied) were quantified using Zh^2 values (variations in signal correlations during post-stimulation periods relative to the background pre-stimulus period). Fig. 1B provides Zh^2 values measured on broadband signals. It can be observed that most Zh^2 values are greater than 0, showing that the cross-correlation between SEEG signals tended to increase after stimulations in a large majority of cases (25 out of 33). A decrease in correlations was observed only in a few of the interactions shown ($Zh^2 < 0$; 8 out of 33).

To address the specificity of these results, we also analysed EEG signals recorded in the same conditions (i.e., during the stimulation of the same region) in the 12 DV− stimulations (see Table 1). Then, we compared the Zh^2 obtained in the two conditions (DV+ vs. DV−). This comparison was done using a non-parametric

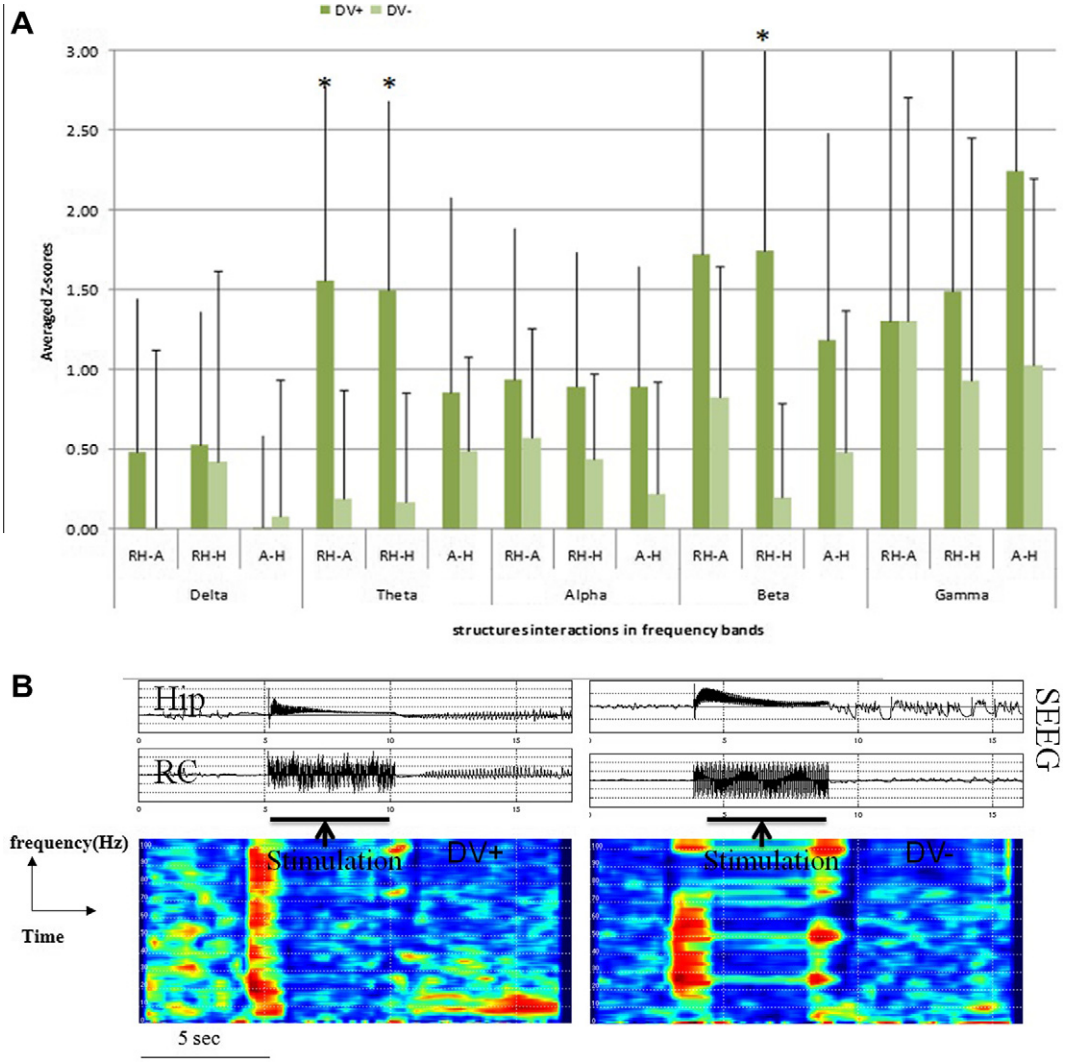

Fig. 2. (A) Interactions between the rhinal cortex (RC), amygdala (A) and hippocampus (H) in EEG sub-bands (see definitions in the text) expressed in *z*-scores of h^2 values obtained in period PS relative to period BKG. An asterisk indicates significant changes. (B) Time frequency representation of EEG correlation changes after stimulation inducing «*déjà vu*» (left, DV+) and stimulation not inducing «*déjà vu*» (right, DV−) in patient 5 after stimulation of the RC. Just after the end of the stimulation, the patient mentioned that he had the strange sensation of reliving the current situation. This sensation was brief and disappeared after several seconds and was associated with an unpleasant sensation of anxiety.

Mann–Whitney *U* test. No statistical difference was observed between stimulation intensity in the two groups ($p = 0.8$).

As shown in Fig. 1C, the cross-correlation increase was more pronounced after DV+ stimulation than after DV− stimulation ($p = 0.01$). Fig. 1C shows the average values of all the interactions between DV+ stimulations and DV− stimulations and Fig. 1D shows the interactions among MTL regions. Differences were significant for interactions RC–H ($p = 0.01$) and A–H ($p = 0.04$).

We then investigated whether these cross-correlation variations take place in specific EEG sub-bands. In this regard, we compared DV+ and DV− Zh^2 values in the five EEG sub-bands defined above. We found that cross-correlation changes were significantly different in the theta band for RC–A ($p = 0.007$) and RC–H ($p = 0.001$) and in the beta band for RC–H ($p = 0.01$) (Fig. 2A). This phenomenon is illustrated in Fig. 2B, which shows time–frequency representations of the nonlinear correlation computed from depth-EEG signals recorded for two different stimulation episodes in a patient. An increase in nonlinear correlation appears clearly in the beta and theta sub-bands when *déjà vu* is induced (Fig. 2B.a), while no clear nonlinear correlation appears when *déjà vu* is not induced (Fig. 2B.b).

4. Discussion

In this study, results show that neural coupling between RCs and H or A was specifically increased in the theta band after stimulations inducing *déjà vu*. In addition, an increase in correlation between the RCs and H was also observed in the beta band. Overall, these results argue against the hypothesis that *déjà vu* is related to the isolated dysfunction of a familiarity coding system depending solely on anterior subhippocampal structures. They argue, on the contrary, for a more complex set of interactions between the different MTL structures.

It has long been known that stimulation of the MTL region may induce typical *déjà vu* in epileptic patients investigated using depth electrodes (Bancaud et al., 1994; Gloor et al., 1982; Halgren et al., 1978; Vignal et al., 2007). H and A were initially proposed as the site of origin of this manifestation. Bancaud et al. (1994) brought evidence that MTL-neocortical interactions underlay *déjà vu* as well as dreamy state phenomena. However, we recently showed that stimulation of the RCs (perirhinal and entorhinal) most reliably triggered *déjà vu* in epileptic patients (Bartolomei et al., 2004). In a series of 24 patients with electrodes exploring the anterior parahippocampal region, 11% of RC stimulations elicited *déjà vu* in comparison with only 2% after hippocampal or amygdala stimulation (Bartolomei et al., 2004). Within subhippocampal structures, stimulation of the entorhinal cortex was even more prone to elicit *déjà vu*. Such results appeared concur with previous assumptions (Spatt, 2002), suggesting that the appearance of *déjà vu* is due to the transient alteration of a "familiarity system." The fact that the rhinal region was the main site to induce *déjà vu*, when stimulated, also appeared in agreement with animal and human studies showing that many neurons in the perirhinal cortex code for familiarity (Brown and Xiang, 1998).

However, it has been argued against the 'altered familiarity' hypothesis that *déjà vu* involves a set of more complex sensations that are not limited to object perception (O'Connor and Moulin, 2008, 2010). We have studied two groups of patients having or not *déjà vu* after stimulation. Stimulations were in the same range of intensities in the two groups. *Déjà vu* was related to increased cross-correlation in the theta and beta frequency bands compared with stimulations in the same brain areas that did not trigger *déjà vu*. Under the hypothesis that the current spread was similar in both conditions, such a result favours the view that *déjà vu* is related to increased correlation among MTL structures rather than being a 'local' phenomenon. Hence, the hypothesis of a dysfunction localised within subhippocampal structures can probably be discarded. New hypotheses have thus to be proposed to account for the set of complex interactions observed among MTL brain regions.

One hypothesis is that the subjective experience of *déjà vu* might be more elaborate than is usually thought, that is, not related to an impression of pure familiarity alone. In this sense, the term '*déjà-vécu*' ('already lived') could be a more appropriate descriptive term (Moulin et al., 2005; O'Connor and Moulin, 2010). It has been observed that temporal lobe epilepsy patients may experience two distinguishable patterns of symptoms, the first being 'pure' *déjà vu* as reported in this study and the other being the vivid reminiscence of a scene from the patient's past involving a visual hallucinatory element (Vignal et al., 2007). This suggests that there could be a continuum between *déjà vu* and recollective episodes, *déjà vu* being considered a low-level recollective episode, and the two conditions probably sharing common mechanisms and highly depending on MTL abnormal activation. In line with this interpretation, we have already demonstrated that recollection of memories induced by stimulation of the perirhinal cortex is associated with increased EEG synchrony between the MTL regions themselves and between MTL and the visual associative cortex (Barbeau et al., 2005). This correlation was significantly modified in the theta EEG band and H appeared as a key region in the network involved in this phenomenon. In the present study, we found that *déjà vu* is specifically associated with increased interactions between RC, A and H. The most significant changes involved RC–H and A–H interactions, thus again placing H in a pivotal role in these interactions. Similar to our previous study, an increase was observed in all EEG bands but predominated in the theta band. These results are in line with two kinds of previous findings. The first is the role of co-operative synchrony between MTL structures during encoding and retrieval of memory, particularly involving theta oscillations (Fell et al., 2001, 2002, 2003; Fernandez et al., 2002; Guderian and Duzel, 2005). Theta oscillations have consistently been proposed to play a prominent role in episodic memory retrieval, both within H and between H and neo-cortical areas (for recent reviews, see Duzel et al. (2010) and Nyhus and Curran (2010)). The second is the key role of H in recollective experience, as has been widely proposed in the literature. Following this hypothesis, "*déjà vécu*" would be a type of weak vivid reminiscence.

However, why should such a phenomenon be elicited more easily by RC than by hippocampal stimulation? Note that we did not report in this study stimulations of H because previous reports have shown that *déjà vu* is rarely elicited after stimulation of this structure (Bartolomei et al., 2004). Recent observation of the crucial role of the entorhinal cortex in long-term memory (Steinvorth et al., 2009) may be relevant to the underlying mechanism of *déjà vu*. As already noted, the entorhinal cortex is probably the structure in which paroxysmal activation most consistently leads to *déjà vu* (Bartolomei et al., 2004). More specifically, (Steinvorth et al. (2009) found, while using micro-electrodes sampling the different cortical layers of the entorhinal cortex in an epileptic patient, that superficial layers II/III, which are afferent to H, showed prominent gamma increase during ecphory (ecphory being the recollection of a past event cued by a trigger, such as a picture or an odour), while deep layer V, which is thought to be an efferent relay between H and the neocortex, showed enhanced theta activity during memory retrieval (Steinvorth et al., 2009). Therefore, stimulation of the RCs could evoke pronounced abnormal local theta activation and/or interference with actual theta oscillations. Because this pattern of theta activation is usually associated with memory retrieval, it could be interpreted as a signal that the system is in a 'retrieval' mode (i.e., oriented towards the internal world). In this situation, H would not be directly activated by the stimulation, and it would thus participate in the process without

activating content retrieval processes. Simply said, one or two abnormal theta cycles could occur during *déjà vu* without the concomitant retrieval of memory content, leading to the very unusual experience of *déjà vu*, a kind of recollection without content. This hypothesis would account both for the importance of the site of stimulation (RC cortices) and the RC/H interactions. Following this hypothesis, *déjà vu* would be close to a vivid reminiscence of scenes, sharing common mechanisms of recollection and clearly different in that no content would be activated.

This hypothesis is related to a recent neurophysiological model that aims at accounting for *déjà vécu* (O'Connor et al., 2010). This model builds upon the proposal that CA1 principal cells fire at different theta phase oscillations, depending on whether they are encoding or retrieving information (Manns et al., 2007). Reading out the mean phase of hippocampal firing by neurons in frontal lobes could signal whether H is in an encoding or a retrieval mode. However, hippocampal theta phase timing disruption (e.g., by seizures) could be wrongly interpreted as a retrieval mode (recollection), whereas H is in reality in an encoding mode. Note, however, that this model involves mainly H rather than anterior subhippocampal structures.

In conclusion, we studied whether the mechanism underlying *déjà vu* was compatible with the hypothesis of an isolated familiarity dysfunction and have provided arguments against this. Even if the precise mechanism of *déjà vu* remains unknown, our results suggest that a coincident occurrence of certain conditions is required: a 'trigger' in anterior subhippocampal structures; and transient functional coupling in the theta range between MTL structures, eventually leading to an activation of the recollection system. The increase in the beta range remains a surprising finding at this stage of our research and will be investigated in future studies.

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