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Déjà-vu in temporal lobe epilepsy: Metabolic pattern of cortical involvement in patients with normal brain MRI

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ABSTRACT

To contribute to the identification of brain regions involved in déjà-vu, we studied the metabolic pattern of cortical involvement in patients with seizures of temporal lobe origin presenting with or without déjà-vu. Using voxel-based analysis of 18FDG-PET brain scans, we compared glucose metabolic rate of 8 patients with déjà-vu, 8 patients without déjà-vu, and 20 age-matched healthy subjects. Patients were selected after comprehensive non-invasive presurgical evaluation, including normal brain MRI and surface electroclinical features compatible with unilateral temporal lobe epilepsy (TLE).

Patients with and without déjà-vu did not differ in terms of age, gender, epilepsy lateralization, epilepsy onset, epilepsy duration, and other subjective ictal manifestations. TLE patients with déjà-vu exhibited ipsilateral hypometabolism of superior temporal gyrus and of parahippocampal region, in the vicinity of perirhinal/entorhinal cortex, in comparison either to healthy subjects or to TLE patients without déjà-vu ($p < 0.05$ FDR-corrected). By contrast, no difference was found between patient subgroups for hypometabolism of hippocampus and amygdala. At an individual-level, in comparison to healthy subjects, hypometabolism of both parahippocampal region and superior temporal gyrus was present in 7/8 patients with déjà-vu. Hippocampal metabolism was spared in 3 of these 7 patients.

These findings argue for metabolic dysfunction of a medial–lateral temporal network in patients with déjà-vu and normal brain MRI. Within the medial temporal lobe, specific involvement of the parahippocampal region, often in the absence of hippocampal impairment, suggests that the feeling of familiarity during seizures greatly depends on alteration of the recognition memory system.

1. Introduction

Déjà-vu is experienced by most people, occurring about once a year in healthy subjects (Brown, 2003). Its frequency decreases with age, and it appears to be promoted by stress and fatigue. Authors have associated this phenomenon to drowsiness or to possible ictal events in normal subjects (Spatt, 2002). On the other hand, déjà-vu is classically reported with similar characteristics by some patients during seizures of temporal lobe origin, suggesting that déjà-vu functionally involves the same temporal structures in epileptic patients and healthy subjects (Bancaud, Brunet-Bourgin, Chauvel, & Halgren, 1994; Gloor, 1990; Spatt, 2002; Wild, 2005).

Ictal déjà-vu was described for the first time by Hughlings Jackson within the spectrum of the "dreamy state", which also included vivid reminiscences of memories. Dreamy state was supposed to be linked to lesions affecting the medial temporal lobe (MTL) (Jackson, 1888; Jackson & Stewart, 1899). Later, Penfield and Jasper associated déjà-vu with sensory illusions and emotional disturbances as experiential hallucinations induced by stimulation of lateral temporal neocortex, particularly the superior temporal gyrus (Penfield & Jasper, 1954). More recently, Bancaud et al. showed that dreamy state depends upon electrical activity of a neural network involving both medial and lateral temporal lobe areas (Bancaud et al., 1994). Among MTL structures, many authors have emphasized the role of the amygdala, the hippocampus (Gloor, Olivier, Quesney, Andermann, & Horowitz, 1982; Vignal, Maillard, McGonigal & Chauvel, 2007) and more recently rhinal cortices (Barbeau, Wendling, et al., 2005; Bartolomei et al., 2004). However, the exact contribution of each of these structures in déjà-vu and dreamy state remains debated (Spatt, 2002).

It has been supposed that déjà-vu occurs due to disruption in the normal operation of two separate but interactive memory processes (Brown, 2003; Spatt, 2002). Déjà-vu, which is characterized by a feeling of familiarity that the current experience is

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the repetition of an episode already seen, could be due to activation of familiarity-based recognition in the absence of retrieval. In this way, déjà-vu suggests possible independence of these two memory processes within the temporal lobes, and provides a rare opportunity to separately study one of the relevant systems for remembering (Brown & Aggleton, 2001; Brown & Xiang, 1998; Spatt, 2002).

On the other hand, recent studies focusing on partial epilepsies suggest good correspondence between interictal PET hypometabolism and the brain regions affected by ictal generation and spreading (Bouilleret, Valenti, Hirsch, Semah, & Namer, 2002; Chassoux et al., 2004; Lee et al., 2009). Only one previous study has investigated the functional metabolic impairment specifically found in temporal lobe epilepsy (TLE) with déjà-vu (Adachi et al., 1999). The authors showed significantly reduced glucose metabolism in medial temporal and parietal cortex, in comparison to TLE patients without déjà-vu. Morphological brain abnormalities were however reported in these patients, and may have influenced the metabolic findings. In addition, the semi-quantitative analysis used in this study was based on circular regions of interest, which were not able to precisely identify the structures involved within the MTL (hippocampal vs. extra-hippocampal structures).

In the present work, we studied, at voxel-level and in comparison to healthy subjects, the metabolic pattern of cortical involvement in patients with normal brain MRI and seizures of temporal lobe origin, presenting with or without déjà-vu. We aimed to contribute to the identification of brain regions involved in déjà-vu, in particular within the mesiotemporal memory system.

2. Materials and methods

2.1. Subjects

Two subgroups of eight consecutive patients were selected according to the presence or the absence of ictal déjà-vu. All patients were enrolled after a comprehensive non-invasive presurgical evaluation, including normal brain qualitative MRI (3DT1-weighted images, T2-weighted axial and FLAIR coronal images, Siemens 1.5T), and surface video-EEG electroclinical features compatible with unilateral TLE as defined in a previous work using depth-recording (Maillard et al., 2004). Patients were interviewed and examined during the course of their seizure by a doctor or a nurse trained in epileptology. Presence or absence of ictal déjà-vu was established by questioning the patient during or just after the seizure. Patients with brain MRI morphological abnormalities were excluded since atrophy and presumed degree of neuronal loss appear to be a primary causal factor in decreased metabolism (Knowlton et al., 2001). Brain MRIs were visually interpreted by the same experienced neuroradiologist specialized in epilepsy. Previous studies have shown good concordance between visual interpretation and volumetric analysis in TLE patients with normal brain MRI (Mueller et al., 2006; Salmenpera et al., 2007).

Twenty right-handed healthy subjects, free of neurological disease and cognitive complaints, and similar to patients in terms of age (35.80 years ± 10.48; $p = 0.9238$, Mann–Whitney test), were also included after confirming normal neurological and neuropsychological evaluation, and normal brain MRI. Informed consent was obtained with a protocol approved by the local ethics committee and conforming to the Declaration of Helsinki on human investigation.

2.2. 18FDG-PET acquisition

Interictal brain metabolism was studied in all patients, under the same conditions as in healthy subjects. PET scan was performed using an integrated PET/CT camera (Discovery ST, GE Healthcare, Waukesha, USA), with 6.2 mm axial resolution, allowing 47 contiguous transverse sections of the brain of 3.27 mm thickness. 150 MBq of 18FDG was injected intravenously in an awake and resting state, with eyes closed, in a quiet environment. Image acquisition started 30 min after injection and ended 15 min later. Images were reconstructed using ordered subsets expectation maximization algorithm, with 5 iterations and 32 subsets, and corrected for attenuation using CT transmission scan.

2.3. Statistical analysis

Whole-brain statistical analysis was performed at voxel-level using SPM2 software (Welcome Department of Cognitive Neurology, University College, London, UK), by flipping the epileptogenic zone (EZ) to the same side, as previously shown (Chassoux et al., 2004). Indeed, we aimed to identify the brain structures specifically involved in déjà-vu, independently of EZ side. Ipsilateral and contralateral brain PET metabolism, related to EZ side, was compared at voxel-level to the mean left and right brain PET metabolism obtained in healthy subjects (Chassoux et al., 2004). The PET images were converted from the DICOM to the Analyze format using the software MRIcro (http://www.sph.sc.edu/comd/rorden/mricro.html), then transferred to SPM2. The data were spatially normalized onto the Montreal Neurological Institute atlas (MNI) using a 12-parameter affine transformation, followed by non-linear transformations and a tri-linear interpolation (Sugiura et al., 1999). The dimensions of the resulting voxel were 2 mm × 2 mm × 2 mm. The images were then smoothed with a Gaussian filter (12 mm FWHM) to blur individual variations in gyral anatomy and to increase signal-to-noise ratio. The resulting PET images were divided by individual FDG uptake value of a specific reference site to control for individual variations in global PET measures (Waxman et al., 2009). We selected the vermis as being a preserved area. The individual vermis value was obtained for each subject using the 'Anatomical ROIs Analysis' toolbox of SPM2 allowing the automatic extraction of the mean value of the labeled region from the Anatomical Automatic Labeling (AAL) atlas (Tzourio-Mazoyer et al., 2002).

Significant regions of hypometabolism were first sought by comparing healthy subjects to the subgroups of TLE patients with and without déjà-vu. Secondarily, brain metabolism was directly compared between TLE patients with and without déjà-vu. We used ANCOVA as statistical model, with age as confounding covariate. The SPM maps were thresholded using $p < 0.05$ corrected for multiple comparisons with the False Discovery Rate method (FDR-corrected). This whole-brain statistical analysis was supplemented at the same statistical threshold by a voxel-based MTL study, with a mask including the ipsilateral amygdala, hippocampus and parahippocampal region from the AAL atlas ($p < 0.05$ FDR-corrected) (Tzourio-Mazoyer et al., 2002). In particular, the parahippocampal region consisted of parahippocampal gyrus and parahippocampal uncus, and included both entorhinal and perirhinal cortices (Tzourio-Mazoyer et al., 2002). The mask of regions of significant hypometabolism obtained in patients with déjà-vu in comparison to healthy subjects was also used to compare brain metabolism between patient subgroups at voxel-level in a final analysis ($p < 0.05$ FDR-corrected): we aimed to search for metabolic differences between patients with and without déjà-vu, within brain areas having previously demonstrated significant hypometabolism in patients with déjà-vu in comparison to healthy subjects.

Anatomical localization of most significant voxels was identified with Talairach Daemon (http://ric.uthscsa.edu/projects/talairachdaemon.html), and regions involved within each significant cluster with the AAL atlas (Tzourio-Mazoyer et al., 2002).

Values of clusters obtained and values of anatomical MTL structures were extracted, and the significance of findings was confirmed using non-parametric tests (Kruskall–Wallis and Mann–Whitney tests). Interaction between clusters of hypometabolism and laterality of epilepsy was secondarily searched using the Mann–Whitney test. At the individual-level, metabolism was considered to be decreased if below the fifth percentile of the control group of healthy subjects.

3. Results

3.1. Patient characteristics

TLE patients with and without déjà-vu did not differ for age, gender, epilepsy lateralization, epilepsy onset and epilepsy duration (Mann–Whitney and Chi-square tests) (Table 1). In the same way, no difference was found for subjective manifestations other than déjà-vu, in particular for viscero-sensitive symptoms ($p = 0.40$), emotional aura ($p = 0.34$) and sensory symptoms (olfactory hallucination or paresthesia; $p = 0.28$) (Fisher exact test).

Visual analysis of PET images showed ipsilateral MTL hypometabolism in all patients. No evidence of bilateral metabolic depression was observed in any patients.

3.2. 18FDG-PET cerebral metabolic rate for glucose

3.2.1. TLE patients with déjà-vu in comparison to healthy subjects

Whole-brain analysis showed significant ipsilateral hypometabolism in patients with déjà-vu, in comparison to healthy subjects, within the parahippocampal region (including entorhinal and perirhinal cortices; BA34, BA35), and the superior temporal sulcus, in particular the superior temporal gyrus (BA22, BA38) (Table 2 and Fig. 1A).

Ipsilateral MTL analysis showed significant hypometabolism, in comparison to healthy subjects, within the parahippocampal region (57% of the cluster volume, including entorhinal and