Pathophysiology of Déjà Vu and Reminiscences in Epilepsy

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Abstract

Illusions of inappropriate familiarity with the current experience or hallucinatory recall of memories have been reported in temporal lobe epilepsies. Pathophysiological hypotheses have been put forward, involving either the limbic regions of the temporal lobe (Jackson), the temporal neocortex ("interpretive cortex", Penfield), or both (Bancaud). New data, acquired in the course of presurgical investigations through intracerebral electrodes recording, demonstrate a critical role of the sub- and para-hippocampal cortices. A new hypothesis of cortico-limbic network is developed. Déjà Vu would result from an abnormal synchronisation between rhinal cortices and hippocampus, and reminiscences (or "dreamy state") from exacerbation of associational function of hippocampus in re-assembling pieces of past experience cortical networks.

Keywords: déja vu, temporal lobe epilepsy, episodic memory, hippocampus, para-hippocampal cortex
INTRODUCTION

The epileptic seizures which are named partial or focal are able to cause perceptive, cognitive, emotional, affective, autonomic, motor, gestural and/or behavioural changes, which are paroxysmal, and develop themselves in the same time dimension as the normal "functions", thus producing a construction of abnormal phenomena (sensory or motor, conscious or unconscious), which can often be viewed as a caricature of normal but for the patient a breakdown of self-control. This production of signs and symptoms which is distinctive of epileptic fits has been carefully studied since the origins of modern neurology. Some of them appeared so close to normal functioning that a pioneer like John Hughlings Jackson was immediately aware that he was studying the effects of a sort of natural stimulation of brain areas provided by the disease, and able to give insight into the way the human brain is working [1].

JACKSON’S DREAMY STATE

One of the most demonstrative illustration of this was provided by the phenomena of déjà-vu and “dreamy state”. Some patients, being conscious of their seizures or at least of their onset, may describe their attacks as follows: “I’m reliving something…but I can see you clearly… It’s as if what is happening now has already happened to me, it’s like an old memory that I am in the middle of living out” or “I see myself playing the drums, with people from my family listening to me” or "It’s exactly the same as the last time, it’s all come back to me…it’s behind, it’s always thoughts from childhood, it’s always visual, it’s a place behind the house, the field where my father put his car, near a lake… It’s not always the same countryside; I’ve forgotten the story of this countryside…” [2].

These illusions of inappropriate familiarity with the present experience (déjà-vu) or hallucinatory recall of (true or false) past experience had been observed and reported by J. Hughlings Jackson at the end of the XIXth century. In fact, his attention towards this phenomenon had been attracted by a physician who suffered from it, and had published himself his own observation. His epilepsy manifested first as “déjà vu” episodes, but their increasing recurrence finally got him worried. He consulted Jackson, who quoted his observation in an article published in 1888 [3]. At this time, in addition of too frequent déjà vu, he experienced abnormal reminiscences that he called “feelings of recollection”. Jackson noticed that “the psychical condition, therefore, is a very complex one”. During these attacks, patients are still aware of the incoming sensory stimuli, so there are remains of normal consciousness and in addition a quasi-parasitical state of consciousness (dreamy state). This double consciousness was named “mental diplopia”. The dreamy state, for Jackson, corresponds to the activation of centers liberated from the control of higher centers impaired by epileptic activity. In his opinion, it arises from an excessive activity that is not epileptic per se, and thus is different from
auras. Having the opportunity to perform autopsy in some of these patients, he concluded that this phenomenon was caused by medial temporal lobe (uncus) « discharging lesions ».

**PENFIELD’S EXPERIENTIAL HALLUCINATIONS**

W. Penfield at the Montreal Neurological Institute inaugurated the modern era of epilepsy surgery in the 1920s. He based the delineation of cortical resections on direct stimulation of the cerebral cortex performed in the awake patient in the operating room [4]. At his great surprise, he could reproduce impressions of familiarity or strangeness or even evoke simple or complex scenes with visual or auditory components like arising from the memory of the patient: « on the first occasion, when one of these « flashbacks » was reported to me by a conscious patient (1933), I was incredulous. On each subsequent occasion, I marvelled. For example, when a mother told me she was suddenly aware, as my electrode touched the cortex, of being in her kitchen listening to the voice of her little boy who was playing outside in the yard. She was aware of the neighborhood noises, such as passing motor cars, that might mean danger to him. » [5]

Penfield did not view these paroxysmal symptoms as a continuum and distinguished between a feeling of familiarity (déjà vu or déjà vécu) and an elaborate visual hallucination. He analysed feelings of familiarity and strangeness as illusions of recognition, classing these together with other sensory illusions (such as visual or auditory) and “emotional” illusions under the denomination “interpretive illusions” (misrepresentation or altered interpretation of present experience, [6]). The phenomena described as defining the “dreamy state” by Jackson were considered as hallucinations by Penfield and were thought of as being the replaying of a past experience, which he termed “experiential hallucinations”, all of which were presumed to be based only upon memories of experiences that the patient had personally lived through. The cortical sites where feelings of familiarity and visual hallucinations might be produced by electrical stimulation were widely distributed over the temporal neocortex [7]. Therefore, the Penfield experience differed from Jackson in anatomical location of the brain structures determinant for producing such phenomena, even though the temporal lobe seemed to be also in cause. However, due to the surgical approach used which privileged the exposed cortex, the access to the deeper areas of the medial temporal lobe was certainly uneasy, limiting the opportunities to stimulate them directly [7].

**SEIZURES AND STIMULATIONS OF THE MEDIAL TEMPORAL LOBE**

The development of stereotaxic methods [8] allowed to deliver stimulations in these MTL structures through multiple lead intra-cerebral electrodes. Certain authors then found that the dreamy state could be provoked by stimulation of the
MTL [9], [10], [11]. Halgren et al. [12] grouped together the mental phenomena provoked by stimulation of the hippocampal formation and amygdala. They noted that obtaining a response depended more upon whether or not an after-discharge occurred, than upon the location of the stimulation site in the MTL. In other words, they found that the dreamy state is not a symptom specific to a single but needs recruitment of several structures, and that its content represents rather an idiosyncratic response that also takes into account the personality of the subject. Gloor et al., [13] could elicit experiential phenomena only by stimulation of the medial limbic areas, and especially of amygdala, which seemed to have the lowest threshold. He made the hypothesis that a given past experience is represented by a specific distributed matrix of neurons linked together through synapses that have been strengthened by plastic changes, this matrix being recruited by amygdala discharge when dreamy state occurs. Halgren and Chauvel [14], and Bangaud et al. [15] analyzed the anatomic-electro-clinical of 57 spontaneous seizures recorded in 16 patients with multiple intracerebral electrodes (Stereoelectroencephalography, SEEG), all of them characterized by déjà vu or dreamy state at their onset, and compared to the same phenomena induced by direct electrical stimulation. They did not follow the classification of Penfield, considering that the illusions of recognition were not at the same level of perceptual/cognitive integration as the unimodal sensory illusions, and observed that if feelings of familiarity/strangeness, feelings of recollection, and reminiscences of elaborated past scenes could be recorded separately in the same patient, they were most of the time reported as successive or even simultaneous in the same experience. Their data were clearly in favor of a paroxysmal alteration of memory processes, sometimes intermingled with negative (more frequent than positive) emotions. They discussed in depth the anatomic-functional basis for their occurrence. These phenomena could be elicited by paroxysmal activation of either amygdala, hippocampus, or temporal neocortex, actually reconciling Jackson’s and Penfield’s views. But this was in fact the co-activation of MTL structures (amygdala and/or hippocampus) with areas of the lateral and posterior temporal cortex that represented the condition for emergence of the dreamy state components. So, the idea of activation of cortical networks, where memories are embedded, through the efferents of the hippocampal/parahippocampal structures driven by the ictal discharge represented the new hypothesis for paroxysmal recollection and reminiscences. This hypothesis was based on the fact that the content of the experiential hallucinations is determined more by the structure which receives the hyperactivated efferences of the MTL rather than by the MTL itself. As a matter of fact, a large majority of the MTL stimulations evoked no psychical phenomenon at all, even when they were intense enough to induce after-discharges [12], [13], [16], [14]. In addition, surgical removal of the MTL structures alone does
not abolish the occurrence of these manifestations. Therefore, activation of MTL neurones is able to produce these memory experiences, but other data indicate that this activation is neither sufficient, nor necessary. Another line of arguments suggests that the neurons whose activity directly underpins experiences evoked by the MTL stimulation are located outside the MTL. This holds to the diversity of the experiences, and the nature of the factors which select them. What is determining the category of the evoked experiences is not the anatomical situation of the stimulating electrode in amygdala, hippocampus or parahippocampal gyrus, but which personality is stimulated and the inter-personal situation at the time of the stimulation. The personal traits and inter-personal relations represent factors susceptible to modify the context in which a remote structure interprets the efferent message from the MTL. Another argument against a sole and direct role of the MTL in elaborating these complex experiences is the fact that, at the very moment when they are occurring its neurons are engaged in an after-discharge which renders them very likely unable to participate in so specific and complex activity. It seems more reasonable to consider that these experiences are produced by a functional “inhibition” of the MTL associated with a paroxysmal dis-organisation remotely induced by its efferent discharge. The main hypotheses proposed and discussed in the literature since Jackson are schematically illustrated in fig.1. Fig.1A represents the Penfield direct activation of long-term memory networks through cortical stimulation. Fig.1B shows, according to Bancaud et al., how amygdala-hippocampus stimulation can synchronize those cortical networks, because of their distributes efferents. Fig.1C emphasizes the Jackson’s conception of an epileptic discharge releasing remote cortical areas thus producing dreamy state phenomena.

**ROLE OF THE RHINAL CORTEXES**

The anatomical organisation of the MTL efferences gives a plausible explanation why a MTL stimulation can synchronize vast territories in the supramodal temporal and temporo-parieto-occipital cortex. The type of discharge and the speed of its propagation are likely to play an important role, given preservation of awareness and current sensory stream access to consciousness maintained in parallel (“mental diplopia”).

This working hypothesis was strengthened by recent data obtained in a series of temporal lobe epilepsy patients investigated with a new strategy of electrode implantation. In order to get recordings directly in epileptogenic lesions situated in the basal temporal cortex, new trajectories of orthogonal multiple lead electrodes were studied to reach this region in addition to the “classical” trajectories targeting amygdala and anterior and posterior hippocampus line. Under these conditions of recording, evoked déjà vu and dreamy state manifestations were obtained by stimulation performed in the course of presurgical investigations [17]. The anatomical situation of the basal temporal electrode allowed stimulation of
Figure 1: Schematic representation of the main hypothesis on the mechanisms of paroxysmal recollections (after [14]). A. Penfield’s hypothesis: cortex stimulation reactivates memory traces embedded in the interpretive cortex (temporal lobe). B. Bancaud et al.’s hypothesis: MTL stimulation synchronizes remote cortical areas, and associates the pieces of the distributed network where memory traces are stored; direct stimulation applied to the cortex can also be successful. C. Jackson’s hypothesis: the “dreamy state” corresponds to the activation of “nervous centers” liberated from the control of higher “centers” impaired by epileptic activity; it arises from an excessive activity that is not epileptic by itself. The nodes connected by lines with arrows represent activated cortical networks; broad arrows with $ and numbers indicate the sites of stimulation.

the rhinal (entorhinal and perirhinal) cortices, in addition to the amygdala and hippocampus. Déjà vu and reminiscences were reported more often by the patients after stimulation of the rhinal cortices than by stimulation of amygdala or hippocampus. Moreover, the most sensitive site to obtain the illusion of familiarity was the entorhinal cortex, and that for reminiscences was the perirhinal cortex. These data are interesting by reference to recent developments in research on anatomo-functional basis of episodic memory. A double system (hippocampal and perirhinal) with distinct but cooperative functions has been hypothesized from convergence of experimental animal and human studies [18]. The perirhinal system is rapid and automatic, and contains familiarity and recency discrimination components of recognition memory; it is also part of a high-level perceptual system coding for visual feature ambiguity [19]. The hippocampal system is slower and associational, more specialised in spatial cognition, and gives access to episodes; it is the system for recollective aspects of recognition memory [18]. The former “knows” that the present event has previously occurred, and the latter “remembers” the previous experience. This
dual organisation of declarative memory could underlie the mechanisms of déjà vu and dreamy state in epileptic patients.

However, the results of rhinal cortices stimulation do not appear in full agreement with experimental data. As a matter of fact, the stimulation of perirhinal rather than entorhinal cortex should induce déjà vu. Two arguments might be developed against a too focal view of these phenomena. First, such stimulations applied intracerebrally with macroelectrodes are considered to inactivate functionally the area close to the electrode and to activate its efferences [14]. Second, clinical observations of the patients presenting with these ictal symptoms show that the two components (déjà vu and recollection) cannot be easily dissociated. If déjà vu may occur in isolation, recollection of memories is, obviously, felt in a context of familiarity [2, 15]. The network hypothesis [14-16] linking medial temporal limbic structures with associative sensory unimodal and polymodal areas remains the most plausible.

Using signal analysis we have studied in one patient functional coupling between the structures discharging after stimulation of the perirhinal region evoking a dreamy state-like hallucination [20]. A déjà vu illusion and experiential phenomena consisting of visual memories could be obtained by stimulation of the same site localised in the perirhinal area, but at distinct levels of intensity, the threshold for déjà vu being the lowest. These visual hallucinations were reported as shapes or pieces of objects, from which a familiar scene is reconstructed. So, a priming effect was exerted by some visual features from which the patient was inferring a complete memory. Interestingly, this associational process seemed to be underlain by significant increase in functional coupling (as measured by cross-correlation) between perirhinal cortex and hippocampus on the one hand, between these two structures and the visual cortex on the other hand. During the stimulation inducing a déjà vu only, there was no correlation with the visual cortex, but synchronisation between the rhinal cortices and the hippocampus. Therefore, déjà vu phenomenon could be related to the abnormal synchronisation between the two systems, i.e. the perirhinal and the hippocampal ones, whereas the “dreamy state” would need an associational mechanism between perceptual/cognitive cortical areas mediated by the hippocampus (and the amygdala, adding the emotional tone of the experience) (fig.2). This hypothesis has been recently confirmed: comparing in the same patients stimulations of the rhinal cortices inducing or not inducing déjà vu, this familiarity experience occurred only when the signal correlation increased between rhinal cortices, amygdala and hippocampus specifically in the theta band [21].

ILLUSIONS OF AUTOBIOGRAPHIC MEMORIES?

The content of the memories pathologically recollected during the dreamy state was especially analysed in 16
Figure 2. Déjà Vu and paroxysmal Recollections of memories: hypothetic mechanisms. An infero-medial aspect of the right hemisphere is represented. Top left (epoch 1): perirhinal cortex (PR) is functionally linked with some areas of the visual cortex (Cx2), whereas hippocampus (H) is in reciprocal relation with two distinct cortical networks (Cx1 and Cx2) representing distributed perceptual/cognitive elements of the current experience. Top right (epoch 2): low-level stimulation applied to rhinal cortex generates a feeling of déjà vu by synchronizing the two systems (dark arrow), perirhinal at the tip of the ventral stream and hippocampal tuned to retrieval; an alternate possibility is that PR stimulation simply signals familiarity to hippocampus. Bottom (epoch 3): a stronger stimulation induces an after-discharge synchronizing the two systems (dark arrow) and cortical associative sensory areas through activation of hippocampal efferences; as a result of this efferent discharge, a distributed cortical network rebuilding memories (Cx1, Cx2) is reactivated (dark dots) because of potentiated synaptic connections.

Subjects submitted to intracerebral recordings prior to epilepsy surgery [2]. Semiological analysis showed a clinical continuity between déjà vu and visual hallucinations, the latter often consisting of a personal memory that was “relived” by the subject; such memories could be recent, distant or from childhood. With one exception, the particular memory evoked differed from one seizure to another, but were always drawn from the same period of the subject’s life. Therefore, these paroxysmal experiences should be viewed as illusions of autobiographic memory. This study also confirmed the mediation of large neural networks that produce recall.
of recent or distant memories via activation of the hippocampus, amygdala and rhinal cortices.

Finally, the modernity of the Jackson’s view of the Dreamy State deserves to be underlined. The fact that the abnormal discharge arises from the MTL network, but the reassembled episode emerges from a remote (normally functioning) cortical network was prefigured: “the elaborate state I call “dreamy state” arises during but slightly raised activities (slightly increased discharges) of healthy nervous arrangements” [3]. Reassembling pieces of a familiar visual scene (as described in most of the stimulation data reports) from basic elements through a priming mechanism might suggest a self-organizing process activated by a loss of normal control from “higher centers impaired by epileptic activity”, a novel hypothesis in accordance with Jackson’s visionary concepts.

Déjà Vu and reminiscences pathophysiology has always been studied by authors having also in mind a search for “normal” déjà vu and episodic memory mechanisms. Similarity between physiological and epileptic déjà vu has been put forward [22], the two phenomena being differentiated rather quantitatively than qualitatively. A grey matter volume reduction in the same areas of the medial temporal lobe as those involved in epileptic déjà vu has recently been demonstrated in normal subjects [23].
LIST OF REFERENCES


