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Neuroimaging and cognitive changes during déjà vu

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ABSTRACT

Objective: The cause or the physiological role of déjà vu (DV) in healthy people is unknown. The pathophysiology of DV-type epileptic aura is also unresolved. Here we describe a 22-year-old woman treated with deep brain stimulation (DBS) of the left internal globus pallidus for hemidystonia. At certain stimulation settings, DBS elicited reproducible episodes of DV.
Methods: Neuropsychological tests and single-photon-emission computed tomography (SPECT) were performed during DBS-evoked DV and during normal DBS stimulation without DV.
Results: SPECT during DBS-evoked DV revealed hyperperfusion of the right (contralateral to the electrode) hippocampus and other limbic structures. Neuropsychological examinations performed during several evoked DV episodes revealed disturbances in nonverbal memory.
Conclusion: Our results confirm the role of mesiotemporal structures in the pathogenesis of DV. We hypothesize that individual neuroanatomy and disturbances in gamma oscillations or in the dopaminergic system played a role in DBS-elicited DV in our patient.

1. Introduction

Déjà vu (DV) is "any subjectively inappropriate impression of familiarity of present experience with an undefined past" [1]. Although 60–80% of the healthy population have experienced déjà vu [2], DV aura is one of the leading symptoms of temporal lobe epilepsy (TLE) [3] occurring in 10% of all epileptic auras [4]. DV aura is the most characteristic symptom of familial mesial temporal lobe epilepsy reported in about one-third of these patients [5,6]. DV occurring in other brain disorders (e.g., depression [7] and schizophrenia [8]) has also been analyzed in more detail.

Studying DV is difficult because of its rarity, unpredictable appearance, and heterogeneity. Contrary to spontaneous DV, induced DV can be examined objectively during presurgical evaluation of epilepsy [3]. Stimulation of the temporal structures [9] or the rhinal cortex [10] often, but not always [11], elicits DV in patients with TLE. Most studies have reported that DV was confined to the nondominant temporal lobe and accompanied by hallucinations or illusions [3,4,9,11]. Furthermore, DV can also be provoked by electrical stimulation of brain structures contralateral to the epileptic focus, suggesting DV can also be elicited in normal brain tissue [12].

Despite numerous investigations, the pathomechanism of DV in healthy people remains unknown. The "small seizure" theory is based on the clinical finding that DV is an aura type in TLE. It is hypothesized that in the nonepileptic population, a "small temporal lobe seizure" may elicit DV without producing clinical seizures [13,14]. However, there are several counterarguments to this theory: DV is much more common than TLE [15,16], and only a portion of patients with TLE experience DV auras [17].

The "tape recorder" theory [18] is one of the best known DV theories applying the dual-processing approach. It assumes that

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two different memory-related processes that normally work synchronously become asynchronous or one process becomes activated in the absence of the other. Under normal conditions, memory encoding (“recording head”) and memory retrieval (“playing head”) work with appropriate timing and synchronization. According to this speculation, if the new sensory information is simultaneously encoded and retrieved, the sensory input is accompanied by familiarity, resulting in a feeling of DV. Based on clinical evaluation of the electrically evoked DV experiences of 16 patients with TLE who underwent presurgical depth electrode implantation, Bancaud and colleagues [9] postulated the neuroanatomical bases for the tape recorder theory. Because association cortical and limbic areas encode the holistic memory of an event, and perceptual information is encoded by the temporal neocortex and stored in the hippocampus, the inappropriate activation of these centers can lead to the experience of DV. Similar electrophysiological results [19] expanded Bancaud’s theory with the complementary assumption of parallel neuronal networks underlying encoding and retrieval [20].

Interestingly, a recent case study described “drug-induced” DV, in which a patient experienced recurrent DV after receiving a combination of amantadine and phenylpropanolamine [21]. Because both drugs can facilitate dopaminergic neurotransmission and recent animal studies have proved that hippocampal dopaminergic systems are involved in spatial memory processes [22], this case suggests that increased dopaminergic activity may play a crucial role in the development of DV [21].

In a very recent case report, hypothalamic deep brain stimulation (DBS) was found to evoke detailed autobiographic memories, but not DV [23].

These data inspired us to systematically analyze the pathophysiology of DV by using functional neuroimaging (SPECT) and neuropsychological batteries in a case in which DBS of the left internal globus pallidum (GPi) elicited DV. As far as the authors are aware, this is the first study using direct, reproducible, and integrative neuropsychological and neuroimaging investigations during DV.

2. Methods

2.1. The patient

The 22-year-old female university student was born with a right-sided spastic hemiparesis due to a perinatal injury. Although the strength of the right limbs normalized, the abnormal posture of the right upper limb, observed at the age of 2 months, developed into a drug-refractory and painful secondary hemidystonia. Locomotive and intellectual development was otherwise normal.

Brain MRI revealed a $4 \times 15 \times 18$-mm lesion in the left globus pallidum. At age 22, she underwent microelectrode-guided implantation of Medtronic quadripolar 3389 DBS electrodes into the left posteroventral GPi without perioperative complications. The patient gave written informed consent to the entire surgical procedure, pre- and postsurgical examinations, and publication of this report; the study was also approved by the local ethics committee.

2.2. Stimulation settings

On the first postoperative day, contact 1 was activated in monopolar mode (C + 1–, 120 μs, 130 Hz, 3.2 V) without any adverse reactions. The patient was admitted to the neurological ward in the third postoperative week to learn how to use the patient controller. During testing of the electrodes, we noticed that monopolar stimulation of contact 0 with an amplitude exceeding 2.7 V elicited several DV episodes. Because turning on or turning off the stimulation had an immediate effect on this experience, we assumed it was a stimulation-related adverse reaction. The impedance of contact 0 (C + 0–, 3.2 V, 120 μs, 130 Hz) was 562 ohms.

2.3. Single-photon-emission computed tomography

Current safety regulations do not permit the use of functional MRI during DBS [24]. Therefore, we performed ^{99m}Tc-hexamethylpropyleneamineoxime (^{99m}Tc-HMPAO) single-photon-emission computed tomography (SPECT) to study the pathophysiology of DV because ^{99m}Tc-HMPAO binds more rapidly (2–10 minutes) compared with positron emission tomography (PET) tracers [25].

SPECT was performed 1 month postoperatively. To exclude the long-term effect of DBS, a baseline SPECT scan was obtained during normal stimulation of contact 1 (C + 1–, 3.2 V, 120 μs, 13 0 Hz). To study the pathophysiology underlying DV, 3 days later we stimulated simultaneously both contact 0 and contact 1 (C + 0–1–, 120 μs, 130 Hz, 3.2 V, referred to as *DV-inducing stimulation*). Analogously to epilepsy studies, we defined this setting as *ictal SPECT*.

As the ^{99m}TcHMPAO tracer (750 MBq) was administered immediately after starting the DV-inducing stimulation and the patient experienced numerous DV episodes during the first 5 minutes of stimulation, we assumed that the tracer binding in ictal SPECT represented the combination of acute DV induction and normal pallidal stimulation. Therefore, the subtraction of baseline from ictal SPECT images theoretically indicated those areas activated during the DV episode. Baseline and ictal SPECT images were compared using the subtraction ictal SPECT co-registered to MRI (SISCOM) method, which is also used in the presurgical evaluation of epilepsy [26].

2.4. Neuropsychological tests

The subject underwent neuropsychological examinations three times: 9 months preoperatively and 2 months postoperatively with and without DV-eliciting stimulation. There was a 1-day difference between the postoperative examinations, during which the Rey and Medical College of Georgia Complex Figure, Rey 8/64 Visual Learning, Benton Visual Retention, Boston Naming, and Rey Auditory Verbal Learning tests were administered [27,28] (see Supplementary Data).

3. Results

3.1. The occurrence of déjà vu

Preoperatively the patient had never experienced DV. Immediately after turning on the DV-inducing stimulation, she experienced an unusual and obscure feeling. In addition to discomfort and a slight disturbance, the subject had an intact sense of reality; she was able to observe what was going on around her and to maintain verbal and behavioral responsiveness. We defined this period as the *standby state for DV* (SSDV). The SSDV persisted until stimulation of contact 0 was turned off or the amplitude of stimulation was lowered below 2.7 V.

During SSDV, she experienced impulse DV episodes lasting 4–5 seconds. On these occasions she felt that the situation seemed familiar. No visual or auditory illusions or hallucinations accompanied the DV. In addition, the patient felt neither the ability to predict the future nor unreality about current circumstances.

DV occurred more frequently immediately after turning on the stimulation (approximately two to five DV episodes during the first 5–10 minutes) and became rarer as time went by (approximately another three to five DV episodes in the first hour and two or three in the second hour). Interestingly, she experienced DV only if her