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Epileptic Disorders

Déjà-vu evoked by electrical stimulation of the insula

Stimulation-induced insular *déjà-vu*

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VIDEOS ONLINE

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ABSTRACT

Objective. *Déjà-vu* is a mental phenomenon commonly experienced during temporal lobe seizures and can be evoked by electrical stimulation of the temporal lobe. We analyzed reproducible *déjà-vu* experiences evoked by stimulating the insula in two patients with pharmacoresistant temporal lobe epilepsy.

Methods. We reviewed video-electroencephalography (EEG) recordings from extraoperative electrical cortical stimulation sessions. In addition, we performed the directed transfer function (DTF) effective connectivity measure of monopolar signals in Patient 1. To highlight elective changes due to each stimulation, we subtracted pre-stimulation DTF matrices from early post-stimulation matrices. This analysis was performed for both non-inducing-*déjà-vu* stimulation (control matrix) and *déjà-vu*-inducing stimulation (active matrix). Finally, the control matrix was subtracted from the active matrix.

Results. Comparison of effective connectivity during control stimulation versus *déjà-vu*-inducing stimulation revealed a reversal of connectivity levels in three main regions: the contralateral inferior insula (the ipsilateral insula could not be analyzed), bilateral mesiotemporal regions and the ipsilateral superior frontal gyrus. The drivers of evoked *déjà-vu* were the mesiotemporal regions (mainly ipsilateral) and the ipsilateral superior frontal gyrus.

Significance. Although our findings are possibly anecdotal, the insula may (in rare instances) remotely generate unexpected *déjà-vu*. If confirmed by further studies, this might change the assessment strategy for possible causes of anterior temporal lobectomy failure.

Key words: insula, epilepsy, *déjà-vu*, electrical stimulation, connectivity

Déjà-vu is a " transitory mental state whereby an objectively novel experience feels subjectively familiar" [1]. Although 60-80% of healthy individuals can occasionally experience such a sensation [2], it is also a well-known and common ictal manifestation of temporal lobe epilepsy [3-6]. Electrical stimulation of the hippocampus, amygdala and temporal neocortex with implanted electrodes has shown to effectively reproduce *déjà-vu* in patients [7-10]. These studies have pointed out the importance of mesiotemporal structures and the rhinal cortex in *déjà-vu* evoked by stimulation [9]. Accordingly, functional coupling analysis of intracranial electroencephalographic signals

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recorded in patients during electrical stimulation has revealed that *déjà-vu* is associated with an increase in neural coupling between rhinal cortices and the hippocampus or amygdala [11]. This suggests an interaction between different medial temporal lobe structures in the production of *déjà-vu*. We report here the elicitation of *déjà-vu* with stimulation of the insula in two patients suffering from drug-resistant temporal lobe epilepsy.

Methods

This study was approved by our research ethics committee. Both patients provided consent for publication in a scientific journal. Details of patients' history were obtained through careful chart review. Video-EEG recordings from extraoperative electrical cortical stimulation sessions from both patients were reviewed. These electrical stimulations were performed for clinical purposes (to elicit habitual auras and map eloquent areas) using the following parameters: 50-Hz frequency; 0.5-msec pulse duration; 5-sec stimulus duration; bipolar fashion. The patients were blinded to the onset and offset of stimulations. Exact locations of stimulated electrode contacts were verified using post-implantation MRI.

To examine the synchrony between different brain areas during symptoms evoked by electrical stimulation, we used the directed transfer function (DTF) effective connectivity measure of monopolar signals. The DTF is a multichannel extension of Granger causality based on a multivariate autoregressive model [12, 13]. The DTF was applied to 5-sec segments prior to and following the electrical stimulation. Due to post-stimulation signal recuperation delay, stimulation contacts were excluded from the analysis due to prolonged local stimulation artifacts. Surrogate data testing (n=20 surrogates) was performed to validate the significance of causal interactions (α = 0.05). In order to highlight connectivity changes triggered by the stimulation, pre- and post-stimulation connectivity matrices were subtracted for a stimulation inducing a *déjà-vu* as well as a stimulation which did not induce a *déjà-vu*. Finally, to highlight changes specific to the *déjà-vu* phenomenon, the two aforementioned connectivity matrices were subtracted. Because of the abundance of post-stimulation artifacts for Patient 2, connectivity analysis could not be performed.

Results

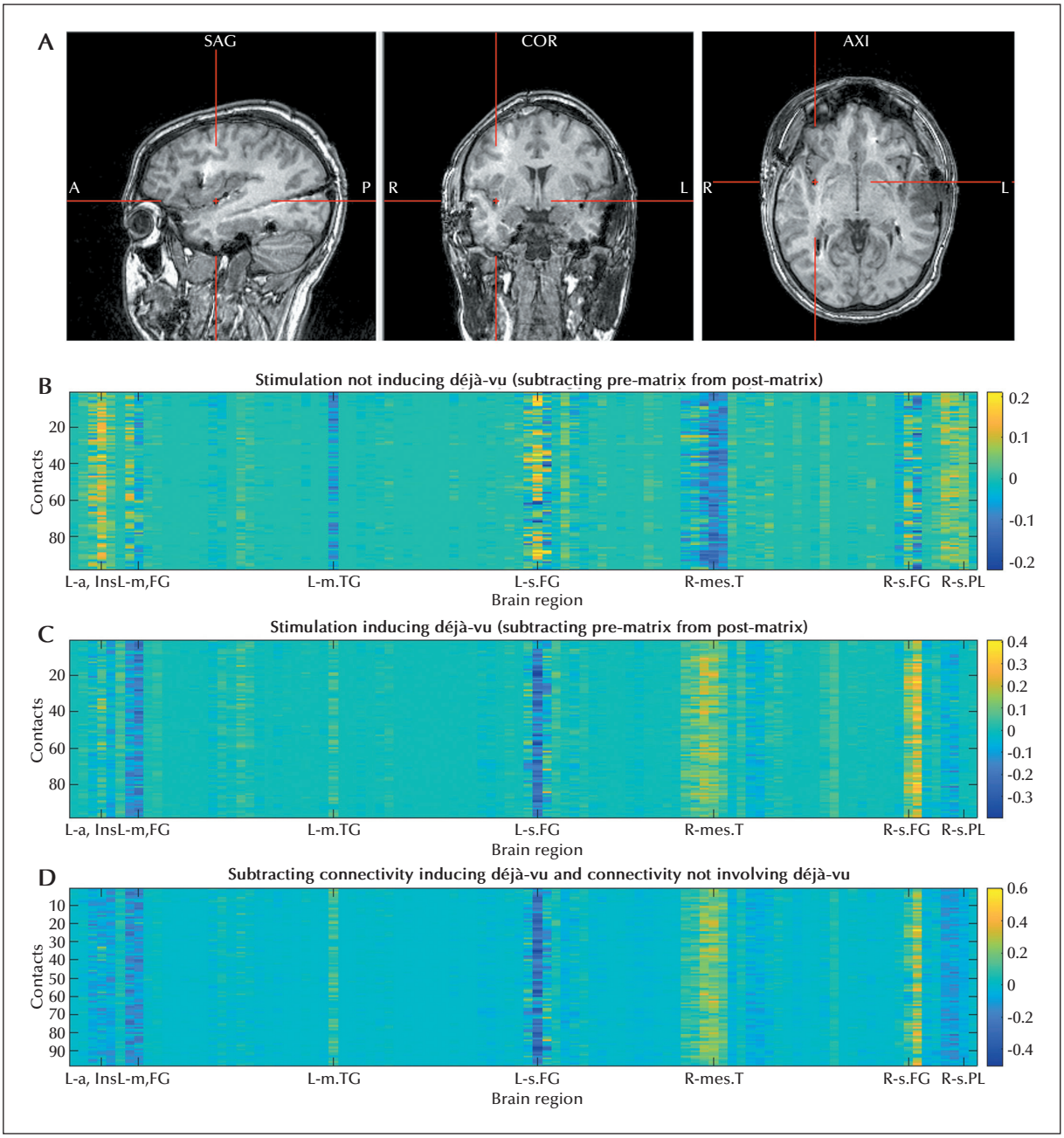
Patient histories

Patient 1 was a 24-year-old, right-handed man who suffered from bilateral temporal epilepsy since age 18 years. Seizures were characterized by an aura of *déjà-vu*, metallic taste and foul odor, followed by impaired awareness, rarely evolving into bilateral tonic-clonic seizures. A presurgical investigation included unremarkable MRI, predominantly left-sided temporal seizures on scalp EEG, left temporo-insular hyperperfusion on ictal single-photon emission computed tomography (iSPECT), and normal cerebral metabolism on 18-FDG positron emission tomography (PET). He subsequently underwent an invasive EEG study. During intracranial EEG monitoring, spontaneous seizures were recorded equally from either the right or left hippocampus with early subsequent spread to the ipsilateral insula. Hence, vagus nerve stimulation was preferred to resective surgery.

Patient 2 was a 32-year-old, ambidextrous woman with seizures since her early 20s, characterized by *déjà-vu*, an epigastric sensation and anxiety followed by impaired awareness with rare evolution to bilateral tonic-clonic seizures. Scalp EEG monitoring revealed interictal and ictal epileptiform discharges over left mid- and anterior temporal leads. Brain MRI showed left hippocampal sclerosis. She underwent a left anterior temporal lobectomy in March, 2016 which rendered her seizure-free for a year. Upon recurrence, the patient mentioned experiencing daily episodes of *déjà-vu* associated with an epigastric sensation and anxiety without impaired awareness; in addition, she experienced three focal to bilateral tonic-clonic seizures during sleep. In a subsequent intracranial EEG study (June, 2018), several stereotypical auras (*déjà-vu* and anxiety) were recorded, some originating from the left inferior insula and others from the posterior-medial margin of the temporal resection (one evolving into a bilateral tonic-clonic seizure). These areas were subsequently removed in a second surgery. Over the last three years, she experienced episodes of *déjà-vu* or foul taste without impairment of awareness. She also presented a probable tonic-clonic seizure during a nap, eight months after the surgery. There has been no attempt to withdraw her phenytoin since the last surgery.

Electrical stimulation findings

In Patient 1, stimulation of the adjacent electrode contact pair, U4(1)-U4(2) (located in the rostral posterior long insular gyrus) (*figure 1A and supplementary table 1*), at 3 mA (and five days later at 2.5 mA) evoked a sensation of *déjà-vu* (" as if he had already been in this situation and performed the same task") without any afterdischarges (*supplementary video 1*). A typical seizure was triggered by stimulating the right and left hippocampus at 1.5 mA and 2 mA, respectively.



■ **Figure 1.** *Déjà-vu* induction area and connectivity study findings for Patient 1. (A) Location of the electrode U4(1) in the ventral portion of the right posterior long insular gyrus. Stimulation of this contact reproduced *déjà-vu* in Patient 1. (B) Subtraction of 5-sec pre-stimulation and 5-sec post-stimulation direct transfer function (DTF) matrices for a stimulation that did not induce *déjà-vu*. (C) Subtraction of 5-sec pre-stimulation and 5-sec post-stimulation direct transfer function (DTF) matrices for a stimulation that induced *déjà-vu*. (D) Subtraction of matrix B from matrix C. The occurrence of *déjà-vu* following insular stimulation is associated with an obvious reversal of DTF connectivity driving, especially in insular, mesiotemporal and frontal (superior frontal gyri) regions. This redistribution of connectivity is led by the mesiotemporal regions bilaterally (but more ipsilateral than contralateral) and the ipsilateral superior frontal gyrus.

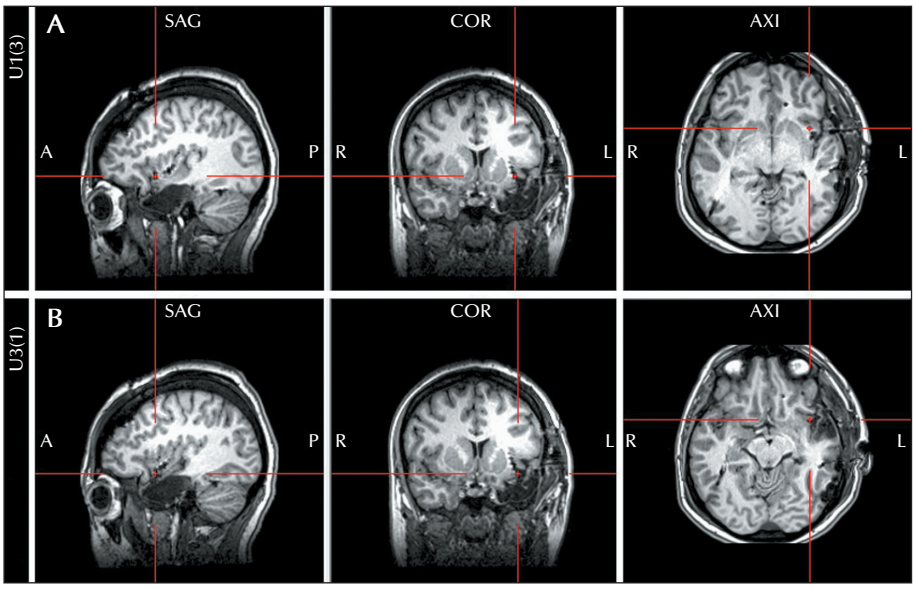
In Patient 2, stimulation of electrode pairs, U1(2)-U1(3) at 3 mA, U1(4)-U1(5) at 2.5 mA, and U3(1)-U3(2) at 3 mA, all evoked *déjà-vu* associated with anxiety and an epigastric sensation. In one instance, she felt as if " the story she was reading was occurring at the same time in her head" (*supplementary video 2*). Wide insular afterdischarges (6-sec) were only observed for the 2.5-mA-stimulation on U1(4)-U1(5). Contact pairs, U1(2)-U1(3) and U1(4)-U1(5), were located, respectively, in the inferior part of the left anterior short insular gyrus and at mid-level of the left middle short insular gyrus (*supplementary table 1*). The contact pair, U3(1)-U3(2), was located in the inferior part of the left posterior short insular gyrus (*figure 2*).

Functional connectivity findings

In Patient 1, visual analysis of subtracted matrices (pre- from post-stimulation DTF) of a non-inducing *déjà-vu* stimulation (2 mA) showed an increase in effective connectivity mainly driven by left anterior insular areas and a bitemporal decrease in effective connectivity (*figure 1B-D*). In order to explore the specific changes related to the occurrence of a *déjà-vu*, we subtracted the following connectivity matrices: a 2-mA stimulation matrix without *déjà-vu* from a 3-mA stimulation matrix which induced a *déjà-vu*. We found an increase in effective connectivity driven by the right superior frontal gyrus and both mesial temporal areas (mainly right areas) (*figure 1D*). We also noticed a considerable decrease in effective connectivity over the left anterior insular and left superior frontal gyrus, as well as right superior parietal lobule. In Patient 2, DTF analysis could not be performed due to technical problems with the recording.

Discussion

In this report, we describe *déjà-vu* evoked by insular electrical stimulation. The sensation was triggered by stimulating the ventral portion of the posterior long insular gyrus for one patient and the ventral portion of anterior insular gyri for the other. With regards to currently available reports of insular stimulation, *déjà-vu* is not an expected response [14-17]. Indeed, this feeling is generally induced by the stimulation of temporal lobe structures, mainly the mesial part [5]. Conversely, stimulation of the insula has rather evoked somatosensory, viscerosensory, olfactory, gustatory, auditory and vestibular responses [16].
In a recent review article, Curot *et al.* (2017) performed a systematic review of reminiscence feelings induced by electrical stimulation (91 patients/273



■ **Figure 2.** *Déjà-vu* induction area for Patient 2: location of the electrode U1(3) (A) and U3(1) (B). Stimulation around these channels (*i.e.* contacts U1 [2, 3, 4, 5] and U3 [1, 2]) evoked a *déjà-vu* sensation in Patient 2. Contact pairs, U1(2)-U1(3) and U1(4)-U1(5), are located, respectively, in the inferior part of the left anterior short insular gyrus and at mid-level of the left middle short insular gyrus. Contact pair, U3(1)-U3(2), is located in the inferior part of the left posterior short insular gyrus.

stimulations) [1]. Reminiscence was defined by the authors as an involuntary recall of a memory distinguished as *déjà-vu* by its longer duration and the fact that it has content (such as visual mental images and/or other sensory characteristics). As expected, reminiscences were mainly evoked by temporal lobe stimulation (94.1%). However, it was briefly mentioned that reminiscences were induced by stimulating the insula in three cases. Unfortunately, the exact localization of the electrodes within the insula was not provided. While *déjà-vu* differs from reminiscence, memory appears to be a common critical support for both; hence, the fact that others have also observed memory experiential phenomena by stimulating the insula is reassuring and in support of the validity of our observations.

Our connectivity analyses for Patient 1 support the notion that a distributed neural network underlies these memory experiential phenomena, most notably structures in the temporal lobe (amygdala, hippocampus, rhinal cortex and lateral temporal neocortex) but also the insula. Supporting this network-based hypothesis, Labate *et al*. (2011), demonstrated the critical role of a mesiotemporal-orbitofrontal-insular network in the genesis of benign mesiotemporal lobe epilepsy [18]. This usually late-onset and familial epilepsy is mainly characterized by the recurrence of focal aware *déjà-vu* seizures [18]. More interestingly, Bradzil *et al*. (2012), using brain volumetry findings of 113 healthy individuals, postulated that *déjà-vu* generation in healthy individuals is due to alterations in this above-described network [2]. However, there are data suggesting a determinant role of perirhinal/entorhinal cortex in the generation of the *déjà-vu* phenomenon, even in the absence of hippocampal impairment [4]. Notably, the study of Guej *et al*. (2010) revealed significant hypometabolism of the insula when comparing 18FDG-PET brain scans of temporal epilepsy patients with and without *déjà-vu* [4]. These observations suggest that *déjà-vu*, although probably centered on mesiotemporal regions, could be elicited by insular stimulation, depending on the bidirectional connectivity of certain subinsular regions with temporal structures. Finally, it must be noted that Patient 2 experienced spontaneous and evoked *déjà-vu* of insular onset despite prior removal of anterior temporal lobe structures. The fact that in both patients, *déjà-vu* was evoked by stimulating the ventral portion of the insula is not necessarily surprising in light of recent tractography findings from our group, which showed that this occurred mainly the inferior portion of the insula that was connected with the temporal lobe, including the amygdala and hippocampus [19].

Why *déjà-vu* has not been evoked more frequently in prior stimulation studies remains difficult to explain. Our observations may be anecdotal, due to exceptional epileptogenic network disorders. As such, one possible explanation for the occurrence of insular *déjà-vu* in our patients is that chronic epilepsy has somehow altered normal cortical and subcortical pathways with aberrant functional reorganization of the insula. This hypothesis is not totally satisfactory as insular stimulation in prior studies was also performed on patients with chronic drug-resistant epilepsy (many of whom had temporal lobe seizures spreading to the insula, similar to our patient) [14, 16]. Because both high and low-frequency stimulations were used in prior studies, it is also unlikely that stimulation parameters explain why others have not reported insular-evoked *déjà-vu*. We speculate that both abnormal efferences from the inferior insula (targeting temporal structures) and aberrant mesiotemporal integration of the afferent influx from the insula may be involved. Moreover, it seems that such a phenomenon recruits mesiotemporal regions bilaterally, as we observed during the connectivity analysis for Patient 1. This might also explain why Patient 2 showed *déjà-vu* episodes despite mesiotemporal resection. This hypothesis does not exclude that a small part of the epileptogenic zone might have been missed by intracranial sampling.

The semiological value of our two-case report study is limited by the small number of observations and its retrospective design. Evoked symptoms during electrical stimulation for clinical purposes are often summarized by a few words, not necessarily scrutinized in detail at the bedside. Moreover, it might have been interesting to also analyze the connectivity of the brain response to low-frequency (1-Hz) stimulation in Patient 1. In addition, DTF analysis could not be performed for Patient 2. We hope that our observations will motivate others to report their experience. If corroborated by others, this notion that the insula may (in rare instances) remotely generate unexpected *déjà-vu* has some interesting clinical implication. Indeed, this could mean that patients who continue to complain of *déjà-vu* auras after an anterior temporal lobectomy could have persistent seizures arising from the ventral portion of the insula and not necessarily from contralateral mesial temporal lobe structures. ■

Key points

- *Déjà-vu* is commonly evoked by temporal stimulation.
- *Déjà-vu* evoked by insular stimulation seems to be remotely triggered via complex networks.
- Contralateral mesiotemporal structures may be activated by insular stimulation.
- The ipsilateral insula should be sampled after unexplained temporal surgery failure.

Supplementary material.
Supplementary table accompanying the manuscript is available at www.epilepticdisorders.com.

Disclosures.
None of the authors have any conflict of interest to declare.

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Legend for video sequences

Video sequence 1

Electrical stimulation-induced *déjà-vu* in Patient 1.

Video sequence 2

Electrical stimulation-induced *déjà-vu* in Patient 2.

Key words for video research on www.epilepticdisorders.com
Phenomenology: not applicable
Localization: insula
Syndrome: not applicable
Aetiology: not applicable