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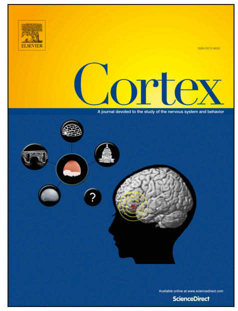

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Vivid memories triggered by odors were particularly well described by the French writer Marcel Proust in his novel *Swann's Way* (*Du Côté de Chez Swann*). The sensorial input provoked by the madeleine cake's odor, flavor and texture immediately transported him into a vivid and rich past childhood episode. Proust constructed a detailed literary description of psychological characteristics of the reminiscence: its unexpected occurrence, the intense positive feeling resembling ecstatic sensation, and the vividness of the memory. Neuroscientific investigation has clarified the characteristics of odor-evoked memories: they evoke more emotional and evocative recollections than memories triggered by any other cue and are exceptionally rich in contextual information (Larsson & Willander, 2009) (Arshamian et al., 2013; Saive, Royet, & Plailly, 2014). The intensity of olfactory recollection and its visceral characteristics have been related to the unique and specific connections of the olfactory system with the neural structures involved in emotion and associative learning (Arshamian et al., 2013; Herz, Eliassen, Beland, & Souza, 2004). The olfactory cortex includes the amygdala, which is also involved in emotional memory and is connected to the hippocampus and in contrast with other sensory modalities, projections from the sensory input onto amygdala do not pass via the thalamus (Cahill, Babinsky, Markowitsch, & McGaugh, 1995; Phelps & Anderson, 1997). A main characteristic of the Proust phenomenon is its unpredictability, rendering it particularly difficult to reproduce in an experimental setting (Jellinek, 2004).

The present case is the first to analyze the induction of Proust phenomenon by focal electrical stimulation of the amygdala, a rare observation in the context of epilepsy presurgical exploration. Our patient was a 27-year-old, right-handed woman who had suffered from drug-resistant left frontal lobe seizures since the age of 5 years. Cerebral magnetic resonance imaging (MRI) disclosed a small lesion in left fronto-polar cortex. Recorded spontaneous seizures showed complex motor semiology without subjective symptoms, notably no olfactory hallucination or déjà vu phenomena. Intracerebral electroencephalographic (EEG) monitoring was undertaken to precisely localize the epileptogenic zone, with 9 intracerebral electrodes (stereoelectroencephalographic (SEEG) method (Bartolomei et al., 2004) implanted within the temporal lobe and the frontal cortex on the left side. Ten seizures were recorded involving the left prefrontal cortex and a left frontal cortectomy was later performed leading to seizure freedom. Pathological examination revealed a type 2 focal cortical dysplasia. Electrical stimulation was performed (50 Hz, 0.5-2 mA, in a bipolar fashion to each contact in the gray matter during a 3 second period) to map functional cortices and trigger habitual seizures (Bartolomei et al., 2004). Two stimulations of the amygdala triggered olfactory hallucination with memory reminiscence. Contacts A'3-4 located in the basolateral region of the amygdala (Fig 1) at 1.5 mA and 2 .5 mA induced a sudden odor of burnt wood, which was immediately followed by the memory of a scene of a campfire on a riverbank during a holiday when she was 15 years old. This scene was associated with a strong feeling of happiness. No electrical after-discharge was noted after stimulations. No other stimulation (including left temporal pole, anterior insula and orbitofrontal cortex) induced such phenomena. Connectivity analysis was performed by measuring interdependencies between SEEG signals before and after stimulations. We performed a nonlinear regression analysis based on the h^2 coefficient (Wendling, Bartolomei, Bellanger, & Chauvel, 2001)(see supplemental material). Figure 1A presents the differences in mean degree (number of significant links) between pre- and post-stim periods. Figure 1B shows connectivity graphs superposed on a 3D rendering of the cortex, with each bipolar channel representing a node of the graph. Link strengths are the h2 values between pairs of nodes, for two positive stimulations (at 1.5 mA and 2.5mA) and one negative stimulation (1 mA) of the amygdala. Positive stimulations induced a significant increase of connectivity values between the amygdala, the temporal pole, and the insular cortex at 1.5 mA. A more extended network was involved at 2.5 mA, including the orbitofrontal and prefrontal cortices. At 1 mA (negative stimulation), only one link between amygdala and temporopolar cortex was elicited without significant change in node degree.

Our observations strongly support the role of the amygdala in inducing the “Proust” phenomenon (Bray, 2013; Jellinek, 2004; Toffolo, Smeets, & van den Hout, 2012), in agreement with the physiological role of the amygdala in processing odor. Autobiographic memories evoked by amygdala stimulation in our case belonged to the adolescent period. A review of mnestic phenomena induced by intracerebral stimulation in patients with temporal lobe epilepsy found that amygdalar stimulation induced déjà-vu more often than hippocampal stimulation (Vignal, Maillard, McGonigal, & Chauvel, 2007) although no olfactory illusion was reported in this series. A large body of data obtained in human beings and animals show that the amygdala participates in various aspects of odor processing, especially in relation to emotion and memory. In particular, during the experience of recollecting an odor-evoked autobiographical memory, the amygdala was more activated than with similar odors that did not evoke a memory (Herz et al., 2004). In patients with epilepsy, depth electrode recordings of the amygdala have revealed that odorant stimulation may induce evoked potentials (Hudry, Ryvlin, Royet, & Mauguiere, 2001). Our connectivity study shows that the amygdala stimulation leads to the activation of a network including ipsilateral orbitofrontal cortex and insular cortex, representing “secondary olfactory cortices”. In particular, the left anterior insula is likely involved in the evaluation of odor properties (Plailly, Radnovich, Sabri, Royet, & Kareken, 2007) (Royet, Plailly, Delon-Martin, Kareken, & Segebarth, 2003). fMRI studies have found that the amygdala could be activated bilaterally by both positive and negative stimuli (Sergerie, Chochol, & Armony, 2008). A study using direct intracerebral electrical stimulation reported that positive and negative emotional feelings could be triggered by left amygdalar stimulation while only negative feelings were triggered by right amygdalar stimulation(Lanteaume et al., 2007). In addition, neuroimaging studies have revealed that anterior insular cortex can be activated during intensely positive feelings, such as joy or maternal and romantic love as well as seeing or making a smile (Craig, 2009). Thus together with the activation of olfactory regions, the activation of the insula may be responsible for the pleasant feeling associated with the Proust phenomenon.

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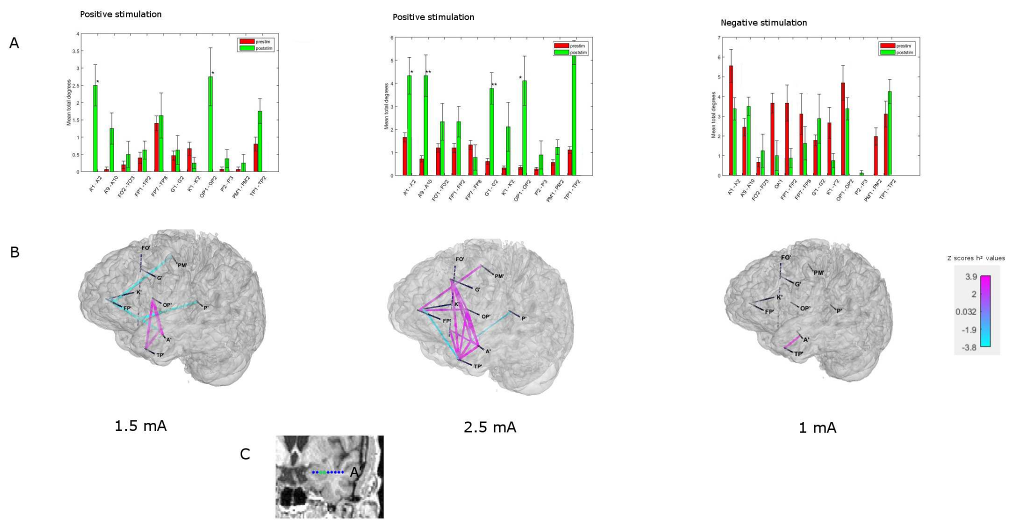
Figure legend:

Connectivity changes associated with Proust phenomenon induced by amygdala stimulations (contacts A'3-4 stimulated at 1.5 mA and 2.5 mA) and in comparison with negative stimulation (1 mA).

A. Node degree connectivity. Connectivity graphs are summarized by a node degrees which consist in thresholding the graph (set empirically to 0.25) and then counting the number of significant links between a given node and the rest of the graph. Comparison were done using a Wilcoxon non-parametric paired test and a Bonferroni correction by comparing a pre-stimulation period and the stimulation period. * shows significant results. Selected regions are indicated by bipolar contacts: A'1-2: Amygdala; A'9-10: Lateral temporal cortex FO'2-3: Orbito-frontal cortex; Fp'1-2: Prefrontal cortex (internal); Fp'7-8: Lateral prefrontal cortex; G'1-2: Cingulate gyrus (area 24); K'1-2: Cingulate gyrus (Area 32); OP'1-2: Anterior insular cortex; P'2-3: Parietal cortex; PM'1-2: Internal premotor cortex; TP'1-2: Temporal pole cortex

B. Changes of connectivity are illustrated on a 3D mesh of the MRI with the position of electrodes. Each graph indicates the significant changes in connectivity between selected contacts of the electrodes (the color scale express the changes relative to the pre-stimulation period in term of Z-scores, here positive values). Color scale indicate the Z-scores of the h^2 values during stimulation period relative to pre-stimulation period

C. Reconstruction of electrode A' within the left amygdala. In green are indicated the two contacts for which bipolar stimulation induced Proust phenomenon


A
Positive stimulation
Positive stimulation
Negative stimulation
B
1.5 mA
2.5 mA
1 mA
C