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The “Proust Phenomenon”: odor-evoked autobiographical memories triggered by direct amygdala stimulation in human

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1 **The “Proust Phenomenon”: odor-evoked autobiographical memories triggered by direct**
2 **amygdala stimulation in human**

3

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28 Vivid memories triggered by odors were particularly well described by the French writer Marcel
29 Proust in his novel *Swann's Way (Du Côté de Chez Swann)*. The sensorial input provoked by the
30 madeleine cake's odor, flavor and texture immediately transported him into a vivid and rich past
31 childhood episode. Proust constructed a detailed literary description of psychological characteristics of
32 the reminiscence: its unexpected occurrence, the intense positive feeling resembling ecstatic sensation,
33 and the vividness of the memory. Neuroscientific investigation has clarified the characteristics of
34 odor-evoked memories: they evoke more emotional and evocative recollections than memories
35 triggered by any other cue and are exceptionally rich in contextual information (Larsson & Willander,
36 2009) (Arshamian et al., 2013; Saive, Royet, & Plailly, 2014). The intensity of olfactory recollection
37 and its visceral characteristics have been related to the unique and specific connections of the olfactory
38 system with the neural structures involved in emotion and associative learning (Arshamian et al.,
39 2013; Herz, Eliassen, Beland, & Souza, 2004). The olfactory cortex includes the amygdala, which is
40 also involved in emotional memory and is connected to the hippocampus and in contrast with other
41 sensory modalities, projections from the sensory input onto amygdala do not pass via the thalamus
42 (Cahill, Babinsky, Markowitsch, & McGaugh, 1995; Phelps & Anderson, 1997). A main
43 characteristic of the Proust phenomenon is its unpredictability, rendering it particularly difficult to
44 reproduce in an experimental setting (Jellinek, 2004).

45 The present case is the first to analyze the induction of Proust phenomenon by focal electrical
46 stimulation of the amygdala, a rare observation in the context of epilepsy presurgical exploration. Our
47 patient was a 27-year-old, right-handed woman who had suffered from drug-resistant left frontal lobe
48 seizures since the age of 5 years. Cerebral magnetic resonance imaging (MRI) disclosed a small lesion
49 in left fronto-polar cortex. Recorded spontaneous seizures showed complex motor semiology without
50 subjective symptoms, notably no olfactory hallucination or déjà vu phenomena. Intracerebral
51 electroencephalographic (EEG) monitoring was undertaken to precisely localize the epileptogenic
52 zone, with 9 intracerebral electrodes (stereoencephalographic (SEEG) method (Bartolomei et
53 al., 2004) implanted within the temporal lobe and the frontal cortex on the left side. Ten seizures were
54 recorded involving the left prefrontal cortex and a left frontal cortectomy was later performed leading
55 to seizure freedom. Pathological examination revealed a type 2 focal cortical dysplasia. Electrical
56 stimulation was performed (50 Hz, 0.5-2 mA, in a bipolar fashion to each contact in the gray matter
57 during a 3 second period) to map functional cortices and trigger habitual seizures (Bartolomei et al.,
58 2004). Two stimulations of the amygdala triggered olfactory hallucination with memory reminiscence.
59 Contacts A'3-4 located in the basolateral region of the amygdala (Fig 1) at 1.5 mA and 2 .5 mA
60 induced a sudden odor of burnt wood, which was immediately followed by the memory of a scene of a
61 campfire on a riverbank during a holiday when she was 15 years old. This scene was associated with a
62 strong feeling of happiness. No electrical after-discharge was noted after stimulations. No other
63 stimulation (including left temporal pole, anterior insula and orbitofrontal cortex) induced such

64 phenomena. Connectivity analysis was performed by measuring interdependencies between SEEG
65 signals before and after stimulations. We performed a nonlinear regression analysis based on the h^2
66 coefficient (Wendling, Bartolomei, Bellanger, & Chauvel, 2001)(see supplemental material). Figure
67 1A presents the differences in mean degree (number of significant links) between pre- and post-stim
68 periods. Figure 1B shows connectivity graphs superposed on a 3D rendering of the cortex, with each
69 bipolar channel representing a node of the graph. Link strengths are the h^2 values between pairs of
70 nodes, for two positive stimulations (at 1.5 mA and 2.5mA) and one negative stimulation (1 mA) of
71 the amygdala. Positive stimulations induced a significant increase of connectivity values between the
72 amygdala, the temporal pole, and the insular cortex at 1.5 mA. A more extended network was
73 involved at 2.5 mA, including the orbitofrontal and prefrontal cortices. At 1 mA (negative
74 stimulation), only one link between amygdala and temporopolar cortex was elicited without significant
75 change in node degree.

76 Our observations strongly support the role of the amygdala in inducing the “Proust” phenomenon
77 (Bray, 2013; Jellinek, 2004; Toffolo, Smeets, & van den Hout, 2012), in agreement with the
78 physiological role of the amygdala in processing odor. Autobiographic memories evoked by amygdala
79 stimulation in our case belonged to the adolescent period. A review of mnemonic phenomena induced by
80 intracerebral stimulation in patients with temporal lobe epilepsy found that amygdalar stimulation
81 induced déjà-vu more often than hippocampal stimulation (Vignal, Maillard, McGonigal, & Chauvel,
82 2007) although no olfactory illusion was reported in this series. A large body of data obtained in
83 human beings and animals show that the amygdala participates in various aspects of odor processing,
84 especially in relation to emotion and memory. In particular, during the experience of recollecting an
85 odor-evoked autobiographical memory, the amygdala was more activated than with similar odors that
86 did not evoke a memory (Herz et al., 2004). In patients with epilepsy, depth electrode recordings of
87 the amygdala have revealed that odorant stimulation may induce evoked potentials (Hudry, Ryvlin,
88 Royet, & Mauguire, 2001). Our connectivity study shows that the amygdala stimulation leads to the
89 activation of a network including ipsilateral orbitofrontal cortex and insular cortex, representing
90 “secondary olfactory cortices”. In particular, the left anterior insula is likely involved in the evaluation
91 of odor properties (Plailly, Radnovich, Sabri, Royet, & Kareken, 2007) (Royet, Plailly, Delon-Martin,
92 Kareken, & Segebarth, 2003). fMRI studies have found that the amygdala could be activated
93 bilaterally by both positive and negative stimuli (Sergerie, Chochol, & Armony, 2008). A study using
94 direct intracerebral electrical stimulation reported that positive and negative emotional feelings could
95 be triggered by left amygdalar stimulation while only negative feelings were triggered by right
96 amygdalar stimulation(Lanteaume et al., 2007). In addition, neuroimaging studies have revealed that
97 anterior insular cortex can be activated during intensely positive feelings, such as joy or maternal and
98 romantic love as well as seeing or making a smile (Craig, 2009). Thus together with the activation of

99 olfactory regions, the activation of the insula may be responsible for the pleasant feeling associated
100 with the Proust phenomenon.

101

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159 **Figure legend:**

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

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

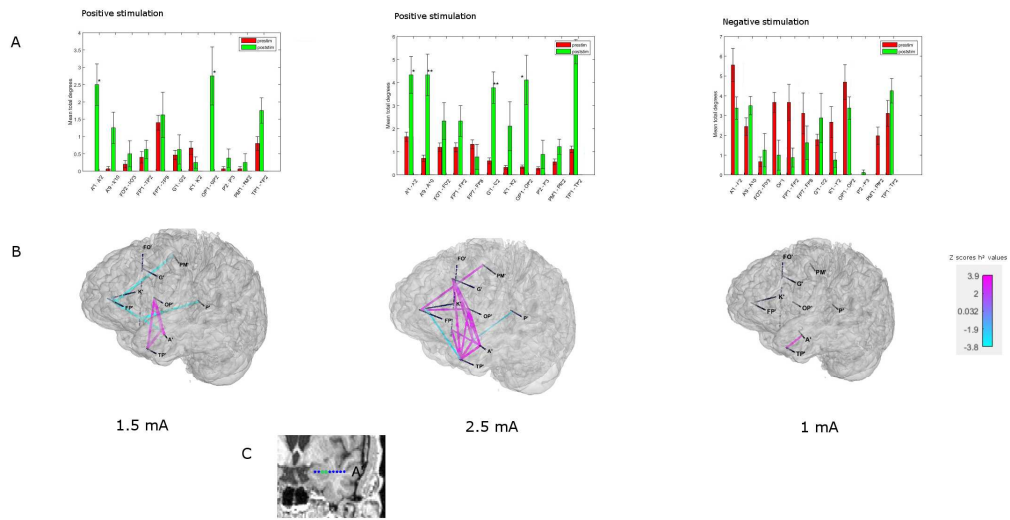
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173 B. Changes of connectivity are illustrated on a 3D mesh of the MRI with the position of
 174 electrodes. Each graph indicates the significant changes in connectivity between selected
 175 contacts of the electrodes (the color scale express the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

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

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