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# How can a focal seizure lead to a dacrytic behavior? A case analyzed with functional connectivity in SEEG

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15 **Abstract**

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17 We present a case of a patient with focal non-motor emotional seizures with dacrystic  
18 expression in the context of drug-resistant Magnetic Resonance Imaging (MRI) negative  
19 epilepsy. The pre-surgical evaluation suggested a hypothesis of a right fronto-temporal  
20 epileptogenic zone. Stereoelectroencephalography (SEEG) recorded dacrystic seizures arising  
21 from the right anterior operculo-insular (*pars orbitalis*) area with secondary propagation to  
22 temporal and parietal cortices during the dacrystic behaviour. We analysed functional  
23 connectivity during the ictal dacrystic behaviour and found an increase of the functional  
24 connectivity within a large right fronto-temporo-insular network, broadly similar to the  
25 "emotional excitatory" network. It suggests that focal seizure, potentially, from various origins  
26 but leading to disorganization of these physiological networks may generate dacrystic  
27 behaviour.

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39 **Introduction**

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41 Among focal seizures with non-motor onset, some are mainly characterized by subjective  
42 and/or objective emotional content. These seizures are grouped as “emotional” in the  
43 International League Against Epilepsy (ILAE) classification of seizures types, and can include  
44 positive or negative emotion <sup>1</sup>. Amongst them, dacrystic seizures are characterized by  
45 paroxysmal manifestations of crying that include lacrimation, grimacing, sobbing, sad facial  
46 expression, yelling, with or without subjective feeling of sadness <sup>2</sup>. Dacrystic seizures may be  
47 observed in epilepsies associated with hypothalamic hamartoma but also in other types of  
48 focal epilepsies <sup>2,3</sup>. The underlying pathophysiology basis of this ictal behaviour is not well  
49 established. It has been hypothesized that a presumed ‘facio-respiratory control centre’ for  
50 emotional expression located in the brainstem is released from voluntary control in reported  
51 cases of cortical lesioning, or by inactivation by seizures <sup>4</sup>. It is known that several regions  
52 (prefrontal cortex, insula, cingulum, amygdala, striatum, hypothalamus, premotor/motor  
53 areas) are functionally connected to this centre and postulated that if a seizure alters the  
54 normal functioning of this network it could lead to dacrystic behaviour by a diaschisis  
55 phenomenon. However, no previous study has precisely investigated the modification of  
56 functional connectivity within this network during dacrystic seizures.

57 We took advantage of stereoelectroencephalography (SEEG) recordings to analyse functional  
58 connectivity changes during ictal dacrystic behaviour.

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## 63 **Case Description**

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65 We present the case of a 57-year-old right-handed man, with drug-resistant focal epilepsy and  
66 negative Magnetic Resonance Imaging (MRI). His seizures are characterized by an aura of the  
67 sensation of electrical discharges in the head, followed by crying behaviour with sad facial  
68 mimicry but without conscious emotion. Scalp video-electroencephalography (EEG) showed  
69 abundant interictal epileptiform discharges over the right fronto-temporal electrodes and ictal  
70 fast activity over the same electrodes. Magnetoencephalography (MEG) source imaging of  
71 abundant interictal spikes found generators within the right inferior frontal gyrus, anterior  
72 ventral insula and orbitofrontal cortex, and slow spikes coming from the right temporal lobe  
73 (superior temporal and temporal pole areas). Cerebral 18F-fluorodeoxyglucose – positron  
74 emission tomography (FDG-PET) showed hypometabolism affecting the right orbitofrontal,  
75 mesial prefrontal and anterior insular regions. At the end of this non-invasive assessment, we  
76 hypothesized a right fronto-temporo-insular epileptogenic network. Due to the absence of an  
77 epileptogenic lesion on MRI and suspicion of extra-temporal epilepsy, we performed a SEEG  
78 to accurately define the epileptogenic zone (EZ) <sup>5</sup>.

79

## 80 **Methods**

81

### 82 1. SEEG recording

83

84 The number and the location of the SEEG electrodes were defined based on our clinical  
85 hypothesis. SEEG exploration was performed using intracerebral multiple-contact electrodes  
86 (Alcis), consisting of 10–15 contacts with length 2mm, diameter 0.8 mm, spaced by 1.5 mm<sup>6</sup>.

87 Signals were recorded on a 256-channel Natus system, sampled at 512 Hz and recorded on a  
88 hard disk (16 bits/sample) using no digital filter. Two hardware filters were present in the  
89 acquisition procedure: a high-pass filter (cut-off frequency = 0.16 Hz at 3 dB), and an anti-  
90 aliasing low-pass filter (cut-off frequency = 170Hz). For the anatomical location of SEEG  
91 contacts, we co-registered pre-implantation cerebral MRI and post-implantation Computed  
92 Tomography (CT) (using the maximization of normalized mutual information and trilinear  
93 interpolation) using the GARDEL (graphical user interface (GUI), [https://meg.univ-  
95 amu.fr/wiki/GARDEL:presentation](https://meg.univ-<br/>94 amu.fr/wiki/GARDEL:presentation))<sup>7</sup>. Long-term video-SEEG monitoring was performed to  
96 record several of the patient's habitual seizures, following a partial withdrawal of antiseizure  
97 medications. Bipolar electrical stimulations of adjacent SEEG contacts were performed to  
98 trigger the habitual aura or seizure and for functional mapping purposes (low frequency  
99 stimulation (1 Hz) for a continuous period of up to 40 s, and high frequency stimulation (50  
100 Hz) during 2–5 s, with intensity ranging from 0.5 to 3 mA<sup>8</sup>).

100

## 101 2. Quantification of ictal activity

102

103 Interictal and ictal activities were firstly analysed visually using a bipolar montage. Then to  
104 define quantitatively the epileptogenic zone (EZ), we used the epileptogenicity index (EI). EI is  
105 a semi-automatic method to quantify the dynamic of the fast-activity genesis at seizure onset.  
106 The epileptogenicity index is based on two important features of the transition from pre-ictal  
107 to ictal activity: (i) the redistribution of signal energy from lower frequency bands (theta,  
108 alpha) toward higher frequency bands (beta, gamma); and (ii) the delay of appearance of  
109 these high frequencies. Briefly the EI quantifies the ability of each structure, involved in the

110 seizure, to generate ictal fast activity (above 12 Hz) with loss of background activity, and the  
111 precocity of this discharge regarding other structures <sup>6</sup>.

112

### 113 3. Evaluation of SEEG signals disorganisation / entropy analyses

114

115 To select the channels for connectivity analyses disclosing a significant level of disorganization  
116 of their signals during dacrytic behaviour, we used “Permutation Entropy” (PE)<sup>9</sup>. PE considers  
117 the complexity of the electrophysiological signals, based on a measure of Shannon entropy of  
118 the relationships between neighbouring values of the time series. It gives a value between 0  
119 and 1, 0 meaning that the signal is perfectly organized (for example in the case of a pure sine  
120 wave) and 1 completely disorganized (completely random noise). The algorithm used to apply  
121 PE on our data is the one developed by Unakafova and colleagues due to its algorithmic  
122 performance<sup>10</sup>. The parameters used were as follows: two-second window, one second steps,  
123 0.1 second max lag, and 0.5 to 256 Hz filters. After calculation of PE, we applied a z-score  
124 normalization of the two periods (1: from electrical seizure onset to dacrytic behaviour onset,  
125 and 2: from dacrytic behaviour onset to electrical seizure offset) in comparison with the  
126 preictal period (baseline). To select channels with a statistically significant change in PE, we  
127 applied a Wilcoxon test comparing the PE values during the periods of interest with those  
128 during the baseline, with a Bonferroni correction.

129

### 130 4. Estimation of changes in brain functional connectivity

131

132 To estimate the changes in brain connectivity during dacrytic behaviour, we analysed the  
133 functional connectivity (FC) for the channels whose entropy was significantly modified using

134 non-linear correlation coefficient  $h^2$ . For each SEEG seizure, we selected two temporal periods  
135 for FC analysis: 1) pre-ictal period, segment selected until 5 seconds before the first SEEG ictal  
136 modification; and 2) period of dacrystic behaviour. Interdependencies between bipolar SEEG  
137 channels were estimated by pairwise nonlinear regression analysis based on the  $h^2$  coefficient  
138 <sup>11</sup>, using Anywave software (<https://meg.univ-amu.fr/wiki/AnyWave>)<sup>12</sup>. Nonlinear regression  
139 analysis aims to estimate the degree of association between two signals X and Y independently  
140 from the linear or nonlinear nature of this association. In a sliding window, a piecewise linear  
141 regression is performed between each pair of signals. The  $h^2$  is the coefficient of  
142 determination, which measures the goodness of fit of the regression (equivalent to the  $r^2$  used  
143 in linear regression). The  $h^2$  is bounded between 0 (no correlation) and 1 (maximal correlation)  
144 and is asymmetric. This method has been shown to be particularly suitable for the analysis of  
145 EEG/SEEG signals in the context of epilepsy (review in <sup>13</sup>) and achieves high accuracy in the  
146 setting of intracranial EEG recordings <sup>14</sup>. We used a sliding window of 2 seconds with a step of  
147 1 second and a maximum delay between signals of 100 ms. We used 0.5 Hz high pass and 256  
148 Hz low pass filters for these analyses. To study FC changes, the z-score values of interactions  
149 comparing the different above-mentioned periods were obtained. We compared the  
150 connectivity during the ictal dacrystic behaviour with the pre-ictal period chosen before the  
151 electrical seizure onset.

152

### 153 **Results of SEEG analysis**

154

155 SEEG was performed with twelve right and two left electrodes (bilateral implantation because  
156 of negative-MRI), which covered the right temporal lobe, prefrontal cortex (especially  
157 orbitofrontal and cingulate), anterior insula and parietal lobe (lower part); and the left orbito-

158 frontal cortex (*Figure 1 and 2*). Interictal activity showed alteration of background activity with  
159 abundant and repetitive spikes suggestive of focal cortical dysplasia (FCD) in anterior insula,  
160 frontal operculum, and orbitofrontal areas. Six spontaneous seizures were recorded, five of  
161 which with dacrystic behaviour. The seizure without dacrystic behaviour consisted only in an  
162 aura without objective semiology and had similar SEEG onset but shorter duration and limited  
163 propagation. Electrical stimulations of pars orbitalis (1 mA, 50 Hz) and anterior insular cortex  
164 (2 mA, 50 Hz) triggered the usual aura of the patient without the dacrystic behaviour or  
165 objective semiology.

166 All dacrystic seizures had similar seizure onset and propagation pattern both in term of  
167 morphology of the discharges and of spatio-temporal organisation. A typical dacrystic seizure  
168 is illustrated in the Figure 1. Seizure onset was characterized by a burst of polyspikes followed  
169 by a low voltage fast activity within the contacts exploring orbitofrontal (almost all contacts  
170 of electrode R), frontal operculum (lateral contacts of R and OF, intermediate contacts of Ia),  
171 and anterior insula (mesial contacts of Ia and Im) areas. About 10 seconds after onset, the  
172 discharge slowed to an alpha sinusoidal discharge in some previously involved structures and  
173 propagated following a similar morphology to right hippocampus (mesial contacts of B), right  
174 neocortical temporal regions (lateral contacts of A and B), right precuneus (mesial contacts of  
175 PI) and right parietal lateral cortex (lateral contacts of PI). The dacrystic behaviour started 5  
176 seconds after the installation of the sinusoidal alpha discharge, therefore 15 seconds after  
177 seizure onset. At that time, we observed: 1) low voltage fast activity in right orbitofrontal (R),  
178 second short gyrus of the anterior insula (mesial contacts of Im) and frontal operculum (OF);  
179 2) sinusoidal alpha discharges in right hippocampus (mesial contacts of B), temporal neocortex  
180 (lateral contacts of A and B), first short gyrus of anterior insula (mesial contacts of Ia),  
181 precuneus (mesial contacts of PI) and lateral parietal cortex (lateral contacts of PI); 3) there

182 were no clear rhythmic or sinusoidal discharge but a modification of background activity with  
183 decrease of amplitude, decrease of low frequencies and increase of high frequency content,  
184 in the left frontal regions (orbito-frontal cortex: OR' and superior frontal cortex: CR'), and right  
185 dorsolateral prefrontal cortex (last contacts of CR and OR).

186 Using the EI to quantify the epileptogenicity of structures during seizures, an orbitofrontal (R),  
187 pars orbitalis (lateral R) and triangularis (lateral OF), anterior insula (Ia) and pars opercularis  
188 (Ia and OF) the epileptogenic zone (EZ) was delineated (*Figure 1*). The patient was operated  
189 with a tailored fronto-insular cortectomy without postoperative complication and is currently  
190 seizure-free for nine months. Histology confirmed a FCD type Ic.

191 Using PE to estimate the level of electrophysiological signals disorganization, we observed  
192 during the dacrytic behaviour a combination of 1) decreased signal complexity in a large  
193 network including the bilateral orbitofrontal cortices, anterior insula, hippocampus, and  
194 precuneus; 2) increased signal complexity in the frontal operculum and middle frontal gyrus  
195 (*Supplementary Figure*).

196 Using  $h^2$  coefficient to estimate the modification of FC, we observed an increased connectivity  
197 within a large network including the EZ (right anterior insula, frontal operculum, and lateral  
198 orbitofrontal cortex) but also remote areas: right orbito-ventro-mesial, right prefrontal  
199 dorsolateral (superior and middle frontal gyri), right precuneus, right hippocampus and left  
200 orbito-ventro-mesial and superior frontal cortices (*Figure 2*).

201

## 202 **Discussion**

203

204 From a physiological point of view, dacrytic / crying behaviours are postulated to involve a  
205 complex system, composed of an “excitatory emotional” network (especially prefrontal

206 cortex, insular, cingulum and amygdala, as well as subcortical structures such as the striatum,  
207 hypothalamus, midbrain and pons), and an “inhibitory voluntary” network (mainly the  
208 premotor/motor areas for facial control) which interact with the periaqueductal grey matter,  
209 itself responsible for control/ coordination of facial expressions, breathing and vocalization  
210 during crying. It is hypothesized that pathological crying occurs when both excitatory and  
211 inhibitory networks are dysfunctional (“two hits theory”)<sup>15</sup>. In our case, we observed an  
212 increase of the functional connectivity within a large right fronto-temporo-insular network,  
213 broadly similar to the "emotional excitatory" network described above. It suggests that a focal  
214 seizure leading to the disorganization of functional connectivity within large network involved  
215 in crying may generate this behaviour during a seizure. A similar mechanism has already been  
216 reported in other complex behaviour observed during focal seizure such as humming  
217 automatisms <sup>16</sup>.

218 Dacrystic seizures can be observed in epilepsies related to hypothalamic hamartomas (often  
219 associated with gelastic seizures), but also in focal epilepsies (especially temporal)<sup>2</sup>. Previous  
220 cases explored with intracerebral EEG showed propagation of the ictal discharge to the medial  
221 frontal structures at the time of dacrystic behaviour <sup>17,18</sup>. Moreover, crying behaviour has also  
222 been reported following electrical stimulation of the orbitofrontal cortex, the internal capsule  
223 and the anterior insula<sup>19</sup>. These data suggest that rather than a specific zone that would cause  
224 this behaviour, seizure-related dysfunction of a large number of functionally connected brain  
225 areas within an emotional network may lead to ictal emotional behaviour.

226 One of the limitations of our study is the limited sampling of contralateral temporo-parieto-  
227 insular regions and subcortical structures, due to obvious clinical limitations in the number of  
228 SEEG electrodes implanted. We report only one patient, and future studies on more patients  
229 analysed invasively and non-invasively (EEG) would be interesting.

230 **Conclusion**

231 Dacrystic behaviour can be seen in focal seizures. This probably does not correspond to the  
232 dysfunction of a unique structure but is rather related to the disorganization of connectivity  
233 within a large fronto-temporo-insular networks associated with the circuit involved in the  
234 physiology of crying. This disorganization may be triggered by the seizure itself or by electrical  
235 stimulation, affecting regions strongly connected to these circuits.

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## Figure Legends

### **Figure 1:**

A. Representation on the patient's 3 dimensions (3D) mesh of the mean epileptogenicity index (EI) across seizures.

*A electrode explored amygdala (mesial part) and middle temporal gyrus (lateral part); B hippocampus and middle temporal gyrus; T: superior temporal gyrus; H: pulvinar, posterior insula and Heschl gyrus; PI: precuneus and supramarginal gyrus; R: orbito-frontal and pars orbitalis; OR orbito-frontal and middle frontal gyrus; OF: anterior insula and pars triangularis; CC: anterior cingulum and middle frontal gyrus; Ia: anterior insula and middle frontal gyrus; Im: middle insula and lateral premotor cortex.*

B. 30 seconds of stereoelectroencephalography (SEEG) recording showing the seizure onset and the beginning of dacrytic behaviour associated to a propagation of the ictal discharge to the orbito-frontal cortex and anterior insula.

*The entire SEEG page has a duration of 30 seconds, there is one second between each yellow vertical line, and the exact timing is indicated by the blue numbers at the top of the SEEG trace.*

**Figure 2:**

Representation on the patient's 3 dimensions (3D) mesh of the changes in entropy during the dacrystic period (z-score compared to pre-ictal period illustrated by the sphere on each channel) and the change in functional connectivity (z-score compared to pre-ictal period illustrate by the links between channels).

*A electrode explored amygdala (mesial part) and middle temporal gyrus (lateral part); B hippocampus and middle temporal gyrus; T: superior temporal gyrus; H: pulvinar, posterior insula and Heschl gyrus; PI: precuneus and supramarginal gyrus; R: orbito-frontal and pars orbitalis; OR orbito-frontal and middle frontal gyrus; OF: anterior insula and pars triangularis; CC: anterior cingulum and middle frontal gyrus; Ia: anterior insula and middle frontal gyrus; Im: middle insula and lateral premotor cortex.*

**Supplementary Figure Legend:**

Boxplot of each change of entropy for each channel during dacrytic or preictal periods (z-score compared to pre-ictal period). The coloured ones are statistically significant, blue means a decrease and red an increase.





