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Transient insular and parietal cortex disconnection during psychogenic non-epileptic seizures (PNES)

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Summary

Psychogenic non-epileptic seizures (PNES) are paroxysmal clinical events that are often misdiagnosed as epileptic seizures, but which are not associated with electrographic discharge. Brain connectivity changes occurring during PNES are not known. We studied functional connectivity (Fc) in two patients with drug-resistant epilepsy, explored by stereotactic-EEG, in whom we recorded both epileptic seizures (ES) and PNES. Functional connectivity using pair-wise non-linear correlation was computed between signals from 7 brain areas: amygdala, hippocampus, lateral temporal cortex, anterior insula, orbitofrontal cortex, prefrontal cortex, lateral parietal cortex. We assessed changes in global Fc during PNES in comparison with a background period. During PNES, a global decrease of Fc occurred between the different brain regions studied, compared with the interictal period. In both patients, decreased functional connectivity was prominent in connections involving anterior insula and parietal cortex. In conclusion, some PNES are associated with ictal functional disconnection between brain areas, particularly involving the parietal cortices and the anterior insula.

Key Words: PNES, epilepsy, functional connectivity, stereotactic-EEG, SEEG, network

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INTRODUCTION

Psychogenic non-epileptic seizures (PNES) are paroxysmal episodes of disruption in consciousness, cognitive control, emotional or behavioral function that may mimic epileptic seizures (ES) but without demonstrable epileptic discharge¹. In addition, PNES and ES may coexist in about 12% of cases (range: 1% to 62%)². The pathophysiology of PNES remains largely unknown. Approximately 75% of patients with PNES have experienced traumatic life events, especially some form of sexual abuse. It has been hypothesized that severe adverse life events could alter interactions between cognitive and emotional brain processes³. Analysis of brain connectivity and network organisation is a robust way to approach pathophysiology of brain disorders. Concerning patients with PNES, studies focused on interictal brain connectivity alterations^{4 5}.

To our knowledge, no studies have yet reported the changes in brain connectivity during PNES. Here, we studied intracerebral EEG functional connectivity (Fc) changes occurring during PNES in two patients explored with stereotactic-EEG (SEEG) for drug-resistant focal epilepsy.

PATIENTS AND METHODS

Patients

Data from two patients explored in the Epileptology Department, Timone Hospital, APHM, Marseille, France, were analyzed. Both patients had detailed evaluation including medical history, neurological examination, cognitive testing, cerebral ¹⁸F-fluorodeoxyglucose-PET and MRI. They had both drug-resistant focal epilepsies requiring SEEG recording after the non-invasive presurgical evaluation. Stereotactic-EEG (SEEG) was carried out as part of patients' usual clinical care, in 2016 and 2017. As well as focal refractory epilepsy, these two patients had co-existing PNES with habitual episodes previously documented during non-invasive investigation. Both patients had given informed consent.

The first patient was affected by a neonatal stroke, causing a right hemiparesis and impaired neurodevelopment. ES began when she was 8 years old, and quickly became drug-resistant. She had experienced physical and psychological abuse at home. Video-EEG was performed in

2015 and found left hemisphere interictal spikes; both PNES and ES were recorded: 1) awake seizures with sudden fall and prolonged period of loss of consciousness without visible epileptic discharges on EEG, corresponding then to PNES; 2) seizures with a tonic posture, and a brief elevation of the right arm sometimes associated with urination, associated with prominent left hemisphere discharges on EEG. Brain MRI revealed left temporo-parietal atrophy. It was decided to perform SEEG, when she was 19 years old. SEEG explored both hemispheres; 2 spontaneous ES affecting the left prefrontal cortex and premotor areas, and 2 spontaneous PNES were recorded. She underwent left frontal tailored disconnection. After 3 years of follow-up, she is free from epileptic seizures as well as from PNES.

The second patient experienced her first epileptic seizures at the age of 15 years, in the course of a family emigration to France during the Kosovan's war in 1999. Epilepsy rapidly became drug-resistant. During ES, she described epigastric discomfort and ascending sensation of warmth, followed by loss of consciousness. Video-EEG displayed interictal spikes over left temporal electrodes, and two seizures were recorded with left centro-temporal discharge. The patient also presented PNES, with generalized tonic posturing and loss of consciousness without EEG changes. Brain MRI displayed a slight left temporal atrophy and cerebral PET showed left anterior temporal hypometabolism. SEEG with bilateral implantation was performed when the patient was 37 years old. She had one spontaneous PNES (with no epileptic discharge) and two spontaneous ES with a left temporo-anterior ictal discharge. She underwent left antero-temporal lobectomy. After two years of follow-up, she is free of epileptic seizures but continues to present PNES.

SEEG recordings

Recordings were performed using intracerebral multiple contact electrodes (10-15 contacts, length = 2 mm, diameter = 0.8 mm, 1.5 mm apart). Signals were recorded on a 256-channel Natus system, sampled at 1024 Hz and recorded on a hard disk (16 bits/sample) using no digital filter. Two hardware filters were present in the acquisition procedure: a high-pass filter (cutoff frequency equal to 0.16 Hz at -3 dB) and an antialiasing low-pass filter (cutoff frequency equal to 340 Hz at 1024 Hz).

Selection of channels

We selected seven areas: amygdala, hippocampus, anterior lateral temporal cortex, anterior insula, orbitofrontal cortex, dorsolateral prefrontal cortex, lateral parietal cortex. These areas were chosen because of clinical relevance, potential pathophysiological implication and sampling in both patients. Our analyses were based solely on electrodes that were ipsilateral to seizure onset zone, because the contralateral hemisphere was less densely explored. To this purpose, we co-registered pre-implantation MRI and post-implantation CT⁶ and visually defined the anatomical areas using the Human Brain Atlas⁷. We analyzed all bipolar channels within these structures (adjacent contacts within grey matter, 12 bipolar signals in patient 1 and 13 bipolar signals in patient 2).

Definition of periods of interest

For both patients, three artefact-free periods of interest were analyzed: 1) background, 2) PNES, 3) ES. We analyzed all spontaneous ES and PNES (2 PNES, 2 ES for patient 1 and 1 PNES and 2 ES for patient 2). The background period was chosen from a period at least 4 hours away from any ES or PNES. The onset of the ES or PNES periods was defined as follows: 1) the beginning of SEEG ictal discharge for ES (which always preceded first clinical signs); 2) the first clinical sign for PNES. We chose the same duration for background, PNES and ES: 90 seconds, corresponding to the minimal length of PNES. For patient 1, we chose a period of voluntary motor activity close to that observed during the PNES (including a version of the body to the right). For patient 2, since the PNES included hypotonic behavior without movement, a quiet rest period without movement and eyes closed was chosen.

Functional Connectivity (Fc) analysis and graph measures

Interdependencies between bipolar SEEG signals were estimated by pairwise nonlinear regression analysis based on the h^2 correlation coefficient⁸ computed using Anywave software⁹. We used a sliding window of 1 second with an overlap of 0.5 second and a maximum delay between signals of 100 ms. We used only a 0.5Hz high pass filter in all analyses. Because h^2 values are asymmetric (h^2 values from a structure X to a structure Y and from a structure Y to a structure X are different), we symmetrized our connectivity matrix using the higher h^2 value between two channels. We only analysed the connections between different brain nodes (brain structures): « link strength » that consists of the mean h^2 of all pairs of bipolar channels

between two nodes. As a measure of centrality, we used the “node strength” that consists of the mean h^2 of connections of one node with all other nodes of the network.

Statistical analysis

We performed three types of statistical analyses: 1) evaluation of the change in global connectivity, 2) evaluation of the change for each specific “link strength”, 3) evaluation of the changes for each specific “node strength”. In order to express the magnitude of these changes between two period, we used the z-score with the background as reference period. For the statistical analyses, at first, we averaged the h^2 values across temporal windows in order to obtain the mean h^2 by pair of bipolar channels. Then, the statistical tests were performed on these mean h^2 values and paired in order to compare the values for each specific link / node between two periods of interest. All statistical tests were made at the patient level. In case of multiple PNES/ES recorded, the values of the different PNES/ES were combined for the statistical tests. We used Wilcoxon sign-test and Mann-Whitney U-test, with a Bonferroni’s correction for multiple comparisons. The significance thresholds were then $p < 0.0024$ ($=0.05/21$) for edge-specific h^2 and $p < 0.007$ ($=0.05/7$) for node strength. Statistical analyses were performed using MATLAB and SPSS.

RESULTS

Patient 1 presented two spontaneous PNES (see details in table 1). During the episode, she did not respond to orders, and the PNES ended gradually after few minutes. There was no electrographic discharge over SEEG recordings during the PNES. Patient 2 presented one spontaneous PNES in which she reported warning symptoms of a feeling of discomfort and dizziness, followed by sudden hypotonia of the head with loss of consciousness and recovered gradually (Table 1).

We first evaluated the global level of brain connectivity during PNES and calculated the mean h^2 of all edges of our graph. We observed a significant decrease in global h^2 during PNES in comparison with background period. For patient 1, the mean h^2 was significantly lower during PNES than during background (0.36 vs 0.39 $p < 0.001$, paired Wilcoxon). Similarly, for patient 2, the mean h^2 over all connections was significantly lower during PNES than during background (0.22 versus 0.24 $p < 0.001$, paired Wilcoxon). Then, we looked at the

pair-wise Fc changes between two regions (namely edges of our graph), during PNES in comparison with background. We found significant reduction of some links between regions in both patients particularly involving the insula and the lateral parietal cortex: anterior insula - parietal; anterior insula - prefrontal; amygdala - parietal; orbitofrontal – parietal; hippocampus – parietal; anterior insula - orbitofrontal; anterior insula - hippocampus; parietal - prefrontal; orbitofrontal - temporal lateral; orbitofrontal – prefrontal (Fig 1A and 2). The changes of node-strength confirmed a significant reduction of the node strength values of anterior insula and parietal cortices in both patients (Fig. 1B and 2).

Finally, we evaluated if the changes in Fc observed during PNES were different from the changes observed during epileptic seizures. For this purpose, we evaluated the global level of brain connectivity during ES in comparison with background and calculated the mean h^2 of all edges of our graph. For patient 1, the mean h^2 increased from 0.39 during background to 0.48 during ES ($p < 0.001$, paired Wilcoxon). For patient 2, the mean h^2 increase significantly from 0.24 during background to 0.28 during ES ($p < 0.001$, paired Wilcoxon).

DISCUSSION

We studied the changes in Fc during PNES serendipitously recorded in epileptic patients undergoing SEEG. We demonstrated in our two patients, in comparison with background activity, a global decrease of Fc, mostly affecting anterior insula and lateral parietal cortex (especially with orbitofrontal cortex, hippocampus and prefrontal cortex). Several studies have previously suggested altered Fc in patients with PNES during the interictal state. EEG studies showed a correlation between PNES frequency and decreased connectivity between frontal and posterior regions¹⁰ or a correlation with poor local (intraregional) connectivity⁵. Several fMRI studies found decreased Fc in patients with PNES, and identified the parietal cortex as one of the regions with altered connectivity in patients¹¹⁻¹⁴. A PET study demonstrated interictal focal hypometabolism in patients with PNES, particularly in the right parietal area¹⁵. Altered consciousness is present in many PNES and has been suggested to result from a process of dissociation¹⁶. One mechanism suggested by our results could be an alteration of long-distance functional brain connections involving parietal cortex. Indeed, pathological alterations of long-distance fronto-parietal networks are associated with

impairments of conscious access¹⁷. Such alterations have been demonstrated in focal seizures with impairment of awareness, characterized by an abnormal hypersynchronisation of these networks¹⁸. Interestingly, alterations have been demonstrated in patients with functional motor disorders¹⁹ with decreased fMRI connectivity between the right temporo-parietal junction and bilateral sensorimotor regions. Another important hub exhibiting hypoconnectivity during PNES in our study is the anterior insula (AI). The insular cortex may constitute a neuroanatomical substrate for subjective feeling states that may underlie a conscious representation of self²⁰ and AI is a key region for predictions related to interoception and emotions²¹. Disconnection of AI observed during PNES could thus lead to altered integration of information and prevent accurate predictions. The lack of normal continuous production of predictions could contribute to a feeling of being “disconnected” from reality, perhaps as a protective mechanism to avoid representations that would be considered threatening.

Our study has some clear limitations, notably analysis of only two patients and three PNES due to the serendipity of PNES recorded during SEEG. SEEG has necessarily limited brain spatial sampling. Moreover, our study does not allow correlation with underlying interictal psychopathology or subjective sensation during PNES. Finally, the mechanisms of PNES in patients with co-existing drug-resistant epilepsy may be different than for patients without epilepsy. Future studies could analyze Fc during PNES extracted by source-connectivity methods on scalp-EEG recordings²², which would allow more extensive brain sampling and analysis of a larger population (with and without epilepsy).

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Legends of Figures

Figure 1: A/ Z-scores values of the functional connectivity changes of the 21 links between selected regions, during PNES and ES, compared to BKG for the two patients. Values during PNES of patient 1 are figured in orange, those during ES in green. Values during PNES of patient 2 are figured in red, those during ES in blue. *: links with significant connectivity changes during PNES in comparison to background ($p < 0.0024$) B/ Z-scores values of the 7 node-strength changes during PNES and ES, compared to background for the two patients. Values during PNES of patient 1 are figured in orange, those during ES in green. Values during PNES of patient 2 are figured in red, those during ES in blue. *: node-strength with significant connectivity changes during PNES in comparison to background ($p < 0.007$).

Figure 2: Changes in functional connectivity during PNES when compared with BKG, in both patients, illustrated on a standard 3D mesh of the MRI with the position of electrodes. Lines represent z-score value of the h2 changes between two regions, Spheres represent z-score values of the mean-strength changes of each sampled region. The thickness/diameter and the colors reflect the value of the z-score. **A.** Changes in connectivity during PNES in patient 1. **B.** Changes in connectivity during PNES in patient 2. Note the important decrease of connectivity in links affecting the anterior insular and parietal cortices. Abbreviations refer to the SEEG electrode names. Left side is labeled with the sign ' after each abbreviation. A': amygdala (medial contacts); anterior part of middle temporal gyrus (MTG, lateral contacts). B': anterior hippocampus (medial contacts); anterior part of middle temporal gyrus (MTG, lateral contacts). GPH': posterior hippocampus (medial contacts); posterior part of MTG (lateral contacts). Ib': insula (deepest contacts), superior part of middle frontal gyrus (lateral contacts). TP': temporal pole mesial part (medial contacts); and lateral part (lateral contacts). OF': anterior insula (medial contacts); operculo-insular cortex (lateral contacts). PA' (patient 1) or PI' (patient 2): lateral parietal cortex (lateral contacts). H': thalamus (medial contacts); superior temporal gyrus (lateral contacts). CR': anterior cingulate region (medial contacts); lateral prefrontal cortex (lateral contacts). OR': orbitofrontal (medial contacts); dorsolateral prefrontal cortex (lateral contacts). TB': entorhinal cortex (medial

contacts); inferior temporal gyrus (ITG, lateral contacts). SA': supplementary motor area (medial contacts); premotor cortex (lateral contacts); SC': central sulcus (medial contacts); middle frontal gyrus (lateral contacts). CU': cuneus (medial contacts); occipital posterior cortex (lateral contacts). OT': fusiform gyrus (medial contacts); posterior part of middle temporal gyrus (MTG, lateral contacts).

Table 1: Clinical characteristics of psychogenic non epileptic seizures (PNES) and epileptic seizures (ES) recorded in the two patients. Loss of consciousness intensity was scored by one of the authors (TM), using an eight criteria scale (CSS: Consciousness Seizure Scale)¹⁸.

DISCLOSURE OF CONFLICTS OF INTEREST

None of the authors has any conflict of interest to disclose. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.