Abnormal Functional Connectivity between Areas involved in Emotion and Executive Control in PNES

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Authors:
Sylvie van der Kruijs¹, Nynke Bodde¹, Maarten Vaessen², Richard Lazeron¹, Paul Hofman², Walter Backes², Albert Aldenkamp¹, Jaap Jansen²

Institutions:
¹Epilepsy Center Kempenhaeghe, Heeze, Netherlands, ²Radiology, Maastricht University Medical Center, Maastricht, Netherlands

Introduction:
Psychogenic non-epileptic seizures (PNES) are episodes of movement or behaviors that resemble epileptic seizures, but are not accompanied by epileptiform activity as seen on EEG. The underlying cause is assumed to be psychological; the episodes may be the somatic manifestations of emotional distress. An important predisposition factor for PNES may be the tendency to dissociate, which is closely related to hypnotic suggestibility and essentially shows the ability to take distance from reality (Bodde, 2009). However, it remains unclear how patients with PNES process information differently than non-affected individuals, resulting in dissociative episodes. We explored whether fMRI could identify biomarkers of brain alterations associated with dissociation in PNES.

Methods:
The study population included 11 patients with PNES (6F, 5M, age 34±11, nr of seizures in previous month 2±3), and 13 healthy volunteers (8F, 5M, age 33±11). All completed the Dissociation Questionnaire (DIS-Q), Dissociative Experiences Scale (DES), and the Somatoform Dissociation Questionnaire (SDQ-20). Global intelligence was tested using the Raven's Progressive Matrices Test. The fMRI paradigms (Philips Achieva 3T) consisted of 4 scans: Resting state fMRI (rsfMRI) 1, picture encoding, Stroop color naming, and rsfMRI 2. All images were co-registered, spatially normalized to MNI space, and smoothed in SPM8. A standard random-effects analysis was performed to assess differences in cerebral activation between groups. Subsequently, ROIs with strong activation were defined, based on the activation patterns during the tasks averaged over all subjects. For the rsfMRI analysis, seed time courses for each region and subject were generated, by averaging the signal within the ROI at each time point. Each seed time course was regressed against all voxel time courses to obtain a functional connectivity (FC) map (Waites, 2005), subsequently transformed using the Fisher-Z transformation. Multiple regression was then performed with subject type (patient or control) and session (1 or 2) as covariates (p<0.05, corrected for multiple comparisons). Finally, Spearman correlations between FC values and dissociation scores were obtained.

Results:
Patients displayed significantly lower performance on the Raven's test (nr correct: 44±7 vs 53±3 (ctrl), p<0.001), and significantly higher dissociation tendency [(DES: 1.7±1.18 vs 0.8±1.01, p=0.016), (DISQ: 1.6±0.24 vs 1.3±0.24, p=0.023), and (SDQ: 26.1±4.76 vs 21.8±6.66, p<0.001)]. No significant differences were found between controls and patients in the fMRI activation maps. For the FC map analysis, 5 ROIs were created: Left parahippocampus and right parahippocampus (based on the encode paradigm), and inferior prefrontal sulcus, cingulate sulcus and supramarginal gyrus (based on Stroop paradigm). Significant group differences were found between the FC maps based on the seed regions inferior prefrontal sulcus (Figure 1) and supramarginal gyrus (Figure 2). Compared to healthy controls, patients had 3 significantly higher functional correlations: Precentral sulcus - cingulate cortex, supramarginal gyrus - insular cortex, and supramarginal gyrus - parietooccipital fissure. Contrasts between the two rsfMRI sessions were not significant. Significant correlations (p<0.05) were found between the parieto-insular FC values during both rsfMRI sessions and DES (Figure 3), DISQ and SDQ scores. The FC values of the other two connections also correlated significantly with at least one of the dissociation scales.

Conclusions:

In this study, patients with PNES displayed a higher dissociation tendency and abnormal functional connectivity (between regions involved in emotion, executive control, and movement). Moreover, a positive relationship between FC values and dissociation scores was found, suggesting an underlying dissociation mechanism where an emotional state can influence executive control, resulting in a seizure-like episode (Baslet, 2010).

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Figure 1: (A) Seed ROI in the motor cortex (inferior precentral sulcus), based on average activation for Stroop paradigm in all subjects. (B) Significant higher correlation with seed region for patients compared to controls during resting state fMRI sessions 1 & 2. Contrast is visible in the cingulate cortex. Coordinates are given in MNI space. Overlays are displayed on top of a normalized T1w of a healthy control.
**Figure 2:** (A) Seed ROI in the parietal lobe (supramarginal gyrus). Contrast is visible in the insula (B) and the parieto-occipital fissure, medial part (C).
Figure 3: Scatter plot of distribution of the parieto-insular functional connectivity values and DES scores in the total study population.

Abstract Information

References
