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Facial emotion processing in patients with seizure disorders

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ABSTRACT

Studies of emotion processing are needed to better understand the pathophysiology of psychogenic nonepileptic seizures (PNES). We examined the differences in facial emotion processing between 12 patients with PNES, 12 patients with temporal lobe epilepsy (TLE), and 24 matched healthy controls (HCs) using fMRI with emotional faces task (EFT) (happy/sad/fearful/neutral) and resting state connectivity. Compared with TLE, patients with PNES exhibited increased fMRI response to happy, neutral, and fearful faces in visual, temporal, and/or parietal regions and decreased fMRI response to sad faces in the putamen bilaterally. Regions showing significant differences between PNES and TLE were used as functional seed regions of interest (ROIs), in addition to amygdala structural seed ROIs for resting state functional connectivity analyses. Whole brain analyses showed that compared with TLE and HCs, patients with PNES exhibited increased functional connectivity of the functional seed ROIs to several brain regions, particularly to cerebellar, visual, motor, and frontotemporal regions. Connectograms showed increased functional connections between left parahippocampal gyrus/uncus ROIs and right temporal ROIs in PNES compared with both the TLE and HC groups. Resting state functional connectivity of the left and right amygdala to various brain regions including emotion regulation and motor control circuits was increased in PNES when compared with those with TLE. This study provides preliminary evidence that patients with PNES exhibit altered facial emotion processing compared with patients with TLE and HCs and increased amygdala functional connectivity compared with TLE. These findings identify potential key differences in facial emotion processing reflective of neurophysiologic markers of neural circuitry alterations that can be used to generate further hypotheses for developing studies that examine the contributions of emotion processing to the development and maintenance of PNES.

1. Introduction

Between 0.5 and 1% of the general population has seizure disorders with an estimated 30–40% of them having seizures that are difficult to control with standard antiepileptic drugs (AEDs). A substantial proportion of them, by some estimates of 10–20%, actually have psychogenic nonepileptic seizures (PNES), rather than epilepsy with up to 50% of patients admitted to epilepsy monitoring units (EMUs) for evaluation, being eventually diagnosed with PNES rather than epilepsy [1,2]. In this study, we refer to both diagnostic groups under the common label of "seizure disorders". Patients with poorly controlled seizure disorders exert a significant financial and emotional burden on the medical system and the society [3,4]. Numerous interventions for treatment-resistant epilepsies are available, and additional efforts are being expanded to develop new and advance the available therapies. At the same time, the treatment for PNES, when compared with epilepsy, remains underdeveloped and underutilized [5–7].

The DSM-5 conversion disorder (CD) (a.k.a. functional neurological symptom disorder) diagnostic criteria include one or more of altered voluntary sensory of motor functions with concurrent presence of incompatibility between the occurring symptoms and a specific medical diagnosis [8]. The PNES fulfill this definition and are, thus, a subtype of CD. They are prevalent, disabling, and costly [2,4]. While there are many similarities between clinical features of PNES and epileptic seizures, the major and consistent differences between the two entities include the lack of epileptiform discharges on the EEG during the recorded/witnessed event in PNES and the lack of sustained response

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to pharmacotherapy with AEDs [9,10]. Semiological differences between PNES and epileptic seizures cannot be used reliably to distinguish between the entities [11,12]. Further, psychiatric and psychological comorbidities are present in PNES and in epilepsy, and both groups of patients report stress and emotional problems as major contributors and triggers to seizures and their recurrence [13–16]. The outcomes of patients with PNES treated with the standard of care, which includes intermittent follow up with reassurance, supportive care, and/or referral to a psychiatrist, are poor [17].

Much is already known about the epidemiology of PNES including incidence, cost of diagnosis, semiology, psychiatric comorbidities, neuropsychological profiles, and quality of life (QOL) [2,4,16,18–20]. But, the neurobiology of PNES remains unclear, with only few studies to date examining the neurofunctional underpinnings of the disorder. Some authors suggest that alterations in emotion processing, including emotional dysregulation, may be one of the pathophysiologic mechanisms that underlie initiation and maintenance of PNES [21,22]. Understanding the abnormalities in the neural networks and signals involved in emotion processing that underlie PNES (and contrasting them against the abnormalities in neural networks and signals that exist in patients with epilepsy) may be an essential step for better understanding of the disorder, for developing other methods of differential diagnosis beyond the gold standard of video-EEG monitoring, and for the development of more efficacious interventions [5,22].

The goal of the present study was to improve the understanding of the mechanisms of emotional control in patients with seizure disorders (PNES vs. temporal lobe epilepsy (TLE)). To address this, we utilized a standard fMRI emotional faces task (EFT), which is frequently utilized for the purpose of evaluating emotional and stress circuits in various healthy and diseased populations, and that typically activates brain areas involved in emotion control, including medial temporal regions and medial orbitofrontal regions, and areas involved in conscious representation of emotional facial expressions including anterior cingulate, prefrontal, and somatosensory cortices [23–25]. Further, various emotions included in the EFT stimuli (happy/sad/fearful/neutral) may activate different nodes of the emotion processing circuit with these differences most prominently expressed in medial and lateral frontal lobes [26]. Different versions of this fMRI task have been used in the previous investigations of the cortical underpinnings of motor CDs to demonstrate differences in activation and/or connectivity patterns between patients with functional movement disorder (FMD) and HCs [27,28], but neither EFT analysis in PNES nor comparisons to epilepsy have been performed to date. Thus, in this exploratory study, we sought to identify differences in neuropathophysiology of facial emotion processing between the two seizure groups and healthy controls. Further, we wanted to determine whether the observed group differences in EFT are associated with altered brain connectivity patterns as further evidence for the presence of differences in emotion processing between groups. Finally, we specifically wanted to examine the connectivity of the amygdala as a brain region that was previously observed to exhibit altered fMRI activation and differences in structural and functional connectivity patterns in patients with CDs when compared with healthy controls [27–30]. The overarching hypothesis guiding this work was that fMRI would show aberrant emotional processing in the medial frontal and/or temporal cortices and aberrant functional connectivity of emotion network including the amygdala, in patients with seizure disorders (i.e., increased in PNES and decreased in TLE) when compared with healthy controls with these differences being more pronounced in PNES.

Table 1
Demographic, clinical, and performance variables for the patients with psychogenic nonepileptic seizures (PNES), patients with left temporal lobe epilepsy (TLE), and healthy control (HC) subjects.

	Patients with PNES (N = 12)[d]	Patients with TLE (N = 12)	Healthy controls (N = 24)	p-Value
Age	36 (12)	40 (12)	36 (11)	0.61
Sex, male	2 (20)	2 (20)	4 (20)	1.0
Education, years	15 (2)	13 (1)	15 (3)	0.12
Age of illness onset	32 (12)	29 (15)	–	0.59
Illness duration, years	4 (4)	11 (8)	–	**0.015**
Monthly seizure frequency	8 (1–60)	2 (0–16)	–	0.16
Beck Depression Inventory	26.5 (17.7)[a,b]	12.8 (10.8)[a]	7.7 (8.6)[b]	**0.0003**
Profile of Mood States (POMS)				
Total Mood Disturbance	77.3 (66.1)[b]	34.4 (44.0)	20.2 (32.5)[b]	**0.0038**
Tension/anxiety subscale	16.4 (10.8)[b]	9.9 (6.7)	6.7 (7.7)[b]	**0.0074**
Depression/dejection subscale	24.8 (20.9)[b]	14.3 (16.8)	6.7 (7.7)[b]	**0.0034**
Anger/hostility subscale	15.3 (15.6)	7.8 (8.3)	7.6 (9.6)	0.12
Vigor/activity subscale	9.1 (6.1)[a,b]	15.3 (5.0)[a]	16.1 (6.7)[b]	**0.0072**
Fatigue/inertia subscale	15.1 (10.1)[b]	9.5 (5.2)	7.3 (5.7)[b]	**0.011**
Confusion/bewilderment subscale	14.8 (8.3)[b]	8.7 (6.0)	6.8 (5.1)[b]	**0.0033**
Faces Task during fMRI				
Accuracy, % correct	91.0 (13.8)	96.4 (2.6)	96.1 (7.7)	0.23
Response time, msec	958 (235)	862 (159)	827 (116)	0.086
Postscan rating of emotions on faces				
Total accuracy, % correct	99.7 (1.0)	96.1 (6.3)	97.4 (6.2)	0.89
Total response time, msec	2107 (703)[a]	2987 (1043)[a,c]	2183 (745)[c]	**0.015**
Happy: accuracy, % correct	99.7 (1.0)	96.1 (6.3)	97.4 (6.2)	0.26
Response time, msec	1663 (476)	2072 (487)[c]	1636 (524)[c]	**0.048**
Fearful: accuracy, % correct	83.3 (12.4)	83.9 (18.1)	82.8 (18.0)	0.98
Response time, msec	2747 (1064)	4192 (3250)	2881 (1237)	0.11
Sad: accuracy, % correct	83.9 (7.4)	78.6 (11.2)	83.6 (9.6)	0.29
Response time, msec	2125 (710)[a]	3042 (944)[a,c]	2258 (841)[c]	**0.017**
Neutral: accuracy, % correct	81.7 (21.6)	88.9 (13.7)	88.8 (12.9)	0.40
Response time, msec	2571 (992)	3178 (625)	2567 (1097)	0.18

Data reported as mean (SD) except for sex, which is reported as frequency (percentages), and for monthly seizure frequency, which is reported as median (range).
[a] Significant difference between PNES and TLE.
[b] Significant difference between PNES and HC.
[c] Significant difference between TLE and HC.
[d] At the time of the fMRI testing, all patients with PNES were already weaned off AEDs hence comparison of number of AEDs to patients with epilepsy is not provided.