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Memory and motor control in patients with psychogenic nonepileptic seizures☆

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ABSTRACT

Psychogenic nonepileptic seizures (PNES) are of the most elusive phenomena in epileptology. Patients with PNES present episodes resembling epileptic seizures in their semiology yet lacking the underlying epileptic brain activity. These episodes are assumed to be related to psychological distress from past trauma, yet the underlying mechanism of this manifestation is still unknown.

Using resting-state functional magnetic resonance imaging (fMRI), we investigated functional connectivity changes within and between large-scale brain networks in 9 patients with PNES, compared with a group of 13 age- and gender-matched healthy controls.

Functional magnetic resonance imaging analyses identified functional connectivity disturbances between the medial temporal lobe (MTL) and the sensorimotor cortex and between the MTL and ventral attention networks in patients with PNES. Within network connectivity reduction was found within the visual network.

Our findings suggest that PNES relate to changes in connectivity in between areas that are involved in memory processing and motor activity and attention control. These results may shed new light on the way by which traumatic memories may relate to PNES.

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1. Introduction

Psychogenic nonepileptic seizures (PNES) were first described by Jean-Martin Charcot in the 19th century who termed the syndrome "hysteria" [1]. Psychogenic nonepileptic seizures are classified by Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [2] as Conversion Disorder (Functional Neurological Symptom Disorder) — With attacks or seizures (F44.5). The criteria for diagnosis include the following: one or more symptoms of altered voluntary motor or sensory function, evidence of incompatibility between the symptom and recognized neurological or medical conditions, and not better explained by another medical or mental disorder. The attacks should cause significant distress or impairment (DSM 5) [2]. Psychogenic nonepileptic seizures include an extensive range of paroxysmal episodes of impaired self-control, associated with a range of motor, sensory, autonomic, and mental manifestations, similar to that of epileptic disorders [3] yet without underlying epileptic activity [4,5]. It occurs in people who never experienced a seizure, as well as in patients suffering from concurrent epilepsy [6–8]. The incidence of PNES has been estimated between 1.4 and 4.9 per 100,000 per year, with a prevalence of between 2 and 33 per 100,000 [6].

Causes for PNES have been hypothesized to be either a psychodynamic mechanism where intolerable affect is "converted" into somatic symptoms, a dissociative process where patients utilize psychological 'compartmentalization' to avoid traumatic memories and experiences, as well as a cognitive process where patients alter their attentional resources leading to dysfunctional sensory and motor activity [9,10]. This is bolstered by the fact that risk factors for PNES include history of traumatic life experiences [11], psychiatric disorders, including depression, anxiety, posttraumatic stress disorder, and personality disorders [5]. One review demonstrated that samples with PNES showed very high rates of trauma (44–100%) and childhood physical or sexual

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abuse (23–77%), which were 15–40% higher than those found in control groups [11]. However, despite the extensive psychological literature on the subject, the underlying physiological mechanism of PNES is still unknown [7].

Characteristically, patients suffering from PNES exhibit unremarkable general medical and neurological assessments, including electrophysiological and neuroimaging studies [5,8,12–14]. However, the relationship of PNES to past traumatic experiences as well as its prominent semiology suggests that PNES will be reflected in brain processing, which may be evident in functional imaging. In recent years, several studies have attempted to detect functional changes underlying PNES (Table 1; for review, see Dworetzky and Baslet [15]). Studies used functional magnetic resonance imaging (fMRI), positron emission tomography (PET), single-photon emission computerized tomography (SPECT), or electroencephalography (EEG), and largely compared patients and healthy controls in their resting state. These studies gave rise to diverged results implicating mostly prefrontal (6/14) and parietal (8/14) abnormalities. Additionally, seven studies found activation changes in sensorimotor areas.

Based on the outlined relations of PNES to comorbid neuropsychiatric disorders and past trauma, conscious or unconscious processes, might be related to underlying neurophysiological changes, which ultimately evolve into abrupt behavioral changes. Therefore, we speculated that patients suffering from PNES will display functional changes in brain regions related to self-processing and retrieval of memories of stressogenic events [32]. We further hypothesized that the connection between these brain regions, such as the salient network, the sensorimotor, and the limbic network would be different in patients with PNES.

2. Methods

2.1. Patients

Nine patients with PNES (25.4 ± 2.6 years old; 6 females) were recruited from the Presurgical Epilepsy Unit at the Department of Neurology of Hadassah Medical Center. All patients underwent detailed neurological and psychiatric evaluation (for clinical details see Table 2). Psychogenic nonepileptic seizures were confirmed by video-

Table 1
Summary of findings from available neuroimaging studies investigating PNES.

Author, year	Journal	No. of patients	Inter/ictal	Modality	Results
Knyazeva et al., 2011 [16]	JNNP	13	Interictal	EEG	Decreased prefrontal and parietal synchronization in patients suffering from PNES as compared with healthy controls.
Barzegaran et al., 2012 [17]	Front Hum Neurosci	13	Interictal	EEG	Weakness of local connectedness in the EEG Alpha band in patients with more frequent PNES attacks per month. Excessive rigidity of cortical networks in EEG Beta bands, in patients suffering from PNES, as compared with healthy controls
Arzy et al., 2014 [18]	Epi Behav	3 (suffering from both PS + ES)	Ictal	ECoG, EEG	Decreased parietal theta activity during psychogenic seizures but not during epileptic seizures in the same patients.
Barzegaran et al., 2016 [19]	JNNP	18	Interictal	EEG	Decrease functional connectivity between BG and limbic, prefrontal, temporal, parietal, & occipital regions in the alpha band in patient with PNES compared with healthy controls.
Van der Kruijs et al., 2012 [20]	JNNP	11	Interictal	Rest fMRI (FC), task fMRI	Stronger connectivity between insula, frontoparietal, and motor areas in patients suffering from PNES than healthy controls. No change in task scores between patients suffering from PNES and healthy controls.
Ding et al., 2013 [21]	PLoS One	17	Interictal	Rest fMRI (FC, DTI)	Reduced structural connectivity in attention, sensorimotor, subcortical, and default-mode networks in patients with PNES as compared with healthy controls.
Ding et al., 2014 [22]	Epilepsy Res	18	Interictal	Rest fMRI (FC),	Decreased functional connectivity density in frontal, ACC, and occipital cortexes as compared to healthy controls.
Van der Kruijs et al., 2014 [23]	J psychiatry Res	21	Interictal	Rest fMRI (FC)	Increased coactivation of orbitofrontal, insular, and subcallosal cortex in the resting-state network; the cingulate gyrus, superior parietal lobe, pre- and postcentral gyri, and supplemental motor cortex in the resting-state network; and the precuneus and (para-) cingulate gyri in the default-mode network. Decreased coactivation of the orbitofrontal cortex and the precuneus in the resting state network — in patients with PNES as compared with healthy controls.
Li et al., 2015 [24]	Brain Topogr	18	Interictal	Rest fMRI – FC	Stronger FC between insular subregions and sensorimotor network, lingual gyrus, superior parietal gyrus, and putamen in patients with PNES
Li et al., 2015 [25]	Sci Rep	18	Interictal	Rest fMRI – FC	Patients with PNES showed significantly increased fractional amplitude of low-frequency fluctuations (fALFF) in the DLPFC, parietal cortices, and motor areas, as well as decreased fALFF in the triangular inferior frontal gyrus; increased connectivity in the DLPFC, sensorimotor, and limbic system; decreased connectivity in ventrolateral prefrontal cortex.
Arthuis et al., 2015 [26]	JNNP	16	Interictal	PET-FDG	Hypometabolism: R parietal/central, bilateral ACC; Hypermetabolism: R parietal/central bilateral ACC, left parahippocampal gyrus. Patients with PNES compared with healthy controls
Labate et al., 2012 [27]	Epilepsia	20	Interictal	VBM MRI	Patients with PNES revealed abnormal cortical atrophy of the motor and premotor regions in the right hemisphere and the cerebellum bilaterally.
Ristic et al., 2015 [28]	Epilepsy Res	37	Interictal	MRI cortical thickness	Increased in cortical thickness in L insula, L PFC; decreased cortical thickness in R precentral, R ERC R occipital regions in patients suffering from PNES compared with healthy controls.
Hernando et al., 2015 [29]	Epilepsy Behav	8	Interictal	MRI DTI	Increased R uncinate fibers in patients with PNES compared with healthy controls
Lee et al., 2015 [30]	Brain Res	16	Interictal	MRI DTI	Significantly higher fractional anisotropy was observed in patients suffering from PNES in the left corona radiata, left internal and external capsules, left superior temporal gyrus, as well as left uncinate fasciculus compared with healthy controls.
Bolen et al. 2016 [31]	Epi Behav	112	Interictal	MRI	Patients suffering from PNES had increased multifocal abnormalities than those suffering from epileptic seizures, including encephalomalacia or chronic infarct, focal T2 hyperintensity, and atrophy.

PubMed served as the main search engine.
ACC, anterior cingulate cortex; BG, basal ganglia; DLPFC, dorsolateral prefrontal cortex; DTI, Diffusion tensor imaging; ECoG, Electrocorticography; ERC, entorhinal cortex; FDG, fluorodeoxyglucose; fMRI, functional magnetic resonance imaging; FC, functional connectivity; mPFC, medial prefrontal cortex; PCC, posterior cingulate cortex; PET, positron emission tomography; PFC, prefrontal cortex; PPC, posterior parietal cortex; SMA, supplementary motor area; SPECT, single-photon emission computerized tomography; TPJ, temporoparietal junction; VBM, Voxel-based morphometry; +, significantly increased activity; −, significantly decreased activity.

Table 2
Clinical details of subjects with PNES.

	Age	Sex	First onset	Psychiatric diagnoses and identified precipitant traumatic event	PNES semiology
1	22	M	22	History of ADHD (Attention deficit hyperactivity disorder)	Presented with episodes of lapses in awareness, confusion, and stupor lasting minutes to hours.
2	20	F	19	Documented history of statutory rape Started peripartum	Presented with paroxysmal episodes of loss of losing consciousness and falling down
3	27	F	25	History of borderline personality disorder Started postpartum	Presented with episodes of flailing of all four limbs and retrograde amnesia regarding events preceding the seizure
4	25	M	22	Started after alleged police brutality	Presented with loss of consciousness and flailing of all limbs as well as patient's head
5	18	F	18	History of panic attacks	Presented with patient screaming and flailing all four limbs
6	36	F	26	History of major depressive disorder and borderline personality disorder	Presented with loss of consciousness, eyes "rolling back", and tremor
7	20	F	18	No prior diagnosis	Presented with flailing action of all four limbs accompanied by "pelvic thrusts"
8	40	F	39	History of major depressive disorder	Presented with loss of consciousness, eyes "rolling back", and flailing of all four limbs
9	21	M	16	Started after alleged police brutality	Presented with loss of consciousness and flailing limbs

EEG recording, all EEGs were without any abnormalities and structural magnetic resonance imaging (MRI) was without pathological findings. None of the patients suffered from comorbid epilepsy. It is worth noting that four out of nine patients have reported a traumatic event prior to developing the PNES symptoms, although no formal post-traumatic stress disorder (PTSD) diagnosis was documented. The control group comprised of 13 healthy subjects without history of neurological or psychiatric disorders (32.2 ± 9.8 years old; 7 females). All subjects gave written informed consent, and the study was approved by the ethical committee of the Hadassah Hebrew University Medical Center.

2.2. MRI acquisition

Subjects were scanned using a Siemens Trio 3 T system (32-channel head coil). Blood oxygen level-dependent (BOLD) fMRI was acquired using a whole brain, gradient-echo (GE) echo-planar (EPI) sequence of 160 volumes (repetition time/echo time = 2000/30 ms; flip angle = 75°; matrix = 64 × 64; 33 axial slices; slice thickness/gap = 4 mm/0 mm; voxel size = 3 × 3 × 4 mm). Functional magnetic resonance imaging was done in a single run. Subjects were instructed to stay awake, keep their eyes open, and remain still. Subjects had their eyes open during imaging and fixated their eyes on a central crosshair during imaging. In addition, high-resolution (1 × 1 × 1 mm) T1-weighted anatomical images were acquired for spatial normalization to standard anatomical space.

2.3. fMRI preprocessing

Preprocessing was conducted with Statistical Parametric Mapping (SPM8,www.fil.ion.ucl.ac.uk/spm, RRID:SCR_007037), Data Processing Assistant for Resting-State fMRI (DPARSF) [33], and MATLAB (MathWorks®, Natick, MA, RRID:SCR_001622) software [34]. All functional time series were slice-time-corrected, motion-corrected to the mean functional image using a trilinear interpolation with six degrees of freedom, coregistered with the anatomical image, normalized to standard anatomical space (Montreal Neurological Institute (MNI) EPI template, resampling to 3 mm cubic voxels), and spatially smoothed (4 mm Full width at half maximum Full width at half maximum (FWHM), isotropic). Additional preprocessing steps included the removal of linear trends to correct for signal drift and filtering with a 0.01 to 0.15-Hz bandpass filter to reduce non-neuronal contributions to BOLD signal fluctuations. In line with recent concerns regarding the effect of subjects' motion on functional connectivity characteristics [35,36], we performed multiple regression of 24 motion parameters: 6 rigid body-head motion parameter values—x, y, and z translations and rotations—their value at the previous time point, and the twelve corresponding squared values. To further reduce motion effects, motion "spikes" were also included as separate regressors (identified by framewise displacement of 1 mm), effectively eliminating ("scrubbing") the data at the spike without further changes to correlation values [35,37]. Finally, regressors for global mean, white matter, and cerebrospinal fluid signals were also included as nuisance sources [37].

2.4. Extraction of region-wise resting-state fMRI time series

To measure functional connectivity, we first defined a whole brain network using the Atlas of Intrinsic Connectivity of Homotopic Areas (AICHA) [38], which defines 384 brain regions across the cerebral cortex. To ensure that voxels in each region were indeed a part of the cerebral cortex, we applied the new-segment algorithm of SPM8, which identifies different tissue types on the T1 anatomical image of each subject. The resulting image was used to create a mask of the gray matter (gray matter segmentation intensity >0.1). To avoid including voxels that are affected by signal dropout, we used intensity-based masking, by fitting a Gaussian model to the voxel intensity graph and creating a mask excluding voxels with low functional signal [39]. Regions containing <10 voxels after masking were removed from further analyses. The BOLD signal was averaged across each brain region (from gray-matter voxels only) resulting in a time series of the average activity within that region. To measure whole brain functional connectivity, we computed the Pearson correlation coefficient between each pair of functional regions in the atlas, resulting in a 384 × 384 functional connectivity matrix for each subject [32].

2.5. Identification of disturbances in large-scale fMRI brain networks

To identify large-scale networks, we used the existing parcellation of Yeo and colleagues to seven large-scale brain networks [40]. For each of the AICHA atlas regions, we determined the network it belongs from the seven networks by maximal overlap. To investigate connectivity disturbances between patients and controls, we computed the mean connectivity within each network in each subject, calculated as the average correlation of all possible pairs of regions in each network. Mean connectivity between networks was additionally calculated as the average correlation between all possible pairs of regions belonging to the two networks. To measure connectivity disturbances between patients and controls, we used two-sample two-tailed t-tests between average connectivity values of patients and controls. Statistical values were corrected for multiple comparisons using the Benjamini–Hochberg false discovery rate (FDR) correction [41]. Networks were visualized using Computerized Anatomical Reconstruction Toolkit (CARET) software [42].

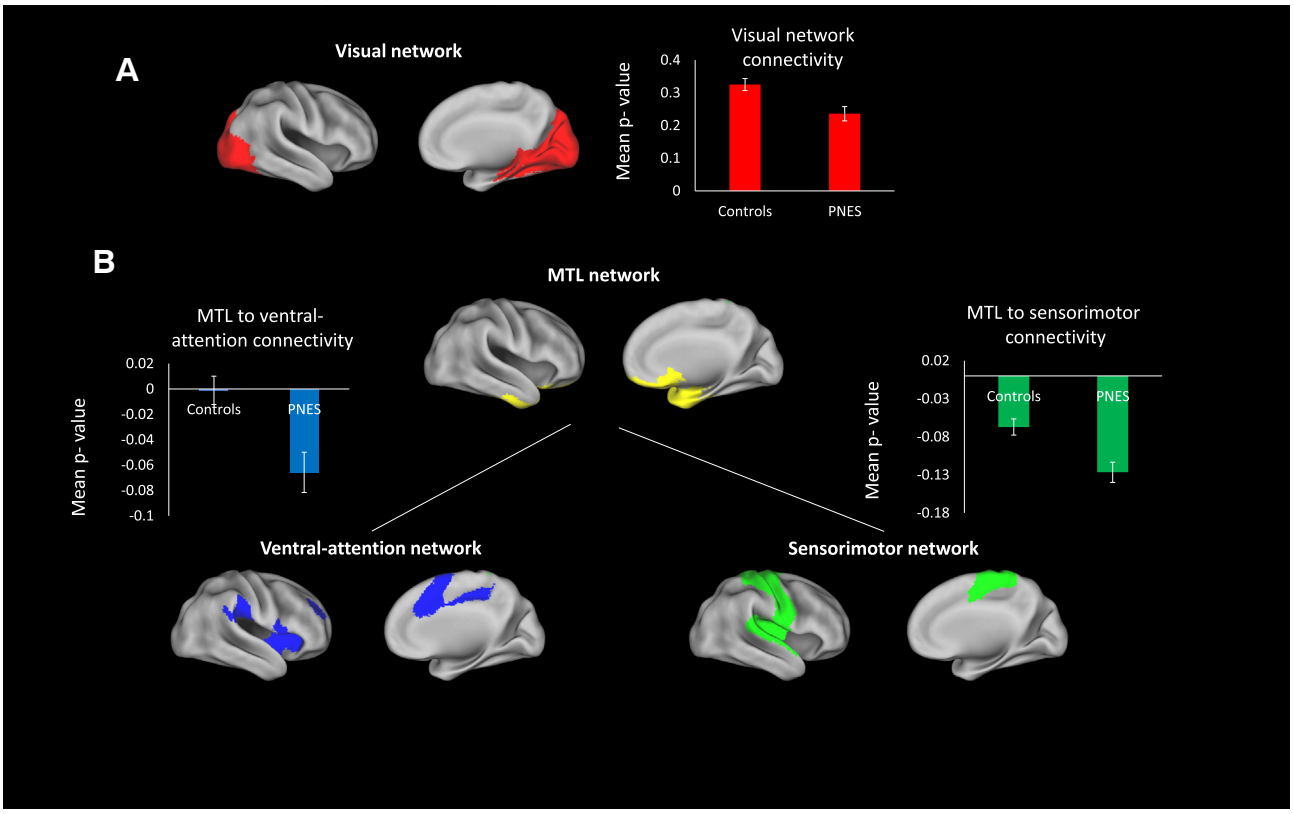

Fig. 1. Connectivity disturbances within and between large-scale resting-state fMRI networks in PNES. A) Disturbed connectivity within the visual network between healthy controls and patients with PNES. B) Disturbed connectivity between networks: MTL to ventral attention networks connectivity and MTL to sensorimotor network connectivity.

3. Results

3.1. Disturbances in large-scale brain networks in patients with PNES

To examine differences in functional connectivity in patients with PNES, we measured the mean connectivity within seven large-scale brain networks [40]. This analysis revealed reduced connectivity in the visual network of patients with PNES in comparison with controls ($p < 0.05$, two-sample two-tailed t-test, FDR-corrected; Fig. 1 and Table 3). Connectivity within these networks did not differ between hemispheres ($p > 0.1$).

3.2. Internetwork disturbances in PNES

To detect internetwork changes in PNES, we looked for differences in functional connectivity between the 7 networks. This analysis revealed a changed connectivity in patients with PNES between the medial temporal lobe (MTL) and the sensorimotor network and between the MTL and the ventral attention network ($p = 0.02$ and $p = 0.03$, respectively, two-sample two-tailed t-test, FDR-corrected) (Fig. 1 and Table 4). Connectivity values did not differ between (all p-values >0.1). Connectivity values were not correlated with illness duration, age, or gender.

4. Discussion

Our study demonstrates impaired connectivity between the MTL and the sensorimotor cortex and between the MTL and the ventral attention network in patients with PNES, as well as within network connectivity reduction in visual network.

Our finding of a changed connectivity between the MTL (involved in autobiographical memory) and sensorimotor networks in PNES is in line with our previous results in patients with conversion disorders [32]. These results support theories which posit that PNES symptoms are a result of the use of psychological defense mechanisms, such as repression or dissociation, used by patients to 'block' awareness of traumatic memories [11,19,23,37,43].

Our results support models which postulate that PNES are a specific dissociative trauma reaction or a subtype of dissociative PTSD [11,44]. In this model, dissociative defense mechanisms used by individuals undergoing severe trauma generate continued use of dissociation as a defense mechanism throughout the life span [45,46]. This, in turn, leads to

Table 3
Average connectivity within the 7 resting-state fMRI networks.

	Visual network		Sensorimotor network		Dorsal attention network		Ventral attention/salience network		Medial temporal/limbic network		Frontoparietal control network		Default-mode network	
t-test — p value (uncorrected)	0.006		0.062		0.111		0.608		0.246		0.214		0.556	
	Control	PNES	Control	PNES	Control	PNES	Control	PNES	Control	PNES	Control	PNES	Control	PNES
Mean	0.325	0.236	0.317	0.263	0.242	0.280	0.327	0.338	0.190	0.214	0.204	0.182	0.243	0.228
SD (standard deviation)	0.065	0.066	0.076	0.053	0.037	0.059	0.055	0.044	0.040	0.051	0.033	0.043	0.053	0.061
S.E. (standard error)	0.018	0.022	0.021	0.018	0.010	0.020	0.015	0.015	0.011	0.017	0.009	0.014	0.015	0.020

Table 4
p-Values of disturbances in connectivity strength between brain networks.

	Visual	Sensorimotor	Dorsal attention	Ventral attention/salience	Medial temporal/limbic	Frontoparietal control
Visual	–	–	–	–	–	–
Sensorimotor	0.226	–	–	–	–	–
Dorsal attention	0.770	0.260	–	–	–	–
Ventral attention/salience	0.637	0.964	*0.023*	–	–	–
Medial temporal/limbic	0.540	***0.003***	*0.011*	***0.002***	–	–
Frontoparietal control	*0.031*	0.100	0.164	0.068	0.108	–
Default mode	0.505	0.905	0.333	0.414	0.610	0.420

Italics: $p < 0.05$ uncorrected; Bold font: $p < 0.05$ when corrected for false discovery rate of multiple comparisons.

sensorimotor disturbances found in conversion disorders in general [47,48] and PNES in particular [49]. The disassociation during the psychogenic episode allows the patient to block out intrusive painful or traumatic memories [50,51]. Similar brain connectivity results were reported in dissociation studies [52]. For example, Krause-Utz et al. reported that dissociation trait positively predicted the connectivity between the amygdala and the dorsolateral prefrontal cortex and negatively predicted the amygdala and the occipital lobe [53]. However, further endeavors in this direction should follow to support this claim.

Despite its promising findings, this study has a few limitations. In our patient group, although the diagnosis of PNES was well established, no direct measures of dissociation, trauma, or PTSD were available. Sample size was small, and the control group did not include patient's suffering from epilepsy. Nevertheless, we saw robust results that passed multiple comparisons correction. Additionally, the size of our experimental group was similar to those used in prior PNES functional neuroimaging studies (see Table 1).

5. Conclusion

In conclusion, our findings suggest that PNES relate to connectivity changes between brain areas that are involved in memory processing and those involved in motor control and activity. These results may shed new light on the way by which traumatic memories may relate to PNES. Future studies may focus on how fMRI data could be used to differentiate between PNES and epileptic seizures as well as how fMRI data can be used to guide in the psychotherapy of this disabling illness.

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