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The application of artificial intelligence to understand the pathophysiological basis of psychogenic nonepileptic seizures☆

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ABSTRACT

Psychogenic nonepileptic seizures (PNES) are episodes of paroxysmal impairment associated with a range of motor, sensory, and mental manifestations, which perfectly mimic epileptic seizures. Several patterns of neural abnormalities have been described without identifying a definite neurobiological substrate. In this multicenter cross-sectional study, we applied a multivariate classification algorithm on morphological brain imaging metrics to extract reliable biomarkers useful to distinguish patients from controls at an individual level.

Twenty-three patients with PNES and 21 demographically matched healthy controls (HC) underwent an extensive neuropsychiatric/neuropsychological and neuroimaging assessment. One hundred and fifty morphological brain metrics were used for training a random forest (RF) machine-learning (ML) algorithm.

A typical complex psychopathological construct was observed in PNES. Similarly, univariate neuroimaging analysis revealed widespread neuroanatomical changes affecting patients with PNES. Machine-learning approach, after feature selection, was able to perform an individual classification of PNES from controls with a mean accuracy of 74.5%, revealing that brain regions influencing classification accuracy were mainly localized within the limbic (posterior cingulate and insula) and motor inhibition systems (the right inferior frontal cortex (IFC)).

This study provides Class II evidence that the considerable clinical and neurobiological heterogeneity observed in individuals with PNES might be overcome by ML algorithms trained on surface-based magnetic resonance imaging (MRI) data.

1. Introduction

Psychogenic nonepileptic seizures (PNES) consist of paroxysmal behavioral manifestations resembling epileptic seizures [1,2] that have been associated with chronic disability and increased risk of morbidity and mortality [1,2]. Current medical nosology mainly categorizes PNES as manifestations of conversion/somatoform (DSM 5) or dissociative disorders (ICD-10), providing no additional insights into the likely neurobiological underpinnings of the disorder (DSM 5). Although, video electroencephalography (vEEG) is the gold-standard diagnostic investigation in PNES, such assessment is considered as not mandatory by psychiatrists, is expensive, is unavailable in many centers, and requires hospitalization. Moreover, PNES, rather than epileptic seizures, occur in more than 20% of the patients referred to epilepsy centers for refractory recurrent seizures [2–5]. Because of the above reasons, identification of reliable biomarkers of this disorder is widely required by both patients and physicians.

Our group demonstrated that neuroanatomical abnormalities, mainly involving the motor network, occur in PNES [6]. In the last five years, several groups have confirmed and extended pathophysiological mechanisms including additional pathways, such as limbic and motor systems. To date, however, several meta-analytic or systematic reviews have failed to identify definite neurobiological substrates for PNES [7–9].

In recent years, artificial intelligence proved to be a novel effective approach to automate the analysis of medical data and extract new combinations of biomarkers useful for early individual diagnosis [10–14]. Compared to the classical univariate perspective of previous studies, the multivariate neurobiological heterogeneity detected in patients

☆ Statistical analysis conducted by Roberta Vasta & Alessia Sarica.

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with PNES might be used to train a multivariate machine-learning (ML) classifier with the aim to predict or classify a specific phenotype or behavior. Identifying potential risk factors for PNES would be of primary importance for planning preventive and therapeutic interventions.

The main purpose of this study was to evaluate the contribution of different anatomical neuroimaging metrics (cortical thickness, volume, surface) combined with artificial intelligence for an automated diagnosis of PNES. As a secondary objective, we attempted to extract the multivariate pattern of brain abnormalities that plays a pivotal role in the pathophysiological mechanisms of PNES.

2. Methods

2.1. Subjects enrolment

Patients with PNES were enrolled from two tertiary epilepsy centers, one from the south and one from the north of Italy: The Institute of Neurology, University Magna Graecia of Catanzaro (center A) and the Neurology Unit of Anna Meyer Children's Hospital, University of Florence (center B). The diagnosis of definite PNES was made when patients with an indicative clinical history had spontaneous or provoked seizures recorded with vEEG, and all attacks in a context of negative ictal EEG recordings were considered typical of habitual seizures by seizure witnesses [6,15]. Psychogenic nonepileptic seizures were characterized by stereotyped motor phenomena. All patients enrolled in the study underwent long-term vEEG monitoring to capture at least two stereotyped spontaneous or provoked nonepileptic events. Furthermore, the entire group was studied based on a protocol routinely used for patients with epilepsy through awake and sleep-deprived EEG [6]. Exclusion criteria were as follows: 1) age < 16 years; 2) inability to communicate with the researcher or to complete questionnaires because of language difficulties; 3) severe learning disability or dementia and any other serious neurological or medical illness; 4) cooccurrence of both a functional disorder and epilepsy; 5) evidence of vascular brain lesions, brain tumor, and/or marked cortical and/or subcortical atrophy on magnetic resonance imaging (MRI) scan; 6) personality disorders assessed by structured clinical interview II (SCID-II) [16]; and 7) severe depressive symptoms.

Twenty-three patients with PNES fulfilled these criteria and were enrolled in the study (mean age: 26.22 ± 12.35 years; 20 females). Additionally, 21 consecutive healthy controls (HC), matched for age (mean age: 28.76 ± 7.61 years) and sex (15 women) with no previous history of neurologic or psychiatric disorders, were enrolled from both centers. All patients and controls provided written informed consent. The study was approved by local ethics committees at both participating centers and was conducted in accordance with the Helsinki Declaration.

2.2. Neuropsychiatric and neuropsychological assessment

All patients completed a comprehensive battery of neuropsychiatric tests [17], administered by an experienced neuropsychologist, lasting around 50 min and extensively described in Supplementary materials (S1). The neuropsychiatric examination included the Toronto Alexithymia Scale (TAS-20) [18], the Hamilton Anxiety Rating Scale (HAM-A) [19], the Beck Depression Inventory (BDI-II) [20], the Dissociative Experiences Scale (DES) [21], the Traumatic Experience Checklist [22], and the Somatoform Dissociation Questionnaire-20 (SDQ-20) [23].

2.3. MRI data acquisition

Imaging data were obtained from two different 3T MRI scanners (voxel size = $1 \times 1 \times 1$ mm^3). Patients with PNES and HC were also matched by a scanner. The detailed MRI protocol routinely used for patients with PNES at both institutions was similar, according to guidelines for epilepsy [6,24]. After visual inspection by expert neuroradiologists, images with prominent ghosting or heavy movement artefacts were excluded. The final dataset included 44 structural MRI scans.

2.4. MRI processing and features extraction

Structural images were preprocessed with the standard FreeSurfer pipeline (recon-all script) (Massachusetts General Hospital, Harvard Medical School; http://surfer.nmr.mgh.harvard.edu — version 5.3), as described elsewhere [25–29]. Automatic parcellation of the cortex into 34 gyral-based regions-of-interest (ROIs) per hemisphere was performed according to the Desikan–Killiany atlas [30]. Thus, for each of the 68 cortical bilateral ROIs, metrics for thickness (in mm) and surface area of the pial (in mm^2) were used as training features. Moreover, normalized volumes (mm^3) of 40 subcortical structures were also added as extracted from automatic subcortical segmentation. In conclusion, after removing metrics of no interest, a total of 167 morphological brain features were extracted and analyzed using double statistical approaches: univariate & multivariate ML analysis.

2.5. Neuroimaging analysis: univariate approach

Statistical methodology consisted of an analysis of covariance (ANCOVA) used to investigate the main effect of diagnosis on gray matter parameters (cortical thickness, cortical surface area, and subcortical volume features). Age, sex, total intracranial volume (ICV), and MR manufacturer were included in the model as covariates of no interest. All statistical analyses were corrected for multiple comparisons (Bonferroni's correction) and a p-level of .05 was considered as significant. We calculated the Cohen's *d* as a measure of the effect size that indicates the magnitude of mean differences (using the estimated marginal means) [31]. Statistical analyses were performed using SPSS (version 12.0). This analysis was made independently from multivariate approach in order to evaluate the overall pattern of morphological brain abnormalities associated with the diagnosis of PNES.

2.6. Neuroimaging analysis: multivariate approach

In order to perform a multivariate pattern analysis by means of T1-weighted structural images, we used a ML algorithm previously implemented by our group in clinical neuroimaging [32]. Generally, ML techniques assess the clinical utility of MRI features, providing a support for clinicians in diagnosis prediction. To evaluate the prediction power of morphological variables, we applied the random forest (RF) algorithm [33], which has already been successfully applied on neuroimaging data, such as in dementia classification [32]. This algorithm is robust to overfitting, and it is considered more stable than other ML algorithms in the presence of outliers and in very high-dimensional parameter spaces [32]. In particular, RF is a collection or ensemble of classification and regression trees (CART) [34] trained on datasets of the same size as training set (called bootstraps) and tested on samples that do not include any particular record from the original (one-third of the total subjects [33]). Once a tree is constructed, a set of bootstraps, which do not include any particular record from the original dataset [out-of-bag (OOB) samples], is used as test set. The error rate of the classification on OOB test sets is an estimation of the generalization error. The concept of variable importance is assessed by the Gini impurity criterion index, which is a measure of prediction power of variables, based on the principle of impurity reduction [35]. A greater decrease in Gini means that a particular predictor feature plays a greater role in partitioning the data into the two classes. Thus, the Gini index can be used to rank the importance of features for a classification problem [32].

Our analyses were conducted using the R language (version 3.3.2) and the RF package [36]. A binary classifier was trained by RF on the entire morphological metrics obtained by FreeSurfer, with 10,000 trees in the forest, as suggested by empirical evidence [37]. Variables were then ranked according to their mean decrease in Gini, and all the features

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Table 1
Neuropsychiatric characteristics of patients with PNES.

Patients with PNES (n°23)	
Age	26.22 ± 12.35
Sex (n° female)	20/23
Disease Duration (y)	15.6 ± 6.7
Neuropsychiatric features	
TAS-20	62.13 ± 7.74[a]
BDI-II	16.87 ± 13.11[a]
HAM-A	22.33 ± 7.72[a]
TEC	3.73 ± 2.89
DES	11.04 ± 9.86
SDQ-20	24.60 ± 11.56[a]

TAS-20: Toronto Alexithymia Scale. BDI-II: Beck Depression Inventory-II. TEC: Traumatic Experience Checklist. DES: The Dissociative Experiences Scale. SDQ-20: Somatoform Dissociation Questionnaire-20. Data are given as mean ± SD.
[a] Score overcoming cutoff values.

with a mean decrease in Gini ≥ 0.24 were selected (feature selection phase). This threshold was chosen to construct a new classifier with the lowest OOB error (10,000 trees in the forest). The accuracy of the new classifier was evaluated as 100 - OOB error. Moreover, in order to show the stability of the classification, the true positive rate on one of the training set generated internally by RF was calculated as the ratio between the number of correctly classified instances and the total number of instances. In order to evaluate the effect of nuisance variables such as age, gender, and scanner, we performed analysis including or excluding those features as main factors to highlight their influence on multivariate classification performance. For additional information and for the evaluation of RF performance with respect to other ML algorithms, see the Supplementary materials.

3. Results

3.1. Clinical data

Demographic and clinical data are summarized in Table 1. Psychogenic nonepileptic seizure semiology was highly stereotyped in each patient, mainly featuring convulsive components, such as tonic, clonic, or bizarre motor manifestations usually involving the upper or lower limbs bilaterally. Five patients manifested nonmotor events such as paralysis, or unresponsiveness, or reported sensory feelings. None of the patients had a family history of psychogenic events. Neurologic examination was unremarkable in all patients. No interictal or ictal EEG changes were observed during vEEG. Neuropsychiatric evaluation revealed a typical heterogeneous psychopathological construct characterized by high level of pathological somatoform dissociation (SDQ-20), alexithymia (TAS-20), anxiety (HAMA), and depression (BDI-II).

3.2. Neuroimaging univariate approach

Patients with PNES exhibited significant morphological abnormalities only in cerebral cortical areas, including the bilateral pars triangularis and the right pars opercularis of the inferior frontal cortex (IFC), the medial and the lateral regions of the orbitofrontal cortex (OFC), the caudal middle (intermediate) region of the frontal cortex, the right precentral gyrus, the left posterior cingulate, and the left insula (Table 2). No significant changes were detected in subcortical regions.

3.3. Neuroimaging multivariate approach

Random forest classifier, trained on all the features, showed a mean OOB error of 51.3% (mean accuracy = 48.7%), calculated on all the 10,000 test sets. After feature selection, the classifier was trained on the most important morphological metrics, for a total of 12 (mean decrease in Gini ≥ 0.24), showing a mean OOB error of 25.5% (mean accuracy = 74.5%) (first two columns of Table 3). The true positive rate on training set without feature selection was of 52%, while with only the most predictive variables, we reached 75% of accuracy.

The analysis of the variable importance (Fig. 1A) showed that anatomical metrics influencing the classification of PNES with respect to HC mainly included the right pars triangularis area, left posterior cingulate thickness, and right medial orbitofrontal area. Additional significant morphological features, useful for PNES discrimination, were detected in the left caudal middle frontal area, right lateral orbitofrontal area, left transverse temporal thickness, right parahippocampal area, left pars triangularis area, right pars opercularis, right transverse temporal thickness, left putamen, and right precentral area (Fig. 1B). The same results were obtained including nuisance variables (such as age, gender, and scanner) as main factor in multivariate analysis, demonstrating that the influence of demographical features on classification performance was negligible.

4. Discussion

The pathophysiological mechanisms underlying PNES are still a matter of debate. In the last few years, several review and meta-analytic studies have tried to summarize the large amount of evidence generated from behavioral and neuroimaging realms, providing different key lectures. In spite of a number of important pathological features having been reported that highlight neurobiological differences in the PNES brain, their subsequent translation into clinical practice has not happened. The implementation of multivariate automatic classification approaches might represent an essential step towards improving clinical diagnosis. Our multivariate approach allows reaching optimal accuracy for individual discrimination between patients with PNES and controls, detecting neural changes in widespread neural systems and highlighting the involvement of the limbic and motor inhibition pathways.

Clinical histories of patients with PNES feature differences in behavioral seizure manifestations, life experiences, personal histories of trauma, and overall high levels of psychiatric comorbidity. All these factors contribute to the widely heterogeneous nature of this yet medically unexplained neurological disorder, where cognitive-behavioral therapy

Table 2
Significant results of ANCOVA on morphological features comparing patients with PNES and HC.

Morphological features	HC	Patients with PNES	p-Value	Effect size (Cohen's *d*)
Left pars triangularis surface (mm^2)	1341.1 ± 190.1	1190.1 ± 192.6	.012	0.79
Right pars triangularis surface (mm^2)	1493.7 ± 149.1	1322.8 ± 178	.001	1.04
Right medial orbitofrontal surface (mm^2)	1772 ± 203.2	1597.8 ± 161.9	.003	0.95
Left caudal middle frontal surface (mm^2)	2281.5 ± 296	2027.1 ± 357.6	.014	0.77
Left lateral orbitofrontal surface (mm^2)	2496.9 ± 308.8	2291.4 ± 320	.036	0.65
Left posterior cingulate thickness (mm)	2.6 ± 0.1	2.7 ± 0.2	.012	0.77
Left insula surface (mm^2)	2054.1 ± 216	1888.2 ± 259.5	.027	0.70
Right pars opercularis surface (mm^2)	1403.8 ± 188.6	1251.5 ± 239.2	.025	0.71
Right precentral surface (mm^2)	4611.1 ± 431.1	4315.2 ± 414.9	.025	0.70

Data are given as mean ± SD.

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Table 3
Performance of RF classifiers, trained on all FreeSurfer features (without feature selection) and on the most important variables (with feature selection, mean decrease in Gini ≥ 0.24). The confusion matrix of the classification of one-random training set is shown in the last two columns (right side). Abbreviations: RF = random forest. OOB = out-of-bag.

RF Classifier	OOB error	Accuracy	Confusion matrix [Random training set]
without feature selection	mean = 51.3% (min=36.4, max=56.8)	mean = 48.7% (min=63.6, max=43.2)	

	Reference		True positive rate
Prediction	**PNES**	**CTRL**	52.3%
PNES	11	12	
CTRL	9	12	

RF Classifier	OOB error	Accuracy	Confusion matrix [Random training set]
with feature selection	mean = 25.5% (min=25.0, max=50.0)	mean = 74.5% (min=75.0, max=50.0)	

	Reference		True positive rate
Prediction	**PNES**	**CTRL**	75.0%
PNES	18	5	
CTRL	6	15	

is the most effective treatment useful for reducing seizure frequency [38]. Most importantly, clinical manifestations in these patients are frequently mistaken as epileptic seizures and treated with multiple drugs, which considerably delays a proper treatment [5]. For this reason, identifying reliable biomarkers of this disorder is highly needed. In the last two decades, researchers have investigated the neurobiological correlates of PNES using different advanced neuroimaging methods [9]. Overall, largely contradictory findings have been reported, mainly concerning structural MRI data. Morphological studies of the gray matter pointed to neural losses in widespread brain regions involving the motor, premotor [6], and limbic systems [39]. Structural connectivity studies have provided proof-of-concepts that nonepileptic seizures characterizing PNES semiology may be associated with damages of fibers connecting the limbic system with prefrontal areas [40,41]. This first evidence, however, was limited by the lack of significant association with clinical data. As suggested by some authors [42], given high rates of psychiatric comorbidity in PNES, it is impossible to infer if the above structural brain abnormalities are specifically associated with seizure attacks or coexisting psychopathologies (such as anxiety, depression, or dissociative disorders). Functional MRI studies have helped in clarifying the pathophysiological mechanisms underlying nonepileptic seizures. Some researchers have reported that connectivity strength in resting-state networks (underlying executive control, sensory-motor, and default-mode) was positively correlated with dissociation scores [43–45]. Similar clinical-imaging relationships were described in a study [46], in which altered communication in patients with PNES were observed between regions involved in emotional elaboration (insula) and motor planning (precentral sulcus), as a function of dissociation scores.

Our results confirm the considerable evidence already gathered suggesting that regions belonging to the primary motor system (putamen; the precentral cortex), motor control (IFC), and limbic network (insula, cingulate cortex, and OFC) are involved in pathophysiological mechanisms of PNES. However, the ML approach allowed us to narrow down our interest on those areas primary involved in clinical expression of PNES. Indeed, an intriguing novelty of our contribution is the use of an

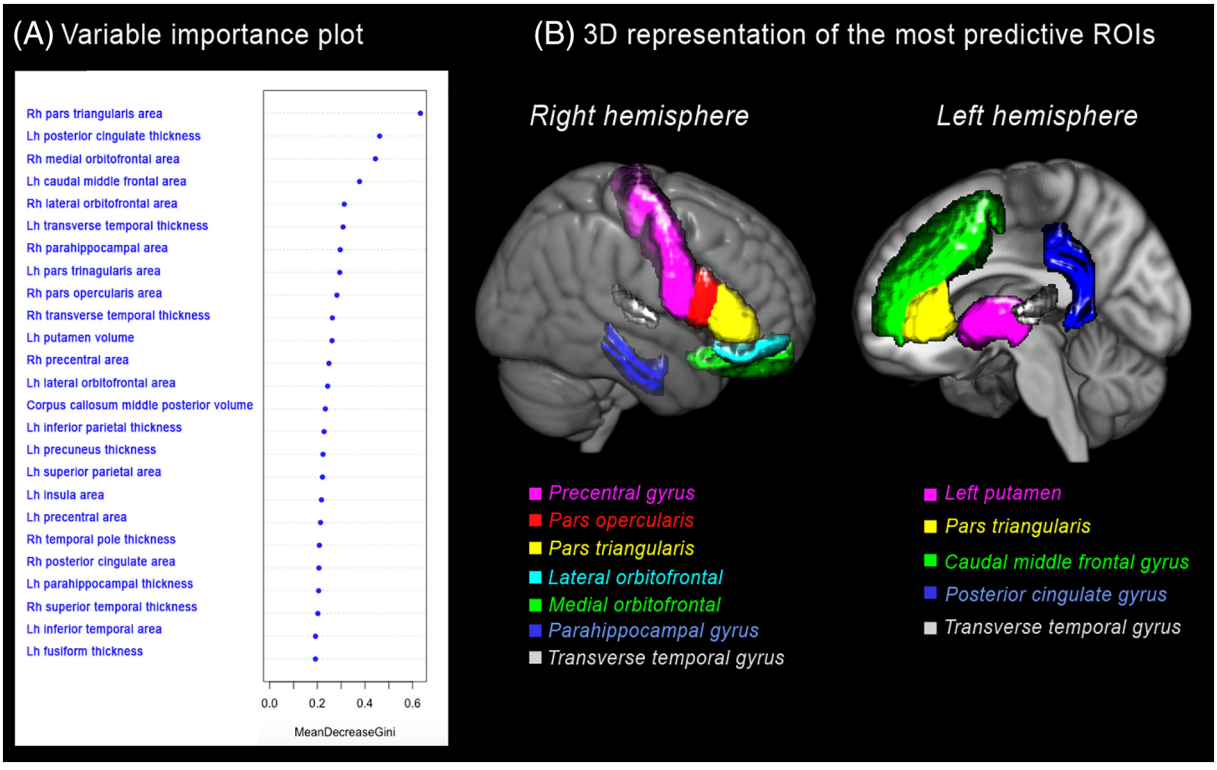

Fig. 1. Machine-learning results and variable importance analysis. (A) Variable importance plot, according to the Gini impurity criterion index; (B) 3D rendering of the most predictive morphological features extracted by FreeSurfer for individual classification between patients with PNES and controls.

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artificial intelligence technique to evaluate the selective influence of anatomical abnormalities on PNES diagnosis by a multivariate statistical approach, with around 75% accuracy. In particular, the advantage of ML application to neuroimaging data is dual: firstly, it allows characterization at the single subject level and is potentially useful for translation to clinical practice; and secondly, being intrinsically multivariate, it is sensitive both to widely distributed and subtle brain effects, which would not be detectable using traditional univariate methods focusing on macroscopic group-wide differences. Therefore, in this context, ML techniques offer the possibility to assess the clinical usefulness of MRI features for diagnostic purposes in clinical practice.

Analysis of the variable importance (the Gini index) highlighted IFC involvement, the posterior cingulate cortex, and medial OFC as more reliable markers to distinguish patients with PNES from controls at the individual level. The IFC is the main brain region involved in the motor control ability [47]. Lesions within this region have been reported in compulsive–impulsive disorders, Tourette syndrome, and Parkinson's disease with levodopa-induced dyskinesias [29]. The posterior cingulate cortex is one of the three brain regions participating in the default mode network, mainly involved in the regulation processes associated with self-awareness/consciousness of one-self [48,49]. Patients with PNES exhibit increased functional connectivity [46] and reduced cortical thickness [39] within this region. Finally, abnormality of the OFC is one of the most consistent findings commonly described by neuroimaging studies [3,39,45]. Increased functional connectivity [45], thinning [6], as well as reduced cortical depth [39] within the OFC have all been described. The most prominent hypothesis about pathophysiological mechanisms underlying PNES symptomatology supports the view of the "dissociative experiences" [39,50], caused by altered communication between brain regions involved in emotion regulation (cingulate cortex, OFC) and frontal regions involved in inhibitory control (IFC). This abnormal mechanism could lead to disruption in information processing and aberrant sensorimotor interactions beyond the conscious control of the individual, resulting in nonepileptic, seizure-like episodes [46,51,52]. These findings have potential implications for treatment, particularly psychological therapies that may be more effective than medication and particularly cognitive-behavior therapy, which proved to be the most effective in reducing seizure frequency in patients with PNES [5,38].

Some possible limitations of our data need to be addressed. The number of subjects in this study was relatively small for ML approach, but the RF algorithm is known to be robust to overfitting and very stable with small sample size and high-dimensional parameter spaces [34]. Although the accuracy we reached is lower with respect to ML application to other neurological disorders such as mild cognitive impairment [32], Alzheimer's disease [13], Parkinson's disease [11,14], and schizophrenia [53], in view of the heterogeneity of PNES, our first attempt on using ML is very promising. Another limitation could be the lack of additional pathological groups matching similar psychopathological or neurological pictures revealed in patients with PNES. The application of ML approach to distinguish patients with PNES from patients with major depression or from patients with epilepsy would be a critical advantage for translating this method in clinical practice. Finally, as for previous neuroimaging studies, we cannot infer causal relationship between neurobiological signs and PNES symptoms. Additional longitudinal and multicentric studies will be useful to monitor the progressive involvement of the limbic and frontal circuits in this pathology and to reconcile neuroimaging findings with clinical phenotypes.

Author contributions

Dr. Vasta took part in the analyses and interpretation of the data, statistical analysis, drafting/revising the manuscript, and the final approval of the version to be published. Dr. Cerasa took part in the data collection and interpretation, drafting/revising the manuscript, and the final approval of the version to be published. Dr. Sarica took part in the data collection, analysis, and interpretation; drafting/revising the manuscript; and the final approval of the version to be published. Dr. Bartolini took part in the data collection, analysis, and interpretation; drafting/revising the manuscript; and the final approval of the version to be published. Dr. Martino took part in the acquisition and analysis of data and the final approval of the version to be published. Prof Quattrone took part in the revision of the manuscript and final approval of the version to be published. Prof Gambardella took part in drafting/revising the manuscript and the final approval of the version to be published. Prof Guerrini took part in the study concept and design; acquisition, analysis, and interpretation of the data; drafting/revising the manuscript for important intellectual content; and the final approval of the version to be published. Prof Labate took part in the study concept and design; acquisition, analysis, and interpretation of the data; drafting/revising the manuscript for important intellectual content; and the final approval of the version to be published.

Declaration of interests

All authors report no disclosures.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Appendix A. Supplementary material

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