



Psychogenic non-epileptic seizures, recent advances and commentary on, Vasta *et al.*, the application of artificial intelligence to understand the biological bases of the disorder

Nash N. Boutros

The Saint Luke's Marion Bloch Neuroscience Institute, University of Missouri-Kansas City, Kansas City, USA

Correspondence to: Nash N. Boutros. The Saint Luke's Marion Bloch Neuroscience Institute, University of Missouri-Kansas City, 4225 Baltimore Avenue, Kansas City, Missouri 64111, USA. Email: boutrosn@umkc.edu.

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As many as 33 per 100,000 people experience episodes of paroxysmal impairment associated with a range of manifestations that can be motor, sensory, and/or mental and closely mimic and frequently mistaken for epileptic seizures (1). These episodes are termed psychogenic non-epileptic seizures (PNES). The prevalence of PNES episodes is much higher in epilepsy practices, reaching as high as 30% (2). The diagnosis of PNES remains a process of excluding epilepsy and thus leads to an average time from onset of these paroxysms to diagnosis of close to seven years. As there are no current biomarkers for the disorder itself (PNES), this delay is inevitable as the diagnosis of PNES is limited to the negative process of ruling out epilepsy (i.e., characterized as a non-disease (not epilepsy) (3). This is further complicated by the fact that the two disorders (PNES and epilepsy) may co-exist in about 10% of epileptic patients (3). The next major advance in caring for individuals with PNES will be the identification of one or more biomarkers that would positively point towards the diagnosis. As the disorder is highly likely to be heterogeneous with subgroups of varying neuro-psychopathologies, biomarkers that would point to one of the subgroups (4) would go a long way towards the development of more targeted and hopefully more effective treatments. Eliminating or significantly reducing the stigma associated with the diagnosis would also be a great benefit not only to the patients, but also their families and caregivers. As anger and resistance tend to frequently be experienced by the patient when informed about the diagnosis, the presence

of a biomarker indicative of an organic basis for the disorder would also be good to help enlist the patient's confidence and cooperation with treatment. In fact anger is one of the significant factors, along with depression, that correlate with a lowered quality of life in PNES patients (5).

The above alluded to heterogeneity of PNES is not surprising as almost all psychiatric disorders tend to be heterogeneous with significant variabilities in both clinical features and treatment responses. The following are possible subgroups within the PNES populations: (I) combined epileptic and PNES; (II) PNES with clear secondary gain; (III) PNES without secondary gain but with neuropsychological deficits; and (IV) PNES without secondary gain nor neuropsychological deficits. Each category could be positive or negative for history of childhood abuse thus making for eight potential subgroups with diagnostic, therapeutic and prognostic implications.

We have recently provided pilot data suggesting that a biomarker can be found for some of the PNES patients (6). In a small sample of PNES patients (with no evidence of comorbid epilepsy), the resting-state magnetoencephalography (MEG recording while resting and without any imposed cognitive tasks) was examined for evidence of increased focal coherence in the frontal temporal cortical regions which can be interpreted as evidence for focal hyper-excitability in these structures. PNES patients were contrasted to age and gender (matched as a group) healthy control (HC) subjects. The data suggested decreased posterior-occipital alpha power while increased power in frontotemporal delta/

theta in people with PNES compared to HC subjects. Furthermore, mean interregional functional connectivity tended to be reduced in extra-frontotemporal but increased in frontotemporal regions in patients with PNES compared to HC. In the same report the authors indicate that all PNES patients had their highest coherence structure within the frontotemporal limbic structures whereas the majority of HC subjects had their highest coherence value structure in the extra-frontotemporal regions. The difference did reach statistical significance despite the small sample size. Perhaps most interestingly are the significant increases in coherences detected in basal ganglia regions (Left Caudate and Putamen). Both left and right Cuneus areas also exhibited increased focal coherence in the PNES patients. The Cuneus is at the frontal end of the cingulate gyrus. The anterior cingulate is one major conflict resolution center.

The recent paper by Vasta and colleagues [2018] (7) represents a major step forward positively identifying (and not just aiming at ruling out epilepsy) at least one of the subgroups of this difficult to treat population. The authors underscore the fact that despite the reported neural abnormalities in PNES patients, no consistent neurobiological substrate that would be useful diagnostically has been identified. The Vasta *et al.* (7) study is unique because although it was a cross-sectional study it was a relatively large multicenter project (23 PNES and 21 demographically matched HCs). It should be noted that secondary to the expensive work up necessary to be confident about ruling out epilepsy, larger size samples could be cost prohibitive. Due to the massive data collected (150 morphological brain metrics) the investigators applied a multivariate classification algorithm on the morphological brain imaging metrics to extract reliable biomarkers useful to distinguish patients from controls at an individual level. To our knowledge, this is the first serious effort at developing a diagnostic marker for PNES. All subjects underwent extensive neuropsychiatric, neuropsychological and neuroimaging assessments. One hundred and fifty morphological brain metrics were used for training a random forest (RF) machine-learning (ML) algorithm. Univariate neuroimaging analysis revealed widespread neuroanatomical changes affecting individuals with PNES. ML 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)].

These findings are in a significant agreement with Boutros *et al.* (6) and thus support the need for further, and perhaps larger, investigations. Furthermore, a typical complex psychopathological construct was observed in PNES. The Vasta *et al.* (7) study thus 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. The above two studies combined would suggest that additional electrophysiological data like from high-density electroencephalography or MEG added to morphological data may further refine the biomarker profile of this group of patients.

A Two-Factor Model (OFC dysfunction + Stress) was proposed by Pillai *et al.* (8). An underlying frontal lobe dysfunction in PNES has been repeatedly postulated and Changes in the frontostriatal circuits have also been postulated. Impaired emotional and self-monitoring functions have been well-described in OFC dysfunctions. OFC dysfunction can lead to inability to integrate positive and negative emotions leading to dissociation. Thus, loss of the inhibitory and integrative functions of OFC could facilitate the emergence of “Dissociation”. The paroxysms experienced by patients with PNES can thus be seen as “episodes” resulting from an unstable/hyper-excitable cognitive-emotional attention system and implicating a super-sensitive limbic-frontal circuitry (9). Autonomous prewired behavioral tendencies, including cognitive and sensorimotor aspects are not properly integrated during the episodes, allowing the emergence of PNES attacks (10).

A three factor model incorporating the frontal-striatal circuits to explain the manifestation of dissociation in a motor fashion like in PNES can be postulated. Based on literature and preliminary data abnormal frontostriatal circuitry may be necessary for the dissociation to manifest in a motoric activity like in PNES.

Conclusions: available data, including the recent findings from Vasta *et al.*, support the need for further investigations of the pathophysiology of PNES and suggest that biomarkers for the disorder are likely to be identified. The identification of a biomarker for PNES would not only provide for more informed therapeutic approaches, but it could also eliminate the stigma and resentment associated with the diagnosis of PNES.

Given the postulated heterogeneity (potentially up to eight subtypes) future studies should either be selective regarding these subgroups or aim at having large enough sample sizes and utilize multimodal neuroimaging

techniques (possibly including EEG, MEG, MRI, and functional MRI) which will then necessitate the utilization of high computing power and machine learning to be able to detect the more than likely subtle differences between the groups. Finally, it is also possible that yet un-described neural systems or circuitries could be contributing to the emergence of medically unexplained symptoms including PNES (11). Careful attention to collected data would facilitate the identification of such systems.

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