



# Clinical Correlation Advised: Measuring Functional Connectivity in PNES

Epilepsy Currents

2021, Vol. 21(1) 30-32

© The Author(s) 2020

Article reuse guidelines:

sagepub.com/journals-permissions

DOI: 10.1177/1535759720975436

journals.sagepub.com/home/epi



## Activation of Functional Brain Networks in Children With Psychogenic Non-Epileptic Seizures

Radmanesh M, Jalili M, Kozłowska K. *Front Hum Neurosci*. 2020. doi:10.3389/fnhum.2020.00339.

**Objectives:** Psychogenic nonepileptic seizures (PNES) have been hypothesized to emerge in the context of neural networks instability. To explore this hypothesis in children, we applied a graph theory approach to examine connectivity in neural networks in the resting-state electroencephalogram in 35 children with PNES, 31 children with other functional neurological symptoms (but no PNES), and 75 healthy controls. **Methods:** The networks were extracted from Laplacian-transformed time series by a coherence connectivity estimation method. **Results:** Children with PNES (vs controls) showed widespread changes in network metrics: increased global efficiency ( $\alpha$  and  $\beta$  bands), increased local efficiency ( $\gamma$  band), and increased modularity ( $\gamma$  and  $\alpha$  bands). Compared to controls, they also had higher levels of autonomic arousal (eg, lower heart variability); more anxiety, depression, and stress on the Depression Anxiety and Stress Scales; and more adverse childhood experiences on the Early Life Stress Questionnaire. Increases in network metrics correlated with arousal. Children with other functional neurological symptoms (but no PNES) showed scattered and less pronounced changes in network metrics. **Conclusion:** The results indicate that children with PNES present with increased activation of neural networks coupled with increased physiological arousal. Although this shift in functional organization may confer a short-term adaptive advantage—one that facilitates neural communication and the child's capacity to respond self-protectively in the face of stressful life events—it may also have a significant biological cost. It may predispose the child's neural networks to periods of instability—presenting clinically as PNES—when the neural networks are faced with perturbations in energy flow or with additional demands.

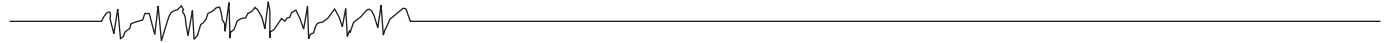
## Commentary

Nearly a third of people with epilepsy have seizures that are refractory to medical management. Physicians and researchers working in the field of epilepsy have dedicated their entire careers to improve this statistic through advances in epilepsy surgery, developments of new therapeutics and cutting edge diagnostics, and better understanding of the long-term consequences of uncontrolled seizures. The ultimate goal is to improve the care and quality of our patients' lives but also to answer several "whys"—why does epilepsy occur, why are some patients refractory to therapy, why do comorbidities arise? Unfortunately, the level of curiosity and research efforts is not equal across all seizure types.

Psychogenic nonepileptic seizures (PNES) are an example of a disorder that has not attracted sufficient attention from the scientific community. Psychogenic nonepileptic seizures are paroxysmal events that involve changes in consciousness, tone, or motor activity and that occur in the absence of epileptiform abnormality on electroencephalography. Psychogenic nonepileptic seizures have incidence rates between 4 and 7.4/100 000, varying by age-group and geographic location, among other

variables.<sup>1,2</sup> Although this may pale in comparison to the annual cumulative incidence of epilepsy at 68/100 000,<sup>3</sup> PNES are likely vastly underdiagnosed; they have a mortality ratio 2.5 times the general population, comparable to drug resistant epilepsy, and nearly 70% of patients with PNES continue to have seizures despite therapy.<sup>4,5</sup> Thus, while the incidence of PNES may be lower than epilepsy, the adverse impact is not. To date, we have failed to understand this condition adequately enough to improve treatment and outcomes, but why? The diagnosis and management of PNES has occupied a wasteland between the fields of psychiatry and neurology for centuries. For neurologists, the diagnosis lacks a signature biomarker; thus, we excel at describing what PNES is not on electroencephalogram (EEG) and less what it is. For psychiatrists, PNES does not fit nicely within boundaries created by criteria in the *Diagnostic and Statistical Manual of Mental Disorders*. That uncertainty leaves the diagnosis and best treatment plans in doubt. Two things are apparent. First, psychiatrists and neurologists will need to collaborate to improve the diagnosis and management of PNES and our patients will be better because of that collaboration. Second, we must understand why PNES occur to





provide widespread legitimacy to the condition and a target for diagnosis and management.

It has been hypothesized that PNES emerge from temporal disruption in brain neural networks, thereby compromising the horizontal and vertical integration of brain function and causing a disconnect between cortical and subcortical systems.<sup>6</sup> The question is whether such a disruption in the neural network can be measured by available clinical tools. Developing sensitive and specific biomarkers for the diagnosis of PNES, monitoring of treatment, and learning more about the underlying pathophysiological mechanisms are essential for understanding this condition. In the past four decades, numerous structural and functional neuroimaging studies have provided an incredible amount of knowledge about the role and function of each human brain region (segregation). More recently, the concept of functional connectivity among segregated brain regions was introduced (integration). Functional connectivity is defined as the temporal coincidence of spatially distant neurophysiological events.<sup>7</sup> As such, two brain regions are considered to show functional connectivity if there is a statistical relationship between measures of brain activity recorded for them. The notion behind this connectivity approach is that areas are presumed to be coupled or are components of the same network if their functional behavior is consistently correlated with each other.

The pathophysiological mechanisms of epileptic seizure generation involve both abnormal brain structures and aberrant connections between these regions, resulting in large-scale network instability.<sup>8</sup> Aberrant network activity in the epileptic brain may also contribute to devastating cognitive and neuropsychological sequelae frequently suffered in this disorder. The question remains whether aberrant connections are a sequela of epilepsy, thus causing these neuropsychological comorbidities, or whether inherent abnormal connectivity is the source of both. Regardless, abnormal functional connectivity is increasingly cited as a potential biomarker in both instances.

A growing body of neuroimaging literature utilizing functional connectivity has focused on PNES, aiming to identify biomarkers for diagnosis, treatment response, and prognosis.<sup>9</sup> The common finding among these studies is altered functional connectivity within various parts of the networks that may be involved in PNES generation and maintenance. These network regions include executive control, frontoparietal, sensorimotor, and default mode networks shown to be significantly associated with dissociative symptomatology. Taken together, these previous studies suggest that neural networks of patients with PNES (when compared with those of healthy controls) may be less resilient in the face of additional demands and more prone to temporary states of disorder or aberrant changes in functional connectivity—resulting in PNES.

In their recent resting-state EEG study, Radmanesh and colleagues<sup>10</sup> used graph theory to examine neural network function in children with PNES, children with other functional neurological symptoms (but no PNES), and healthy controls. Graph theory is a relatively new tool that has been widely applied to characterize human brain network architecture.


It provides quantitative measurements for each node to depict integrated nature of local brain activity and to describe the global properties of brain networks. Radmanesh and colleagues<sup>10</sup> found that children with PNES showed widespread changes in network metrics compared to controls: increased global efficiency, local efficiency, and modularity in several frequency bands (ie, alpha, beta, and gamma). Moreover, they found that children with other functional neurological symptoms (but no PNES) showed scattered and less pronounced changes in network metrics. Radmanesh and colleagues<sup>10</sup> also observed that increases in some of the functional network metrics were correlated with increased arousal in children with PNES.

These findings pave the path for the development of a signature biomarker that captures PNES-related EEG changes which are invisible to the naked eye of the EEG reader but require the use of advanced signal processing tools to be estimated. Such a biomarker would be able to diagnose PNES and monitor treatment based on a relatively inexpensive diagnostic tool that is available in every epilepsy center; it may also be sensitive enough to discriminate different types of functional neurological disorders. The presented findings advance our understanding about the underlying pathophysiological mechanisms of PNES by its conceptualization as a stress system disorder. More importantly, they highlight the need for arousal decreasing interventions on multiple system levels that will likely help the child's neural network shift back to physiological equilibrium.

Like many of the functional neurological disorders, PNES is undergoing a renaissance of clinical interest, particularly among neurologists. Essential to any advancements in care, a reliable measurement must be developed to aid diagnosis, guide therapy, and answer the “whys.” Although we are far from defining the EEG pattern of PNES, exploration of functional connectivity with methods such as graph theory represents a positive step forward for a group of patients whose sojourn across the diagnostic wasteland has gone on too long.

M. Scott Perry  and Christos Papadelis

## ORCID iD

M. Scott Perry  <https://orcid.org/0000-0002-1825-846X>

## References

1. Hansen AS, Rask CU, Rodrigo-Domingo M, Pristed SG, Christensen J, Nielsen RE. Incidence rates and characteristics of pediatric psychogenic nonepileptic seizures. *Pediatr Res*. 2020;88(5):796-803.
2. Szaflarsk JP, Ficker DM, Cahill WT, Privitera MD. Four-year incidence of psychogenic nonepileptic seizures in adults in Hamilton County, OH. *Neurology*. 2000;55(10):1561-1563.
3. Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy. *Neurology*. 2017;88(3):296-303.



4. Nightscales R, McCartney L, Auvrez C, et al. Mortality in patients with psychogenic nonepileptic seizures. *Neurology*. 2020;95(6): e643-e652.
5. Reuber M, Pukrop R, Bauer J, Helmstaedter C, Tessedorf N, Elger CE. Outcome in psychogenic nonepileptic seizures: 1 to 10-year followup in 164 patients. *Ann Neurol*. 2003;53(3):305-311.
6. Knyazeva MG, Jalili M, Frackowiak RS, Rossetti AO. Psychogenic seizures and frontal disconnection: EEG synchronisation study. *J Neurol Neurosurg Psychiatry*. 2011;82(5):505-511.
7. Friston KJ. Functional and effective connectivity: a review. *Brain Connect*. 2011;1(1):13-36.
8. Jiruska P, de Curtis M, Jefferys JG, Schevon CA, Schiff SJ, Schindler K. Synchronization and desynchronization in epilepsy: controversies and hypotheses. *J Physiol*. 2013;591(4): 787-797.
9. Szaflarski JP, LaFrance WC Jr. Psychogenic nonepileptic seizures (PNES) as a network disorder—evidence from neuroimaging of functional (Psychogenic) neurological disorders. *Epilepsy Curr*. 2018;18(4):211-216.
10. Radmanesh M, Jalili M, Kozłowska K. Activation of functional brain networks in children with psychogenic non-epileptic seizures. *Front Hum Neurosci*. 2020. doi:10.3389/fnhum.2020.00339