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Differentiating epilepsy from psychogenic nonepileptic seizures using neuropsychological test data

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ABSTRACT

Objective: Differentiating epileptic seizures (ES) from psychogenic nonepileptic seizures (PNES) represents a challenging differential diagnosis with important treatment implications. This study was designed to explore the utility of neuropsychological test scores in differentiating ES from PNES.
Method: Psychometric data from 72 patients with ES and 33 patients with PNES were compared on various tests of cognitive ability and performance validity. Individual measures that best discriminated the diagnoses were then entered as predictors in a logistic regression equation with group membership (ES vs. PNES) as the criterion.
Results: On most tests of cognitive ability, the PNES sample outperformed the ES sample (medium–large effect) and was less likely to fail the Reliable Digit Span. However, patients with PNES failed two embedded validity indicators at significantly higher rates (risk ratios (RR): 2.45–4.16). There were no group differences on the Test of Memory Malingering (TOMM). A logistic regression equation based on seven neuropsychological tests correctly classified 85.1% of patients. The cutoff with perfect specificity was associated with 0.47 sensitivity.
Conclusions: Consistent with previous research, the utility of psychometric methods of differential diagnosis is limited by the complex neurocognitive profiles associated with ES and PNES. Although individual measures might help differentiate ES from PNES, multivariate assessment models have superior discriminant power. The strongest psychometric evidence for PNES appears to be a consistent lack of impairment on tests sensitive to diffuse neurocognitive deficits such as processing speed, working memory, and verbal fluency. While video-electroencephalogram (EEG) monitoring is the gold standard of differential diagnosis, psychometric testing has the potential to enhance clinical decision-making, particularly in complex or unclear cases such as patients with nondiagnostic video-EEGs. Adopting a standardized, fixed neuropsychological battery at epilepsy centers would advance research on the differential diagnostic power of psychometric testing.

1. Introduction

Psychogenic nonepileptic seizures (PNES) are episodes of altered sensory and/or motor functioning that resemble epileptic seizures (ES) but are not due to epileptiform discharges. Instead, they are thought to be elicited by psychological factors. The history of PNES dates as far back as the first descriptions of epilepsy and are termed conversion disorder (functional neurological symptom disorder) with attacks or seizures in the newest iteration of the *Diagnostic and Statistical Manual of Mental Disorders* [1]. Patients with PNES commonly have comorbid psychiatric conditions such as depression, anxiety, panic attacks, posttraumatic stress, dissociation and/or personality disorders [2]. The precise prevalence of the disorder is unknown, though the incidence of individual persistent conversion symptoms is estimated to be 2–5/100,000 per year [1]. Among patients referred to tertiary epilepsy centers, approximately 25–30% are diagnosed as having PNES [3], although the lower limit of some estimates ranges from 10% to 15% [4,5]. The onset of PNES can occur throughout the life course but peaks in the third decade of life [6]. Psychogenic nonepileptic seizures are two to three times more common in women [1].

Differentiating patients with ES from those with PNES represents a challenging differential diagnosis with important treatment implications. Further complicating matters, PNES may coexist with other neurologic disorders, and approximately 10% of patients with PNES also have ES [1,7–9]. These confounding factors may explain why it takes an average of seven to eight years for an accurate diagnosis of PNES [10]. During this delay in diagnosis, patients are often treated with antiepileptic drugs (AEDs), many of which have negative side effects [7,9,10]. While video-

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EEG monitoring is the gold standard of differential diagnosis, psychometric testing has the potential to enhance clinical decision-making. All aspects of the neuropsychological assessment can offer important clues to differential diagnosis in an astute examiner, including aspects of clinical history-taking, behavioral observations of seizure semiology (should seizures occur during the examination), and self-reported symptoms on structured psychological inventories [11–17]. However, research on the diagnostic power of neuropsychological tests of cognitive ability and performance validity has historically produced inconsistent results.

Dodrill succinctly summarized the literature investigating cognitive differences between ES and PNES into a few key points [18]. First, the majority of published studies show no significant differences between patients with ES and PNES on tests of cognitive functioning. Second, when differences are found, patients with PNES outperform those with ES. However, these differences are typically small and not specific to a given test or even cognitive domain, greatly limiting their diagnostic utility. Finally, both ES and PNES are often associated with some degree of cognitive impairment and demonstrate lower neuropsychological performances than healthy controls.

A plausible explanation for this pattern of findings in PNES is *psychogenic interference* — a hypothesized mechanism through which fleeting psychiatric symptoms (anxiety, emotional distress, dissociative episodes, a cognitive version of somatization) disrupt performance during cognitive testing, resulting in scores that underestimate true ability levels [19–22]. The vast majority of patients with PNES have a history of complex psychological trauma [23], and the base rate of sexual abuse was found to be significantly higher among patients with PNES as compared with patients with ES [24]. Symptoms of unresolved traumatic experiences (intrusive thoughts, emotional numbing, and dissociation) in turn may disrupt examinees' ability to demonstrate their best (or even typical) performance on tests of attention, processing speed, and memory [25].

The psychogenic interference hypothesis would also predict increased vulnerability to failing performance validity tests (PVTs) [26–28]. Performance validity tests are objective measures of the credibility of a given response set, that is, the extent to which the neurocognitive data are likely to reflect the examinee's true ability level. They can be free-standing instruments specifically designed to measure performance validity or embedded validity indicators within existing tests of cognitive ability that were later co-opted as PVTs. Since establishing the credibility of psychometric data is a prerequisite for clinical interpretation, PVTs are instrumental in evaluating cognitive functioning. This realization has been formally recognized in consensus statements by professional organizations within clinical neuropsychology, emphasizing the administration of several PVTs as an essential component of a comprehensive neurocognitive assessment [29,30].

Empirical investigations of the specificity of PVT failures to psychogenic interference (and hence, their potential contribution to the differential diagnosis of ES and PNES) remain inconclusive. Kemp et al. [31] reported a relatively low base rate of invalid neuropsychological profiles (11%) among 45 patients with medically unexplained symptoms referred to an outpatient neurology clinic, in line with broad-based prevalence estimates of noncredible responding [32]. In contrast, participants in the experimental malingering condition produced very high failure rates (94%–100%), serving as a reminder that psychogenic interference and medically unexplained symptoms are not always associated with a marked increase in PVT failure rates. The research evidence is comparably equivocal within populations with ES and PNES. Several studies report that a large portion of patients with PNES produce invalid profiles during neuropsychological evaluations [27,33–36] while other well-designed studies challenge these findings [20,37,38]. To further complicate matters, some investigators have found elevated rates of PVT failure in patients with ES [39–42].

In sum, the existing evidence suggests that, despite sporadic reports of between-group differences, ES and PNES cannot be reliably distinguished on neuropsychological testing. A notable limitation of previous research is that test scores were typically used in isolation, even though neuropsychologists interpret the pattern of performance across several tests to draw conclusions about an examinee's overall cognitive functioning [43]. As such, previous studies may have inadvertently underestimated the cumulative discriminant power of neuropsychological tests by relying on univariate contrasts. The current study was designed to investigate the hypothesis that a multivariate approach would improve diagnostic accuracy.

Given the cumulative evidence in performance validity research that combining multiple indicators improves overall classification accuracy [26,44–46], we expected the effect to replicate when applied to a different signal detection challenge (i.e., ES vs. PNES). We predict that a multivariate assessment model using test scores that provide nonredundant information would augment its discriminant power over individual measures [47–49].

2. Materials and methods

2.1. Participants

Data were collected through retrospective clinical chart reviews at an academic medical center in the Northeastern US on neuropsychological assessments performed between 2001 and 2016. The sample included 72 patients with electroencephalographic evidence of ES and 33 patients with PNES. The two subsamples did not differ on age, gender, education, handedness, or self-reported level of depression (Table 1). Although the specific reason for neuropsychology referral varied on a case-by-case basis (presurgical assessment, investigating subjective cognitive complaints, monitoring medication side effects on cognitive functioning, informing clinical management), the most common purpose was correlating results of biometric and behavioral data obtained by epileptologists (neurological exam, EEG, seizure semiology, neuroradiological findings) with the outcome of psychometric testing. Each patient was individually administered a core battery of widely used neuropsychological tests by a trained master's level psychometrist, predoctoral intern, or postdoctoral fellow under the supervision of a licensed psychologist board-certified in clinical neuropsychology. Testing was performed in an outpatient setting and typically lasted between 4 and 6 h.

In order to be diagnosed as having PNES, patients had to meet several criteria: (1) Evaluated with video-EEG monitoring in an inpatient epilepsy monitoring unit, during which they experienced an event that involved altered motor activity and/or sensory perception typical of their usual episodes while their EEG remained normal; (2) Background EEG remained normal during video-EEG monitoring and/or there was no evidence of EEG abnormalities across repeated examinations; (3) Semiology was judged by the epileptologist to be typical of PNES and atypical of ES. The study was approved by the Institutional Review Boards of Dartmouth-Hitchcock Medical Center and the University of Windsor.

2.2. Materials

Commonly used standardized tests designed to measure intellectual functioning, attention, memory, processing speed, language skills,

Table 1
Results of independent *t*-tests comparing patients with ES and PNES on demographic variables and BDI-II.

	ES		PNES		*p*
	$n = 72$		$n = 33$		
	M	SD	M	SD	
Age	35.7	11.3	39.5	13.0	0.14
Education	12.8	2.0	13.2	2.2	0.30
BDI-II	13.2	10.7	16.9	13.5	0.16
% Male	45.8		45.5		0.97
% Right-handed	85.9		84.8		0.33

Note: ES: epileptic seizures; PNES: psychogenic nonepileptic seizures; BDI-II: Beck Depression Inventory — Second Edition (raw score).