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Psychiatric and Behavioral Comorbidities in Epilepsy: A Critical Reappraisal

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Abstract

Psychiatric and behavioral disorders are important aspects of epilepsy and have received increasing attention in the last several years. The literature upon which most of the field relies contains some biases that must be carefully examined and resolved in future studies: (1) In the pediatric epilepsy literature, many reports find children with epilepsy have high levels of behavioral and psychiatric disorders when compared to appropriate controls. Most of these studies rely on parent-proxy completed instruments to assess these behavioral endpoints. Parents' reports are not objective but reflect parents' reactions and emotions. Increasing evidence suggests inherent biases in proxy reports and highlights the need to assess children directly. (2) Peri-ictal phenomena may be mischaracterized as underlying mood disorders. (3) Many studies report elevated levels of psychiatric morbidity before and after the diagnosis of epilepsy suggesting an inherent relation between the two types of disorders. Psychogenic nonepileptic seizures, while widely recognized as posing a diagnostic dilemma in the clinic, may account for some of these research findings. Diagnostic errors between epilepsy and PNES need careful consideration when evaluating studies demonstrating associations between psychiatric disorders and epilepsy or poorer seizure control in association with psychiatric disorders in people who have epilepsy. Mental health concerns are important for everyone. An accurate, undistorted understanding of the relation between mental health disorders and epilepsy is essential to insure appropriate therapy and avoid unnecessary and potentially harmful treatments and avoid common misconceptions.

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Keywords

Diagnostic errors; mood disorders; proxy-report; psychogenic nonepileptic seizures; bias

The interest in and awareness of various behavioral and psychiatric difficulties in association with epilepsy has waxed and waned over the past 150 years. Gowers (1881) recognized that the cognitive and behavior disorders are common interictally and result from combinations of the underlying disorder, medications, and seizures. In the 1930's, Lennox commented that "*Many persons subject to ordinary grand mal or petit mal seizures also have disturbances in mood or behavior … which may only be a result of difficult circumstances…*".[1] Livingston echoed this 30 year later: "*The most serious hazard of an epileptic disorder is frequently not the seizures, but the associated emotional disturbances which are prone to develop in a youngster as a result of mismanagement by his family, by his classmates and friends and by society.*"[2] Although clinicians such as Gastaut (1955) and Geschwind (1975) recognized biological factors contributing to a diverse set of psychiatric disorders and behavioral changes, the difficulties associated with epilepsy, however were still largely attributed to factors outside the patient.

The Bi-Directional Hypothesis

Beginning around 2000, studies started to raise other explanations. Specifically, investigators began reporting that psychiatric disorders and behavioral problems were already present at or near the time when people were first diagnosed with epilepsy and suggested these disorders predated the onset of seizures.[3–7] Other studies demonstrated higher rates of psychiatric diagnoses both before and after the diagnosis of epilepsy. [8–10] This has been termed the "bi-directional" association between epilepsy and psychiatric comorbidity, [11; 12] and was recently employed in reference to autism spectrum and attention deficit hyperactivity disorders.[13] In all, the repeated findings that psychiatric diagnoses and behavioral problems predated the onset of epilepsy suggested that the psychiatric and behavioral disorders were not simply due to the reactions to epilepsy and its consequences but might, in some patients, actually be related to expression of the same underlying pathophysiology that is involved in the seizures (epilepsy) themselves. Much research has since been devoted to demonstrating this association in different populations. The notion of psychiatric and behavioral disorders as part of the spectrum of the expression of epilepsy has become generally accepted. [12; 14–18]

In theory, a disorder or associated dysregulation that drives a brain to have seizures could also affect other aspects of brain function including behavior and mood.[19] This is because some epilepsies implicate common networks involved in the expression and regulation of mood. For instance, frontal-temporal dysfunction has been implicated in mood and anxiety disorders,[20; 21] including suicide related behavior and post-traumatic stress disorder.[22; 23] It is likely that seizure foci in frontal or temporal regions as well as white matter changes affecting functions in or between those regions could disrupt those pathways. The epilepsies, however, are a diverse set of disorders, and studies should reflect the different specific diseases that are grouped together as epilepsy.

A Critical Look at the Bi-directional Hypothesis

A more nuanced approach to the now-accepted relationship between epilepsy and its psychiatric "comorbidities" is required in light of at least three considerations: (1) the source of information and specifically the reliance on parent-proxy reports when making behavioral assessments, especially in children; (2) the occurrence in some patients of peri-ictal mood and anxiety symptoms which can complicate the assessment of behavioral and psychiatric symptoms and disorders; and (3) the role of psychogenic nonepileptic seizures (PNES) and misdiagnosis of epilepsy in general in muddying the data.

(1) Reliance on proxy-reports

In children, parent-proxy reports are often used to assess behavior and make inferences about psychiatric disorders. [4; 5; 24–26] These studies all tend to demonstrate a greater burden of such disorders or symptoms of these disorders in children with epilepsy compared to sibling, [4; 25] cousin, [6; 26] or other types of controls. [5; 27; 28] Austin et al. used the Child Behavior Checklist (CBCL), a well-known and well-respected instrument for assessing current behavioral problems. Although this instrument is not diagnostic and only reflects recent behavior, it is convenient to use and useful for tracking behavior over time. The CBCL reports total, internalizing, and externalizing problems scores. Internalizing problems are mood disorders (anxiety and depression predominately). Externalizing disorders reflect disruptive behaviors (aggression and rule-breaking behaviors). The study reported that parents rated their case children as having higher levels of internalizing disorders relative to control siblings.[4] Externalizing disorders were not elevated in the cases relative to sibling-controls, however. Almane reported substantial differences between children with epilepsy and cousin controls on every CBCL scale with all findings indicating greater behavioral problems and poorer social competence in the case children.[26] The Dutch group followed a small cohort of children with epilepsy and a group of controls and documented higher (worse) behavioral problem scores in children with epilepsy than in controls. For individual children, however, the scores varied substantially from one time point to another.

Mood Disorders in Children—Assessment of mood disorders in children through parent-proxy report is complicated by many factors. First, mood disorders may aggregate in families. To the extent that they do, children whose parents have mood disorders may be at heightened risk of mood disorders themselves.[29; 30] Being at risk, however, is not the same as having a mood disorder. In an analysis of cross-informant comparisons, proxy reports by depressed mothers of their children's psychopathology were higher than ratings of the same children performed by teachers and therapists who evaluated the children. This phenomenon of maternal depression being associated with worse parent-proxy reports of child behavior, is termed the "depression distortion hypothesis.[31]"

Second, even in the absence of psychopathology, parental reports may be influenced by factors other than the child him or herself. Canadian investigators found that, in children with newly diagnosed epilepsy, parental stress translated into more negative parent-proxy assessment of the child's quality of life.[32] Although this is not the same as behavior, this

study still demonstrates how proxy assessments are contaminated by factors that can systematically distort assessments of subjective outcomes.

Proxy vs. Self-Report—Recently, Eom compared case-control differences in behavior based on parent-proxy and self-report in young people with epilepsy and healthy sibling controls.[33] Similar to other reports that utilized parent-proxy measures, cases (under 18 years) had substantially higher levels of behavioral problems than controls across all parent-reported CBCL scales. When adjustment was made for a measure of parental emotional impact (impact associated with the child him or herself) the case-control differences reported by the parents all but disappeared. Further, when cases and control were compared based on self-reported measures either as older adolescents or as young adults, there was no evidence of greater behavioral burden in the epilepsy versus control group. The study strongly suggested that parental emotional factors seeped into the parental assessment of children's behavior and differentially affected assessments of cases and sibling controls. Parental stress and other factors may explain the substantial differences seen in the impact of epilepsy on children based on child self-report versus parent proxy-report for quality of life[34; 35] and felt stigma. [36]

Related to the above, the child psychiatry literature, in general, reveals considerable differences between child self-report and parent-proxy reports of behavior, [37–43] Critical to interpreting parental reports in children with and without a disorder such as epilepsy are the systematic biases in parental report that have been documented. In general (nonclinical) samples, parents are not especially sensitive to internalizing (mood) symptoms and disorders reported by children themselves,[41] thus reports for "control" children would be expected to under-estimate levels of mood (internalizing) problems. Further, in clinical studies of children with epilepsy, family factors and parent reactions have a large impact on the parents' assessments of their children.[32; 44; 45] This likely leads to higher levels of parent-reported mood and related problems in children with epilepsy. These systematic biases (under-ascertainment in controls and over-ascertainment in cases) may be influencing our understanding of psychiatric-behavioral problems associated with childhood epilepsy.

Child-self report is an important perspective to obtain, yet, in the field of epilepsy, few studies have gathered information directly from children. [6; 28] Two studies in school-aged children used the Kiddie Schedule for Affective Disorders (K-SADS) and found a strong association between epilepsy and mood disorders. In the first instance, a subsequent extension of the study reported only on the parent-proxy assessments of children (based on the CBCL).[26] It is unclear how the children themselves responded or how their responses correlate with their parents' assessments. In the second study, children had incompletely controlled seizures (all had to have one or more seizures in the past year, and over 90% were on therapy), prevalent epilepsy (average duration 4.7 years). Controls were screened for neurologic, psychiatric, hearing, and language disorders and excluded if they had symptoms of these disorders. Thus, the control group was constructed such that children with the disorders of interest were largely excluded. Consequently, neither study provides strong evidence for a higher level than expected of mood disorders in children with epilepsy.

Baldin compared levels of life-time and current mood disorders and history of suicidal ideations and attempts in young adults cases prospectively followed since the onset of epilepsy in childhood-onset and compared their responses to those of their sibling controls as well as to a population-based sample of controls.[46] The self-reported Diagnostic Interview Schedule (DIS) was used for these purposes. No evidence of increased current or life-time psychiatric difficulties was found in cases compared to either control group. The subjects were studied approximately 15 years after the onset of epilepsy, and most were seizure-free and off medication at the time of assessment. If there were a comorbid association between childhood epilepsy and mood disorders, one would expect at very least to see a higher prevalence of life-time disorders, but that was not the case.

In all, these findings indicate that caution must be exercised when drawing conclusions about behavioral and psychiatric problems in children with epilepsy based on parent-proxy reports.

(2) Peri-ictal psychiatric symptoms

Pre-ictal and postictal behavioral changes occur in many patients with temporal lobe and other forms of epilepsy. Affective auras (e.g., anxiety, fear, pleasure) occur in 10–15% of patients with temporal lobe epilepsy;[47] the mechanisms underlying these episodic symptoms remain poorly understood. Pre-ictal changes may result from environmental (eg, sleep deprivation, missed medication, alcohol) or physiological (e.g., premenstrual) factors that increase seizure susceptibility. Alternatively, these behavioral changes could result from neurochemical (e.g., altered neurotransmitter) or neurophysiological changes (e.g., hormonal fluctuations, progressive alteration of seizure threshold, active inhibition, postictal depression or disinhibition). [48] Limited evidence from patients with motor seizures demonstrates cortical excitability changes within the seizure-onset zone during the 24 hours before (increased) and 24 hours after (decreased) a seizure.[49] The implications in terms of impact on the functions subserved by these regions is unclear; however the findings suggest a neurophysiological basis for peri-ictal changes that could affect other regions of the brain involved in seizures.

Before a Seizure—Premonitory symptoms, defined as occurring at least 30 minutes before a seizure, were reported by 29% of patients with focal epilepsy[50] and occur less frequently among patients with generalized epilepsies.[51] The premonitory symptoms were continuous and lasted up to 3 days. The most frequently reported symptoms were irritability, depression, headache, ‘funny feeling’, and confusion. Another study identified insidious onset prodromal symptoms in 39% of patients; behavioral, mood and cognitive changes were most frequent. However, when selected patients with stereotypic prodromal symptoms used a personal digital device to report these symptoms, there was no relation between prodromal symptom and seizure occurrence.[52] This finding emphasizes the limits of self- or proxy-report for symptoms that occur around the time of seizures, since 1) a common human bias is finding causal patterns in chance occurrences,[53] and 2) memory is often impaired peri-ictally, limiting the validity of self-reports.

After a seizure—Diverse cognitive and behavioral symptoms occur postictally, with dysphoric symptoms occurring within 24–72 hours after seizures in more than 50% of patients.[54] Postictal psychosis may affect as many as 2–6% of people with some epilepsies,[55] often following a cluster of complex partial or tonic-clonic seizures. Unlike other postictal behavioral symptoms that typically resolve within hours or days, postictal psychosis can last up to three months (mean duration, 9–10 days).[56] The few studies that examined post-ictal mood used symptom checklists.[54; 57] While reporting several mood and anxiety related symptoms post-ictally does not meet clinical criteria for a mood or anxiety disorder, patients with a history of depressive or anxiety disorders was associated with worse post-ictal symptoms.[54] These studies are conducted in the setting of the epilepsy monitoring unit (EMU) where patients are participating in pre-surgical work up. People with seizures emerging from temporal lobe regions and neighboring structures were significantly more likely to describe post-ictal dysphoric symptoms than people with seizures limited to the temporal lobe (39.1 versus 6.8%).[57]

Limitations of common measurement scales—Most psychometric scales, including structured psychiatric assessments, do not distinguish between episodic, ictally-related phenomena and an ongoing, underlying mood disorder. This may confound assessments of psychiatric co-morbidities, especially when behavioral symptoms fluctuate, data on seizure frequency and severity is incomplete, and antiepileptic and psychotropic medication regimens are in flux. The mechanisms, frequency and treatment of peri-ictal behavioral studies remain ripe for study.[58]

(3) Misdiagnosis of Nonepileptic seizures and events

In adults, psychogenic non-epileptic seizures (PNES) have risen in prominence as a nexus between psychiatry and epileptology.[59–64] PNES present tremendous diagnostic challenges [65] but even greater therapeutic challenges.[66] A comprehensive evaluation – including video EEG and psychiatric assessment –is generally reserved for patients who, consistent with current recommendations, [67–69] have already failed two or more trials of medications. Well-documented observations from the EMU need to be incorporated into our thinking about epilepsy and psychiatric comorbidities. Five to 33% of patients referred and evaluated for refractory epilepsy and surgical evaluation don’t have epilepsy; instead, they have PNES, a conversion disorder. [59; 70] Such disorders are a means of coping with severe trauma and generally do not occur in complete isolation from other psychiatric symptoms. Among over 800 EMU-evaluated patients from the Portland, OR VA Medical Center, one fourth of the patients evaluated for epilepsy were found to have PNES without epilepsy. In addition, other nonepileptic events were diagnosed in 3% of civilians and 12% of veterans. The EMU evaluation confirmed the diagnosis of epilepsy without PNES in only 40% of civilians and 18% of veterans. [62] Further, in veterans, a group with a high prevalence of combat-related head trauma and at very high risk for post-traumatic stress disorder (PTSD), PNES misdiagnosed as epilepsy were recognized in many patients whose epilepsy had been attributed to mild traumatic brain injury. [71] The association is seen in the civilian population as well. [72] Such findings raise further questions about reports of mild TBI as a risk factor for epilepsy.[73]

PNES are not reserved for adults and occur in children as well. Although PNES are uncommon in the pre-school years, they begin to appear in older children, and their frequency increases with age.[74] As in adults with PNES, PTSD is a common finding, although in adolescents, it is often secondary to sexual or physical abuse.[75] A history of multiple psychiatric diagnoses, particularly internalizing disorders, is also associated with an increased risk of PNES in children.[60; 76]

PTSD, Suicidality and PNES—Suicidal tendencies (ideation or attempt) have been linked to the risk of developing epilepsy, and the risk of suicidal behavior, including completed suicide, is higher in adults with epilepsy. [10; 77] Psychiatric disorders, particularly depression and PTSD, are a substantial risk factor for suicidality by themselves. They are also risk factors for PNES. [60; 78; 79] A heightened risk of suicidality has not been specifically reported in children with epilepsy. Studying suicidality in children and adolescents is complicated by the fact that the symptoms of suicidality (expressed wishes to die or of plans to take one's life) are often indications of poor frustration tolerance or attention seeking behavior. While they should never be ignored and require careful clinical assessment, they are often nonspecific and do not reliably identify children who are truly suicidal. A full understanding of any association between epilepsy and suicidality must first take these complexities into account.

Impact on epidemiological studies—Accurate diagnosis of PNES has important implications for interpreting large population surveys. For example, the Behavioral Risk Factors Surveillance Survey contains questions such as "Have you ever been told by a doctor or other health professional that you had seizures?" as a means of identifying people in the population who have epilepsy. [80] Resulting data are likely contaminated by a proportion of people who endorse such questions but who have a psychiatric disorder that has been mislabeled as epilepsy. While people with PNES (with or without co-occurring epilepsy) express cluster B personality traits,[81] are more likely to suffer from mood and anxiety disorders, and are more likely to express dissociative symptoms,[82] there is no characteristic psychological profile that is sensitive or specific enough to distinguish people with PNES from epilepsy.[83, 84; 85] Therefore, even validating such questions against the medical record diagnoses may not correct the problem as errors are often repeated within the records and misdiagnosis can persist for years. It is unclear how such errors are ultimately corrected in the administrative records that many researchers depend upon. To the extent that patients with PNES are labeled as having epilepsy, this may both increase the prevalence of epilepsy and the prevalence of drug-resistant epilepsy in the population as well as enrich the census of people with "epilepsy" who have psychiatric disorders. Further, PNES may, in a proportion of individuals, co-exist with epileptic seizures. If the two different events are not recognized and distinguished, this may further complicate the assessment of therapeutic success and failures.[62; 86] Such diagnostic errors cannot usually be definitively corrected without a video monitoring evaluation in which a stereotypical episode is recorded. Judging from the results reported from EMUs, these individuals may represent a substantial proportion of the patients in the population with "uncontrolled" "epilepsy." Any epidemiological or administrative records-based study reporting an association between epilepsy and psychiatric disorders must be interpreted in light of these concerns.

The literature on the relationship between pre-surgical psychiatric disorders and post-surgical seizure outcomes may also be contaminated by misdiagnosed PNES. For example, one report found that patients with psychiatric disorders prior to surgery may be less likely to experience remission after surgery.[87] PNES, however, may be a new post-surgical finding, particularly in individuals with a presurgical history of psychiatric disorders.[88]

Recent trends in the evaluation and referral for epilepsy surgery may partly reflect the frequency of PNES. There has been an increase in the numbers of patients evaluated for surgery following the publication of the AAN Practice Parameter.[69; 89–91] The number of surgeries, however, did not rise proportionately. These studies demonstrate the decrease in surgeries for mesial temporal lobe epilepsy and increase in surgeries for extra-temporal and nonlesional cases. They also demonstrate a larger proportion of patients overall being referred for evaluation but not having surgery. Given the large proportion of PNES caught during EMU admission,[59; 62] one contributing factor may be that PNES patients who had been misdiagnosed as having refractory epilepsy have been more firmly encouraged to have a comprehensive evaluation. Once accurately diagnosed, such patients would not then go on to have surgery.

Impact on Bi-Directionality Hypothesis—Diagnostic errors that lead patients with PNES to be misdiagnosed as having epilepsy need careful consideration when evaluating studies purportedly demonstrating bidirectionality between psychiatric disorders and epilepsy or reporting poorer seizure control in association with psychiatric disorders. Such data suggest that, in some patients, the psychiatric manifestations prior to seizure onset may in fact represent a neuropsychiatric prodrome phase to the epilepsy or the epilepsy a neurologic prodrome phase to the psychiatric disorders. If so, this could mean that implicated psychiatric disorders and epilepsy share some aspects of their underlying pathophysiology. While this could have tremendous implications for treatment and prevention, the errors of misdiagnosis of PNES, which affect a sizable proportion of adults with uncontrolled epilepsy, must first be addressed. This concept is distinct from auras or immediate postictal phenomena that manifest as psychic or mood disruption only circa a seizure.

Implications

Mental health disorders and epilepsy are closely related with overlapping risk factors and etiologies. We need greater precision in articulating and testing hypotheses as well as in developing policies and practice.

Investigations into the associations between epilepsy and various psychiatric and behavioral co-morbidities and consequences must become more sophisticated to reflect the complexities of epilepsy diagnosis, the ictal manifestations of epilepsy, and how information is acquired. Perhaps one of the most striking lessons in the literature so far is that there are diagnosis and treatment gaps that occur even while we think excellent care is being provided. Over-diagnosis of epilepsy occurs in individuals with autism[92] and intellectual disability.[93] In both instances, the error results in unnecessary treatment with medications that can potentially cause or exacerbate behavioral or cognitive problems. Our discussion

highlights the same concern in relation to psychiatric disorders, particularly PNES. Such patients tend to receive the wrong diagnosis (epilepsy), are treated for a disorder they do not have (sometimes for years), and do not receive the treatment they need for a conversion disorder that they actually do have, therapies for which, particularly Cognitive Behavioral Therapy (CBT) are appropriate but only if the nature of the events is correctly diagnosed.[94] The magnitude of this problem is evident in the results from the monitoring unit studies.[59; 62; 95] These data argue strenuously for the inclusion of psychiatric services and routine evaluation in many (perhaps most) patients presenting with new-onset seizures. These findings also emphasize the need to be aware of the psychiatric history when assessing presumed treatment failure of seizure medications to control the events. Correcting these diagnostic errors could potentially alter the current estimates of the number of people in the population with epilepsy and the proportion of patients with epilepsy who have refractory seizures.

For children, there is also much to learn. The US Preventive Services Task Forces recommends depression screening for adolescents 12–18 [96] and such recommendations of course apply equally to young people with epilepsy. In the setting of a diagnosis of epilepsy in a child, current evidence suggests there may be an important role for educational interventions and perhaps counseling directed not just to the child but to the parents, or even the entire family. Children live with and are affected by the way they are viewed by their parents and the expectations that their parents have for them. Addressing apprehensions and correcting the misconceptions of parents early may help optimize outcomes for children later.

Finally, as so exquisitely described by Lennox and later Livingston, there are ample situational factors that must surely have a negative impact on the individual with epilepsy. The loss of control and autonomy, the need to take medications, the embarrassment or awkwardness occasioned by a seizure, the stigmatizing misconceptions, and, sometimes, the cruelty with which those who are different are treated, even in our post-ADA society –these cannot be ignored. These are larger issues beyond the diagnosis and medical encounter; they require a public health framework to address.[97]

Mental health is a key consideration for everyone. For people with epilepsy, there are many reasons to infer that mental health and related concerns may be more common than in people who do not have epilepsy. We should never deny or ignore problems that are truly there. Understanding their nature and origins, however, is essential to addressing and resolving difficulties effectively. It is essential that we not set up an expectation of limitations, barriers, and ultimately failure that may not exist. A full and accurate understanding of the extent and nature of the relation between epilepsy and behavioral-psychiatric problems is essential.

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Key Points

1. Biases in the current literature must be addressed to provide an accurate understanding of epilepsy-behavioral disorders associations.
2. Parent-proxy report of children's behavior is biased by parental perceptions and reactions to illness.
3. Psychogenic non-epileptic seizures misdiagnosed as epilepsy may induce errors in the assessment of psychiatric disorders and epilepsy.
4. Peri-ictal phenomenon can be misinterpreted as underlying mood disorders.
5. These errors can lead to under and over treatment and misconceptions that may cause further problems for individuals with epilepsy.