Scared or scarred: could ‘dissociogenic’ lesions predispose to nonepileptic seizures after head trauma?

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Title:
Scared or scarred: could ‘dissociogenic’ lesions predispose to nonepileptic seizures after head trauma?

Category:
Focused review

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Highlights

- Traumatic brain injury (TBI) is common in psychogenic nonepileptic seizures (PNES).
- A possible connection is seen in maladaptive symptom modelling.
- Effects of mild brain injury can include disruption of functional connectivity.
- This disruption might temporarily fascilitate dissociation and PNES development.
- Mild TBI might be a cause of “dissociogenic” lesions in some patients.
Abstract
A history of head injury is common in patients with psychogenic nonepileptic seizures (PNES). This association has so far been interpreted as either spurious or psychologically mediated. Biased recall and misattribution could foster illness beliefs about brain damage that promote symptom production. Furthermore, the emotional impact of head injury could induce long-term changes in stress responsivity. Lastly, maladaptive cognitive-behavioural processes involving symptom modelling and aversive conditioning, known to play a role in functional neurological disorders, could contribute to the development of PNES after head trauma. Lesional effects of head injury, on the other hand, remain unexplored in the context of PNES. However, even mild traumatic brain injury without structural MRI abnormalities on routine imaging can lead to disruptions of network connectivity that correlate with short-term cognitive impairments and psychiatric symptoms. Since alterations in global functional connectivity have been demonstrated in PNES patients using imaging and electroencephalography, we hypothesize that, in some patients, TBI and the associated disruption of long-range association fibres could contribute to the individual propensity for dissociative experiences in general and PNES in particular. This possibility is explored in the context of new cognitive-behavioural models of PNES pathogenesis, and the concept of a "dissociogenic" brain lesion is introduced.

Keywords
traumatic brain injury; concussion; psychogenic nonepileptic seizures; dissociative seizures; dissociation; functional connectivity

Introduction
Psychogenic nonepileptic seizures (PNES) are paroxysmal episodes of dissociation that can superficially resemble epileptic seizures or syncope, but do not arise from neuronal hypersynchronisation or ischaemia. They can occur in isolation as a form of functional neurological (dissociative) disorder, or in association with various neurological and psychiatric conditions such as epilepsy or posttraumatic stress disorder (PTSD). The underlying psychophysiological processes are still a matter of controversial debate, and closely associated constructs such as somatization, conversion and dissociation remain themselves inconsistently defined (see [1] for review). Recently accelerated efforts to elucidate the neural ("biological") underpinnings of PNES have shed some light on specific physiological dysfunctions and anatomical predispositions for PNES, challenging a dualistic view of a disorder often seen as purely psychogenic.1,2 Using the common association of traumatic
brain injury (TBI) and PNES as a starting point, this article aims to expand our understanding of PNES pathophysiology with the proposition of “dissociogenic” brain lesions. In analogy to epileptogenic lesions, which can (but do not always) cause focal epileptic seizures, it will be argued that dissociogenic lesions can predispose individuals to PNES in addition to known risk factors such as childhood trauma, anxiety or personality disorder.

TBI preceding PNES

Early case note reviews from epilepsy centres demonstrated an unexpectedly high comorbidity of PNES and TBI.3,4 Studies have since then confirmed this observation with rates of co-occurrence varying between 16-83%, and a weighted average of 43% among 1039 adult PNES patients across 17 studies (Table 1).3-21 While TBI preceding PNES are mild (mTBI) in a majority of cases, moderate and severe TBI can also be associated with PNES.6 The fact that mTBI is much more common in PNES than moderate or severe TBI could lead to the perception that mTBI is somehow more pathogenic in relation to PNES compared to more severe trauma; however, this distribution more likely reflects the overall incidence of mild, moderate and severe TBI, with 80-90% of TBI in the general population categorized as mTBI.22 The latency between TBI and PNES onset varies greatly. In the two studies on adults which report this information (sample size 33 and 37) 81-89% patients developed PNES within the first year after TBI.3,4

The epidemiology of TBI-PNES co-occurrence should be set against the general prevalence of both disorders. A meta-analytic study has calculated that 12% of the general population in developed countries reports a history of TBI (mostly mild), with men affected twice as often as women.23 The incidence of hospital-treated cases of mTBI is about 100-300/100,000.24 PNES is diagnosed at a rate of 1.4-4.9/100,000/year, has an estimated prevalence of 2-33/100,000, and shows a clear preponderance of women.25 Clearly, when analysing the co-occurrence of TBI and PNES, these epidemiological data indicate that part of the correlation might be coincidental rather than causal, and that any causal relationship would be far from universal.
Table 1: History of TBI in patients with PNES

<table>
<thead>
<tr>
<th>Year</th>
<th>PNES, n</th>
<th>TBI-Hx, n (%)</th>
<th>average age (range or ±SD), gender of TBI-Hx subgroup</th>
<th>Latency</th>
<th>mTBI</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1993</td>
<td>27</td>
<td>18 (67%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>15</td>
</tr>
<tr>
<td>1993</td>
<td>93</td>
<td>15 (16%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>16</td>
</tr>
<tr>
<td>1998</td>
<td>157</td>
<td>37 (24%)</td>
<td>34 y (15-56), 68% women</td>
<td>89% within 1 y</td>
<td>78%</td>
<td>3</td>
</tr>
<tr>
<td>1998</td>
<td>102</td>
<td>33 (32%)</td>
<td>34 y (17-57), 48% women</td>
<td>81% within 1 y</td>
<td>91%</td>
<td>4</td>
</tr>
<tr>
<td>1999</td>
<td>100</td>
<td>52 (52%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>14</td>
</tr>
<tr>
<td>2000</td>
<td>16 a</td>
<td>7 (44%)</td>
<td>10.5 y (5-18), 31% girls</td>
<td>71% within 7 mo</td>
<td>57%</td>
<td>13</td>
</tr>
<tr>
<td>2001</td>
<td>40</td>
<td>33 (82.5%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>17</td>
</tr>
<tr>
<td>2002</td>
<td>23</td>
<td>20 (83%)</td>
<td>-</td>
<td>-</td>
<td>100%</td>
<td>12</td>
</tr>
<tr>
<td>2004</td>
<td>-</td>
<td>34 b</td>
<td>36 y, 53% women</td>
<td>-</td>
<td>0% b</td>
<td>6</td>
</tr>
<tr>
<td>2005</td>
<td>63</td>
<td>16 (26%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>2006</td>
<td>21</td>
<td>10 (48)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>19</td>
</tr>
<tr>
<td>2010</td>
<td>64</td>
<td>13 (20%)</td>
<td>-</td>
<td>-</td>
<td>&quot;most&quot;</td>
<td>8</td>
</tr>
<tr>
<td>2010</td>
<td>44</td>
<td>13 (44%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>20</td>
</tr>
<tr>
<td>2013</td>
<td>92</td>
<td>41 (45%)</td>
<td>38.9 y (±12.6), 66% women</td>
<td>-</td>
<td>73%</td>
<td>11</td>
</tr>
<tr>
<td>2014</td>
<td>324</td>
<td>119 (37%)</td>
<td>37.3 y (±12.2), 71% women</td>
<td>-</td>
<td>-</td>
<td>10</td>
</tr>
<tr>
<td>2015</td>
<td>77</td>
<td>38 (57%)</td>
<td>49 y, 19% women c</td>
<td>-</td>
<td>87%</td>
<td>5</td>
</tr>
<tr>
<td>2017</td>
<td>51</td>
<td>26 (51%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7</td>
</tr>
<tr>
<td>2017</td>
<td>49</td>
<td>13 (27%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9</td>
</tr>
<tr>
<td>2017</td>
<td>17</td>
<td>10 (59%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>21</td>
</tr>
</tbody>
</table>

a Paediatric population
b Study recruited only patients with moderate or severe TBI preceding seizure disorder
c Study from veteran’s hospital
PNES, psychogenic nonepileptic seizures; TBI, traumatic brain injury; TBI-Hx, positive history of head injury; mTBI, mild traumatic brain injury; y, years; mo, months; SD, standard deviation

Table 2: Potential aetiological factors underlying PNES and antecedent TBI

<table>
<thead>
<tr>
<th>Non-lesional phenomena</th>
<th>Possible effect on mTBI-PNES correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recall bias and misattribution</td>
<td>promotes illness belief that can perpetuate dysfunction</td>
</tr>
<tr>
<td>Emotional trauma</td>
<td>affective stressor can induce long-term changes in stress-responsivity and metacognitive function akin to the development of posttraumatic stress disorder (PTSD)</td>
</tr>
<tr>
<td>Maladaptive emotional learning</td>
<td>acute stress and concussive symptoms lead to averingly conditioned neuropsychiatric dysfunction (“seizure scaffold”) that is adapted as a response to emotional, somatic or trauma-related cues</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesional phenomena</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Axonal injury and alteration of global functional connectivity</td>
<td>disruption or destabilization of metacognitive faculties such as cognitive inhibition and self-awareness which predisposes to dissociation</td>
</tr>
</tbody>
</table>

PNES, psychogenic nonepileptic seizures; mTBI, mild traumatic brain injury
Non-lesional effects of head trauma

Most authors of correlational studies on TBI and PNES have offered only restrained speculations on causality. While a structural component in PNES development after TBI has been entertained, psychological phenomena and confounders are much more commonly cited (Table 2 and Fig. 1). One possible factor is recall bias. PNES patients are often given imprecise explanations of their attacks and can find themselves actively searching for conceivable causes of their symptoms. Inconsistent definitions of what constitutes TBI and concussion can further add to this, with harmless “knocks to the head” being reinterpreted as disease triggers. In one study, 39% of patients ascribed their PNES to antecedent TBI independent of (and usually contrary to) their physician’s assessment. This might especially be the case in the veteran community, where the causal association between TBI and (epileptic) seizures is common knowledge. In a disorder where symptom expectations play a key role (see below), etiological misattributions of this sort may gain secondary importance by promoting relevant illness beliefs.

TBI is a significant stressor that could precipitate PNES due to its emotional impact alone following established models of psychological trauma and dissociation. High rates of traumatic experiences in general and physical injury in particular have been associated with PNES. Mild TBI can induce high levels of stress and anxiety, so it might trigger neuropsychiatric dysfunction in predisposed individuals on an emotional level as would any other traumatic event. In line with this explanation, a study on veterans with seizures attributed to head trauma revealed that 57% of all patients with PNES after TBI had documented PTSD. Since PTSD has been identified as a strong independent predictor of PNES, mTBI might be one step removed from PNES or entirely unrelated. Highlighting the role of emotional stress in presumed head injury sequelae, a prospective study on 175 trauma patients found that acute post-concussion syndrome is as likely to occur patients with mTBI as it is in non-head-injured trauma controls.

Accidental head trauma combines a highly stressful situation (e.g. sports competition, vehicle accident, brawl, injury- and treatment-related pain and dysfunction) with acute neuropsychiatric impairments in motor control, sensory faculties, consciousness or memory. In this context of acute stress, maladaptive emotional learning (especially aversive conditioning) combined with affect-biased attentional prioritization can thus result in symptom modelling: a repertoire of dysfunction or "seizure scaffold" is coupled with an abnormal stress response to perceived threats. Put in computational terms, the expectation of seizure-like dysfunction, both consciously due to illness beliefs and unconsciously in response to conditioned emotional and somatic cues, is allotted such disproportionately high confidence (or “precision”), that it can override through active inference contradicting perceptual information and produce symptoms. Such maladaptive behavioural cascades have been proposed to underlie other functional neurological disorders such as functional...
dizziness\textsuperscript{35} and sensory and motor conversion disorder.\textsuperscript{34,36} In a study of 50 patients with functional movement disorders, 80\% reported a precipitating peripheral trauma and 39\% of those retrospectively fulfilled the criteria for a panic attack in association with the trauma.\textsuperscript{37} In a study of 869 cases of motor and sensory conversion disorder, 37\% were preceded by some kind of physical injury.\textsuperscript{38} Lastly, in a study of 100 consecutive patients with motor functional neurological disorders (PNES, functional weakness, functional movement disorders and mixed presentations), 42\% of all patients reported antecedent head trauma, with a higher incidence in PNES and functional movement disorders patients than in functional weakness.\textsuperscript{7} These observations would support a cognitively and emotionally mediated connection between antecedent head trauma and PNES, independent of any structural neuronal dysfunction.

**The pathology of mTBI**

Mild TBI results from an external force to the head that generates intracranial pressure gradients through the inertia of the brain inside the skull.\textsuperscript{22} This can lead to shearing and strain forces which in turn cause microtubule disruption and primary and secondary damage to axons. Some neuropathological investigations have described multifocal axonal injury (typical for moderate and severe TBI) after mTBI, but confounders remain difficult to control for. Routine clinical neuroimaging is normal after mTBI, but axonal dysfunction and network connectivity alterations can be detected and quantified using diffusor tensor imaging (DTI).\textsuperscript{39,40} Even though mediators or confounders such as opiate use or anxiety disorders might be part of the causal chain linking TBI with brain connectivity alterations, the basic association itself has been well established. Furthermore, the degree of white matter abnormalities detected on DTI correlates well with cognitive performance following mTBI.\textsuperscript{39} Several studies on patients with mTBI using tractography show that frontal association pathways are primarily (though not exclusively) affected. It is beyond the scope of this article to review the potential neuropsychiatric implications of each commonly affected tract, but the uncinate fasciculus, which is affected in 29\% of patients after mTBI,\textsuperscript{41} will be discussed as an example. It connects anterior temporal structures such as the amygdala to prefrontal cortices and has been directly implicated in psychiatric disorders.\textsuperscript{42} Interestingly, in a study of moderate and severe TBI in children, DTI-measured injury to the uncinate fasciculus reliably predicted emotional and behavioural dysregulation.\textsuperscript{43} Since the uncinate fasciculus undergoes developmental maturation well into the third decade of life\textsuperscript{42} post-concussive development of psychiatric disorders could in part be connected to its vulnerability and microstructural damage in both children and adults. Another way to visualize the neurophysiological consequences of disruptions of long-range association fibres after mTBI is through functional magnetic resonance imaging (fMRI).\textsuperscript{44} Studies using resting-state protocols have repeatedly demonstrated reduced functional connectivity of the
default mode network (DMN), which is closely associated with self-reflective mental activity, after mTBI. Albeit mostly in subjects with moderate to severe TBI, Ham and colleagues have convincingly shown impairments of self-awareness to result from breakdown of functional interactions within the DMN, and not from focal posttraumatic lesions. The same group has also shown DMN dysfunction after TBI to correlate with inefficient inhibitory cognitive control as assessed in a Stroop task. Lastly, both electroencephalography (EEG) and magnetoencephalography (MEG) studies have shown disruptions of functional connectivity after mTBI. In conclusion, even though mTBI may often leave no traces on routine structural MRI, the disruption of functional network connectivity due to injury to long-range association fibres can have direct short- and medium-term effects on metacognitive functioning.

Dysconnectivity in PNES
To assess the possibility of a structural predisposition to PNES after mTBI, a pathophysiological commonality has to be demonstrated. While current conceptual frameworks for the development of PNES are supported by a wealth of clinical and psychometric data, empirical advances in search of the neurobiological underpinnings are still discordant. Furthermore, the heterogeneity of PNES and their association with different neurological and psychiatric conditions makes a unique focal neural dysfunction unlikely. Still, PNES are dissociative events that invariably entail certain (meta-)cognitive deficits such as loss of inhibitory control, reduced sense of agency and emotion dysregulation, which could be assumed to be related to distinct neurophysiological disruptions.

Several groups have investigated PNES pathology with structural and functional MRI. Using DTI, Hernando and colleagues showed a rightward asymmetry of uncinate fasciculus streamlines in PNES patients that was not seen in age- and sex-matched healthy controls. Interestingly, age at PNES onset was correlated with asymmetry indices of fractional anisotropy. Since the average age at disease onset was 35 years, these correlations might be related to the prolonged maturation process of the uncinate fasciculus mentioned above. Another DTI study also found altered white matter structural connectivity in the left uncinate fasciculus, as well as in the left corona radiata, left internal and external capsules, and left superior temporal gyrus. Ding and colleagues performed DTI and fMRI in PNES patients and found decreased network connectivity strength in both structural and functional connectivity networks compared to healthy controls. Using high-density EEG, Knyazeva and colleagues found that psychogenic seizure frequency was correlated with hypo-synchronization of prefrontal and parietal regions, which, as the authors note, are both integral parts of the DMN. Several studies using various imaging and electrophysiological methods have assessed neural alterations in PNES populations, but their findings have yet to converge around a coherent model. While a unifying neural signature of PNES predisposition has yet to be defined, studies suggest that
network connectivity alterations could be a potentially defining feature. Metacognitive processes that rely on top-tier recursive large-scale networks might be most susceptible to such disruptions, facilitating dissociation, disinhibition, amnesia and loss of volition during moments of abnormal stress and neurohumoral activation.

**Dissociogenic brain lesions: a hypothesis**

With this in mind, a plausible pathophysiological link between mTBI-related disruptions of long-range connectivity and the development of PNES emerges which is additional rather than oppositional to the non-lesional mechanisms described earlier (Fig. 1). Conscious awareness of sensory input and behaviour requires global integration of brain signals, which is assumed to rely on finely tuned recursive long-range connectivity. A disruption of global connectivity and metacognitive functioning following mTBI might predispose individuals to dissociative experiences in general and PNES in particular. Focusing on specific vulnerable pathways such as, for example, the uncinate fasciculus, further reveals possible biological links of this nature. Just as certain life events or psychiatric diseases can be seen as clear precursors or catalysts of PNES, certain brain insults could well be considered “dissociogenic” (in analogy to those considered “epileptogenic”). Multifocal injury and disruption of long-range axonal fibres after mTBI would be a good example for this.

Dissociative symptoms and disorders other than PNES can sometimes be observed following mTBI. In a prospective study of 1116 acute trauma patients, the group that had suffered an mTBI (n = 476) were significantly more likely to report dissociative symptoms such as derealization, restricted affect, and reduced awareness. In a similar study on 131 road traffic accident victims (aged 18-65 years, no known pre-existing psychological disorder) with (n = 66) and without (n = 65) mTBI, the mTBI-group reported significantly more dissociation since the trauma (excluding peri-traumatic dissociation) compared to non-mTBI participants. Another study on 80 mTBI patients found exceptionally high scores on the Dissociative Experiences Scale a median of 24.5 weeks after injury, though potential biases in patient sampling limit the interpretability of this study.
Fig. 1. Potential pathways linking mTBI and PNES. Misattribution can foster illness beliefs that shape symptom expectations. Acute post-concussive symptoms can serve as a symptom model ("seizure scaffold") that is aversively conditioned to emotional, somatic or trauma-related cues as part of a maladaptive stress response. The acute stress of mTBI, despite promoting peri-traumatic dissociation, could also lead to changes in metacognition through pathways described in PTSD. Lastly, mTBI-related axonal injury, which is thought to underlie some of the acute symptoms, can also alter global connectivity in ways that affect metacognition and promote dissociation. Abbreviations: PNES, psychogenic nonepileptic seizures; mTBI, mild traumatic brain injury; PTSD, posttraumatic stress disorder.

Testing and expanding the hypothesis

Previous attempts to localize specific brain lesions associated with dissociative phenomena besides PNES should be considered when formulating our hypothesis. Research into states and traits of dissociation in dissociative disorders (derealization and depersonalization disorder, dissociative identity disorder) and trauma-associated disorders (dissociative subtype of PTSD, borderline personality disorder) has relied mainly on functional task-related or resting-state imaging. A long list of potentially relevant brain regions has thus been assorted, but questions of predisposition, causality, adaptation and compensation have yet to be elucidated. Since our hypothesis specifically regards brain injury, the "lesion method" of neuroanatomical localization seems more promising.

One mTBI study which comes close to addressing our hypothesis was performed by Niogi and colleagues and ingeniously applied a combination of trait-mapping and the lesion method using DTI. In a first step, target cognitive domains (memory and attention) in healthy controls were found
to correlate significantly with specific white matter regions of interest (left hemisphere anterior corona radiata and uncinate fasciculus, respectively). In a second step, thus identified white matter tracts were studied in mTBI patients at least 1 month post-injury (range 1-53 months). Changes in microstructural white matter integrity (measured by fractional anisotropy) in the regions of interest indeed correlated with the respective cognitive faculties in the pathological range. There was no "cross-correlation" – uncinate fasciculus disruption did not correlate with attentional dysfunction and vice versa. This type of mechanistic studies using imaging and electrophysiology will be needed to test our hypothesis, in addition to large-scale epidemiological studies that more closely distinguish reported, suspected and confirmed TBI and register the presence and length of posttraumatic amnesia and loss of consciousness to allow for better classification.

What other types of dissociogenic brain insults could there be? New onset of PNES has been observed anecdotally after general neurosurgery\textsuperscript{71}, as well as systematically after epilepsy surgery, affecting 2.4 – 8.8\% of patients.\textsuperscript{72,74} Most of the preceding operations in epilepsy patients were complete or partial temporal lobe resections, in which the uncinate fasciculus and its limbic connections are routinely resected. In discussing the post-operative development of PNES, many reports cite the psychosocial stress of being seizure-free after surgery or the stress of surgical morbidity as potential psychological factors.\textsuperscript{72,73} However, the potentially deleterious effect of resective epilepsy surgery on global network connectivity has received little attention so far. Other examples of potentially dissociogenic pre-existing conditions in PNES patients include perinatal brain injury, anoxic brain damage and various epileptogenic lesions.

In conclusion, the idea of dissociogenic brain lesions predisposing to PNES does not negate or oppose established cognitive-behavioural mechanisms (Fig. 1), but rather emphasizes the inextricable concurrence of structural predispositions and functional disturbances in neuropsychiatric disorders. Recognizing and studying lesional effects on PNES pathology will enable a more comprehensive understanding of the disorder and help in devising treatment strategies. Furthermore, this train of thought can lead to a better conceptualization of other functional neurological disorders, as well as other lesional predispositions.

Declaration of interest statement:
Dr. Popkirov reports no disclosures relevant to this study. Dr. Carson gives independent testimony in court on a range of topics that include functional neurological symptoms. Dr. Stone runs a free non-profit self-help website www.neurosymptoms.org.

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