Psychotic Disorder Due to Traumatic Brain Injury: Analysis of Case Studies in the Literature

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The present study utilized methodology from a previous descriptive study that analyzed case studies of psychotic disorder due to traumatic brain injury (PD-TBI) reported in psychiatry and neurology journals. The purpose was to replicate findings from the PD-TBI literature and to elucidate a pattern of characteristics that would differentiate PD-TBI from schizophrenia. The findings supported both objectives. PD-TBI data were highly consistent with previous studies: PD-TBI differed from schizophrenia in showing more focal frontal and temporal abnormalities on neurological studies and a lower rate of negative symptoms. The authors discuss implications of these findings for conceptualizing psychosis as a neurobiological syndrome.

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There is a growing literature supporting the idea of traumatic brain injury (TBI) as a risk factor for psychosis. An earlier review of case studies in the literature before 1969 reported incidence rates of post-traumatic psychosis ranging from 0.07 % to 9.8 %.[1] More recent epidemiological studies from a number of different countries, including the United States, Taiwan, Denmark, and Sweden, all report significantly elevated levels of TBI in persons with a psychotic disorder, some only for subgroups of the total sample. Harrison et al.[2] found a small but significant incidence of nonaffective psychosis in persons sustaining a head injury (odds ratio [OR]: 1.37). Nielsen et al.[3] reported ORs of 3.964 and 3.189 for women developing schizophrenia within 1 year of sustaining a concussion and severe head injury, respectively. A study from Taiwan following persons hospitalized with a TBI for 5 years reported an OR of 1.99 for developing schizophrenia, as compared with a matched sample.[4] Data from an American health-maintenance organization (HMO) reported an increased risk for developing a psychotic disorder after sustaining a moderate-to-severe head injury; 5.9 for an occurrence from 13 to 24 months after the injury, and 3.6 for an occurrence between 25 and 36 months.[5] Results from a community survey of severe head trauma with loss of consciousness reported a significant increased risk for developing schizophrenia (OR: 1.8) when controlling for demographic factors of age, gender, race, socioeconomic status, and quality of life. The risk was of borderline

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significance when also controlling for alcohol abuse (OR: 1.7).[6]

Higher incidence rates of TBI are found in persons with schizophrenia before onset of illness, with rates ranging from 8.8% to 39.6%.[7–12] Other studies suggest that neurological conditions, particularly those with congenital or childhood onset,[7,12,13] and psychiatric illness[5,14,15] may also be predisposing factors. Taken together, these studies would suggest that persons who develop a psychotic disorder due to traumatic brain injury (PD-TBI) have a premorbid vulnerability including genetic predisposition for schizophrenia or other neurological or psychiatric conditions.[7,9,10]

Despite strikingly consistent findings, with 13/13 studies reporting some type of significant relationship, the idea of TBI as a risk factor for psychosis has been criticized. David and Prince[16] questioned this relationship, arguing that many earlier studies suffer from weak methodologies, such as questionable diagnostic criteria and lack of a control group. By comparison, more recent, better-designed epidemiological studies with larger sample sizes (in which the authors admit having important methodological shortcomings that could affect finding a relationship between TBI and psychosis) fail to demonstrate global significant findings. Instead, the researchers propose that psychosis is a risk factor for sustaining a head injury and cite findings from a study reporting a very large OR of 10 for this directional relationship.[5] A closer examination of this study, however, indicated that 57% of subjects who sustain a TBI after being identified as having a psychotic disorder were age 65 years or older. Elderly persons have both higher incidence rates of psychosis, with one community sample estimating a rate of 5.7%,[17] and head injury with hospitalizations for TBI being 2.5 times that of younger adult populations.[18] Given these numbers and the use of antipsychotic medications, which pose a fall risk for elderly patients,[19] as one of the diagnostic criteria for psychosis, it is probably more accurate to state that psychosis is a strong risk factor for sustaining a TBI in persons older than 65. Indeed, a similar study by the same authors reported a more modest OR of 1.9, where organic psychiatric disorders had the highest risk for sustaining a subsequent head injury (OR: 3.7–4.4).[20] Given the literature, it is likely that both directional relationships exist.

Studies examining persons with PD-TBI report much variability in the type and severity of the triggering TBI and course of illness, including the latency from TBI to onset of psychosis and chronicity of symptoms. PD-TBI can occur from both open and closed head injuries, the former primarily found in earlier studies on World War II veterans,[1,15,21] the latter in more recent studies.[3,5,7,8,22,23] Psychotic disorders can occur after both mild and moderate-to-severe TBI, and findings are mixed as to which severity of TBI is more prevalent.[2,3,7,8,22–24] The majority of PD-TBI cases report onset in persons age 20–30,[4,15,22,23] although onset from the teen years to the 80s has been described.[15] There is generally a latency from the time of TBI to the onset of psychosis. Several studies suggest that most cases occur within the first year,[1,15,22,24] whereas other studies report that a significant number of cases develop psychosis after 5 years[1,3,15,24] or even after 10 years, suggesting a bimodal distribution.[21,24] The mean appears to be between 4 and 5 years.[7,22,23] Several studies report an elevated family history of psychiatric illness, ranging from 2.9% to 18%;[1,23] by contrast, one PD-TBI study with a small sample size reported no family history.[24] Comorbid seizure disorder ranges from 9% to 44%, with the higher percentages from studies including a higher proportions of open head-injury patients.[7,15,22,23]

The lone study describing prodromal symptoms indicated that the majority of PD-TBI patients experienced a pre-psychotic phase similar to schizophrenia.[23] The most common symptoms were bizarre behaviors (50%), followed by affective instability (39%), antisocial behaviors (36%), scholastic or work deterioration (33%), and social withdrawal (31%).

The long-term course of PD-TBI is also highly variable. Although most studies report that persons with PD-TBI improve, particularly after treatment,[14,21–23] studies with longer follow-ups suggest that many experience a chronic course.[14,21] Antipsychotics appear to be the most efficacious treatment, followed by anticonvulsants, and lithium.[22]

Although onset factors and course of psychosis may vary, studies converge on the presentation of PD-TBI. Men are overrepresented[1,7,8,15,23,24] even when controlling for gender ratio for sustaining TBI.[22] The most common symptoms are persecutory delusions (22%–80%),[1,7,14,15,22,23] and auditory hallucinations (47%–84%),[7,22,23] whereas negative symptoms are much less prominent (15%–22%).[1,22,23] Most persons with PD-TBI sustain neuropsychological impairments, although not as severe as in persons with schizophrenia.[8] The most common deficits are found in memory and executive functioning,[8,22,23] and general intelligence and verbal

skills are also affected[22,23] Lesions to temporal[1,14,15,22,23,25] and frontal lobes[15,22,25] are the most commonly implicated in PD-TBI, as determined by location from missile wounds[1,15] and findings on MRI/CT and EEG.[22,23]

Given the overlap in presentation with schizophrenia, Fujii and Ahmed[22] attempted to identify characteristics that may assist in differential diagnosis between PD-TBI and schizophrenia. As compared with persons with schizophrenia (PWS), persons with PD-TBI appear less likely to demonstrate negative symptoms (14% versus 25%–84%), and more likely to demonstrate positive findings on MRI/CT (65% versus 12%–35%) that are more focal in nature (62%). Frontal (42%) and temporal (27%) abnormalities are the most common finding in PD-TBI, versus enlarged ventricles for persons with schizophrenia (22%–35%). Persons with PD-TBI are also more likely to demonstrate positive findings on EEG (70% versus 20%–60%), with the most common finding being temporal slowing, versus frontal slowing for persons with schizophrenia.[22]

The current study replicates methodology of an earlier study by Fujii and Ahmed[22] that examined characteristics of PD-TBI by analyzing case studies in the literature before 2000. In the present study, the focus is on newer case studies, published after 2000, although non- duplicative cases before 2000 are also included. The purpose is to determine the robustness of earlier findings of the PD-TBI literature. Also, similar to the initial study, select characteristics will be compared with the literature on schizophrenia to aid in differential diagnosis.

General hypotheses include the following:

1. PD-TBI results from both mild and moderate head injuries.
2. There is a bimodal distribution of time between TBI and onset of psychosis. Many persons develop psychosis within the first year after sustaining a brain injury or after 5 years. The mean latency between the TBI and onset of psychotic symptoms is 4–5 years.
3. Seizure disorder is more common in PD-TBI than in general TBI.
4. Most persons with PD-TBI improve in presentation, with antipsychotics being the most efficacious medication.
5. Male gender and family history of schizophrenia are risk factors for developing PD-TBI.
6. The most common psychotic symptoms associated with PD-TBI are persecutory delusions and auditory hallucinations. Negative symptoms are less pronounced.
7. PD-TBI is associated with cognitive impairments, most commonly in memory and executive functioning.
8. PD-TBI is associated with lesions to frontal and temporal areas of brain as identified by neurological studies.
9. PD-TBI patients will differ from PWS in the following manner: Persons with PD-TBI are 1) less likely to present with negative symptoms; 2) more likely to demonstrate positive findings on CT/MRI, with the most common findings being focal lesions to temporal and frontal lobes, versus PWS, who commonly present with enlarged ventricles; and 3) more likely to demonstrated positive findings on EEG, with the most common findings being temporal slowing, versus PWS, who most commonly demonstrate frontal slowing.

METHOD

Articles were obtained from case studies in the psychiatric and neurologic literature found through PubMed searches with the following keywords: psychotic disorder, schizophrenia, delusions, and hallucinations—combined with traumatic brain injury and case studies. Case studies were included if a subject developed a psychosis after sustaining a TBI and met the DMS-IV criteria for Psychotic Disorder Due to a General-Medical Condition (TBI).[26] Exclusionary criteria included: history of psychosis before the brain injury, inclusion in the original sample of PD-TBI case studies in the literature,[22] and publication in a journal written in a language other than English. Also, we included four case studies from the first author's practice.

A total of 30 articles were included, yielding 64 cases. The article authors are listed in Table 1. The following data were procured from each case: gender, etiology of TBI, loss of consciousness, age when sustained TBI, age at onset of psychotic symptoms, presence of seizure disorder, family history of mental illness, medication category, clinical outcome, presence of negative symptoms, inpatient/outpatient status, diagnosis, presence and type of delusions, presence and type of hallucinations, EEG findings, MRI/CT findings, PET/SPECT findings, presence of neurological signs, and neuropsychological test findings.

Data criteria are the same as in the original Fujii and Ahmed study.[22] Severity of TBI was based on criteria set by the Mild Traumatic Brain Injury Committee of the

TABLE 1. Articles Included in Analysis

Campbell and Panicker, 2011[29]
Tremeau et al., 2011[30]
Webb et al., 2010[31]
De Mattos Viana et al., 2010[32]
Bennouna-Greene et al., 2010[33]
Guerreiro et al., 2009[34]
Miller and Roache, 2009[35]
Catalano et al., 2009[36]
Guenedi et al., 2009[37]
Zaidi and Faruqui, 2008[38]
Sheehan and Thurber, 2006[39]
Bennouna et al., 2005[40]
Stewart and Brennan, 2005[41]
Stephane et al., 2004[42]
Duggal, 2004[43]
Koponen and Larmo, 2003[44]
Kim and Humaran, 2002[45]
Jaskiw and Kenny, 2002[46]
Fujii and Ahmed, 2001[7]
Butler, 2000[47]
Feinberg et al., 1999[48]
Mattioli et al., 1999[49]
Burke et al., 1999[50]
Bloom and Kraft, 1998[51]
Schreiber et al., 1998[52]
Francisco and Ivanhoe, 1996[53]
Rousseaux et al et al., 1994[54]
Michals et al., 1992[55]
Fornazzari et al., 1992[56]
Ritchie et al., 1989[57]

Head Injury Interdisciplinary Special Interest Group of the American Congress of Rehabilitation Medicine (ACRM)[27] which considers a head injury as mild if the duration of loss of consciousness (LOC) is 30 minutes or less and moderate-to-severe if LOC is longer than 30 minutes.

Psychotic symptoms were rated as present or absent on the basis of the descriptions in the case studies. Also, subtypes of each symptom were tallied. Because a subject can demonstrate more than one type of symptom within a category, for example, paranoid and bizarre delusions, subtype tallies exceed the number of the actual number of subjects reporting the symptom. Positive findings and localization on EEG, CT/MRI, and PET/SPECT were calculated in a similar manner, with the total localization of abnormalities exceeding the total number of positive findings. Clinical outcome was based on rating case descriptions, based on a 3-point system—1: improved; 2: no improvement; or 3: decline in status. Family history of psychotic illness was only calculated if mentioned specifically in the case study. Thus, absence of reporting was not considered to be absence of family history. Psychiatric diagnosis was only included if stated in case study and was not inferred from the title of article. Negative symptoms were deemed absent if there was adequate description of the presentation and negative symptoms were not mentioned.

In many case studies, there were missing data due to differences in case description. All data-points for each variable were included in individual analyses despite missing data for a case; thus sample sizes for specific characteristics of PD-TBI are highly variable and often less than the total sample size of 64. Statistical analyses were primarily chi-square tests, as most data were categorical. Chi-square calculations were based on chance differences unless base rates were known or appropriate. T-tests were also conducted when appropriate. As in the original study, because of its exploratory nature, small sample sizes, and the relatively lower power of nonparametric (versus parametric) statistics to detect significant differences between groups, a less conservative significance level was set at 0.05.

Demographics

Demographic data are presented in Table 2. The sample consisted of 56 men and 8 women. The gender ratio is significantly different from the expected (2:1) base rate for TBI[28] ($\chi^2[1]=11.97$; $p<0.001$). The most frequent cause of TBI was motor vehicle accidents (42%), followed by assault (23%), falls (23%), gunshot wounds (5%), and unspecified (7%). The distribution of causes was significantly different from chance ($\chi^2[4]=30.77$; $p<0.001$). Of all known cases, 91% of patients sustained closed head injuries, and 9% sustained open head injuries ($\chi^2[1]=42.24$; $p<0.001$). A significant majority of the sample (73%) lost consciousness because of their injury ($\chi^2[1]=10.08$; $p<0.01$). No differences were found in the frequency of mild (62%) or moderate–severe (28%) head injury, based on ACRM criteria ($\chi^2[1]=2.38$; NS). An overwhelming majority of the sample (86%) were inpatients ($\chi^2[1]=32.37$; $p<0.001$), with 83% admitted to a psychiatric hospital ($\chi^2[2]=68.40$; $p<0.001$) and the remaining coming from medical (14%) and rehabilitation facilities (13%).

The mean age for sustaining a TBI was 23.7 (standard deviation [SD]: 12.84), whereas the mean age at onset of psychosis was 27.3 (SD: 11.64). There was a bimodal distribution in the duration of latency between TBI and onset of psychosis, with 38% developing a psychosis within 1 year and 36% 4 years after sustaining a TBI. Known diagnoses were fairly evenly distributed ($\chi^2[1]=2.88$; NS). PD-TBI was the most common (35%), followed by schizophrenia (29%), organic mental

TABLE 2. Demographic Data

Variable	Data	χ^2
Gender (N=64)	56 men; 8 women	11.97***
TBI: etiology (N=60)	25 motor vehicle accidents; 14 assault; 3 gunshot wound; 14 falls; 4 unspecified	30.77***
TBI: type (N=64)	58 closed head injury; 6 open head injury	42.24***
TBI: loss of consciousness (N=48)	35 yes; 13 no	10.08**
TBI: severity (N=42)	26 mild; 16 moderate–severe	2.38
Setting (N=60)	52 inpatient; 8 outpatient	32.37***
	50 psychiatric; 8 rehab.; 2 medical	68.40***
TBI: age at onset (N=63)	23.7 (SD: 12.84); range: 3–61	
Psychosis (N=61)		
Age at onset	27.3 (SD: 11.64); range: 14–61	
Delay of onset, years (N=61)	3.6 (SD: 4.26); range: 0–15	
	<1: 23; 1: 7; 2: 5; 3: 4, 4+ years: 22	
Diagnosis (N=17)	Psychotic Disorder Due to General-Medical Condition/ TBI: 6; Schizophrenia: 5; Organic Mental Disorder With Psychosis: 3; Psychotic Disorder, NOS: 2; Major Depression with Psychosis: 1	2.88
Family history of mental illness (N=17)	Yes: 3; No: 14	8.46**

**p<0.01; ***p<0.001.

disorder with psychosis (18%), psychotic disorder NOS (12%), and major depression with psychosis (6%). As compared with the base rate in the general population for having a first-degree relative with schizophrenia (3.7%),[28] the ratio of the sample reporting a family history of schizophrenia (17.6%) for the available data were significantly larger than chance (χ^2[1]=8.46; p<0.01).

Clinical Presentation and Course

Data for the clinical presentation and course of illness are presented in Table 3. Posttraumatic seizures were reported in 23.6% of our sample. Studies indicate that the base rate for posttraumatic seizures varies with severity of brain injury, occurring in 4.4% of mild, 7.6% or moderate, and 13.6% of severe TBI.[59] Using these figures as multipliers for the different levels of TBI severity, the expected frequency of posttraumatic seizures in our sample was 7%. The percentage of seizure disorder in our sample was significantly larger than chance (χ^2[1]=21.84; p<0.001). Delusions were reported in 92% of our sample (χ^2[1]=18.62; p<0.001). Persecutory delusions was the most common, occurring in 77% of subjects, followed by bizarre delusions (10%), grandiose (8%), delusions of reference (6%), religious and Capgras (5%), Cotard's and Fregoli (3%), and delusional jealousy (2%). The proportion of paranoid delusions was significantly greater than chance (χ^2[8] =147.43; p<0.001).

Hallucinations were reported in 87% of our sample, which was significantly greater than chance (χ^2[1] =25.13; p<0.001). Ninety-three percent experienced auditory-hallucinations, followed by visual (15%), olfactory (5%), and tactile (3%). There was a significantly greater proportion of auditory hallucinations than any other type (χ^2[3]=76.67; p<0.001). Negative symptoms were reported in 37% of the cases, which was not different from chance (χ^2[1]=2.13; NS). The most common negative symptom was blunted affect, found in 23% of cases, followed by social isolation (17%), poor hygiene (7%), and apathy and avolition (4%). The proportion of negative symptoms was greater than chance (χ^2[4]=13.60; p<0.01). Thought disorder/loose associations was much less common, with only 8% reporting these symptoms, which was significantly below chance level (χ^2[1]=37.23; p<0.001).

A majority of PD-TBI cases (87%) displayed signs of improvement, which was significantly greater than chance (χ^2[1]=17.06; p<0.001). Of the 28 patients who were prescribed efficacious medications, 87% received antipsychotics; 11%, anticonvulsants; and 11%, antidepressants. The number of patients prescribed antipsychotics was significantly higher than chance (χ^2[2]=29.40; p<0.001).

Laboratory Findings

Data for laboratory findings are shown in Table 4. EEG data were reported in only 14 cases, with 79% positive for abnormalities, which was significantly greater than chance (χ^2[1]=4.57; p<0.05). A significant majority of abnormalities were localized to the left hemisphere (73%; χ^2[2]=28.67; p<0.001). No significance was found for localization (χ^2[3]=7.33; NS) or type of abnormality (χ^2[1]=0.033; NS).

Of the 24 cases with CT/MRI data, a majority (79%) reported positive findings (χ^2[1]=8.17; p<0.01). The hemispheric location of the lesions also proved to be significant, with 47% involving the left hemisphere; 47%, bilateral lesions; and only 5%, right hemisphere (χ^2[2] =42.67; p<0.001). By far, most subjects with CT/MRI demonstrated frontal lobe lesions (74%), followed by temporal lobe (47%), subcortical lesions (32%), enlarged ventricles (21%), parietal and occipital lobes (16%), and

TABLE 3. Clinical Presentation and Course

Variable	Data	χ^2
Seizure disorder (N=55)	13 Yes; 42 No	21.84***
Delusions (N=52)	48 Yes; 4 No	18.62***
Type (N=63)	37 persecutory; 6 bizarre; 5 grandiose; 4 reference; 3 religious; 3 Capgras; 2 Fregoli; 2 Cotard's; 1 jealousy	147.43***
Hallucinations (N=46)	40 yes; 6 no	25.13***
Type (N=46)	37 auditory; 6 visual; 2 olfactory; 1 tactile	76.67***
Thought disorder; disorganized/loose associations (N=52)	Yes: 4; No: 48	37.23***
Negative Symptoms (N=30)	Yes: 11; No: 19	2.13
	7 blunted affect; 5 isolation; 2 poor hygiene; 1 apathy; 1 avolition	13.60**
Course (N=31)	27 improved; 4 no improvement	17.06***
Efficacious Medications (N=28)	24 neuroleptics; 3 anticonvulsants; 3 antidepressants	29.40***

**p<0.01; ***p<0.001.

brainstem lesions (5%). Lesion location was significantly different from chance (χ^2[6]=25.20; p<0.001). All 13 subjects with SPECT/PET data showed positive findings which is greater than chance (χ^2[1]=13.00; p<0.001). The breakdown in localization was 46% for temporal lobes; 38%, frontal lobes; 8%, parietal lobe and brainstem, which was not significant (χ^2[3]=6.38; NS).

Although 71% of subjects were positive for abnormal findings on a neurological examination, this statistic did not reach significance (χ^2[1]=2.88; NS). A significant number of subjects did demonstrate impairments on neuropsychological testing (94%; χ^2[1]=13.24; p<0.001). Memory was the most commonly impaired function (76%), followed by executive functioning (65%), attention (53%), language (29%), and visuospatial skills (18%). This distribution was not significantly greater than chance (χ^2[4]=8.40; NS). Overall, 95% of subjects demonstrated at least one abnormal finding on neurological or neuropsychological studies, which is significantly greater than chance (χ^2[1]=33.39; p<0.001).

PD-TBI Versus Schizophrenia

Differences between PD-TBI and schizophrenia, based on a comparison of our data and the literature on schizophrenia, are presented in Table 5. PD-TBI appears to be less likely to demonstrate negative symptoms than schizophrenia (37% vs. 50%-90%), with subtle differences in most common symptoms.[60] For PD-TBI, the common negative symptoms are blunted affect (64%) and social withdrawal (45%), whereas the order is reversed in schizophrenia.[61]

Several differences were found on neurological studies. PD-TBI is more likely to show positive findings on MRI/CT than schizophrenia (70% vs. 12%-35%).[62–66] For PD-TBI, findings are more focal in nature, with frontal (74%) and temporal (47%) lesions the most prevalent. By contrast, schizophrenia is most commonly associated with whole-brain and hippocampal atrophy and enlarged ventricles.[71] On PET/SPECT scans, PD-TBI demonstrates abnormalities in both temporal (46%) and frontal areas (38%), whereas, in schizophrenia, hypofrontality is the most common finding, and temporal areas are generally normal.[72] EEG abnormalities are more prevalent in PD-TBI (77%) versus schizophrenia (20%–60%).[73] The most common EEG finding in PD-TBI is temporal spiking or slowing, whereas schizophrenia is associated with general slowing.[74]

DISCUSSION

Findings will be discussed within the context of each hypothesis:

1. PD-TBI results from both mild and moderate head injuries.

Mild and moderate-to-severe head injuries were represented evenly in our sample, although most cases of PD-TBI suffered a loss of consciousness. Our current finding differs from the previous analysis of case studies where moderate-to-severe injuries were overrepresented.[22] However, it mirrors the mixed results found in the literature where PD-TBI resulted from predominantly mild[7,8] or moderate-to-severe TBI,[5,14,22,] or were evenly distributed between mild and moderate-to-severe TBI.[23,24]

2. There is a bimodal distribution of time between TBI and onset of psychosis. Many persons develop psychosis within the first year after sustaining a brain injury, or after 5 years. The mean latency between the TBI and onset of psychotic symptoms is between 4 and 5 years.

In our sample, 38% developed a psychosis within the first year after sustaining a TBI, whereas 36% developed

TABLE 4. Laboratory Findings

Variable	Data	χ^2
EEG abnormalities (N=14)	Yes: 11; No: 3	4.57*
Hemisphere (N=11)	8 left; 2 bilateral; 1 right	28.67***
Localization (N=10)	5 temporal; 3 frontal; 1 occipital; 1 parietal	7.33
Type of abnormality (N=12)	7 slowing; 5 spiking;	0.33
CT/MRI: positive (N=24)	Yes: 19; No: 5	8.17**
Hemisphere (N=19)	9 left: 9 bilateral; 1 right	42.67***
Localization (N=37)	14 frontal; 9 temporal; 6 subcortical; 4 ventricles; 3 parietal; 3 occipital, 1 brainstem	25.20***
SPECT/PET (N=13)	Yes: 13; No: 0	13.00***
(N=13)	6 temporal; 5 frontal; 1 parietal; 1 brainstem	6.38
Neurological signs (N=17)	Yes: 12; No: 5	2.88
Neuropsychological testing: impairment (N=17)	Yes: 16; No: 1	13.24***
Domain (N=37)	13 memory; 11 executive functions; 9 attention; 5 language; 3 visual-spatial	8.40
Any abnormality (N=39)	Yes: 37; No: 2	33.39***

*p<0.05; **p<0.01; ***p<0.001.

a psychosis after 5 years. This bimodal distribution was consistent with the previous literature.[1,3,15,21,22,24] The mean latency of onset of psychosis was 3.6 years after TBI, which was slightly lower than the predicted mean of 4–5 years found in the literature.[7,22,23]

TABLE 5. Potential Characteristics Discriminating Between PD-TBI and Schizophrenia

	PD-TBI	Schizophrenia
Presence of Negative Symptoms	37%	50%–90%[60]
	64% blunted affect	46% social withdrawal
	45% social withdrawal	33% blunted affect[61]
MRI/CT: Positive Findings	70%	12%–35%[62–66]
Atrophy	0%	12%–35%[67,68]
Focal abnormalities	100%	6%–9%[69,70]
Most common finding	74% frontal	Whole brain
	47% temporal	Hippocampal atrophy
	21% enlarged ventricles	Enlarged ventricles[71]
SPECT/PET	46% temporal	Hypofrontality[72]
	38% frontal	
EEG: Positive Findings	77%	20%–60%[73]
Most common finding	Temporal spiking/slowing	Slowing (delta)[74]
	PD-TBI	**Schizophrenia**
Presence of Negative Symptoms	14%	25%–84%[61,62]
MRI/CT: Positive Findings	65%	12%–35%[63–67]
Atrophy	60%	12%–35%[68,69]
Focal abnormalities	62%	6%–9%[70,71]
Most common finding	42% frontal	22%–35%[63–65]
	27% temporal	
	20% ventricles	Enlarged ventricles
EEG: Positive Findings	70%	20%–60%[72]
Most common finding	Temporal slowing	Frontal slowing[74]

3. Seizure disorder is more common in PD-TBI than in TBI.

The percentage of subjects sustaining a posttraumatic seizure was 23.6%, which was significantly greater than prorated base rate of 7%. The higher rate of posttraumatic seizures is consistent with studies examining World War II veterans with primarily open head injuries,[14] and state hospital patients with primarily closed head injuries,[7] as well as previous case studies in the literature.[22] The lone study without a higher posttraumatic seizure rate (9%) was based on patients from a tertiary neuropsychiatric unit and medico-legal cases.[23]

4. Most persons with PD-TBI improve in presentation, with antipsychotics the most efficacious medications.

As with our previous analysis of PD-TBI case studies in the literature, as well as neuropsychiatric patients, a majority of subjects improved with antipsychotic medications.[22,23] Unfortunately, long-term course cannot be determined by our data, and there is evidence that for many, PD-TBI has a chronic course. One study with predominantly open head injuries reported that 40% sustained chronic delusions,[21] and another, with 1–10 year follow-up reported that most subjects did not demonstrate improvement.[14]

5. Male gender and family history of schizophrenia are risk factors for developing PD-TBI.

There was an overrepresentation of men in our PD-TBI sample, even when controlling for the (2:1) gender base rate. Our data are consistent with the previous literature; this is a highly robust finding.[1,7,8,15,22–24]

Interestingly, the preponderance of men who develop PD-TBI parallels the slightly higher risk for men to develop schizophrenia (OR: 1.4).[75]

About 17.6% reported a family history of schizophrenia, which is significantly higher than the base rate for persons without schizophrenia (3.7%).[58] This percentage is lower than reported in Sachdev et al.(24%),[23] in which family history of psychosis was the strongest statistical predictor of PD-TBI. However, it is also almost identical (17.6%) to the Roscommon study that identified percentage of first-degree relatives in a large-scale schizophrenia sample.[58]

A potential implication of the similar family history percentages is that PD-TBI, like schizophrenia, results from an interaction between genetic vulnerability and environmental stressor.[76] This interaction would account for the much higher percentage of head injury before onset of psychosis in schizophrenic populations, which ranges from 8.8% to 39.6%,[7–12] as well as both premorbid neurological conditions[7,12,13] and psychiatric illness[5,14,15] being predisposing factors for PD-TBI. PD-TBI develops only after a threshold of damage is sustained to key brain areas.[77,78]

6. The most common psychotic symptoms associated with PD-TBI are persecutory delusions and auditory hallucinations. Negative symptoms are less pronounced.

In our sample, the most prominent symptoms were delusions (92%) and hallucinations (87%), with persecutory delusions (77%) and auditory hallucinations (92%) the most common subtypes. A much smaller percentage demonstrated negative symptoms (37%). These findings are consistent with the PD-TBI literature that reports a modal presentation of persecutory delusions (22%–80%),[1,7,14,15,22,23] and auditory hallucinations (47%–84%),[7,22,23] whereas negative symptoms are much less prominent (15%–22%).[1,22,23] A slight difference between our data and previous studies is the much higher percentage of patients showing negative symptoms in our study. It is believed that this increase can be attributed to changes from DSM-III to DSM-IV criteria for schizophrenia, in which negative symptoms became more prominent diagnostic criteria.[26] Data from the current study were procured from cases reported in the 2000s, whereas data from earlier studies were primarily cases in the 1980s and early 1990s, before the publication of DSM-IV.

7. PD-TBI is associated with cognitive impairments, most commonly in memory and executive functioning.

In our study, 94% of known cases demonstrated impairments in neuropsychological functioning. This percentage is similar to a previous study conducted by Fujii and Ahmed,[22] which reported a finding of 88%. In both studies, the most common impairments were executive functioning and memory—a robust finding in the literature.[8,23] Unlike the findings in other studies, deficits in vocabulary or verbal skills were much less pronounced.[8,23]

8. PD-TBI is associated with lesions to frontal and temporal areas of the brain as identified by neurological studies.

Our study reported 79% positive findings in the EEG and CT/MRI and 100% on PET/SPECT scans, with 95% of patients demonstrating an abnormality on any neurological study. The most consistent finding for all neurological studies were focal abnormalities in frontal and temporal areas: EEG (frontal: 21.4%, temporal: 35.7%), MRI/SPECT (frontal: 38.4%, temporal: 46%.), CT/MRI (frontal: 58.3%, temporal: 37.8%). Lesion localization in these areas is uniform within the PD-TBI literature, with localization determined by distance from missile wounds[1,15] and findings on MRI/CT[14,22,23,25]and EEG.[22,23]

9. PD-TBI will differ from PWS in the following manner: Persons with PD-TBI are 1) less likely to present with negative symptoms; 2) more likely to demonstrate positive findings on CT/MRI, with the most common findings being focal lesions to temporal and frontal lobes, versus patients with schizophrenia (PWS), who commonly present with enlarged ventricles; and 3) more likely to demonstrated positive findings on EEG, with the most common finding of temporal slowing, versus PWS, who most commonly demonstrate frontal slowing.

Our findings are generally consistent with the previous study analyzing case studies in the literature,[22] with some minor differences in percentages. Both studies suggest that PD-TBI and schizophrenia demonstrate a pattern of differences on neurological studies. PD-TBI is associated with more focal lesions in frontal and temporal areas on structural (CT/MRI) and functional imaging (PET/SPECT), whereas temporal areas are implicated on EEG. By contrast, schizophrenia is associated with more global neuropathology, including global cortical atrophy and enlarged ventricles in addition to hippocampal atrophy on CT/MRI, and EEG characterized by general slowing. PET/SPECT in

schizophrenia is associated with hypofrontality without abnormalities in temporal areas. Also, schizophrenia is more likely to present with negative symptoms. These differences would be useful to discriminate the two disorders and provide evidence that PD-TBI is a distinct subtype of psychotic disorder.

A broader implication is that our findings, in combination with the general PD-TBI literature, provide support for conceptualizing psychosis as a neurobiological syndrome. According to Fujii and Ahmed,[79,80] a disorder is a neurobiological syndrome if it meets the following criteria:

1. A constellation of symptoms is reliably associated with neuropathology in a circumscribed structural location or neural circuit.

Evidence from schizophrenia imaging research indicates that both delusions[81] and auditory hallucinations[82] are associated with abnormalities to frontal and temporal-hippocampal areas.

2. Similar neurobiological disturbances (location or neural circuit) secondary to different etiologies would result in similar cognitive or behavioral symptoms.

The presentation of delusions and auditory hallucinations in PD-TBI are very similar to the positive symptoms commonly found in schizophrenia. A robust finding in PD-TBI is frontal and temporal lesions found in neurological studies.[1,14,15,22,23,25] The onset and course of the two disorders are also similar. Schizophrenia is commonly preceded by a prodrome in which a person demonstrates a decline in functioning and increase in psychiatric symptoms before the onset of a full-blown psychotic disorder. Prodromes are highly variable in duration, ranging from days to years, with some evidence for a bimodal distribution of less than 1 year to more than 4.5 years.[83] A consistent finding in PD-TBI is a latency period from the time of TBI to the onset of psychotic symptoms, with a similar bimodal distribution. One study reported that all their cases of PD-TBI was preceded by a prodrome.[23]

3. Less neurobiologic disturbance is associated with milder symptoms.

Our findings suggest that schizophrenia is associated with more global brain abnormalities than PD-TBI. Not surprisingly, schizophrenia also appears to be associated with a more severe presentation as evidenced by a greater likelihood of negative symptoms[22,23] and more severe and global cognitive impairment.[8] Both negative symptoms[84,85] and cognitive functioning[86,87] have been found to be highly correlated with illness severity and long-term prognosis in schizophrenia.

4. Additional symptoms, such as cognitive, mood, psychiatric, or other associated neurological symptoms, are related to other networks' simultaneously being affected by underlying neurochemical or neuropathologic processes.

As reported previously, frontal (PET) and temporal (CT/MRI) abnormalities were among the most common found in schizophrenia. Lesions to these areas are reliably associated with cognitive deficits in executive functioning and memory, two of the most frequently reported neuropsychological deficits in schizophrenia.[88] In PD-TBI, frontal and temporal abnormalities[1,14,15,22,23,25] and impairments in executive functioning and memory[8,22,23] are robust findings.

5. Aside from treating underlying disease process, treatment for the associated symptoms of a neurobiological disorder of different etiologies is similar.

Similar to schizophrenia, the most efficacious treatment for the positive symptoms of PD-TBI is the use of antipsychotic medications.[22,23]

The current study has several limitations, primarily associated with potential biases in using archival data. For example, differences in reporting data across studies resulted in various missing data-points for each case. Accuracy or comparability of data can be affected by the subjectivity of the researchers. Published case studies may be biased toward those with positive findings or perhaps shorter latency for onset of symptoms. Finally, our comparison of PD-TBI and schizophrenia is based on observation of descriptive statistics, versus inferential statistical analysis, as the ranges reported from the schizophrenia literature do not lend themselves to statistical comparison.

Future directions for research include replicating our findings with prospective studies using objective measures for data-gathering. Given the rarity of PD-TBI, studies may need to employ multicenter methodologies or utilize institutions with large samples of TBI, such as the military or veteran affairs treatment centers. Another direction for research is to extend beyond the focus of PD-TBI as a distinct entity, and instead attempt to elucidate the conceptualization of psychosis as a neurobiological syndrome. Studies could examine whether those

who develop PD-TBI have the same genetic predisposition to schizophrenia,[89] and, if so, whether this predisposition interacts with TBI severity or latency between TBI and onset of psychosis. The prodrome in PD-TBI would be another area of interest, particularly if the pattern and characteristics of progression mirror those of schizophrenia. Knowledge from these types of studies would not only assist in understanding of psychotic disorders in general, but may also set the groundwork for prevention of PD-TBI in high-risk individuals.

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