

Traumatic Brain Injury as a Risk Factor for Schizophrenia

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Abstract: Traumatic brain injury (TBI) is associated with schizophrenia, but the causal nature of this relationship is not clear. Three models for their association exist: 1) TBI causes a phenocopy of schizophrenia (parallelism); 2) TBI is a marker of schizophrenia vulnerability (spurious association); and 3) TBI interacts with genetic vulnerability to cause schizophrenia (interaction or effect modification). We found that TBI is a causal component of some cases of schizophrenia, specifically those with enhanced genetic vulnerability. This has biological plausibility. Prevention of 50% of these cases could lead to a savings of \$313 million annually in the United States. Further research on critical windows for traumatic brain injury in vulnerable individuals could shed light on the developmental pathophysiology of schizophrenia.

Keywords: Traumatic brain injury, schizophrenia, prevention, gene-environment interaction, risk.

INTRODUCTION

An association between traumatic brain injuries (TBI) and later serious psychopathology, including psychosis, has been observed since the 19th century [1]. Early in the 20th century, Emil Kraepelin [2] hypothesized that head injuries in childhood might either cause or release predisposition to schizophrenia, implicating a causative role for TBI in psychotic illness. Psychotic symptoms occur more frequently in individuals who have had TBI, and patients with psychotic disorders are consistently more likely to have prior TBI than the general population [3]. Understanding the association of TBI with psychosis is important as 1) it has implications for prevention and 2) it may shed light on the pathophysiology of both psychosis and TBI.

Although the more common psychiatric sequelae of TBI are mood disorders [4], personality changes [5], and cognitive deficits [6,7], psychosis is a disturbing and disabling outcome of TBI with great morbidity and cost. About three million people incur TBI in the U.S. each year: these individuals are estimated to have a two to five-fold greater risk of developing psychosis compared with the general population [8].

The differential diagnosis for psychosis subsequent to TBI includes “psychotic disorder following traumatic brain injury” (PDFBTBI) [9], a diagnosis made only if the psychosis cannot better be accounted for by a primary psychotic disorder (i.e. schizophrenia) and only if there is “evidence from the history, physical examination or laboratory findings that the disturbance is the direct physiological consequence” of the TBI (DSM-IV). In practice, differential diagnosis for the phenomenon of posttraumatic psychosis is challenging. Although focal brain pathology may distinguish PDFBTBI from schizophrenia in some cases [9], both disorders share temporal lobe abnormalities and ventricular enlargement [10]. Likewise, a relative dearth of negative symptoms may char-

acterize PDFBTBI, but both disorders share qualitatively similar positive symptoms of hallucinations and paranoid delusions, cognitive deficits in memory and executive function, increased prevalence of family history of psychosis, and even prodromal symptoms (reviewed in [9]). Further, while a causal role for TBI is explicit in the diagnosis of PDFBTBI, TBI may also be an etiological factor for the complex multifactorial disorder of schizophrenia.

Psychosis is a plausible outcome of traumatic brain injury. The period of greatest risk for a TBI is from the mid-teens through the mid-twenties, prior to the onset of most psychotic disorders, with males having a several fold higher risk for TBI than females [11,12]. Brain regions implicated in schizophrenia, such as the prefrontal cortex, temporal lobes and hippocampus, are particularly vulnerable to TBI. The bony protrusions adjacent to the orbitofrontal and anterior temporal lobes render these areas vulnerable to damage from the differential motion of the brain within the fixed skull. Axons are stretched and sheared from the rotation of the brain, which may injure important corticocortical pathways [13]. Secondary damage to brain regions remote from the point of impact in TBI is evident, including the cerebellum in animal models [14] and the hippocampus in clinical studies [15].

Evidence of a correlation between TBI and subsequent psychosis (and schizophrenia) in the existing literature is strong, though not definitive. Schizophrenia and other “primary” psychotic disorders are complex heterogeneous illnesses that likely arise from the interaction of multiple etiologies, including genes, obstetric complications, and other exposures. Schizophrenia has a large genetic component; nonetheless, among identical twins, there is only a 50% concordance rate of schizophrenia, suggesting that environmental factors may also play a role [16]. There is evidence that in utero exposures, such as infections like influenza or rubella [17], or malnutrition [18], is associated with later schizophrenia. Perinatal events such as obstetric complications have also been linked to increased risk for schizophrenia [19]. Candidates for postnatal exposures that increase risk of schizophrenia include early trauma and life events [20], as well as traumatic brain injury. TBI may be an etio-

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logical factor with small or large effects on risk for psychosis and schizophrenia, depending on inherent genetic vulnerability and other exposures.

EVIDENCE FOR AN ASSOCIATION OF TRAUMATIC BRAIN INJURY AND SUBSEQUENT PSYCHOSIS

Beginning in the early 20th century, a number of studies found that brain-injured individuals have increased rates of ensuing psychosis, as compared with the general population. For example, in 1920, Kornilov [21] followed 340 patients with brain injury and found "psychotic symptoms" and a "personality transformation" consistent with negative symptoms in 26.5% of these patients. In another ten to fifteen year follow-up study of forty patients who incurred severe brain injury, 20% were found to develop posttraumatic psychosis (undefined), and many patients had features characteristic of the deficit symptoms of schizophrenia, including loss of social contact (68%), lack of interest (55%), asponaneity (53%) slowness (53%) and speech abnormalities [22]. A Finnish study found a somewhat lower rate of posttraumatic psychosis - 7.95% - in randomly ascertained Finnish soldiers with brain injury [23]. It is important to note that no clear diagnostic criteria for psychosis were used in any of these studies.

In contrast, a much lower rate of posttraumatic psychosis is found when using more contemporary diagnostic criteria. In a retrospective chart review study of 670 World War II British soldiers with penetrating brain injuries only five of the veterans (0.7%) developed psychosis during the four years of follow-up [24]. This rate is comparable to the population risk for schizophrenia and argues against an association between brain injury and ensuing psychosis. This study by Lishman was among the first to use contemporary diagnostic criteria, and notably, mood disorders, dementias and amnesic disorders were counted separately. The patients were all evaluated and treated at the same brain-injury unit and vigorous efforts were made to follow the patients, with annual questionnaires sent to patients, relatives, employers, general practitioners and social service agencies. However, psychotic patients were not contrasted with other groups and the follow-up period was only four years.

An analysis of consolidated data from eight long-term follow-up studies published between 1917 and 1964 yielded an overall rate of psychosis following brain trauma of 0.7 to 9.8%, with a median rate of 1.35% [25]. As mentioned before, there are a number of methodological limitations to these studies, and they vary in terms of subject population, ascertainment strategies, extent of blinding of investigators, attention to potential confounding factors, diagnostic criteria, and lengths of follow up [26]. The subjects of these reports ranged from civilians incurring concussions to soldiers suffering combat injury. Frequently, confounding variables such as age, gender and exposure to combat were not controlled for. Many of the studies had low statistical power and contained imprecise data on traumatic brain injury and diagnosis of subsequent psychiatric disorders; different diagnostic criteria were employed and were typically not standardized or specified. Durations of follow-up ranged from as little as three months to more than twenty years. The two lowest rates of posttraumatic psychosis came from two studies with

follow-ups of only 3 months and 2 years. Davison and Bagley noted that the incidence of psychosis increased over time and that many individuals did not become psychotic until years after the injury, demonstrating the need for lengthy follow-up in assessing true rates of posttraumatic psychosis. In comparing this range of 0.7 to 9.8% (with a median of 1.35%) to the .8% lifetime incidence of psychosis in the general population over a period of 25 years, Davison and Bagley concluded that brain trauma increased the observed incidence of psychosis by two to three fold over a period of ten to twenty years. A more recent prospective study, however, suggests a smaller increase in incidence of schizophrenia from TBI, with odds ratios of ~1.3 – 1.4 [27].

Of note, retrospective studies of premorbid traumatic brain injury in schizophrenia patients also suggest a relationship between traumatic brain injury and subsequent primary psychotic disorders. For example, Wilcox and Nasrallah [28] conducted a blinded chart review study that included only traumatic brain injury with loss of consciousness before age 10 with medical complications severe enough to warrant medical evaluation. They found premorbid brain injury in 11% of schizophrenia patients, compared to 4.9% of mania patients, 1.5% of depressed patients and 0.7% of surgical controls.

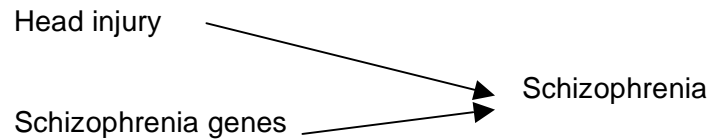
Case control studies also suggest an association of TBI with schizophrenia. For example, schizophrenia cases have a more than doubled prevalence of childhood TBI as compared with controls, specifically family members without psychosis [29]. TBI patients with psychosis (cases) appear to have a pre-existing neural vulnerability as compared with TBI patients without psychosis (controls), characterized either by family history of psychosis [30] or by earlier TBI or neurological conditions [31]. These case-control studies are all consistent with TBI interacting with latent vulnerability to yield psychosis.

The association of specific types and locations of TBI with subsequent psychosis has been examined. Severity of injury is related to risk for psychosis in most but not all studies (reviewed in [32]). Other characteristics of TBI (i.e. closed vs open) and age at injury are not predictive of psychosis [30,31]. Several studies, however, suggest a link between left hemisphere injury, particularly of the temporal lobe, with psychosis (reviewed in [32]), a pattern found in other neurological conditions [33,34].

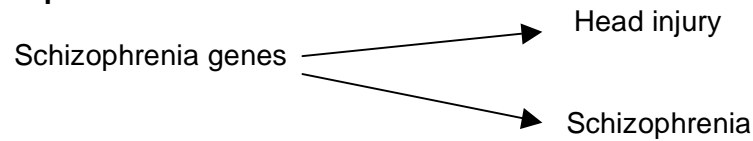
EXPLANATORY MODELS FOR THE ASSOCIATION OF TRAUMATIC BRAIN INJURY AND SCHIZOPHRENIA

Carefully designed recent pedigree studies also demonstrate an association between TBI and subsequent psychosis. In a study of members of schizophrenia and bipolar pedigrees, schizophrenia patients had a threefold greater rate of reported brain injury as compared with family members who were never mentally ill [35]. (Of note, the association of brain injury and psychopathology was not specific to schizophrenia, as subjects with bipolar and unipolar depression had a twofold greater rate of brain injury than family members without mental illness.) There are several possible models that might explain the association of brain injury and schizophrenia, including (1) TBI leads to a phenocopy of genetic schizophrenia, (2) TBI and schizophrenia are spuriously as-

1) Phenocopy/parallelism



2) Spurious relationship



3) Gene-environment interaction

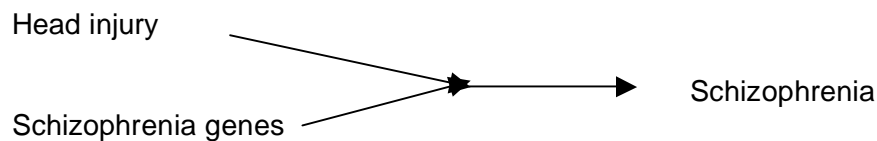


Fig. (1). Models of associations between head injury and genes in schizophrenia risk.

sociated, in that they are both related to a third factor, or (3) TBI interacts with genetic vulnerability to cause schizophrenia (Fig. 1). These models are described below, and then a strategy for distinguishing among them is defined, specifically the exploration of the associations among TBI and schizophrenia in genetically high and low risk populations.

1) Post-Traumatic Psychosis as a Phenocopy of Schizophrenia: Parallel Pathways to Causation

It has been hypothesized that TBI can cause a schizophrenia-like illness directly, yielding a nongenetic **phenocopy** of the illness [36]. A model in which both genetic vulnerability and TBI can contribute to schizophrenia risk independently is consistent with parallelism or parallel pathways to causation as defined by Darroch [37]. In this model, risk for schizophrenia is the sum of the individual genetic and environmental effects, which affect the same system and thus both add to risk. For example, if genetic variability affected frontolimbic circuitry through neurotransmitter receptor function, and TBI altered the same circuitry neuroanatomically, then genetic expression and TBI may combine in an additive fashion to increase the risk of disease.

This model of parallel causation would predict that highly familial cases of schizophrenia would have lower rates of premorbid TBI than would non-familial cases. In fact, Edith Zerbin-Rudin found that the risk for schizophrenia was particularly low in siblings of probands whose onset of illness occurred within a year of major brain trauma [38].

2) Could TBI and Schizophrenia have a Spurious Association?

In addition to the phenocopy/parallelism model, another possibility is that the relationship between TBI and schizophrenia is **spurious**. What this means is that the environmental factor – TBI – may simply be a marker of disease vulnerability, and not contribute to causation or the actual risk for the disorder. In this model, genes for schizophrenia

influence the chances of exposure to TBI. A vulnerability to schizophrenia could entail a vulnerability to TBI through premorbid factors. Factors predisposing to TBI may include premorbid impulsivity, attentional abnormalities, subtle cognitive dysfunction, motor dyscoordination and sensory-motor integration deficits. Pandysmaturation, a putative neurointegrative defect in cognitive and motor development, has been identified in high-risk schizophrenia samples [39] and may in and of itself increase the risk for incurring TBI.

In the spurious association model, unaffected family members with unexpressed genetic vulnerability should have elevated rates of TBI. Of note, unaffected family members of schizophrenia probands have been found to have a number of neurological problems found in patients, including motor abnormalities [40], which adds to the plausibility of this model. In fact, elevated rates of TBI in unaffected relatives of schizophrenia patients have been found in multiplex pedigrees [35].

3) Gene-Environment Interaction: A Model for Synergistic Effects Between Genes and TBI in Schizophrenia Causation

A third model is that TBI could interact with genetic or other vulnerability factors to lower the threshold for expressing psychotic illness. One model for this type of gene-environment interaction is “effect modification”, wherein the TBI and genetic factors each alter the other’s effect in a non-additive fashion, also known as synergy (Fig. 2) [3]. This means that genes have a different effect in people with and without the exposure, and conversely, exposure has a different effect in people with and without a particular genotype. This model could explain an increase in schizophrenia following TBI, if illness were more likely to ensue in those who had a certain genetic vulnerability.

The gene-environment model predicts that the odds ratio for schizophrenia expression based on history of TBI would differ among low and high genetic risk populations.

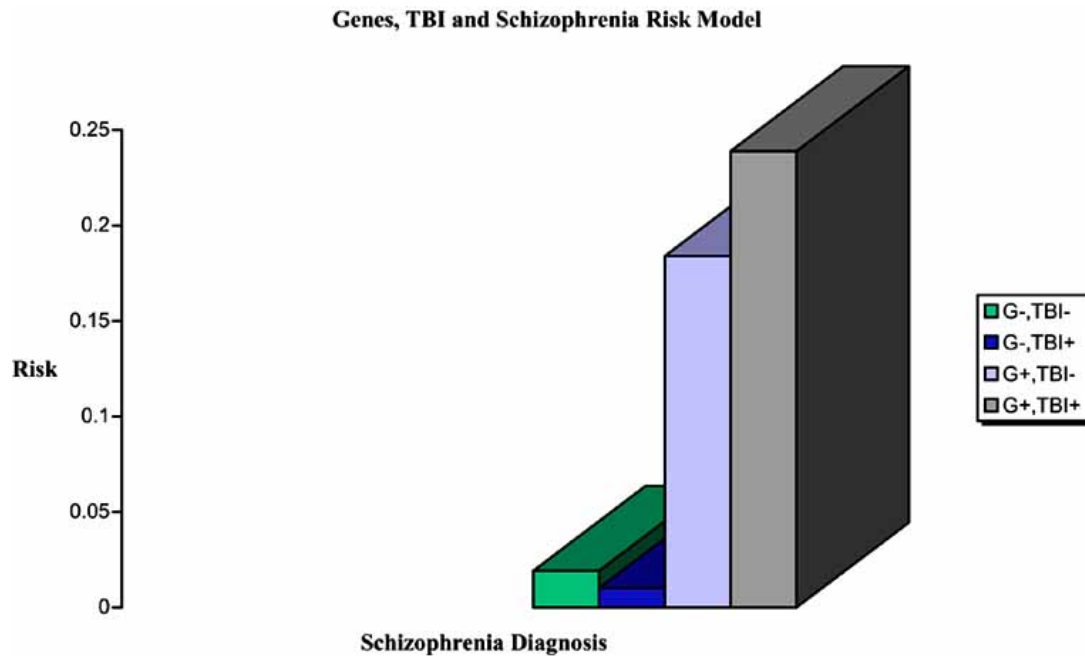


Fig. (2). Risk of schizophrenia according to presence of genetic risk and traumatic brain injury. G- represents membership in bipolar pedigree and presumed low genetic risk. G+ represents membership in schizophrenia pedigree and presumed high genetic risk. TBI- and TBI+ represent respectively no exposure, or exposure to traumatic brain injury. Copyright M.E. Sharpe, International Journal of Mental Health.

Testing these Models in a Study of TBI and Subsequent Psychosis in High-Risk and Low-Risk Pedigrees

We have been able to test these three models/hypotheses using data on TBI exposure in schizophrenia and bipolar multiplex pedigrees [35]. Our assumption is that membership in the schizophrenia pedigree reflects relatively *higher* genetic vulnerability for schizophrenia and membership in the bipolar pedigree reflects relatively *lower* genetic vulnerability for schizophrenia. TBI exposure was assessed in all members of both types of pedigree, including individuals with schizophrenia and their unaffected relatives.

Of note, the subjects were members of the NIMH Genetics Initiative schizophrenia and bipolar multiplex pedigrees. They came from families with at least two biologically related first-degree relatives diagnosed with core illness [41]. Diagnostic interviews were conducted with the Diagnostic Interview for Genetic Studies [42], which specifically inquired about serious TBI. The bipolar and schizophrenia sites had adopted common diagnostic procedures so that joint analyses of these two pedigree sets could be undertaken.

We examined whether genetic loading and TBI interact to increase the risk for disease more than either factor alone. We proposed that genes and environmental exposures might work independently to cause disease (parallel pathways) and/or have joint effects (synergy). The three models/hypotheses have the following predictions about this data set:

1. The “phenocopy/ parallelism” hypothesis predicts that schizophrenia patients in the bipolar pedigree (lower genetic vulnerability) would have a *greater* incidence of premorbid TBI than schizophrenia patients

in the schizophrenia pedigree (higher genetic vulnerability).

2. The “spurious association” hypothesis predicts that there would be equivalent rates of TBI among schizophrenia patients in the two pedigrees.
3. The “joint effects/synergy” hypothesis predicts that schizophrenia patients in the bipolar pedigree (lower genetic vulnerability) would have a *lower* incidence of premorbid TBI than schizophrenia patients in the schizophrenia pedigree (higher genetic vulnerability).

In this study, the bipolar pedigree sample had 1271 subjects and the schizophrenia pedigree sample included 561 subjects. Compared to the never mentally ill subjects, the exposure odds ratios for TBI was increased for schizophrenia (OR=3.32, $p=.001$), in line with other cross-sectional studies of schizophrenia patients, suggesting an association between TBI and schizophrenia. Risk was unrelated to the severity of the TBI. We compared the association of TBI and schizophrenia between pedigree types. Only 4.5% (1/22) of schizophrenia subjects from bipolar pedigrees (non-genetic schizophrenia) had TBI, vs 19.6% (21/107) of those from schizophrenia pedigrees. Therefore, the presumed “schizophrenia phenocopies” (from the bipolar pedigree) were less likely to have TBI exposure than were the schizophrenia subjects from schizophrenia pedigrees. This finding is inconsistent with both the purely spurious association model and the phenocopy model and instead supports the hypothesis for gene-environment interaction.

Further, using data from the multiplex pedigrees and an approach from Darroch [37], we have compared models of gene-exposure associations based on 1) joint effects of genes and TBI (synergism) and 2) additive and independent effects of genes and TBI (parallelism or phenocopy model). This

analysis showed that a greater magnitude of gene-environment interaction accounted for the risk for schizophrenia from TBI than did parallel actions of genes and TBI [3].

In sum, being in a high-genetic-risk schizophrenia pedigree (as opposed to a low-genetic-risk bipolar pedigree) increased one's risk for schizophrenia by 9.68. Among subjects in schizophrenia pedigrees, TBI further increased the risk for schizophrenia by 2.89 fold. In contrast, TBI did not increase the risk for schizophrenia for those with low genetic risk [35].

TBI AND SCHIZOPHRENIA: ATTRIBUTABLE RISK OF APPROXIMATELY 1%

The observed relationship between TBI and schizophrenia suggests that gene-environment interaction rather than phenocopy induction accounts for the association. TBI had a different effect in people with and without the predisposing genotype: posttraumatic psychosis primarily ensued in those who had a genetic vulnerability for schizophrenia. Membership in a schizophrenia pedigree raised the risk of schizophrenia and TBI exposure further enhanced that risk. Subjects with both genetic vulnerability and TBI had a .24 probability of schizophrenia, compared to .18 in those with only genetic vulnerability (and no TBI) and .01 in those with only TBI (and no genetic vulnerability). The latter 1% schizophrenia prevalence is consistent with that found in most population studies, and suggests that TBI without genetic vulnerability may not substantially increase the risk of schizophrenia over the published population prevalence.

Based on these data, the actual attributable risk would depend on the prevalence of schizophrenia genes. Schizophrenia vulnerability is likely polygenic and widely disparate rates for the frequency and penetrance of schizophrenia have been proposed. To be conservative, and for simplicity, we can assume a disease gene frequency of 0.005 and a penetrance for affected phenotype of .45 at age 35 [43]. The genes alone would account for $.0005 \times .45 = 2.25$ cases/1000 (roughly a quarter of cases.) TBI in these subjects would increase the risk by .33 to 3 cases/1000 (calculation = $2.25 \times .24/.18$). To remain conservative, we assume independence of schizophrenia genes and TBI and assume a cumulative prevalence of .10 for TBI. Then, in the 90% of schizophrenia patients who have genetic vulnerability but no TBI exposure the risk would be 2.25 cases/1000 and in the 10% of those with both genetic vulnerability and TBI it would be 3/1000. The risk would be increased by TBI by .105 cases/1000 (from $2.25/1000$ to $2.325/1000$; 2.325 is the sum of $.9 \times 2.25 + .1 \times 3$). Therefore, the attributable risk from TBI would be .105 cases/1000 population. In this conservative model, assuming a .01 prevalence of schizophrenia, TBI may account for about 1% of all schizophrenia cases.

This analysis is intended to represent an approach to examining effects of genes and TBI without knowing the identity or presence of particular vulnerability genes. These data were generated with simplistic models and caution should be taken in interpreting these findings. First, we assumed that subjects from bipolar pedigrees did not have genes for schizophrenia. Next, we assumed a unitary genetic risk for schizophrenia in all pedigree members. We also ignored the

temporal relationships of TBI and disease onset in these analyses, which would be necessary to examine causality.

EFFORTS AT PREVENTION OF TBI: IMPLICATIONS FOR SCHIZOPHRENIA RISK

Secondary Prevention

There may be public health implications to these data if immediate medical approaches to TBI can minimize resultant neurotoxicity for those with schizophrenia vulnerability. The prevention of TBI or the modification of the brain response to the trauma might decrease the incidence of the major psychiatric disorders in those already vulnerable. New medications now given at the time of severe brain trauma to stop oxidative damage from evolving may minimize the exposure-related disease. However, we have not yet fully characterized the nature of brain injuries that are related to schizophrenia, specifically the timing, severity or means of trauma. These will be important data to obtain before specific prevention programs can be developed and implemented.

Primary Prevention

The NIH Consensus Development Panel on Rehabilitation of Persons with Traumatic Brain Injury [11] reports the highest incidence of TBI is among individuals ages 15 to 24 (and the elderly), with another peak in children younger than five. Motor vehicle accidents are a major cause of TBI across all age groups, accounting for 50% of all TBI.

Among very young children, falls are the second most frequent cause of TBI. The NIMH panel estimates that changes in the design of strollers, walkers and shopping carts may have prevented the occurrence of some TBI in this age group [11]. Another significant cause of TBI in the very young is assault – both shaken baby syndrome and domestic violence [6]. A literature search using the terms “shaken baby syndrome” with psychosis and schizophrenia did not yield any reports. However, reported rates of prior child abuse are 20/38 or 52% of patients with first-episode psychosis [44] and 27/61 or 44% of patients with chronic psychosis [45]. Among infants and young children, programs aimed to reduce violence and child abuse should significantly reduce TBI. Of note, although it was once considered that TBI in infants and young children might create less morbidity than in older individuals as the young brain is more plastic, in fact very young children may be more vulnerable, especially to cognitive effects [6].

In teens, TBI incurred during sports, including mild brain trauma, have been shown to have clear neurological consequences. Collins *et al.* [46] found a significant interaction of learning disorder and multiple concussions on performance in Trail-Making Test B and Symbol Digit Modalities. In a cross-sectional study of 33 amateur soccer players vs 27 amateur swimmers and track athletes, soccer players were found to have impaired memory, as assessed by several measures (presumably from heading the ball) with concussion further worsening performance [47]. Sports-related TBI, broadly defined and reported by school trainers in an observational cohort study, affected at least 1 per 100 player-seasons in not only football, but wrestling, girls' soccer and girls' basketball as well [48]. Collision was the operative factor, including both with other players and with objects

(i.e. field hockey sticks, heading a soccer ball). Powell and Barber-Foss, the authors of this observational cohort study, suggest that the morbidity of sports-related TBI in teens could be reduced through 1) the focus on development of player skills, modifications of rules and improved teaching methods and 2) the provision of accurate and consistent medical management of any TBI [48]. Of note, the use of helmets has likely reduced TBI-related morbidity among sports players in the past few decades. Gerberich *et al.* [49] found 19 concussions per 100 players in the late 70's among high school football players, before the implementation of the National Operating Committee for Safety in Athletic Equipment helmet protection standards. In more recent years, McCrea *et al.* [50] and Powell *et al.* [48] reported concussion rates in high school football players of 4.3% and 3.9% respectively.

For adolescents and young adults, traumatic brain injuries largely result from violence (1/2 firearm and 1/2 non-firearm related) [11] and motor vehicle accidents [6], similar to the main causes of mortality in this age group. Alcohol use is a predictor of traumatic brain injury in teens and young adults [51] and is related to both violence and motor vehicle accidents (reviewed in [52,53]). Alcohol use characterizes ~1/3 of motor vehicle accidents in youth ages 15-20 [54]. Preventive interventions have proven successful in reducing alcohol-related traffic fatalities and injuries among teens in the past few decades, including 1) the activism of citizen groups such as Mothers Against Drunk Driving (MADD), who raised public attention, mobilized grassroots support, and lobbied for increases in the minimum age for purchase of alcohol, and 2) deterrence, such as zero tolerance laws for any alcohol use in young drivers [55]. It is plausible that similar approaches – grassroots activism and new statutes – could reduce the morbidity and mortality related to teen violence.

PREVALENCE OF TBI AND ITS COSTS IN CARE AND QUALITY OF LIFE

The NIH [11] panel estimates that the annual cost of care and rehabilitation for new cases of TBI in the United States approaches \$10 billion, principally as a result of motor vehicle accidents, falls, acts of violence and sports injury. The incidence of TBI is 100 per 100000 persons and the prevalence is estimated at 2.5 to 6.5 million people. 1.5 to 2 million people incur TBI each year in the United States. The morbidity associated with TBI reduces quality of life and creates health problems. Effects of TBI can be estimated by an overall crude health index, in which a specific state of health is considered to lie on a continuum between 0 (death) and 1 (perfect health) [56]. Quality-adjusted life years or QALYs are calculated by multiplying life expectancy in years by this overall health index (estimated as lying between 0 and 1). QALYs are used to estimate the health effects of different preventive intervention strategies in a population. For example, in a study in Taiwan, it was estimated that each TBI leads to a mean loss in 4.8 QALYs [57]. Assuming the health effects of TBI are similar in Taiwan and the US, TBI in the US leads to a total loss each year in quality-adjusted life years of 7.2 to 9.6 million (i.e. 4.8 QALYs per TBI case X 1.5-2.0 million TBI cases); this represents significant morbidity and suffering.

SAVINGS OF CASES OF SCHIZOPHRENIA

In a conservative model employed earlier, we calculated that TBI may account for about 1% of all schizophrenia cases. The total cost of schizophrenia (both direct and indirect costs) in the U.S. in 2002 was \$62 billion [58]. If 50% of all TBI-induced schizophrenia was prevented through primary or secondary means, this would mean a savings of \$313 million each year.

FUTURE RESEARCH

For prevention efforts, it will be important to more fully characterize the nature of traumatic brain injuries (types and timing) that are associated with schizophrenia and to further delineate the relationship of TBI and genetic vulnerability in developing schizophrenia. This has important clinical implications. If TBI augments the effect of genetic vulnerability, then parents of children at risk may be counseled to take extra precautions. If there is an important window in development for the effects of TBI, then at-risk individuals who incur TBI during this critical period might be more carefully monitored for early symptoms of schizophrenia.

Future research should also focus on how TBI can contribute to the pathophysiology of schizophrenia and other psychotic disorders. Schizophrenia is a complex disorder that involves synaptic abnormalities [59], gray matter reduction [60], disturbance of white matter tracts [61], pathology in GABAergic inhibitory interneurons [62], glutamatergic dysfunction [63] and dopamine dysregulation [64]. TBI can contribute to aberrant synaptic pruning during adolescence *via* pro-apoptotic mechanisms, leading to a reduction in neuropil, and generation of schizophrenia symptoms. This may be reflected in reduced hippocampal size, common to both TBI [15] and schizophrenia [60]. TBI could also contribute to schizophrenia pathophysiology through its effects on white matter. Van Hoesen *et al.* [13] hypothesize that TBI injures, through tearing and shearing, white matter tracts that are important both for sensory experience and for decisions from hippocampus output structures regarding relevancy and novelty. TBI can lead to loss of inhibitory interneurons in the hippocampus, a feature seen in postmortem schizophrenia brains [60]. It has been hypothesized that excitotoxicity may underlie schizophrenia pathophysiology [65]. TBI also causes a breach of the blood-brain barrier, creation of toxic free radicals, activation of catabolizing enzymes, and edema and increased vulnerability to ischemia and apoptosis (a programmed cell death) (reviewed in [66]).

CONCLUSION

Many of the similarities between TBI and schizophrenia are intriguing. Yet not everyone who suffers TBI goes on to develop schizophrenia and not each patient with schizophrenia has a history of TBI. Future research that characterizes their relationship more clearly in humans, in the context of genetic vulnerability, will be of important clinical utility. Such studies may clarify the biochemical and anatomical substrates of their relationship, which will be supported by animal research.

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