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Traumatic Brain Injury in Individuals at Clinical High Risk for Psychosis

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Abstract

Background—Recent research suggests that a traumatic brain injury (TBI) can significantly increase the risk of later development of psychosis. However, it is unknown whether people at clinical high risk (CHR) of psychosis have experienced TBI at higher rates, compared to otherwise healthy individuals. This study evaluated the prevalence of mild TBI, whether it was related to past trauma and the relationship of mild TBI to later transition to psychosis.

Methods—Seven-hundred forty-seven CHR and 278 healthy controls (HC) were assessed on past history of mild TBI, age at first and last injury, severity of worst injury and number of injuries using the Traumatic Brain Injury Interview. Attenuated psychotic symptoms were assessed with the Scale of Psychosis-risk Symptoms. IQ was estimated using the Wechsler Abbreviated Scale of Intelligence and past trauma and bullying were recorded using the Childhood Trauma and Abuse Scale.

Results—CHR participants experienced a mild TBI more often than the HC group. CHR participants who had experienced a mild TBI reported greater total trauma and bullying scores than those who had not, and those who experienced a mild TBI and later made the transition to psychosis were significantly younger at the age at first and most recent injury than those who did not.

Conclusion—A history of mild TBI is more frequently observed in CHR individuals than in HC. Inclusion or study of CHR youth with more severe TBI may provide additional insights on the relationship between TBI and later transition to psychosis in CHR individuals.

1. Introduction

A traumatic brain injury (TBI) is characterized as an alteration in brain functions caused by an external force (Reis et al., 2015). A TBI is known to lead to a variety of psychiatric problems in as high as one third of those who suffer a TBI, such as mood and anxiety disorders, personality changes, as well as impairments in Intelligence Quotient (IQ) and neurocognition (Deb et al., 1999; Kim et al., 2007; Konigs et al., 2015; Masel and DeWitt, 2010; Nicholl and LaFrance, 2009). More recent work suggests that a TBI may also be a risk factor for psychosis. In particular, a recent meta-analysis reported that a TBI significantly increased the risk of later development of schizophrenia by approximately 60% (Molloy et al., 2011). However, estimates of increased risk vary widely according to sample selection, with risk estimates typically elevated and more likely to be inaccurate in psychotic samples where TBI history is taken retrospectively, relative to estimates drawn from patients with a TBI who later develop psychosis (Batty et al., 2013). Moreover, it is difficult to determine whether a TBI leads to psychosis or whether an individual was already on a course towards psychosis prior to the injury (David and Prince, 2005). Interpretation is further complicated by the retrospective manner in which data on TBI were collected in schizophrenia samples (Molloy et al., 2011).

The risk of psychosis following a TBI is highest in individuals with a family history of the disorder (Kim, 2008) suggesting that the relationship of TBI to schizophrenia may involve a

combination of a genetic predisposition to psychosis and environmental insult to the brain (Abdel Malik et al., 2003). Even in those at risk for psychosis, those with a family history reportedly experienced a greater number of lifetime head injuries compared to a healthy control group as evaluated with the Traumatic Brain Injury Interview, a 24 question clinician-rated scale (Stowkowy and Addington, 2013). Moreover, people at CHR of psychosis reported higher rates of trauma and bullying compared to healthy controls (Addington et al., 2013; Bechdolf et al., 2010) and it has been found that adolescents with a history of TBI are vulnerable to psychological and behavioral harms that co-occur with their history of TBI (Ilie et al., 2014).

However, it is unknown whether CHR individuals who had experienced a mild TBI also report significantly greater rates of trauma and bullying. This is an important consideration, as approximately 35% of people at CHR of psychosis will go on to develop a full blown psychotic disorder (Fusar-Poli et al., 2012). Thus this population offers a window of opportunity to evaluate the presence of TBI in people who have a greater risk of developing psychosis compared to the general population. These individuals present with attenuated psychotic symptoms, brief intermittent psychotic symptoms, or have a genetic risk for the disorder and a recent decline in functioning (McGlashan et al., 2010). The CHR cohort offers a unique opportunity to examine the prevalence of TBI and its impact on IQ prior to the onset of psychosis in people with a greater probability of developing a psychotic disorder relative to the general population, but who do not have a full blown psychotic disorder as in the retrospective research described above. However, TBI is typically an exclusion criteria in studies of clinical high risk. In the North American Prodromal Longitudinal Study (NAPLS 2) there were clear exclusion criteria with respect to moderate and severe TBI, typical of other studies (Brewer et al., 2005). The aims of the current study were to evaluate, in a large sample of youth at CHR of psychosis the prevalence of mild TBI, whether it was related to positive symptoms, differences in IQ, past experiences of trauma and bullying, and the relationship of mild TBI to later transition to psychosis.

2. Materials and Methods

2.1 Participants

All participants were recruited as part of the eight-site NAPLS 2 study (Addington et al., 2012), which was established to investigate predictors and mechanisms of transition to psychosis. As described in Addington et al., (2012) all participants are help-seekers and were responding to similar recruitment strategies across sites. All participants were screened for TBI at the initial screening visit. This paper reports on the 747 CHR participants that completed the Traumatic Brain Injury questionnaire (Abdel Malik et al., 2003) at the baseline assessment. All CHR participants were required to meet the Criteria of Psychosis-risk Syndromes (COPS) using the Structured Interview for Psychosis-risk Syndromes (SIPS) (McGlashan, Walsh, and Woods, 2010). Participants were excluded if they met criteria for any current or lifetime axis I psychotic disorder, IQ <70 based on the WASI (Wechsler, 1999), past or current history of central nervous system disorder or DSM-IV criteria for current substance dependence disorder. HC participants were excluded if they had a first degree relative with a current or past psychotic disorder or any other disorder involving

psychotic symptoms, met criteria for any prodromal syndrome, any current or past psychotic disorder or a Cluster A personality disorder diagnosis, or were currently using psychotropic medication. A more detailed description of participant details is provided elsewhere (Addington et al., 2012).

Informed consent was obtained from those who met criteria and were judged fully competent to give consent. Parental consent was obtained from parents/guardians of participants who were under age 16. The study was approved by the Institutional Review Boards of all eight NAPLS-2 sites.

2.2 Measures

The SIPS and the Scale of Psychosis-risk Symptoms (SOPS) (McGlashan, Walsh and Woods, 2010) were used to assess criteria for a prodromal syndrome and severity of attenuated positive symptoms and negative symptoms.

IQ was assessed with the block design and vocabulary subtests of the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler, 1987).

Trauma and bullying was assessed using the Childhood Trauma and Abuse Scale (Janssen et al., 2004). This measure is a semi-structured interview in which the interviewer inquires about trauma and abuse before the age of 16 including any emotional, physical, psychological or sexual abuse they may have experienced. Participants are also asked about any psychological or physical bullying.

The Family Interview for Genetic Studies (FIGS) (Maxwell, 1996) was used to determine the presence of a psychotic disorder in a first degree relative.

The Traumatic Brain Injury (TBI) Interview (AbdelMalik et al., 2003) was used to assess previous history of head injury. This interview captures the age at the first TBI, age at most recent TBI, number of TBIs reported, and the rating of the most severe TBI. Ratings of the most severe TBI were based on a scale of 1 (No head injury) to 8 (head injury with loss of consciousness/coma lasting 6 hours or more, and/or skull fracture, and/or positive findings on head CT/MRI). Participants were excluded from NAPLS 2 if they experienced a moderate to severe TBI (i.e. ratings of 7 and above), any head injury that resulted in greater than 30 minutes loss of consciousness. Participants were also excluded if they had sustained 3 or more, mild TBI with loss of consciousness of more than 5 minutes, their symptoms persisted for greater than 2 months or the TBI had occurred in the 2 months prior to recruitment.

2.3 Statistical Analysis

Chi-square analyses for categorical variables and t-tests for continuous variables were used to compare CHR and HC groups on demographic variables. The age at first and most recent TBI, severity of the most recent TBI, and number of TBIs variables were non-normally distributed; therefore, the non-parametric Mann Whitney U test was used for analysis involving these variables. Univariate analysis of variance was used to compare CHR and controls with and without a history of mild TBI on IQ. Chi Square was used to compare

CHR and controls with and without a history of mild TBI on sex, and in CHR with and without a history of mild TBI on family history of psychosis. T-tests were used to compare CHR with and without a history of mild TBI on SOPS symptom severity. Kruskal-Wallis was used to compare CHR and controls with and without a history of mild TBI on trauma and bullying scores. Statistical analyses were conducted using SPSS 22.

2.4 Procedures

All eight sites (Emory University, Harvard University, University of Calgary, University of California at Los Angeles, University of California at San Diego, University of North Carolina at Chapel Hill, Yale University, and Zucker Hillside Hospital) recruited CHR individuals and HC participants. Raters were experienced research clinicians who demonstrated adequate reliability at routine reliability checks. Gold standard post-training agreement on the critical threshold for determining initial eligibility and subsequent transition status based on the SIPS was excellent (kappa=.90). The Principal Investigator or clinical psychiatrist or psychologist at each site conducted a comprehensive clinical assessment to determine if entry criteria were met. JA chaired weekly conference calls to review criteria for all individuals admitted to the study. Clinical assessments that included the SOPS were conducted at baseline. Assessments including the IQ, Childhood Trauma and Abuse and Traumatic Brain Injury (TBI) Interview were conducted at baseline only. If the Presence of Psychotic Symptoms Criteria (POPS) (McGlashan, Walsh and Woods, 2010) was met suggesting the transition to psychosis, then the complete assessment was done at the time of conversion with a one year post conversion assessment to determine diagnosis (Addington et al., 2012).

3. Results

The sample consisted of 278 HC participants (140 males, 138 females) and 747 CHR participants (428 males, 319 females). Groups did not significantly differ on sex. HC's were significantly older (M=19.8, SD=4.7 vs M=18.5, SD=4.2, t=4.16, p<0.01) and had more years of education (M=12.7, SD=3.6 vs. M=11.3, SD=2.8, t=6.71, p<0.001) than CHR participants. Groups did not significantly differ on race and the majority of each group, approximately 60%, were White, Middle Eastern or Latin American.

As shown in Table 1, CHR participants experienced a significantly greater number of mild TBIs than the HC groups. CHR and HC groups did not significantly differ on the age at first or last TBI, severity of TBI or the number of TBIs across the lifetime.

When examining differences in IQ for CHR and HC participants who did vs did not have a history of mild TBI, the ANOVA indicated a significant group effect, F=15.24(3,940), p<0.001. Tukey's post-hoc tests indicated that HC participants without a history of mild TBI (M=111.1) had significantly higher IQ than CHR participants with (M=103.2) and without (M=103.9) a history of mild TBI (p<0.001 and p=0.01, respectively). HC participants with (M=110.6) a history of mild TBI also had higher IQ than CHR participants with and without a history of mild TBI (p=0.006 and p=0.01, respectively). There was no significant difference in IQ between those who had and had not experienced a mild TBI in the CHR

group (M=103.2 and M=103.9, respectively; t=0.23, p=0.13), nor in the HC group (M=110.6 and M=111.1, respectively; t=0.60, p=0.53).

There were no sex differences in those who had experienced a mild TBI vs. those who had not in the CHR group (χ^2=0.94, p=0.33) nor in the HC group (χ^2=0.99, p=0.32).

In the CHR group, there was no significant difference in those who had experienced a mild TBI versus those who had not on SOPS total attenuated positive (M=11.7 and M=11.9, respectively; t=0.66, p=0.88) or negative symptoms (M=11.7 and M=12.0, respectively; t=0.56, p=0.63).

When examining differences in total trauma scores in CHR and HC participants who did vs did not have a history of mild TBI, the Kruskal Wallis was significant, χ^2=116.16, p<0.001. Follow-up Mann-Whitney tests indicated that HC participants without a history of mild TBI (M=0.2) had significantly lower total trauma scores than CHR participants with (M=1.3) and without (M=1.1) a history of mild TBI (both p<0.001). HC participants with a history of mild TBI (M=0.2) also had lower total trauma scores than CHR participants with and without a history of mild TBI (both p<0.001). CHR with a history of mild TBI had significantly higher total trauma scores than CHR without a history of mild TBI (p=0.04).

When examining differences in total bullying scores in CHR and HC participants who did vs did not have a history of mild TBI, the Kruskal Wallis was significant, χ^2=59.30, p<0.001. Follow-up Mann-Whitney tests indicated that HC participants without (M=0.5) a history of mild TBI had significantly lower total bullying scores than CHR participants with (M=1.0) and without (M=0.8) a history of mild TBI (both p<0.001). HC participants with (M=0.5) a history of mild TBI also had lower total bullying scores than CHR participants with and without a history of mild TBI (p<0.001 and p=0.009, respectively). CHR with a history of mild TBI had significantly higher total bullying scores than CHR without a history of TBI (p<0.001).

A significantly greater proportion of CHR participants with a family history for psychosis reported experiencing a mild TBI (n=112, 40.2%) relative to those with no family history (n=633, 29.5%; χ^2=5.02, p<0.05). There were no differences between those with and without a family history of psychosis in the age at first or last TBI, severity of TBI or the number of TBIs across the lifetime.

Of the 747 CHR participants, 85 made the transition to psychosis within 2 years. As shown in Table 2, there was no difference between those who made the transition and those who did not in having a history of a mild TBI. Of the 232 CHR participants who had experienced a mild TBI, the 24 who made the transition to psychosis were significantly younger at the age of first and most recent TBI than CHR participants who did not make the transition to psychosis (n=207). CHR participants who made the transition to psychosis did not significantly differ on the number of mild TBIs experienced across the lifetime nor the severity rating of the most severe TBI compared to CHR participants who did not make the transition to psychosis.

4. Discussion

The purpose of this study was to investigate, in a large sample of individuals at CHR of psychosis, the prevalence of mild TBI, whether it was related to past trauma and other relevant correlates and the relationship of mild TBI to later transition to psychosis.

The finding that a greater proportion of CHR participants reported experiencing a mild TBI than HCs is consistent with the literature in people with schizophrenia, who are more likely to have a history of TBI in comparison to their healthy siblings (AbdelMalik et al., 2003) and to healthy people (Malaspina et al., 2001). One possible explanation for these findings is that head injuries occur more frequently in young people already displaying subtle premorbid features associated with schizophrenia (AbdelMalik et al., 2003). The direction of the relationship between TBI and psychosis, however, is difficult to determine, i.e. if participants were already on course to developing an illness or if the TBI played a role in the emergence of the illness (David and Prince, 2005). In the present study, CHR and HC participants did not differ in age at the first and most recent TBI, number of mild TBIs and severity of the worst TBI, corroborating findings from a recent meta-analysis which found no evidence for a dose dependent relationship of the severity of TBI and risk of schizophrenia (Molloy et al., 2011). Exclusion of people with moderate and severe TBI in the current study may have precluded ability to detect an effect with the severity of TBI variable.

No sex differences emerged between participants who had experienced a mild TBI versus those who had not for all participants. There is limited evidence that otherwise healthy males are more likely to experience a TBI than females (Langlois et al., 2006; Schmidt et al., 2012), although this pattern may not extend to people with a diagnosis with schizophrenia (Malaspina et al., 2001). There were no IQ differences between those who had and had not experienced a mild TBI in either group, although we did find that CHR participants with and without a history of mild TBI had significantly lower IQ compared to both HC groups with and without a history of mild TBI. There is some evidence that people who developed a psychotic disorder following a TBI show lower IQ and other cognitive functions compared to controls (Fujii et al., 2004). However, there is also meta-analytic evidence that otherwise healthy individuals who experience a mild TBI do not show impairments in IQ compared to healthy controls or Wechler normative means (Konigs et al., 2015). An investigation that may be of interest in future research is whether individuals at CHR of psychosis with more severe TBI exposures may be more sensitive to IQ differences compared to CHR individuals with mild or no history of TBIs.

CHR participants with a history of mild TBI reported experiencing increased trauma and bullying compared to those without a history of mild TBI, a result not observed in the control group. CHR participants both with and without a history of mild TBI reported experiencing increased trauma and bullying compared to both healthy controls without a history of mild TBI and with a history of mild TBI. It has been reported that those at risk for psychosis have a high prevalence of history of trauma and bullying compared to healthy controls (Addington et al., 2013; Bechdolf et al., 2010). Adolescents with a history of TBI are vulnerable to a range of psychological and behavioral harms that co-occur with their

history of TBI, for example those who reported a lifetime TBI had a greater chance of experiencing cyberbullying and bullying at school (Ilie et al., 2014). People at CHR of psychosis show poor social functioning (Addington et al., 2008) and also movement abnormalities (Callaway et al., 2014), and this could possibly contribute to the increased rate of TBIs and bullying in this population. Future studies may wish to gather information on the specific incidences surrounding how the TBI was acquired to test this hypothesis.

There was no significant difference in CHR participants who had experienced a mild TBI versus those who had not on SOPS attenuated positive or negative symptom severity. Furthermore, a positive history of a mild TBI was not a differentiating factor between CHR participants who made the transition to psychosis compared to those who did not transition. However, it should be noted that a recent meta-analysis reported that a TBI significantly increased the risk of later development of schizophrenia by approximately 60% (Molloy et al., 2011), in the current sample this effect was not observed. Moreover, CHR participants who did or did not make the transition to psychosis did not differ on the number of mild TBIs experienced across the lifetime, nor the severity rating of the most severe TBI. This result is consistent with findings of Molloy et al. (2011) who did not find a dose-response relationship between severity of TBI and subsequent risk for schizophrenia. There is research showing a significant risk-modifying effect of TBI in people who have a family history for schizophrenia (Kim, 2008), suggesting that both a family history and environmental insult to the brain may contribute an additive effect in these individuals. We did observe that a higher percentage of CHR participants with a family history of psychosis had mild TBI than those with no family history. It may be that a combination of a mild TBI and a family history of psychosis may increase an individual's vulnerability to at least being at risk for psychosis. However, in this sample since only six participants with both a mild TBI and a family history made the transition to psychosis we were unable to determine if there was an additive effect.

Interestingly, however, for CHR participants who had experienced a mild TBI, those who made the transition to psychosis were significantly younger at the age of first and most recent TBI than CHR participants who did not make the transition to psychosis. It is possible that an environmental insult to the brain at a particular period in development may negatively impact the course of illness in people who first develop CHR symptoms and then ultimately develop a psychosis. However, as noted in other studies (David and Prince, 2005), it is difficult to determine the directionality of the effect i.e. whether the TBI caused the individual to develop a psychosis, or if the individual was already on the path to develop a psychosis.

Several limitations should be noted. First, history of mild TBI was assessed retrospectively, and was not corroborated through medical records. The retrospective manner in which data was acquired raises the question of recall bias in our CHR and healthy control participants. Clearly, prospective studies are needed to ensure accurate evaluation of TBI occurrences in all populations. Secondly, people who experienced a moderate to severe TBI were excluded from the present study. Including participants with more severe TBI history may provide additional insights on the relationship between TBI and sex, IQ, trauma, symptom severity and later conversion to psychosis. The restricted range of SOPS symptoms used in the

current study (i.e., scores of 3–5 as defined by the CHR status) may have reduced ability to detect an association between TBI and symptom severity. Additionally, we did not collect information on the specific incidences surrounding how the TBI was acquired, which may help clarify the observed relationship between increased trauma and bullying in those with a positive history of mild TBI in the CHR group. Unfortunately, we did not ascertain data on accident proneness in our CHR participants, and therefore we cannot evaluate whether higher accident proneness is associated with higher rates of TBI in our sample. Finally, we do not have access to participants with other disorders or risk of other disorders with whom to compare TBI history with our participants at CHR of psychosis. Despite these limitations, the findings from this study provide novel evidence that people at CHR of psychosis may be more vulnerable to experiencing a mild TBI than healthy people, and this is consistent with findings in people with a full blown psychosis, suggesting a similar pattern across the schizophrenia spectrum. These findings further suggest that an environment insult to the brain at a particular period in development may negatively impact the course of illness in people who first develop CHR symptoms and then ultimately develop a psychosis.

Acknowledgments

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Table 1

TBI measures for Clinical High Risk and Healthy Control participants

	CHR n=747 N (%)	HC n=278 N (%)	χ^2	*p*-value
TBI (Yes)	232 (31.0)	55 (19.8)	12.77	<0.001
	Mean (SD)	**Mean (SD)**	**U**	**p-value**
Age at first TBI	10.3 (5.4)	11.2 (6.3)	5918.50	0.46
Age at last TBI	12.2 (5.9)	12.5 (6.2)	6245.50	0.89
Number of TBIs	1.5 (0.9)	1.3 (0.6)	5730.50	0.14
Severity of worst TBI	2.9 (1.2)	2.6 (0.9)	5823.50	0.29

Note. CHR, Clinical High Risk; HC, Healthy Controls; SD, Standard Deviation, TBI=traumatic brain injury

Table 2

TBI measures in clinical high risk of psychosis participants who did and did not make the transition to psychosis.

	Made the transition to psychosis n=85 N (%)	Did not make the transition to psychosis N=654 N (%)	χ^2	*p*-value
TBI (Yes)	24 (28)	207 (32)	0.41	0.52
	Mean (SD) n=24	**Mean (SD) n=207**	**U**	***p*-value**
Age at first TBI	7.8 (3.0)	10.6 (5.6)	1732.00	0.02
Age at last TBI	10.1 (5.5)	12.4 (6.0)	1818.50	0.04
Number of TBI	1.7 (1.2)	1.5 (0.8)	2263.50	0.40
Severity of TBIs	2.8 (1.2)	2.9 (1.2)	2282.00	0.50

Note. CHR, Clinical High Risk; HC, Healthy Controls; SD, Standard Deviation.