Childhood Trauma and Hippocampal and Amygdalar Volumes in First-Episode Psychosis

Katrina Hoy[1], Suzanne Barrett[2], Ciaran Shannon[*,1], Clodagh Campbell[1], David Watson[3], Teresa Rushe[4], Mark Shevlin[4], Feng Bai[5], Stephen Cooper[2], and Ciaran Mulholland[2]

[1]School of Psychology, Queen's University Belfast, Belfast, N. Ireland; [2]Department of Psychiatry, Queen's University Belfast, Belfast, N. Ireland; [3]Computational Neuroscience, University of Ulster, Londonderry, N. Ireland; [4]Psychology, University of Ulster, Londonderry, N. Ireland; [5]School of Medicine, South East University, Nanjing, China

*To whom correspondence should be addressed; tel: +44-28- 90975447, fax: +44-28-90974222, e-mail: ciaran.shannon@qub.ac.uk

Objective: A history of childhood trauma is common in individuals who later develop psychosis. Similar neuroanatomical abnormalities are observed in people who have been exposed to childhood trauma and people with psychosis. However, the relationship between childhood trauma and such abnormalities in psychosis has not been investigated. This study aimed to explore the association between the experience of childhood trauma and hippocampal and amygdalar volumes in a first-episode psychosis (FEP) population. *Methods*: The study employed an observational retrospective design. Twenty-one individuals, who had previously undergone magnetic resonance imaging procedures as part of the longitudinal Northern Ireland First-Episode Psychosis Study, completed measures assessing traumatic experiences and were included in the analysis. Data were subject to correlation analyses (r and r_{pb}). Potential confounding variables (age at FEP and delay to scan from recruitment) were selected a priori for inclusion in multiple regression analyses. *Results*: There was a high prevalence of lifetime (95%) and childhood (76%) trauma in the sample. The experience of childhood trauma was a significant predictor of left hippocampal volume, although age at FEP also significantly contributed to this model. There was no significant association between predictor variables and right hippocampal volume. The experience of childhood trauma was a significant predictor of right and total amygdalar volumes and the hippocampal/amygdalar complex volume as a whole. *Conclusions*: The findings indicate that childhood trauma is associated with neuroanatomical measures in FEP. Future research controlling for childhood traumatic experiences may contribute to explaining brain morphology in people with psychosis.

Key words: psychosis/trauma/hippocampus/amygdala

Introduction

A history of traumatic events, childhood abuse in particular, is common in psychosis populations.[1,2] The Traumagenic Neurodevelopmental (TN) model of psychosis[3] hypothesizes that abnormal neurodevelopmental processes can originate in traumatic events in childhood. It has been theorized that these traumatic events may lead to biological changes such as a pathological alteration in the hypothalamic-pituitary-adrenal (HPA) axis[4] and to the high responsivity to stress observed in a sizeable percentage of people with schizophrenia. The model is based upon research demonstrating a similar profile of neurological and biochemical abnormalities in individuals with schizophrenia and in those exposed to childhood abuse.[3] Indeed, a recent test of the TN model indicates greater HPA axis dysregulation, as measured by cortisol levels, in individuals with a diagnosis of schizophrenia abused as children (especially those emotionally abused) as compared with their nonabused counterparts.[5]

A number of imaging studies have identified similar brain abnormalities in traumatized individuals with a diagnosis of Post-Traumatic Stress Disorder (PTSD),[6] Dissociative Identity Disorder,[7] Borderline Personality Disorder (BPD),[8] and Major Depression[9] to those observed in psychosis. This suggests that trauma may have specific effects on the brain. There is also evidence to suggest that early life stressors, such as childhood abuse and neglect, can result in a reduction in the volume of the hippocampus, which is a prominent substrate for glucocorticoid-mediated negative feedback on HPA activity and that this reduction is observable in adulthood.[10,11] A large body of research has demonstrated hippocampal volume reductions in schizophrenia,[12–14] although some studies are contradictory.[15] It is significant, from a neurodevelopmental perspective, that reductions in hippocampal volume have been observed in first-episode schizophrenia[12,16] and in

ultrahigh risk (UHR) groups[17] because they cannot be explained as a consequence of medication effects or disease chronicity. Read et al[3] have therefore posited that such structural abnormalities observed in schizophrenia could in fact be caused by childhood trauma. There is also indirect behavioral evidence of greater temporal/hippocampal dysfunction associated with childhood trauma in this population: explicit verbal memory impairments have been reported to be greater in individuals with chronic schizophrenia who have a significant trauma history.[18]

It has also been suggested that a '"critical period" exists for the normative development of an emotional regulatory system that is able to appropriately differentiate threatening from nonthreatening environmental stimuli and that trauma exposure during development may impact function of the HPA axis through effects at the level of the amygdala.[4] While there is evidence of increased limbic functional sensitivity in individuals who have experienced childhood trauma, [4,10,11] results regarding amygdalar volumes in traumatized and psychotic groups lack consensus. In people who have experienced childhood abuse, some studies report minor volume reductions,[8] whereas others report significant amygdalar size reductions.[19,20] Meta-analyses of magnetic resonance imaging (MRI) findings in schizophrenia provide evidence of amygdalar reductions,[21] but these conflict with more recent research.[15]

Despite evidence indicating a high prevalence of childhood maltreatment in psychotic populations and neurobiological consequences of such stress, morphometric studies in psychosis have neither reported nor controlled for a history of childhood trauma, opting instead to highlight possible etiological explanations that are vague or reflect biological reductionism. The present study assessed the experience of childhood maltreatment and its association with hippocampal and amygdalar volumes in a subsample of individuals who participated in the longitudinal Northern Ireland First-Episode Psychosis (NIFEPS) study.[22] To our knowledge, this is the only study that has examined the association between childhood trauma and brain morphology in a psychosis sample to date. We hypothesized that the experience of such trauma would significantly predict hippocampal and amygdalar volumes at illness onset in these patients.

Methods

Participants

Participants were recruited from the NIFEPS[22] which recruited cases of first-episode psychosis (FEP) from psychiatric services between January 2004 and December 2004 in the Northern and Belfast Health and Social Care Catchment Areas in Northern Ireland (population; 782 979). From these referrals, 90 participants consented to and underwent MRI scanning procedures. Exclusion criteria were evidence of psychosis resulting from an organic etiology, history of a traumatic brain injury or

neurodegenerative disorder, a previous episode of psychosis, evidence of a learning disability, or a contraindication for an MRI (eg, metal in the body around the scan area).

The 90-scanned participants satisfied International Classification of Diseases (10th edition: ICD-10)[23] criteria for schizophrenia/schizoaffective disorder ($n = 25$), bipolar disorder/mania ($n = 24$), and psychotic depression ($n = 11$), while the remainder were '"other psychotic disorders" ($n = 30$).

All available participants with an MRI (from NIFEPS) were invited to take part in the current study through their keyworkers. Ethical approval for this study was obtained from a local research ethics committee regulated by a statutory research governance framework. Written informed consent was obtained from all participants after they had a received a complete description of the study. Participants were also excluded if they were unable to participate due to current mental state.

Twenty-seven participants (30%) were lost to follow-up due to not being contactable, relocation, or death. Sixty-three (70%) participants were contacted. Of these, 41 (19 males [46%] and 22 females [54%]) declined to participate. The 21 individuals who participated satisfied ICD-10 criteria for schizophrenia ($n = 10$), bipolar disorder/mania ($n = 3$), psychotic depression ($n = 2$), and "other psychotic diagnoses" ($n = 6$). One further individual was interviewed but excluded from statistical analysis as they were judged to be an extreme outlier based on their volumetric measurements.

Characteristics for participants are shown in table 1. Those interviewed were relatively similar in respect of age, gender, and gross brain volumes to those who declined to participate (age at first episode [$t = 0.67$, $df = 60$, $P = .51$], gender [$X^2 (1) = 0.65$ $P = .42$], white matter [WM] [$t = 1.2$, $df = 60$, $P = .24$], gray matter [GM] [$t = 0.9$, $df = 60$, $P = .37$], and cerebrospinal fluid (CSF) [$t = 0.89$, $df = 60$, $P = .38$]). People who declined interview were less likely to have a diagnosis of schizophrenia but this did not reach significance (Declined Interview—SCZ/Other = 11/30; $X^2 (1) = 2.68$, $P = .1$).

Materials

Symptom Measures. At both the time of MRI scan and administration of trauma measures, depression was measured using the "Beck Depression Inventory (BDI) II"[24] and psychotic symptoms were assessed using the "Positive and Negative Symptom Scale (PANSS)."[25] These measures have good psychometric properties.[26,27] In addition, we reported on an "excitement-mania" factor from the PANSS[28] (see table 1). At follow-up, the "Dissociative Experiences Scale II" (DES II)[29] was employed to assess for current symptoms of dissociation. This measure has high levels of reliability and validity.[29]

Trauma Measures. "The Traumatic Experiences Checklist" (TEC)[30] was administered to assess traumatic

Table 1. Demographic and Clinical Characteristics of Participants

n	21		
Gender (female; %)	12	(57%)	
At first episode/time of scan			
Age at first episode (mean y; SD; range)	31.86	10.35	18–60
Delay to MRI scan from initial presentation to services (mean wk; SD; range)	52.07	39.8	2–122
Medication at scan (olanzapine/risperidone/ quetiapine/aripiprazole/ clozapine/none)	7/6/4/1/1/2		
PANSS positive symptoms at first presentation (mean; SD)	14.57	4.99	7–26
PANSS negative symptoms at first presentation (mean; SD)	12.43	6.19	7–26
PANSS general symptoms at first presentation (mean; SD)	30	6.68	21–40
PANSS excitement-mania factor at first presentation (mean; SD)[a]	5.14	1.53	4–9
BDI symptoms at first presentation (mean; SD)	23	15	0–60
Alcohol (DSM IV dependence/ abuse/use/abstention/never used)	2/4/11/2/2		
At trauma interview			
Currently employed (yes; %)	8	(38.1%)	
Age (mean years; SD; range)	39.52	11.42	26–64
PANSS positive symptoms (mean; SD)	11.81	4.88	7–25
PANSS negative symptoms (mean; SD)	14.33	5.38	7–27
PANSS general symptoms (mean; SD)	32.71	12.4	16–63
PANSS excitement-mania factor (mean; SD)[a]	5.25	1.59	4–10
Beck depression symptoms (mean; SD)	17.5	14.71	0–55
Dissociation symptoms	19.38	14	
Number of hospital admissions	2.43	2.18	0–8
Psychological therapy (any reason: yes)	9	(42.9%)	
Alcohol units (0/1–10 per wk; %)	7/14	(33.3/66.6%)	

Note: PANSS, Positive and Negative Symptoms Scale; BDI, Beck Depression Inventory; MRI, magnetic resonance imaging; DSM-IV, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition.*
[a]PANSS excitement—mania factor: excitement, hostility, poor impulse control, and uncooperativeness items.[28]

experiences. The TEC is a 33-item self-report questionnaire designed to measure 29 types of potential trauma and the perceived impact of these events. The TEC yields a childhood trauma composite score, comprising various domains of trauma (eg, emotional abuse, sexual abuse, physical abuse. "Childhood trauma: is defined as '"trauma occurring before the age of 18 y."). It has been shown to have good levels of reliability and validity.[30]

"The Post-Traumatic Diagnostic Scale"[31] is a 49-item self-report instrument and is designed to aid in the detection and diagnosis of PTSD. It was administered twice to assess for PTSD in relation to the most significant traumatic experiences in childhood and again in adulthood. This measure has been shown to have high levels of test-retest reliability and of validity.[32]

The experience and impact of civil conflict was assessed using the "Troubles Related Experiences Questionnaire".[33] This is a 30-item self-report questionnaire designed to assess exposure to, and perceived impact of, civil conflict in Northern Ireland in child and adulthood. Preliminary research suggests high internal reliability.[33]

MRI Procedures and Measurements

MRI Data Acquisition MRI scans were obtained using a GE Sigma 1.5 T scanner (General Electric, Milwaukee, WI). The scan protocol consisted of a coronal high-resolution T1 volume acquisition, axial dual echo PD/T2, and axial FLAIR scans. All scans were reviewed by a consultant neuroradiologist for gross anomalies. The T1 volume scan was used for regions of interest (ROI) analyses. A 3D Inversion-Recovery-prepared Fast Spoiled Gradient echo (IR-Prepped FSPGR) sequence was used, with the following parameters: TR/TE = 9.6/2.4, TI = 450, FOV = 220 × 165 mm, 0.87 mm pixel size, flip angle 20°, slice thickness 1.5 mm, acquisition time 6 minutes 51 seconds. Two-dimensional DICOM T1 magnetic resonance images were subsequently combined into three-dimensional volume (NifTI file format) and interpolated to create 1 × 1 × 1 mm isotropic voxels using SPM5 (Wellcome Institute, London, UK). All brain images were globally spatially normalized to MNI space to remove gross differences in brain size, position, and orientation. Between-subject head size variance is large so inclusion of a head size measure as a covariate is important in morphometric analysis. It has been shown that spatial normalization is an effective alternative method[34] and may have benefits in determining volume differences between populations[35] including for the hippocampus.[34]

Parcellation of the Hippocampus and Amygdala

Manual drawing of the 2 structures involved outlining the periphery of the ROI, delineated separately for the left and right hemispheres from the T1-weighted, spatially normalized coronal images lying on a plane perpendicular to the hippocampus major axis. This process was performed in Analyze 7.5 Imaging Software (Biomedical Imaging Resource, Mayo Clinic). All ROIs were drawn by one experienced researcher (F.B.) who was blinded to group membership. A random subset of 5 participants had their structures redrawn (both right and left hippocampi and amygdala) to test consistency of parcellation. The correlation coefficients for

hippocampus and amygdala volumes were 0.93 and 0.89, respectively. Anatomic guidelines for the hippocampus were based on a standard neuroanatomical atlas.[36] The hippocampal regions measured included the CA1 to CA4 fields of the cornu ammonis, dentate gyrus, the subiculum, the alveus, and the fimbria. Parahippocampal gyrus, tail of the caudate, amygdala, CSF around the hippocampus, and the fornix were excluded. Tracing of the hippocampus started caudally anteriorly in the section where the crura of the fornices depart from the lateral wall of the lateral ventricles and ended rostrally where the hippocampus disappears below the amygdale.

Anatomic guidelines for the delineation of the amygdala were taken after Brierley.[37] The anterior border was identified where the lateral sulcus closed to form the entorhinal sulcus. The posterior border excluded the tail of the caudate nucleus, the globus palladus and putamen, and lateral geniculate body. In cases where the border of the putamen could not be defined clearly, only the medial halves of the structures in the roof were included inside the amygdala boundary. The medial border was drawn to include uncus, but the inferior entorhinal cortex to the uncal notch was excluded. The lateral border was defined by the inferior horn of lateral ventricle or adjacent WM. The superior border was drawn: (1) anteriorly, as a straight line laterally from entorhinal sulcus to the fundus of the inferior portion of the circular sulcus of insula; (2) posteriorly, as a straight line laterally from the superolateral aspect of the optic tract to the fundus of the circular sulcus of insula. Finally, the inferior border was defined by the uncal recess of the lateral ventricle.

Design and Statistical Analyses

This observational study employed a retrospective correlational design. Examination of the MRI data revealed one participant who was judged to be an outlier by distance (standard residual = 2.54) and by influence (Cook's distance = 2.51) and was excluded from subsequent analyses. The total childhood trauma composite score from the TEC, assessing severity of childhood trauma, was not normally distributed and hence, simplified to a Yes/No binary variable "Experience of Childhood Trauma" (no childhood trauma group [$n = 5$; TEC score = 0]; childhood trauma group [$n = 16$; TEC median score = 10 IQR = 3–33.5]) for the purposes of a priori sta-

tistical testing using parametric methods. Associations between variables were tested using Pearson's parametric correlations (r and r_{pb}). A series of regression analyses were then conducted to determine if 3 predictor variables of theoretical interest (experience of childhood trauma, age at first episode of psychosis, delay to scan) predicted neuroanatomical volumes. "Age at first episode" was added as a covariate as onset of psychosis most commonly occurs in late adolescence/early adulthood, an observation that is often thought to be a reflection of abnormal neurodevelopmental processes. "Delay to scan was included primarily as a proxy measure for duration of exposure to antipsychotic medication as all participants were commenced on antipsychotics shortly after first presentation to psychiatric services.

Results

Traumatic Experiences

Twenty participants (95%) reported experiencing one or more traumatic life events (mean = 7, SD = 4.7, range 0–16). Sixteen participants (76%) reported experiencing "childhood trauma" ie, trauma occurring prior to 18 years, and 5 participants did not (24%). Of those reporting childhood trauma, 5 (31.25%) reported traumatic experiences to have first occurred between age 0–6 years (all reporting further childhood trauma subsequent to this), 10 (62.5%) between 7 and 12 years (7 reporting further childhood trauma between 13 and 18 y), and 1 (6.25%) between 13 and 18 years. There was little evidence in this small sample that a first trauma experienced earlier (0—6 y) rather than later influenced amygdalar or hippocampal volumes in people with a childhood trauma history, hence this variable was not considered further in these analyses. Fisher's Exact Test indicated that rates of childhood trauma did not significantly differ between participants with a diagnosis of schizophrenia vs 'other' diagnoses ($P = 0.31$; trauma/no trauma: SCZ $n = 9/1$; Other 7/4). The sample characteristics in respect of trauma domains (frequencies of events), as assessed by the TEC, are shown in table 2.

In respect of exposure to conflict related to civil conflict, 17 (85%) participants reported experiencing

Table 2. Frequencies of Participants Who Experienced Different Childhood Traumas (TEC)

Age Range (y)	Emotional Neglect (%)	Emotional Abuse (%)	Bodily Threat (%)	Sexual Harassment (No Physical Contact) (%)	Sexual Abuse (Physical Contact) (%)
0–18	11 (52)	12 (57)	9 (42)	4 (19)	5 (24)
0–6	4 (19)	3 (14)	1 (5)	0 (0)	0 (0)
7–12	8 (38)	11 (52)	6 (29)	2 (9)	3 (14)
13–18	7 (33)	8 (38)	8 (38)	4 (19)	5 (24)

Note: TEC, Traumatic Experiences Checklist

Table 3. Brain Volumes for Regions of Interest in Participants

Brain Region	Mean Volume	SD	Z Scores[a]
Grey matter cm^3	680.61	59.14	−0.09
White matter cm^3	474.95	47.48	−0.13
Cerebrospinal fluid (CSF) cm^3	361.04	43.15	0.28
Right hippocampus mm^3	2845.28	336.22	−0.12
Left hippocampus mm^3	2786.8	359.99	−0.81*
Total hippocampus mm^3	5632.09	635.01	−0.48
Right amygdala mm^3	2320.02	341.54	0.27
Left amygdala mm^3	2196.08	357.73	−0.13
Total amygdala mm^3	4516.10	652.34	0.09
Hippocampus/amygdala total mm^3	10148.19	1167.86	−0.06

[a]Z Scores derived to contextualize participants results using data from controls ($n = 21$) from Northern Ireland First-Episode Psychosis Study, selected to individually match study participants for both sex and age. Controls were scanned concurrently and neuroanatomical data were generated contemporaneously, using identical methods to those described herein.
*Significant reduction, $P < .05$.

exposure as an adult and 18 (90%) as a child. A high prevalence of trauma was apparent; however, 5 participants (24%) met the criteria for PTSD related to traumatic event that occurred in childhood, only 2 participants (10%) met the criteria for PTSD related to traumatic events that occurred in adulthood, and only 1 participant met the criteria for PTSD related to both. Nine (43%) participants' scores on the DES-II fell with the 'high range', suggesting significant dissociative experiences within the sample.

Trauma and Gross Brain Regions

The volumetric means of all ROIs are shown in table 3. The experience of childhood trauma was not significantly associated with any gross volumetric regions including: total GM ($r_{pb} = .161$, $P = .486$), total WM ($r_{pb} = −.003$, $P = .99$), total CSF ($r_{pb} = −.143$, $P = 0.537$), and intracranial volume ($r_{pb} = .026$, $P = .909$).

Regression Analyses

Hippocampus/Amygdala Complex Total Volume. Using the enter method, the regression model for the hippocampus/amygdala complex volume was significant, accounting for 31.9% of the variance (adjusted $R^2 = .319$; df (3, 17); $F = 4.128$; $P = .023$). The significant variable within the model was the experience of childhood trauma (β = −.451, $P = .027$; age at first episode β = .385; delay to scan β = .07).

Hippocampus. The model for total hippocampus volume approached, but did not achieve, significance, and accounted for 22.5% of the variance (adjusted $R^2 = .225$; df (3, 17); $F = 2.933$; $P = .063$; predictors—experience of childhood trauma β = −.315; age at first episode β = −.445; delay to scan β = −.033). The model for the right hippocampus was not significant (adjusted $R^2 = −.012$; df (3, 17); $F = 0.919$; $P = .453$; predictors—experience of childhood trauma β = −.164; age at first episode β = −.362; delay to scan β = −.153). The regression model for the left hippocampus was however significant, accounting for 45.1% of the variance (adjusted $R^2 = .451$; df (3, 17); $F = 6.468$; $P = .004$). The 2 significant variables within the model were the experience of childhood trauma (β = −.402, $P = .028$) and age at first episode (β = .446, $P = .027$). Delay to scan was not significant in this model (β = .2).

Amygdala. The regression model for total amygdala volume was significant, accounting for 27.3% of the variance (adjusted $R^2 = .273$; df (3, 17); $F = 3.5$; $P = .038$). The only significant variable within the model was the experience of childhood trauma (β = −.5, $P = .019$; age at first episode β = .256; delay to scan β = .094). The regression model for right amygdala volume was significant, accounting for 28.4% of the variance (adjusted $R^2 = .284$; df (3, 17); $F = 3.639$; $P = .034$). The significant variable within the model was the experience of childhood trauma (β = −.419, $P = .042$; age at first episode β = −.358; delay to scan β = .11). The regression model for left amygdala volume approached, but did not achieve, significance, and accounted for 18.8% of the variance (adjusted $R^2 = .188$; df (3, 17); $F = 2.545$; $P = .09$). The significant variable within the model was the experience of childhood trauma (β = −.512, $P = .022$; age at first episode β = .124; delay to scan β = .066).

The relationships between childhood trauma composite scores from the TEC (ranked by severity) and neuroanatomical variables were also examined using simple, nonparametric correlations (Spearman's Rho): all findings were upheld in these secondary analyses.

Trauma and Symptomatology

Post hoc analyses between childhood trauma experience and symptomatology were conducted to determine whether there was evidence of interrelationships between the experience of childhood trauma, severity of patients' illness, and volumetric measures. They were primarily conducted to check whether illness severity in the sample could be a potential confounding factor in these analyses. Given the primary purpose of these secondary analyses was conservative (ie, search for confounds), the large number of correlations being conducted and the small sample size, effect sizes of $r > .35$ were considered further.

Results indicated that there were no relationships of note (all $r_{pb} < .35$) between the experience of childhood

trauma in these participants and their initial, current, or change in, PANSS scores (positive, negative, and general), current dissociation symptoms, current BDI scores, or change in depression once baseline scores were controlled for. BDI scores at presentation correlated with the experience of childhood trauma ($r_{pb} = -.39$) and a number of neuroanatomical volumes: left hippocampus $r = .4$; right amygdala $r = .49$; and total amygdala $r = .44$. These suggested that higher levels of depression at onset was associated with the absence of a childhood trauma history in the patients sampled as well as larger, rather than smaller, anatomical structures, the opposite of what was observed for the experience of childhood trauma. Effects sizes for these relationships were small to moderate however.

Regressions models were then repeated for all anatomical structures with experience of childhood trauma, baseline symptoms, and change in symptoms (ie, baseline positive symptoms, change in positive symptoms, etc.) as predictor variables. These were undertaken to further ensure that the relationship between the experience of childhood trauma and brain volumes could not be accounted for by indicators of greater illness severity in participants. All findings were upheld, aside from when severity of depression at presentation, and change in depression were examined as additional predictor variables in some models. Changes were thought to be best understood with reference to a degree of multicollinearity in, and/or the additional explanatory terms disimproving aspects of, the regression models.

Discussion

To our knowledge, this study represents the first investigation of childhood trauma and brain morphology in psychosis. The use of a FEP group largely eliminates potential study confounders such as disease chronicity and the effects of long-term antipsychotic medication, which may affect brain morphology.[37] Moreover, a recent innovation in MRI modulation techniques that removes the need to control for brain size was utilized.

The findings support our hypothesized association between the experience of childhood trauma and decreased hippocampal volume, particularly left hippocampal volume. Decreased right, left, and total amygdala volumes were also associated with the experience of childhood traumatic experiences against a background of minimal evidence of amygdalar volume alteration in these patients relative to healthy controls. It would be hypothesized from these data that amygdalar volume enlargement would most likely be observed in psychosis samples with a negligible history of childhood trauma, while no change, or volumetric reductions in the amygdala, would be observable in those cohorts with a high prevalence of childhood trauma. Hence, the findings represent evidence that the neuroanatomical

abnormalities observed in some psychosis studies may, in part, be due to the uncontrolled inclusion of individuals with a history of childhood trauma. Moreover, traumatic experiences in childhood may play an important role in brain morphology in FEP, relatively independent of psychotic symptoms.

The literature is replete with research indicating associations between trauma and neuroanatomical variables, irrespective of diagnosis. A meta-analysis[6] has confirmed that a diagnosis of PTSD is associated with decreased hippocampal and left amygdalar volumes, while also revealing a similar influence of trauma in the absence of PTSD. In a BPD sample,[8] volume differences between controls and those with BPD were only found when the BPD group also had a history of childhood abuse. Smaller hippocampal volumes have been observed in adult women with major depressive disorder with a history of childhood abuse.[9]

Our results, when considered with an earlier neurocognitive article,[18] suggest that specific neurocognitive deficits and neuroanatomical abnormalities observed in psychosis may at least in part be a consequence of childhood trauma. Difficulties arise when comparing the studies because of variations in illness trajectory and diagnostic groups as the previous neurocognitive articles predominantly focus on samples with chronic difficulties. However, the combined findings, irrespective of study variations, strengthen the proposition that childhood trauma is exerting an effect.

If reported structural abnormalities are sometimes a product of the experience of early childhood trauma and the inclusion of traumatized individuals in study samples, then we would expect to find some similar structural abnormalities in UHR and FEP groups. While one study suggests that structural changes occur only after the onset of psychotic symptoms,[14] this is not supported by other research reporting hippocampal reductions in a UHR and first-episode groups as compared with controls.[17]

This study is limited by a number of factors. The small sample size reduces the statistical power of the study but is however comparable to other FEP MRI studies[12]. In addition, from the observations reported here, while associations can be determined, causality cannot be inferred.

A number of additional factors that were not controlled for in the analyses may also play an important role in brain morphology in psychosis. Diagnostic category may be important as research suggests that while the amygdala may facilitate hippocampal-dependant memory processes in BPD, it may impair these same processes in schizophrenia.[38] Younger age of traumatic experience may also be important because the consequences of trauma appear more detrimental at an earlier stage of brain development.[39] We examined this variable in a rudimentary way (an early versus later first childhood

trauma experience) in people who had experienced childhood trauma but did not find evidence to support this conclusion. There are numerous potential reasons for this however, eg, a small sample size/minimal statistical power as well as the potential for other characteristics of those sampled exerting a more pervasive effect on neuroanatomical variables (problematically, ICV differed between these groups and had to be controlled for).

Factors that may have been considered confounds in these analyses (eg, age of onset; psychosis severity) may also be influenced by trauma history and both drug abuse and depression are likely to have a complex relationship with trauma and neuroanatomical variables in psychosis groups. Moreover, while antipsychotic medication effects were deemed to be limited, we did not control for antidepressant treatments, the prescription of which may have predated the onset of psychosis, which have been found to block the effects of stress and/or promote neurogenesis.[40]

The retrospective design is also a limitation. The trauma measures were administered a few years following the MRI scanning procedures and rely on the accurate self-report of trauma. Participants may have underestimated their experience of trauma due to it being repressed, dissociated, or forgotten or may not have been prepared to disclose their experiences due to feeling ashamed or being mistrustful of the researcher and/or the interview situation. Conversely, overreporting may have occurred, possibly as a by-product of the participants' mental state. However, the trauma measures utilized in this research have excellent psychometric properties, indicating high test-retest reliability and thus stability over time.[32] Several studies have reported fair to moderate test-retest reliability for trauma measures in populations with severe mental illnesses, including one in the same geographical region as this study.[41] Moreover, recent research indicates that self-reported histories of adversity in a psychosis population were both reliable and valid when they were measured over time (7-year period) and compared with other sources of data (eg, case notes) and also were not associated with current severity of psychotic symptoms.[42]

Irrespective of the study limitations, there are a number of important implications. This study contributes to current theorizing by providing support for the TN model of psychosis.[3] The high prevalence of trauma within the sample provides further evidence for the implementation of new policy guidelines in the United Kingdom, which stipulate that trauma enquiries by trained mental health professionals should form a part of all routine psychiatric assessments (National Health Service Confederation).[1] The results further suggest that trauma-focused interventions for traumatized individuals with psychosis may be an important avenue for intervention. Indeed, Read et al[1] note that "the fact that early trauma affects the brain does not imply that those brain changes are irreversible."

This study provides evidence that childhood trauma is a potentially important explanatory variable for neuroanatomical observations in FEP. However, many questions remain regarding the exact nature of the relationship. The use of longitudinal studies with UHR and traumatized groups offers a promising method of disentangling the conflicting morphometric findings in psychosis populations.

Funding

Acknowledgments

References

1. Read JP, Rudegeair T, Fellitti V, Whitfield CL. Child maltreatment and psychosis: a return to a genuinely integrated bio-psycho-social model. *Clin Schizophr Relat Psychoses*. 2008;2:235–254.
2. Morgan C, Fisher H. Environment and schizophrenia: environmental factors in schizophrenia: childhood trauma—a critical review. *Schizophr Bull*. 2007;33:3–10.
3. Read JP, Perry BD, Moskowitz A, Connolly J. The contribution of early traumatic events to schizophrenia in some patients: a traumagenic neurodevelopmental model. *Psychiatry*. 2001;64:319–346.
4. Gillespie CF, Phifer J, Bradley B, Ressler KJ. Risk and resilience: genetic and environmental influences on development of the stress response. *Depress Anxiety*. 2009;26:984–992.
5. Braehler C, Holowka D, Brunet A, et al. Diurnal cortisol in schizophrenia patients with childhood trauma. *Schizophr Res*. 2005;79:353–354.
6. Karl A, Schaefer M, Malta LS, Dörfel D, Rohleder N, Werner A. A meta-analysis of structural brain abnormalities in PTSD. *Neurosci Biobehav Rev*. 2006;30:1004–1031.
7. Stein MB, Koverola C, Hanna C, Torchia MG, McClarty B. Hippocampal volume in woman victimised by childhood sexual abuse. *Psychol Med*. 1997;7:95–959.
8. Brambilla P, Soloff PH, Sala M, Nicoletti MA, Keshavan MS, Soares JC. Anatomical MRI study of borderline personality disorder patients. *Psychiatry Res*. 2004;131:125–133.
9. Vythilingam M, Heim C, Newport J, et al. Childhood trauma associated with smaller hippocampal volume in women with major depression. *Am J Psychiatry*. 2002;159:2072–2080.
10. Grassi-Oliveira R, Ashy M, Stein LM. Psychobiology of childhood maltreatment: effects of allostatic load? *Rev Bras Psiquiatr*. 2008;30:60–68.
11. Neigh GN, Gillespie CF, Nemeroff CB. The neurobiological toll of child abuse and neglect. *Trauma Violence Abuse*. 2009;10:389–410.
12. Vita A, De Peri L, Silenzi C, Dieci M. Brain morphology in first-episode schizophrenia. A meta-analysis of quantitative magnetic resonance imaging studies. *Schizophr Res*. 2006;82:75–88.

13. Velakoulis D, Pantelis C, Mc Gorry P, et al. Hippocampal volume in first episode psychosis and chronic schizophrenia. *Arch Gen Psychiatry*. 1999;56:133–141.

14. Velakoulis D, Wood SJ, Wong MT, et al. Hippocampal and amygdala volumes according to psychosis stage and diagnosis: a magnetic resonance imaging study of chronic schizophrenia, first-episode psychosis, and ultra-high-risk individuals. *Arch Gen Psychiatry*. 2006;63:139–149.

15. Tanskanen P, Veijola J, Piippo U, et al. Hippocampus and amygdala volumes in schizophrenia and other psychoses in the Northern Finland 1966 birth cohort. *Schizophr Res*. 2005;75:283–294.

16. Verma S, Sitoh YY, Lynn YC, et al. Hippocampal volumes in first-espisode psychosis. *J Neuropsychiatry Clin Neurosci*. 2009;21:24–29.

17. Witthaus H, Mendes U, Brüne M, et al. Hippocampal subdivision and amygdalar volumes in patients in an at-risk mental state for schizophrenia. *J Psychiatry Neurosci*. 2010;35:33–40.

18. Shannon C, Douse K, Mc Cusker CG, Feeney L, Barrett S, Mulholland C. The association between childhood trauma and memory functioning in schizophrenia. *Schizophr Bull*. 2011;37:531–537.

19. Schmahl CG, Vermetten E, Elzinga BM, Bremner JD. Magnetic resonance imaging of hippocampal and amygdala volume in women with childhood abuse and borderline personality disorder. *Psychiatry Res*. 2003;122:193–198.

20. Weniger G, Lange C, Sachsse U, Irle E. Amygdala and hippocampal volumes and cognition in adult survivors of childhood abuse with dissociative disorders. *Acta Psychiatr Scand*. 2008;10:1–10.

21. Wright IC, Rabe-Hesketh S, Woodruff WR, David AS, Murray RM, Bullmore ET. Meta-analysis of regional brain volumes in schizophrenia. *Am J Psychiatry*. 2000;157:16–25.

22. Barrett S, Mulholland C, Cooper S, Rushe T. Patterns of neurocognitive impairment in first episode bipolar disorder and schizophrenia. *Br J Psychiatry*. 2009;195:67–72.

23. World Health Organization. *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva, Switzerland: *WHO*; 1992.

24. Beck AT. *Beck Depression Inventory-II*. London, UK: The Psychological Corporation; 1996.

25. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13:261–276.

26. Groth-Marnat G. *Handbook of Psychological Assessment*. 4th ed. Hoboken, NJ: Wiley; 2003.

27. Kay SR, Opler LA, Lindenmayer JP. Reliability and validity of the positive and negative syndrome scale for schizophrenics. *Psychiatry Res*. 1988;23:99–110.

28. Lindenmayer JP, Brown E, Baker RW, et al. An excitement subscale of the positive and negative syndrome scale. *Schizophr Res*. 2004;68:331–337.

29. Carlson PW, Putnam FW. An update on the dissociative experiences scale. *Dissociation*. 1993;6:16–26.

30. Nijenhuis RS, van Der Hart O, Kruger K. The psychometric characteristics of the Traumatic Experiences Questionnaire (TEC): first findings among psychiatric outpatients. *Clin Psychol Psychother*. 2002;9:200–210.

31. Foa EB. *Post Traumatic Diagnostic Scale Manual*. Minneapolis, MN: National Computer Systems, Inc; 1995.

32. Foa EB, Cashman L, Jaycox L, Perry K. The validation of a self-report measure of posttraumatic stress disorder: the Posttraumatic Diagnostic Scale. *Psychol Assess*. 1997;9:445–451.

33. Dorahy M, Shannon C, Maguire C. The Troubles Related Experiences Questionnaire (TREQ): a clinical and research tool for Northern Irish samples. *Ir J Psychol*. 2007;38:185–195.

34. Buckner RL, Head D, Parker J, et al. A unified approach for morphometric and functional data analysis in young, old, and demented adults using automated atlas-based head size normalization: reliability and validation against manual measurement of total intracranial volume. *Neuroimage*. 2004;23:724–738.

35. Mathalon DH, Sullivan EV, Rawles JM, Pfefferbaum A. Correction for head size in brain-imaging measurements. *Psychiatry Res*. 1993;50:121–139.

36. Duvernoy HW. *The Human Hippocampus: Functional Anatomy, Vascularization and Series Sections with MRI*. 2nd ed Berlin, Germany: Springer-Verlag; 1998.

37. Brierley B, Shaw P, David AS. The human amygdala: a systematic review and meta-analysis of volumetric magnetic resonance imaging. *Brain Res Brain Res Rev*. 2002;39:84–105.

38. Killgore WD, Rosso IM, Gruber SA, Yurgelun-Todd DA. Amygdala volume and verbal memory performance in schizophrenia and bipolar disorder. *Cogn Behav Neurol*. 2009;22:28–37.

39. Glaser JP, Van Os J, Portegijis PTM, Myin-Germeys I. Childhood trauma and emotional reactivity to daily life stress in adult frequent attenders of general practitioners. *J Psychosom Res*. 2006;61:229–236.

40. Bremner JD. Traumatic stress: effects on the brain. *Dialogues Clin Neurosci*. 2006;8:445–461.

41. Klewchuk E, McCusker CG, Mulholland C, Shannon C. Cognitive biases for trauma stimuli in people with schizophrenia. *Br J Clin Psychol*. 2007;46:333–345.

42. Fisher HL, Craig TK, Fearon P, et al. Reliability and comparability of psychosis patients' retrospective reports of childhood abuse. *Schizophr Bull*. 2011;37:546–553.