Untangling pathways between childhood trauma and psychosis

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Childhood trauma in patients with psychotic disorders is associated with hippocampal volume: a sMRI study


Submitted
Abstract

**Background.** It has been suggested that childhood trauma (ChT) may contribute to the development of psychosis through structural alterations observed in hippocampal and amygdala volume. This study examined whether ChT – differentiating between type I and type II ChT and childhood bullying – is associated with smaller hippocampal and amygdala volume in patients with psychosis.

**Methods.** Of 172 patients recently diagnosed with schizophrenia or a related disorder, structural 3T MRI scans were acquired. We assessed single incident trauma (type I ChT) with the List of Threatening Events (LTE) and complex trauma (type II ChT) and childhood bullying with the Childhood Experience of Care Abuse Questionnaire (CECA.Q).

**Results.** Linear mixed model analysis showed ChT was associated with smaller hippocampal volume ($d = .33, p = .025$). Furthermore, patients with a history of type II ChT showed smaller hippocampal volumes than patients with only a history of type I ($d = .39, p = .195$). Last, we found that being bullied as a child was also associated with smaller hippocampal volume ($d = .63, p = .01$). No differences were found in amygdala volume.

**Conclusions.** Especially type II ChT is associated with substantially smaller hippocampal volume in patients with psychotic disorders. Moreover, patients who have been bullied in childhood show a loss in hippocampal volume that is comparable to that of patients with a history of type II ChT. This finding supports the hypothesis that being bullied can be considered as a type II ChT.

Introduction

The association between childhood trauma (ChT) and psychotic disorders is well-established. However, it is still not clear which factors account for this relationship. Both reductions of hippocampal and amygdala volumes and a history of ChT are highly prevalent in patients with psychosis and it has been suggested that one way ChT could contribute to the development of psychosis is through structural alterations observed in these brain regions.

There is accumulating evidence that ChT has lasting effects on brain systems and circuits that mediate the stress response, including the hypothalamic-pituitary-adrenal (HPA) axis. In case of prolonged exposure to stress, which coincides with chronic heightened glucocorticoid release, permanent changes in the HPA axis occur. These changes in the HPA axis are related to structural alterations in brain regions as the hippocampus and amygdala, areas with high densities of glucocorticoid receptors. In turn, stress induced dysregulation of the HPA axis results in an increase of dopamine receptor densities and dopamine release in the brain. This dopaminergic system is proposed to be important in the interpretation of (stress and) threat-related stimuli. In case of prolonged exposure to stressful events, this could contribute to a generalized ‘oversensitivity’ to (later) stress, often seen in patients with a psychotic disorder.

Possibly due to relatively small samples, studies that have addressed brain volume in patients with both psychosis and a history of ChT have yielded inconsistent findings. Of three studies comparing hippocampal and amygdala volume of patients with ChT to patients without a history of ChT, one study found decreased hippocampal volume and two studies found reduced amygdala volume. The discrepancy between these findings emphasizes the need for studies in larger samples.

When investigating trauma, a distinction can be made between ‘type I’ single-incident trauma and ‘type II’ complex trauma. Type I trauma refers to isolated traumatic events that are not directly caused by a (closely) related person and include for example natural disasters or being in an accident. Type II trauma refers to events that are often chronic and caused by the actions of a (closely) related person (such as abuse and neglect), and is considered to have more pervasive consequences than type I trauma because of associated psychobiological and developmental mechanisms.

To date, type II trauma types ‘abuse’ and ‘neglect’ are most consistently associated with psychosis. However, growing evidence indicates that childhood bullying, when severe, can also be considered a significant form of type II ChT. Recent studies on childhood bullying and psychosis, showed that the risk of psychotic symptoms to be twice as high in individuals who were childhood victims of bullying, independent of previously diagnosed psychiatric disorders and other psychosocial stressors. This relationship was even stronger in case of chronic and/or severe bullying.
In the present study therefore we aim to examine hippocampal and amygdala brain volumes in a large sample of patients with recent onset psychotic disorders, with and without a history of ChT, considering both type I and type II ChT and childhood bullying.

**Methods**

**Participants**
Participants were patients admitted to the Early Psychosis Department of the Academic Medical Centre (AMC, University of Amsterdam) in the Netherlands, a specialized clinic for young adults with recent-onset psychotic disorders. Our sample is part of a larger cohort\(^3\). We included all patients aged 16-39 who underwent a sMRI scan in the period December 2004 and December 2010 as part of standard clinical procedure and gave informed consent. Patients with brain lesions, neurological or endocrine disorders were excluded. Data management was done in accordance with the institutional ethical protocols for data protection. Removing all retraceable information and encrypting all identifiers in the final datasets maintained confidentiality.

**Materials**

**Symptomatology and functioning**
Experienced clinicians conducted all diagnostic interviews. The Comprehensive Assessment of Symptoms and History (CASS)\(^8\) was used to assess DSM-IV diagnosis. The CASH includes the Scale for the Assessment of Positive Symptoms (SAPS, with 34 items measured on a Likert scale ranging from 0 (absent) to 5 (severe))\(^4\) and the Scale for the Assessment of Negative Symptoms (SANS, with 21 items)\(^1\). All diagnoses were assessed using the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 4th edition\(^1\).

To assess the severity of symptoms we used the PANSS Remission Tool\(^5\). For the Remission Tool eight major symptoms of the PANSS were selected (delusions, conceptual disorganization, hallucinations, blunted affect, passive/apathetic social withdrawal, lack of spontaneity and flow of conservation, poor impulse control and unusual thought content). Remission is defined as having a score of ≤ 3 on the 7-point severity scale of the PANSS (mild or less) for a period of at least six months. We dichotomized the scores on the remission tool according to the guidelines; with a group in remission (with a score ≤ 3) and a group not in remission (with a score ≥ 4).

Current social, psychological and symptomatic functioning of the patients was assessed using the interviewer-rated DSM-IV-TR Axis V 100-point scales, the Global Assessment of Functioning (GAF)\(^2\).

The number and duration of the psychotic episodes were assessed by combining the information collected from the interviews of patients and their significant others.

**Childhood trauma**

Information about type I ChT (single incidence trauma) was assessed with the List of Threatening Events (LTE)\(^2\), which reflects the presence of moderate and major life stressors. In the current study, the questionnaire was completed retrospectively using the patients’ case records. We only included the items related to major stress, including serious illness, death of parents or family, victim of assault, robbery, burglary or threat and to witnessing a severe traumatic event (for example war experience or a natural disaster) before the age of 17.

Type II ChT (complex trauma) and bullying were obtained with the Childhood Experience of Care Abuse Questionnaire (CECA.Q)\(^2\). This is a self-report questionnaire measuring a broad range of adverse childhood experiences before the age of 17. In the current study, also this questionnaire was completed retrospectively using the patients’ case records. Fisher and colleagues showed that childhood abuse documented in clinical case notes is reliable\(^3\). Childhood abuse (physical, emotional and sexual), childhood neglect (physical and emotional) and witnessing domestic violence between the parents were classified as type II ChT.

**MRI acquisition and processing**

All structural MRI scans were acquired on the same 3T MRI scanner (Intera, Philips Healthcare, Best, The Netherlands) with a phased array SENSE six/eight-channel receiver head coil. For each participant, a T1-weighted structural MRI image was acquired. Except for bullying, the scan parameters differed slightly between scans, but not significantly between groups (see Supplementary Table 1 for scanning sequences). T1-weighted images were visually inspected for motion and other artefacts. Cortical reconstruction and volumetric segmentation was performed with the FreeSurfer image analysis suite (version 5.0.0) (http://surfer.nmr.mgh.harvard.edu/), using the e-Bioinfra Gateway\(^4\), a web application that provides facilitated access to the Dutch Grid infrastructure to analyse large data collections.

Briefly, FreeSurfer processing includes motion correction\(^5\), skull stripping\(^6\), automated Talairach transformation, segmentation of the subcortical white matter and deep grey matter volumetric structures\(^5\), intensity normalization\(^5\), tessellation of the grey/white matter boundary, automated topology correction\(^6\), and surface deformation\(^5\).
Data analysis

Demographic and clinical data were compared between groups using $\chi^2$ and One-Way ANOVA’s. The above described FreeSurfer processing steps generate a volumetric output variable for each individual subject. These output variables were extracted from the FreeSurfer output files from the subcortical segmentation step from the FreeSurfer processing pipeline using Matlab (R2009a, Mathworks, Inc., Natick, MA) and transferred into SPSS version 20 (SPSS Inc., Chicago, IL).

Regions of interest (ROIs) were the hippocampus and amygdala, which were selected prior to analysis according to the literature. The results were controlled for age, gender and intracranial volume (ICV). No differences (between group analyses and post-hoc analyses) were found between demographics, clinical variables (Table 1) and scan parameters (Supplementary Table 1) and therefore were not added to the model.

First, we compared hippocampal and amygdala volume between patients with and without ChT. Second, we differentiated between type I, type II ChT and childhood bullying. For these second analyses we classified five groups: 1) patients without ChT; 2) patients with a history of type I ChT; 3) patients with a history of type II ChT; 4) patients with a history of both type I and type II or type I ChT and bullying; and 5) patients with a history of childhood bullying without a history of other forms of ChT.

For each brain region the effect of ChT was assessed using a linear regression model with hippocampus or amygdala volume as dependent variable, and ChT (modelled as a function of the type of ChT experienced), age, gender and ICV as predictors. To assess whether the effect of ChT on hippocampal or amygdala volume was modified by age, gender and/or ICV we added all possible interaction terms as predictors to the regression model. Subsequently, all non-significant interaction terms were removed from the model. Age and ICV were centered around the grand mean. To compare the magnitudes of the effects, we calculated Cohen’s $d$ scores (based on beta’s and standard deviations thus controlled for age, gender and ICV).

Results

Demographic variables

Data were available for 172 patients (mean age = 22.08; SD = 3.06). 103 patients (60 %) reported to have experienced ChT. Of those, 33 (32%) patients reported a history of type I ChT, 16 (16%) patients reported a history of type II ChT, 35 (34%) a history of both type I and type II ChT or type I ChT and bullying and 19 patients reported only a history of bullying (18%). No significant group differences were found in terms of gender, age at time of MRI scan, highest educational level, diagnosis, ethnicity, age at first psychosis, number of psychotic episodes, number of months psychotic, use of antipsychotics, PANSS remission tool score and GAF scores. Descriptives are presented in Table 1.
Chapter 6

Hippocampus

**ChT versus no ChT**

Linear mixed model analysis showed that patients with a history of ChT showed smaller hippocampal volume compared to patients without a history of ChT (Cohen's \( d = .33, p = .025 \)). Results of the linear mixed model analysis are described in Table 2 and 3.

**Type I versus type II ChT**

When we differentiated between the types of ChT, we found type of ChT (type I versus type II) to be differentially associated with hippocampal volume. Patients with a history of type II ChT had smaller hippocampal volumes than patients with only a history of type I ChT (Cohen's \( d = .39, p = .195 \)). Patients with type I ChT did not differ from those without a history of ChT (Cohen's \( d = .09, p = .675 \)). However, a large difference in hippocampal volume was found when comparing patients without a history of ChT with patients that experienced type II ChT (Cohen's \( d = .50, p = .08 \)). Results of the linear mixed model analysis are described in Table 2 and 3.

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**Childhood bullying**

Being bullied was significantly associated with a smaller hippocampal volume. Patients with a history of bullying (without any other forms of ChT) showed smaller hippocampal volume compared to patients without any history of trauma (Cohen's \( d = .63, p = .01 \)). Moreover, no significant difference was found between those with a history of type II ChT and those with a history of childhood bullying (Cohen's \( d = .15, p = .583 \)). Results of the linear mixed model analysis are described in Table 2 and 3.

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**Table 2.** Means, standard deviations and results of the mixed model analyses of the effect of ChT on hippocampal and amygdala volume

<table>
<thead>
<tr>
<th></th>
<th>Mean (SD)</th>
<th>( F )</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hippocampal volume</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ChT-</td>
<td>4325 (439)</td>
<td>5.10</td>
<td>.025*</td>
</tr>
<tr>
<td>ChT+</td>
<td>4175 (511)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amygdala volume</strong></td>
<td></td>
<td>.014</td>
<td>.905</td>
</tr>
<tr>
<td>ChT-</td>
<td>1672 (202)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ChT+</td>
<td>1671 (199)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hippocampal volume</strong></td>
<td></td>
<td>2.260</td>
<td>.065</td>
</tr>
<tr>
<td>ChT-</td>
<td>4325 (439)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>4318 (464)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>4038 (455)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both I and II</td>
<td>4159 (496)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only bullying</td>
<td>4070 (624)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Amygdala volume</strong></td>
<td></td>
<td>.091</td>
<td>.985</td>
</tr>
<tr>
<td>ChT-</td>
<td>1672 (202)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type I</td>
<td>1700 (234)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type II</td>
<td>1658 (211)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Both I and II</td>
<td>1643 (165)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Only bullying</td>
<td>1683 (185)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1The beta estimate is the deviation from the volume of the reference group. The estimated volume of the reference group is depicted below.

2ChT-: no history of childhood trauma, ChT I: history of type I trauma, ChT II: a history of type II trauma

3Beta (SE) from the reference group ChT: 4342.45 (55.87)

4Beta (SE) from the reference group ChT: 4343.02 (55.56)

5Beta (SE) from the reference group ChT II: 4121.53 (117.00)

6Beta (SE) from the reference group only bullying: 4036.33(104.28)

7\( \* p < 0.05, ** p < 0.01 \)
**Amygdala**

We found no significant differences in amygdala volumes between patients with and without a history of ChT (supplementary Table 2).

**Discussion**

This study provides evidence for a loss in hippocampal volume in patients with psychosis and a history of ChT. This finding is in line with the recent literature reporting on brain volume loss in people with ChT\textsuperscript{246-248,250,253}. Moreover, our finding that especially type II ChT is related to a loss in hippocampal volume is in agreement with the suggestion that the consequences of type II ChT are more pervasive than those of type I ChT\textsuperscript{56,58,95,127,272}. Although not all the findings reach the level of significance (probably due to a power problem as a result of small subsamples), we did find large effect sizes. An important finding of this study is that patients who have been bullied in childhood show decreased hippocampal volume comparable to the smaller volume of patients with a history of type II ChT. This finding supports the hypothesis that being bullied may be considered a type II ChT.

Our finding that patients with a history of type II ChT and patients with a history of childhood bullying had significantly smaller hippocampal volume than patients with a history of type I ChT, underscores the theory that especially prolonged exposure to stress is related to structural alterations in certain brain regions\textsuperscript{56,58,271}. It is suggested that type II ChT is more pervasive than type I ChT because of underlying psychobiological and developmental mechanisms\textsuperscript{2,11}. Type II ChT, including bullying, is caused by the actions of a person who expresses the intention to harm and humiliate the victim. Moreover, perpetrators are often closely related to their victims. This type of ChT has been related to the development of negative beliefs about self and others (e.g. negative self-esteem and/or a disruption in the ability to trust others)\textsuperscript{56,58,271}. Negative beliefs have in turn been associated with reduced experience of internal control and (because of that) higher levels of (experienced) distress\textsuperscript{56,58,95,127,272}. Furthermore, ChT can give rise to social defeat, the negative experience of being excluded, which is also associated with increased levels of stress\textsuperscript{273}.

We did not find differences in amygdala volumes between patients with and without a history of ChT. Of the other three studies comparing amygdala volume of patients with psychotic disorders\textsuperscript{56,231,234}, two studies provided evidence for a loss in amygdala volume in those patients with a history of ChT\textsuperscript{246,248}\textsuperscript{274}. Efforts to identify effects of ChT on amygdala structure are inconclusive, and have linked abuse to both smaller, larger or no differences in amygdala volumes\textsuperscript{246,248,274}.

One of the strengths of this study is the large sample size. Possibly due to relatively small samples, previous studies that have addressed brain volume in patients with both psychosis and a history of ChT have yielded inconsistent findings. Our data suggest that a history of ChT in patients with psychotic disorders is associated with smaller hippocampal volume, but not with amygdala volume. Because we made use of a large sample, these findings are more robust and reliable. Moreover, by using a large MRI sample of patients with psychotic disorders, we were also able to differentiate between type I and type II ChT and bullying. However, these different groups were small and therefore these findings need to be replicated in larger samples.

When interpreting these findings, certain limitations have to be considered. The most important limitation is that traumatic experiences were measured retrospectively on the basis of clinical charts. Most of the files were comprehensive but although standard clinical procedure entails that the interviewers inquire about traumatic experiences, it is possible that not all traumatic experiences were included in the clinical files.

A second limitation is the small number of females in our sample, and therefore we were not able to examine possible gender differences. Investigating possible gender differences is an important aspect for future research.

Third, the cross-sectional design of the study does not allow for any conclusions about causation. To make inferences about causality, longitudinal and prospective studies are needed.

This study provides evidence for a loss in hippocampal volume in patients with psychosis and a history of ChT. Moreover, our findings suggest that bullying can be considered a type II ChT. This highlights the importance of early (school-based) interventions, designed to prevent and stop bullying. School bullying is a worldwide problem that affects about one-third of children, and approximately 11% are bullied on a regular basis\textsuperscript{59}. Furthermore, negative appraisals about self and others may be important subjects for discussion in the classroom to change existing cognitive schema\textsuperscript{92}.

For clinical purposes it is important is that researchers and clinicians need to comprise attention for ChT, including bullying. It is important that clinicians address dysfunctional interpersonal interaction styles and dysfunctional beliefs and help their patients to change them. Research has suggested that early detection and intervention may have the potential to change the course of early psychopathology\textsuperscript{279}.

**Author contributions**

D. van Dam, L. Koenders, W. Vingerhoets, M. Machielsen, E. Velthorst, C. Meijer and L. de Haan conceived and designed the experiments. D. van Dam, L. Koenders and W. Vingerhoets analyzed and interpreted the data. D. van Dam wrote the article. All authors reviewed the article and approved for publication.
### Supplementary Table 1. Scan parameters

<table>
<thead>
<tr>
<th>Scan parameter</th>
<th>Patients ChT-¹ (N = 69)</th>
<th>Patients ChTI (N = 33)</th>
<th>Patients ChTI (N = 16)</th>
<th>Patients ChT both I and II (N = 35)</th>
<th>Only bullying (N = 19)</th>
<th>Statistics</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TR² in ms (m:s.d)</td>
<td>9.56 (0.36)</td>
<td>9.56 (0.35)</td>
<td>9.49 (0.39)</td>
<td>9.54 (0.37)</td>
<td>9.37 (0.40)</td>
<td>F = 1.09</td>
<td>0.365</td>
</tr>
<tr>
<td>TE³ in ms (m:s.d)</td>
<td>4.34 (0.40)</td>
<td>4.36 (0.39)</td>
<td>4.26 (0.45)</td>
<td>4.31 (0.42)</td>
<td>4.12 (0.47)</td>
<td>F = 1.30</td>
<td>0.272</td>
</tr>
<tr>
<td>Slice thickness in mm (1.0/1.2: N)</td>
<td>20/49</td>
<td>9/24</td>
<td>6/10</td>
<td>11/24</td>
<td>10/9</td>
<td>X²=4.51</td>
<td>0.342</td>
</tr>
<tr>
<td>Flip angle in degrees (8.0: N%)</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rows columns (in mm)</td>
<td>256*256</td>
<td>256*256</td>
<td>256*256</td>
<td>256*256</td>
<td>256*256</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ChT- no history of childhood trauma, ChTI a history of type I trauma, ChTI a history of type II trauma
²TR = repetition time
³TE = echo time