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Hippocampal development in youth with a history of childhood maltreatment

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ABSTRACT

Childhood maltreatment (CM) is associated with enhanced risk of psychiatric illness and reduced subcortical grey matter in adulthood. The hippocampus and amygdala, due to their involvement in stress and emotion circuitries, have been subject to extensive investigations regarding the effect of CM. However, the complex relationship between CM, subcortical grey matter and mental illness remains poorly understood partially due to a lack of longitudinal studies. Here we used segmentation and linear mixed effect modelling to examine the impact of CM on hippocampal and amygdala development in young people with emerging mental illness. A total of 215 structural magnetic resonance imaging (MRI) scans were acquired from 123 individuals (age: 14–28 years, 79 female), 52 of whom were scanned twice or more. Hippocampal and amygdala volumes increased linearly with age, and their developmental trajectories were not moderated by symptom severity. However, exposure to CM was associated with significantly stunted right hippocampal growth. This finding bridges the gap between child and adult research in the field and provides novel evidence that CM is associated with disrupted hippocampal development in youth. Although CM was associated with worse symptom severity, we did not find evidence that CM-induced structural abnormalities directly underpin psychopathology. This study has important implications for the psychiatric treatment of individuals with CM since they are clinically and neurobiologically distinct from their peers who were not maltreated.

1. Introduction

Child abuse and neglect are widespread global phenomena (Stoltenborgh et al., 2015) and represent a major public health challenge due to the enduring negative impact they have on social, academic, mental and physical health outcomes (McLeod et al., 2014; Rapoza et al., 2014; Romano et al., 2014). Maltreated children have double the risk of developing a psychiatric illness in adulthood (Scott et al., 2010; Spauwen et al., 2006). Furthermore, amongst people with depressive, bipolar, psychosis or anxiety disorder, childhood maltreatment (CM) has been linked to worse symptom severity and poor treatment response (Kuhn et al., 2015; Miniati et al., 2010; Nanni et al., 2012; Simon et al., 2009).

Across studies of the past two decades CM has been strongly related to reduced hippocampal volume in adulthood (for meta-analysis see Paquola et al. (2016)), however the largest study to date did not find CM to be associated with hippocampal volume in healthy and depressed individuals (Frodl et al., 2017). There has been no evidence of differences in hippocampal volume between children with abuse related post-traumatic stress disorder (PTSD) and healthy non-abused children (De Bellis and Keshavan, 2003; De Bellis et al., 1999; De Bellis et al., 2002). Additionally, while numerous studies of institutionally-raised children have shown enlarged amygdala volumes (Lupien et al., 2011; Mehta et al., 2009; Tottenham et al., 2010), only two studies have reported greater amygdala volumes in adults with a history of CM (Kuhn et al., 2015; Pechtel et al., 2013). Conversely, several studies have shown no difference (Andersen et al., 2008; Brambilla et al., 2004; Bremner et al., 1997; Cohen et al., 2006; Driessen et al., 2000; Frodl et al.,

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2017; Schmahl et al., 2003) or smaller amygdala volumes (Aas et al., 2012; Hoy et al., 2012; Malykhin et al., 2012; Sodre et al., 2014) among adults with a history of CM. Furthermore, our recent meta-analysis revealed greater CM-related reductions in amygdala volume amongst older cohorts (Paquola et al., 2016). During normal brain development, amygdala and hippocampal volumes increase throughout adolescence (Lenroot and Giedd, 2010; Ostby et al., 2009).

To date, only three longitudinal studies have investigated the impact of CM on the development of subcortical brain structures. One small longitudinal study of 10–13 years old children did not detect any difference in hippocampal or amygdala volume changes between healthy children and those with PTSD secondary to child abuse (De Bellis et al., 2001). In contrast, Whittle et al. (2013) reported that young teens with high levels of CM had reduced left amygdala growth compared to non-maltreated counterparts. In the same study the authors reported that there was no difference in hippocampal development. This result was replicated in a recent extension of the study to late teens, which also assessed development of hippocampal subregions (Whittle et al., 2016). Childhood maltreatment was, however, found to be indirectly related to reduced left hippocampal development via increased risk of psychopathology (Whittle et al., 2013).

Numerous links have been established between CM and subcortical volumes (Paquola et al., 2016), between CM and psychiatric risk (Scott et al., 2010; Spauwen et al., 2006) and between subcortical volume and mental health (Schmaal et al., 2016; van Erp et al., 2016). However, few studies have investigated the three factors in conjunction (for an interesting exception see Rao et al. (2010)). It has been suggested that abnormal subcortical development during youth may confer enhanced psychiatric risk and contribute to the clinical differentiation of individuals with a history of CM from those without (Teicher and Samson, 2013). This effect may be particularly important between late adolescence and young adulthood when the symptoms and diagnosis of three quarters of lifetime psychiatric disorders emerge (Kessler et al., 2005) and subcortical development is coupled to pubertal changes (Goddings et al., 2012).

The primary aim of the present study was to determine whether CM impacts hippocampal and amygdala development in young people with emerging mental illness. In addition, we aimed to quantify the clinical differentiation of individuals with CM, and examine whether clinical differences were related to aberrant hippocampal or amygdala development. To this end we performed a mixed cross sectional/longitudinal study of 123 young people exhibiting an admixture of psychiatric symptoms and reporting varied CM histories. We used linear mixed effect modelling to explore the differences in subcortical development and clinical trajectories of young people with high and low levels of reported CM. Furthermore, we assessed whether subcortical development was related to symptom severity. We hypothesised that people with CM would have reduced rates of hippocampal grey matter growth compared to people without CM, and that this reduced rate of brain development would be related to worse psychiatric symptoms.

2. Method

2.1. Participants

Participants were recruited from a specialised clinic ('headspace') for assessment and early intervention of mental health problems in young people (Scott et al., 2012) at the Brain and Mind Centre, Sydney, Australia. Given the instability and high co-morbidity of psychiatric diagnoses in young people (Hafner et al., 2008), we followed the Research Domain Criteria recommendations of the National Institute of Mental Health (Cuthbert and Insel, 2013) and recruited a wide range of individuals from a specialised mental health clinic for young people. The advantages of using this trans-diagnostic approach in research are discussed at length elsewhere (Casey et al., 2013; Cuthbert, 2014; Cuthbert and Insel, 2013). The present study included 215 MRI scans from 123 individuals, of whom 52 were scanned at least twice (see Supplementary Table 1 for further information). All patients were receiving clinician-based case management and relevant psychosocial interventions at the time of assessment. Patients who were treated with psychotropic medications were assessed under 'treatment as usual' conditions, that is, medications were not interrupted in any way. Exclusion criteria for all participants were medical instability (as determined by a psychiatrist), history of neurological disease (e.g. tumour, head trauma, epilepsy), medical illness known to impact cognitive and brain function (e.g. cancer, electroconvulsive therapy in last 3 months), intellectual and/or developmental disability (a predicted IQ score < 70), insufficient English for testing or psychiatric assessment and current substance dependence. The study was carried out in accordance with the Declaration of Helsinki, was approved by the University of Sydney Human Research Ethics Committee and all participants gave written informed consent.

2.2. Clinical assessment

At baseline a retrospective self-report questionnaire, the Childhood Trauma Questionnaire (CTQ) short form, was used to measure exposure to maltreatment prior to the age of 16 (Bernstein et al., 1997). The CTQ separately assesses experiences of sexual abuse, physical abuse, emotional abuse, physical neglect and emotional neglect using a rating system along a five point Likert scale from 1 (never true) to 5 (very often true). Each participant produces a score from 5 to 25 for each subscale and an additive score from 25 to 125 for total CTQ. Participants were assigned to the CM group if they exceeded the moderate-severe cutoff score on one or more CTQ subscales; sexual abuse $\geq$8, physical abuse $\geq$10, emotional abuse $\geq$13, physical neglect $\geq$10 and emotional neglect $\geq$15. Thirteen participants reported sexual abuse, 24 participants reported physical abuse, 50 participants reported emotional abuse, 30 participants reported physical neglect and 34 participants reported emotional neglect. Notably, 55 participants did not report any CM, 25 participants reported one type of CM, 17 participants reported three types of CM, 10 participants reported four types of CM and 2 participants reported five types of CM.

At each time point a trained research psychologist conducted the clinical assessment (in a semi-structured interview format) to inform the diagnostic classification and to determine the nature and history of any mental health problems (see Supplementary Table 1 for more information on clinical data acquired at each time point). Primary diagnoses of participants included depressive ($n = 58$), bipolar ($n = 32$), psychosis ($n = 17$), and anxiety disorders ($n = 16$). Since 84% of the participants presented with a co-morbid axis-1 psychiatric disorder, we characterised the cohort on the basis of having any mood disorder diagnosis, any psychosis disorder diagnosis and any anxiety disorder diagnosis. Age of illness onset was collected for 94 participants. 64 participants experienced early disorder onset; defined as disorder onset at or before 15 years of age. 30 participants experienced late disorder onset; defined as disorder onset after 15 years of age. The assessment also included the Hamilton Depression Rating Scale (HDRS, 17-item) (Hamilton, 1967) to quantify current mood symptoms, the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) to quantify current general psychiatric symptoms and the Social and Occupational