Schizophrenia Research xxx (2016) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Childhood adversity and hippocampal and amygdala volumes in a population at familial high risk of schizophrenia

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ARTICLE INFO

Article history:
Received 12 October 2015
Received in revised form 13 April 2016
Accepted 18 April 2016
Available online xxxx

Keywords:
Familial high risk
Schizophrenia
Childhood adversity
Hippocampus
Amygdala

ABSTRACT

Background: There is an established link between childhood adversity (CA) and schizophrenia. Hippocampus and amygdala abnormalities pre-date onset in those at high familial risk (fHR) of schizophrenia, but it is not clear whether these alterations are associated with CA in those at elevated risk of schizophrenia.
Methods: We examined hippocampal and amygdala volumes in those at fHR who had been referred to a social worker or the Children's Panel compared to those who had not.
Results: The right hippocampus and left amygdala were significantly smaller in those that had been referred to social work and Children's Panel.
Conclusions: Our findings suggest that CA can influence structural changes in the brain in a cohort at fHR of schizophrenia. These findings provide further evidence that while genetic factors contribute to the structural changes found in schizophrenia, environmental factors such as CA can have a lasting impact on specific brain regions.

1. Introduction

The stress-diathesis model suggests that a biologically driven (genetic) predisposition interacting with environmental factors produces an individual's phenotype(Zubin and Spring, 1977). It is well established that childhood adversity (CA) increases the risk of developing psychosis (Varese et al., 2012), and other psychiatric disorders including affective and anxiety disorders. It is unclear what determines an individual's vulnerability to different psychiatric disorders given similar environmental exposures but one likely influence is genetic vulnerability.

Neurodevelopmental abnormalities in the hippocampal formation have been implicated in the development of Schizophrenia (Cannon et al., 2003; Weinberger, 1999). Reductions in hippocampal volume and alterations in the amygdalae of individuals with both first episode and chronic psychosis and in those at familial high risk of schizophrenia have been demonstrated (Boos et al., 2007; Francis et al., 2013; Honea et al., 2005; Koolschijn et al., 2010a; Lawrie et al., 2001; Steen et al., 2006; Velakoulis et al., 1999; Velakoulis et al., 2006; Verma et al., 2009; Vita et al., 2006; Witthaus et al., 2010; Wright et al., 2000) and it has also been shown that left amygdala volume is reduced in those at familial high risk of schizophrenia (Cooper et al., 2014). It is also well established that there are hippocampal and amygdala volume alterations in adults in response to CA (Andersen et al., 2008; Bremner et al., 1997; Edmiston et al., 2011; McCrory et al., 2011; Stein et al., 1997; Teicher et al., 2003; Vythilingam et al., 2002; Woon et al., 2010) (Dannlowski et al., 2012). Interestingly these volume reductions are not seen in children and adolescents who have experienced CA (Carrion et al., 2001; De Bellis et al., 1999; Jackowski et al., 2009; Woon and Hedges, 2008) and translational studies have shown that exposure to early stress affects synaptic density in the hippocampus but that these effects do not emerge until after puberty (Andersen and Teicher, 2004). Furthermore it has also been demonstrated that hippocampal, particularly left hippocampal and amygdala volumes were significantly reduced in those individuals with first episode psychosis who had experienced CA compared to those that had not (Aas et al., 2012; Hoy et al., 2011).

Hypothalamic-Pituitary-Adrenal (HPA) axis activation occurs in response to environmental stress and has been implicated as a mechanism by which chronic stress such as CA influences a variety of psychiatric disorders. Read et al. were among the first to propose a traumagenic neurodevelopmental model of schizophrenia mediated by the HPA axis (Read et al., 2001). Adults who have suffered CA show hyper-reactivity and persistent sensitisation of the HPA stress response (Heim et al., 2000) as do those with schizophrenia (Mondelli et al., 2010a; Walker et al., 2008). The hippocampus is involved in terminating

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http://dx.doi.org/10.1016/j.schres.2016.04.028
0920-9964/

Table 1
Table showing population demographics for those with and without social work or Children's Panel involvement.

	Social work involvement ($n = 41$)	Children's Panel involvement ($n = 18$)	No involvement ($n = 97$)	p
Age	21.0 (0.44)	21.2 (0.67)	21.2 (0.29)	S/W v's none = 0.783 CP v's none = 0.95
Gender	20 male 21 female	7 male 11 female	52 male 45 female	
WAIS IQ	96.3 (2.27)	89.8 (2.1)	99.8 (1.23)	S/W v's none = 0.164 CP v's none = 0.0016*
Affected mother	21 (52%)	8 (44%)	20 (21%)	
Affected parent	28 (70%)	13 (72%)	30 (31%)	
Affected sibling	2 (5%)	2 (11%)	30 (31%)	

* $p < 0.005$.

the stress response through glucocorticoid mediated negative feedback on the HPA axis. Whereas the effects of stress on the adult hippocampus are generally transient, stress that occurs in early life can permanently alter the hippocampus (Brunson et al., 2003). The enduring effects of early life stress may either reflect the occurrence of stress during a sensitive developmental period in the hippocampus or the cumulative effects of both early and continuing processes of progressive injury to hippocampal neurons. It has been shown that in those at familial high risk of schizophrenia among the subfields of the hippocampal formation, the subicula are bilaterally reduced. This area plays a prominent role in inhibition of the hypothalamo-pituitary-adrenocortical (HPA) axis which may suggest that these individuals are particularly sensitive to stress and stress related hippocampal alterations (Herman and Mueller, 2006). These findings support the idea that genetic factors and CA may both contribute to reductions in hippocampal and amygdala volume, structural changes which are found in individuals with psychosis. The presence of reduced hippocampal volume in unaffected relatives of those with schizophrenia suggests that these changes are not due to the disease process.

The aim of the present study was to examine whether indices of CA derived from the Edinburgh High Risk Study (EHRS) were associated with volumetric indices of the hippocampus and amygdala, which are pre-specified subcortical regions of interest (ROIs) known to be susceptible to early adverse events. The EHRS consists of a large cohort at familial high risk of developing schizophrenia. Our hypothesis was that alterations in the hippocampal and amygdala volumes seen in those at familial high risk of schizophrenia would be significantly associated with CA as indicated by social work involvement in childhood or appearance before the Children's Panel.

A Children's Panel hears cases as part of the legal and welfare systems in Scotland and makes decisions about vulnerable children and young people in need of care; it aims to combine justice and welfare for children and young people. The majority of children are referred on care and protection grounds. The most common grounds of referral in 2013/14 were 'lack of parental care'. Referral to social work or the Children's Panel represents a level of concern regarding the adversity that a child is exposed to such that intervention is deemed necessary. This is an objective indicator of exposure to adversity as compared to more subjective retrospective self-report methods.

2. Methods

2.1. Participants

The recruitment and clinical assessment process for the EHRS have been described in detail elsewhere (Johnstone et al., 2005). The Edinburgh High Risk Study was a prospective longitudinal study where individuals at high familial risk of developing schizophrenia were identified throughout Scotland. Informed consent was obtained from all participants, as approved by the Psychiatry and Clinical Psychology subcommittee of the Multi-Centre Research Ethics Committee for Scotland. High Risk individuals aged 16 to 25 years with no personal history of psychiatric disorder were contacted, throughout Scotland, based on the criteria that they had at least two first- and/or second-degree relatives with a diagnosis of schizophrenia. The Edinburgh high risk study included full clinical and imaging data on 150 individuals at baseline. This study includes all those with grossly normal structural Magnetic Resonance Imaging scans ($n = 147$) which generated adequate

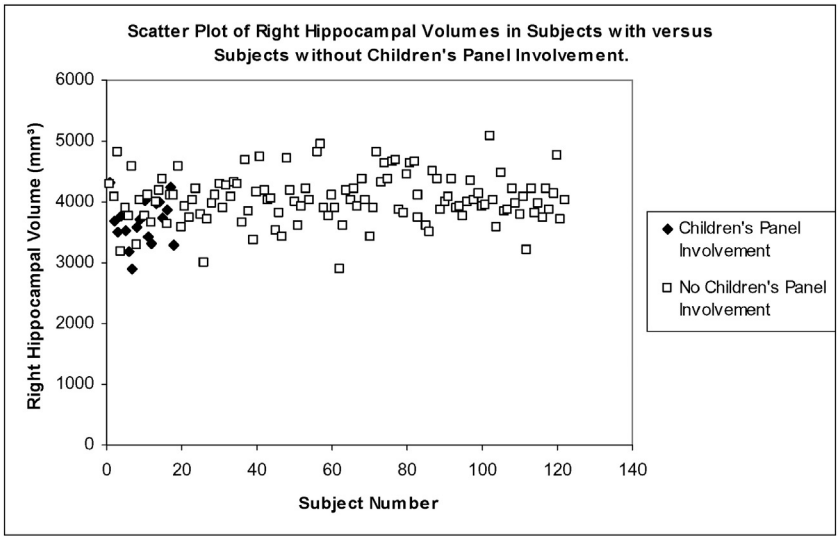

Fig. 1. Right hippocampal volume in those with and without Children's Panel involvement. Those who had Children's Panel involvement have significantly smaller right hippocampi than those that had not.

Please cite this article as: Barker, V., et al., Childhood adversity and hippocampal and amygdala volumes in a population at familial high risk of schizophrenia, Schizophr. Res. (2016), http://dx.doi.org/10.1016/j.schres.2016.04.028