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Meta-analysis of associations between childhood adversity and hippocampus and amygdala volume in non-clinical and general population samples

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ABSTRACT

Background: Studies of psychiatric populations have reported associations between childhood adversity and volumes of stress-related brain structures. This meta-analysis investigated these associations in non-clinical samples and therefore independent of the effects of severe mental health difficulties and their treatment.
Methods: The MEDLINE database was searched for magnetic resonance imaging studies measuring brain structure in adults with and without childhood adversity. Fifteen eligible papers (1781 participants) reporting hippocampal volumes and/or amygdala volumes were pooled using a random effects meta-analysis.
Results: Those with childhood adversity had lower hippocampus volumes (hedges $g = -0.15$, $p = 0.010$). Controlling for gender, this difference became less evident (hedges $g = -0.12$, $p = 0.124$). This association differed depending on whether studies included participants with some psychopathology, though this may be due to differences in the type of adversity these studies examined. There was no strong evidence of any differences in amygdala volume.
Discussion: Childhood adversity may have only a modest impact on stress-related brain structures in those without significant mental health difficulties.

Contents

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1. Introduction

Childhood adversity, defined as difficult and unpleasant situations and experiences in childhood including physical, sexual, or emotional abuse, neglect and poverty, is highly prevalent worldwide (Kessler et al., 2010). In a recent UK survey (Radford et al., 2013), 24.5% of young adults reported experiencing abuse or neglect by a parent or caregiver during childhood. Childhood abuse and neglect is associated with a range of negative physical and mental health outcomes (see (Wilson, 2010) and (Norman et al., 2012) for reviews), including posttraumatic stress disorder (Kessler et al., 1995), psychosis (Varese et al., 2012), depression and anxiety (Lindert et al., 2014), diabetes (Huffhines et al., 2016) and obesity (Danese and Tan, 2014). Growing up in poverty, another highly prevalent form of childhood adversity, is also related to a range of negative health consequences (Schickedanz et al., 2015).

These negative health outcomes may be due in part to the effects of childhood adversity on brain development. Childhood adversity can be a form of stress at a time where brains are especially sensitive to the neurotoxic effects of excessive release of stress hormones and stress-related epigenetic changes (Lupien et al., 2009). Evidence for altered neurodevelopment comes from several studies that have now shown associations between childhood adversity and neuroanatomical changes (for reviews, see (Hart and Rubia, 2012) and (McLaughlin et al., 2014)). The neurotoxic effect of stress has been demonstrated experimentally in animal studies and importantly, the neuroanatomical effects of stress in these studies are similar to those found to be related to childhood adversity in humans, particularly in the hippocampus and corpus callosum (Teicher et al., 2006).

Research on the neuroanatomy of childhood adversity has often been carried out in samples recruited for their mental health difficulties, for example, demonstrating altered volumes in stress-related brain structures such as the hippocampus and the amygdala in people with post-traumatic stress disorder (Bremner et al., 1997), depression (Vythilingam et al., 2002) and psychosis (Hoy et al., 2012); (Aas et al., 2012). It must be noted that the majority of people who experience childhood adversity do not go on to develop psychiatric illness, though they are of course at much higher risk of doing so (Macmillan et al., 2001). The present study focuses on general population samples, and control groups without a psychiatric disorder included in case-control studies. This is in order to examine whether evidence of the impact of childhood adversity on neuroanatomy can be detected in the absence of selection for mental health difficulties. Childhood adversity may have less impact on brain structures of those who do not go on to develop mental health difficulties, i.e. those resilient to the development of mental ill health in the face of childhood adversity may also have been less affected on a neuroanatomical level. If so, a meta-analytical approach is ideal as it provides increased statistical power to detect more subtle effects. This is particularly relevant for control groups of case-control studies as these individuals have relatively low levels of childhood adversity (Chaney et al., 2014). The focus on non-psychiatric samples also allows for the effect of childhood adversity to be investigated unconfounded by the stress of experiencing severe mental health difficulties and the effect of receiving treatment for these difficulties (such as psychotropic medication and hospitalisation). Overall, this study will therefore allow us to examine whether neuroanatomical changes associated with childhood adversity and psychopathology are not simply a consequence of experiencing or receiving treatment for mental health difficulties.

There are important differences in prevalence of childhood adversity by gender, particularly childhood sexual abuse, which is more common in females (Barth et al., 2013). In addition, women on average have lower hippocampal (Tan et al., 2016) and amygdala (Goldstein et al., 2001) volumes. Therefore, gender could confound the relationship between brain volumes and childhood adversity.

The current study aimed to clarify the impact of childhood adversity on brain structure in a large number of diverse non-psychiatric samples and to present the results adjusted for gender. This was accomplished by conducting a meta-analysis to estimate the association between childhood adversity and volume of specific brain structures in general population or control samples. Specific regions of interest were included if they were reported in enough studies and were highlighted as potentially relevant in preclinical literature. Gender was taken into account as a potential confounder.

2. Methods

2.1. Study database

Included in the study database were peer-reviewed studies that measured the volume of specific regions of interest using Magnetic Resonance Imaging (MRI) in control or general population samples of working age adults with and without a history of childhood adversity. Medline was searched up to 24th April 2015 using a combination of relevant expanded subject headings and free text searches (see supplementary material for detailed search terms). In total, 1458 records of publications were initially examined. Three studies were later identified via the references of included papers. Studies were excluded if they were case studies or reviews, if they concerned traumatic head injury rather than adversity, if they did not include volumetric data as means and standard deviations (for example, voxel-based morphometry studies that only reported co-ordinates), if they were not studies of working age adults, or if the sample overlapped with another larger study sample. The amygdala and hippocampus were the most commonly studied regions and have previously been highlighted by animal studies as regions effected by psychosocial stress and were therefore chosen for analysis. Fifteen publications fulfilled the inclusion criteria and were included in the database (see PRISMA Flowdiagram in Fig. 1 in supplementary material). Authors were contacted for more information if their paper indicated that they had collected but not reported the relevant data.

The following data were recorded from each study where available: number of subjects with and without a history of childhood adversity, type of childhood adversity studied, mean age of participants at interview and at time of adversity, percentage of female participants, percentage of participants with a psychiatric illness, severity of adversity experienced and mean and standard deviation for hippocampus and amygdala volume.

2.2. Defining childhood adversity

Childhood adversity was defined as any difficult and unpleasant situations and experiences in childhood. Studies captured this using either specific measures of trauma, abuse, neglect, poverty or more general measures of adversity and early life stress. Abuse can be physical, sexual or emotional and is usually defined as the action of intentionally