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Childhood adversity predicts earlier onset of Major Depression but not reduced hippocampal volume

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Abstract

Childhood adversity may influence severity and age of onset of depression, potentially mediated by greater vulnerability to an existing biochemical or neural mechanism. Prior studies have suggested that reduced hippocampal volume is a result of childhood adversity. This study examined the relationship between childhood adversity, hippocampal volumes and clinical characteristics in women *who were recruited for depression history rather than abuse experiences*. Thirty-one women with remitted unipolar depression and 24 psychiatrically healthy women completed the Childhood Experience of Care and Abuse (Bifulco et al 1994). High resolution MRI scans and hippocampal volumetric determination by stereological assessment were obtained. We found that childhood adversity was associated with a history of recurrent depression and with earlier age of depression onset. We did not find a relationship between childhood adversity and hippocampal volumes in this sample with mild childhood adversity. Our results suggest that the decreased hippocampal volume seen in Major Depressive Disorder may be mediated by additional factors. Further research is needed to more fully understand the interrelationships among childhood adversity, hippocampal morphology, neuroendocrine regulation, and other genetic and environmental factors influencing vulnerability to depression.

Keywords

Magnetic resonance imaging; depression; abuse; CECA

1. Introduction

The link between childhood adversity and the development of Major Depressive Disorder (MDD) has been widely studied. MDD has been associated with experiencing physical or sexual abuse, poor parenting, marital discord, and family violence in childhood (Parker 1979; Bifulco et al., 1994; 1998; Parker et al., 1995; Parker et al., 1997; Harkness and Monroe 2002). Prevalence rates of childhood abuse or adversity range from 8% to 83% in clinical samples of depressed patients and 23% to 68% in community studies depending on

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the sample characteristics and on the definitions used to measure the adversity (Brown and Anderson, 1991; Carlin et al., 1994; Mullen et al., 1996; Kessler et al., 1997). For example, definitions of sexual abuse range from “some kind of sexual experience with another while growing up” (Sedney and Brooks 1984) to “sexual contact between a girl under 15 and an individual at least 5 years older” (Briere and Runtz 1988). Most research has focused on the adult outcomes of childhood sexual abuse. Other forms of childhood adversities including physical abuse, emotional abuse, or parental neglect are receiving increased attention and also have important implications for depression. It should be noted that many different terms are used throughout the literature to describe childhood adverse experiences including, adversity, abuse, and trauma. For simplicity, we will use the term adversity.

Several studies have suggested that childhood adversity is associated with age of onset, course, and treatment response of MDD (Brown and Moran, 1994; Brown et al., 1994; Zlotnick et al., 1995; Kessler et al., 1997; Young et al., 1997; Bifulco et al., 1998; Bernet and Stein, 1999; Sakado et al., 1999; Kaplan and Klinetob 2000; Lara et al., 2000). Some studies have found a link between childhood adversity and increased chronicity of depressive episodes (Brown et al., 1994; Brown and Moran, 1994; Zlotnick et al., 1995; Lara et al., 2000). Other studies have found an association between childhood adversity and earlier age of onset of depression (Kessler et al., 1997; Young et al., 1997; Bifulco et al., 1998; Bernet and Stein, 1999; Widom et al., 2007). Recent reports have suggested that early adversity is associated with an increased risk of depressive episode recurrence, decreased chance of remission, increased suicidality, and overall poorer prognosis (Dube et al., 2001, Gilman et al., 2003; McHolm et al., 2003).

Our previous work, as well as that of other studies has found an association between MDD and hippocampal volume loss (Sheline et al., 1996; 1999; for reviews see Sheline 2003; Videbech and Ravnkilde 2004). There have also been reports of hippocampal volume changes in adults with childhood abuse histories and other psychiatric diagnoses (Bremner et al., 1997; Stein et al., 1997; Driessen et al., 2000). Bremner and colleagues found smaller hippocampal volumes in adults meeting criteria for PTSD secondary to childhood abuse (1997). Stein and colleagues selected an abuse sample and found smaller hippocampal volumes in women who reported sexual abuse compared to those with no prior abuse (1997). Others have found an association between abuse experiences and smaller hippocampal volumes in women with Borderline Personality Disorder (Driessen et al., 2000; Brambilla et al., 2004) and Dissociative Identity Disorder (Vermetten et al., 2006). Because these studies found a relationship between childhood adversity and decreased hippocampal volumes, it was hypothesized that the observed hippocampal volume deficits in MDD may also be related to childhood adversity. To our knowledge, only one study has looked at the association of hippocampal volumes and childhood adversity in MDD (Vythilingam et al., 2002). Vythilingam and colleagues found smaller hippocampal volumes only in the women with MDD who had experienced severe and prolonged sexual and/or physical abuse in childhood. They did not find hippocampal volume differences in women with MDD without abuse histories.

The goal of this study was to investigate the differences in the severity of childhood adversity in a sample of women with a history of MDD and matched controls. Second, we investigated whether the severity of childhood adversity is related to depression severity, age of onset of MDD, number of past depressive episodes, and number of lifetime days depressed. Finally, we investigated the relationship between childhood adversity severity and depression status and hippocampal volumes. In order to minimize subjective bias in reporting early experiences, we utilized a rigorous investigator based rating instrument, the Childhood Experience of Care and Abuse (CECA; Bifulco et al., 1994). Childhood adversity in the core scales of the CECA is conceptualized as caregiver lack of warmth or positive

regard, emotional or material neglect, physical abuse, sexual abuse, and psychological abuse. The CECA is advantageous over self-report ratings in several ways (Bifulco et al., 1994). It includes detailed information on a wide range of childhood experiences for all household members, and it takes into account duration of experiences to allow for more precise hypothesis testing.

We hypothesized that women with a history of recurrent depression would report more severe levels of childhood adversity than women without histories of depression. We also hypothesized that more severe levels of childhood adversity would be associated with earlier age of onset of depression, greater number of depressive episodes, and more lifetime days depressed. Finally, we hypothesized that more severe levels of childhood adversity would be associated with lower hippocampal volumes.

2. Methods

2.1 Participants

Participants in this study were recruited to take part in one of two neuroimaging studies of depression (24 participants from Sheline et al., 1999 and 7 participants from Mintun et al., 2004). The data presented in this paper represents additional analyses to those already published (see Sheline et al., 1999 and Mintun et al., 2004). Remitted depressed participants were recruited to the outpatient psychiatry service at Washington University School of Medicine (WUSM), from referrals from other psychiatrists (17 subjects) and also from advertisements to the general public (14 subjects). Control participants were recruited from the Aging and Development Project maintained by the Psychology Department at Washington University (13 subjects) and also from notices posted at the medical center (11 subjects). Participants ranged in age from 23-86 (mean=48.47; SD = 14.88; n=5 over age 70). Inclusion criteria were a history of recurrent major depression, with at least one prior episode requiring psychiatric treatment, female gender, right handed, and no medical illness potentially affecting the central nervous system. No participants with current acute depression were included and none had been acutely depressed within the past four months. Only women were selected to decrease the incidence of occult cardiovascular disease and to minimize gender-based brain differences (Aboitiz et al., 1992). Groups were matched for age, education and post-hoc for height, a predictor of general brain size (Andreasen et al., 1994). Potential participants were screened using a questionnaire, medical history, review of medical records and physical exam. Exclusion conditions included a current or past neurological disorder, head trauma, uncontrolled hypertension, myocardial infarction or ischemia, diabetes, Cushings Disease, steroid use, or drug/alcohol abuse. The senior author (YIS) used the Clinical Dementia Rating scale (Morris, 1993) to screen participants for incipient dementia. All participants had documented normotension. In addition, participants who had received more than three courses of electroconvulsive therapy (ECT) were excluded. Five participants had received ECT prior to the study; as previously reported, there were no brain volumetric differences between participants who received ECT and those that did not (Sheline et al., 1999). The Washington University School of Medicine Institutional Review Board approved this investigation. All participants gave written informed consent prior to their participation.

Clinical assessment was conducted by a psychiatrist (YIS) experienced in the use of the Diagnostic Interview for Genetic Studies (DIGS). The DIGS is a structured interview with high reliability (Nurnberger et al., 1993) encompassing DSM-IV criteria. It was used to make the diagnosis of past episodes of recurrent major depressive disorder for depressed participants and to exclude other psychiatric diagnoses for all participants. In addition, Life Charting (Post et al., 1988) was used to anchor all episodes of depression and to determine the duration of depressive episodes. Current antidepressant status and dosage was

determined; the majority of participants in the remitted depression group were currently taking antidepressant medication (24/31). To determine the presence and severity of any current depressive symptoms all participants were assessed using the 17-item Hamilton Rating Scale for Depression (HAMD; Hamilton 1960).

2.2 Measures

2.2.1 Childhood Experience of Care and Abuse—The Childhood Experience of Care and Abuse (CECA; Bifulco et al., 1994) is a retrospective semi-structured instrument designed to measure the quality of childhood experiences (ages 0-18). The ratings are divided up into sections called “family arrangements”. A family arrangement consists of a particular combination of caregivers with whom the child resides for at least one year. Each subject has one or more family arrangements; if the composition of the household changes, a new family arrangement is documented. Ratings are given for each caregiver in the household. This interview format not only serves to enhance retrospective recall, but also assesses more than just experiences from mother and father. This format also does not require participants to average their experiences over their entire childhood. Ratings were made on five core domains. The core domains are defined as follows:

Antipathy: criticism, dislike, coldness, rejection, or hostility towards the child

Indifference/Neglect: the degree to which the caretaker provides for the child’s emotional needs (interest in school, friends, child’s happiness, health and well-being) and basic material needs (food, clothing, shelter, protection)

Physical Abuse: violence directed towards the child by any other person (including strangers, peers, parents, etc.); severity ranges from pushing or slaps on bottom, hits on head, hit with object, kicked, bitten, or burned, to threats with gun or knife

Sexual Abuse: age-inappropriate sexual contact. Sexual abuse includes intercourse, violation or penetration with object, oral sex, touching of breasts/genitals, requiring subject to watch sexual activity or pornography, and verbal solicitations or age inappropriate verbal content

Psychological Abuse: cruel or distressing behavior, either verbal or non-verbal. This includes denigration, humiliation, ridicule, cruelty, deprivation of basic things (food, light, sleep), deprivation of treasured objects (social contacts, comfort objects, tormenting or killing pets), threats of abandonment, emotional blackmail, terrorizing, and corruption or exploitation.

A CECA rating manual, developed by Bifulco and colleagues, contains rules for rating and precedent examples. This manual was used to guide all ratings. The CECA uses an investigator-based approach to rating, behavioral indicators rather than the subject’s own feelings or reports of severity are taken into account for the rating. Ratings are made on a 1-4 scale (4-little/none, 3-some, 2-moderate, 1-marked) for all of the domains. Two raters rated each interview transcript, with at least one rater blind to diagnosis. The primary rater was trained in the use of the CECA by A. Bifulco. The two other raters were trained by the primary rater using taped recordings of the training workshop and written training materials. Discrepant ratings were agreed upon in consensus meetings where reviewers were blind to diagnosis and reporting style of the subject. Final ratings were based upon the reviewer consensus.

The CECA has been shown to be reliable in community studies conducted in Great Britain (Bifulco et al., 1994). Content validity has been established using a sibling corroboration study (Bifulco et al., 1997). All subjects were in remission of depression before receiving the CECA interview.

2.22 Magnetic Resonance Imaging—MRI scans were obtained using a Magnetom SP-4000 1.5T imaging system (Siemens Medical Systems, Inc., Iselin, New Jersey), and a standard Siemens 30 cm circularly polarized rf head coil. Anatomic images consisted of 128 contiguous 1.25 mm thick sagittal slices and were acquired using magnetization prepared rapid gradient echo (MPRAGE) acquisition. Specific MPRAGE scanning parameters were: TR=10 ms, TE=4 ms, inversion time = 300ms, flip angle = 8, matrix = 256 × 256 pixels, voxel size = 1×1×1.25 mm, slice thickness = 1.25 mm. Hippocampal gray matter volumes were determined using an identical protocol and identical measurement techniques to those previously described (Sheline et al., 1999) with hippocampal anatomical boundaries defined by specific rules (Bartzokis et al., 1993; Sheline et al., 1999) using stereological estimation methods. Means for gray matter volumes were determined from an average of two independent measures by the same rater, who was blind to subject identity. Intra-rater reliabilities were greater than 0.9 using the intraclass correlations.

2.3 Data Analysis

To reduce the CECA data, average scores were constructed for each of the five adversity domains. These average scores accounted for both the degree of adversity and the duration of the rating for each caregiver. Adversity from the mother figure was calculated by summing the five domain average scores for the mother ratings. Adversity from the father figure was calculated by summing the five domain average scores for the father ratings. To obtain an indicator of total adversity, scores needed to account for the potential of other caregivers/perpetrators, not just mother and father. Therefore, for each CECA domain the domain score of each caregiver was summed and then divided by the number of caregivers scored in that domain. These average scores were then summed across the five domains, yielding a Total Adversity Index. This method of data reduction accounts for change in adversity ratings over time, as well as varying number of caregivers present.

Another method of data reduction commonly used employs the use of “peak scores”. The CECA is well suited to this method since the rating system was designed as a dichotomous measure with a large difference between a rating of ‘3 –some’ and ‘2-moderate’. Using this dichotomy, adversity was classified as “present” if at anytime during childhood the participant received a rating of ‘2’ or ‘1’ on any of the CECA domains. Adversity was classified as ‘absent’ if no ratings of ‘2’ or ‘1’ occurred.

All data were analyzed using SAS System for Windows, version eight.

3. Results

3.1 Preliminary Analyses

Demographic, clinical characteristics and brain volumetric data are summarized in Table 1. Two-tailed t-tests were used to compare remitted depressed and control subjects on all demographic and MRI measures. There were no significant differences between remitted depressed participants and controls on age or education. Remitted depressed patients scored significantly higher on HAMD scores than controls. Table 2 summarizes the CECA ratings. Remitted depressed patients score significantly lower (more severe adversity) than the controls on a majority of the CECA domains. When using the peak score dichotomy to classify participants, a majority (19/31) of the remitted depressed participants reported having at least one adversity experience in the marked or moderate range; whereas, only two control participants reported having adversity experiences in this range ($\chi^2(1, N=55) = 16.07, P<0.0001$).

Univariate analyses were conducted to detect the presence of outliers as well as the distribution of the data. Two outliers for age of onset of depression were detected.

Subsequent analyses were run both with and without these outliers. Results were the same for all of the analyses when excluding the outliers; therefore, we only report results including the full sample. 3.2 Hypothesis 1: Severity of adversity and MDD diagnosis

Analysis of Covariance was used to test the relationship between remitted depressed participants and controls on the adversity indices (see Table 2). After controlling for age and HAMD (these variables were found to be correlated with adversity and hippocampal volume, see Spearman correlations below), remitted depressed participants were significantly more likely than controls to experience more severe levels of adversity overall ($F(1, 51) = 6.86, P=0.01$) and more severe levels of adversity from father ($F(1, 51) = 5.61, P=0.02$). There were no significant differences between groups on levels of adversity from mother ($F(1, 51) = 2.07, P=0.16$).

3.3 Hypothesis 2: Severity of adversity and MDD characteristics

Spearman correlations were used to test the relationship between demographic and clinical variables with the adversity indices. Significant correlations were found between age and total adversity ($r_s = 0.39, P=0.03$) in the remitted depressed participants, but not adversity from mother alone ($r_s = 0.32, P=0.08$) or father alone ($r_s = 0.25, P=0.17$). Adversity indices were not significantly correlated with HAMD scores (total $r_s = -0.07, P=0.69$; mother $r_s = -0.20, P=0.29$; father $r_s = -0.01, P=0.95$). Number of previous depressive episodes was not related to adversity scores (mother $r_s = 0.03, P=0.88$; father $r_s = 0.18, P=0.32$; total $r_s = 0.07, P=0.71$). Nor was there a relationship between number of days depressed and adversity scores (mother $r_s = 0.04, P=0.84$; father $r_s = 0.07, P=0.71$; total $r_s = 0.13, P=0.50$). In the control participants, significant correlations were found between HAMD scores and adversity from mother ($r_s = -0.52, P=0.009$) and total adversity ($r_s = -0.49, P=0.02$). Age was significantly related to adversity from mother ($r_s = -0.47, P=0.02$) and total adversity ($r_s = -0.49, P=0.02$).

In order to examine the association between the adversity and age of depression onset, we used Cox's proportional hazards models (Kalbfleisch and Prentice 1980). In this model the rate of progression to depression is examined. Since control participants have not "yet" developed depression, they are considered statistically censored at their current age. When total adversity score from both mother and father is used in the model, the estimated hazard ratio associated with a unit increase of the total adversity score is 0.731 with a 95% confidence interval from 0.626 to 0.855, indicating a significant association between the higher total adversity score (i.e., less adversity—score of 1 denotes highest and score of 4 denotes lowest adversity) and a slower rate of developing depression. When adversity from mother is used in the model, the estimated hazard ratio associated with a unit increase of the adversity score is 0.743 with a 95% confidence interval from 0.612 to 0.902. When adversity from father is used in the model, the estimated hazard ratio associated with a unit increase of the adversity score is 0.901 with a 95% confidence interval from 0.847 to 0.958.

3.4 Hypothesis 3: Adversity and Hippocampal Volume

Spearman correlations were used to examine the relationship between adversity and total hippocampus measurements. Total hippocampus was not significantly related to any of the adversity indices in either the remitted depressed group (total $r_s = -0.12, P=0.53$; mother $r_s = -0.07, P=0.72$; father $r_s = -0.10, P=0.60$) or the control group (total $r_s = -0.05, P=0.81$; mother $r_s = -0.12, P=0.57$; father $r_s = -0.09, P=0.69$). We also examined whether hippocampal volume is associated with diagnosis and total adversity after adjusting the effect of age using an analysis of covariance model (Milliken and Johnson 2001). We first tested the interaction effects between the diagnosis and both the adversity score and age, and found that none of these interaction effects was significant ($F(1, 49) = 1.02$ and $0.20, P=0.317$ and 0.656 ,

respectively). Therefore we fitted the analysis of covariance model without these interactive effects, and found that the remitted depressed subjects have a different mean hippocampal volume as compared to the control subjects after adjusting the effect of adversity and age ($F(1,51)=4.70$, $P=0.035$). This analysis indicated a significant age effect on hippocampal volume ($F(1,51)=9.61$, $P=0.003$), whereas the effect of total adversity score on hippocampal volume was not statistically significant ($F(1,51)=0.92$, $P=0.343$).

We also used the peak score method to categorize participants into either present or absent for adversity, regardless of depression diagnosis, to determine whether the presence of severe adversity was related to hippocampal volume. These results were also non-significant (data not shown). It should be noted that due to the small sample size, we had limited power to show an effect in this model.

4. Discussion

4.1 Adversity and MDD characteristics

In this sample of women selected for depression diagnosis rather than abuse experience, we tested the relationships between childhood adversity, clinical characteristics of depression, and hippocampal volumes. As expected, we found significant differences in experiences of childhood adversity between women with a history of recurrent major depression and healthy control participants. We also found a significant relationship between childhood adversity and earlier age of depression onset. However, while hippocampal volumes were smaller in depressed subjects compared to controls, there was no association between mild childhood adversity and hippocampal volume, suggesting that in our sample, hippocampal volume decreases were mediated by additional factors.

Our finding of a relationship between childhood adversity and subsequent depression in adult life confirms and extends findings in other studies of early life stress. Poor parenting has been shown to increase the risk of depression 1.4 to 2.6 times (Kessler and Magee 1993). A recent longitudinal study found that childhood physical abuse and neglect were associated with an increased risk of developing depression in young adulthood (Widom et al., 2007). Research in both children and adults suggests that greater frequency, severity, and duration of sexual abuse increase the risk for depression (for a review see Weiss et al., 1999). Additionally, childhood adversity may influence the onset and course of depression. Several studies using longitudinal, epidemiological, or clinical samples suggest that childhood adversity is associated with an earlier age of onset of depressive symptoms (Kessler et al., 1997; Young et al., 1997; Bernet and Stein 1999; Widom et al., 2007). Importantly, compared with other samples with MDD, our subjects experienced relatively lower severity of childhood adversity, yet even this mild adversity was associated with recurrent depression and younger age of depression onset.

4.2 Adversity and hippocampal volume

In this study we did not find evidence for a contribution of mild childhood adversity independent of MDD on predicting smaller hippocampal volumes. This finding contrasts with some previous research examining the relationship between hippocampal volumes and childhood adversity in patients who had both MDD and PTSD (Vythilingam et al., 2002) or severe sexual abuse (Bremner et al., 1997; Bremner et al., 2003). There are a few key differences between our sample and those described by previous investigators which may help explain the differing findings. First, the investigators in these studies used strict criteria for abuse experiences, which selected for a sample with more severe abuse experiences than our sample. Second, in contrast to previous studies, we used an objective measure of childhood adversity that does not account for any subjective impact of abuse experiences. Additionally, rather than comparing group differences between participants with and without

abuse, our analyses used a continuous measure adversity experience. It should be noted that Vythilingam and colleagues (2004) did not find significant correlations between hippocampal volumes and their adversity measure total score or subscale scores. Finally, our sample did not include women with other comorbid psychiatric diagnoses, including PTSD.

A potential consequence of early life adversity is that it sensitizes the individual to stressors occurring later in life (Hammen et al., 2000). Although our study does not directly bear on this question a number of studies in the literature, both in rodents and humans suggest that stress acts on developmental pathways altering neuroendocrine and neurochemical signaling. For example, studies in rats that experienced low maternal care or separation have shown multiple CNS changes that likely underlie sensitization to stress, including: increased CRF mRNA expression, sensitization of CRF neurons in hypothalamic and limbic regions, decreased glucocorticoid receptor density in hippocampus, decreased neurogenesis in hippocampus, decreased GABA and oxytocin receptor binding, and increased norepinephrine (NE) activity in locus coeruleus (Plotsky and Meaney 1993; Meaney et al., 1996; Liu et al., 1997, 2000; Caldji et al., 1998, 2000; Ladd et al., 2000; Jimenez-Vasquez et al., 2001; Plotsky et al., 2001; Francis et al., 2002; Huot et al., 2002). Additionally, decreased adrenocortical activity and changes in Hypothalamic-Pituitary-Adrenal (HPA) axis function have been noted in non-human primates as a consequence of early life stress (Rosenblum et al., 1994, 2002; Coplan et al., 1996; Maestripieri 1999; Lyons et al., 1999, 2000; Dettling et al., 2002). In humans, weight at birth (a proxy for prenatal stress) was associated with hippocampal volume only in women who reported low maternal care during childhood, suggesting that the postnatal environment may play a role in modulating prenatal risk factors (Buss et al., 2007). Studies in humans have also shown increased plasma ACTH response to stress, a finding that was more pronounced in concurrently depressed women, altered feedback properties of the HPA axis, and altered NE and serotonin functioning in response to early life stress (Heim et al., 2000; Heim and Nemeroff 2001; Rinne et al., 2002). As proposed by Heim and colleagues (2004), neurobiological changes that occur as a consequence of early life can result in changes that eventually trigger repeated depressive episodes after exposure to additional stress. For example, sensitized CRF and NE systems along with altered hippocampal function may lead to enhanced and sustained cortisol responses, thereby causing brain damage and impairment in neurogenesis, which could lead to further disinhibition of the stress response (Heim et al., 2004). Thus, the childhood stresses experienced by our subjects may have been sufficient to confer vulnerability to depression through alteration in neurobiological pathways. Our data argue that this vulnerability to depression from childhood adversity was not accounted for by structural effects on the hippocampus; suggesting other factors may also be responsible for the decreased hippocampal volume in MDD. For example, genetic studies in non-human primates have suggested that differences in adult hippocampal volumes were reflective of inherited variation in hippocampal morphology rather than postnatal stress (Lyons et al., 2001). Recent studies in humans have also suggested genetic variations associated with hippocampal volumes in both PTSD (Pitman et al., 2006) and depression (Frodl et al., 2004; Taylor et al., 2005). Because we previously found that the course of depression (i.e. total days depressed) was associated with hippocampal size, an alternative conclusion is that the depressive state itself has a negative effect on hippocampal volume; however, no consistent findings have been reported to date (O'Brien et al., 2004).

4.3 Limitations

Several limitations of the current report need to be addressed. First, reports of childhood experiences are retrospective. In a comprehensive review of the reliability of retrospective reports of childhood experiences, Brewin, Andrews, and Gotlib (1993) concluded that, although claims that retrospective reports are unreliable are exaggerated, limitations to

retrospective reports must be addressed in order to improve their reliability. Although certain techniques contained in the CECA were used to enhance recall in the current study, these techniques do not address all of the problems with retrospective reporting. The small sample size may limit the power of the statistical analyses; we may not have been able to detect any additional contribution adversity may have to hippocampal changes. It must be noted that the majority of the participants with remitted MDD underwent the MRI scan while on antidepressant medication. Longitudinal studies in animal models have reported that SSRI treatment increases hippocampal neurogenesis (Jacobs et al., 2000; Malberg et al., 2000; Czeh et al., 2001; Manev et al., 2001; D'Sa and Duman 2002). However, this has not been found in humans with MDD (Vythilingam et al., 2004). Finally, the findings of this study may not be generalizable to other populations. This sample consisted of primarily white, middle class, highly educated women. Our sample may not have experienced the severity of abuse as has been found in other reports of adversity in MDD. In comparison to other studies of depression using the CECA, we found lower rates of sexual abuse and neglect, but similar rates of antipathy, physical abuse, and psychological abuse than those found by Bifulco and colleagues (1994) and Harkness and Monroe (2002). Additionally, the women in this sample were treatment responders; all of the participants had to reach remission in order to receive the CECA interview. It is possible that treatment non-responders would have more severe reports of childhood adversity (Sakado et al., 1999; Dube et al., 2001).

4.4 Summary and future directions

Despite these limitations, we used a rigorous measure of childhood adversity to rate the experiences of a well-characterized group of women with recurrent MDD and a group of healthy controls. Although our study supports that finding that there is a relationship between childhood adversity and MDD, the nature of this relationship is still not fully understood. To understand this relationship, future studies must combine assessment of childhood adversity with genetics, neuroendocrine challenges, functional neuroimaging tasks and structural MRI studies, preferably in a longitudinal design. This would allow the determination of the interrelationships among childhood stressors, inherited variation in hippocampal morphology, stress levels of cortisol and neuroendocrine regulation, behavioral vulnerability to stress and brain morphology and would further elucidate the interactions between genetic dispositions and environmental factors in influencing vulnerability to depression.

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Table 1

Demographic, clinical characteristics, and brain volumetric data (N=55).

Variable	Remitted MDD (N=31)		Controls (N=24)		unpaired <i>t</i> -test	
	Mean	SD	Mean	SD	<i>t/z</i>	<i>p</i>
Age at time of Interview	50	15	46	14	0.96	0.34
Education (in years)	16	4	16	4	-0.06	0.95
HAMD	7	5	1	1	5.69	<.0001
Age at First Episode	29	15				
Number Days Depressed	1394	1377				
Number of Previous MDD Episodes	5	4				
Hippocampal gray matter						
Left, mm ³	2169	311	2482	305	-2.43	0.02
Right, mm ³	2171	326	2468	309	-1.78	0.07
Total, mm ³	4340	606	4951	601	-2.00	0.04
Whole Brain Volumes, cm ³	1018	148	1005	109	-0.23	0.82

Note: HAMD= Hamilton Rating Scale for Depression 17-item MDD = Major Depressive Disorder

Table 2

Childhood adversity differences between remitted depressives and controls.

CECA Scale	Remitted MDD (n=31)		Controls (n=24)	
	Mean	SD	Mean	SD
Antipathy **	2.9	0.80	3.7	0.50
Neglect **	3.2	0.70	3.8	0.33
Sexual Abuse **	3.6	0.76	4.0	0.08
Physical Abuse **	3.2	0.83	3.8	0.29
Psychological Abuse *	3.7	0.46	4.0	0.00
CECA Adversity Index (average scores)				
Mother †	18	2	20	0.90
Father ††	17	5	20	0.69
Total ††	18	2	20	0.69

Note: The highest level of adversity rated in a domain is considered to be the peak score. Lower scores signify more severe adversity.

* Comparison of remitted depressed vs. controls $p=0.07$

** Comparison of remitted depressed vs. controls $p<0.005$

† ANCOVA controlling for age and HAMD [$F(1,51)=2.07$, $p=0.16$]

†† ANCOVA controlling for age and HAMD [Father $F(1,51)=5.61$, $p=0.02$ Total $F(1,51)=6.86$, $p=0.01$]