The association between financial hardship and amygdala and hippocampal volumes: results from the PATH through life project

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This study examined whether middle-aged adults exposed to poverty in childhood or current financial hardship have detectable brain differences from those who have not experienced such adversity. Structural magnetic resonance imaging (MRI) was conducted as one aspect of the Personality and Total Health (PATH) through life study: a large longitudinal community survey measuring the health and well-being of three cohorts from south-eastern Australia. This analysis considers data from 431 middle-aged adults in the aged 44–48 years at the time of the interview. Volumetric segmentation was performed with the Freesurfer image analysis suite. Data on socio-demographic circumstances, mental health and cognitive performance were collected through the survey interview. Results showed that, after controlling for well-established risk factors for atrophy, adults who reported financial hardship had smaller left and right hippocampal and amygdalar volumes than those who did not report hardship. In contrast, there was no reliable association between hardship and intra-cranial volume or between childhood poverty and any of the volumetric measures. Financial hardship may be considered a potent stressor and the observed results are consistent with the view that hardship influences hippocampal and amygdalar volumes through hypothalamic–pituitary–adrenal axis function and other stress-related pathways.

Keywords: hippocampus; amygdale; socio-economic position; financial hardship; hypothalamic–pituitary–adrenal axis; depression

INTRODUCTION

The effects of hardship, socio-economic disadvantage and deprivation during both childhood and adulthood on mental functions are well-established. On average, children from disadvantaged socio-economic backgrounds have poorer language (Noble et al., 2005), executive (Ardila et al., 2005), memory (Farah et al., 2006) and attention skills (Mezzacappa, 2004). Adults who endured difficult socio-economic conditions during their childhood have a higher risk of cognitive impairment (Zhang et al., 2008) and poorer physical health (Painter et al., 2005). Current socio-economic disadvantage and particularly the experience of deprivation, is associated with increased risk of psychiatric disorders (Weich and Lewis, 1998; Butterworth et al., 2009). Individuals who experienced deprivation and/or social disadvantage during their adult life have lower cognitive abilities and higher risk of dementia (Basta et al., 2008; Nguyen et al., 2008; Gao et al., 2009).

Despite such evidence linking socio-economic disadvantage across the life course with mental function, relatively little research has examined the influence of the socio-economic environment on brain development and how this impacts on brain function to create vulnerabilities to mental and cognitive disorders (Raizada and Kishiyama, 2010). In animals, sensory, social and dietary deprivation has been associated with decreased axonal complexity and connectivity particularly in the hippocampus, amygdala, corpus callosum and medial pre-frontal cortex (Andrade et al., 1996; Innocenti, 2007; McEwen, 2008b). Such findings have been demonstrated in very young, pubescent and adult animals with effects detected with relatively short exposures. For instance, chronic stress initiated by physical restraint for 21 days in 8 week-old rats (puberty = 50–60 days, life expectancy 2–3 years) produced significant dendritic retraction in the medial pre-frontal cortex. In humans such effects cannot be investigated systematically, however, extreme visual sensory deprivation (blindness before 2 years of age) is associated with decreased grey matter volume and white matter connectivity (Noppeney et al., 2005). Early social deprivation in children reared in orphanages was found to be associated with cerebral white matter microstructural abnormalities and correlated with inattention and hyperactivity scores (Govindan et al., 2009). Poor nutrition, particularly the absence of certain micronutrients and starvation, in early and late life was found to be related to greater brain atrophy, lower intra-cranial volumes (ICV), larger white matter hyperintensities and more cerebral

abnormalities (Hulshoff Pol *et al.*, 2000; Casella *et al.*, 2005; Vogiatzoglou *et al.*, 2008).

While the pathophysiological mechanisms mediating the effect of hardship and deprivation on brain structure and cognition are unclear, both factors, particularly when enduring, can be conceptualized as sources of chronic stress which influence neuroendocrine function (e.g. Brunner *et al.*, 2002; Dowd *et al.*, 2009). Thus, the neurobiological system likely to be involved is the limbic system and other related structures through their involvement in the modulation of the hypothalamus–pituitary–adrenal (HPA) axis and autonomic cardiovascular reactivity in response to stress. HPA function is well understood: detection of threat is mediated by the medula, the amygdala and other cerebral structures (pre-frontal cortex, cingulate, hippocampus). Threats and perceived threats lead to production of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP) in the hypothalamus. These hormones trigger the secretion of adrenocorticotropin hormone (ACTH) in the pituitary, which leads to the production of glucocorticoid in the adrenal cortex. In addition, based on input from limbic structures, the autonomic nervous system also modulates cardiovascular and visceral responses to stress via the vagal nerve and stimulates the production of catecholamines in the adrenal medulla through increased sympathetic activation (see McEwen, 2008a; Dedovic *et al.*, 2009; Ulrich-Lai and Herman, 2009; Pruessner *et al.*, 2010 for a review).

In an isolated, acute situation, this cascade of responses raises blood pressure and heart rate, redirects blood flow to essential organs, increases alertness and leads to fast adaptive responses that increase the odds of avoiding the threat or of successfully confronting it and is, therefore, beneficial to the organism. However, when stress becomes chronic, normal physiological responses can have deleterious effects. For example, a study investigating stress reactivity to social stress (public speaking) found that women who had a history of childhood abuse and suffering from major depression had a 6-fold increased ACTH response as well as increased cortisol and heart rate responses (Kirschbaum *et al.*, 1993). However, because the stress response of women with a history of abuse but no depression was not different from controls it was unclear whether this effect was due to variation in resilience across individuals and/or depressive pathology related or unrelated to childhood abuse. Another study clarified this question and showed that women with a history of childhood abuse with and without depression showed an abnormal response to stressors at a level thought to be associated with increased risk (Heim *et al.*, 2002). Similar effects were also reported in maltreated non-depressed men (Carpenter *et al.*, 2007) but are known to differ between males and females (Young and Korszun, 2010; see also, Heim *et al.*, 2008 for a review).

Sustained cerebral exposure to glucocorticoids has been shown to lead to dendritic retraction, and neuronal death in the hippocampus, cingulate and medial pre-frontal cortex as well as decreased neurogenesis in the hippocampus, while in the amygdala neuronal hypertrophy is observed, at least in a first stage (see Radley and Morrison, 2005; McLaughlin *et al.*, 2009; Ulrich-Lai and Herman, 2009 for a review). In rats, chronic stress exposure has been found to produce hippocampal shrinkage and in humans PTSD and depression have been associated with hippocampal atrophy (McEwen, 2000; Roozendaal *et al.*, 2009). In ageing individuals, higher cortisol levels are associated with smaller hippocampal volumes and poorer memory function (Raskind *et al.*, 1994). The picture is less clear for the amygdala. As mentioned above, sustained stress can initially lead to amygdala hypertrophy, however, it appears that high corticosteroid exposure and depressive illness ultimately lead to amygdala atrophy (Brown *et al.*, 2008; Desai *et al.*, 2009). Thus, it is possible that amygdala volume is modulated by the level and length of exposure to stressors. However, it is also possible that individuals with larger amygdala are protected against some of the effects of chronic stress, thus any causal relationship must be considered with care. Total brain atrophy and smaller corpus callosum surface have been reported in PTSD and therefore might also be present in other forms of chronic stress. Finally, the neurobiological changes produced by chronic stress have been shown to be associated with enhanced excitability of the HPA axis (Akana *et al.*, 1992) which is likely to compound the effects of pre-existing stressors and further harm the brain (see Pruessner *et al.*, 2010 for a review of neuroimaging findings). Recent research also found an association between stress and increased amyloid plaque, one of the hallmark of Alzheimer's disease (Dong and Csernansky, 2009) which is consistent with findings discussed above showing associations between deprivation, low SES and increased risk of dementia.

In summary, based on the proximal and distal effects of chronic stress reviewed above it would be expected that hardship would be associated with specific brain changes, particularly in the hippocampus and amygdala. The aim of this study was to use data from a community-based survey of middle-aged adults to assess whether individuals exposed to poverty in childhood or current hardship (being excluded from minimally accepted ways of life due to a lack of resources) present with detectable brain differences from those who did not experience such adversity. It was hypothesized that hardship would be associated with hippocampal and amygdala atrophy even after controlling for an extensive range of previously identified correlates of atrophy. If smaller medial temporal lobe volume occurs in the context of smaller ICV, this may be best explained as a generalized effect reflecting compromised early brain development in childhood. Alternatively, if the experience of poverty and hardship is associated with medial temporal lobe atrophy in the absence of ICV differences, the results would more likely be a consequence of sustained exposure to environmental stressors and the corresponding HPA axis response.

METHODS

Study design

The data used for this analysis are drawn from the Personality and Total Health (PATH) through life study. This is a large longitudinal community survey measuring the health and well-being of three cohorts, born in 1975–79, 1956–60 and 1937–41 and originally residing in Canberra and the neighbouring town of Queanbeyan in south-eastern Australia. The sampling frame was the electoral roll (registration on the electoral roll is compulsory for Australian citizens). It is planned to follow-up each cohort every 4 years over a 20-year period.

This analysis considers data from the middle-aged cohort. The current data are largely drawn from the second wave interview, conducted in 2004, when respondents were in the age group of 44–48 years. However, some retrospective information on childhood experiences collected during the Wave 1 interview (conducted in 2000) is also used in analysis. The Wave 1 response rate was 64.6% and the follow-up rate at Wave 2 was 93.0%. At Wave 2 there were 2354 respondents.

A randomly selected subsample of 656 participants was offered an MRI scan, which 503 accepted and 431 eventually completed. There were no differences in age, sex and years of education between those who had an MRI scan and those who did not ($P > 0.05$). One scan was lost due to a technical fault, giving a total number of 430 scans. The reasons for not undergoing an MRI scan after having initially agreed, included subsequent withdrawal of consent, medical conditions precluding MRI and claustrophobia or other anxiety about the procedure.

All participants provided written informed consent. The Human Research Ethics Committee of The Australian National University approved the study protocol. Further details of the survey including the sampling procedure and the MRI substudy are reported elsewhere (Jorm *et al.*, 2003; Cherbuin *et al.*, 2009).

MRI acquisition

MRI data were acquired on a 1.5 Tesla Gyroscan scanner (ACS-NT, Philips Medical Systems, Best, The Netherlands). T1-weighted 3D structural MRI images were acquired in coronal plane using Fast Field Echo (FFE) sequence. About mid-way through this study, for reasons outside the researchers' control, the original scanner (scanner A) was replaced with a similar Philips scanner (scanner B). The scanning parameters were kept essentially the same. The first 164 subjects were scanned on scanner A with TR = 8.84 ms, TE = 3.55 ms, a flip angle of 8°, matrix size = 256 × 256, slices 160 and the field of view (FOV) 256 × 256 mm. Slices were contiguous with slice thickness of 1.5 mm. For the remaining 268 subjects scanned on scanner B, the TR = 8.93 ms, TE = 3.57 ms values were slightly different in order to improve image quality, but all other parameters were exactly the same. No significant differences were observed between scanners (Cherbuin *et al.*, 2009).

Image analysis

Volumetric segmentation was performed with the Freesurfer image analysis suite (Figure 1), which is documented and freely available for download online (http://surfer.nmr.mgh .harvard.edu/). This processing includes motion correction, removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Ségonne *et al.*, 2004), automated Talairach transformation and segmentation of the subcortical white matter and deep grey matter volumetric structures (including for the present investigation hippocampus, amygdala, total grey and white matter for each hemisphere, as well as a measure of ICV; Fischl *et al.*, 2002, 2004). The validity and reliability of the Freesurfer package has been assessed in a number of recent studies and was found to be very good (Tae *et al.*, 2008; Cherbuin *et al.*, 2009). The scans of 27 participants were excluded from the sample due to poor scan quality, low signal-to-noise ratio, or movement artefacts which did not allow for normal processing with the standard Freesurfer pipeline, leaving 403 cases for MRI analysis. Each segmented volume was inspected slice by slice and reprocessed with additional parameters if errors were detected.

Other measures

Participants completed the majority of the PATH questionnaire on a hand-held computer, with the interviewer administering physical and cognitive tests. Only measures used in the current analysis are described.

The key independent measure in this analysis assessed the experience of financial hardship. Four dichotomous hardship items that assessed lack of basic goods and opportunities due to limited financial resources—(over the past year have the following happened because you were short of money: pawned or sold something; went without meals, unable to heat home, asked for help from welfare/community organizations;—see Butterworth *et al.*, 2009). We also considered a fifth item which assessed whether respondents had to—go without things they really needed because they were short of money—over the past 12 months. We focus on those who reported 'yes' often. An overall measure representing any experience of hardship (any of the five items) was constructed for this analysis (0 hardships reported *vs* 1 or more). A dichotomous measure of childhood poverty (yes or no) was based on a single item from Wave 1 which asked respondents whether they had 'grown up in poverty'. Other measures of contemporaneous (Wave 2) socioeconomic status included: labour force status (employed, unemployed or not participating in the labour force), educational attainment (years of full-time education corresponding with highest level of educational attainment) and low-skilled occupational background (those employed in elementary clerical and labouring jobs).
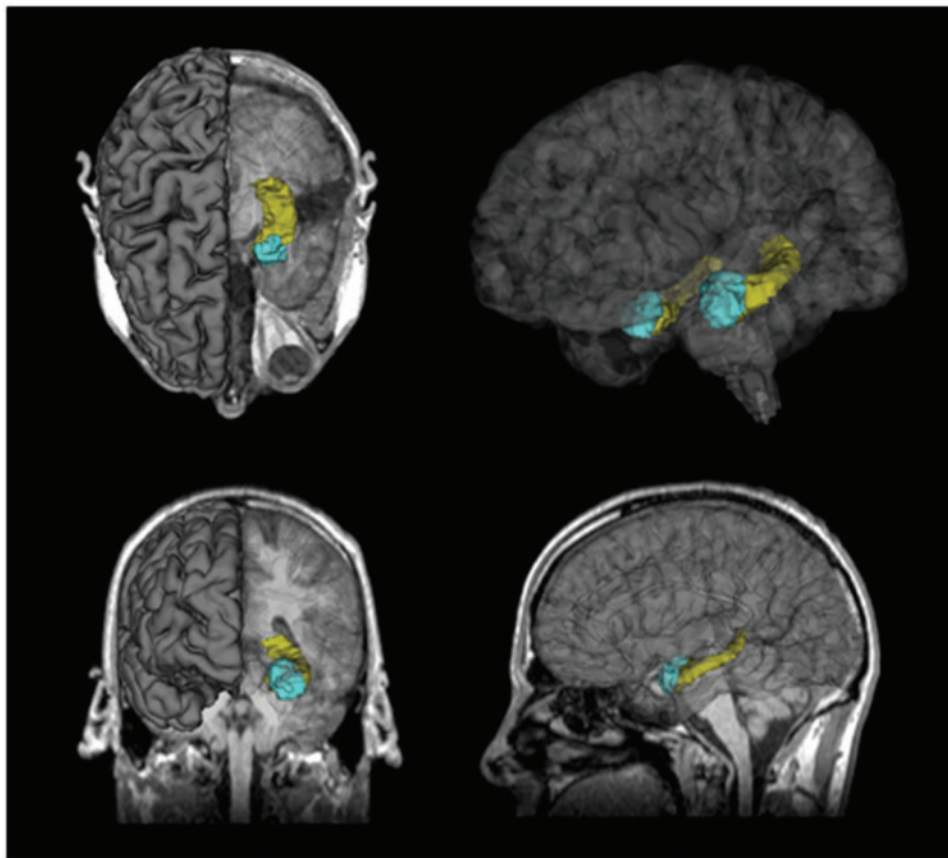
Fig. 1 Three-dimensional model of the segmented hippocampus (yellow) and amygdala (blue) using Freesurfer and displayed in Slicer (www.slicer.org).

Socio-demographic characteristics included in the analyses were age, gender and partner status (married or de facto relationship *vs* other). A range of covariates, previously shown to be associated with atrophy of medial temporal lobe structures were included in analyses including current (the Alcohol Use Disorders Identification Test; Saunders *et al.*, 1993) and previous (Anstey *et al.*, 2006) hazardous or harmful alcohol consumption (Wrase *et al.*, 2008), experience of trauma (e.g. rape, sexual molestation and physical assault; Brewin *et al.*, 2002) or childhood adversity (including neglect, physical abuse and sexual abuse; Vythilingam *et al.*, 2002; Rosenman and Rodgers, 2006; Woon *et al.*, 2010) and conditions such as diabetes (based on reported use of medication), stroke, hypertension (no evidence, borderline or definite), heart disease and stroke (Korf *et al.*, 2004; Gold *et al.*, 2007). We also included a measure of self-rated health (excellent or very good *vs* other). The scale score from the Patient Health Questionnaire (PHQ; Spitzer *et al.*, 1999) was used as a measure of depression symptoms. Various domains of cognitive functioning were also evaluated. As the focus of the current study is on cognitive functioning broadly defined, a composite measure was constructed which represented the mean standardized score across measures of episodic memory (assessed by the

immediate recall task from the first trial of the California Verbal Learning Test; Delis *et al.*, 1987), working memory (the Digits Backwards subtest of the Wechsler Memory Scale; Wechsler, 1945) and processing speed (the Symbol-Digit Modalities Test; Smith, 1982). Finally, current use of anti-depressive medication was assessed.

Statistical analysis

As a preliminary analysis, a series of linear regression models assessed whether the relationship between each measure of socio-economic circumstance and mental functioning (depression and cognition) was evident in the restricted MRI sample after controlling for age and sex. The primary focus of this study, however, was analysis of the volumetric measures and an initial regression model tested whether the hardship measures were associated with overall ICV. In the key analyses, measures of left and right hippocampus and amygdala volumes (adjusted for/divided by ICV) were regressed on financial hardship, childhood poverty and the range of covariates described above. Aside from the variables critical to the hypotheses tested, non-significant terms were eliminated from models in a step-wise procedure to arrive at the most parsimonious final model for each dependent measure. Because of the low prevalence of

hardship in the sample and concern to ensure the comparability of the hardship and the control groups, the analyses were rerun using a subsample of 'control' respondents who were selected to closely match the respondents in the hardship group (matching variables were sex, partner status, labour-force status, depression medication, experience of traumatic life events, depression symptoms, cognitive performance and ICV). Further sensitivity analyses examined whether the inclusion of an interaction between current hardship and childhood poverty, or the interaction between sex and financial hardship, improved overall model fit.

Missing data for most of the items examined in this analysis were minimal. One measure (hypertension) had missing data for 2.5% of respondents. Missing data for all other scales/items were <1% of cases. Missing data were imputed using a multivariate regression approach.

RESULTS

Table 1 presents data on the characteristics of the 403 respondents in the MRI substudy and contrasts those who did and did not report hardship. Overall, the sample represents a relatively advantaged population, with very low levels of financial hardship and unemployment, skilled occupational backgrounds and high levels of educational attainment. Compared to the control group, those who did experience

hardship were more likely to be unemployed or not participating in the workforce, to have previously consumed alcohol at hazardous/harmful levels, to have experienced rape or physical assault, to currently experience depression, to be less likely to have a partner and to have lower levels of cognitive performance.

The preliminary series of analyses, controlling for age and sex, confirmed that socio-economic position was related to mental function in this sample (Table 2). The experience of financial hardship and not participating in the workforce were associated with greater depression symptoms and poorer cognitive functioning. Reported poverty in childhood and low-skilled occupational background were each associated with greater depression symptoms but not with cognitive functioning. Similar results were obtained for cognitive functioning when controlling for depressive symptoms (a potential mediator of the relationship between socio-economic position and cognitive functioning).

Analysis of simple and multivariate linear regression models demonstrated that neither the experience of financial hardship (coefficient from full multivariate model = 21 670, s.e. = 30 037, n.s.) nor reported childhood poverty (coefficient = 11 630, s.e. = 19 136, n.s.) were associated with overall ICV. Table 3 presents mean volumes and results of a series of multivariate linear regression models examining predictors of left and right hippocampus and amygdala

Table 1 Characteristics of the sample

Characteristics	Overall	Hardship	No hardship	*P*-value
N	403	19	384	
Sex (men) (%)	44.2	47.4	44.0	0.77
Age (years) (mean, s.e.)	46.7 (0.07)	46.8 (0.28)	46.7 (0.07)	0.76
Partnered (married or *de facto*) (%)	81.4	63.2	82.3	0.04
Experienced financial hardship (%)	3.7	100	0.0	
Grew up in poverty (%)	12.4	21.1	12.0	0.24
Educational attainment (mean years)	14.7 (0.11)	14.2 (0.66)	14.7 (0.11)	0.40
Low skilled occupational background (%)	5.0	5.3	5.0	0.95
Unemployed (%)	1.7	5.3	1.6	0.000
Not participating in labour force (%)	7.0	31.6	5.7	
Hypertensive (borderline or definite) (%)	38.5	52.6	37.8	0.08
Heart disease (%)	2.7	5.3	2.6	0.49
Diabetes (%)	2.0	5.3	1.8	0.29
Stroke (%)	0.7	0.0	0.8	0.70
Current hazardous/harmful alcohol consumption (%)	5.7	21.1	5.4	0.35
Previous history of hazardous/harmful alcohol consumption (%)	26.3	47.4	25.3	0.03
Lifetime experience of:				
Rape (%)	6.5	21.1	5.7	0.008
Sexual molestation (%)	15.4	14.8	15.4	0.18
Physical attack/assault (%)	9.7	31.6	8.6	0.001
Childhood adversity:				
Neglect (%)	2.5	5.6	2.3	0.43
Physical abuse (%)	8.2	15.8	7.8	0.22
Sexual abuse (%)	1.2	1.3	1.2	0.62
Depression—from PHQ (%)	10.0	33.3	8.9	0.001
Taking depression medication (%)	6.5	15.8	6.0	0.09
Cognition	2.08 (.31)	1.11 (1.44)	2.24 (.32)	0.023

Table 2 Association between measures of socio-economic position and depression symptoms (PHQ depression score) and cognitive function, reporting regression β-coefficients and standard errors from a series of regression models controlling for age and sex

	Depression symptoms Coefficient (and standard error)	Cognitive functioning Coefficient (and standard error)
Experience of financial hardship	3.60 (0.86)***	−3.31 (1.47)*
Grew-up in poverty	1.49 (0.56)**	1.78 (0.95)
Labour-force status (employed)		
Unemployed	−0.66 (1.42)	−0.93 (2.38)
Not participating in the labour force	1.64 (0.74)*	−3.00 (1.24)**
Low-skilled occupational background	1.99 (0.86)*	−2.25 (1.44)

***$P < 0.001$; **$P < 0.01$; *$P < 0.05$.

Table 3 Mean volume (in mm³ and standard error) and regression results (β-coefficient and s.e.) for series of models examining association of hardship and childhood poverty with volume of medial-temporal lobe structures, including covariates[a]

	Financial hardship			
	No	Yes	Coefficient	P-value
	Full sample ($n = 384$)	($n = 19$)		
Left hippocampus[a]	3691 (18.9)	3619 (92.2)	−9.9 (5.00)	0.049
Right hippocampus[b]	3981 (19.4)	3850 (85.2)	−12.7 (5.04)	0.012
Left amygdala[c]	1462 (11.1)	1341 (47.3)	−7.6 (2.76)	0.007
Right amygdala[d]	1628 (11.2)	1527 (43.2)	−7.9 (2.59)	0.003
	Matched control group ($n = 42$)	($n = 19$)		
Left hippocampus[a]	3756 (50.1)	3619 (92.2)	−11.4 (6.55)	0.087
Right hippocampus[b]	4057 (58.1)	3850 (85.2)	−14.4 (6.22)	0.025
Left amygdala[c]	1492 (37.7)	1341 (47.3)	−6.19 (3.08)	0.050
Right amygdala[d]	1664 (35.7)	1527 (43.2)	−6.39 (2.81)	0.027

	Childhood poverty			
	No	Yes	Coefficient	P-value
	($n = 353$)	($n = 50$)		
Left Hippocampus[a]	3690 (20.1)	3674 (48.4)	−2.9 (3.18)	0.362
Right Hippocampus[b]	3968 (20.3)	4017 (52.4)	2.7 (3.23)	0.401
Left Amygdala[c]	1453 (11.6)	1476 (30.4)	1.4 (1.78)	0.429
Right Amygdala[d]	1620 (11.8)	1650 (26.7)	1.8 (1.72)	0.289

Covariates in final models are:
[a] sex, years of education, labour-force status, diabetes, experience of physical assault, experienced physical abuse as child, depression and cognition.
[b] Sex, years of education, diabetes, depression and cognition.
[c] Sex, labour-force status, reported heart disease, neglect during childhood, experienced physical abuse as child, depression and cognition.
[d] Sex, diabetes, stroke, experience of sexual molestation, experience of physical assault, depression and cognition.

volume (adjusted for ICV). The experience of current financial hardship was associated with smaller volume in each of the medial temporal lobe structures after controlling for covariates. There was no evidence that reported childhood poverty was associated with hippocampal or amygdalar volume. Overall, these models accounted for between 8% and 11% of variance in adjusted volume.

A number of sensitivity analyses were conducted. Respondents who reported financial hardship were matched with a subsample of 42 similar respondents who had not experienced hardship. The matching procedure was effective: repeating the series of comparisons presented in Table 1 confirmed that there were no significant differences between the two groups on any of the reported characteristics apart from the experience of hardship. Analysis of adjusted volumetric measures using the matched sample confirmed that hardship was associated with smaller hippocampus and amygdala volume (though the effect on left hippocampus was only marginally significant; Table 3). The current results were also consistent with those from analyses in which all covariates were included and analyses which used the actual measures of hippocampus and amygdala volume as the dependent variable and included ICV as a covariate (vs analysis of volume adjusted for ICV). However, again in these last two analyses, the effect of hardship on left hippocampus volume was of marginal significance ($P = 0.057$ and $P = 0.091$, respectively). Finally, the results were similar when cases with missing data were excluded from the analysis rather than using data imputation.

The cognitive measures were only significant predictors in the analysis of right amygdalar volume (0.18, s.e. = 0.088, $P = 0.047$) and marginally significant for left amygdalar volume (.16, s.e. = 0.093, $P = 0.089$). The measure of depression was not a significant independent predictor in any of the analyses. There was also no evidence in any of these models that the inclusion of the interaction term between current financial hardship and childhood poverty (i.e. entrenched disadvantage) or the interaction between sex and financial hardship improved model fit.

DISCUSSION

This study examined the consequences in adulthood of recent and early life socio-economic adversity. Our analyses focused on a retrospective measure of childhood poverty and 12-month prevalence of financial hardship. The initial analysis sought to verify the well-established association between socio-economic adversity and mental function (both cognition and depression) in this cohort of middle-aged adults from a community survey. Consistent with expectations, the results showed that financial hardship was associated with higher levels of current depression symptoms and poorer cognitive performance. The effects of childhood poverty were more modest and restricted to an association with depression. The primary and unique aim of this article, however, was to extend this behavioural analysis and examine whether the effects of adverse socio-economic circumstances were observable in measures of global intra-cranial or more specific medial-temporal lobe volumes. The critical findings were that middle-aged adults who reported current financial

hardship had smaller left and right hippocampal and amygdalar volumes than those who did not report hardship after controlling for a comprehensive range of well-established risk factors. This was the case in the full sample and also in an analysis using a control group more closely matched to those respondents who experienced financial hardship.

The observed pattern of results is consistent with the view that hardship can be conceptualized as a potent stressor and that the association between hardship and smaller hippocampal and amygdalar volumes reflects the impact of HPA function and corticosteroid exposure. The notion of hardship as a source of severe stress is supported by the well-established association between hardship and depression and consistent with past research demonstrating smaller hippocampal and amygdalar volumes in depression (Kronmuller *et al.*, 2009; Rigucci *et al.*, 2009). Further, the hypothesized effect of hardship on the brain is consistent with recent results in rats showing that repeated experimental stressors led to detectable proteomic expression changes in the adult hippocampus which are associated with neuroplasticity, metabolism and apoptosis pathways. Confidence in the hypothesized biological consequences of the experience of hardship is enhanced by finding that hardship was only associated with the volume of medial-temporal lobe structure but not with overall ICV, suggesting the results were not due to more generalized early developmental differences.

The measure of financial hardship examined in this study focused on difficulties satisfying basic requirements of daily living due to limited financial resources. These types of hardship measures are strongly associated with depression and psychological distress (Lewis *et al.*, 1998; Weich and Lewis, 1998; Lorant *et al.*, 2007; Butterworth *et al.*, 2009) and have been found to mediate the relationship between other measures of socio-economic position and depression (Lewis *et al.*, 1998). Experiencing difficulties satisfying basic requirements may impact on mental function because it is such a fundamental concern and likely to be associated with ongoing worry and stress and feelings of hopelessness, lack of control and demoralization (Brown, 2002). The current study, therefore, provides biological evidence to support the hypothesized pathway between hardship and mental function. It is interesting, however, that the depression and cognitive measures were generally not independently associated with hippocampal/amydgala volume. The fact that hardship was more strongly associated with right hippocampal volume than with other medial-temporal lobe structures warrants further investigation to examine if this reflects a localized effect. Previous findings have also reported asymmetrical effects (Kronmuller *et al.*, 2009) and investigations in animals have found that gene expression is different in the left and right hippocampi which may modulate their susceptibility to stressor (Samara *et al.*, 2009).

There are a number of limitations which must be considered when interpreting the current findings. Firstly, our data were cross-sectional and although we posit a theoretic model in which hardship has biological consequences on brain structure, it may be that respondents with smaller medial temporal lobe structures are selected into financial hardship. It may be that effects attributed to hardship may reflect that hardship is an effective marker of underlying social and economic disadvantage. So, for example, hardship in midlife may be associated with childhood adversity and social selection, life long behaviours (poor diet, limited exercise, etc.), poor social support, a lack of marketable job skills, under-employment and/or low income. Better data are needed to differentiate the volumetric correlates of short-term *vs* persistent and sustained hardship (Lynch *et al.*, 1997). The lack of association between poverty in childhood and the volumetric measures may reflect that this measure, based on retrospective report of childhood circumstances, lacks precision.

In conclusion, the current study has shown the association between financial hardship and poorer mental function is paralleled by an association between hardship and medial temporal lobe volume. These findings suggest that hardship may have a significant impact on an individual brain as well as observable effects on mental function. Importantly, evidence of neurological correlates of hardship suggests the adverse behavioural effects of financial deprivation do not simply reflect a mood-induced reporting bias. There remains a need to consider these effects longitudinally to contrast persistent and short-term hardship and examine whether the medial temporal lobe effects can be overcome by a more positive social environment. This sort of evidence is critical to ascertain whether social interventions aimed at reducing poverty can be considered as a tertiary intervention or whether interventions need to be preventative in nature.

Conflict of Interest

None declared

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