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Amygdala, hippocampal and corpus callosum size following severe early institutional deprivation: The English and Romanian Adoptees Study Pilot

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The adoption into the UK of children who have been reared in severely deprived conditions provides an opportunity to study possible association between very early negative experiences and subsequent brain development. This cross-sectional study was a pilot for a planned larger study quantifying the effects of early deprivation on later brain structure. We used magnetic resonance imaging (MRI) to measure the sizes of three key brain regions hypothesized to be sensitive to early adverse experiences. Our sample was a group of adoptee adolescents (N = 14) who had experienced severe early institutional deprivation in Romania and a group of non-institutionalised controls (N = 11). The total grey and white matter volumes were significantly smaller in the institutionalised group compared with a group of non-deprived, non-adopted UK controls. After correcting for difference in brain volume, the institutionalised group had greater amygdala volumes, especially on the right, but no differences were observed in hippocampal volume or corpus callosum mid-sagittal area. The left amygdala volume was also related to the time spent in institutions, with those experiencing longer periods of deprivation having a smaller *left* amygdala volume. These pilot findings highlight the need for future studies to confirm the sensitivity of the amygdala to early deprivation. **Keywords:** Corpus callosum, hippocampus, amygdala, deprivation, neurodevelopment, institution rearing, adolescence, brain imaging, brain development.

Maltreatment, neglect or other stressful experiences early in life are known to produce impairments in social, behavioural and cognitive functioning (Rutter & O'Connor, 2004; Teicher et al., 2003). The hippocampus, amygdala and corpus callosum have been identified as key brain structures sensitive to the consequences of exposure to early negative or stressful experience in experimental animals and humans (Teicher et al., 2003; Sanchez, Hearn, Do, Rilling, & Herndon, 1998; Suomi, 1997). In human studies, negative experiences have typically included neglect and physical/sexual abuse, with average ages of onset around 3 years or later (e.g., Tupler & De Bellis, 2006; Teicher et al., 2004). The English and Romanian Adoptees (ERA) study (Rutter et al., 2007a) provides a good opportunity to study the effects of global deprivation limited to the first three and a half years of life, which is a period of dramatic growth in the hippocampus, amygdala and corpus callosum (Hayakawa et al., 1989; Nishida et al., 2006; Pfluger et al., 1999). In this pilot study we examined the relationship between regional brain volume and early institutional deprivation in order to guide our future strategy for research linking brain, behaviour and developmental context within the larger ERA cohort.

Our sample was drawn from the large cohort of children who had spent their early years living in the extremely deprived conditions of state institutions of the Ceauşescu regime in Romania at the end of the 1980s and who were subsequently adopted into families living in the UK. The conditions of care in the Romanian institutions that these children had experienced varied from poor to appalling. Typically, they remained in cots all day, had few if any toys or playthings, and were fed gruel through bottles with large teats; there was no personalised care-giving and very little talk or interaction with caregivers (Castle et al., 1999). Despite showing significant catch-up [both physical and cognitive (Rutter, 1998)] at the first longitudinal assessments (at ages 4 and 6), a substantial number of adoptees still

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showed difficulties in a number of areas; specifically quasi-autism, disinhibited attachment, impaired cognition and inattention/overactivity (Rutter et al., 2001). Ames (1997) conducted a similar study of Romanian children adopted into Canada and found the emergence of comparable behavioural problems. There is also considerable heterogeneity in outcome; while some children have very severe problems, others do not exhibit any problems at all (Rutter et al., 2001). While animal studies of social isolation cannot be directly compared to these 'natural human experiments', it is interesting to note that similar behavioural abnormalities have been found in socially deprived primates (Sanchez et al., 1998; Suomi, 1997).

The brain structures to be studied were chosen because of previous evidence from human and experimental animals demonstrating their sensitivity to early stressful experiences (Bremner, 1999; Eluvathingal et al., 2006; Kaufman, Plotsky, Nemeroff, & Charney, 2000; Karl et al., 2006; Suomi, 1997; De Bellis et al., 2002; Tupler & De Bellis, 2006; Bremner, 2001, 2007; Bremner, Elzinga, Schmahl, & Vermetten, 2008; Bremner et al., 1995, 1997; Teicher et al., 2004; Vythilingam et al., 2005), and because of their putative role in mediating cognitive and emotional processes that may underlie some of the difficulties experienced by institutionally deprived individuals (Rutter et al., 2007a; Teicher et al., 2003). There have been two reports of alterations in brain structure and function in a sample of children aged between 7 and 11 with a history deprivation in Romanian institutions. Despite the small sample sizes and some methodological limitations, these provide preliminary evidence for a role for our candidate structures. In the first (Eluvathingal et al., 2006), diffusion tensor imaging was used to examine white matter tracts in seven children. This showed reduced integrity of the uncinate fasiculus, which connects the inferior frontal lobe with the anterior temporal lobe areas including the amygdala. In the second, brain metabolism in 10 children was investigated using positron emission tomography (Chugani et al., 2001). In comparison to a group of healthy adults and children of similar age with medically intractable partial epilepsy, reduced metabolism was detected in the left orbitofrontal cortex and left medial temporal lobe area (including hippocampus and amygdala). The hippocampus and the amygdala are medial temporal lobe structures that play crucial roles in memory formation, including emotional memories, as well as guiding behaviour based on emotional/threat-related stimuli (Adolphs & Spezio, 2006; Strange & Dolan, 2006). While early experiences are thought to influence the function of the hippocampus and amygdala in both experimental animals and humans, the effects of very early deprivation in humans as experienced by the Romanian adoptees included here are unknown. Early experiences are also known to influence corpus callosum (CC) size in both experimental animals (Juraska & Kopcik, 1988; Sanchez et al., 1998) and humans. The CC is the major commissure connecting homologous areas of the cerebral hemispheres and plays a crucial role in interhemispheric connectivity (Gazzaniga, 2000; Tomasch, 1954), with studies in humans showing diminished CC size in adolescents following childhood physical/sexual abuse or neglect (De Bellis et al., 1999; Teicher et al., 2004; Teicher et al., 1997). The effects of very early deprivation in humans are not known, although theoretically important because the CC goes through its most dramatic period of growth between 6 months and 3 years of age (Hayakawa et al., 1989), encompassing the period of time spent in institutions of the cohort included in this study.

The aim of the present study was to pilot the use of structural MRI to explore the influence of early adverse experiences on brain structure in the ERA cohort. Given the rarity of cohorts of this sort and their potential research value, a pilot study such as this one is essential in order to ensure that we address the most informative research questions with the most appropriate methodology in future studies of the full ERA cohort. Based on the previous research described above, we hypothesised that the sizes of the corpus callosum, amygdala and hippocampus would all be affected in the Romanian adoptees. Not enough is currently known about the role of very early adversity on these brain regions to specifically hypothesise increases or decreases in size. As described above, early adversity is often associated with reduced volumes in our target regions. However, increased hippocampal volumes have also been reported as being associated with trauma in childhood (Tupler & De Bellis, 2006). We therefore made no apriori predictions in this regard.

Methods

Participants

The Romanian adoptees were drawn from the 165 children in the ERA sample, from which we recruited 14 participants. Initial contact was made with 25 adoptees who lived within relative geographical proximity to London and agreement to participate was obtained from 17. Of these, three were not enrolled because of failing to meet the selection criteria for MRI scanning, or being unable to travel to London on the available scanning dates. The details of the remaining 14 participants are given in Table 1. At the time of participant selection extensive information was available for each participant from parent/child interviews, questionnaires and behavioural assessments, the details of which are given elsewhere (Croft et al., 2007; Beckett et al., 2006; Rutter et al., 2007c; Stevens et al., 2008; Beckett et al., 2007; Kreppner et al., 2007; Rutter et al., 2007b). In order to ensure that the sample was representative of the broad range of problems typically seen in the ERA group, half of those contacted scored highly at age 11 assessments (in the top 15% of the ERA full sample) in

Table 1 Participant information for the Romanian adoptees and comparison group

	Controls	Romanian adoptees	Statistical significance
N	11	14	–
Age in years	16.0 (.85)	16.2 (.72)	NS
Gender (#male)	6	6	NS
Handedness (#right)	8	11	NS
Verbal IQ	107 (16)	93 (18)	$t_{23} = 2.10$, $p = .048$
Performance IQ	101 (15)	78 (17)	$t_{23} = 3.54$, $p = .002$
Full-scale IQ	105 (15)	83 (14)	$t_{23} = 3.81$, $p = .001$
Time spent in institutions (months)	N/A	24.7 (8.8)	–

Values in brackets are standard deviations for the corresponding means.

at least one out of four areas of difficulty (quasi-autism, inattention/overactivity, cognitive impairment and disinhibited attachment) while the other half did not. For the healthy comparison group we recruited 11 UK-born, non-adopted age- and sex-matched adolescents from local schools ($p = .53$ and $p = .56$ respectively).

The study was approved by The Institute of Psychiatry and South London & Maudsley NHS Trust (Bethlem & Maudsley Hospitals) Research Ethical Committee. All participants and one parent for each participant provided written informed consent.

Image acquisition

A 1.5T GE Excite Scanner (General Electric Medical Systems, Milwaukee, WI) was used to acquire an inversion recovery prepared SPGR sequence of 1.1 mm thick slices and in-plane resolution of .9 mm × .9 mm (TR = 10.8 ms, TE = 5.0 ms, TI = 300 ms, 146 slices, matrix size 256^2).

Regional assessments

The CC area was measured on the mid-sagittal slice and hippocampal and amygdala volumes were delineated using stereological measurement. Corpus callosum (CC) mid-sagittal slice area was rated for each participant using the image analysis software Analyze™, Biomedical Imaging Resource, Mayo Foundation (http://www.analyzedirect.com). The CC was subdivided into four subregions by drawing lines perpendicular to its antero-posterior length as described previously (Nosarti et al., 2004; Woodruff, Pearlson, Geer, Barta, & Chilcoat, 1993), and these 'quarters' were corrected for total mid-sagittal area prior to statistical analysis. Hippocampal and amygdala volumes were measured using an unbiased point-counting technique implemented in stereological assessment software (Barta, Dhingra, Royall, & Schwartz, 1997). Hippocampal measurements were taken from a posterior boundary of clear fornix definition on the coronal orientation to the appearance of the amygdala as the anterior boundary, with details available in Nosarti et al. (2002). The amygdalae were defined according to the protocol in Mackay et al. (1998). Amygdala definition extended from the coronal slice where a clearly identifiable boundary from the neighbouring white matter of the temporal lobe was visible to the most posterior coronal slice where the grey matter superior to the hippocampus can be identified. Total grey and white matter volumes were determined using SPM2 (http://www.fil.ion.kcl.ac.uk/spm). All regions were assessed blind to group affiliation and interrater (two raters) and intrarater reliability estimates were high for 10 randomly selected independent ratings: total CC area and four subregions ICCs > .94; hippocampus ICCs > .95; amygdala ICCs > .89. Spatial reliability (intersection/union) was greater than .89 across all three regions, which is in line with previous literature (Nacewicz et al., 2006).

Cognitive assessment

The Wechsler Intelligence Scale for Children-Revised (WISC-R) was administered to all participants (Wechsler, 1991) either on the day of scanning or within 6 months of being scanned. The WISC-R score was unavailable for one of the Romanian adoptees and their score was substituted with the IQ determined from assessment at age 11.

Statistical analyses

Data were analysed with SPSS 15 (SPSS Inc., Chicago, USA). Differences in CC mid-sagittal length, height and surface area (adjusted and unadjusted for white matter volume) between Romanian adoptees and controls were assessed by univariate analysis of variance (ANOVA). CC sub-regions and lateralised hippocampal and amygdala volumes were assessed using repeated-measures ANOVA. Values presented represent means with standard deviations.

Results

The Romanian adoptees (882 ± 78 ml) had significantly reduced brain volumes compared with the control group (1051 ± 83 ml; $F_{1,23} = 27.1$, $p < .001$). The Romanian adoptee grey and white matter volumes were reduced by 15% and 18% respectively, with no effects of handedness or gender. These reduced volumes are in keeping with the known reduction in head circumference previously described for the ERA sample (Sonuga-Barke et al., 2008). Indeed there was a significant correlation between brain volumes measured in this sample and previous head circumference measurements (rs > .62, ps < .01). Overall, CC area did not differ between the Romanian adoptees and controls ($F_{1,23} = .60$, $p = .45$), even after controlling for total white matter volume (Jancke & Steinmetz, 1998; Figure 1). Absolute and adjusted values are given in Table 2. Across these analyses there were no effects of CC subregion, handedness or gender. Mean absolute hippocampal volumes were smaller in the Romanian group (4.72 ± .74 cm^3) compared with the control group (5.62 ± 1.00 cm^3); $F_{1,22} = 6.69$,

Table 2 Mean values and standard deviations for absolute and adjusted region sizes for the corpus callosum, hippocampus and amygdala

Region	Healthy comparison group	Romanian adoptees	Statistical significance
Corpus callosum			
Mid-sagittal area (absolute – cm^2)	4.77 ± 99.3	4.46 ± 96.0	$P = .45$
Normalised area[a]	8.74 ± 1.46	9.39 ± 1.95	$P = .37$
Hippocampus			
Left absolute volume (cm^3)	2.82 ± .58	2.34 ± .35	$P = .017$[c]
Right absolute volume (cm^3)	2.80 ± .53	2.38 ± .46	
Left adjusted volume (cm^3)[b]	2.58 ± .53	2.54 ± .33	$P = .98$[c]
Right adjusted volume (cm^3)[b]	2.55 ± .43	2.59 ± .52	
Amygdala			
Left absolute volume (cm^3)	1.43 ± .27	1.41 ± .37	$P = .89$[d]
Right absolute volume (cm^3)	1.09 ± .21	1.40 ± .40	$P = .029$
Left adjusted volume (cm^3)[b]	1.30 ± .23	1.54 ± .41	$P = .10$[e]
Right adjusted volume (cm^3)[b]	.99 ± .18	1.53 ± .43	$P = .001$

[a]Normalisation against white matter volume; [b]Adjusted by total grey/white matter volume and scaled to the grand mean; [c]p value shown is for main effect of group across both left and right hemisphere – the interaction with side was non-significant. [d]Group by side interaction $F_{1,23} = 7.37$, $p = .012$ – p-value shown is for post-hoc tests for left and right side separately. [e]Group by side interaction $F_{1,23} = 4.94$, $p = .036$ – p-value shown is for post-hoc tests for left and right side separately.

$p = .017$. There were no effects of hemisphere, age or gender. The reductions observed were accounted for by the reduced total grey/white matter volume (after adjustment: $p = .76$); see Figure 2 and Table 2.

Mean absolute amygdala volumes did not differ between the groups (control: 2.52 ± .39 cm^3, Romanian adoptees 2.80 ± .68; $F_{1,23} = 1.57$, $p = .22$), although there was a significant interaction between hemisphere and group ($F_{1,23} = 6.40$, $p = .019$). This was due to (1) a hemisphere effect for controls (L:R = 1.34:1; $F_{1,10} = 16.14$, $p = .002$), but not the Romanian group (L:R = 1.01:1; $F_{1,13} = .02$, $p = .90$) and (2) a group effect for the right amygdala ($F_{1,23} = 5.41$, $p = .029$, controls <Romanian adoptees), but not the left amygdala ($p = .89$). After adjustment for total grey/white matter volume (Figure 2) there was a significant main effect of group ($F_{1,23} = 10.17$, $p = .004$), and an interaction between hemisphere and group ($F_{1,23} = 4.94$, $p = .036$). The significant group effect was due to a 33.5% larger adjusted amygdala volume in the Romanian adoptees. The interaction between group and hemisphere was due to the group effect being greater for the right amygdala (right: $F_{1,23} = 15.02$, $p = .001$; left: $F_{1,23} = 2.90$, $p = .10$). In summary, the Romanian groups had enlarged relative amygdala volumes compared to the control group, particularly on the right. There were no significant effects of handedness or gender.

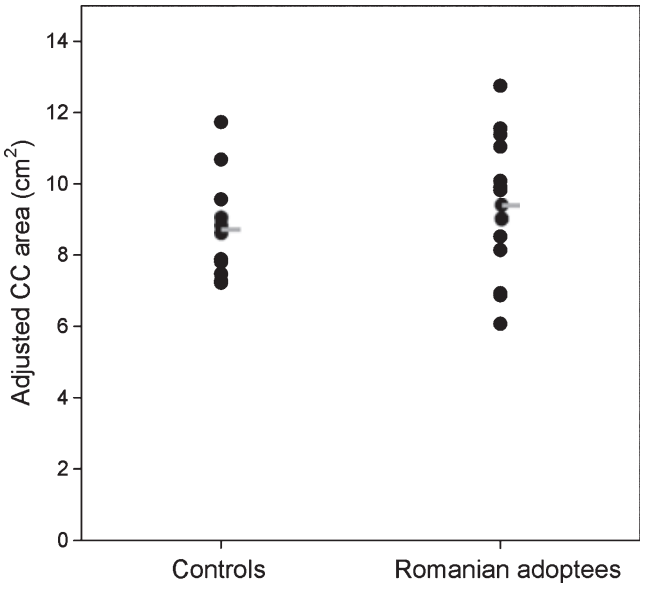

Figure 1 Adjusted sizes of the corpus callosum for controls and Romanian adoptees. Circular symbols represent individual values. Grey horizontal marks represent means for each group

Correlations with time spent in institutions

Spearman's rho was used to examine possible relationships between the measured size of structures and the length of time spent in institutions prior to being adopted within the UK (Table 3). The left amygdala volume was the only region that correlated significantly with time in institutions. As Figure 3 illustrates, those with smaller left amygdala volumes experienced longer stays in institutions. The effect remained significant after correcting for IQ differences (Spearman's rho = –.68, $p = .003$) and Bonferroni correction for multiple comparisons. Multiple linear regression analysis confirmed the significant association between left amygdala volume and time spent in institutions with adjusted hippocampal and corpora callosal volumes also included as independent variables.

Discussion

This pilot study demonstrated that volumetric changes in brain structure are detectable in

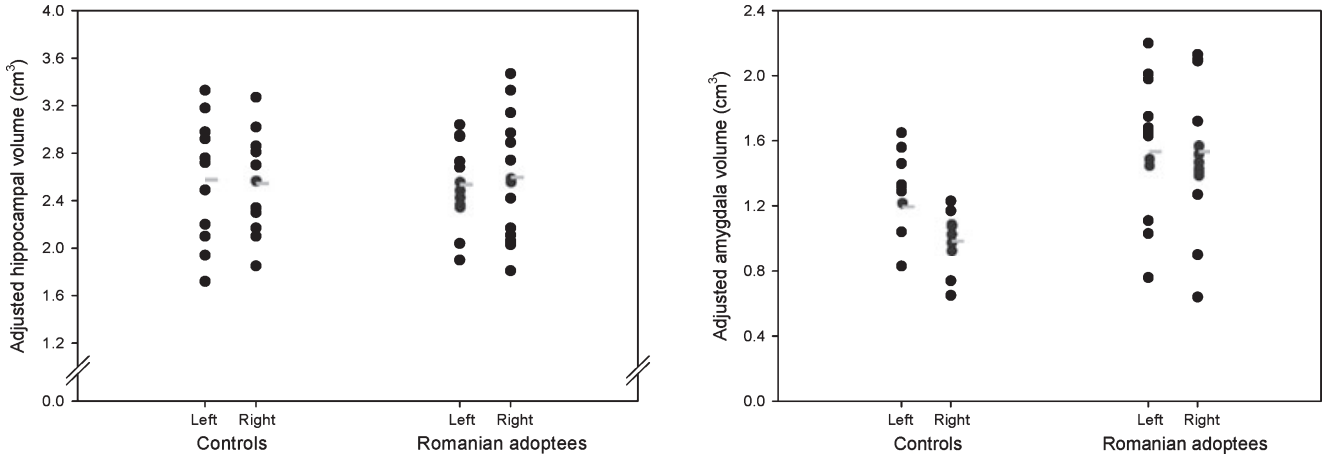

Figure 2 Individual values for left and right hippocampal (left panel) and amygdala (right panel) volumes, adjusted for total grey and white matter volume. Mean values are shown as grey bars. There is no difference in hippocampal volumes, while amygdala volumes are larger in the Romanian adoptees, particularly on the right

Table 3 Relationships between the measured size of structures and the length of time spent in institutions prior to being adopted within the UK

Brain region	Correlation[1]	Statistical significance
Total grey/white matter volume	−.08	.79
CC mid-sagittal area	−.40	.16
Left Hippocampus	−.01	.97
Right Hippocampus	−.22	.67
Left Amygdala	−.72	.003*
Right Amygdala	−.24	.41
Hippocampal laterality coefficient[2]	.18	.53
Amygdalar laterality coefficient[2]	−.23	.43

[1]Spearman's rho is shown for each area. [2]Laterality coefficients are left volume/right volume. Regions are corrected for total brain volume, and results are similar for absolute regional sizes. *Significant correlation after correction for multiple comparisons.

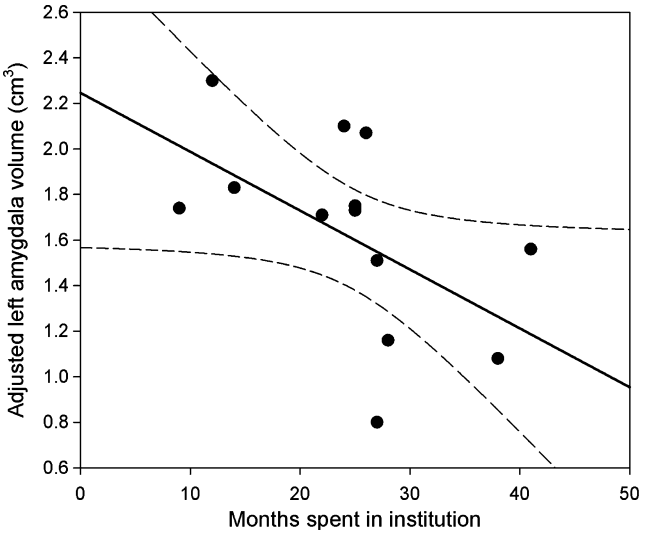

Figure 3 Scatter plot and regression line for the significant relationship between time spent in institutions prior to adoption into the UK against the left amygdala volume, adjusted for total grey/white matter volume. The relationship remains significant after controlling for potential outliers identified using Cook's D (Cook, 1977)

adolescents who had experienced severe deprivation in the early years of their lives. Taken together with previous studies suggesting changes in cerebral metabolic rate in widespread brain regions and reduced white matter integrity, this study provides a compelling argument for continuing this work in larger cohorts. In addition to the reduced grey and white matter volumes – expected from previous findings of reduced head circumference – the deprived group had a larger relative amygdala volume potentially underpinning disrupted affective processing. These were greater for the right amygdala, with the left amygdala showing a more subtle increase in relative volume. A significant negative relationship between the left amygdala volume and time spent in institutions indicates that this structure may have particular sensitivity to the deprivation experienced.

As mentioned in the introduction, amygdala abnormalities have previously been suggested in Romanian adoptees. Chugani et al. (2001) reported that brain metabolism was reduced in medial temporal lobe regions compared with adult and childhood epileptic controls and in subgroup of seven Romanian adoptees, showed reduced white matter integrity in the left uncinate fasciculus, which connects anterior temporal lobe regions and the amygdala to inferior regions of the frontal cortex (Eluvathingal et al., 2006). The relationship with the integrity of the uncinate fasciculus and volume of proximal grey matter structures, including the amygdala, is not known, but when taken together with our findings a degree of convergence is suggested. An important next step will be to conduct multimodal imaging in the full ERA cohort allowing

mapping of grey and white matter structural differences as well as functional imaging differences. Functionally, the amygdala has a role in basic emotional processing, guiding social behaviours, probably by attentional modulation of other areas of the cortex (Adolphs, 2007; Adolphs & Spezio, 2006). The inclusion of specific paradigms designed to delineate components of emotional reactivity will therefore be important to fully understand the effects of deprivation and adoption on emotional function mediated by the amygdala and connected brain networks.

The developmental trajectory of the CC and hippocampal formation suggests that they may be highly sensitive to early negative or stressful experiences (Lavenex, Banta LaVenex, & Amaral, 2007; Hayakawa et al., 1989; Pfluger et al., 1999). However, we did not find evidence of altered CC area or hippocampal volume. The possibility that such effects may emerge later in life in this sample cannot be ruled out. Such age-dependent effect could result from pre-existing differences (Vythilingam et al., 2005), age-related atrophy (Pruessner, Collins, Pruessner, & Evans, 2001), or as a result of an interaction between early negative experiences and pre-existing genetic predispositions that emerge later in life due to the cumulative effects of ongoing neural and endocrine activity and life experiences (McEwen, 2001, 2002).

There are a number of limitations in this study. First, the comparison group were healthy adolescents that were not adopted. Nonetheless, the full ERA sample (Rutter, 1998) includes children who were born within the UK prior to adoption and inclusion of this group within the larger cohort study is planned. Second, although adolescents with a broad range of deprivation-related problems were included, we were underpowered to examine the extent to which these modulated the impact of deprivation of brain structure. As such the future strategy will incorporate exploration of similarities and differences between brain changes in Romanian adoptees and other trauma/adversity-related changes, in particular post-traumatic stress disorder. Third, the volumetric measurements were limited to three brain regions. Voxel-based approaches in the larger sample will allow determination of the possible wider impact of deprivation on regional brain structures, thus contributing not only to hypothesis testing, but also hypothesis generation.

These initial findings in 14 adolescents from the ERA cohort highlight the amygdala as a possible marker of adaptation to severe global early deprivation during the first few years of life. This adaptation could relate to either protective or compensatory mechanisms following early deprivation acting as a 'trigger' for an alternative neuro-developmental pathway for the deprived children, or early deprivation occurring during a sensitive period of amygdala development. Extension of this work into the full sample will allow the relative roles of adoption, deprivation, genetic polymorphisms and associated factors such as IQ and profiles of cognitive deficits to be determined. Thus, in addition to the assessment of pre-existing differences (e.g., genetic), which may moderate the early response to stress (Caspi et al., 2002; Kumsta et al., 2008), the larger cohort will also allow analysis of post-adoption environmental factors (ascertained prospectively), which may either compound or ameliorate the risk accrued in the institutions. We hypothesise that the effects of very early negative or stressful experiences on brain structure and function will be qualitatively different from negative experiences later in childhood or adulthood and anticipate that a complete understanding of the development of brain structures in relation to negative experiences will be dependent not only upon the experiences early in life, but also upon the outcome of those experiences.

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Key points

- The English and Romanian Adoptees study provides an opportunity to study the effects of early global deprivation on brain development.
- Structural MRI scans showed smaller overall brain volumes and larger relative amygdala volumes.
- Changes in the corpus callosum and hippocampus were not evident after correction for overall brain volumes.
- The amygdala may therefore be a valuable target for studies of the effects of early deprivation.
- Extension of our findings into larger populations is now needed.

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