Associations of perceived adverse lifetime experiences with brain structure in UK Biobank participants

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Background: Adversity experiences (AEs) are major risk factors for psychiatric illness, and ample evidence suggests that adversity-related changes in brain structure enhance this vulnerability. To achieve greater understanding of the underlying biological pathways, increased convergence among findings is needed. Suggested future directions may benefit from the use of large population samples which may contribute to achieving this goal. We addressed mechanistic pathways by investigating the associations between multiple brain phenotypes and retrospectively reported AEs in early life (child adversity) and adulthood (partner abuse) in a large population sample, using a cross-sectional approach. Methods: The UK Biobank resource was used to access imaging-derived phenotypes (IDPs) from 6,751 participants (aged: $M = 62.1$, $SD = 7.2$, range = 45-80), together with selected reports of childhood AEs and adult partner abuse. Principal component analysis was used to reduce the dimensionality of the data prior to multivariate tests. Results: The data showed that participants who reported experiences of childhood emotional abuse (‘felt hated by family member as a child’) had smaller cerebellum and ventral striatum volumes. This result was also depicted in a random subset of participants; however, we note small effect sizes ($\eta^2_p < .01$), suggestive of modest biological changes. Conclusions: Using a large population cohort, this study demonstrates the value of big datasets in the study of adversity and using automatically preprocessed neuroimaging phenotypes. While retrospective and cross-sectional characteristics limit interpretation, this study demonstrates that self-perceived adversity reports, however nonspecific, may still expose neural consequences, identifiable with increased statistical power. Keywords: Brain imaging; adversity; early life experience; large data.

Introduction

Among the risk factors for psychopathology, childhood adverse experiences (AEs) may account for approximately 30% of adult mental illness (Kessler et al., 2010). Furthermore, AEs occurring in adulthood, such as intimate partner abuse, are also linked to multiple psychiatric outcomes (Pill et al., 2017). Although the biological mechanisms are not fully understood, it is argued that adversity-related neuroendocrine dysregulations may determine structural brain changes (Meaney et al., 1991), thus contributing to the neuropathology of mental illness (Lupien et al., 2018; McLaughlin & Lambert, 2017).

Indeed, there are many studies demonstrating that children exposed to adversity show structural and functional changes in putative emotion-regulation areas (McCrory et al., 2017). For example, a recent review shows that adversity related to threat (e.g. abuse) is primarily associated with alterations in fronto-striatal-limbic circuits, while fronto-parietal regions are more often affected by experiences of deprivation (e.g. neglect) (McLaughlin et al., 2019).

Adversity-related changes are also frequently observed in other brain regions, such as the corpus callosum (McCarthy-Jones et al., 2018), occipital cortex (Lim et al., 2014) and cerebellum (De Bellis & Kuchibhatla, 2006). There is also evidence that such alterations are present in the absence of psychopathology (Edmiston et al., 2011) and even with more mild forms of adversity (Walsh et al., 2014). Research on the neurobiological consequences of various adult AEs also implicates regions of the frontal cortex, limbic and paralimbic structures such as the amygdala and cingulate cortex, particularly in studies of post-traumatic stress disorder (Akiki et al., 2017; Fonzo et al., 2010). Across these findings, there are discrepancies related to adversity type, the presence of comorbidities, the use of moderators and statistical power.

To increase convergence among findings, systematic reviews suggest that large sample sizes, greater consistency in the quantification of adversity and implementation of longitudinal approaches, are needed (McLaughlin, 2016; McLaughlin et al., 2019). The current study contributes to this literature by looking at the associations between retrospective adversity reports related to childhood and adult partner abuse (e.g. familial/partner physical abuse, respectively) and a multitude of brain imaging phenotypes, using a cross-sectional design.

While being limited in interpretation due to its retrospective nature, the study aims to determine the presence and strength of associations between AEs and brain structures in a large sample of adults (aged: $M = 62.1$, $SD = 7.2$, range = 45–80). Indeed, more subtle, adversity-related changes in brain structure in the general population with smaller

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effect sizes can be identified in large datasets (Calem et al., 2017). These also provide enough statistical power to employ multivariate approaches and to control for multiple confounding variables. However, there are important statistical challenges in ‘Big Data’ studies associating imaging with nonimaging variables, described at length elsewhere (Smith & Nichols, 2018).

Of relevance here, these challenges relate to exactly the strength of this study, that is simultaneously investigating the associations between adversity reports and multiple neuroimaging phenotypes (imaging-derived phenotypes – IDPs, i.e. quantitative measures of brain structure). To address this, we employ multivariate tests to minimize the loss of statistical sensitivity. Furthermore, to avoid overfitting the models, we used feature extraction (principal component analysis – PCA) to reduce the number of neuroimaging variables. Indeed, UK Biobank researchers have implemented this approach previously, illustrating advantages for using imaging data that are consistently acquired and preprocessed (Miller et al., 2016). For example, of the IDPs made available, microstructural measures of white matter tract integrity share a considerable proportion of variance (Cox et al., 2016; Shen et al., 2017), and age-related differences were shown to relate more closely to the features that these measures share, rather than their unique characteristics (Cox et al., 2016). In addition, performing PCA on IDPs also has the advantage that results can be easily mapped back to the original structures. The use of PCA also addresses other aspects related to statistical robustness. Specifically, with unbalanced group sizes (see Figure S1), reducing the number of dependent variables also reduces the risk of violating the assumption of homogeneity of covariance in multivariate tests (Coombs et al., 1996) and limits multicollinearity.

Therefore, we investigated the relationship between AEs and multiple neuroimaging measures in a large cohort population. We aimed to identify the number of affected neural structures and the strength of their associations, given (a) ample evidence that AEs can affect the brain’s integrity and function, (b) the need to achieve greater understanding and consistency into the underlying biological pathways and (c) the statistical advantages of using a large dataset to address current knowledge gaps (McLaughlin, 2016).

Methods

Participants

The data in this study are from the UK Biobank resource (http://www.ukbiobank.ac.uk), a large epidemiological cohort collecting extensive genetic, biomarker, cognitive, psychometric and lifestyle measures. 502,591 participants were successfully recruited into the UK Biobank. Participants were aged 40–69 years at the time of recruitment in 2006–2010 (Sudlow et al., 2015). In 2015, the imaging phase of the study began with the aim to scan 100,000 cohort participants by 2022 (Miller et al., 2016). UK Biobank received ethical approval from the Research Ethics Committee (11/NW0382). Volunteers gave informed consent for their participation. The current analysis was conducted on 6,751 individuals on complete cases (no imputation was performed): 3,960 females, aged 45–79 (M = 61.28, SD = 7.09), and 2,791 males, aged 46–80 (M = 63.25, SD = 7.12). Selection of the final sample and further details of demographics and data preprocessing are provided in Appendix S1, Figures S2 and S3, Tables S1–S3.

Measures and questionnaires

An online mental health questionnaire was administered as a follow-up self-assessment (2016), wherein selected items on AEs occurring in childhood or adult life were administered. Childhood adversity items were based on the short version of the Childhood Trauma Questionnaire (CTS-5) (Glaesmer et al., 2013), and adult partner abuse was evaluated using bespoke (custom-built) questions on domestic abuse, adapted from the British Crime Survey (Khalifeh et al., 2015). The online questionnaire also measured current depression and anxiety disorder at the time of completion, using two well-established tools: the Patient Health Questionnaire-9 questions (PHQ-9) (Manea et al., 2012) and the Generalized Anxiety Disorder-7 questions (GAD-7) (Kroenke et al., 2010) versions, respectively. The AE items (Table 1) on a 5-point Likert scale: never true, rarely true, sometimes true, often true and very often true. Given the distribution of responses (Figure S1), showing that most participants reported never having experienced adverse events (EAc: 85%; ENc: 52%; Pac: 79%; Pnc: 85%; Eap: 76%; and Pap: 86%), the items were dichotomized and recorded as either 0 (never true: AEs=0) or 1 (any other option: AEs+). For PHQ-9/GAD-7, we used the summed scores, based on 5-point responses (1–4). Complete information on these web-based scales is available online (http://biobank.ndph.ox.ac.uk/showcase/showcase/doc/ssl/mental_health_online.pdf).

Brain imaging

Brain images were acquired on a Siemens Skyra 3T scanner with a 32-channel RF receive head coil (Siemens Medical Solutions, Germany). Scanning was conducted in Cheadle, Manchester (n = 6,493), and Newcastle (n = 258) using identical protocols. For preprocessing and output generation, an automated pipeline was applied using tools primarily from the FSL library (Jenkinson et al., 2012).

Our study made use of IDPs generated by an image-processing pipeline developed and run on behalf of UK Biobank (Alfaro-Almagro et al., 2018). IDPs represent meaningful quantities extracted from the imaging data in the form of numerical variables. Grey matter structures and total brain volumes were segmented from T1-weighted images. Specifically, separation among tissue types using FAST (FMRIB’s Automated Segmentation Tool (Zhang et al., 2001)) was employed to obtain total grey, white matter and cerebrospinal fluid volumes, together with 139 grey matter IDPs (65 bilateral). Microstructural white matter tract integrity was investigated here by looking at the diffusion tensor imaging (DTI) outputs: fractional anisotropy (FA) and mean diffusivity (MD). This technique measures the ability of water molecules to move within a specific tissue. Specifically, FA provides information about the directionality of white matter molecule diffusion, while MD indicates the magnitude of diffusion (Cox et al., 2016). The AutoPtx tool was used to define 27 white matter tracts (12 bilateral) for each derived microstructural parameter (De Groot et al., 2013).
Table 1 Childhood adversity and partner abuse items

| Childhood Adversity: ‘When I was growing up...’ | Variable name | Acronym |
|-------------------------------------------------|---------------|---------|
| I felt that someone in my family hated me        | Childhood     | EAc     |
| I loved a child                                 | Emotional     | EnC     |
| People in my family hit me so hard that it left me with bruises or marks | Physical Abuse | PaC |
| There was someone to take me to the doctor if I needed it* | Physical Abuse | PAc |
| Partner Abuse (Adverse events in adult life): Since I was sixteen...* | Variable name | Acronym |
| A partner or ex-partner repeatedly belittled me to the extent that I felt worthless | Partner Emotional Abuse | EAp |
| A partner or ex-partner deliberately hit me or used violence in any other way | Partner Physical Abuse | Pap |

*Variables were recoded (higher values represent more frequent adversity events); variable names were selected for convenience and are based on known nomenclature (Gilbert et al., 2009).

Complete details of the scanning protocol and analysis pipeline are available on the UK Biobank website (http://biobank. nkc.ndph.ox.ac.uk/showcase/label.cgi?id=100) and have been previously documented (Alfaro-Almagro et al., 2018; Miller et al., 2016; Shen et al., 2017). A summary is available in Appendix S2.

Analysis strategy

Analyses were conducted using Stata V16.1 (StataCorp, College Station, TX, USA). All bilateral IDPs were averaged. Observations were excluded for IDPs $\pm3$SD from the sample mean. The imaging data were adjusted for several variables, by regressing out demeaned confounds as per UK Biobank recommendations (link above). IDPs were adjusted for age and sex, variables known to be associated with brain volume differences, including in UK Biobank participants (Cox et al., 2016; Ritchie et al., 2018). To minimize the risk of identifying nonmeaningful effects given the large sample size (Smith & Nichols, 2018), the IDPs were also adjusted for variables known to influence brain imaging biomarkers, that is, handeness (Anstey et al., 2004), ethnicity (Brickman et al., 2008) and education (Shen et al., 2018). In addition, given the retrospective nature of the adversity information in our study and existing evidence that retrospective self-reports are associated with concurrent psychopathology (Newbury et al., 2018), we also adjusted for depression and anxiety symptoms at the time of adversity reporting, using the summary scores obtained from PHQ-9 and GAD-7 (however, we note that this adjustment may not substantially account for recall bias (Fergusson et al., 2000)). Furthermore, with a cross-sectional design, pre-existing differences in brain volume cannot be ruled out (Lupien et al., 2018). Therefore, we used comparative morphometric measures of height and body size at age 10 (acquired retrospectively; thinner/plumper; shorter/taller; average), as a proxy measure of normative development (Seitz et al., 2015) in the IDP adjustment. While birthweight is also associated with brain volume in later life (Allin et al., 2004), given the degree of missingness in this variable (32% of total N) and the absence of significant differences in birthweight between participants with and without reported AEs (all: $t < 1.42, p < .156$), we decided to exclude this variable from the analysis. Finally, we corrected for head size and head position during scanning, using the head size scaling factor and x-, y- and z-axis positions of the head in scanner coordinates, respectively, provided as IDPs in the dataset. The head size scaling variable is estimated based on the external surface of the skull, to normalize the brain IDPs (Alfaro-Almagro et al., 2018).

Of the IDPs, nine were excluded (Appendix S2). The remaining measures were as follows: 67 grey matter IDPs, 13 white matter tracts for each integrity measure (26 total) and total volumes of grey/white matter (Appendix S3 for list). Given their putative association with early adversity neurobiology (e.g. Edmiston et al., 2011), the analysis considered limbic, paralimbic and basal ganglia structures (13 IDPs) individually. All other grey matter structures (54 IDPs) and DTI IDPs were included in the PCA, to reduce the dimensionality of the data (Tables S4–S8). Separate PCAs were conducted to obtain one latent measure for each type of tract measurement (FA/MD). For grey matter, the Harvard–Oxford and the Diedrichsen (cerebellum) atlases were initially used to group IDPs (Diedrichsen et al., 2009; Smith et al., 2004), and separate PCAs were conducted within each lobe and the cerebellum. This would facilitate mapping the results back to individual measures, given the unsupervised nature of this analysis. To determine the number of factors, we considered Kaiser’s criterion of 1 and the point of inflection in scree plots, using Horn’s parallel analysis (Horn, 1965). When more than one component was identified, orthogonal (varimax) rotation was used (Laubach et al., 1999). A value $>.60$ for the Kaiser–Meyer–Olkin measure was considered adequate (Kaiser, 1970), and variables with small loadings (<.3) were removed from the analysis. The latent measures together with the individual structures were all included as outcomes in separate MANO- VAs, with each of the six adversity items as the predictors, using primarily the Wilk’s $\lambda$ result. The significance level was set at .0083 ($\alpha = .05/6$). The same threshold was considered for the univariate tests following a significant MANOVA. Partial eta-squared ($\eta^2_p$) was reported to describe effect sizes. We used SPSS (IBM, Armonk, NY, USA) to run Box’s test for the assumption of equal covariance matrices with $p < .001$ (Hahn-Vaughn, 2016). Where this was violated, results refer to Pillai’s trace statistic (see Table S9 for MANOVA tests on IDPs without outlier exclusion). Independent t-tests were conducted where a significant result was identified on the latent measures, using Bonferroni correction. All analyses are conducted on standardized residuals after adjusting for the variables described above. For clarity of interpretation, means and standard deviations are reported together with tests referring to brain volumes, adjusted for total brain volume only: IDP (white + grey matter + CSF)*100. The Supporting Information file includes supplementary Figures/Tables/Appendices annotated ‘S’. Results

Description of participants

Participant characteristics and group differences are summarized in Table 2.

Latent measures

For the white matter microstructural measures, a single unrotated factor explained 51.05% (global
Table 2 Description of participants based on childhood adversity and partner abuse

|                          | Emotional Abuse (child adversity) | Emotional Neglect (child adversity) | Physical Abuse (child adversity) | Physical Neglect (child adversity) | Emotional Abuse (partner abuse) | Physical Abuse (partner abuse) |
|--------------------------|-----------------------------------|-------------------------------------|----------------------------------|-----------------------------------|--------------------------------|-------------------------------|
| N                        | 5,722                             | 1,029                               | 5,388                            | 1,363                             | 5,739                          | 1,012                         |
| Age (M, SD, range)       | (62.4, 60.5, t = 7.80)            | (7.1, 7.1, p < .001)                | (7.2, 7.2, p = .083)             | (7.0, 7.0, p < .001)              | (7.1, 7.1, p < .001)           | (7.1, 7.1, p < .001)          |
| Gender (%)               | 57.3                              | 59.8                                | 57.8                             | 60.2                              | 53.9                           | 57.0                          |
| Education (%)            | 45.3                              | 51.3                                | 47.5                             | 45.6                              | 45.6                           | 44.6                          |
| Ethnicity (%)            | 97.6                              | 97.7                                | 97.7                             | 97.8                              | 97.3                           | 97.1                          |
| Handedness (Right-handed)| 89.4                              | 88.7                                | 89.1                             | 89.4                              | 89.5                           | 89.0                          |
| PHQ-9 (M, SD)            | 11.2                              | 13.3                                | 11.4                             | 12.3                              | 11.1                           | 13.0                          |
| GAD-7 (M, SD)            | 8.7                               | 10.3                                | 8.8                              | 9.6                               | 8.6                            | 10.1                          |
| Body size 10yo (% short: tall) | 32.16                              | 36.20                               | 32.16                            | 36.15                             | 32.16                          | 36.05                         |
| Height 10yo (cm)         | 20.2                              | 22.7                                | 20.2                             | 22.7                              | 20.2                           | 22.7                          |
| GM (M, SD)               | 36.6                              | 37.8                                | 36.6                             | 37.8                              | 36.6                           | 37.8                          |
| WM (M, SD)               | 32.6                              | 32.5                                | 32.6                             | 32.5                              | 32.6                           | 32.6                          |
| CSF (M, SD)              | 30.7                              | 30.7                                | 30.7                             | 30.7                              | 30.7                           | 30.7                          |

GM, cerebrospinal fluid; GM, grey matter; M, mean; SD, standard deviation; WM, white matter.

*Flags significant results (notably: participants who report Ε score higher on depression and anxiety (PHQ-9/GAD-7); there are no group differences on overall brain volumes). Comparisons on brain volumes are performed on standardized residuals after adjusting for demographics, psychopathology, body size (above), as well as head size and position during scanning (for ease, M and SD are shown after adjusting for brain size only).
fractional anisotropy: gFA) and 57.42% (global mean diffusivity: gMD) of the total integrity variance, with large positive loadings in all tracts (Figure S4, Table S7). Fifty-four grey matter IDPs were grouped for each lobe (frontal: 10; temporal: 16; parietal: 7; occipital: 7), together with the cerebellum (14), resulting in 8 latent measures of grey matter, representing middle-superior region of the frontal gyrus (MSFG – 21.86% variance), inferior region of the frontal gyrus (IFG – 20.66%), superior region of the temporal gyrus (STG – 16.84%), inferior region of the temporal gyrus (ITG – 15.63%), temporo-occipital region of the temporal gyrus (TOG – 13.03%), parietal lobe (PL – 33.29%), occipital lobe (OC – 39.41%) and cerebellum (CBL – 44.02%) (Figure S4, Table S8). Within each latent factor, IDPs correlated significantly in the same positive direction (all \( p < .001 \); Tables S4–S6) (Appendix S3).

**Multivariate analyses**

Each AE was included separately in one-way MANOVAs with 10 latent factors, 13 individual measures (thalamus, putamen, caudate, hippocampus, amygdala, ventral striatum, insula, cingulate gyrus anterior/posterior, subcallosal cortex, paracingulate gyrus and parahippocampal gyrus anterior/posterior) and 2 IDPs of total grey/white matter as the outcomes (25 total). There was a significant effect of AE for emotional abuse in childhood, EAc: \( F(25,6725) = 1.92, \ p = .004, \eta_p^2 = .007 \). Separate tests of between-subjects effects on the outcome variables showed a significant effect of EAc on CBL (\( F(1,6749) = 7.53, \ p = .006, \eta_p^2 = .001 \)) and ventral striatum (EAc+: \( M = .0337, SD = .01 \); EAc–: \( M = .0338, SD = .01 \); \( F(1,6749) = 10.19, \ p = .001, \eta_p^2 = .002 \)). To identify which cerebellar regions were associated with EAc, we ran independent t-tests on the 14 structures included in the analogous latent variable, considering \( p < .0036 \) (\( \alpha = .05/14 \)). There were significant volume differences in cerebellar lobules I–IV between individuals who reported EAc (EAc+: \( M = .116; SD = .02 \), compared to those who did not (EAc–: \( M = .117; SD = .02 \); \( t(6749) = 2.92, \ p = .0035 \)). A trend in the same direction was also observed in Crus I (EAc+: \( M = .658, SD = .08 \); EAc–: \( M = .660, SD = .08 \); \( t(6749) = 2.65, \ p = .008 \)) and to a lesser extent in cerebellar lobule IX (\( t(6749) = 2.55, \ p = .011 \)), vermis lobules VIIa (\( t(6749) = 2.52, \ p = .012 \)) and VIIb (\( t(6749) = 2.50, \ p = .013 \)).

All other AEIs did not reach the adjusted significance threshold, although a trend can be observed for physical neglect in childhood, PNC: \( F(25,6725) = 1.63, \ p = .026, \eta_p^2 = .006 \), and partner physical abuse, PAP: \( F(25,6725) = 1.53, \ p = .043, \eta_p^2 = .006 \). The effects of emotional neglect and physical abuse in childhood and partner emotional abuse were nonsignificant: ENC: \( F(25,6725) = .97, \ p = .513, \eta_p^2 = .004 \); PAC: \( F(25,6725) = 1.05, \eta_p^2 = .004 \); and EAP: \( F(25,6725) = 1.04, \ p = .407, \eta_p^2 = .004 \). Box’s M-statistic was significant for PAP only (\( M = 419.2, \ p < .001 \)). Although IDPs were adjusted for gender, we noted that more females reported partner abuse compared to males (Table 2). Partner adversity analyses conducted on females only remained nonsignificant (PAP: \( F(25,3934) = 1.46, \ p = .067, \eta_p^2 = .009 \); EAP: \( F(25,3934) = 1.29, \ p = .153, \eta_p^2 = .008 \)).

**Robustness of statistical results**

Given the small effect sizes observed, we reran the MANOVAs on a random selection of 80% of the observations (\( N = 5,401 \)), while keeping the same distribution of adversity scores (EAc+: 15%; EAc–: 85%). There was a significant effect of EAc on the outcome measures (\( F(25,5375) = 2.06, \ p = .001, \eta_p^2 = .010 \)). Between-groups effects remained significant at the adjusted \( \alpha \) for CBL (\( F(1,5399) = 8.70, \ p = .003, \eta_p^2 = .002 \)) and ventral striatum (EAc+: \( M = .0336, SD = .01 \); EAc–: \( M = .0338, SD = .01 \); \( F(1,5399) = 9.74, \ p = .002, \eta_p^2 = .002 \)). Bonferroni-corrected t-tests on the individual cerebellar IDPs showed only a trend towards significance in cerebellar lobules I–IV (\( p = .008 \)), lobe IX (\( p = .009 \)), Crus I (\( p = .011 \)), vermis VIIIa (\( p = .007 \)) and VIIib (\( p = .016 \)). All other multivariate tests on the remaining AEIs remained nonsignificant (\( p > .1 \)). Finally, we reran the significant MANOVA to test whether acquiring the images on two scanners introduced bias (Newcastle observations dropped: 258; \( N = 6,493 \)). The multivariate test remained significant (\( F(25,6467) = 1.93, \ p = .004, \eta_p^2 = .007 \)), as did the univariate tests (CBL: \( F(1,6491) = 7.65, \ p = .006, \eta_p^2 = .001 \); ventral striatum: \( F(1,6491) = 10.93, \ p = .001, \eta_p^2 = .002 \)). Individual analyses on all IDPs are shown in Table S10 (Appendix S4).

**Discussion**

This study used multiple brain phenotypes and retrospectively reported AEIs in childhood and adulthood, reflecting early adversity and partner abuse, respectively, in a large population sample of adults, aiming to contribute to current efforts of understanding the neural consequences of adversity. We found that participants who experienced emotional abuse in childhood had smaller global cerebellar volumes and ventral striatum. Cerebellar lobules I–IV were particularly affected, and to a lesser extent, Crus I. While this result remained significant in a random subsample, we note the small effect sizes (\( \eta_p^2 < .01 \)). We also report uncorrected individual associations in Table S10 to illustrate the presence of other putative findings (e.g. amygdala–physical neglect, \( \beta = -0.1 \)). Such associations did not meet the current statistical rigours, lending further support to the conclusion that associations between AEIs...
and brain structures in our sample showed small effects. Finally, there were no significant differences in total grey and white matter volumes on either of the adversity items, suggestive of localized effects.

The finding that the volumes of the cerebellum and ventral striatum were smaller in individuals exposed to childhood adversity is in agreement with previous reports (De Bellis & Kuchibhatla, 2006; Edmiston et al., 2011; Walsh et al., 2014). Indeed, the cerebellum supports emotional processing (Schmahmann & Sherman, 1998), has abundant glucocorticoid receptors (Sanchez et al., 2000), and it has a protracted developmental time course, thus remaining vulnerable to environmental factors for longer (Giedd et al., 2007). The ventral striatum is implicated in reward processing, a function which is affected by childhood AEs, predicting depressive symptoms (Hanson et al., 2015) and neuroendocrine hyperactivation (Pruessner et al., 2004). Interestingly, the cerebellum and basal ganglia are strongly connected via disynaptic projections, suggesting that changes in one node may influence the other. While it is yet to be determined whether the ventral striatum part of the basal ganglia receives these projections (Bostan & Strick, 2018), empirical evidence lends support in this direction (Li et al., 2014). Computationally, the striatum associates reward/punishment signals to cerebellar processes (Doya, 2000). Conversely, cerebellar granule cells compute expectations of reward (Wagner et al., 2017). Having identified associations between both structures and reports of childhood emotional abuse (albeit small in magnitude), this finding may further support the argument of their interconnected activity, specifically in the realm of emotional processing.

We acknowledge a series of important weaknesses, which caution the interpretation of these results beyond the limitations imposed by the use of retrospective and nonstandard adversity measures in a cross-sectional design. First, the adversity information available in UK Biobank is limited. We refer here to individual items, using convention, such as ‘emotional abuse’, given ‘yes’ responses on the item: ‘felt hated by family member as a child’ (anywhere on the spectrum: rarely—very often). Indeed, to qualify as adversity the quantifiable experiences need to suggest chronicity (e.g. institutional rearing) or represent single events of increased severity (e.g. sexual abuse) (McLaughlin et al., 2019). Furthermore, evidence on the effects of childhood AEs on the brain is consistent with a dimensional model of adversity related to the concepts of threat and deprivation (McLaughlin et al., 2014), which, arguably, may not be reflected in all items used here. This might explain why some consistent findings, such as reductions in the prefrontal cortex, were not replicated. Second, by assessing adversity retrospectively, the analysis does not account for other probable sources of pre-existing vulnerability in brain phenotypes (Lupien et al., 2018). A recent meta-analysis demonstrated that childhood AEs collected prospectively identify a different group of individuals based on mental illness risks, compared to studies including adults who recall AEs retrospectively from their childhood (Baldwin et al., 2019). It is plausible that the associated neural signatures are also different. Third, a longitudinal design, as opposed to the current cross-sectional approach, would be more suitable to capture neural changes and their timing, without being confounded by other factors influencing brain structure. Fourth, we acknowledge the small effect sizes observed throughout, which suggest that the biological effects in this sample, while significant, may not translate in altered behaviour. Finally, it is important to note that given the volume of neuroimaging data, identification of the IDPs included here cannot be ensured by expert human operators. Therefore, while there is comparable overlap between the phenotypes obtained using hand tracing vs automated processes, we acknowledge the potential biases introduced by the latter (Morey et al., 2009).

In conclusion, this cross-sectional study shows that retrospective reports related to emotional abuse are associated with small reductions in the cerebellum and ventral striatum, in a large population of adults. Future studies should continue to use large samples to build on a literature consensus. However, longitudinal cohort designs acquiring prospective and precise assessments of adversity are needed.

Supporting information
Additional supporting information may be found online in the Supporting Information section at the end of the article:

Appendix S1. Selection of the analytical sample and descriptives.
Appendix S2. Brain imaging.
Appendix S3. Principal component analysis.
Appendix S4. Supplemental results.
Figure S1. Distribution of scores for AEs (%).
Figure S2. Selection of the analytical sample.
Figure S3. Number of observations with datapoints outside \pm 3SD.
Figure S4. Scree plots of parallel analysis for each PCA based on the grey matter IDPs.
Table S1. Demographics.
Table S2. Comparative morphometrics.
Table S3. Group comparisons between participants included and those excluded from the dataset.
Table S4. Pearson correlations between white matter microstructural measures (FA).
Table S5. Pearson correlations between white matter microstructural measures (MD).
Table S6. Latent factors of grey matter structure – Pearson correlations.
Table S7. Principal Component Analysis: tract loadings for Fractional Anisotropy and Mean Diffusivity.
Table S8. Principal Component Analysis: factor loadings for grey matter IDPs.

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Table S9. MANOVA tests including IDPs without outlier exclusion.
Table S10. Logistic regressions on all investigated IDPs.

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Key points
- Adversity-related changes in brain structure increase vulnerability to psychopathology.
- Larger sample sizes are needed to increase convergence among findings.
- We demonstrate that retrospective reports of self-perceived emotional abuse in childhood are associated with smaller cerebellum and ventral striatum.
- Future studies should continue using large datasets together with longitudinal designs and comprehensive assessments of adversity.

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